Cascade Metathesis Reactions for the Synthesis of Taxane and Isotaxane Derivatives

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Abstract: Tricyclic isotaxane and taxane derivatives have been synthesized by a very efficient cascade ring-closing diene-yne metathesis (RCDEYM) reaction, which formed the A and B rings in one operation. When the alkyne is present at C13 (with no neighboring gem-dimethyl group), the RCDEYM reaction leads to 14,15-isotaxanes 16a,b and 18b with the gem-dimethyl group on the A ring. If the alkyne is at the C11 position (and thus flanked by a gem-dimethyl group), RCDEYM reaction only proceeds in the presence of a trisubstituted olefin at C13, which disfavors the competing diene ring-closing metathesis reaction, to give the tricyclic core of Taxol 44.

Introduction

Taxol® (paclitaxel), together with its derivatives Taxotere® (docetaxel) and Jevtana® (cabazitaxel) are the largest selling anticancer drugs of all time, with sales of over three billion USD per year for Taxotere alone in 2010.[1] Originally indicated for the treatment of ovarian and breast cancers, they are now widely prescribed to treat a broad range of malignancies.[2] The structures of these three compounds only differ in terms of the functionalization of the amine on the side chain and the hydroxyl groups at C10 and C7 (Scheme 1). Taxol is currently being manufactured through plant-cell fermentation by Phyton Biotech, LLC, a DBP Pharmaceuticals Company for Bristol–Myers Squibb, whilst Taxotere and Jevtana are produced by semisynthesis from 10-deacetylbaccatin III by Sanofi, which still requires an expensive extraction process of natural resources. There have been six total syntheses of Taxol by the groups of Holton,[3] Nicolaou,[4] Danishefsky,[5] Wender,[6] Mukaiyama[7] and Kuwajima,[8] as well as three formal syntheses by the groups of Takahashi,[9] Nakada[10] as well as Sato and Chida,[11] but they all comprise at least 37 steps.[12] An efficient synthesis of active taxoid analogues has yet to be achieved, because of the sterically hindered, complex and highly functionalized structure of these compounds.

A rapid synthesis of the tricyclic core of Taxol where all of the functional groups required for activity are present or in an atent form would facilitate access to a diverse array of novel taxoids with potential anticancer activity. We report here a synthetic strategy featuring a cascade ring-closing dienyne metathesis (RCDEYM) reaction that allows access to the ABC tricyclic
Results and Discussion

Our initial retrosynthesis is outlined in Scheme 1. We aimed for a formal synthesis of Taxol, so we chose the intermediate 4 described by Holton during his synthesis of this natural product as our primary target. The A ring would be closed by a pinacol coupling between the ketones at C11 and C12 in compound 5, as previously described by Mukaiyama on a similar substrate. The ketone at C12 would be installed by hydration of alkyne 6. The eight-membered B ring would be formed by a ring-closing metathesis (RCM) reaction between the alkenes at C10 and C11 in compound 7. This key step was successful in our synthesis of model BC bicyclic systems of Taxol (with no hydroxyl group at C7 and a butyl side chain at C1). Finally, the metathesis precursor 7 would be assembled by a Shapiro reaction between hydrazone 8 and aldehyde 9. This coupling reaction has proved to be very diastereoselective on similar substrates during our previous approaches to taxoids.

Our synthesis commenced with the preparation of aldehyde 9 (Scheme 2). Commercially available 3-pentyn-1-ol was oxidized with the Dess–Martin periodinane (DMP) and the resulting aldehyde was subjected to a Barbier reaction with prenyl bromide under the Luche conditions to furnish alcohol 10 in excellent yield. Oxidation of alcohol 10 gave the corresponding ketone 11, which was submitted to trimethylsilyl cyanide in the presence of a chiral tertiary amine, 1,4-diazabicyclo[2.2.2]octane (DABCO) as a catalyst. The resulting cyanoalcohol was reduced to the intermediate imine, which was hydrolyzed to give the racemic aldehyde (±)-9 by exposure to silica gel. Optically active aldehyde 9 was also prepared in 99% ee in a similar fashion using a chiral amine base for the cyanation reaction, but we chose to pursue the synthesis of the metathesis precursors with the racemic aldehyde to widen the array of taxoids generated, and to study the influence of the stereochemistry of the precursor on the RCM reaction outcome.

In order to test the key metathesis reaction, we decided to use a 7-deoxy C ring as a coupling partner in the Shapiro reaction. It is worth noting that the removal of the functional group at C7 in Taxol did not result in a significant loss of bioactivity. When hydrazone 12 (Scheme 3), prepared in 76% yield from the corresponding known ketone, was submitted to tBuLi for the Shapiro coupling, only degradation was observed. We surmised that this was due to the deprotonation at the allylic position, and thus the alkene was masked as a protected primary alcohol. Enantiopure hydrazine 13 was treated with aldehyde (±)-9 using conditions we had developed previously. To our surprise, the reaction only proceeded in 20% yield. Several additives were screened. Addition of MgBr₂ and ZnCl₂ did not lead to any of the desired product, but we observed a dramatic increase in yield when dry CeCl₃ was stirred for 30 min with the vinylithium reagent derived from hydrazine 13 before addition of aldehyde (±)-9. and diols 14a,b were obtained in 85% combined yield after hydrolysis of the TMS ether. The reason for this difference in reactivity between the model aldehyde (butyl side chain at C1) and (±)-9-(2-butyl) side chain at C1 is unclear.

As had been observed previously for the model aldehydes, this reaction was highly diastereoselective, giving the trans dial compounds 14a and 14b after hydrolysis of the trimethylsilyl ether. The stereochemistry of these compounds was assigned by comparing their proton NMR spectra with those of the corresponding model Shapiro adducts possessing a butyl side chain at C1. Diols 14a and 14b were then submitted separately to trityl ether hydrolysis, elimination of the resulting primary alcohol using the Grieco protocol and protection of the C1–C2 diol as the cyclic carbonate ester to furnish the metathesis precursors 15a and 15b in 75% and 65% overall yields for the four steps, respectively. No intermediate purification was required for these transformations.

We first tried out the key RCM reaction on carbonate 15a, which possesses the opposite configuration at C1 and C2 compared to Taxol. Treatment of this compound with 10 mol% of the second-generation Grubbs precatalyst in toluene at reflux for 24 h did not lead to the desired cyclooctene, but gave a tricyclic derivative 16a instead of Scheme 4. This product resulted from an enyne metathesis reaction between the alkene at C10 and the alkyne at C13, furnishing the intermediate bicyclic...
16a’, which further cyclized by a diene metathesis to give 16a in good yield. This intermediate 16a’ could be isolated as a 1:1 mixture with 16a if only 5 mol% of the precatalyst was used for the reaction. The first enyne metathesis reaction was not unexpected,\(^\text{27}\) what was more surprising to us was the ease of formation of the strained tricyclic system in compound 16a. This 14,15-isotaxane has an unprecedented skeleton, which is very similar to that of taxane derivatives, except that the C14 and C15 carbons have swapped positions, which places the gem-dimethyl group in the A-ring alone. In addition, the C2 stereogenic center possesses the undesired configuration for Taxol.

In an effort to assess the influence of the nature of the diol protecting group on the outcome of the metathesis reaction, which was shown to be crucial for model compounds,\(^\text{11b}\) the benzoate 17a was prepared by addition of phenyllithium to the carbonate 15a (Scheme 4). Unfortunately, benzoate 17a did not undergo metathesis when treated with the Grubbs 2 precatalyst, but slowly decomposed.

A similar cascade diene metathesis reaction was observed with stereoisomer 15b, but the reaction proceeded under milder conditions and gave tricycle 16b in 91% yield (Scheme 4). This time, RCM of benzoate 17b, obtained by phenyllithium addition to 15b, furnished isotaxane 18b in 57% yield, underscoring the influence of the configuration at C1 and C2 on the outcome of the metathesis reactions.\(^\text{11b}\) These isotaxanes possess the undesired configuration at C1. Isotaxane 16b was crystalline, and its X-ray crystallographic analysis\(^\text{28}\) (Figure 1) established its tricyclic structure and confirmed the configuration of the carbonate-bearing stereocenters at C1 and C2.

The isotaxanes 16a, 16b and 18b represent a novel class of Taxol analogues, and could be transformed into potentially active compounds. Indeed, taxanes such as tasumatrols E, F and G (Figure 2), isolated from Taxus sumatrana, do not possess the classical ABC 6,8,6-tricyclic system of Taxol; however, they exhibit more potent activity than Taxol in vitro against four human cancer cell lines.\(^\text{29}\)

An easy way to circumvent the unwanted dienyn metathesis cascade is to perform the alkyne hydration before the RCM step, and this has been achieved in excellent yield (Scheme 5). Diol 19 was prepared in three steps from the Shapiro adduct 14b in 68% overall yield. Treatment of alkyne 19 with the Gagosz catalyst\(^\text{30}\) in the presence of water did not give the corresponding ketone but hemiketal 20.\(^\text{31}\) Fortunately, compound 20 underwent ring-closing metathesis in 98% yield to form the BC ring system of Taxol 21. Work is in progress for the completion of the synthesis of the tricyclic core of Taxol according to the retrosynthesis shown in Scheme 1.

On the other hand, we also wanted to take advantage of this very efficient metathesis cascade to synthesize the ABC tricycle of Taxol, and our revised retrosynthesis is shown in Scheme 6. The 2-ene-1,4-diol unit of compound 4 would be installed by a Ti\(^\text{16}\) radical-mediated opening of the corresponding 1,3-diepoxide, which can be generated from the 1,3-diene moiety at C10-C13 of compound 22.\(^\text{12}\) A hydroboration/oxi-

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**Scheme 4.** Attempts at metathesis and synthesis of isotaxanes. a) 5 mol% Grubbs 2, toluene, 110° C, 48 h; 1:1 16a/16a’ 30%; b) 10 mol% Grubbs 2, toluene, 110° C, 24 h; 16a 62%; c) PhLi, THF, −78° C, 17a 54%; 17b 70%; d) 5 mol% Grubbs 2, toluene, 80° C, 2 h, 91%; e) 5 mol% Grubbs 2, toluene, 110° C, 1 h, 57%. For the structure of Grubbs 2, see Table 1.

**Scheme 6.** The revised retrosynthesis for the ABC tricyclic core of Taxol.

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**Figure 1.** ORTEP (50% probability) representation of compound 16b.

**Figure 2.** Structures of tasumatrols E, F and G.
The synthesis of aldehyde 24 in its racemic form was not as straightforward as the synthesis of the corresponding aldehyde 9. It started with ester 26 obtained by propargylation of ethyl isobutyrate (Scheme 7). Attempts to isomerize the terminal alkyne of 26 into the internal one with potassium tert-butoxide only resulted in degradation products. Fortunately, this isomerization reaction was successful on the corresponding acid 27, and acid 28 was obtained in 94% yield. Addition of crotylmagnesium chloride to the corresponding Weinreb amide (compound 41, see Scheme 9 for structure) furnished a complex mixture of products, so we next turned to the cyclization of aldehyde 29. Treatment of this aldehyde with crotyl magnesium chloride in the presence of aluminum trichloride led to a 1:1.5 mixture of α and γ crotylation products. Fortunately, allyl transfer from 2,3-dimethyl-4-penten-2-ol catalyzed by tin(II) triflate gave the desired alcohol 30 (as an inescapable 3:1 mixture of E/Z isomers) in 76% yield after 2 days. Oxidation of 30 with 2-iodoxybenzoic acid (IBX) followed by homologation of the resulting ketone 31 furnished aldehyde (±)-24 in good overall yield.

The dienynes 32a,b and 34a,b were prepared using a similar reaction sequence to the one used for compounds 15a,b and 17a,b, as described in the preliminary account of our work. Metathesis reactions of carbonates 32a,b and benzoates 34a,b with Grubbs 2 catalyst did not produce tricyclic compounds, but led to the bicycles 33a,b and 35a,b, respectively, from a simple diene RCM between the olefins at C10 and C13 (Scheme 8).

Compound 33a was crystalline, and its X-ray crystallographic analysis (Figure 3) confirmed the configuration at C1 and C2 of the metathesis precursors 32a and 34a.

We had assumed that in the case of compounds 15 and 17, the initial enyne metathesis (between C10 and C13) would be favored compared to the alternative diene metathesis (between C10 and C11) because it would lead to a more stable tricyclic product after subsequent diene metathesis, but it seems that in all cases the first RCM takes place at C13, so the undesired diene RCM is disfavored. We thus embarked on the synthesis of metathesis precursors bearing a trisubstituted olefin at C13. The synthesis of
the aldehyde (±)-36 required for their preparation is shown in Scheme 9. Prenyl transfer to aldehyde 29 from 2,3,3-trimethyl-4-penten-2-ol was unreliable, with yields of 15 to 61%. Ketone 38 was then obtained by IBX oxidation. An umpolung synthesis of 38 was also achieved. Prenylation of dithiane 39, prepared from aldehyde 29, furnished 40 in excellent yield. Hydrolysis of the dithiane moiety gave ketone 38. However, this route was not very convenient on large scale, so as a last resort prenylation of the Weinreb amide 41 derived from acid 28 (Scheme 7) was also attempted. To our surprise, this reaction was very clean and afforded ketone 38 in 95% yield. In this fashion, aldehyde (±)-36 was obtained after homologation of 38 in 7 steps and 66% overall yield from ethyl isobutyrate.

Compounds 42a,b and 43a,b bearing a trisubstituted olefin at C13 were synthesized in the same way as compounds 32a,b and 34a,b as previously described, then subjected to the Grubbs 2 precatalyst in toluene at reflux (Scheme 10). We were disappointed to find out that carbonate 42a and benzoate 43a,b possessing the undesired configurations at C1 and C2, furnished the bicyclic compounds 33a and 35a that we had already observed for the metathesis reactions of 32a and 34a (Scheme 8). Taxol-like benzoate 43b also underwent diene RCM to produce 35b. However, Taxol-like carbonate 42b furnished compound 44 after RCDEYM, which corresponds to the tricyclic core of Taxol, along with the undesired bicyclic compound 33b.

In order to confirm the structure of the highly strained tricyclic product 44, we converted it to the crystalline p-nitrobenzoate derivative 45 by hydrolysis of the carbonate and acylation of the resulting secondary alcohol (Scheme 11). X-ray crystallographic analysis of 45 not only confirmed the tricyclic structure, but also established without ambiguity the configurations at C1 and C2 for the Taxol-like series of compounds. We then set to optimize the yield of the desired tricyclic compound 44. The 44/33b ratio was the same under different concentrations ranging from 3×10⁻³ to 15×10⁻³ M, so all metathesis reactions were performed at 5×10⁻³ M. Toluene at reflux proved to be a better choice than 1,2-dichloroethane at reflux (80°C) or xylene at reflux (140°C). Various precatalysts were then screened (Table 1). No reaction was observed with the less reactive Grubbs 1 precatalyst, so we tested second-generation ruthenium complexes. The Hoveyda–Grubbs precatalyst HG2 gave an improved yield of the desired compound 44 compared to the Grubbs 2 precatalyst (69 vs. 45%), and so did the Grela complex, which possesses an imidazolidino group attached to the benzylidene ligand. Pleasingly, the HG2 derivative Zhan1B, which possesses a N,N-dimethylcyanamido group gave the desired product 44 in 86% yield.
The best yield (70%) of compound 44. It seems that RCDYEM is favored with precatalysts possessing high initiation rates.

The different ratios observed with the Hoveyda–Grubbs-type precatalysts cannot be easily rationalized. Indeed, metathesis of substrate 42b with any precatalyst will result in the same carbene (Scheme 12). This intermediate should then lead to the same ratios of 44 and 33b after cyclization, releasing the same isopropylidene catalyst. The only difference between the reactions is the ligand released after the first catalytic cycle, which could recombine with the isopropylidene catalyst to reform the precatalyst. To probe the influence of the ligand, a metathesis experiment was run with 10 mol% of the Hoveyda–Grubbs 2 precatalyst and 300 mol% of the corresponding ligand, but the observed ratio of 44 and 33b was very similar to the one observed without any added ligand.

Attempts to convert bicyclic product 33b to the desired tricycle 44 by heating it in toluene at reflux in the presence of the Grubbs 2 or Zhan-1B precatalyst were unsuccessful, even

| Precatalyst       | Yield of 44 [%] | Yield of 33b [%] |
|-------------------|----------------|-----------------|
| Grubbs 1          | 0%             | 0               |
| Grubbs 2          | 45             | 45              |
| Hoveyda–Grubbs 2  | 59             | 38              |
| Grela             | 55             | 45              |
| Zhan-1B           | 70             | 20              |

[a] Reaction conditions: a) 10 mol% precatalyst, toluene, 5 × 10⁻⁵ M, 110°C. (b) No reaction was observed.

Scheme 12. Metathesis scheme. Conditions: toluene, reflux.
under microwave conditions. When 10 mol% of precatalyst was used, only \( 33b \) was recovered, and with 100 mol% of precatalyst decomposition occurred. Ring opening of \( 33b \) in the presence of ethylene was not considered, because it would lead to a carbene unsubstituted at C13, \text{carbene}' (Scheme 13), which would undergo diene metathesis preferentially. In an effort to regenerate the carbene with a trisubstituted olefin at C13, bicycle \( 33b \) was submitted to the above conditions in the presence of 2-methyl-2-buten, the reagent which Grubbs and co-workers have employed for the synthesis of trisubstituted olefins from their terminal homologues by cross metathesis,[13] but to no avail (Scheme 13). These results seem to indicate that the formation of compound \( 33b \) is not reversible, and that the metathesis reactions leading to \( 33b \) and 44 are under kinetic control.

**Scheme 13.** Equilibration attempts.

**Conclusions**

In summary, we have synthesized Taxol analogues with an unprecedented skeleton as well as the tricyclic core of Taxol in a very efficient fashion. The key step in these syntheses is a cascade ring-closing diyne metathesis (RCDEYM) reaction, leading to either 14,15-isotaxane tricyclic ring systems or the tricyclic ring system of Taxol in one operation from simple precursors, by judicious choice of the position of the alkyne (C13 for isotaxanes or C11 for taxanes). Furthermore, in the case of the taxane synthesis, we have shown that we can direct the course of the crucial metathesis reaction by adding a temporary methyl substituent to the olefin at C13, which does not appear in the structure of the tricycle. Calculations rationalizing the different outcomes of the metathesis reactions of compounds 42a,b and 43a,b, which strongly depend on the stereochemistry and the protecting group of the diol at the C1 and C2 positions in the metathesis precursors, will be reported in due course.

**Experimental Section**

All experimental details can be found in the Supporting Information. The material includes compound characterization, crystal structures of \( 16b \) and \( 33a \), and copies of spectra for all new compounds.

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