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Formal Total Synthesis of (−)-Taxol through Pd-Catalyzed Eight-Membered Carbocyclic Ring Formation

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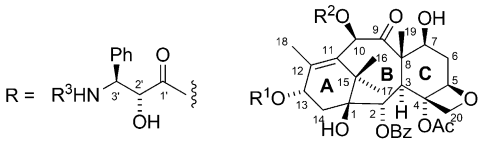
Abstract: A formal total synthesis of (−)-taxol by a convergent approach utilizing Pd-catalyzed intramolecular alkenylation is described. Formation of the eight-membered carbocyclic ring has been a problem in the convergent total synthesis of taxol but it was solved by the Pd-catalyzed intramolecular alkenylation of a methyl ketone affording the cyclized product in excellent yield (97%), indicating the high efficiency of the Pd-catalyzed intramolecular alkenylation. Rearrangement of the epoxy benzyl ether through a 1,5-hydride shift, generating the C3 stereogenic center and subsequently forming the C1–C2 benzylidene, was discovered and utilized in the preparation of a substrate for the Pd-catalyzed reaction.

Introduction

(−)-Taxol (Figure 1), which was isolated from the bark of the Pacific yew tree (Taxus brevifolia) by Wani et al.,[1,2] has been widely used as an anticancer drug.[3] In addition to the potent bioactivity of taxol, its complex structural features—a highly distorted 6-8-6 taxane scaffold with nine stereogenic centers including an all-carbon quaternary stereogenic center, diverse functional groups such as oxetane, *trans*-1,2-diol, acyloin, and a bridgehead double bond—make taxol an attractively challenging synthetic target. Indeed, over 200 papers describing synthetic studies of taxol have been published so far,[4–13] and further studies on the total synthesis of taxol are underway.[5] However, only seven total syntheses including a formal synthesis have been accomplished so far,[6–12] indicating the difficulties encountered in its total synthesis.



(–)-taxol (R^1 = R, R^2 = Ac, R^3 = Bz); taxotere (R^1 = R, R^2 = H, R^3 = Boc)
baccatin III (R^1 = H, R^2 = Ac)

Figure 1. Structures of (−)-taxol, taxotere, and baccatin III. Boc = *tert*-butoxycarbonyl.

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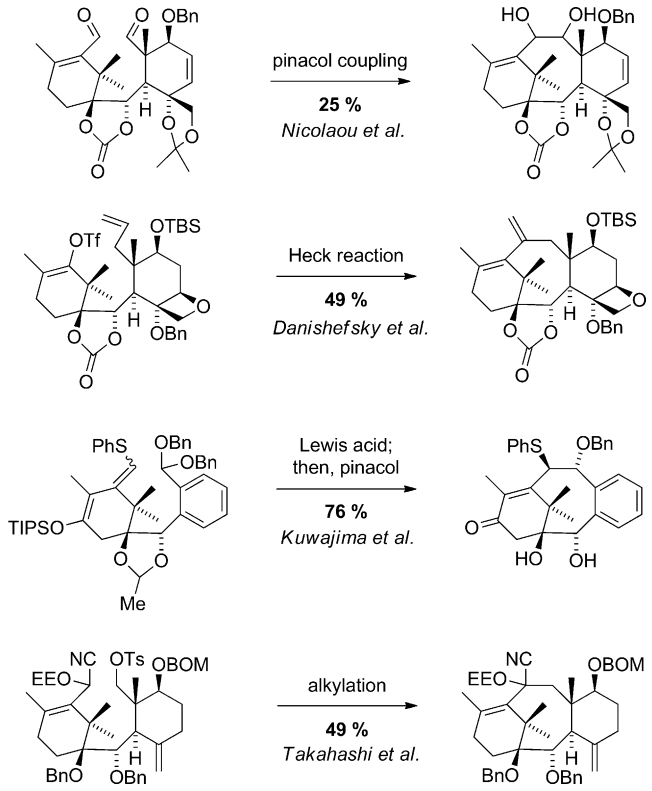
Although taxol and its congener, taxotere (Figure 1), are clinically important anticancer agents, some problems have been reported such as low water solubility, side effects, and the emergence of taxol-resistant tumors.[2] Thus, new derivatives of taxol have been studied to solve these problems; however, most of the structure-activity relationship studies have been initiated from baccatin III (Figure 1), thus, the diversity of derivatives is limited.

We envisioned that a convergent total synthesis of taxol would enable the synthesis of diverse taxol derivatives. Herein, we report the formal total synthesis of (−)-taxol through a convergent approach based on the stereoselective construction of the C3 stereogenic center by a 1,5-hydrogen shift–benzylidene formation sequence and the highly efficient formation of the eight-membered carbocyclic B-ring of taxol by Pd-catalyzed intramolecular alkenylation of a methyl ketone.

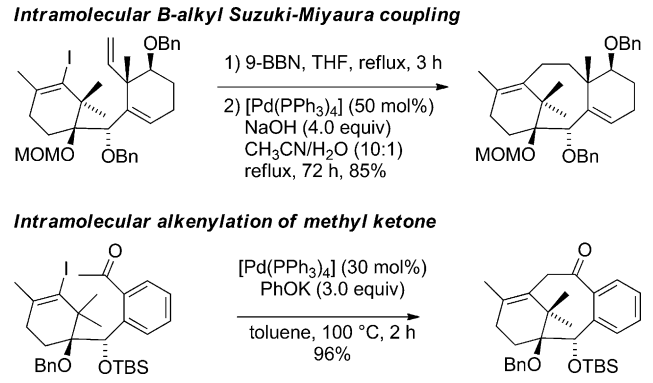
Results and Discussion

A convergent total synthesis allows the parallel preparation of building blocks, thus reducing time and also providing the advantage of the independent transformations of functional groups that are otherwise incompatible with each other. Moreover, a convergent synthesis is useful for affording derivatives with diverse structures. Thus, the convergent syntheses of taxol, that is, the preparation and coupling of the A- and C-rings, followed by the formation of the eight-membered B-ring and further transformations, have been studied by many research groups, and four convergent total syntheses of taxol[7,8,11] including a formal synthesis[12] have been reported.

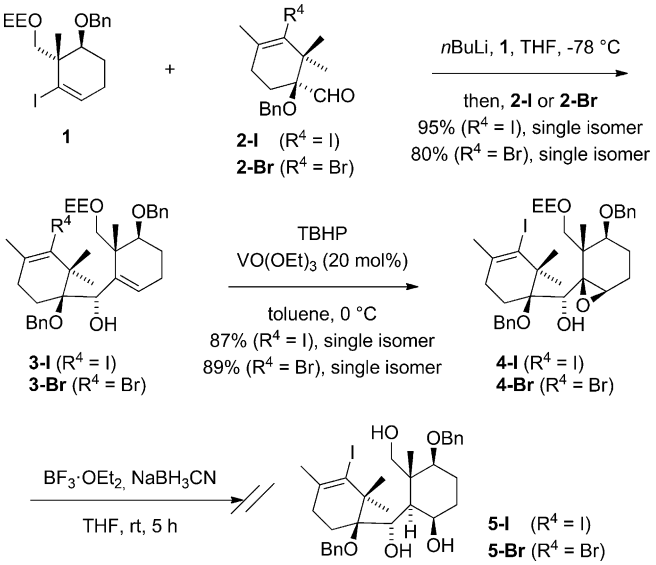
The formation of the eight-membered carbocyclic ring has been a synthetic problem because of its highly strained nature arising from the transannular strain. Indeed, the three convergent total syntheses of taxol suffered from difficulties in the formation of the eight-membered carbocyclic B-ring (Scheme 1). Thus, pinacol coupling,[7] the Heck reaction,[8] and



Scheme 1. Eight-membered carbocyclic B-ring formation in convergent total syntheses of taxol. Bn = benzyl; OTf = triflate; TBS = *tert*-butyldimethylsilyl; TIPS = triisopropylsilyl; EE = ethoxyethyl; Ts = tosyl; BOM = benzyloxymethyl.



Scheme 2. Eight-membered carbocyclic ring formations by Pd-catalyzed reactions reported by our group. 9-BBN = 9-borabicyclo[3.3.1]nonane.



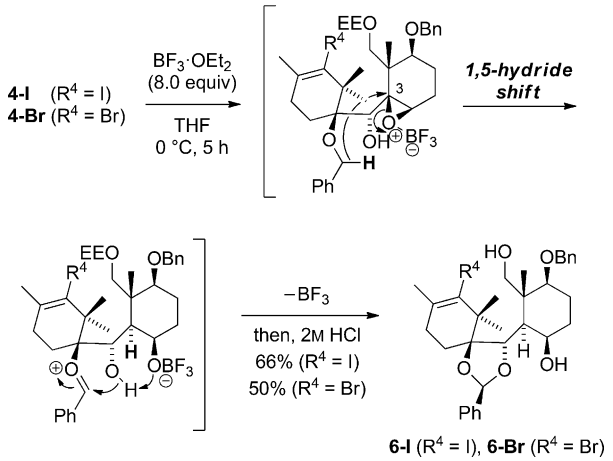
Scheme 3. Coupling reaction of **1** and **2**, and attempted preparation of **5**.

alkylation[12] were used for formation of the B-ring. However, the yield did not exceed 49%, indicating that the formation of the B-ring is challenging. An exceptional example is the efficient closure of the B-ring in Kuwajima's total synthesis,[11] which afforded the desired product in at least 76% yield, although the substrate is relatively simple and it required many further steps to realize the total synthesis.

We reported C–C bond-forming reactions using transition-metals that effectively formed eight-membered carbocyclic rings.[13c,e,g,14] In particular, Pd-catalyzed reactions; that is, intramolecular *B*-alkyl Suzuki–Miyaura coupling reactions[13c] and intramolecular alkenylation of methyl ketone[13g] to efficiently afford taxol model compounds (Scheme 2). Whereas the former reaction product has an ethylene at the C9–C10 position, which is difficult to selectively functionalize because our substrate possesses oxidation- and radical-sensitive functional groups such as a benzylidene acetal and a benzyl ether, the latter reaction product has a keto group at the C10 position, which enables facile functionalization. Therefore, to examine the applicability of the latter method for the formation of the B-ring of taxol, the substrate was prepared starting with the coupling reaction of compounds **1** with **2**-I and **2**-Br (Scheme 3), which were, in turn, prepared from known compounds[13b–d,i,15] reported by us.

The coupling reaction of **1** with **2**-I was successfully carried out through a halogen–Li exchange reaction to afford compound **3**-I as the sole product (Scheme 3). Sharpless epoxidation of olefin **3**-I using TBHP and $VO(acac)_2$[16a,b] afforded epoxide **4**-I as a single isomer, but the yield was improved (87%) by using $VO(OEt)_3$[16c] as the catalyst. Construction of the C3 stereogenic center was then attempted by the reduction of epoxide **4**-I. The reduction of **4**-I with $NaBH_3CN$ and $BF_3{\cdot}OEt_2$[17] was expected to take place at the more substituted carbon to afford compound **5**-I under acidic conditions. However, extensive structural analysis of the major product using NMR techniques revealed that compound **6**-I (Scheme 4) was obtained instead of **5**-I. The oxidation state of **6**-I was the same as that of **4**-I, indicating that the reaction proceeded without the action of the reducing agent, $NaBH_3CN$. Further optimization of the reaction under several acidic conditions improved the yield of **6**-I to 66%.[18]

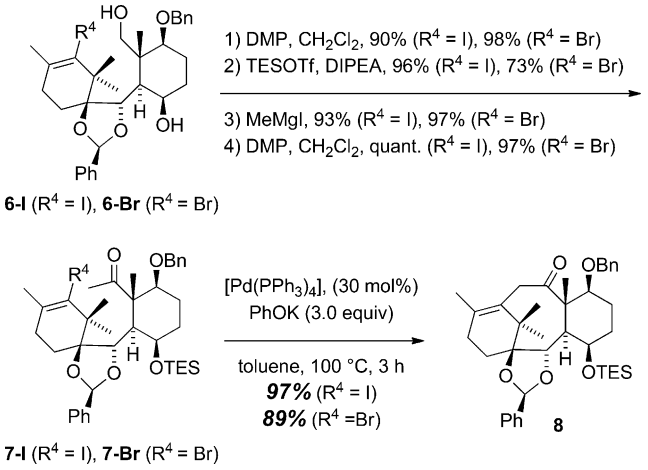
The reaction of compound **4**-I can be explained as follows (Scheme 4): First, $BF_3{\cdot}OEt_2$ activated epoxide **4**-I, thus inducing the 1,5-hydride shift from the proximal benzylic hydrogen of the C1 benzyl ether to the C3 position; that is, a hydride derived from the C1 benzyl ether underwent backside attack at



Scheme 4. The $BF_3{\cdot}OEt_2$ induced 1,5-hydride shift–benzylidene formation cascade.

the C3 position. Next, benzylidene formation, proton transfer, and treatment with 2 M HCl afforded compound **6**-I.

To investigate the Pd-catalyzed intramolecular alkenylation, compound **6**-I was converted into methyl ketone **7**-I (Scheme 5). The primary hydroxyl group of **6**-I was selectively oxidized to an aldehyde group, followed by TES ether formation at the C4 axial secondary hydroxyl group to an OTES



Scheme 5. Eight-membered carbocyclic B-ring formation by Pd-catalyzed intramolecular alkenylation. DMP = Dess–Martin periodinane; TES = triethylsilyl; DIPEA = *N*,*N*-diisopropylethylamine.

group, the reaction of the aldehyde group with methylmagnesium bromide to form the CH(OH)Me group, and Dess–Martin oxidation of the CH(OH)Me group to the COMe group, thus affording **7**-I. Compound **7**-Br was also successfully prepared from **2**-Br[13j] according to the transformations used to prepare **7**-I from **2**-I.

The Pd-catalyzed intramolecular alkenylation of compound **7**-I under the optimized reaction conditions previously reported by us[13h] afforded the desired product, **8**, in 97% yield (Scheme 5).[19] The reaction of compound **7**-Br required 6 h to complete under the same reaction conditions, and the yield was 89%. The maximum yield of the B-ring formation in the convergent total syntheses of taxol reported so far was 76% (Scheme 1); therefore, the Pd-catalyzed intramolecular alkenylation was highly efficient.

As shown in Figure 2, X-ray crystallographic analysis of **8** clearly confirmed its highly distorted taxane scaffold and the stereochemistry of the C1–C2 benzylidene.

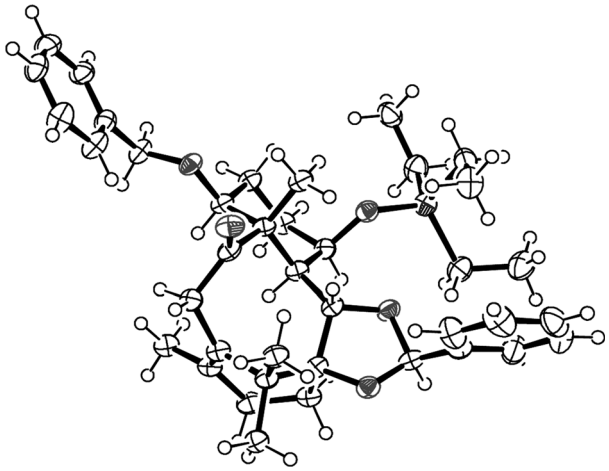
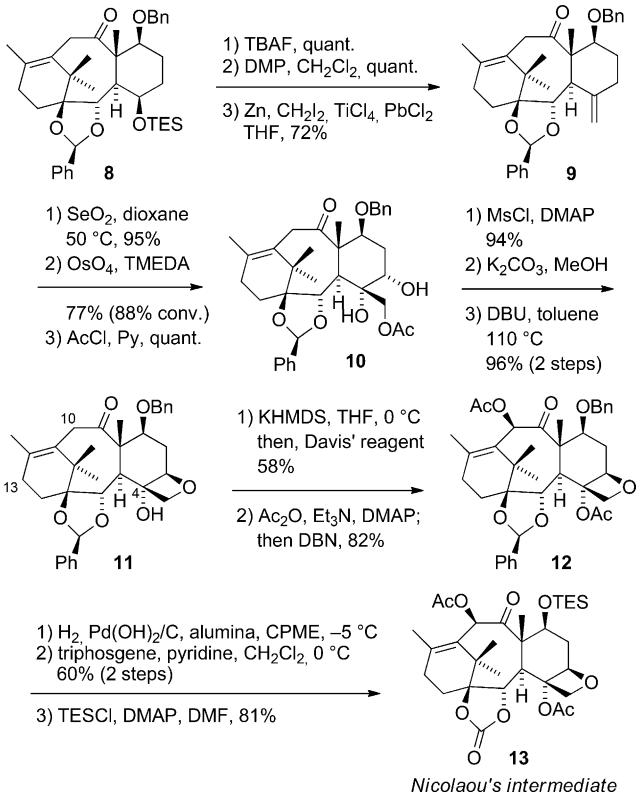


Figure 2. X-ray crystallographic structure of **8**.

We next addressed the introduction of a hydroxy group at the C10 position and carried out oxidation of the enolate of ketone **8**. Considering the structure of ketone **8**, the oxidation was expected to occur from the less hindered side of the enolate to introduce an α-hydroxy group at the C10 position. Thus, epimerization of the C10 configuration would be required after introduction of the C10 hydroxy group.

Hence, we screened a range of derivatives that were suitable for C10 epimerization by considering the stereochemistry of the substrate. After extensive studies, the derivative of **11** (Scheme 6) afforded satisfactory results. Thus, compound **8** was converted into **9** by removal of the TES group, Dess–Martin oxidation, and Takai methylenation, then **9** was converted into **11** via intermediate **10**, based on the reported reaction conditions.[7] The hydroxylation at the C10 position of **11** with potassium hexamethyl disilazide (KHMDS) and Davis' reagent[20] afforded the product with an α-hydroxy group at the C10 position, as expected. Gratifyingly, acetylation of the C4 and C10 hydroxyl groups of the resultant diol and subsequent treatment with DBN in the same pot induced C10 epimerization to afford **12**. Notably, the compounds with C1 hydroxy and C2 benzoate moieties did not undergo C10 epimerization and C4 acetylation under the conditions used for the preparation of **12**.

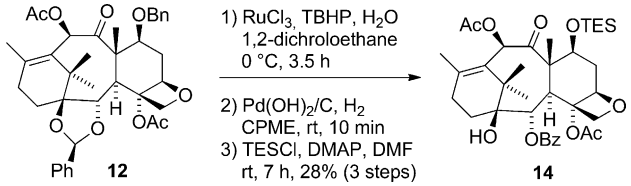
Removal of the C1–C2 benzylidene moiety on the taxane scaffold under catalytic hydrogenation conditions has been known to form the tetrahydrofuran (THF) ring,[12] which can be attributed to the reaction of the liberated C2 hydroxyl group with the adjacent oxetane moiety. However, the reaction using



Scheme 6. Formal total synthesis of (−)-taxol. TBAF = tetrabutylammonium fluoride; TMEDA = *N,N,N′,N′*-tetramethylethylenediamine; Py = pyridine; Ms = methane sulfonyl; DMAP = 4-dimethylaminopyridine; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DBN = 1,5-diazabicyclo[4.3.0]non-5-ene.

Pearlman's catalyst with basic alumina in cyclopentyl methyl ether (CPME) at −5 °C in a hydrogen atmosphere cleanly cleaved the benzylidene acetal and the C-7 benzyl ether of **12** without forming the THF ring. Finally, formation of C1–C2 carbonate and C7 TES ether afforded **13**, which was found to be spectroscopically identical to the synthetic intermediate of taxol reported by Nicolaou,[7] confirming that the formal total synthesis of (−)-taxol has been achieved.

Compound **12** was also converted into compound **14**, which is a more advanced Nicolaou's synthetic intermediate derived from **13** (Scheme 7). Thus, a Ru-catalyzed oxidation, which was reported to be used for allylic oxidation,[21] was found to convert the C1–C2 benzylidene moiety of **12** into C2 benzoate. The Ru-catalyzed reaction afforded only the C2 benzoate because the C1 benzoate was probably difficult to form



Scheme 7. Conversion of **12** into the more advanced Nicolaou's synthetic intermediate **14**. TBHP = *tert*-butyl hydroperoxide; Bz = benzoyl.

because of steric strain. Allylic oxidation at the C13 position was not observed in the Ru-catalyzed reaction. The reaction of **12** using $KBrO_3/Na_2S_2O_3$[22a,b] resulted in no reaction and the reaction with Ph_3CBF_4[22c] caused ring-opening reaction of the oxetane. Subsequent removal of the benzyl group and formation of a TES ether afforded **14**. The yield from **12** to **14** was low, but further optimization may improve the yield.

Conclusion

The problem of forming the eight-membered carbocyclic ring in the convergent total synthesis of taxol was solved by using the Pd-catalyzed intramolecular alkenylation of a methyl ketone, thus affording the cyclized product in an excellent yield (96%), which allowed the efficient formal total synthesis of (−)-taxol by a convergent approach. To our knowledge, this is a first example of Pd-catalyzed intramolecular alkenylation that is used for the formation of an eight-membered carbocyclic ring in natural product synthesis. The maximum yield for B-ring formation of taxol in the convergent total syntheses reported so far was 49%, indicating the high efficiency of the Pd-catalyzed intramolecular alkenylation reaction. During the preparation of a substrate for the Pd-catalyzed reaction, the rearrangement of the epoxy benzyl ether including a 1,5-hydride shift, generating the C3 stereogenic center and subsequently forming the C1–C2 benzylidene, was discovered and successfully utilized. The longest linear steps via **14** from a commercially available compound to (−)-taxol based on this synthesis was 37 when **2**-Br was used, although some steps require optimization to improve the overall yield.[23] Further efforts towards reducing the number of synthetic steps as well as improving the overall yield are underway.

Experimental Section

A full account of the experimental procedures, characterization data and spectra for compounds reported in this manuscript can be found in the Supporting Information.

Acknowledgements

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Keywords: cyclization · enantioselectivity · natural products · palladium · total synthesis

[1] M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, A. T. McPhail, *J. Am. Chem. Soc.* **1971**, *93*, 2325 – 2327.
[2] Y.-F. Wang, Q.-W. Shi, M. Dong, H. Kiyota, Y.-C. Gu, B. Cong, *Chem. Rev.* **2011**, *111*, 7652 – 7709.
[3] A. K. Singla, A. Garg, D. Aggarwal, *Int. J. Pharm.* **2002**, *235*, 179 – 192.
[4] K. C. Nicolaou, W. M. Dai, R. K. Guy, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15 – 44; *Angew. Chem.* **1994**, *106*, 38 – 69.

[5] For synthetic studies reported within the last five years, see: a) T. Serizawa, S. Miyamoto, Y. Numajiri, S. Fuse, T. Doi, T. Takahashi, *Tetrahedron Lett.* **2009**, *50*, 3408 – 3410; b) W. P. D. Goldring, G. Pattenden, S. L. Rimmington, *Tetrahedron* **2009**, *65*, 6670 – 6681; c) C. Ma, S. Schiltz, J. Prunet, *Collect. Czech. Chem. Commun.* **2011**, *76*, 1579 – 1594; d) J. Petrignet, A. Boudhar, G. Blond, J. Suffert, *Angew. Chem. Int. Ed.* **2011**, *50*, 3285 – 3289; *Angew. Chem.* **2011**, *123*, 3343 – 3347; e) A. Mendoza, Y. Ishihara, P. S. Baran, *Nat. Chem.* **2011**, *4*, 21 – 25; f) N. C. Wilde, M. Isomura, A. Mendoza, P. S. Baran, *J. Am. Chem. Soc.* **2014**, *136*, 4909 – 4912.

[6] a) R. A. Holton, C. Somoza, H.-B. Kim, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile, J. H. Liu, *J. Am. Chem. Soc.* **1994**, *116*, 1597 – 1598; b) R. A. Holton, H. B. Kim, C. Somoza, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile, J. H. Liu, *J. Am. Chem. Soc.* **1994**, *116*, 1599 – 1600.

[7] a) K. C. Nicolaou, Z. Yang, J. J. Liu, H. Ueno, P. G. Nantermet, R. K. Guy, C. F. Claiborne, J. Renaud, E. A. Couladouros, K. Paulvannan, E. J. Sorensen, *Nature* **1994**, *367*, 630 – 634; b) K. C. Nicolaou, P. G. Nantermet, H. Ueno, R. K. Guy, E. A. Couladouros, E. J. Sorensen, *J. Am. Chem. Soc.* **1995**, *117*, 624 – 633; c) K. C. Nicolaou, J.-J. Liu, Z. Yang, H. Ueno, E. J. Sorensen, C. F. Claiborne, R. K. Guy, C.-K. Hwang, M. Nakada, P. G. Nantermet, *J. Am. Chem. Soc.* **1995**, *117*, 634 – 644; d) K. C. Nicolaou, Z. Yang, J.-J. Liu, P. G. Nantermet, C. F. Claiborne, J. Renaud, R. K. Guy, K. Shibayama, *J. Am. Chem. Soc.* **1995**, *117*, 645 – 652; e) K. C. Nicolaou, H. Ueno, J.-J. Liu, P. G. Nantermet, Z. Yang, J. Renaud, K. Paulvannan, R. Chadha, *J. Am. Chem. Soc.* **1995**, *117*, 653 – 659.

[8] a) J. J. Masters, J. T. Link, L. B. Snyder, W. B. Young, S. J. Danishefsky, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1723 – 1726; *Angew. Chem.* **1995**, *107*, 1886 – 1888; b) S. J. Danishefsky, J. J. Masters, W. B. Young, J. T. Link, L. B. Snyder, T. V. Magee, D. K. Jung, R. C. A. Isaacs, W. G. Bornmann, C. A. Alaimo, C. A. Coburn, M. J. D. Grandi, *J. Am. Chem. Soc.* **1996**, *118*, 2843 – 2859.

[9] a) P. A. Wender, N. F. Badham, S. P. Conway, P. E. Floreancig, T. E. Glass, C. Gränicher, J. B. Houze, J. Jänichen, D. Lee, D. G. Marquess, P. L. McGrane, W. Meng, T. P. Mucciaro, M. Mühlebach, M. G. Natchus, H. Paulsen, D. B. Rawlins, J. Satkofsky, A. J. Shuker, J. C. Sutton, R. E. Taylor, K. Tomooka, *J. Am. Chem. Soc.* **1997**, *119*, 2755 – 2756; b) P. A. Wender, N. F. Badham, S. P. Conway, P. E. Floreancig, T. E. Glass, J. B. Houze, N. E. Krauss, D. S. Lee, D. G. Marquess, P. L. McGrane, W. Meng, M. G. Natchus, A. J. Shuker, J. C. Sutton, R. E. Taylor, *J. Am. Chem. Soc.* **1997**, *119*, 2757 – 2758.

[10] a) T. Mukaiyama, I. Shiina, H. Iwadare, H. Sakoh, Y. Tani, M. Hasegawa, K. Saitoh, *Proc. Jpn. Acad. Ser. B* **1997**, *73*, 95 – 100; b) T. Mukaiyama, I. Shiina, H. Iwadare, M. Saitoh, T. Nishimura, N. Ohkawa, H. Sakoh, K. Nishimura, Y. Tani, M. Hasegawa, K. Yamada, K. Saitoh, *Chem. Eur. J.* **1999**, *5*, 121 – 161.

[11] a) K. Morihira, R. Hara, S. Kawahara, T. Nishimori, N. Nakamura, H. Kusama, I. Kuwajima, *J. Am. Chem. Soc.* **1998**, *120*, 12980 – 12981; b) H. Kusama, R. Hara, S. Kawahara, T. Nishimori, H. Kashima, N. Nakamura, K. Morihira, I. Kuwajima, *J. Am. Chem. Soc.* **2000**, *122*, 3811 – 3820.

[12] T. Doi, S. Fuse, S. Miyamoto, K. Nakai, D. Sasuga, T. Takahashi, *Chem. Asian J.* **2006**, *1*, 370 – 383.

[13] a) M. Nakada, E. Kojima, Y. Iwata, *Tetrahedron Lett.* **1998**, *39*, 313 – 316; b) M. Iwamoto, H. Kawada, T. Tanaka, M. Nakada, *Tetrahedron Lett.* **2003**, *44*, 7239 – 7243; c) H. Kawada, M. Iwamoto, M. Utsugi, M. Miyano, M. Nakada, *Org. Lett.* **2004**, *6*, 4491 – 4494; d) M. Iwamoto, M. Miyano, M. Utsugi, H. Kawada, M. Nakada, *Tetrahedron Lett.* **2004**, *45*, 8647 – 8651; e) M. Iwamoto, M. Miyano, M. Utsugi, H. Kawada, M. Nakada, *Tetrahedron Lett.* **2004**, *45*, 8653 – 8657; f) M. Utsugi, M. Miyano, M. Nakada, *Org. Lett.* **2006**, *8*, 2973 – 2976; g) M. Utsugi, Y. Kamada, H. Miyamoto, M. Nakada, *Tetrahedron Lett.* **2007**, *48*, 6868 – 6872; h) M. Utsugi, Y. Kamada, H. Miyamoto, M. Nakada, *Tetrahedron Lett.* **2008**, *49*, 4754 – 4757; i) S. Hirai, N. Urushizako, M. Miyano, T. Fujii, M. Nakada, *Tetrahedron Lett.* **2013**, *54*, 1888 – 1892.

[14] K. Tsuna, N. Noguchi, M. Nakada, *Tetrahedron Lett.* **2011**, *52*, 7202 – 7205.

[15] H. Watanabe, M. Iwamoto, M. Nakada, *J. Org. Chem.* **2005**, *70*, 4652 – 4658.

[16] a) K. B. Sharpless, T. R. Verhoeven, *Aldrichimica Acta* **1979**, *12*, 63 – 74; b) A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307 – 1370; c) K. C. Nicolaou, S. T. Harrison, *Angew. Chem. Int. Ed.* **2006**, *45*, 3256 – 3260; *Angew. Chem.* **2006**, *118*, 3334 – 3338.

[17] a) R. O. Hutchins, I. M. Taffer, W. Burgoyne, *J. Org. Chem.* **1981**, *46*, 5214 – 5215; b) D. F. Taber, J. B. Houze, *J. Org. Chem.* **1994**, *59*, 4004 – 4006.

[18] The rearrangement of C1 *p*-methoxybenzyl and *p*-methylbenzyl derivatives of **4**-I also afforded **6**-I after acidic workup, but yields were not improved. The rearrangement of **4**-I and **4**-Br accompanied ring-contraction, forming a cyclopentyl aldehyde derivative, which could be derived from Wagner–Meerwein type rearrangement of **4**-I and **4**-Br.

[19] The intramolecular *B*-alkyl Suzuki–Miyaura coupling was also used to construct the taxane scaffold in 71% yield. For α-alkenylation and α-arylation of ketones, see Ref. [13h].

[20] a) F. A. Davis, J. Lamendola Jr., U. Nadir, E. W. Kluger, T. C. Swdergran, T. W. Panunt, R. Billmers, R. Jenkins Jr., I. J. Turchi, W. H. Watson, J. S. Chen, M. Kimura, *J. Am. Chem. Soc.* **1980**, *102*, 2000 – 2005; b) F. A. Davis, S. Dayay, J. C. Towson, S. Lal, T. Reddy, *J. Org. Chem.* **1988**, *53*, 2087 – 2089.

[21] R. Miller, W. Li, R. Humphrey, *Tetrahedron Lett.* **1996**, *37*, 3429 – 3432.

[22] a) M. Adinolfi, G. Barone, L. Guariniello, A. Iadonisi, *Tetrahedron Lett.* **1999**, *40*, 8439 – 8441; b) P. M. Senthilkumar, A. Aravind, S. Baskaran, *Tetrahedron Lett.* **2007**, *48*, 1175 – 1178; c) H.-P. Wessel, D. R. Bundle, *J. Chem. Soc. Perkin Trans. 1* **1985**, 2251 – 2260.

[23] The 37 longest linear steps from a commercially available compound to (−)-taxol via **14** is one of the shortest synthesis of (−)-taxol; however, the overall yield (0.22%) needs improvement. In our syntheses, the longest linear steps from a commercially available compound to (−)-taxol via **13** was 42 in 0.75% overall yield when **2**-I was used and 38 in 0.31% overall yield when **2**-Br was used.

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FULL PAPER

Natural Products

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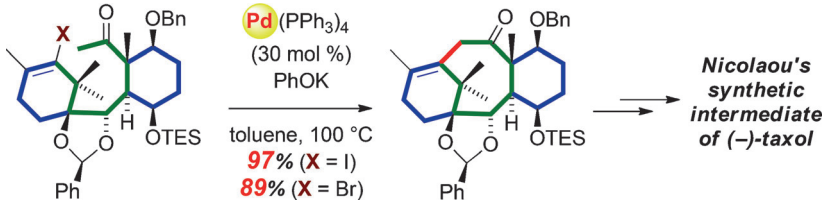
Formal Total Synthesis of (−)-Taxol through Pd-Catalyzed Eight-Membered Carbocyclic Ring Formation



A less taxing route to taxol: The Pd-catalyzed intramolecular alkenylation of a methyl ketone affords a key cyclized intermediate for the synthesis of (−)-taxol in excellent yield (97%) (see scheme; Bn = benzyl; TES = triethylsilyl). Rearrangement of an epoxy benzyl ether through a 1,5-hydride shift, generating the C3 stereogenic center and subsequently forming the C1–C2 benzylidene, was discovered during the preparation of a substrate for the Pd-catalyzed reaction.