Synthetic Methods

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Step-Economical Synthesis of Taxol-like Tricycles through a Palladium-Catalyzed Domino Reaction**

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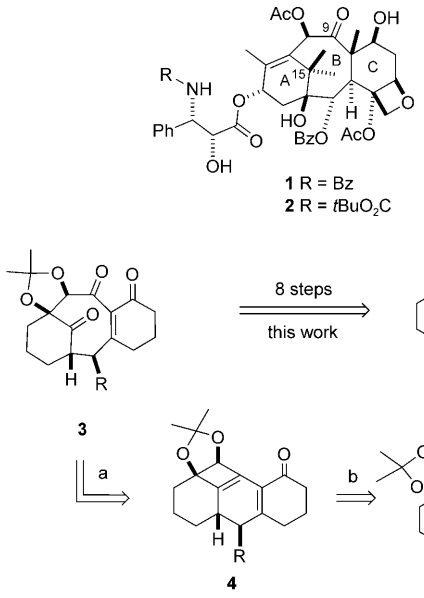
The world of natural bioactive products offers a large variety of structurally complex molecules.[1] Two main factors slow their study and clinical advancement: 1) the scarcity and variability of the natural sources and 2) their availability by synthesis which often requires many steps and therefore time and effort. In contrast, knowledge of how a natural product functions could allow for the design of simpler, more synthetically accessible, and more effective agents. Several studies on this function-oriented synthesis (FOS) concept[2] have been published, and have resulted in affording simplified active drug leads inspired by the more complex natural products.[3] A key to success in an FOS approach is the design of a step-economical route to the core scaffold. Typically, cascade or domino reactions[4] offer efficient ways to quickly achieve scaffold complexity. Herein, we describe a facile route to the taxane tricyclic core that is part of a larger program to ultimately produce simplified agents exhibiting superior functional activity.

The aim of this work is not to access the natural product but a core scaffold which could be decorated to achieve activity comparable or superior to taxol. Since its discovery in 1971 by Wani, Wall, and co-workers, taxol (**1**; see Scheme 1 for structure) has generated great research interest and significant therapeutic benefit.[5] The inherent chemical complexity of this polycyclic compound has also stimulated much synthetic interest, and has led to six total syntheses of taxol reported to date.[6] Notwithstanding the value of **1** and taxotere (**2**) for the treatment of various cancers, development of cellular resistance to these agents is a major cause of failure in therapy. Recent investigations have focused on the development of new taxanes or taxane modifications that would overcome this resistance.[7] Step-economical access to new taxanes, particularly those that would overcome resistance, is thus a goal of great clinical importance.[8] In recent years, our research group has developed efficient cascade reactions that provide rapid access to new polycyclic compounds. These processes are initiated through a 4-*exo*-dig cyclocarbo-palladation and subsequent Stille cross-coupling and/or intramolecular Heck reaction. Completion of the domino process with a 8π and/or 6π electrocyclization, leads to three new rings overall and multiple stereogenic centers on a densely functionalized framework.[9]

Herein, we describe a new, rapid, and efficient strategy for accessing the highly functionalized taxane ring system **3** in two key steps (Scheme 1). With this strategy, the tricyclic skeleton of taxol (**1**) was expected to be derived by a regioselective oxidative cleavage of the most strained double bond of the diene **4**. Based on our method, this racemic tetracyclic structure would be obtained in a two-step process through a palladium-catalyzed domino sequence reaction using propargylic alcohol **5** and subsequent oxidation of the hydroxy group.



Scheme 1. General strategy: a) oxidative cleavage; b) 1. 4-*exo*-dig/6-*exo*-trig/6π electrocyclization palladium-catalyzed cascade; 2. oxidation. Bz = benzoyl.

Significantly, polycycle **3** is potentially available in only eight steps from 2-bromocyclohexenone through this strategy. In exploring our plan, a range of propargylic alcohols **5** with various R groups and different alkene geometries (*Z* or *E*) were prepared in one step from alkyne **6**, which in turn was synthesized in four steps from 2-bromocyclohexenone. Alkyne **6** was treated with *n*BuLi at −78 °C, then with aldehydes **7**[10] to afford precursors **5** in 60–90 % yield (Scheme 2). All chiral compounds described in this study are in racemic form.

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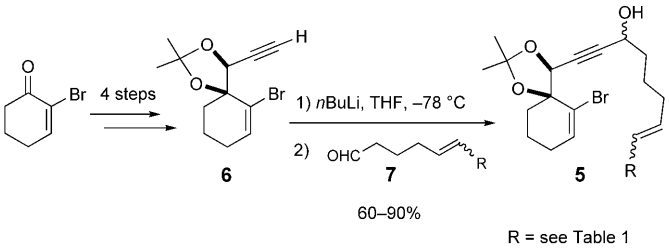
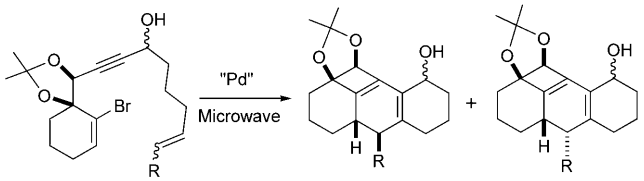


Scheme 2. Preparation of domino precursors **5**. THF = tetrahydrofuran.

As summarized in Table 1, the alkenylbromides **5** were then treated with $[Pd(PPh_3)_4]$ (5 mol%) as catalyst in the presence of diisopropylamine in benzene under microwave heating to afford in a single process and three steps the

Table 1: Microwave-assisted domino reaction of **5**.[a]

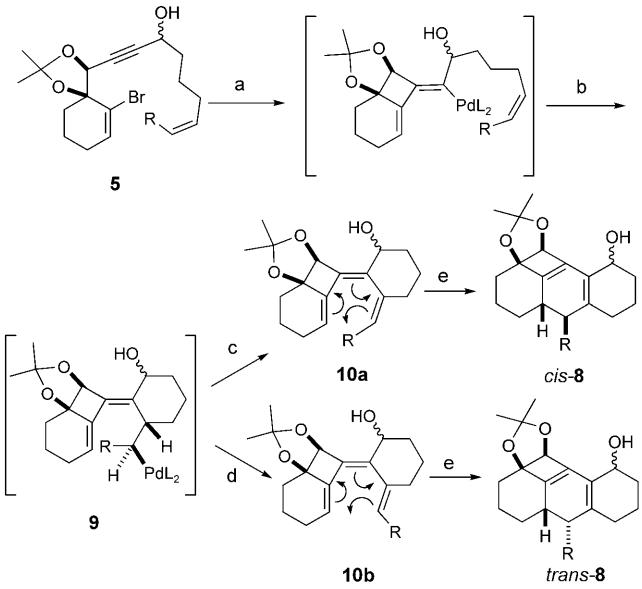


Entry	R	Configuration of **5** (*Z*/*E*)	*cis*/*trans*[b]	Yield [%][c]
1	H	–	–	35 (**8a**)
2	$SiEt_3$	10:90	0:100	23 (**8b**)
3	$SiMe_3$	100:0	100:0	65 (**8c**)
4	Ph	40:60	30:70	65 (**8d**)
5	Ph	0:100	0:100	52 (**8d**)
6	Ph	100:0	83:17	62 (**8d**)
7	4-$OMeC_6H_4$	90:10	70:30	63 (**8e**)
8	4-$CF_3C_6H_4$	100:0	90:10	57 (**8f**)
9[d]	CO_2Me	0:100	0:100	52 (**8g**)
10	CO_2Me	100:0	100:0	60 (**8g**)

[a] Reaction conditions: $[Pd(PPh_3)_4]$ (5 mol%), iPr_2NH (20 equiv), benzene, microwave 160°C, 20 min. [b] Determined by ^1H NMR spectroscopy. [c] Yield of isolated product. [d] Reaction carried out at 130°C.

tetracyclic ring **8** as a mixture of two or four diastereoisomers. In this domino reaction, the yields of the products varied mainly owing to the nature of the R olefinic group. By using H or $SiEt_3$, **8a** and **8b** were obtained in modest yields (35% and 23%, respectively: Table 1, entries 1 and 2), whereas $SiMe_3$, CO_2Me, or any aryl group afforded the corresponding polycycles **8c**–**g** in yields between 52% and 65% (Table 1, entries 3–10). These quantities were sufficient to supply structure-function studies.

It is especially noteworthy that in this one-flask operation, three new carbon–carbon bonds, two new stereogenic centers, and one double bond common to three rings including a four-membered ring, are formed. These results show also that an *E* configuration for the double bond in the starting material, only slightly decreased the yields of the final polycycles (compare Table 1, entries 5 and 6 as well as entries 9 and 10). Furthermore and significantly, the double-bond geometry can be used to control the relationship between the bridgehead and pro C2 center. The *Z* olefins bearing a non-aromatic substituent gave, as a sole adduct, compound **8** with the *cis* configuration between the R group and the bridgehead hydrogen atom, whereas the *E* olefins gave exclusively compound *trans*-**8** (Scheme 3).

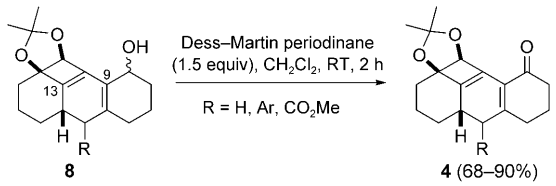


Scheme 3. Proposed mechanism for the palladium-catalyzed domino sequence. General reaction conditions: a) oxidative addition then 4-*exo*-dig; b) 6-*exo*-trig; c) *syn* dehydropalladation elimination; d) *anti* dehydropalladation elimination; e) 6π electrocyclization.

The excellent diastereoselectivity obtained in each of these specific cases can be rationalized by: 1) the stereospecificity of the disrotatory 6π electrocyclization according to the Woodward–Hoffmann rules,[11] and 2) the total torquoselectivity determined by the *cis*-protected diol **9**.[12] However, one can observe that the diastereoselectivity slightly decreased in favor of the *trans* adduct when R is a "*Z*-aromatic" substituent (Table 1, entries 6–8). This unusual selectivity is a possible consequence of an *anti*-hydride elimination of the palladium(II) intermediate **9** prior to the electrocyclization of **10** into **8** (Scheme 3).[13] The *anti*-hydride elimination in **9** produced the compound **10b**, where the stereoelectronic interactions between the aromatic moiety and the cyclohexene ring are minimized. The relative stereochemistry of these compounds has been fully established by using NMR spectroscopy. To control subsequent chemoselectivity, we oxidized the hydroxy group present in **8** to provide enones **4**. Such derivatives were easily prepared using Dess–Martin periodinane as the oxidant (Scheme 4).

The structure of the *cis*-**4f** derivative was confirmed by X-ray crystallographic analysis[14] (Figure 1) and the others by spectroscopic analogy.

It is worth noting that this oxidation did not work as well with **8c** (R = $SiMe_3$; Table 1, entry 3). Regardless of the oxidant used, a subsequent loss of the silyl group with an aromatization of the central ring was observed to afford ketone **11** in 64% yield. Thus, we tried to remove the silyl group before oxidation to avoid this problem by using



Scheme 4. Oxidation of the allylic alcohol **8**.

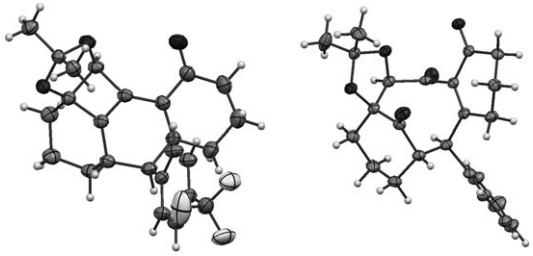
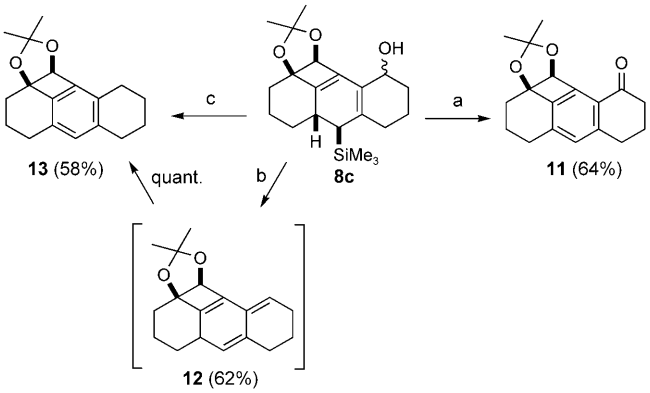


Figure 1. ORTEP drawings of **4 f** and **3 d** with ellipsoids at 50% probability.

classical conditions for desilylation.[15] All of these conditions afforded, with good yield, the triene **12** by vinylogous Peterson elimination,[16] which spontaneously aromatized into **13** (Scheme 5).

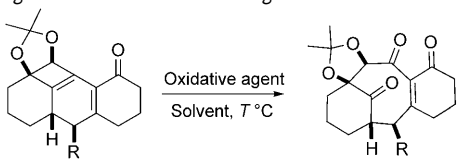
Polycycle **4** incorporates the core-ring system of taxanes with C9 and C15 "protected" as a tetrasubstituted double bond (Scheme 1 and 4). To remove this protection and reveal the eight-membered B-ring in the form of **3**, we investigated the regioselective oxidative cleavage of dienes **4**. Preliminary results showed that dienes *trans*-**4** led to complicated mixtures of products owing to a nonselective cleavage of the double bonds of starting material. However, in contrast, *cis*-**4** dienes underwent chemoselective cleavage of the desired double bond to produce taxane **3**. As summarized in Table 2, various oxidative agents were employed to perform this reaction.[17]

While a classical ozonolysis afforded a low yield of 19% of **3 d** (Table 2, entry 1), ruthenium tetroxide generated in situ



Scheme 5. Oxidation of domino product **8**. Reagent and conditions: a) pyridinium chlorochromate (2 equiv), celite, CH_2Cl_2, RT, 18 h; b) TBAF (1.1 equiv), THF, −78 °C, 1 h; c) *t*BuOK (5 wt%) in DMSO, H_2O, RT, 2 h. DMSO = dimethyl sulfoxide, TBAF = tetra-*n*-butylammonium fluoride.

Table 2: Regioselective oxidative cleavage of **4**.[a]



4 **3**

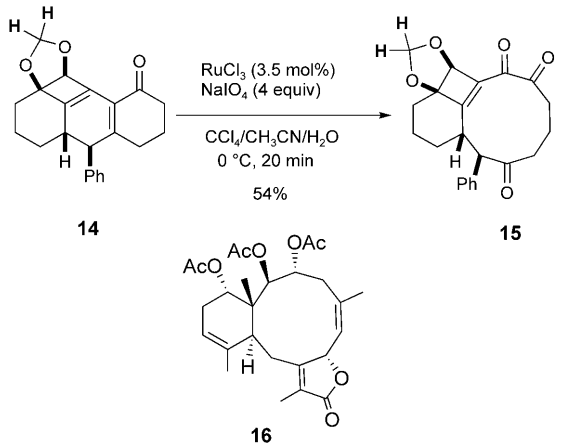
Entry	R	Oxidative agents	Solvent	Yield [%][b]
1[c]	Ph	O_3/pyridine	CH_2Cl_2	19 (**3 d**)
2[d]	Ph	$RuCl_3$/oxone/$NaHCO_3$	AcOEt/CH_3CN/H_2O	42 (**3 d**)
3[e]	Ph	$RuCl_3$/$NaIO_4$	CCl_4/CH_3CN/H_2O	44 (**3 d**)
4[f]	Ph	$RuCl_3$/$NaIO_4$	CCl_4/CH_3CN/H_2O	57 (**3 d**)
5[g]	4-$OMeC_6H_4$	$RuCl_3$/oxone/$NaHCO_3$	AcOEt/CH_3CN/H_2O	40 (**3 e**)
6[h]	4-$OMeC_6H_4$	$RuCl_3$/$NaIO_4$	CCl_4/CH_3CN/H_2O	44 (**3 e**)
7[h]	4-$CF_3C_6H_4$	$RuCl_3$/$NaIO_4$	CCl_4/CH_3CN/H_2O	62 (**3 f**)
8[h]	CO_2Me	$RuCl_3$/$NaIO_4$	CCl_4/CH_3CN/H_2O	50 (**3 g**)

[a] All reactions were carried out at 0 °C, except where noted. [b] Yield of isolated product. [c] Reaction was carried out at −78 °C, ozone, pyridine (20 equiv). [d] $RuCl_3$ (3.5 mol%), oxone (4 equiv), $NaHCO_3$ (8 equiv), AcOEt/CH_3CN/H_2O (1:1:1), 1 h. [e] $RuCl_3$ (3.5 mol%), $NaIO_4$ (2 equiv),CCl_4/CH_3CN/H_2O (1:1:1), 1 h. [f] $RuCl_3$ (3.5 mol%), $NaIO_4$ (4 equiv), CCl_4/CH_3CN/H_2O (1:1:1), 30 min. [g] $RuCl_3$ (3.5 mol%), oxone (4 equiv), $NaHCO_3$ (8 equiv), AcOEt/CH_3CN/H_2O (1:1:1), 1 h. [h] $RuCl_3$ (3.5 mol%), $NaIO_4$ (4 equiv), CCl_4/CH_3CN/H_2O (1:1:1), 30 min.

with an excess amount of oxidant such as sodium periodate or oxone was able to properly cleave the most strained tetrasubstituted double bond to afford taxane skeleton **3**. After some optimization of the reaction conditions, taxanes **3 d**–**g** were obtained in acceptable yields (up to 62%; Table 2, entries 3–7). Compound **3 d** gave crystals suitable for X-ray crystallographic analysis,[16] thus confirming unambiguously the structure and configuration of the newly synthesized taxanes (Figure 1). The excellent regioselectivity of this reaction could be explained by electronic effects: the double bond conjugated with the ketone moiety is electron-deficient and would thus not be expected to undergo a facile cleavage with electrophilic oxidants.

We expected to obtain the same results with **14** as the starting material, but were surprised to observe the exclusive formation of the ten-membered ring polycycle **15** in 54% yield when a less bulky protective group such as methylene unit was used for the diol protection instead of the *gem*-dimethyl (Scheme 6). Clearly, steric effects also influence the selectivity that is achieved in this cleavage process. Compound **15** represents the basic structure of brianthein A (**16**), which is a novel brianane-type diterpene recently isolated from the *gorgonian Briareum excavatum*.[18] Brianthein A is known for reversing multidrug resistance in human carcinoma cell lines.[18]

In summary, we have successfully developed a new, concise, and efficient strategy for accessing the taxane tricyclic scaffold. These new tricyclic structures are obtained using two key steps: the first step involves a palladium-catalyzed domino reaction based on methods previously



Scheme 6. Oxidative cleavage of **14**.

developed in our research group. The second step also involves a novel process in which a regioselective oxidative cleavage of a novel octasubstituted diene is achieved along with the production of a diketone. This step-economical route to highly functionalized taxane scaffolds allows for rapid access to new analogues and more generally to other polycycles possessing the bicyclo[5.3.1]undecane core of taxol. In addition, the basic carbon structure of brianthein A (**16**) has also been prepared by a slight modification of the starting compound. Activity studies and application of this method for the preparation of other polycyclic systems is actively being pursued in our laboratory and will be reported in due course.

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[14] CCDC 783559 (**4f**) and 783560 (**3d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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