Macrocycle Formation by Ring-Closing Metathesis. Application to the Syntheses of Novel Macrocyclic Taxoids

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Abstract: A series of novel macrocyclic taxoids **6** and **6′** bearing 16-, 17-, and 18-membered rings connecting the substituents at the C-2 and C-3′ positions were designed and synthesized. The syntheses of these macrocycles **6** and **6′** were accomplished using the highly efficient ruthenium-catalyzed ring-closing metathesis (RCM) of taxoid-ω,ω'-dienes **7** in the key step. Taxoid-ω,ω'-dienes **7** were obtained through the ring-opening coupling of 4-alkenyl-β-lactams **9** with 2-alkenoylbaccatins **8** in good to high yields. Although various novel pentacyclic macrocycles **6** and **6′** were successfully synthesized, there were cases in which the desired RCM did not proceed. The scope and limitation of RCM in its application to highly functionalized complex substrates are discussed. All macrocyclic taxoids **6** and **6′** were found to be cytotoxic, with some of them exhibiting submicromolar IC_{50} values against a human breast cancer cell line.

Although there are many methods for cyclization and macrocyclization in organic synthesis, ring-closing metathesis (RCM) has recently emerged as a powerful tool for the formation of a variety of ring systems.[1−3] While macrocycle formation by RCM has proven to be effective in the synthesis of various natural products[4−17] and macrocyclic amino acids or peptides,[18−24] it is obvious that the complexity and functional group tolerance of substrates in this process need to be further investigated to expand its applicability in organic syntheses.

In the course of our study on the bioactive conformation of paclitaxel (**1**) and its congeners,[25−27] we have proposed[28] a plausible common pharmacophore for paclitaxel (**1**),[29] epothilones (**3** and **4**)[30] (Figure 1), eleutherobin,[31] and discodermolide,[32] which share the same mechansim of action, i.e., inhibition of the cell division cycle by stabilizing microtubules. On the basis of this common pharmacophore model, we recognized that macrocyclic taxoids **6** (unsaturated) and **6′** (saturated) which connected the C2 and C3′ positions of taxoids such as docetaxel (**2**)[33] and nonataxel (**5**)[34] (Figure 1) would provide hybrid constructs of taxoids and epothilone.[28] Accordingly, a series of macrocyclic taxoids **6** and **6′** were designed.

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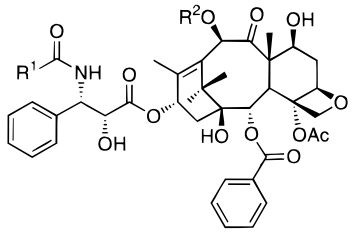
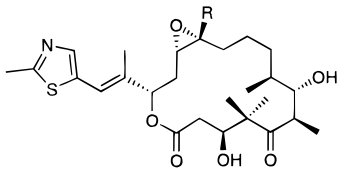
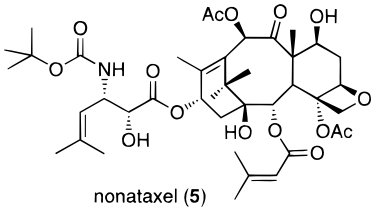


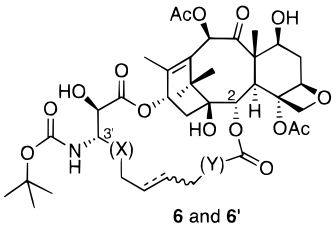
paclitaxel (**1**): R^1 = Ph; R^2 = Ac
docetaxel (**2**): R^1 = *t*-BuO, R^2 = H



epothilone A (**3**): R = H
epothilone B (**4**): R = Me



nonataxel (**5**)



6 and **6'**

Figure 1.

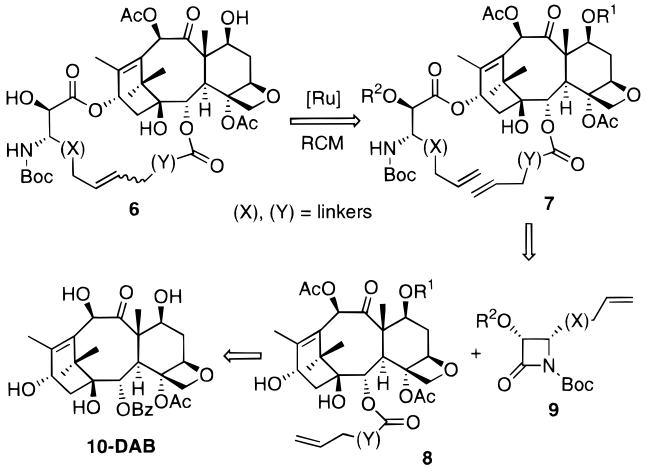
To synthesize these macrocyclic taxoids, we chose to use the Ru-catalyzed RCM in the key step. Since the designed RCM precursor taxoids bearing two olefinic tethers involve many functional groups and possess highly complex structures, such a study would provide valuable information about the scope and limitation of the RCM methodology.

We describe here our successful syntheses of a series of novel macrocyclic taxoids **6** and **6′** using RCM in the key step and discuss the scope and limitation of this method observed. All these novel macrocyclic taxoids were found to be cytotoxic, which provides supporting evidence for the proposed common pharmacophore.[28]

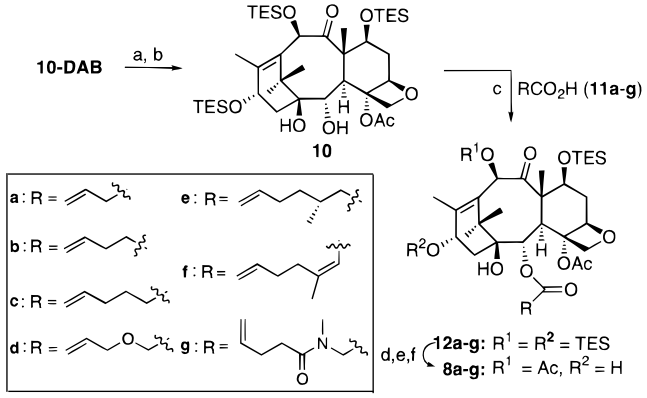
Results and Discussion

The retrosynthetic analysis of the target macrocyclic taxoid **6** bearing 16-, 17-, 18-membered rings is shown in Scheme 1. As Scheme 1 illustrates, novel taxoid **6** should be obtained through a Ru-catalyzed RCM of the open-chain precursor, taxoid-ω,ω'-diene **7**, which can be synthesized from C-2-alkenoylbaccatin **8** and enantiopure 4-alkenyl-β-lactam **9** using the "Ojima−Holton" ring-opening coupling protocol.[26,35−39] The C-2-modified baccatin **8** can be obtained from naturally occurring 10-deacetylbaccatin III (DAB), while enantiopure β-lactam **9** should be obtained through the highly efficient chiral enolate−imine cyclocondensation established in these laboratories.[35,38−40]

Scheme 1



Scheme 2[a]



[a] Key: (a) TES−Cl, imidazole, DMF, room temperature (rt), 96%; (b) Red-Al (2 equiv), THF, −10 °C, 20 min, quantitative; (c) DCC or DIC, DMAP, rt to 50 °C, 67−95%; (d) HF/Pyr, rt; (e) TES−Cl (3 equiv), imidazole (4 equiv), 0 °C to rt; (f) LiHMDS (1.1 equiv), AcCl (1.2 equiv), THF, −40 °C; 50-84% (three steps).

The synthesis of macrocyclic taxoids **6** started from the preparation of a series of C-2-modified baccatins. Reaction of DAB with TES−Cl and imidazole followed by the removal of the C-2 benzoyl group with Red-Al gave 7,10,13-triTES-2-debenzoylbaccatin (**10**) in 96% yield for two steps (Scheme 2). Esterification of **10** was carried out using unsaturated carboxylic acids **11a**−**g** in the presence of DCC/DMAP or DIC/DMAP as the coupling agents, which gave the desired C-2-modified baccatins **12a**−**g** in 67−95% yields. The silyl protecting groups at C-7, C-10, and C-13 were then removed using HF/pyridine. Selective reprotection of the C-7 hydroxyl group with TES−Cl and imidazole, followed by acetylation of the C-10 hydroxyl group using acetyl chloride and LiHMDS gave the desired baccatins **8a**−**g** in high yields (Scheme 2).

While the coupling method using DCC or DIC/DMAP worked well with less bulky alkenoic acids, the reactions of

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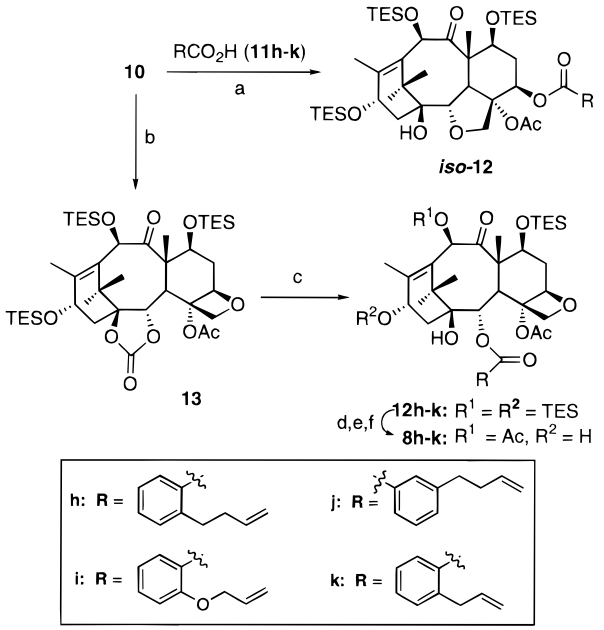
Scheme 3[a]



[a] Key: (a) DCC or DIC, DMAP, rt to 50 °C; (b) triphosgene/Pyr, 0 °C to rt, 97%; (c) RMgBr, THF, −78 °C, 79−96%; (d) HF/Py, rt; (e) TES−Cl (3 equiv), imidazole (4 equiv), 0 °C to rt; (f) LiHMDS (1.1 equiv), AcCl (1.2 equiv), THF, −40 °C; 55-76% (three steps).

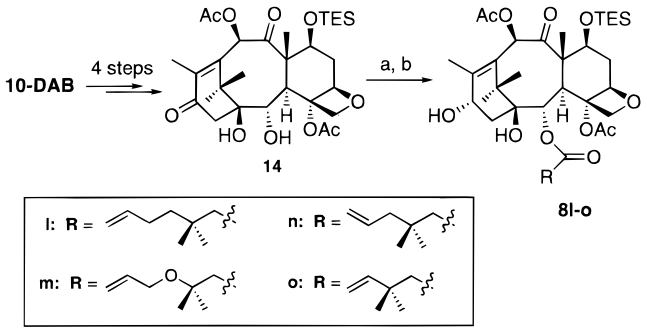
bulky *ortho*- or *meta*-substituted benzoic acids **11h**−**k** with **10** were very sluggish, forming predominantly the D-ring-opened products **iso**-**12**.[41] To circumvent this problem, we employed the regioselective ring-opening coupling of baccatin-1,2-carbonate **13** with *ortho*- or *meta*-substituted phenylmagnesium bromides.[28,41] Baccatin-1,2-carbonate **13** was prepared in 97% yield from **10** by treatment with triphosgene in the presence of pyridine at 0 °C.[42] Treatment of **13** with the *ortho*- or *meta*-substituted phenylmagnesium bromides afforded baccatins **12h**−**k** in good to high yields (Scheme 3).[28,41] Baccatins **12h**−**k** thus obtained were converted to **8h**−**k** in high yields following the same three-step procedure as that described above for the syntheses of **8a**−**g**.

For the coupling of bulky alkenoic acids **11l**−**o** bearing a *gem*-dimethyl group β to the carboxyl group, less bulky 2-debenzoyl-7-TES-13-oxobaccatin (**14**)[34] was employed. Thus, the reaction of 13-oxobaccatin **14** with alkenoic acids **11l**−**o** in the presence of DCC/DMAP or DIC/DMAP gave baccatins **14l**−**o** in 67−85% yields (Scheme 4). Finally, the reduction of the 13-keto moiety of **14l**−**o** with $NaBH_4$ gave the desired baccatins **8l**−**o** in 84−90% yields.

The syntheses of β-lactams **9** began with the preparation of (3*R*,4*S*)-1-PMP-3-TIPSO-4-(2-methylprop-1-enyl)azetidin-2-one (**15**) (PMP = *p*-methoxyphenyl, TIPSO = triisopropylsiloxy) with high enantiopurity (>96% ee) in excellent yield using a highly efficient chiral enolate−imine cyclocondensation reaction.[35,38−40,43,44] Ozonolysis of the 4-alkenyl moiety of **15** gave 4-formyl-β-lactam **16** in quantitative yield. Reaction of aldehyde **16** with a Wittig reagent generated in situ from (but-3-enyl)triphenylphosphonium bromide and *n*-BuLi afforded 4-(penta-1,4-dienyl)-β-lactams **17a** (*E*/*Z* = 1/7) in 93% yield. The PMP group was removed by treatment with ceric ammonium nitrate (CAN), followed by protection of the resulting NH group with (*t*-Boc)$_2$O, affording β-lactams **18a** in excellent yield. The *Z*- and *E*-isomers of **18a** were separated by column chromatography on silica gel. The TIPS group was then removed by HF/pyridine, followed by reprotection with a smaller TES group to afford β-lactams **9a**-***Z*** and **9a**-***E*** in 88% and 77% yields, respectively (Scheme 5). 4-[(*E*)-2-Methylhexa-1,5-dienyl)]-β-lactam **9b** and 4-(but-3-enyl)-β-lactam **9c** were synthesized in good overall yields through cyclocondensation of chiral TIPS-ester **19** with *N*-PMP-(*E*)-3-methylhept-2,6-dienaldimine and *N*-PMP-pent-4-enaldimine, giving **17b** (97% ee) and **17c** (97% ee), followed by functional group manipulation analogous to that for **9a** (Scheme 6).

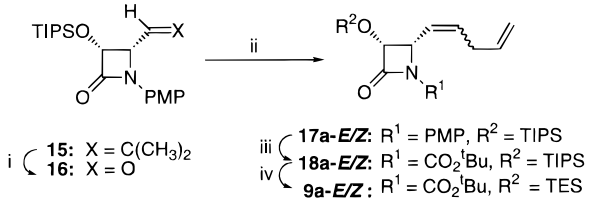
4-(Prop-2-enyl)-, 4-vinyl-, 4-(1-hydroxylprop-2-enyl)-, and 4-(3-vinylphenyl)-β-lactams (**9d**−**g**) were synthesized according to the synthetic routes illustrated in Schemes 7 and 8. Thus, the reaction of 4-formyl-β-lactam **16** with vinylmagnesium bromide followed by in situ protection of the resulting alcohol with acetic anhydride gave β-lactam **20a** in 98% yield. β-Lactam **20a** was subjected to $Pd_2(dba)_3$-catalyzed hydrogenolysis using

Scheme 4[a]



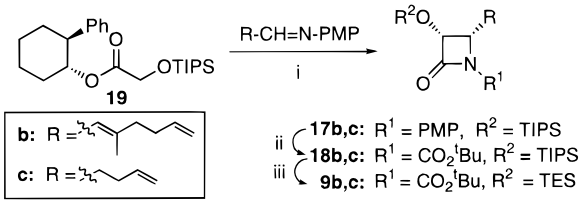
[a] Key: (a) acid **11l**−**o**, DCC or DIC, DMAP, rt to 50 °C, 67-85%; (b) $NaBH_4$, 0 °C to rt; 84−90%.

Scheme 5[a]



[a] Key: (i) O_3/Me_2S, −78 °C to rt, 3 h, quantitative; (ii) $Ph_3P{=}CHCH_2CH{=}CH_2$, −78 °C to rt, 2 h, 93%; (iii) CAN, −10 °C, 2 h, 83%; (*t*-Boc)$_2$O, Et_3N, DMAP, rt, 9 h, 96% (*Z*, *E* separable); (iv) HF/Py, rt, 17−24 h; TES−Cl, Et_3N/DMAP, rt, 1 h; *Z*, 88%; *E*, 77% (two steps).

Scheme 6[a]



[a] Key: (i) LDA, −84 °C; R−CH=N−PMP, −84 °C to rt, overnight; a, 63%; b, 56%; (ii) CAN, −10 °C, 3 h; (*t*-Boc)$_2$O, Et_3N/DMAP, rt, 15 h; a, 88%; b, 72% (two steps); (iii) HF/Py, rt, 20 h; TES-Cl, Et_3N/DMAP, rt, 1 h; a, 88%; b, 90% (two steps).

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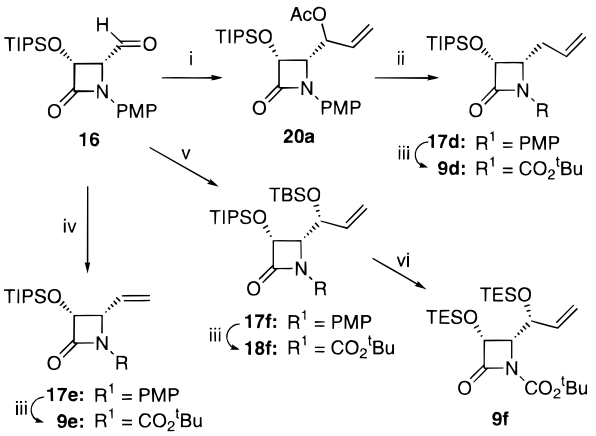
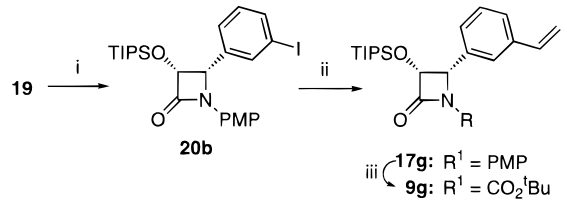
Scheme 7[a]



[a] Key: (i) CH_2═$CHMgBr$ (1.1 equiv), THF, −78 °C; then Ac_2O, −78 °C to rt: 98 % (two steps, *R*/*S* = 11/1); (ii) $Pd_2(dba)_3CHCl_3$ (0.1 equiv), HCO_2NH_4 (3 equiv), PBu_3 (0.2 equiv), dioxane, reflux, 65%; (iii) CAN, −10 °C; (*t*-Boc)$_2$O, Et_3N/DMAP, rt; 82−96% (two steps); (iv) Ph_3P═ (1.5 equiv), −78 to 0 °C, 90%; (v) CH_2═$CHMgBr$, THF, −78 °C; then TBSCl (9 equiv), Et_3N (excess), reflux, 2 d; 82% (two steps); (vi) HF/Py, rt; TES−Cl, Et_3N/DMAP, rt, 90% (two steps).

Scheme 8[a]

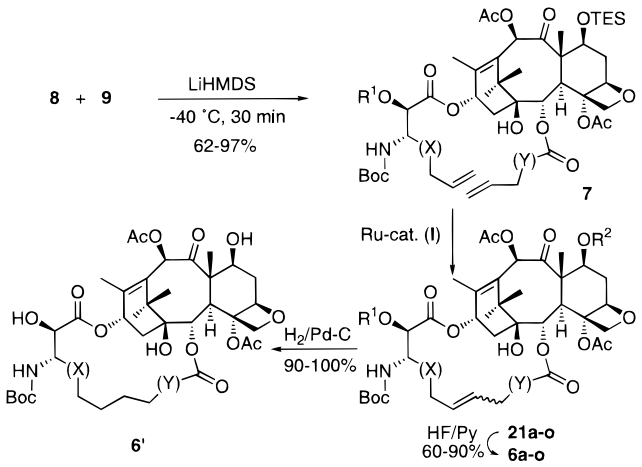


[a] Key: (i) LDA, −84 °C; *m*-I-Ph−CH═N−PMP, −84 °C to rt, overnight, 79%; (ii) $Pd_2(dba)_3$, vinyl tributyltin, PPh_3, dioxane, 80 °C, overnight, 87%; (iii) CAN, −10 °C, 1.5 h; (*t*-Boc)$_2$O, Et_3N/DAMP, rt; 70% (two steps).

HCO_2NH_4 as the hydride source[45] to give 4-allyl-β-lactam **17d** in 65% yield. Reaction of **16** with the same Grignard reagent, followed by protection of the resulting alcohol as the TBS ether, afforded β-lactam **17f** in 82% yield. Reaction of 4-formyl-β-lactam **16** with methylenetriphenylphosphorane gave 4-vinyl-β-lactam **17e** in 90% yield. Removal of the PMP group of β-lactams **17d**−**f** with CAN followed by protection of the resulting free NH with (*t*-Boc)$_2$O afforded β-lactams **9d**, **9e**, and **18f** in high yields. To reduce the steric bulk of **18f** for efficient ring-opening coupling with C-2-modified baccatin **8**, both the TIPS and TBS groups were replaced with TES to give β-lactam **9f** in 90% overall yield (Scheme 7). 4-(3-Iodophenyl)-β-lactam **20b** was synthesized using cyclocondensation of TIPS ester **19** with the PMP-aldimine of *m*-iodobenzaldehyde in 70% yield (Scheme 8). Stille coupling of β-lactam **20b** with vinyltributyltin catalyzed by $Pd_2(dba)_3$ afforded 4-(3-vinylphenyl)-β-lactam **17g** in 78% yield, which was then converted to 1-*t*-Boc-4-(3-vinylphenyl)-β-lactam **9g** in 70% yield for two steps in the same manner as mentioned above.

The ring-opening coupling of 4-alkenyl-β-lactams **9a**−**g** with C-2-alkenoylbaccatins **8a**−**o** was carried out under the standard conditions,[26,36−40,44,46] which gave the corresponding taxoid-ω,ω'-dienes **7a**−**t** bearing two olefinic tethers at the C-2 and C-3′ positions (Scheme 9). Results are summarized in Table 1. With taxoid-ω,ω'-dienes **7a**−**t** in hand, the stage is set for macrocyclization by means of RCM.

Scheme 9



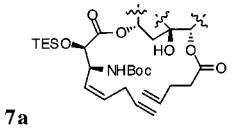
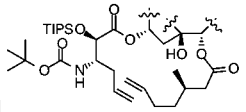
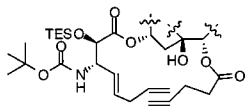
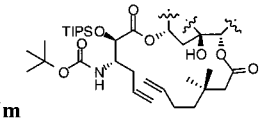
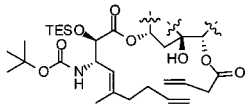
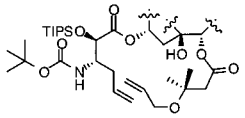
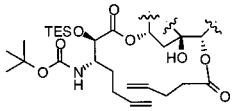
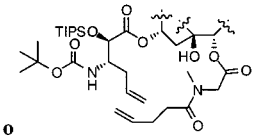
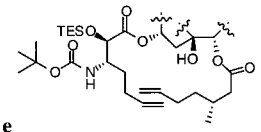
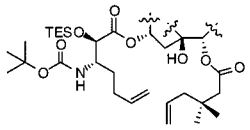
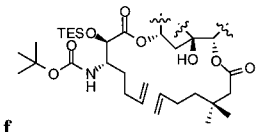
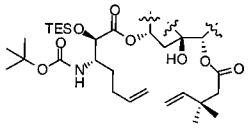
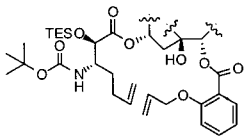
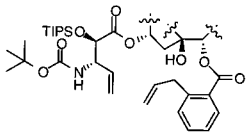
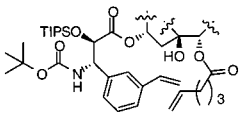
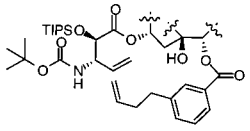
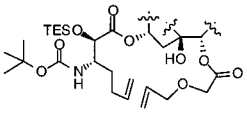
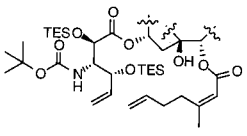
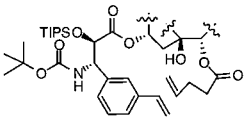
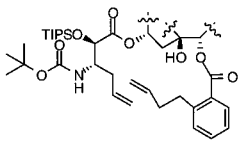
The RCM of taxoid-ω,ω'-diene **7a**, bearing a (*Z*)-penta-1,4-dienyl group at C-3′ and a pent-4-enoyl group at C-2, catalyzed by $RuCl_2$(═CHPh)$(PCy_3)_2$ (**I**) ("Grubb's catalyst",[47] 20 mol %) in CH_2Cl_2 (1.3 mM) at room temperature for 14 h proceeded smoothly to afford the desired 17-membered macrocycle **21a** in 92% yield (*Z*/*E* = 9/1) (Scheme 9). The stereochemical assignment of the newly formed carbon−carbon double bond was unambiguously determined on the basis of *J* coupling constants (major (*Z*), *J* = 9.5 Hz; minor (*E*), *J* = 15.5 Hz). Encouraged by this exciting result, we carried out the RCM of taxoid-ω,ω'-dienes **7b**−**t**. Results are summarized in Table 2.

As Table 2 shows, the RCM of taxoid-ω,ω'-dienes **7** gives the desired macrocyclic taxoids **21** in moderate to high yields for 15 out of the 20 cases studied (entries 1−15). It was previously reported that the RCM of ω,ω'-diene substrates bearing a γ,δ- or β,γ-unsaturated carbonyl moiety did not proceed at all. These negative results were ascribed to the formation of a very stable and thus inactive five- or six-membered Ru−chelate complex (e.g., structures **A** and **B**, Figure 2) that blocks the catalytic cycle, which was presented as a general rule characterizing the scope and limitation of RCM.[2,48] However, we have found that this general rule proposed on the basis of the studies for simpler systems is not applicable to the RCM of highly functionalized taxoids **7a**−**d**, **7j**, and **7o** wherein each substrate possesses a γ,δ- or β,γ-unsaturated carbonyl moiety in the molecule. Thus, these RCM reactions catalyzed by the Ru−carbene complex **I** gave the desired 16- and 17-membered macrocyclic taxoids **21a**−**d**, **21j**, and **21o** in 67−92% yields (entries 1−4, 10, and 15). It is noteworthy that the Ru-catalyzed RCM is found to be applicable to the macrocyclization of highly complex and multifunctionalized systems, further expanding the scope of this synthetic method.

Another unique feature observed in these RCM reactions is the stereoselective double bond formation. As Table 2 shows, the stereochemistry of the double bond in **21** formed by the RCM of taxoids **7** is predominantly or exclusively *E* in all cases examined except for the case of **21a** in which the *Z*-isomer is the predominant product (*Z*/*E* = 9/1). These results make sharp contrast to the very low or no stereoselectivity previously reported for the formation of the olefin moiety, which is a characteristic feature and weakness of the RCM method,[2,17] as

(45) Minami, I.; Nisar, M.; Yuhara, M.; Shimizu, I.; Tsuji, J. *Synthesis* **1987**, 992−998.
(46) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383−389 and references therein.
(47) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041.
(48) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792−803.

Table 1. Synthesis of Dienyl Taxoid **7**[a]

entry	baccatin	β-lactam	Taxoid-ω,ω-diene **7**	yield(%)	entry	baccatin	β-lactam	Taxoid-ω,ω-diene **7**	yield(%)
1	**8b**	**9a*Z***	 **7a**	94	12	**8e**	**9d**	 **7l**	97
2	**8b**	**9a*E***	 **7b**	84	13	**8l**	**9d**	 **7m**	90
3	**8a**	**9b**	 **7c**	69	14	**8m**	**9d**	 **7n**	92
4	**8b**	**9c**	 **7d**	86	15	**8g**	**9d**	 **7o**	62
5	**8e**	**9c**	 **7e**	96	16	**8n**	**9c**	 **7p**	88
6	**8l**	**9c**	 **7f**	84	17	**8o**	**9c**	 **7q**	82
7	**8i**	**9c**	 **7g**	64	18	**8k**	**9e**	 **7r**	85
8	**8c**	**9g**	 **7h**	70	19	**8j**	**9e**	 **7s**	90
9	**8d**	**9c**	 **7i**	69	20	**8f**	**9f**	 **7t**	68
10	**8b**	**9g**	 **7j**	66					
11	**8h**	**9d**	 **7k**	92					

[a] The reaction was carried out with 1.0 equiv of baccatin **8** and 1.5 equiv of β-lactam **9** with 1.5 equiv of LiHMDS in THF at −40 °C for 30 min (see Scheme 9).

exemplified by the formation of *E*/*Z* mixtures of 16-membered rings in the total synthesis of epothilones.[8−10,12,49]

It is also worthy of note that the Ru-catalyzed RCM takes place exclusively at the terminal olefin moieties of a taxoid-ω,ω′-diene **7** bearing an additional inner olefin moiety (entries 1−3). Thus, the inner olefin moieties of **7a**, **7b**, and **7c** are not involved in these RCM reactions, giving the desired RCM products **21a**, **21b**, and **21c**, respectively, in high yields. As expected, the tetrasubstituted olefin moiety at the C11−C12 position of the baccatin skeleton is also completely intact in all cases.

Table 2 also indicates that the RCM reaction is very sensitive to the substitution pattern in the proximity of the terminal double bonds. When the ω-alkenyl moiety at the C-3′ position is a 3-butenyl group (entries 4−7), the RCM reaction proceeds very smoothly. However, the reaction becomes sluggish, and a higher catalyst loading (40−60 mol %) and higher temperatures (60−70 °C) are required to complete the reaction when the ω-alkenyl

(49) It should be noted that stereoselective RCM reactions have recently been reported; see refs 11, 13, 16, 17, and 19.

Table 2. Macrocyclic Taxoid Formation by Ru-Catalyzed Ring-Closing Metathesis[a]

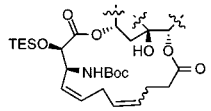
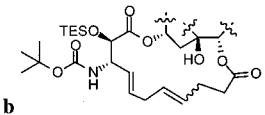
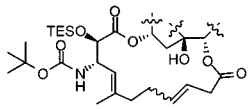
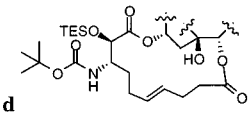
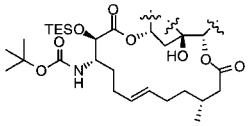
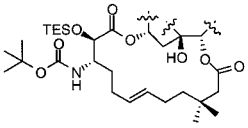
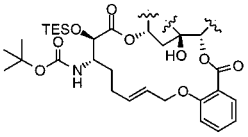
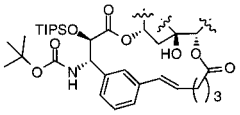
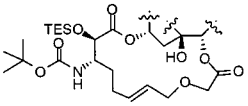
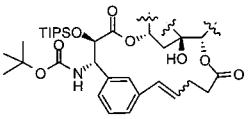
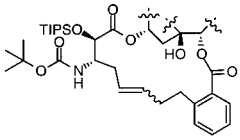
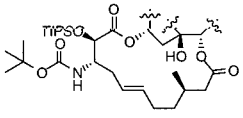
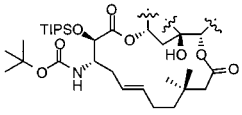
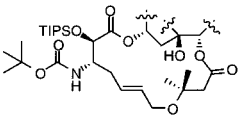
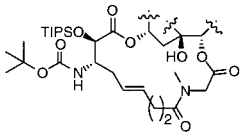
entry	taxoid-diene	catalyst (mol%)	solvent	T (°C)	reaction time (h)	macrocyclic taxoid[b]	ring size[c]	*E*/*Z*[d]	yield(%)
1	**7a**	20	CH_2Cl_2	25	14	 **21a**	17	1/9	92
2	**7b**	25	CH_2Cl_2	25	21	 **21b**	17	3/1	80
3	**7c**	30	CH_2Cl_2	25	20	 **21c**	17	3/1	78(90)[e]
4	**7d**	40	CH_2Cl_2	reflux	25	 **21d**	16	*E* only	67
5	**7e**	20	CH_2Cl_2	25	9	 **21e**	18	*E* only	91
6	**7f**	20	CH_2Cl_2	25	14	 **21f**	18	*E* only	82(75)[e]
7	**7g**	20	CH_2Cl_2	25	14	 **21g**	18	*E* only	82
8	**7h**	20	CH_2Cl_2	reflux	36	 **21h**	18	*E* only	82
9	**7i**	20	CH_2Cl_2	25	8	 **21i**	17	*E* only	94
10	**7j**	20	CH_2Cl_2	reflux	15	 **21j**	17	3/1	65
11	**7k**	40	toluene	70	24 x 2	 **21k**	17	3/1	55
12	**7l**	30	CH_2Cl_2	reflux	22	 **21l**	17	*E* only	96(84)[e]
13	**7m**	40	CH_2Cl_2	reflux	24	 **21m**	17	*E* only	88(84)[e]
14	**7n**	50	toluene	65	24 x 3	 **21n**	17	*E* only	50

Table 2. (Continued)

entry	taxoid-diene	catalyst (mol%)	solvent	T (°C)	reaction time (h)	macrocyclic taxoid[b]	ring size[c]	*E*/*Z*[d]	yield(%)
15	**7o**	20	CH_2Cl_2	25	24	 **21o**	18	4/1	92
16	**7p**	60	CH_2Cl_2	reflux	24 x 8	dimer[f]	(17)	----	0
17	**7q**	60	CH_2Cl_2	reflux	24 x 7	dimer[f]	(16)	----	0
18	**7r**	20	CH_2Cl_2	reflux	24 x 2	dimer[f]	(15)	----	0
19	**7s**	40	CH_2Cl_2	reflux	32	dimer[f]	(17)	----	0
20	**7t**	60	CH_2Cl_2	reflux	24 x 5	dimer[f]	(17)	----	0

[a] The reactions were carried out using $RuCl_2(=CHPh)(PCy_3)_2$ (**I**) as the catalyst (see Scheme 9). [b] Macrocyclic taxoids **21a**−**o** give **6a**−**o** after deprotection. [c] The number in parentheses is the expected ring size if RCM is successful. [d] Determined by NMR. [e] The number in parentheses indicates the percentage of conversion. [f] Supported by mass spectrometry (MH^+ peak observed).

Figure 2.

moiety is an allyl group (entries 11−15). The RCM reactions of taxoid-ω,ω'-dienes **7r**−**t** bearing a vinyl group or 1-TESO-prop-2-enyl group at the C-3′ position do not take place (entries 18−20). However, substrates with a vinyl group attached to a phenyl moiety (**7h** and **7j**) retain good reactivity (entries 8 and 10). The results clearly indicate that the substitution at the allylic position of the terminal olefin moiety imposes serious limitations for the scope of RCM with the exception of the vinylphenyl group. Similar substituent effects are observed for the ω-alkenyl moiety at the C-2 position.

In the cases in which RCM−macrocyclization does not occur (entries 16−20), it appears that a dimerization process prevails at the less sterically hindered ω-olefin moieties. It has been shown that $(2,6\text{-}^iPr_2C_6H_4N{=})Mo(=CHCMe_2Ph)[OMe(CF_3)_2]_2$ ("Schrock's catalyst")[50] possesses a significantly higher activity than that of Ru catalyst in the RCM of sterically demanding dienes.[3] Accordingly, we examined the activity of the Mo catalyst in the RCM of taxoid-ω,ω-diene **7s**. Unfortunately, the attempted RCM reaction resulted in the ring-opening of the oxetane ring, leading to the formation of a complex mixture of products.

RCM−macrocyclization products **21a**−**o** were treated with HF/pyridine to remove the silyl protecting groups at the C-7 and C-2′ positions to afford the desired macrocyclic taxoids **6a**−**o**, possessing different substitution and double bond distribution patterns in the C2−C3′ tether. Hydrogenation of **6a**, **6d**, **6e**−**g**, **6l**, **6m**, and **6o** on palladium−carbon provided the corresponding macrocyclic taxoids bearing saturated C2−C3′ tethers, **6′a**, **6′d**, **6′e**−**g**, **6′l**, **6′m**, and **6′o**, in excellent to quantitative yields (Scheme 9).

These macrocyclic taxoids were evaluated for their cytotoxicities against a human breast cancer cell line, MDA-435/LCC6-WT.[51] All of these novel macrocyclic taxoids are found to be cytotoxic, and three of them, **6f**, **6g**, and **6h**, exhibit strong activity with submicromolar level IC_{50} values, i.e., $IC_{50} = 0.48$, 0.39, and 0.50 μM, respectively.[52] Macrocyclic taxoids, **6c**, **6e**, **6k**, **6l**, **6m**, **6′d**, **6′e**, **6′f**, **6′g**, **6′l**, and **6′m**, also show substantial activity, i.e., $IC_{50} = 1.40-4.10$ μM. However, macrocyclic taxoids, **6a**, **6b**, **6d**, **6i**, **6j**, **6o**, **6′a**, and **6′o**, possess a substantially lower level of activities ($IC_{50} \geq 10$ μM). Several taxoids were also assayed for their tubulin-polymerization activity,[51] and it has been found that **6e**, **6g**, and **6′l** show relative activities of 19%, 36%, and 21%, respectively, as compared to that of paclitaxel in the same assay. Although the biological activity profiles of these macrocyclic taxoids have not exceeded that of paclitaxel (0.0031 μM) yet, it certainly provides supporting evidence for the validity of the common pharmacophore proposed by these laboratories,[28] which serves as the basis for the design and development of paclitaxel−epothilone hybrids and de novo anticaner agents. Further studies on the structure−activity relationships of macrocyclic taxoids are actively underway and will be reported in due course.

Conclusion

A series of novel macrocyclic taxoids bearing various tethers between the C-2 and C-3′ positions has been designed and synthesized. The syntheses of these macrocycles were accomplished using Ru-complex-catalyzed RCM as the key reaction. Successful construction of the 16-, 17-, and 18-membered macrocycles using RCM of the highly functionalized, complex tetracyclic terpenoid substrates is particularly noteworthy. These results have clearly expanded the scope of the RCM methodology. Observation of substantial biological activity of these highly constrained macrocyclic taxoids provides

(50) Bazan, G. C.; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899−6907.

(51) The cytotoxicity assay was performed by Dr. Ralph J. Bernacki and Ms. Paula Pera, Roswell Park Cancer Institute, and the tubulin-polymerization activity assay was performed by Dr. Susan B. Horwitz and Mr. Lifeng He, Albert Einstein College of Medicine. The detailed results will be reported elsewhere.

(52) Recently, a couple of C2−C3′ connected paclitaxel analogues were reported, but these compounds did not show any cytotoxicity. See: Boge, T. C.; Wu, Z.-J.; Himes, R. H.; Vander, D. G.; Georg, G. I. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3047−3052.

(53) Marder-Karsenti, R.; Dubois, J.; Bricard, L.; Guénard, D.; Guéritte-Voegelein, F. *J. Org. Chem.* **1997**, *62*, 6631−6637.

strong supporting evidence for the existence of the proposed common pharmacophore for microtubule-stabilizing agents. Further studies along this line should reveal the way that paclitaxel binds to microtubules, i.e., the biologically active conformation of paclitaxel, and provide a solid basis for the design and synthesis of the next generation antitumor agents targeting tubulin/microtubules.

Experimental Section

For general methods, materials, and the synthesis of **10** see the Supporting Information.

General Procedure for the Syntheses of 7,10,13-Tris(triethylsilyl)-2-debenzoyl-2-alkenoyl-10-deacetylbaccatin III (12a−k). Method A (for the Syntheses of 12a−g). A typical procedure is described for the synthesis of 7,10,13-tris(triethylsilyl)-2-debenzoyl-2-(pent-4-enoyl)-10-deacetylbaccatin III (**12b**). To a solution of **10** (207 mg, 0.255 mmol), pent-4-enoic acid (130 μL, 1.275 mmol), and 4-(dimethylamino)pyridine (DMAP; 31 mg, 0.255 mmol) in dichloromethane (3 mL) was added 1,3-dicyclohexylcarbodiimide (DCC; 526 mg, 2.55 mmol), and the reaction mixture was stirred for 16 h at room temperature. The precipitate was filtered off and washed with ethyl acetate (30 mL). The filtrate was diluted with ethyl acetate (30 mL), washed with saturated aqueous sodium bicarbonate (15 mL × 2), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified on a silica gel column using hexane/ethyl acetate (8/1 followed by 4/1) as the eluant to give **12b** as a white solid (204 mg, 89% yield): mp 110−112 °C; $[\alpha]^{20}_{D}$ −28.6° (*c* 0.35, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.63 (m, 18 H), 0.97 (m, 27 H), 1.06 (s, 3 H), 1.10 (s, 3 H), 1.49 (bs, 1 H), 1.58 (s, 3 H), 1.86 (m, 1 H), 1.93 (s, 3 H), 2.00 (s, 1 H), 2.04 (s, 1 H), 2.16 (s, 3 H), 2.39 (m, 4 H), 2.46 (m, 1 H), 3.71 (d, J = 7.0 Hz, 1 H), 4.14 (d, J = 7.9 Hz, 1 H), 4.36 (dd, J = 10.4, 6.6 Hz, 1 H), 4.42 (d, J = 7.9 Hz, 1 H), 4.88 (t, J = 8.5 Hz, 1 H), 4.93 (d, J = 8.2 Hz, 1 H), 5.02 (d, J = 9.7 Hz, 1 H), 5.07 (d, J = 16.0 Hz, 1 H), 5.14 (s, 1 H), 5.37 (d, J = 7.0 Hz, 1 H), 5.81 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 4.8, 5.2, 5.9, 6.85, 6.91, 10.3, 14.5, 20.5, 22.3, 24.7, 26.4, 28.5, 34.1, 37.2, 39.6, 43.0, 46.8, 58.2, 68.3, 72.5, 75.0, 75.7, 76.7, 79.3, 80.5, 84.1, 115.7, 135.7, 136.6, 139.4, 170.0, 174.0, 205.6; HRMS (FAB, MeOH/NBA/PPG) *m*/*z* calcd for $C_{45}H_{80}O_{10}Si_3{\cdot}H^+$ 865.5138, found 865.5174 (Δ = −4.2 ppm).

Method B (for the Syntheses of 12h−k). A typical procedure is described for the synthesis of 7,10,13-tris(triethylsilyl)-2-debenzoyl-2-(2-allyloxybenzoyl)-10-deacetylbaccatin III (**12i**). To a solution of 2-allyloxyphenylmagnesium bromide (0.36 M solution in THF, 4 mL, 1.44 mmol, prepared from allyl 2-bromophenyl ether and magnesium) was added a solution of 7-TES-2-debenzoylbaccatin-1,2-carbonate (**13**)[42] (293 mg, 0.361 mmol) in THF (2 mL) at −78 °C, and the reaction mixture was stirred for 2 h at the same temperature. The reaction was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (20 mL × 3). The combined extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified on a silica gel column using hexane/ethyl acetate (10/1 followed by 5/1) as the eluant to afford **12i** as a white solid (267 mg, 79% yield): mp 182 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.47−0.67 (m, 18 H), 0.87−0.99 (m, 27 H), 1.11 (s, 3 H), 1.14 (s, 3 H), 1.63 (s, 3 H), 1.83 (m, 1 H), 1.92 (s, 3 H), 1.95 (m, 1 H), 2.09 (s, 3 H), 2.44 (m, 2 H), 3.73 (d, J = 6.5 Hz, 1 H), 4.18 (d, J = 8.3 Hz, 1 H), 4.26 (d, J = 8.3 Hz, 1 H), 4.34 (dd, J = 10.3, 6.5 Hz, 1 H), 4.64 (d, J = 4.2 Hz, 2 H), 4.84 (d, J = 8.9 Hz, 1 H), 4.91 (m, 1 H), 5.13 (s, 1 H), 5.23 (d, J = 10.6 Hz, 1 H), 5.37 (d, J = 17.4 Hz, 1 H), 5.58 (d J = 6.5 Hz, 1H) 5.81 (m, 1 H), 6.91 (m, 2 H), 7.37 (t, J = 7.9 Hz, 1 H), 7.74 (d, J = 7.6 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 4.9, 5.2, 5.9, 6.8, 6.9, 10.4, 14.6, 20.7, 22.3, 26.4, 37.4, 40.8, 42.8, 46.8, 58.4, 68.4, 69.1, 72.6, 75.9, 78.5, 80.7, 84.0, 113.4, 117.9, 120.2, 120.5, 131.7, 132.3, 133.6, 136.0, 139.2, 157.7, 166.9, 205.8; HRMS (FAB, MeOH/NBA/PPG) *m*/*z* calcd for $C_{50}H_{82}O_{11}Si_3{\cdot}Na^+$ 965.5063, found 965.5065 (Δ = −0.2 ppm).

For other baccatins **12**, see the Supporting Information.

General Procedure for the Syntheses of 7-Triethylsilyl-2-debenzoyl-2-alkenoylbaccatin III (8a−o). Method A (for the Syntheses of 8a−k). A typical procedure is described for the synthesis of 7-triethylsilyl-2-debenzoyl-2-(pent-4-enoyl)baccatin III (**8b**). To a solution of baccatin **12b** (111 mg, 0.235 mmol) in pyridine−acetonitrile (1/1, 4 mL) was added dropwise HF/pyridine (70/30, 1.2 mL) at 0 °C, and the mixture was stirred for 23 h at room temperature. The reaction was quenched with saturated aqueous sodium carbonate (10 mL). The reaction mixture was then diluted with ethyl acetate (60 mL), washed with saturated aqueous copper sulfate (10 mL × 3) and water (10 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford 2-debenzoyl-2-(pent-4-enoyl)-10-deacetylbaccatin III as a white solid (118 mg, 96% yield): mp 75−77 °C; $[\alpha]^{20}_{D}$ −27.3° (*c* 0.33, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$/D_4-MeOH) δ 0.75 (s, 3 H), 0.80 (s, 3 H), 1.39 (s, 3 H), 1.58 (m, 1 H), 1.74 (s, 3 H), 1.85 (s, 1 H), 1.89 (s, 1 H), 1.92 (s, 3 H), 2.13 (m, 4 H), 2.24 (m, 1 H), 3.57 (d, J = 6.8 Hz, 1 H), 3.94 (d, J = 7.6 Hz, 1 H), 3.95 (m, 1 H), 4.19 (d, J = 7.8 Hz, 1 H), 4.50 (t, J = 7.8 Hz, 1 H), 4.73 (m, 1 H), 4.75 (d, J = 10.3 Hz, 1 H), 4.81 (d, J = 16.1 Hz, 1 H), 4.98 (s, 1 H), 5.11 (d, J = 6.8 Hz, 1 H), 5.58 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$/[D_4]MeOH) δ 9.0, 14.0, 19.2, 21.6, 24.1, 25.9, 28.0, 33.6, 35.8, 38.5, 42.1, 46.5, 57.2, 66.4, 74.4, 74.7, 76.3, 77.7, 80.0, 84.4, 115.0, 133.5, 136.3, 143.3, 170.5, 173.4, 210.8; HRMS (FAB, MeOH/NBA/PPG) *m*/*z* calcd for $C_{27}H_{38}O_{10}{\cdot}Na^+$ 545.2363, found 545.2341 (Δ = 4.0 ppm).

To a solution of 2-debenzoyl-2-(pent-4-enoyl)-10-deacetylbaccatin III thus obtained (118 mg, 0.226 mmol) and imidazole (52.1 mg, 0.765 mmol) in dry DMF (3 mL) was added chlorotriethylsilane (96.3 μL, 0.574 mmol) dropwise via syringe at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C and diluted with ethyl acetate (60 mL). The mixture was then washed with water (15 mL × 3) and brine (10 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude product was purified on a silica gel column using hexane/ethyl acetate (4/1 followed by 1/1) as the eluant to give 7-triethylsilyl-2-debenzoyl-2-(pent-4-enoyl)-10-deacetylbaccatin III as a white solid (132 mg, 92%): mp 90−92 °C; $[\alpha]^{20}_{D}$ −47.8° (*c* 0.23, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.53 (m, 6 H), 0.91 (m, 9 H), 1.00 (s, 3 H), 1.05 (s, 3 H), 1.51 (br s, 1 H), 1.66 (s, 3 H), 1.89 (m, 1 H), 2.03 (s, 3 H), 2.10 (m, 2 H), 2.16 (s, 3 H), 2.41 (m, 5 H), 3.80 (d, J = 7.0 Hz, 1 H), 4.15 (d, J = 7.9 Hz, 1 H), 4.22 (s, 1 H), 4.34 (dd, J = 10.5, 6.6 Hz, 1 H), 4.45 (d, J = 7.9 Hz, 1 H), 4.81 (t, J = 7.8 Hz, 1 H), 4.94 (d, J = 8.2 Hz, 1 H), 5.02 (d, J = 9.1 Hz, 1 H), 5.07 (d, J = 15.8 Hz, 1 H), 5.11 (s, 1 H), 5.33 (d, J = 7.0 Hz, 1 H), 5.85 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 5.1, 6.7, 9.8, 15.1, 19.3, 22.5, 26.9, 28.5, 34.1, 37.2, 38.4, 42.6, 46.8, 57.9, 67.8, 72.8, 74.8, 74.6, 75.5, 78.5, 80.4, 84.4, 115.8, 135.0, 136.6, 141.9, 170.8, 173.9, 210.3; HRMS (FAB, MeOH/NBA/PPG) *m*/*z* calcd for $C_{33}H_{52}O_{10}Si{\cdot}Na^+$ 659.3227, found 659.3216 (Δ = 1.7 ppm).

To a solution of 7-triethylsilyl-2-debenzoyl-2-(pent-4-enoyl)-10-deacetylbaccatin III (130 mg, 0.204 mmol) thus obtained in dry THF (13 mL) was added 1.0 M LiHMDS in THF (0.225 mL, 0.225 mmol) dropwise via syringe at −40 °C. The mixture was stirred at −40 °C for 5 min, and freshly distilled acetyl chloride (17.4 μL, 0.245 mmol) was added dropwise. After 20 min, the reaction was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with dichloromethane (20 mL × 3). The combined extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified on a silica gel column using hexane/ethyl acetate (2/1 followed by 1/1) as the eluant to afford **8b** as a white solid (131 mg, 95% yield): mp 186−187 °C; $[\alpha]^{20}_{D}$ −46.7° (*c* 0.30, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.57 (m, 6 H), 0.90 (m, 9 H), 1.00 (s, 3 H), 1.11 (s, 3 H), 1.55 (br s, 1 H), 1.66 (s, 3 H), 1.86 (m, 1 H), 2.10 (m, 2 H), 2.15 (m, 9 H), 2.39 (m, 4 H), 2.51 (m, 1 H), 3.73 (d, J = 7.1 Hz, 1 H), 4.15 (d, J = 8.0 Hz, 1 H), 4.43 (m, 1 H), 4.45 (d, J = 8.0 Hz, 1 H), 4.79 (t, J = 7.8 Hz, 1 H), 4.94 (d, J = 8.6 Hz, 1 H), 5.03 (d, J = 9.3 Hz, 1 H), 5.08 (d, J = 15.9 Hz, 1 H), 5.37 (d, J = 7.1 Hz, 1 H), 5.83 (m, 1 H), 6.40 (s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 5.2, 6.7, 9.9, 14.9, 19.9, 20.9, 22.6, 26.8, 28.5, 30.1, 37.2, 38.1, 42.7, 47.1, 58.6, 67.8, 72.2, 74.3, 75.7, 76.6, 78.5, 80.5, 84.4, 115.8, 132.5, 136.5, 144.0, 169.3, 170.8, 173.9, 202.2; HRMS (FAB, MeOH/NBA/PPG) *m*/*z* calcd for $C_{35}H_{54}O_{11}Si{\cdot}Na^+$ 701.3333, found 701.3345 (Δ = −1.7 ppm).

Method B (for the Syntheses of 8l−o). A typical procedure is described for the synthesis of 7-triethylsilyl-2-debenzoyl-2-(3,3-dimethylhept-6-enoyl)baccatin III (**8l**). To a solution of 7-TES-13-

oxobaccatin **14**[34] (143 mg, 0.24 mmol), DMAP (29 mg, 0.24 mmol), and 3,3-dimethylhept-6-enoic acid **11l** (187 mg, 1.20 mmol) in dichloromethane (3 mL) was added *N*,*N*′-diisopropylcarbodiimide (DIC; 0.23 mL, 1.44 mmol), and the mixture was allowed to stir overnight. The precipitate was filtered off and washed with ethyl acetate (30 mL). The filtrate was diluted with ethyl acetate (30 mL), washed with a saturated aqueous sodium bicarbonate (15 mL × 2), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified on a silica gel column using hexane/ethyl acetate (8/1 followed by 4/1) as the eluant to give 7-TES-2-debenzoyl-2-(3,3-dimethylhept-6-enoyl)-13-oxo-baccatin III as a white solid (153 mg, 85% yield): mp 190 °C; $[\alpha]^{20}_D$ −9.1° (*c* 0.22, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.57 (t, J = 7.5 Hz, 6 H), 0.89 (t, J = 8.1 Hz, 9 H), 1.02 (s, 3 H), 1.04 (s, 1.04), 1.14 (s, 3 H), 1.19 (s, 3 H), 1.43 (m, 2 H), 1.58 (s, 3 H), 1.68 (m, 1 H), 1.84 (m, 1 H), 2.03 (m, 1 H), 2.04 (s, 3 H), 2.12 (s, 3 H), 2.19 (s, 3 H), 2.20 (s, 2 H), 2.51 (m, 1 H), 2.58 (d, J = 20.1 Hz, 1 H), 2.74 (d, J = 20.1 Hz, 1 H), 3.79 (d, J = 6.6 Hz, 1 H), 4.14 (d, J = 8.0 Hz, 1 H), 4.42 (dd, J = 10.5, 6.6 Hz, 1 H), 4.51 (d, J = 8.0 Hz, 1 H), 4.90 (d, J = 9.6 Hz, 1 H), 4.94 (d, J = 11.7 Hz, 1 H), 5.01 (dd, J = 17.1, 1.5 Hz, 1 H), 5.38 (d, J = 6.6 Hz, 1 H), 5.80 (m, 1 H), 6.54 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.2, 6.7, 9.5, 13.5, 18.0, 20.8, 21.6, 24.9, 25.6, 27.2, 27.3, 28.5, 33.1, 33.6, 33.9, 37.1, 40.9, 42.2, 43.5, 46.2, 46.5, 49.1, 59.4, 72.2, 76.0, 76.4, 78.4, 80.2, 84.0, 114.4, 138.8, 140.2, 152.8, 168.8, 170.2, 173.3, 198.4, 200.3; HRMS (FAB) *m*/*z* calcd for $C_{39}H_{60}O_{11}Si{\cdot}H^+$ 733.3983, found 733.3985 (Δ = −0.2 ppm).

7-TES-2-debenzoyl-2-(3,3-dimethylhept-6-enoyl)-13-oxo-baccatin III thus obtained (80 mg, 0.11 mmol) was dissolved in 4 mL of MeOH and 1 mL of THF, and $NaBH_4$ (100 mg, 2.0 mmol) was added in small portions at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and quenched by saturated aqueous ammonium chloride (5 mL). The aqueous layer was extracted with ethyl acetate (20 mL × 3). The combined extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified on a silica gel column using hexane/ethyl acetate (4/1 followed by 2/1) as the eluant to afford 40 mg (50% recovery yield) of 7-TES-2-debenzoyl-2-(3,3-dimethylhepta-6-enoyl)-13-oxo-baccatin III and 34 mg of **8l** (85% yield based on 50% conversion) as a colorless film: mp 73−74 °C; $[\alpha]^{20}_D$ −72.2° (*c* 0.18, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.58 (t, J = 7.7 Hz, 6 H), 0.91 (t, J = 7.9 Hz, 9 H), 1.02 (s, 3 H), 1.04 (s, 3 H), 1.06 (s, 3 H), 1.13 (s, 3 H), 1.42 (m, 2 H), 1.60 (s, 3 H), 1.88 (m, 1 H), 2.01−2.25 (m, 6 H), 2.16 (s, 9, H), 2.50 (m, 2 H), 3.75 (d, J = 6.0 Hz, 1 H), 4.13 (d, J = 7.9 Hz, 1 H), 4.44 (dd, J = 10.5, 6.4 Hz, 1 H), 4.50 (d, J = 7.9 Hz, 1 H), 4.79 (m, 1 H), 4.96 (m, 3 H), 5.34 (d, J = 6.9 Hz, 1 H), 5.82 (m, 1 H), 6.41 (s, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ5.3, 6.7, 9.9, 14.9, 19.9, 20.9, 22.6, 26.9, 27.3, 28.6, 29.7, 33.6, 37.2, 38.0, 41.0, 42.9, 46.7, 47.4, 58.6, 68.0, 72.3, 74.0, 75.7, 76.5, 78.6, 80.6, 84.4, 101.9, 114.2, 132.6, 139.1, 143.9, 169.3, 170.6, 170.9, 173.6, 202.3; HRMS (FAB) *m*/*z* calcd for $C_{39}H_{62}O_{11}Si{\cdot}H^+$ 735.4140, found 735.4137 (Δ = 0.4 ppm).

For other baccatins **8**, see the Supporting Information.

(3*R*,4*S*)-1-(4-Methoxyphenyl)-3-triisopropylsiloxy-4-formylazetidin-2-one (16). Nitrogen gas was bubbled into a solution of 4-(2-methylprop-2-enyl)-β-lactam **15** (500 mg, 1.239 mmol) in MeOH/CH_2Cl_2 (1/2, 27 mL) at −78 °C for 3 min. Then, ozone gas was bubbled into the solution until the color of the solution turned blue (2 min), and nitrogen gas was bubbled into the solution for another 3 min. Dimethyl sulfide (0.458 mL, 6.194 mmol) was added to the solution, and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred for 3 h at room temperature. The solvents were removed in vacuo, and the residue was purified on a neutral alumina column using hexane/ethyl acetate (4/1 followed by 2/1) as the eluant to afford **16** as a white solid (467.5 mg, 100%): mp 78−80 °C; $[\alpha]^{20}_D$ +158.0° (*c* 0.50, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.06 (m, 21 H), 3.74 (s, 3 H), 4.43 (dd, J = 5.2, 3.8 Hz, 1 H), 5.25 (d, J = 5.2 Hz, 1 H), 6.81 (d, J = 8.8 Hz, 1 H), 7.22 (d, J = 8.8 Hz, 1 H), 9.72 (d, J = 3.8 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 11.6, 17.4, 55.3, 64.2, 78.6, 114.4, 117.8, 130.7, 156.7, 164.2, 199.6. Anal. Calcd for $C_{20}H_{31}NO_4Si$: C, 63.63; H, 8.28; N, 3.71. Found: C, 63.80; H, 8.05; N, 3.72.

(3*R*,4*S*)-1-(4-Methoxyphenyl)-3-triisopropylsiloxy-4-(penta-1,4-dienyl)azetidin-2-one (17a-*E*,*Z*). To a suspension of (3-butenyl)-triphenylphosphonium bromide (147.3 mg, 0.371 mmol) in anhydrous THF (3 mL) at −78 °C was added *n*-BuLi (0.195 mL, 2.5 M in hexane, 0.371 mmol) under nitrogen. The solution was allowed to warm to room temperature and stirred for 20 min. The solution was cooled to −78 °C, and a solution of 4-formyl-β-lactam **16** (70 mg, 0.185 mmol) in THF (2 mL) was added dropwise at that temperature. The reaction mixture was allowed to warm to room temperature over a period of 2 h with stirring. The reaction was then quenched with water (10 mL), extracted with dichloromethane (15 mL × 3), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude product was purified on a silica gel column using hexane/ethyl acetate (10/1) as the eluant to afford **17a** as a colorless oil (72 mg, 93% yield; *Z*/*E* > 9/1 based on ^{1}H NMR).

***Z*-isomer (17a-*Z*):** ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.11 (m, 21 H), 3.04 (m, 2 H), 3.76 (s, 3 H), 4.88 (dd, J = 10.0, 4.9 Hz, 1 H), 5.09 (d, J = 4.9 Hz, 1 H), 5.12 (dd, J = 9.5, 1.4 Hz, 1 H), 5.15 (dd, J = 15.3, 1.4 Hz, 1 H), 5.63 (dd, J = 10.9, 10.1 Hz, 1 H), 5.86 (m, 2 H), 6.82 (d, J = 9.0 Hz, 2 H), 7.33 (d, J = 9.0 Hz, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 11.9, 17.6, 17.7, 31.9, 55.3, 56.1, 77.5, 114.2, 115.8, 118.3, 125.8, 128.6, 133.8, 135.5, 156.1, 165.3.

***E*-isomer (17a-*E*):** ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.11 (m, 21 H), 2.87 (m, 2 H), 3.76 (s, 3 H), 4.55 (dd, J = 8.6, 5.0 Hz, 1 H), 5.03 (d, J = 10.5 Hz, 1 H), 5.11 (m, 2 H), 5.64 (m, 1 H), 5.86 (m, 2 H), 6.83 (d, J = 9.0 Hz, 2 H), 7.34 (d, J = 9.0 Hz, 2 H); HRMS (DCI/NH_3/PPG) *m*/*z* calcd for $C_{24}H_{37}O_3SiN{\cdot}H^+$ 416.2621, found 416.2633 (Δ = −2.9 ppm).

(3*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-3-triisopropylsiloxy-4-(penta-1,4-dienyl)azetidin-2-one (18a-*E*,*Z*). To a solution of *N*-PMP-β-lactam **17a** (154 mg, 0.371 mmol) in acetonitrile (17 mL) and water (3.5 mL) was added dropwise a solution of CAN (673 mg, 1.227 mmol) in water (13.5 mL) at −10 °C. The reaction mixture was stirred at −10 °C for 2 h. The reaction was then quenched with saturated aqueous sodium sulfite (15 mL). The aqueous layer was extracted with ethyl acetate (40 mL × 3), and the combined organic layers were washed with aqueous sodium sulfite and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude product was purified on a silica gel column using hexane/ethyl acetate (4/1 followed by 2/1) as the eluant to afford (3*R*,4*S*)-3-triisopropylsiloxy-4-(penta-1,4-dienyl)-azetidin-2-ones as a colorless oil (95 mg, 83% yield; *Z*/*E* = 7/1 based on ^{1}H NMR).

***Z*-isomer:** ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.07 (m, 21 H), 2.84 (m, 2 H), 4.50 (dd, J = 8.9, 4.7 Hz, 1H), 4.96−5.07 (m, 3 H), 5.73 (m, 3 H), 6.36 (br s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 11.8, 17.6, 31.7, 52.1, 79.3, 115.4, 126.9, 132.4, 135.8, 169.9.

***E*-isomer:** ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.08 (m, 21 H), 2.88 (m, 2 H), 4.16 (dd, J = 7.8, 4.7 Hz, 1H), 4.94−5.07 (m, 3 H), 5.70 (m, 3 H), 6.45 (br s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 12.3, 17.6, 36.5, 58.0, 79.3, 116.0, 127.7, 133.5, 135.7, 169.9.

To a solution of the NH-β-lactams thus obtained (92 mg, 0.307 mmol), di-*tert*-butyl dicarbonate (80.4 mg, 0.368 mmol), and DMAP (9.4 mg, 0.077 mmol) in dichloromethane (5 mL) was added dropwise triethylamine (0.128 mL, 0.921 mmol) at room temperature. The mixture was stirred for 9 h at room temperature, and the reaction was quenched with saturated aqueous ammonium chloride (15 mL). The reaction mixture was then extracted with ethyl acetate (30 mL × 3). The combined extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified on a silica gel column using hexane/ethyl acetate (20/1 followed by 10/1) as the eluant to afford **18a-*Z*** (102.5 mg) and **18a-*E*** (14.5 mg) as colorless oils (total 117 mg, 96% yield).

***Z*-isomer (18a-*Z*):** $[\alpha]^{20}_D$ +20.0° (*c* 0.15, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.05 (m, 21 H), 1.48 (s, 9 H), 2.97 (m, 2 H), 4.82 (dd, J = 9.7, 5.7 Hz, 1H), 5.04 (m, 3 H), 5.57 (dd, J = 10.9, 9.9 Hz, 1 H), 5.81 (m, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 11.8, 17.60, 17.65, 31.9, 55.3, 77.3, 83.2, 115.6, 123.9, 134.2, 135.9, 165.1; HRMS (FAB) *m*/*z* calcd for $C_{22}H_{39}O_4SiN{\cdot}H^+$ 410.2727, found 410.2734 (Δ = −1.8 ppm).

***E*-isomer (18a-*E*):** ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.05 (m, 21 H), 1.48 (s, 9 H), 2.85 (m, 2 H), 4.49 (dd, J = 8.4, 5.8 Hz, 1H), 5.04 (m,

3 H), 5.57 (dd, J = 15.4, 8.5 Hz, 1 H), 5.83 (m, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 11.8, 17.6, 36.5, 61.0, 77.4, 83.2, 115.9, 124.6, 135.4, 135.6, 166.1; HRMS (FAB) m/z calcd for $C_{22}H_{39}O_4SiN\cdot H^+$ 410.2727, found 410.2734 (Δ = −1.8 ppm).

(3*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-3-triethylsiloxy-4-[(*Z*)-pent-1,4-dienyl]azetidin-2-one (9a-*Z*). To a solution of **18a-*Z*** (70 mg, 0.171 mmol) in pyridine−acetonitrile (1/1, 2 mL) was added dropwise HF/pyridine (70/30, 0.3 mL) at 0 °C, and the mixture was allowed to warm to room temperature. The mixture was stirred for 17 h at room temperature. The reaction was quenched with saturated aqueous sodium carbonate (10 mL), and the reaction mixture was diluted with ethyl acetate (60 mL), washed with saturated aqueous copper sulfate (15 mL × 3), water, and brine, dried over anhydrous magnesiun sulfate, and concentrated in vacuo to afford (3*R*,4*S*)-1-(*tert*-butoxycarbonyl)-3-hydroxy-4-[(*Z*)-pent-1,4-dienyl]azetidin-2-one as a colorless oil (40 mg).

To a solution of the 3-OH-β-lactam thus obtained (40 mg, 0.158 mmol) and DMAP (4.8 mg, 0.039 mmol) in dichloromethane (2 mL) were added dropwise chlorotriethylsilane (32 μL, 0.190 mmol) and triethylamine (66 μL, 0.474 mmol) at room temperature, and the mixture was stirred for 1 h at the same temperature. The reaction was quenched with saturated aqueous ammonium chloride (5 mL), and the reaction mixture was extracted with dichloromethane (15 mL × 3). The combined extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (10/1) as the eluant, affording **9a-*Z*** as a colorless oil (55.5 mg, 88% yield for two steps): $[\alpha]^{20}_D$ +36.4° (c 0.22, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.63 (m, 6 H), 0.93 (m, 9 H), 1.47 (s, 9 H), 2.94 (m, 2 H), 4.77 (dd, J = 9.2, 5.6 Hz, 1H), 4.87 (d, J = 5.6 Hz, 1 H), 5.01 (dd, J = 10.0, 1.4 Hz, 1 H), 5.06 (dd, J = 16.7, 1.4 Hz, 1 H), 5.52 (dd, J = 10.9, 9.5 Hz, 1 H), 5.83 (m, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 4.7, 6.4, 28.0, 31.8, 55.1, 76.8, 83.1, 11.5, 123.9, 133.8, 135.8, 147.9, 166.0; HRMS (FAB) m/z calcd for $C_{19}H_{33}O_4SiN\cdot H^+$ 368.2257, found 368.2252 (Δ = 1.4 ppm).

In the same manner, **9a-*E*** was synthesized.

(3*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-3-triethylsiloxy-4-[(*E*)-pent-1,4-dienyl]azetidin-2-one (9a-*E*): 77% yield from **18a-*E*** (two steps); colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.64 (m, 6 H), 0.95 (m, 9 H), 1.48 (s, 9 H), 2.85 (m, 2 H), 4.46 (dd, J = 8.4, 5.8 Hz, 1H), 4.87 (d, J = 5.6 Hz, 1 H), 5.06 (m, 2 H), 5.54 (dd, J = 15.5, 8.5 Hz, 1 H), 5.82 (m, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 4.6, 6.5, 28.0, 36.5, 64.7, 76.9, 83.1, 115.8, 124.5, 136.4, 136.7, 147.7, 166.0; HRMS (FAB) m/z calcd for $C_{19}H_{33}O_4SiN\cdot H^+$ 368.2257, found 368.2252 (Δ = 1.4 ppm).

For the synthesis and characterization data for other β-lactams **17**, **18**, **20**, and **9**, see the Supporting Information.

General Procedure for the Synthesis of taxoids 7. A typical procedure is described for the synthesis of 2-debenzoyl-2-(pent-4-enoyl)-7-triethylsilyl-13-[(2*R*,3*S*,*Z*)-3-*tert*-butoxycarbonylamino-2-triethylsiloxyocta-4,6-dienoyl]baccatin III (**7a**). To a solution of **8b** (53 mg, 0.078 mmol) and β-lactam **9a-*Z*** (43 mg, 0.117 mmol) in dry THF (3 mL) was added a solution of 1.0 M LiHMDS in THF (0.12 mL, 0.12 mmol) dropwise at −40 °C, and the solution was stirred at −40 °C for 35 min. The reaction was quenched with saturated aqueous ammonium chloride (10 mL), and the aqueous layer was extracted with dichloromethane (25 mL × 3). The combined extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified on a silica gel column using hexane/ethyl acetate (8/1 followed by 4/1) as the eluant to afford the coupling product **7a** as a white solid (77 mg, 94%): mp 82−83 °C; $[\alpha]^{20}_D$ −55.0° (c 0.20, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.59 (m, 12 H), 0.94 (m, 18 H), 1.14 (s, 6 H), 1.38 (s, 9 H), 1.61 (s, 3 H), 1.86 (m, 1 H), 1.94 (s, 3 H), 2.14 (s, 3 H), 2.18 (m, 2 H), 2.21 (s, 3 H), 2.41 (m, 4 H), 2.52 (m, 1 H), 2.90 (m, 2 H), 3.68 (d, J = 6.8 Hz, 1 H), 4.17 (d, J = 7.9 Hz, 1 H), 4.24 (d, J = 2.8 Hz, 1 H), 4.40 (dd, J = 8.2, 6.6 Hz, 1 H), 4.44 (d, J = 7.9 Hz, 1 H), 4.76 (br t, 1 H), 4.90 (br d, 2 H), 5.06 (m, 4 H), 5.42 (d, J = 6.8 Hz, 1 H), 5.60 (m, 2 H), 5.81 (m, 2 H), 6.05 (t, J = 8.5 Hz, 1 H), 6.40 (s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 4.6, 5.2, 6.7, 9.9, 14.1, 20.8, 21.1, 22.6, 26.4, 28.2, 28.4, 32.1, 34.0, 35.0, 37.1, 43.2, 46.5, 50.5, 58.3, 71.5, 72.1, 74.1, 74.5, 75.0, 76.6, 78.5, 79.6, 80.7, 84.3, 115.5, 115.9, 126.9, 131.1, 133.3, 135.8, 136.5, 140.7, 154.9, 169.1, 169.9, 171.6, 173.7, 201.8; HRMS (FAB, $CHCl_3$/NBA/NaCl) m/z calcd for $C_{54}H_{87}NO_{15}Si_2\cdot Na^+$ 1068.5512, found 1068.5546 (Δ = −3.2 ppm).

In the same manner, **7b**−**t** were synthesized. See the Supporting Information.

General Procedure for the Synthesis of Macrocyclic Taxoids 21 by Ring-Closing Metathesis. A typical procedure is described for the synthesis of 7-triethylsilyl-2-debenzoyl-2,13-[(10*R*,9*S*,7*Z*)-9-*tert*-butoxycarbonylamino-10-triethylsiloxy-1,11-diketoundeca-4,7-dienylene]-baccatin III (**21a**). To a solution of taxoid **7a** (63 mg, 0.060 mmol) in dry dichloromethane (30 mL) was added dropwise a solution of bis-(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride (catalyst **I**; 7.4 mg, 0.009 mmol) in dry dichloromethane (15 mL) via cannula over a period of 2 h at room temperature, and the solution was stirred for 14 h. The solvents were removed in vacuo to afford a deep brown residue. The residue was purified on a silica gel column using hexane/ethyl acetate (3/1) as the eluant to afford macrocyclic taxoid **21a** as a white solid (56.5 mg, 92% yield; Z/E = 9/1 as indicated by ^{1}H NMR): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.56 (m, 6 H), 0.64 (m, 6 H), 0.92 (m, 9 H), 0.97 (m, 9 H), [1.09 (major), 1.13 (minor)] (s, 3 H), [1.11 (major), 1.15 (minor)] (s, 3 H), [1.38 (major), 1.40 (minor)] (s, 9 H), 1.64 (s, 3 H), 1.88 (m, 1 H), [1.99 (major), 2.02 (minor)] (s, 3 H), 2.14 (s, 3 H), 2.34−2.57 (m, 4 H), 2.62 (m, 2 H), 2.73 (m, 1 H), 3.11 (m, 2 H), [3.78 (minor), 3.80 (major)] (d, J = 8.0 Hz, 1 H), [4.12 (minor), 4.15 (major)] (s, 1 H), 4.24 (d, J = 8.0 Hz, 1 H), [4.42 (major), 4.43 (minor)] (d, J = 8.0 Hz, 1 H), 4.49 (dd, J = 11.0, 6.5 Hz, 1 H), 4.88 (br t, 1 H), 4.90 (d, J = 8.5 Hz, 1 H), [5.03 (minor), 5.05 (major)] (d, J = 9.5 Hz, 1 H), 5.30 (d, J = 8.0 Hz, 1 H), [5.42 (d, J = 15.5 Hz) (minor), 5.47 (d, J = 9.5 Hz) (major)] (1 H), [5.44 (d, J = 15.5 Hz) (minor), 5.47 (d, J = 9.5 Hz) (major)] (1 H), 5.48 (d, J = 9.5 Hz, 1 H), 5.52 (dd, J = 10.5, 9.5 Hz, 1 H), 5.67 (dt, J = 10.5, 7.0 Hz, 1 H), 5.80 (t, J = 8.5 Hz, 1 H), [6.39 (major), 6.41 (minor)] (s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 4.6, 5.2, 6.6, 6.7, 10.4, 14.2, 20.8, 21.0, 21.3, 22.6, 23.4, 25.8, 26.8, 28.2, 35.5, 36.5, 36.8, 42.9, 47.0, 50.6, 57.9, 60.3, 71.7, 73.9, 74.7, 75.6, 76.1, 79.6, 80.1, 80.7, 84.4, 127.2, 128.0, 128.8, 130.9, 133.5, 140.4, 155.1, 169.1, 169.6, 172.3, 172.5, 201.2; HRMS (FAB, $CHCl_3$/NBA/NaCl/PPG) m/z calcd for $C_{52}H_{83}NO_{15}Si_2\cdot Na^+$ 1040.5199, found 1040.5170 (Δ = 2.8 ppm).

In a similar manner, macrocyclic taxoids **21b**−**o** were synthesized from **7b**−**o**. Toluene was used as the solvent instead of dichloromethane wherever a higher reaction temperature (>40 °C) was necessary. Catalyst loading ranges from 20 to 60 mol %. See the Supporting Information.

General Procedure for the Synthesis of Macrocyclic Taxoids 6. A typical procedure is described for the synthesis of taxoid 2-debenzoyl-2,13-[(10*R*,9*S*,7*Z*)-9-*tert*-butoxycarbonylamino-10-hydroxy-1,11-diketoundeca-4,7-dienylene]baccatin III (**6a**). To a solution of **21a** (50 mg, 0.049 mmol) in pyridine−acetonitrile (1/1, 5 mL) was added dropwise HF/pyridine (70/30, 0.4 mL) at 0 °C, and the mixture was stirred at room temperature for 11 h. The reaction was quenched with saturated aqueous sodium carbonate solution (5.0 mL). The mixture was then diluted with ethyl acetate (70 mL), washed with saturated aqueous copper sulfate (10 mL × 3), water (10 mL), and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude product was purified on a silica gel column using hexane/ethyl acetate (1/1 followed by 1/2) as the eluant to afford macrocyclic taxoid **6a** as a white solid (35.0 mg, 90% yield; Z/E = 9/1 based on ^{1}H NMR): ^{1}H NMR (250 MHz, $CDCl_3$) δ [1.02 (major), 1.05 (minor)] (s, 3 H), [1.16 (major), 1.20 (minor)] (s, 3 H), 1.37 (s, 9 H), 1.62 (s, 3 H), 1.85 (m, 1 H), 1.89 (s, 3 H), 2.11 (s, 3 H), 2.22 (s, 3 H), 2.52 (m, 6 H), 2.85 (m, 1 H), 3.06 (m, 2 H), 3.77 (d, J = 8.0 Hz, 1 H), 4.06 (s, 1 H), 4.23 (d, J = 8.0 Hz, 1 H), 4.42 (d, J = 8.0 Hz, 1 H), 4.43 (m, 1 H), 4.79−4.94 (m, 3 H), 5.28 (d, J = 8.0 Hz, 1 H), [5.40 (minor), 5.46 (major)] (m, 2 H), 5.60 (m, 1 H), 5.70 (m, 1 H), 5.86 (t, J = 8.2 Hz, 1 H), [6.19 (major), 6.22 (minor)] (s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 9.8, 15.2, 20.8, 22.1, 22.5, 23.2, 26.1, 26.8, 28.2, 35.0, 35.4, 36.8, 42.8, 45.7, 50.6, 58.1, 71.6, 72.0, 72.8, 75.5, 75.7, 76.0, 80.1, 80.5, 80.6, 84.7, 126.4, 127.7, 128.9, 131.9, 132.8, 142.4, 155.0, 169.7, 171.3, 172.3, 174.2, 203.4; HRMS (FAB, $CHCl_3$/NBA/NaCl/PPG) m/z calcd for $C_{40}H_{55}NO_{15}\cdot Na^+$ 812.3469, found 812.3459 (Δ = 1.3 ppm).

In the same manner, macrocyclic taxoids **6b**−**o** were synthesized. For the characterization data of **6b**−**o**, see the Supporting Information.

General Procedure for the Synthesis of Macrocyclic Taxoids 6′. A typical procedure is described for the synthesis of 2-debenzoyl-2, 13-[(2*R*,3*S*)-3-*tert*-butoxycarbonylamino-2-hydroxy-1,11-diketoundecylene]baccatin III (**6′a**). A solution of **6a** (15.0 mg, 0.019 mmol) in ethyl acetate (2 mL) was added to 10% palladium on carbon (10 mg) under a hydrogen atmosphere, and the reaction mixture was stirred for 18 h at room temperature. The reaction mixture was then filtered through Celite and concentrated in vacuo. The crude product was purified on a silica gel column using hexane/ethyl acetate (1/2) as the eluant to afford macrocyclic taxoid **6′a** as a white solid (15.0 mg, 100%): mp 156−158 °C; $[\alpha]^{20}_{D}$ −76.2° (*c* 0.21, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.04 (s, 3 H), 1.19 (s, 3 H), 1.38 (s, 9 H), 1.39−1.44 (m, 8 H), 1.60 (s, 3 H), 1.72 (m, 2 H), 1.86 (m, 1 H), 1.90 (s, 3 H), 2.221 (s, 3 H), 2.224 (s, 3 H), 2.28 (m, 2 H), 2.40 (dd, J = 6.9, 6.4 Hz, 2 H), 2.53 (m, 2 H), 2.70 (m, 1 H), 3.03 (br s, 1 H), 3.78 (d, J = 7.7 Hz, 1 H), 3.98 (s, 1 H), 4.02 (br s, 1 H), 4.17 (d, J = 7.8 Hz, 1 H), 4.42 (m, 1 H), 4.46 (d, J = 7.8 Hz, 1 H), 4.53 (d, J = 9.7 Hz, 1 H), 4.96 (d, J = 7.9 Hz, 1 H), 5.33 (d, J = 7.7 Hz, 1 H), 5.90 (t, J = 8.1 Hz, 1 H), 6.21 (s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 9.7, 15.2, 20.8, 21.9, 22.5, 23.6, 24.3, 26.1, 28.2, 28.4, 29.7, 30.6, 35.1, 35.4, 36.4, 43.0, 45.7, 51.2, 58.2, 71.8, 73.4, 75.0, 75.3, 75.6, 76.1, 79.9, 80.8, 84.6, 87.2, 132.5, 142.8, 155.8, 169.5, 171.3, 173.2, 174.8, 203.5; HRMS (FAB, $CHCl_3$/NBA/NaCl) *m*/*z* calcd for $C_{40}H_{59}NO_{15}\cdot Na^+$ 816.3782, found 816.3822 (Δ = −4.8 ppm).

In the same manner, macrocyclic taxoids **6′d**, **6′e**, **6′f**, **6′g**, **6′l**, **6′m**, and **6′o** were obtained. For the characterization data, see the Supporting Information.

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Supporting Information Available: Characterization data for new compounds **7**−**10**, **12**, **17**, **18**, **20**, and **21** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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