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# Novel Dimeric Taxoids via Highly Regio- and Stereospecific Diels–Alder Cycloadditions of Taxinine B and Taxicine I Derivatives

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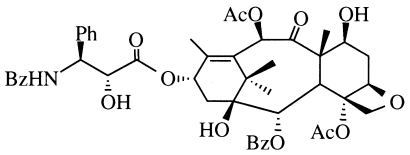
**Abstract**—Oxidation of 20-hydroxy-4,5-ene-7-oxotaxinine **4** derived from a natural taxoid taxinine B via four steps gave a corresponding aldehyde **5**, which afforded a new dimeric taxoid **6** through regio- and stereospecific hetero Diels–Alder cycloaddition. Similar hetero Diels–Alder reaction of 4:5,6:7-diene aldehyde **13** gave two new dimeric taxoids **14** and **15**. In addition, Lewis acid-catalyzed Diels–Alder reaction of 20-hydroxy-4:5,6:7-diene taxoid **12** with *N*-methylmaleimide led to cycloadduct *exo*-**16** and γ-butyrolactone *endo*-**17**, while a similar Lewis acid-catalyzed Diels–Alder reaction of **12** with taxoid **7a** yielded only cycloadduct *exo*-**18**. **7a** and **7b**, the two isomers of alcohol **4**, yielded two 5-ethyl substituted derivatives **8** and **9** through highly stereoselective Michael addition in the presence of diethylaluminum chloride. The structure and stereochemistry of the dimers were established by spectroscopic experiments including 2D NMR studies. 

## Introduction

The novel diterpenoid paclitaxel (Taxol®), first isolated from the Pacific yew tree *Taxus brevifolia* by Wani et al.,[1] is a powerful therapeutic drug for cancer chemotherapy[2] and exhibits remarkably high cytotoxicity and strong antitumor activity against different tumors resistant to existing anticancer drugs.[3] Paclitaxel is now approved for treatment of advanced ovarian and breast cancers[4,5] and shows promise also for treatment of lung, skin, and head and neck cancers with encouraging results.[2,6] In the past two decades, particularly in the recent ten years, structural complexity, important biological activity and novel mechanism of action[7] of paclitaxel have stimulated extensive chemical, biological and medicinal research[2,8] and a number of research groups have attempted to synthesize it and its improved analogs for clinical use. To data, six total syntheses of paclitaxel have been reported.[9] However, one of the major problems[4,10] having been encountered in the pharmaceutical development of paclitaxel is scarcity of the drug owing to its low abundance in yew tissue and none of the total synthetic approaches have been suitable for large-scale production. The major current commercial production methods are that of direct isolation from *Taxus brevifolia* bark and the needles of various *Taxus* species[11] and partial synthesis from 10-deacetylbaccatin III,[12] which is available in reasonable yield from the needles of *Taxus baccata* and other *Taxus* species.[13]




***Taxol***

Although the partial synthesis of paclitaxel from 10-deacetylbaccatin III has alleviated the immediate paclitaxel supply problem, 10-deacetylbaccatin III is still obtained by direct isolation from *Taxus* species. This process yields not only paclitaxel and 10-deacetylbaccatin III but also other useful taxoids. Thus, chemical conversion of more readily available taxoids to 10-deacetylbaccatin III, to paclitaxel or to its analogs is still an interesting research area. In our continuing studies[14] on various chemical conversions of taxoids available from Japanese yew to paclitaxel and analogs for clinical use or other biological activity, several novel taxoid dimers and derivatives were obtained via regio- and stereospecific Diels–Alder cycloadditions of taxinine B and taxicine I derivatives. These interesting results have prompted us to present our observations here because so far very few

*Keywords*: biologically active compounds; taxoids; regiospecificity; stereospecificity; Diels–Alder reactions.

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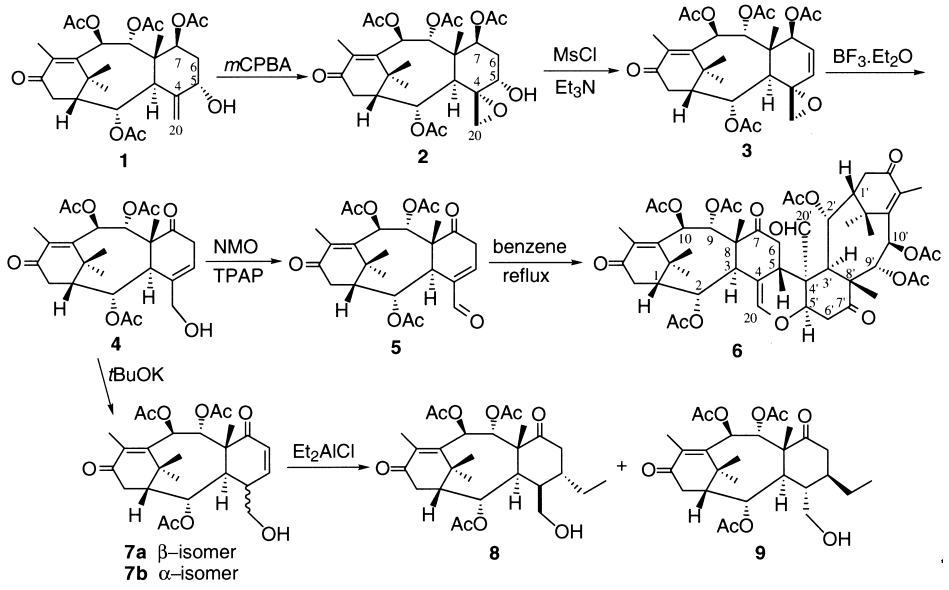



**Scheme 1.**

studies on the synthesis and biological activity of taxoid dimers have been reported.[15]

5-Hydroxytaxinine B **1** was readily prepared following the known method[16] from taxinine B, one of the taxoids obtained from Japanese yew *Taxus cuspidata* and other *Taxus* species.[17] Epoxidation of **1** using *m*-chloroperbenzoic acid (Scheme 1) (*m*CPBA)[14,18] gave a sole product which was determined to be the α-4(20)-epoxy-5-hydroxytaxinine **2** by NOESY correlations of H-20a (δ 2.87, d) to H-2 (δ 5.58, dd) and $H_3$-19 (δ 1.00, s), plus H-20b (δ 2.65, d) to H-5 (δ 3.47, brt) and H-6β (δ 1.96, m). Dehydration of **2** by means of methanesulfonyl chloride ($MsCl/Et_3N$)[19] led to α-4(20)-epoxy-5,6-ene-taxinine B **3**, which subsequently was treated with boron trifluoride diethyl etherate in dichloromethane at −78°C for 2 h, resulting in the rearranged alcohol **4** in 62% yield.[20] The latter can be explained by complexation of the Lewis acid with the α-epoxide followed by double bond migration, 1,2-hydride shift and deacetylation generating the carbonyl group at C-7 in **4**. It was found that oxidation of **4** with tetrapropylammonium perruthenate along with 4-methylmorpholine *N*-oxide (TPAP/NMO)[21] easily yielded α,β-unsaturated aldehyde **5**, which readily afforded a new dimeric compound **6** as a sole product in 90% yield, through regio- and stereospecific Diels–Alder cycloaddition in benzene for 8 h under reflux. Only 50% conversion of **5** to **6** was observed when **5** was allowed to stand at room temperature for two days. However, treatment of **4** with potassium *t*-butoxide gave a mixture of β-isomer **7a** and α-isomer **7b** in a 4:1 ratio.[22] This reaction did not occur in benzene at room temperature or even under reflux for 24 h, but led only to recovery of starting materials. However, a mixture of **7a** and **7b** underwent stereoselective Michael addition instead of Diels–Alder reaction in the presence of diethylaluminum chloride leading to 4β-hydroxymethylene-5α-ethyl-7-oxotaxinine B **8** and 4α-hydroxymethylene-5β-ethyl-7-oxotaxinine B **9** as determined by NMR data and NOESY experiments.[23] The NOESY data of **8** revealed NOE correlations of H-20a (δ 3.52, dd) to H-2 (δ 5.62, dd) and $H_3$-19 (δ 0.97, s), and H-3 (δ 3.12, dd), H-6α (δ 2.32, d) and $H_3$-18 to $CH_2$ (δ 1.24-1.26, m) of the ethyl including H-3 and H-14α (δ 2.48, d) to H-4 (δ 1.92, m). The NOE correlations of H-2 (δ 5.58, dd), H-6β (δ 2.68, dd) and $H_3$-19 (δ 0.96, s) to H-4 (δ 2.01, m), H-3 (δ 3.19, dd) and H-6α (δ 2.24, dd) to H-5 (δ 1.90–1.93, m) and H-20b(δ 3.21, dd), and H-14α (δ 2.54, d) to $H_2$-20 (δ 3.21, 3.60, dd) were observed in **9**. Michael additions of $Et_2AlCl$ to β-isomer **7a** and α-isomer **7b**, respectively leading to **8** and **9** can be explained via the transition states shown in Fig. 1, proposed for the preferred conformations of **7a** and **7b** based on minimum energy calculations.[24] The α-face provides more favorable access for nucleophilic attack by ethyl anion in the β-chelated state derived from β-isomer **7a**, whereas the β-face is more favorably accessed for nucleophilic attack by ethyl anion in the α-chelated state derived from α-isomer **7b**. Similar Michael addition products have been obtained as by-products in a

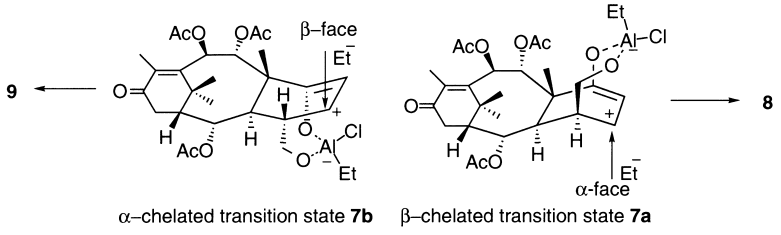



**Figure 1.** Transition states for Michael addition of β-isomer **7a** and α-isomer **7b**.

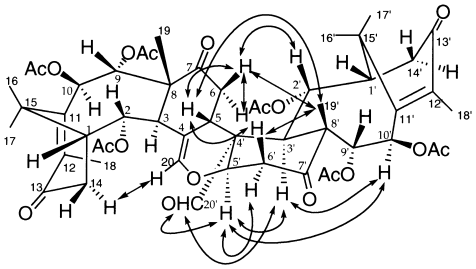


**Figure 2.** Relative stereochemistry of **6** deduced from NOESY experiment (only key NOE correlations donated).

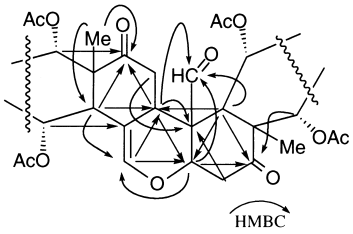



**Figure 3.** Key $^{1}H-^{13}C$ long-range correlations of **6**.

Diels–Alder reaction of Evans's acrylamine[25] with 1-methylpyrrole catalyzed by $Et_2AlCl$.[26]

The structure and stereochemistry (Fig. 2) of **6** were identified by spectroscopic experiments including 2D NMR. Compound **6** was found to have a molecular formula $C_{52}H_{64}O_{18}$, a dimer of **5**, by HRFABMS *m/z* 977.4159 ($MH^+$). The $^1H$ NMR (Table 1) spectrum of **6** showed characteristic signals for each pair of three acetyl methyls, three oxymethines, and four methyls which were unambiguously assigned to each half moiety of the dimer by $^{13}C$ NMR (Table 1) and 2D NMR ($^1H-^1H$ COSY, HMQC, and HMBC) data. HMBC correlations of:H-3, H-5, $H_2$-6, and $H_3$-19 to C-7; H-3 to C-4 and C-5; H-5 to C-3 and C-6, plus H-3′, H-5′, $H_2$-6′, and $H_3$-19′ to C-7′; H-3′ to C-4′ and C-5′; H-5′ to C-3′ and C-6′ indicated the presence of two respective cyclohexanone for each half of the dimer. The presence of a dihydropyran ring (O-20↔C-20↔C-4↔C-5↔C-4′↔C-5′) was established by HMBC (Fig. 3) correlations of: H-20 to C-4 ($\delta$ 102.8), C-5 and C-5′; H-5 to C-4, C-20 ($\delta$ 145.2), C-4′ and C-5′; H-5 to C-20 and C-4′. This was supported by comparison with the olefin chemical shift ($\delta$ 103.4–107.3 and $\delta$ 142.3–145.4) of a reported dihydropyran.[27] In addition, an aldehyde group connected to C-4′ was determined by HMBC correlations of H-5, H-3′ and H-5′ to C-20′ ($\delta$ 203.4). The stereochemistry of **6** was deduced from NOESY studies (Fig. 2). For example, NOESY correlations of H-5 to H-6β, H-6′β, and $H_{13}$-19′ indicated H-5 as possessing the β-orientation, while the α-orientations were assigned to both H-5′ and aldehyde group (CHO) by NOESY correlations of H-3′, H-6′α, and H-10′ to H-5′ as well as H-5′ and H-3′α to a proton of aldehyde group.

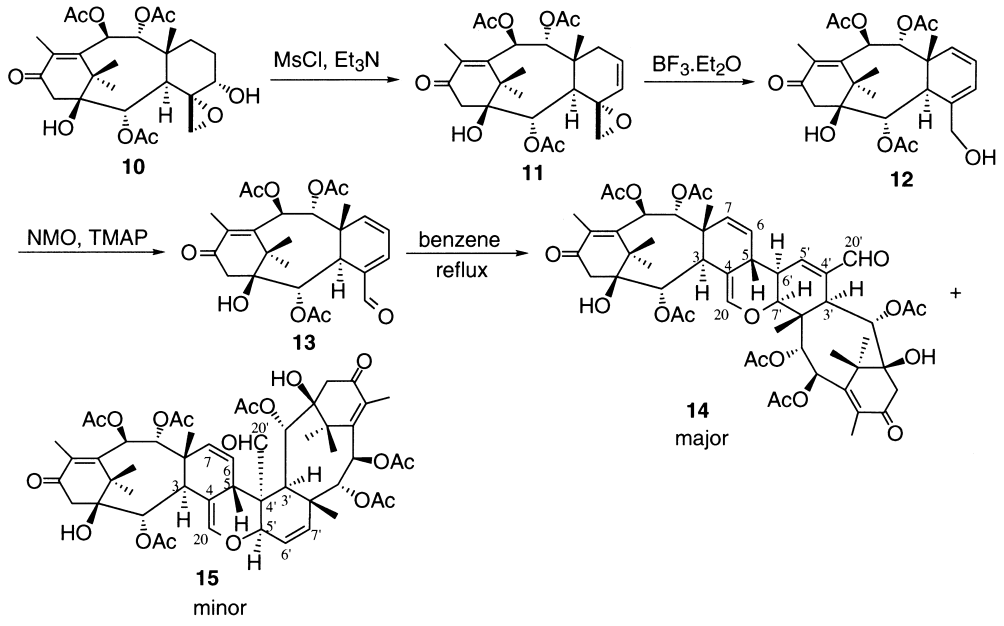
Formation of **6** from **5** is explained via a highly regio- and stereospecific hetero Diels–Alder cycloaddition between the α,β-unsaturated aldehyde moiety of one molecule and the ethylene (C-4′ and C-5′) of another. In fact, a similar dimerization has been reported for formation of bistheonellasterone from theonellasterone.[28]

This high regio- and stereospecificity observed in the

**Table 1.** $^1H$ NMR, $^{13}C$ NMR and $^1H-^1H$ COSY of the dimer **6**

| No. | $^1H$ | *J* (Hz) | $^{13}C$ | $^1H-^1H$ COSY | No. | $^1H$ | *J* (Hz) | $^{13}C$ | $^1H-^1H$ COSY |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2.14 (dd) | 6.5, 2.2 | 48.3 (d) | H-2, H-14β | 1′ | 2.17 (dd) | 6.9, 2.5 | 48.4 (d) | H-2′, H-14′β |
| 2 | 5.58 (dd) | 6.5, 2.2 | 69.8 (d) | H-1, H-3 | 2′ | 5.64 (dd) | 6.7, 2.5 | 72.4 (d) | H-1′, H-3′ |
| 3 | 3.47 (d) | 6.5 | 46.1 (d) | H-2 | 3′ | 3.11 (d) | 6.7 | 44.5 (d) | H-2′ |
| 4 | | | 102.8 (s) | | 4′ | | | 59.7 (s) | |
| 5 | 3.31 (d) | 7.5 | 32.1 (d) | H-6β, H-6α | 5′ | 4.12 (dd) | 11.6, 4.5 | 71.2 (d) | H-6′α, H-6′β |
| 6β | 2.90 (dd) | 18.2, 7.5 | 34.0 (t) | H-5, H-6α | 6′β | 2.88 (dd) | 14.5, 11.6 | 33.7 (t) | H-5′, H-6′α |
| 6α | 2.24 (d) | 18.2 | | H-5, H-6β | 6′α | 2.27 (dd) | 14.5, 4.5 | | H-5′, H-6′β |
| 7 | | | 211.5 (s) | | 7′ | | | 208.6 (s) | |
| 8 | | | 56.2 (s) | | 8′ | | | 54.8 (s) | |
| 9 | 5.99 (d) | 11.0 | 75.6 (d) | H-10 | 9′ | 5.97 (d) | 10.8 | 76.2 (d) | H-10′ |
| 10 | 6.09 (d) | 11.0 | 72.7 (d) | H-9 | 10′ | 6.12 (d) | 10.8 | 73.0 (d) | H-9′ |
| 11 | | | 150.1 (s) | | 11′ | | | 149.6 (s) | |
| 12 | | | 140.6 (s) | | 12′ | | | 139.8 (s) | |
| 13 | | | 198.6 (s) | | 13′ | | | 198.3 (s) | |
| 14β | 2.82 (dd) | 19.8, 6.5 | 37.8 (t) | H-1, H-14α | 14′β | 2.98 (dd) | 19.8, 6.9 | 37.2 (t) | H-1′, H-14′α |
| 14α | 2.48 (d) | 19.8 | | H-14β | 14′α | 2.56 (d) | 19.8 | | H-14′β |
| 15 | | | 39.7 (s) | | 15′ | | | 38.5 (s) | |
| 16 | 1.69 (s) | | 25.2 (q) | | 16′ | 1.74 (s) | | 23.6 (q) | |
| 17 | 1.28 (s) | | 36.1 (q) | | 17′ | 1.19 (s) | | 34.2 (q) | |
| 18 | 2.19 (s) | | 13.9 (q) | | 18′ | 2.18 (s) | | 14.1 (q) | |
| 19 | 1.01 (s) | | 18.5 (q) | | 19′ | 0.97 (s) | | 17.8 (q) | |
| 20 | 6.34 (s) | | 145.2 (d) | | 20′ | 9.67 (s) | | 203.4 (d) | |
| Ac | 2.12 (s) | | 170.9 (s)[a] | | Ac | 2.11 (s) | | 171.0 (s)[b] | |
| | 2.08 (s) | | 169.9 (s)[a] | | | 2.08 (s) | | 169.9 (s)[b] | |
| | 2.06 (s) | | 169.6 (s)[a] | | | 2.04 (s) | | 169.7 (s)[b] | |
| | | | 21.3 (q) | | | | | 21.2 (q) | |
| | | | 20.9 (q) | | | | | 20.9 (q) | |
| | | | 20.7 (q) | | | | | 20.8 (q) | |

[a] Interchangeable.
[b] Interchangeable.




**Scheme 2.**

Diels–Alder cycloaddition has stimulated us to further investigation into the Diels–Alder reactivity of other available taxoids (Scheme 2). Compound **10**,[14a] derived from 5-cinnamoyltriacetyltaxicin-I[29], which is another major taxoid isolated from the needles of a Japanese yew *Taxus cuspidata*, underwent dehydration leading to **11**, which was followed by boron trifluoride-induced ring opening to give 20-hydroxy-4:5,6:7-diene taxicine I **12**.[20] Oxidation of **12** by the TPAP/NMO system yielded a corresponding aldehyde **13**. Interestingly, **13** was allowed to stand at room temperature for two days to afford a separable mixture ratio (5:1) of two dimeric taxoids **14** and **15** in 74% yield (based on 90% conversion of **13**), whereas a mixture ratio (ca. 11:1) of **14** and **15** was observed under reflux for 7 h in 86% total yield. The structure and stereochemistry of dimers **14** (Figs. 4 and 5) and **15** (Figs. 6 and 7) were fully characterized by their spectra data including wide 2D NMR studies. HRFABMS indicated a molecular formula $C_{52}H_{64}O_{18}$ for both **14** and **15** by *m/z* 999.3980 $(M+Na)^+$ and 977.4163 $(MH)^+$, respectively. The $^1H$ and $^{13}C$ NMR along with HMQC of **14** (Table 2) showed signals for each pair of three acetyl methyls, three oxymethines, and four methyls which were assigned to each half moiety of the dimers. These tentative assignments were further confirmed by $^1H$–$^1H$ COSY (Table 2) and HMBC experiments. Fortunately, similar signals of two pairs of three acetyl methyls, three oxymethines, and four methyls belonging to each half

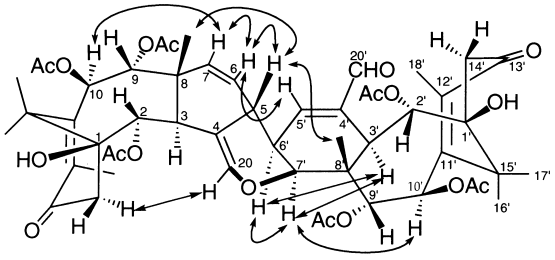


**Figure 4.** Relative stereochemistry of **14** deduced from NOESY experiment (only key NOE correlations donated).

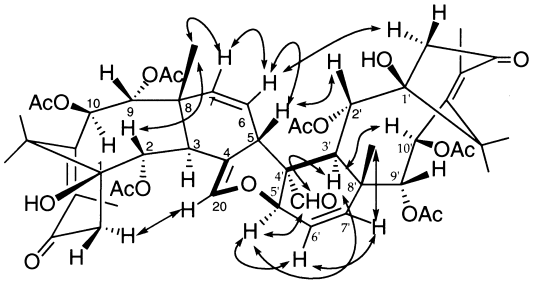


**Figure 6.** Relative stereochemistry of **15** deduced from NOESY experiment (only key NOE correlations donated).

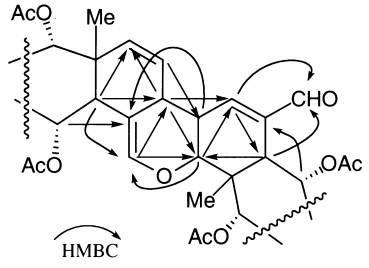



**Figure 5.** Key $^1H$–$^{13}C$ long-range correlations of **14**.

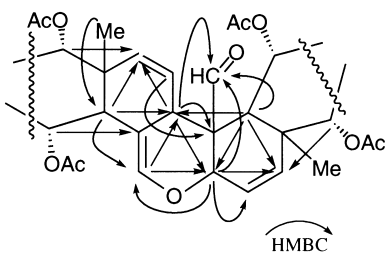



**Figure 7.** Key $^1H$–$^{13}C$ long-range correlations of **15**.

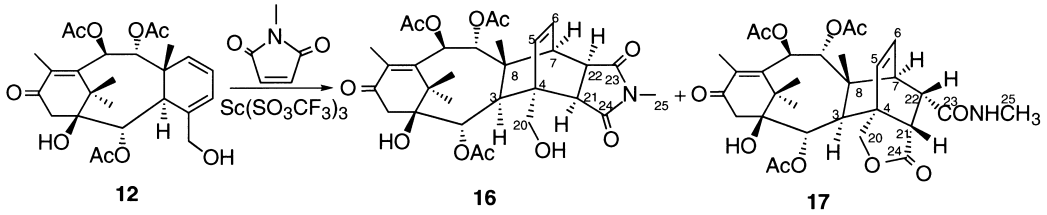
**Table 2.** $^{1}H$ NMR, $^{13}C$ NMR and $^{1}H$–$^{1}H$ COSY of the dimer **14**

| No. | $^{1}H$ | *J* (Hz) | $^{13}C$ | $^{1}H$–$^{1}H$ COSY | No. | $^{1}H$ | *J* (Hz) | $^{13}C$ | $^{1}H$–$^{1}H$ COSY |
|---|---|---|---|---|---|---|---|---|---|
| 1 | | | 77.6 (s) | | 1′ | | | 78.1 (s) | |
| 2 | 5.56 (d) | 4.8 | 71.9 (d) | H-3 | 2′ | 5.63 (d) | 4.5 | 73.1 (d) | H-3′ |
| 3 | 3.58 (d) | 4.8 | 45.4 (d) | H-2 | 3′ | 3.45 (d) | 4.5 | 43.8 (d) | H-2′ |
| 4 | | | 105.2 (s) | | 4′ | | | 139.4 (s) | |
| 5 | 3.94 (d) | 1.7 | 44.1 (d) | H-6 | 5′ | 5.88 (d) | 1.5 | 138.1 (d) | H-6′ |
| 6 | 5.60 (dd) | 9.5, 1.7 | 127.6 (d) | H-5, H-7 | 6′ | 3.65 (dd) | 7.0, 1.5 | 36.7 (d) | H-5′, H-7′ |
| 7 | 5.68 (d) | 9.5 | 128.7 (d) | H-6 | 7′ | 4.21 (d) | 7.0 | 74.6 (d) | H-6′ |
| 8 | | | 48.4 (s) | | 8′ | | | 49.9 (s) | |
| 9 | 5.94 (d) | 10.8 | 75.7 (d) | H-10 | 9′ | 5.90 (d) | 10.5 | 76.1 (d) | H-10′ |
| 10 | 6.15 (d) | 10.8 | 72.4 (d) | H-9 | 10′ | 6.10 (d) | 10.5 | 72.7 (d) | H-9′ |
| 11 | | | 150.2 (s) | | 11′ | | | 151.7 (s) | |
| 12 | | | 139.6 (s) | | 12′ | | | 140.6 (s) | |
| 13 | | | 199.7 (s) | | 13′ | | | 198.7 (s) | |
| 14β | 2.98 (d) | 19.8 | 38.8 (t) | H-14α | 14′β | 2.95 (d) | 19.8 | 39.6 (t) | H-14′α |
| 14α | 2.64 (d) | 19.8 | | H-14β | 14′α | 2.59 (d) | 19.8 | | H-14′β |
| 15 | | | 42.1 (s) | | 15′ | | | 42.8 (s) | |
| 16 | 1.69 (s) | | 20.2 (q) | | 16′ | 1.65 (s) | | 19.8 (q) | |
| 17 | 1.21 (s) | | 34.2 (q) | | 17′ | 1.24 (s) | | 33.7 (q) | |
| 18 | 2.21 (s) | | 14.2 (q) | | 18′ | 2.17 (s) | | 13.7 (q) | |
| 19 | 0.98 (s) | | 17.8 (q) | | 19′ | 0.95 (s) | | 16.8 (q) | |
| 20 | 6.36 (s) | | 145.8 (d) | | 20′ | 9.56 (s) | | 192.6 (s) | |
| Ac | 2.13 (s) | | 171.4 (s)[a] | | Ac | 2.13 (s) | | 171.5 (s)[b] | |
| | 2.09 (s) | | 170.1 (s)[a] | | | 2.11 (s) | | 169.9 (s)[b] | |
| | 2.07 (s) | | 169.6 (s)[a] | | | 2.08 (s) | | 169.5 (s)[b] | |
| | | | 21.4 (q) | | | | | 21.3 (q) | |
| | | | 21.0 (q) | | | | | 20.9 (q) | |
| | | | 20.6 (q) | | | | | 20.7 (q) | |

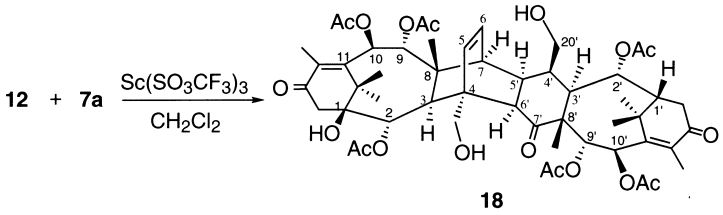
[a] Interchangeable.
[b] Interchangeable.

moiety of the dimer **15** were also observed in $^{1}H$ and $^{13}C$ NMR (see Experimental section). The presence of a dihydropyran ring had been found in both **14** and **15** as **6**, was established by HMBC data (Figs. 5 and 7). That the dihydropyran ring in **14** was fused via (O-20↔C-20↔C-4↔C-5↔C-6′↔C-7′↔O-20) was evident from HMBC correlations of: H-20 to C-7′, C-4 and C-5; H-5 to C-4, C-20, C-6′ and C-7′; H-6′ to C-4 and C-5 plus H-7′ to C-20 and C-5, while the HMBC correlations of H-20 ($\delta$ 9.62, s) to C-5′ ($\delta$ 80.1, d), H-5 ($\delta$ 3.92, d) to C-4′ ($\delta$ 48.7, s) and C-5′, and H-5′ ($\delta$ 4.56, d) to C-20 ($\delta$ 145.4, d) and C-5 ($\delta$ 45.7, d) suggested that the dihydropyran ring was fused via (O-20↔C-20↔C-4↔C-5↔C-4′↔C-5′↔O-20) in **15**. The stereochemistry of **14** and **15** was suggested by NOESYs experiments as illustrated in Figs. 4 and 6. The NOE correlations of H-5 to $H_3$-19 and $H_3$-19′, H-7′ to H-3′ and H-10′ as well as H-6′ to H-7′ indicated that H-5 possessed the β-orientation and both H-6′ and H-7′ were in the α-orientation in **14**. That H-5, H-5′ and the aldehyde group in **15** possessed the same stereochemistry as that of **6** was shown by NOE correlations of $H_3$-19 and H-2′ to H-5, both H-5′ and a proton of aldehyde to H-3′. The dimeric taxoids **14** and **15** may have arisen from **13** through regio- and stereospecific hetero Diels–Alder reactions of the 4,5-unsaturated aldehyde (O-20, C-20, C-4, and C-5) moiety of one molecule with either the 6,7 or the 4,5 ethylene of another molecule.

Although the above results have demonstrated that α,β-unsaturated aldehydes, such as **5** and **13**, can easily undergo Diels–Alder cycloaddition producing dimeric taxoids, all reactions are hetero Diels–Alder cycloadditions in which the diene is the 4,5-ene-20-oxo moiety (open chain) and not the 4:5,6:7-diene of the C-ring. In order to study the reactivity of the 4:5,6:7-diene in a Diels–Alder reaction, the 20-hydroxy-4:5,6:7-diene taxicine I **12** was selected to react with the monodentate dienophile *N*-methylmaleimide. The reaction was monitored by TLC. Unfortunately, no cycloadducts were observed in either benzene under reflux or $CH_2Cl_2$ at room temperature even under reflux for 12 h. However, this Diels–Alder cycloaddition took place successfully in the presence of a catalytic amount of $Sc(OTf)_3$[30] at room temperature in $CH_2Cl_2$ for 4 h to give a cycloadduct **16** and a rearranged cycloadduct γ-butyrolactone **17** in a 89:11 ratio (Scheme 3). The products were identified as *exo* adduct **16** and *endo*-γ-butyrolactone **17** by means of spectra data and NOESY experiments[31] ($^{1}H$ and $^{13}C$ NMR data see Experimental section). The presence of a




**Scheme 3.**




**Scheme 4.**

bicyclo[2,2,2]octene moiety in both **16** and **17** was established by HMBC correlations of H-3 and H-21 to C-4, C-5, and C-7; H-7 and H-22 to C-6, C-8, and C-21; H-5 to C-3, C-4, C-6, and C-21 and H-6 to C-5, C-7, C-8, and C-22. In addition, HMBC correlations of H-7 ($\delta$ 2.96, d) and H-22 ($\delta$ 3.19, d) to C-23 plus H-21 ($\delta$ 3.29, d) and H-22 to C-23 and C-24 indicated a 1-methyl-3,4-dihydro-2,5-dioxopyrrolidine ring fused by C-21 and C-22 to the cyclohexane ring in **16**. The NOE correlations observed between H-2 ($\delta$ 5.62, d) and H-5 ($\delta$ 6.21, d), $H_3$-19 ($\delta$ 1.01, s) and H-6 ($\delta$ 6.31, d), H-3 ($\delta$ 3.21, d) and H-21 plus H-21 and H-22 as well as the absence of NOE between H-7 and H-22 suggested a β-orientation of the 5,6-ene moiety and α-orientations (*endo* position) of H-21 and H-22 for the *exo*-cycloadduct **16**. In comparison to that of **16**, the NMR data of **17** showed chemical shifts of $H_2$-20 ($\delta$ 4.23 and 3.89, d, $J_{HH}$ 9.6 Hz) and C-20 ($\delta$ 69.5) moving to downfield by $\nabla\delta_H$ 0.60 ppm and $\nabla\delta_C$ 7.9 ppm and signals for an amide proton NH ($\delta$ 6.30, brs) as well as $\delta$ 171.4 (C=O) and 178.5 (C=O) assigned for $CONHCH_3$ and γ-butyrolactone by comparison with the chemical shifts of saturated amide $\delta$ 171.6 and γ-butyrolactone $\delta$ 178.0,[32] respectively. This indicated the presence of a γ-butyrolactone (O-20↔C-20↔C-4↔C-21↔C-24↔O-20) in **17** fused by C-4 and C-21 to a cyclohexane ring, and was confirmed by HMBC correlations of H-21 to C-4, C-20, and C-24 and H-20 to C-4, C-21 and C-24. No NOE relationship was observed between H-3 and H-21 and NOE correlations of both H-5 and H-20a to H-21 was consistent with a γ-butyrolactone ring possessing an α-orientation via C20–C4 and C24–C21 bonds fused to cyclohexane ring (C-ring). Furthermore, the $J_{HH}$ 1.6 Hz coupling observed between H-7 and H-22, the presence of NOE between H-7 and H-22 and NOE correlation of H-22 to H-21 all indicated H-22 possessing the β-orientation (*exo* position). Thus, the formation of γ-butyrolactone **17** can be explained to arise from cycloadduct *endo*-**16** in situ followed by intramolecular nucleophilic addition. The carbon (C-24) in the *endo* position of *endo*-**16** is positioned for nucleophilic attack by the oxygen of 20-hydroxy group leading to the γ-butyrolactone **17**.

Based on the fact that 20-hydroxy-4:5,6:7-diene taxicine I **12** could act as the diene in a Diels–Alder cycloaddition with *N*-methylmaleimide giving cycloadducts **16** and **17**, we expected that the diene **12** could undergo Diels–Alder cycloaddition with taxoid dienophile **7a** to give an *endo*- or *exo*-cycloadduct. Indeed, we observed that Lewis acid-catalyzed Diels–Alder cycloaddition between **12** and **7a** (Scheme 4) took place successfully in the presence of $Sc(OTf)_3$ for 12 h, to give *exo*-cycloadduct **18** as a sole product in 75% yield. The structure and stereochemistry of **18** were unambiguously established by full NMR spectra data (see Experimental section) and 2D NMR (Figs. 8 and 9). It was worthy to note that no coupling ($J_{HH}$) was observed in the resonances at $\delta$ 2.95 (d) and $\delta$ 2.87 (dd) assigned, respectively, to be the bridgehead proton H-7 and H-5′ by $^1H$–$^1H$ COSY, which was supported by the absence of NOE. In addition, strong NOE correlations of H-3 ($\delta$ 3.25, d) to H-6′ ($\delta$ 3.35, d), H-3′ ($\delta$ 3.17, dd) to H-5′ and H-5′ to H-6′ demonstrated that both H-5′ and H-6′ possessed the α-orientation (*endo*-position).

In conclusion, several taxoid dimers obtained through highly regio- and stereospecific hetero Diels–Alder or Lewis acid-catalyzed Diels–Alder cycloaddition have been demonstrated. The structure and stereochemistry of all new dimers have been elucidated by spectroscopic experiments including 2D NMR. This chemistry can be expected to be applied for the synthesis of other dimeric taxoids. Moreover, the formation of *exo*-adduct **16** and of γ-butyrolactone **17** probably might be applicable to the synthesis of new taxoid analogs possessing biological activity. Biological studies of all new dimers and compounds are in progress.

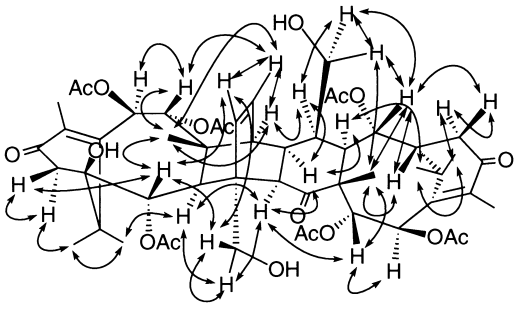


**Figure 8.** Relative stereochemistry of **18** deduced from NOESY experiment.

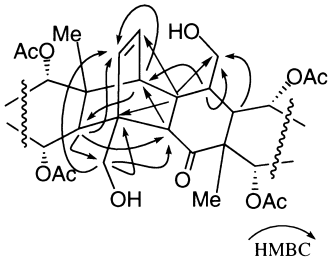



**Figure 9.** Key $^1H$–$^{13}C$ long-range correlations of **18**.

## Experimental

$^1$H NMR (500 MHz), $^{13}$C NMR (125 MHz) and 2D NMR were performed on a Varian Unity INOVA 500 spectrometer in $CDCl_3$ using TMS as an internal standard. Chemical shifts are expressed in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz). Optical rotations were recorded on a HORIBA SEPA-300 Polarimeter. MS and HRMS were measured on a JEOL JMS-700 spectrometer using EI and FAB modes. Dichloromethane was refluxed and distilled from $CaH_2$ under nitrogen. Benzene was distilled from and kept over sodium. All commercially available reagents were used without further purification. Chromatography was carried out on a Merck silica gel 60 (230–400 mesh). Preparative TLC was performed on Merck silica gel 60 $F_{254}$ plates (0.85 mm thickness).

**4,20-Dihydro-4α(20)-epoxy-5-hydroxytaxinine B (2).** To a solution of 5-hydroxytaxinine B **1** (0.25 g, 0.47 mmol) in $CH_2Cl_2$ (20 mL), was added *m*-chloroperbenzoic acid (0.28 g, 1.64 mmol) and $Na_2HPO_4$ (0.47 g, 3.29 mmol). The reaction mixture was stirred at room temperature for 3 h under nitrogen, and was then extracted with ethyl acetate (20 mL×3). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$ and removed under reduced pressure. The residue was chromatographed on silica gel (ethyl acetate–hexane 2:1 v/v) to give **2** as a white amorphous solid in 91% yield (0.235 g). $^1$H NMR $\delta$: 1.00 (s, 3H, $H_3$-19), 1.27 (s, 3H, $H_3$-17), 1.67 (m, 1H, H-6), 1.70 (s, 3H, $H_3$-16), 1.96 (m, 1H, H-6), 2.01 (s, 3H, Ac), 2.07 (s, 3H, Ac), 2.08 (s, 3H, Ac), 2.14 (s, 3H, Ac), 2.18 (dd, 1H, *J*=7.0, 2.2, H-1), 2.24 (s, 3H, $H_3$-18), 2.45 (d, 1H, *J*=19.8, H-14), 2.65 (d, 1H, *J*=4.5, H-20b), 2.69 (brs, 1H, OH-5), 2.85 (dd, 1H, *J*=19.8, 7.0, H-14), 2.87 (d, 1H, *J*=4.5, H-20a), 3.47 (brt, 1H, H-5), 3.61 (d, 1H, *J*=6.5, H-3), 5.58 (dd, 1H, *J*=6.5, 2.2, H-2), 5.78 (dd, 1H, *J*=11.5, 5.0, H-7), 5.92 (d, 1H, *J*=11.0, H-9), 6.09 (d, 1H, *J*=11.0, H-10). $^{13}$C NMR $\delta$: 14.5 (q, C-18), 18.7 (q, C-19), 20.6, 20.8, 20.9, 21.4 (4×q, 4×$CH_3$ of Ac), 24.7 (q, C-16), 35.6 (q, C-17), 36.7 (t, C-6), 37.8 (t, C-14), 38.4 (s, C-15), 44.6 (d, C-3), 47.8 (s, C-8), 48.6 (d, C-1), 52.5 (t, C-20), 63.6 (d, C-5), 69.8 (d, C-7), 71.2 (d, C-2), 72.7 (d, C-10), 75.4 (s, C-4), 75.6 (d, C-9), 140.5 (s, C-12), 151.2 (s, C-11), 169.4, 169.9, 170.1, 171.4 (4×s, 4×CO of Ac), 199.6 (s, C-13). HREIMS *m/z* found 550.2402, Calcd for $C_{28}H_{38}O_{11}$ $(M)^+$ 550.2412.

**4,20-Dihydro-4α(20)-epoxy-5,6-enetaxinine B (3).** To a solution of **2** (0.225 g, 0.41 mmol) in $CH_2Cl_2$ (10 mL) cooled to 0°C under $N_2$ was added methanesulfonyl chloride (0.03 mL, 0.43 mmol) followed by slow injection of triethylamine (0.3 mL, 2.15 mmol) in 15 min. After stirring for additional 3 h at 35°–40°C and being cooled to room temperature, $CH_2Cl_2$ (20 mL) was added. The organic phase was separated, washed with water, 5% HCl and brine solution, and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the residue was chromatographed (ethyl acetate–hexane 2:3 v/v) to give **3** as a white amorphous solid in 68% yield (0.15 g). $^1$H NMR $\delta$: 0.96 (s, 3H, $H_3$-19), 1.23 (s, 3H, $H_3$-17), 1.68 (s, 3H, $H_3$-16), 2.02 (s, 3H, Ac), 2.07 (s, 3H, Ac), 2.08 (s, 3H, Ac), 2.13 (s, 3H, Ac), 2.15 (dd, 1H, *J*=6.6, 2.4, H-1), 2.21 (s, 3H, $H_3$-18), 2.58 (d, 1H, *J*=19.8, H-14), 2.67 (d, 1H, *J*=4.0, H-20b), 2.82 (dd, 1H, *J*=19.8, 6.6, H-14), 3.01 (d, 1H, *J*=4.0, H-20a), 3.45 (d, 1H, *J*=6.7, H-3), 5.56 (dd, 1H, *J*=6.7, 2.4, H-2), 5.76 (d, 1H, *J*=10, H-5), 5.87 (dd, 1H, *J*=10, 2.5, H-6), 5.89 (d, 1H, *J*=11.0, H-9), 6.10 (d, 1H, *J*=11.0, H-10), 6.24 (d, 1H, *J*=2.5, H-7). $^{13}$C NMR $\delta$: 14.7 (q, C-18), 17.9 (q, C-19), 20.6, 20.8, 21.1, 21.3 (4×q, 4×$CH_3$ of Ac), 24.7 (q, C-16), 34.7 (q, C-17), 37.8 (t, C-14), 38.2 (s, C-15), 44.2 (d, C-3), 48.4 (d, C-1), 48.7 (s, C-8), 53.1 (t, C-20), 70.3 (d, C-7), 71.1 (d, C-2), 72.6 (d, C-10), 75.4 (d, C-9), 76.4 (s, C-4), 127.6 (d, C-5), 128.1 (d, C-6), 140.1 (s, C-12), 150.4 (s, C-11), 169.4, 169.8, 169.9, 171.5 (4×s, 4×CO of Ac), 199.2 (s, C-13). FAB-MS *m/z* 555 $(M+Na)^+$, 533 $(MH)^+$, 473 $(MH-AcOH)^+$, 413 $(MH-2AcOH)^+$, 395 $(MH-H_2O-2AcOH)^+$. HRFABMS *m/z* found 555.2201, calcd for $C_{28}H_{36}O_{10}Na$ $(M+Na)^+$ 555.2204.

**20-Hydroxy-4,5-ene-7-oxotaxinine B (4).** To a solution of **3** (0.177 g 0.33 mmol) in $CH_2Cl_2$ (5 mL) was added boron trifluoride diethyl etherate (abt. 47% solution, 0.2 mL) at −78°C. The resulting mixture was stirred for 2 h under nitrogen and then partitioned between chloroform (15 mL) and saturated aqueous $NaHCO_3$ (2 mL). The organic phase was separated, washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed (ethyl acetate–hexane 3:2 v/v) to give **4** as a colorless oil in 62% yield (0.102 g). $^1$H NMR $\delta$: 0.97 (s, 3H, $H_3$-19), 1.21 (s, 3H, $H_3$-17), 1.72 (s, 3H, $H_3$-16), 2.08 (s, 3H, Ac), 2.09 (s, 3H, Ac), 2.13 (s, 3H, Ac), 2.14 (dd, 1H, *J*=6.5, 2.2, H-1), 2.19 (s, 3H, $H_3$-18), 2.58 (d, 1H, *J*=19.8, H-14), 2.60 (brs, 1H, OH), 2.64 (dd, 1H, *J*=18.6, 1.5, H-6), 2.80 (dd, 1H, *J*=19.8, 6.5, H-14), 3.18 (dd, 1H, *J*=18.6, 2.5, H-6), 3.72 (d, 1H, *J*=5.5, H-3), 4.24 (d, 1H, *J*=10.2, H-20b), 4.47 (d, 1H, *J*=10.2, H-20a), 5.64 (dd, 1H, *J*=5.5, 2.2, H-2), 5.76 (m, 1H, H-5), 5.96 (d, 1H, *J*=10.8, H-9), 6.14 (d, 1H, *J*=10.8, H-10). $^{13}$C NMR $\delta$: 13.8 (q, C-18), 18.2 (q, C-19), 20.7, 20.9, 20.9 (3×q, 3×$CH_3$ of Ac), 24.7 (q, C-16), 33.8 (q, C-17), 37.5 (t, C-14), 38.2 (t, C-6), 38.6 (s, C-15), 47.2 (d, C-3), 48.7 (d, C-1), 54.6 (s, C-8), 67.3 (t, C-20), 69.8 (d, C-2), 72.9 (d, C-10), 76.1 (d, C-9), 129.8 (d, C-5), 136.1 (s, C-4), 140.4 (s, C-12), 150.8 (s, C-11), 169.5, 170.0, 171.1 (3×s, 3×CO of Ac), 198.8 (s, C-13), 209.8 (s, C-7). FAB-MS *m/z* 491 $(MH)^+$, 431 $(MH-AcOH)^+$, 353 $(MH-2AcOH-H_2O)^+$. HRFABMS *m/z* found 491.2274, calcd for $C_{26}H_{35}O_9$ $(MH)^+$ 491.2279.

**7,20-Dioxo-4,5-enetaxinine B (5).** To a solution of **4** (25 mg 0.05 mmol) in dry $CH_3CN$ (2.0 mL) was added 4-methylmorpholine *N*-oxide (17 mg, 0.15 mmol), molecular sieves 4A (activated 12 mg) and tetrapropylammonium perruthenate (5 mg, 0.015 mmol). The reaction mixture was stirred at room temperature for 3 h and chromatographed by preparative TLC (ethyl acetate–hexane 3:1 v/v) to give **5** as a colorless oil in 96% yield (23 mg). $^1$H NMR $\delta$: 0.95 (s, 3H, $H_3$-19), 1.24 (s, 3H, $H_3$-17), 1.70 (s, 3H, $H_3$-16), 2.07 (s, 3H, Ac), 2.09 (s, 3H, Ac), 2.11 (s, 3H, Ac), 2.17 (dd, 1H, *J*=6.5, 2.4, H-1), 2.21 (s, 3H, $H_3$-18), 2.52 (dd, 1H, *J*=18.5, 1.5, H-6), 2.61 (d, 1H, *J*=19.5, H-14), 2.78 (dd, 1H, *J*=19.5, 6.5, H-14), 3.21 (dd, 1H, *J*=18.5, 2.0, H-6), 3.78 (d, 1H, *J*=6.0, H-3), 5.60 (dd, 1H, *J*=6.0, 2.4, H-2), 5.87 (dd, 1H, *J*=2.0, 1.5, H-5), 5.97 (d, 1H, *J*=11.0, H-9), 6.15 (d, 1H, *J*=11.0, H-10), 10.52 (s, 1H, CHO). $^{13}$C NMR $\delta$: 13.6 (q, C-18), 17.6 (q, C-19), 20.7, 20.9, 21.0 (3×q,

3×$CH_3$ of Ac), 24.3 (q, C-16), 33.7 (q, C-17), 38.4 (t, C-14), 38.7 (t, C-6), 39.1 (s, C-15), 45.2 (d, C-3), 48.7 (d, C-1), 54.8 (s, C-8), 70.2 (d, C-2), 72.9 (d, C-10), 76.2 (d, C-9), 138.9 (s, C-4), 141.0 (s, C-12), 142.3 (d, C-5), 151.8 (s, C-11), 169.6, 169.9, 170.9 (3×s, 3×CO of Ac), 193.2 (d, C-20), 198.4 (s, C-13), 208.6 (s, C-7). HREIMS *m/z* found 488.2039, calcd for $C_{26}H_{32}O_9$ $(M)^+$ 488.2044.

**Dimer of 7,20-Dioxo-4,5-enetaxinine B (6).** A solution of **5** (20 mg, 0.041 mmol) in dry benzene (2 mL) was heated at 80°C for 8 h (the reaction was monitored by TLC). The reaction mixture was cooled to room temperature and purified by preparative TLC (ethyl acetate–hexane 3:1 v/v) to give **6** as white solid in 90% (18 mg). mp 232–234°C, $[\alpha]_D^{20}$=+64.3 (c 0.02, $CHCl_3$), FAB-MS *m/z* 977 $(MH)^+$, 959 $(MH-H_2O)^+$, 857 $(MH-2AcOH)^+$, 839 $(MH-H_2O-2AcOH)^+$, 821 $(MH-2H_2O-2AcOH)^+$, 471, 411, 351. HRFABMS *m/z* found 977.4159, calcd for $C_{52}H_{65}O_{18}$ $(MH)^+$ 977.4167. $^1$H NMR and $^{13}$C NMR are shown in Table 1.

**20-Hydroxy-5,6-ene-7-oxotaxinine B (β-isomer 7a) and (α-isomer 7b).** To a solution of **4** (59 mg 0.12 mmol) in methanol (5 mL) was added potassium *t*-butoxide (10 mg, 0.09 mmol). The resulting mixture was stirred at room temperature for 12 h (the reaction was monitored by TLC). $CH_2Cl_2$ (10 mL) was added after removal of methanol under reduced pressure. The organic layer was separated, washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed by preparative TLC (ethyl acetate–chloroform 2:3 v/v) to give **7a** and **7b** as a colorless oil in 74% yield (44 mg). **7a**: $^1$H NMR $\delta$: 1.01 (s, 3H, $H_3$-19), 1.25 (s, 3H, $H_3$-17), 1.72 (s, 3H, $H_3$-16), 2.07 (s, 3H, Ac), 2.09 (s, 3H, Ac), 2.11 (s, 3H, Ac), 2.13 (dd, 1H, *J*=6.5, 2.4, H-1), 2.17 (s, 3H, $H_3$-18), 2.48 (m, 1H, H-4), 2.50 (d, 1H, *J*=19.5, H-14), 2.56 (brs, 1H, OH), 2.74 (dd, 1H, *J*=19.5, 6.5, H-14), 3.14 (dd, 1H, *J*=8, 6.5, H-3), 3.25 (dd, 1H, *J*=10.3, 3.0, H-20b), 3.59 (dd, 1H, *J*=10.3, 2.5, H-20a), 5.56 (dd, 1H, *J*=6.5, 2.4, H-2), 5.84 (d, 1H, *J*=7.0, H-6), 5.94 (d, 1H, *J*=10.8, H-9), 6.12 (d, 1H, *J*=10.8, H-10), 6.44 (m, 1H, H-5). $^{13}$C NMR $\delta$: 14.1 (q, C-18), 17.9 (q, C-19), 20.7, 20.9, 20.9 (3×q, 3×$CH_3$ of Ac), 23.1 (q, C-16), 34.5 (q, C-17), 38.2 (t, C-14), 39.2 (s, C-15), 44.1 (d, C-3), 48.3 (d, C-1), 51.2 (d, C-4), 54.2 (s, C-8), 63.2 (t, C-20), 69.7 (d, C-2), 72.6 (d, C-10), 75.9 (d, C-9), 129.1 (d, C-6), 139.9 (s, C-12), 149.7 (d, C-5), 150.1 (s, C-11), 169.5, 169.8, 171.3 (3×s, 3×CO of Ac), 197.4 (s, C-7), 198.6 (s, C-13). FAB-MS *m/z* 514 $(MH+Na)^+$, 513 $(M+Na)^+$, 490 $(M)^+$, 430 $(M-AcOH)^+$. HRFABMS *m/z* found 513.2088, calcd for $C_{26}H_{34}O_9Na$ $(M+Na)^+$ 513.2098. **7b** in mixture with **7a**, $^1$H NMR $\delta$: 0.99 (s, 3H, $H_3$-19), 1.27 (s, 3H, $H_3$-17), 1.70 (s, 3H, $H_3$-16), 2.06 (s, 3H, Ac), 2.09 (s, 3H, Ac), 2.11 (s, 3H, Ac), 2.15 (dd, 1H, *J*=6.7, 2.4, H-1), 2.20 (s, 3H, $H_3$-18), 2.40 (m, 1H, H-4), 2.44 (d, 1H, *J*=19.8, H-14), 2.81 (dd, 1H, *J*=19.8, 6.7, H-14), 3.26 (d, 1H, *J*=6.5, H-3), 3.42 (dd, 1H, *J*=10.3, 2.5, H-20b), 3.67 (dd, 1H, *J*=10.3, 3.0, H-20a), 5.57 (dd, 1H, *J*=6.5, 2.4, H-2), 5.83 (d, 1H, *J*=6.9, H-6), 5.90 (d, 1H, *J*=10.8, H-9), 6.11 (d, 1H, *J*=10.8, H-10), 6.42 (d, 1H, *J*=6.9, H-5).

**4β-Hydroxymethylene-5α-ethyl-7-oxotaxinine B (8) and 4α-Hydroxymethylene-5β-ethyl-7-oxotaxinine B (9).** To a solution of **7a** and **7b** (30 mg, 0.06 mmol) in $CH_2Cl_2$ (1.5 mL) was added diethylaluminum chloride (1.0 M solution in hexanes, 0.06 mL) at 0°C under nitrogen. The mixture was stirred at room temperature for 2 h (the reaction was monitored by TLC). Saturated aqueous $NH_4Cl$ (0.1 mL) was added, followed by extraction with $CH_2Cl_2$ (5 mL×2). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was chromatographed by preparative TLC (ethyl acetate–chloroform 1:1 v/v) to give **8** in 59% yield (19 mg) and **9** in 22% yield (7 mg) as a colorless oil. **Compound 8:** $[\alpha]_D^{20}$=+18.5 (c 0.04, $CHCl_3$) $^1$H NMR $\delta$: 0.81 (t, 3H, *J*=7.0, $CH_3$), 0.97 (s, 3H, $H_3$-19), 1.24–1.26 (m, 2H, $CH_2$), 1.27 (s, 3H, $H_3$-17), 1.68 (s, 3H, $H_3$-16), 1.83 (m, 1H, H-5), 1.92 (m, 1H, H-4), 2.06 (s, 3H, Ac), 2.10 (s, 3H, Ac), 2.12 (s, 3H, Ac), 2.16 (dd, 1H, *J*=6.5, 2.2, H-1), 2.19 (s, 3H, $H_3$-18), 2.32 (d, 1H, *J*=18.4, H-6), 2.45 (brs, 1H, OH), 2.48 (d, 1H, *J*=19.6, H-14), 2.74 (dd, 1H, *J*=18.4, 7.0, H-6), 2.80 (dd, 1H, *J*=19.6, 6.5, H-14), 3.12 (dd, 1H, *J*=6.7, 4.5, H-3), 3.17 (dd, 1H, *J*=10.2, 2.5, H-20b), 3.52 (dd, 1H, *J*=10.2, 1.8, H-20a), 5.62 (dd, 1H, *J*=4.5, 2.2, H-2), 5.92 (d, 1H, *J*=10.5, H-9), 6.10 (d, 1H, *J*=10.5, H-10). $^{13}$C NMR $\delta$: 13.5 (q, $CH_3$), 14.2 (q, C-18), 18.1 (q, C-19), 20.6, 20.9, 21.2 (3×q, 3×$CH_3$ of Ac), 22.4 (t, $CH_2$), 23.6 (q, C-16), 34.2 (q, C-17), 35.5 (t, C-6), 38.7 (t, C-14), 39.9 (s, C-15), 40.4 (d, C-5), 41.6 (d, C-4), 43.7 (d, C-3), 48.2 (d, C-1), 53.8 (s, C-8), 63.6 (t, C-20), 72.1 (d, C-2), 72.8 (d, C-10), 76.2 (d, C-9), 169.6, 170.1, 171.5 (3×s, 3×CO of Ac), 199.4 (s, C-13), 210.6 (s, C-7). FAB-MS *m/z* 543 $(M+Na)^+$, 520 $(MH)^+$, 460$(MH-AcOH)^+$. HRFABMS *m/z* found 543.2568, calcd for $C_{28}H_{40}O_9Na$ $(M+Na)^+$ 543.2567. **Compound 9:** $[\alpha]_D^{20}$=+34.2 (c 0.01, $CHCl_3$) $^1$H NMR $\delta$: 0.85 (t, 3H, *J*=7.0, $CH_3$), 0.96 (s, 3H, $H_3$-19), 1.23–1.25 (m, 2H, $CH_2$), 1.31 (s, 3H, $H_3$-17), 1.65 (s, 3H, $H_3$-16), 1.90–1.93 (m, 1H, H-5), 2.01 (m, 1H, H-4), 2.07 (s, 3H, Ac), 2.10 (s, 3H, Ac), 2.13 (s, 3H, Ac), 2.12 (dd, 1H, *J*=6.5, 2.4, H-1), 2.21 (s, 3H, $H_3$-18), 2.24 (dd, 1H, *J*=14.6, 4.8, H-6), 2.50 (brs, 1H, OH), 2.54 (d, 1H, *J*=19.5, H-14), 2.68 (dd, 1H, *J*=14.6, 11.5, H-6), 2.84 (dd, 1H, *J*=19.5, 6.5, H-14), 3.19 (dd, 1H, *J*=11.0, 4.5, H-3), 3.21 (dd, 1H, *J*=10.2, 2.6, H-20b), 3.60 (dd, 1H, *J*=10.2, 3.0, H-20a), 5.58 (dd, 1H, *J*=4.5, 2.4, H-2), 5.94 (d, 1H, *J*=10.8, H-9), 6.08 (d, 1H, *J*=10.8, H-10). $^{13}$C NMR $\delta$: 13.7 (q, $CH_3$), 13.9 (q, C-18), 17.8 (q, C-19), 20.7, 20.9, 21.1 (3×q, 3×$CH_3$ of Ac), 21.8 (t, $CH_2$), 23.1 (q, C-16), 33.8 (q, C-17), 35.4 (t, C-6), 39.1 (t, C-14), 39.6 (s, C-15), 40.1 (d, C-5), 42.4 (d, C-4), 44.2 (d, C-3), 47.9 (d, C-1), 53.4 (s, C-8), 64.0 (t, C-20), 72.2 (d, C-2), 72.8 (d, C-10), 75.9 (d, C-9), 169.6, 170.0, 171.3 (3×s, 3×CO of Ac), 198.7 (s, C-13), 208.4 (s, C-7). FAB-MS *m/z* 543 $(M+Na)^+$, 502 $(MH-H_2O)^+$, 460 $(MH-AcOH)^+$, 382 $(MH-H_2O-2AcOH)^+$. HRFABMS *m/z* found 543.2561, calcd for $C_{28}H_{40}O_9Na$ $(M+Na)^+$ 543.2567.

**4,20-Dihydro-4α(20)-epoxy-5-hydroxytaxicin-I (10).** To a solution of 5-hydroxytriacetyltaxicin-I (500 mg, 1.0 mmol) in $CH_2Cl_2$ (50 mL), was added *m*-CPBA (600 mg, 3.5 mmol) and $Na_2HPO_4$ (1.04 g, 7.3 mmol). The reaction mixture was stirred at room temperature for 3 h, and then extracted with EtOAc and washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (ethyl acetate–hexane 2:1 v/v) to give 480 mg (92%) of **10** as a white amorphous solid. Its spectroscopic data

were identified as those of the compound previously described in Ref. 14a.

**4,20-Dihydro-4α(20)-epoxy-5,6-enetaxicin-I (11).** Following the procedure for preparation of **3**, using **10** (0.40 g, 0.79 mmol) gave **11** in 62% (0.239 g) as a white amorphous solid after chromatography (ethyl acetate–hexane 1:1 v/v). $^1$H NMR $\delta$: 0.97 (s, 3H, $H_3$-19), 1.20 (s, 3H, $H_3$-17), 1.65 (s, 3H, $H_3$-16), 2.07 (s, 3H, Ac), 2.10 (s, 3H, Ac), 2.10–2.13 (m, 1H, H-7), 2.14 (s, 3H, Ac), 2.24 (s, 3H, $H_3$-18), 2.42–2.44 (m, 1H, H-7), 2.46 (d, 1H, *J*=4.5, H-20b), 2.67 (d, 1H, *J*=19.5, H-14), 3.02 (d, 1H, *J*=4.5, H-20a), 3.14 (d, 1H, *J*=19.5, H-14), 3.61 (d, 1H, *J*=4.5, H-3), 5.60 (d, 1H, *J*=4.5, H-2), 5.75 (d, 1H, *J*=10.0, H-5), 5.78 (m, 1H, H-6), 5.94 (d, 1H, *J*=10.5, H-9), 6.17 (d, 1H, *J*=10.5, H-10). $^{13}$C NMR $\delta$: 14.2 (q, C-18), 17.4 (q, C-19), 19.6 (q, C-16), 20.7, 20.9, 21.3 (3×q, 3×$CH_3$ of Ac), 28.1 (t, C-7), 33.9 (q, C-17), 38.2 (t, C-14), 43.1 (s, C-15), 44.4 (d, C-3), 44.8 (s, C-8), 52.8 (t, C-20), 72.3 (d, C-2), 72.7 (d, C-10), 75.5 (d, C-9), 76.8 (s, C-1), 77.8 (s, C-4), 126.5 (d, C-5), 127.3 (d, C-6), 141.9 (s, C-12), 151.6 (s, C-11), 169.6, 170.0, 171.7 (3×s, 3×CO of Ac), 199.6 (s, C-13). HRFABMS *m/z* found 491.2276, calcd for $C_{26}H_{35}O_9$ $(MH)^+$ 491.2279.

**20-Hydroxy-4:5,6:7-dienetaxicin-I (12).** Following the procedure for preparation of **4**, using **11** (0.295 g, 0.6 mmol) and boron trifluoride diethyl etherate (abt. 47% solution, 0.35 mL) gave **12** in 51% yield (0.15 g) as a white amorphous solid after chromatography (ethyl acetate–hexane 2:1 v/v). $^1$H NMR $\delta$: 0.95 (s, 3H, $H_3$-19), 1.17 (s, 3H, $H_3$-17), 1.67 (s, 3H, $H_3$-16), 2.07 (s, 3H, Ac), 2.10 (s, 3H, Ac), 2.22 (s, 3H, $H_3$-18), 2.54 (brs, 1H, OH), 2.58 (d, 1H, *J*=19.5, H-14), 3.07 (d, 1H, *J*=19.5, H-14), 3.87 (d, 1H, *J*=10.4, H-20b), 4.03 (d, 1H, *J*=5.0, H-3), 4.21 (d, 1H, *J*=10.4, H-20a), 5.59 (d, 1H, *J*=9.8, H-7), 5.62 (d, 1H, *J*=5.0, H-2), 5.70 (d, 1H, *J*=5.4, H-5), 5.76 (dd, 1H, *J*=9.8, 5.4, H-6), 5.98 (d, 1H, *J*=10.3, H-9), 6.09 (d, 1H, *J*=10.3, H-10). $^{13}$C NMR $\delta$: 13.8 (q, C-18), 18.1 (q, C-19), 20.3 (q, C-16), 20.7, 21.0, 21.4 (3×q, 3×$CH_3$ of Ac), 34.2 (q, C-17), 39.2 (t, C-14), 42.9 (s, C-15), 47.2 (d, C-3), 47.9 (s, C-8), 65.6 (t, C-20), 72.4 (d, C-2), 72.8 (d, C-10), 75.7 (d, C-9), 77.0 (s, C-1), 122.8 (d, C-5), 128.9 (d, C-7), 129.7 (d, C-6), 137.2 (s, C-4), 140.4 (s, C-12), 150.7 (s, C-11), 169.5, 169.9, 171.5 (3×s, 3×CO of Ac), 199.2 (s, C-13). FAB-MS *m/z* 491 $(MH)^+$, 473 $(MH-H_2O)^+$, 413 $(MH-AcOH-H_2O)^+$. HRFABMS *m/z* found 491.2280, calcd for $C_{26}H_{35}O_9$ $(MH)^+$ 491.2279.

**4:5,6:7-Diene-20-oxotaxicin-I (13).** Following the procedure for preparation of **5**, using **12** (0.1 g, 0.2 mmol) gave **13** in 92% yield (0.092 g) as a colorless oil after chromatography (ethyl acetate–hexane 1:1 v/v). $^1$H NMR $\delta$: 0.99 (s, 3H, $H_3$-19), 1.20 (s, 3H, $H_3$-17), 1.69 (s, 3H, $H_3$-16), 2.07 (s, 3H, Ac), 2.11 (s, 3H, Ac), 2.14 (s, 3H, Ac), 2.19 (s, 3H, $H_3$-18), 2.54 (d, 1H, *J*=19.5, H-14), 2.96 (d, 1H, *J*=19.5, H-14), 3.89 (d, 1H, *J*=4.8, H-3), 5.60 (d, 1H, *J*=4.8, H-2), 5.74 (dd, 1H, *J*=9.8, 5.2 H-6), 5.80 (d, 1H, *J*=9.8, H-7), 5.83 (d, 1H, *J*=5.2, H-5), 5.97 (d, 1H, *J*=10.5, H-9), 6.12 (d, 1H, *J*=10.5, H-10), 10.31 (s, 1H, CHO). $^{13}$C NMR $\delta$: 14.1 (q, C-18), 17.7 (q, C-19), 20.2 (q, C-16), 20.6, 20.9, 21.3 (3×q, 3×$CH_3$ of Ac), 33.9 (q, C-17), 38.7 (t, C-14), 42.6 (s, C-15), 46.5 (d, C-3), 48.2 (s, C-8), 71.9 (d, C-2), 72.6 (d, C-10), 75.7 (d, C-9), 76.9 (s, C-1), 125.6 (d, C-6), 133.2 (d, C-7), 138.3 (s, C-4), 140.2 (s, C-12), 143.3 (d, C-5), 149.8 (s, C-11), 169.5, 170.2, 171.4 (3×s, 3×CO of Ac), 193.6 (d, C-20), 198.8 (s, C-13). HREIMS found 488.2040, calcd for $C_{26}H_{32}O_9$ $(M)^+$ 488.2044.

**Dimers of 4:5,6:7-diene-20-oxotaxicin-I (14) and (15).** Following the procedure for preparation of **6**, using **13** (70 mg, 0.143 mmol) at 80°C for 7 h (the reaction was monitored by TLC) gave **14** in 79% yield (55 mg) and **15** in 7% yield (5 mg) after chromatography (ethyl acetate–hexane 3:1 v/v). **Dimer 14:** mp 251–253°C, $[\alpha]_D^{20}$=+54.7 (c 0.015, $CHCl_3$) FAB-MS *m/z* 999 $(M+Na)^+$, 977 $(MH)^+$, 941 $(MH-2H_2O)^+$, 857 $(MH-2AcOH)^+$, 839 $(MH-H_2O-2AcOH)^+$, 779 $(MH-H_2O-3AcOH)^+$, 737 $(MH-4AcOH)^+$, 489, 429, 411. HRFABMS found 999.3980, calcd for $C_{52}H_{64}O_{18}Na$ $(M+Na)^+$ 999.3986. $^1$H and $^{13}$C NMR see Table 2. **Dimer 15:** $[\alpha]_D^{20}$=+72.6 (c 0.01, $CHCl_3$), $^1$H NMR $\delta$: 0.96 (s, 3H, $H_3$-19), 0.98 (s, 3H, $H_3$-19′), 1.23 (s, 3H, $H_3$-17′), 1.27 (s, 3H, $H_3$-17), 1.67 (s, 3H, $H_3$-16′), 1.70 (s, 3H, $H_3$-16), 2.06 (s, 3H, Ac′), 2.07 (s, 3H, Ac), 2.09 (s, 3H, Ac′), 2.10 (s, 3H, Ac), 2.13 (s, 3H, Ac), 2.13 (s, 3H, Ac′), 2.17 (s, 3H, $H_3$-18′), 2.22 (s, 3H, $H_3$-18), 2.55 (d, 1H, *J*=19.5, H-14′), 2.64 (d, 1H, *J*=19.8, H-14), 2.96 (d, 1H, *J*=19.5, H-14′), 3.02 (d, 1H, *J*=19.8, H-14), 3.38 (d, 1H, *J*=4.5, H-3′), 3.54 (d, 1H, *J*=5.0, H-3), 3.92 (d, 1H, *J*=1.8, H-5), 4.56 (d, 1H, *J*=2.0, H-5′), 5.58 (d, 1H, *J*=5.0, H-2), 5.59 (dd, 1H, *J*=10.1, 2.0, H-6′), 5.61 (dd, 1H, *J*=9.8, 1.8, H-6), 5.66 (d, 1H, *J*=9.8, H-7), 5.68 (d, 1H, *J*=10.1, H-7′), 5.72 (d, 1H, *J*=4.5, H-2′), 5.89 (d, 1H, *J*=11.0, H-9), 5.91 (d, 1H, *J*=10.8, H-9′), 6.09 (d, 1H, *J*=11.0, H-10), 6.14 (d, 1H, *J*=10.8, H-10′), 6.30 (s, 1H, H-20), 9.62 (s, 1H, H-20′). $^{13}$C NMR $\delta$: 13.7 (q, C-18′), 14.0 (q, C-18), 17.8 (q, C-19′), 18.2 (q, C-19), 19.8 (q, C-16′), 20.0 (q, C-16), 20.6, 20.7, 21.0, 21.0, 21.3, 21.4 (6×q, 6×$CH_3$ of Ac and Ac′), 33.8 (q, C-17), 34.2 (q, C-17′), 38.6 (t, C-14′), 39.4 (t, C-14), 42.6 (s, C-15), 43.2 (s, C-15′), 43.8 (d, C-3), 44.1 (d, C-3′), 45.7 (d, C-5), 47.9 (s, C-8′), 48.4 (s, C-8), 48.7 (s, C-4′), 72.3 (d, C-2), 72.4 (d, C-10′), 72.6 (d, C-2′), 72.7 (d, C-10); 75.2 (d, C-9′), 75.4 (d, C-9), 76.9 (s, C-1), 77.4 (s, C-1′), 80.1 (d, C-5′), 103.6 (s, C-4), 127.4 (d, C-6), 127.6 (d, C-6′), 128.7 (d, C-7′), 128.9 (d, C-7), 139.6 (s, C-12), 140.7 (s, C-12′), 145.4 (d, C-20), 149.8 (s, C-11), 151.4 (s, C-11′), 169.6, 170.1, 171.4 (3×s, 3×CO of Ac) 169.5, 170.0, 171.4 (3×s, 3×CO of Ac′), 198.8 (s, C-13′), 199.7 (s, C-13), 202.7 (d, C-20′). FAB-MS *m/z* 977 $(MH)^+$, 917 $(MH-AcOH)^+$, 881 $(MH-2H_2O-AcOH)^+$, 841 $(MH-H_2O-2AcOH)^+$, 839 $(MH-H_2O-2AcOH)^+$, 761 $(MH-2H_2O-3AcOH)^+$, 489, 453, 393. HRFABMS *m/z* found 977.4163. calcd for $C_{52}H_{65}O_{18}$ $(MH)^+$ 977.4167.

**Cycloadduct (*exo*-16) and γ-butyrolactone (*endo*-17).** A solution of **12** (40 mg, 0.082 mmol), *N*-methylmaleimide (13 mg, 0.12 mmol) and scandium trifluoromethanesulfonate (6 mg, 15 mol%) in $CH_2Cl_2$ (2 mL) was stirred at room temperature for 5 h under nitrogen. The reaction mixture was chromatographed directly by preparative TLC (ethyl acetate–chloroform 3:1 v/v) to give **16** (37 mg, 76%) and **17** (5 mg, 10%) in 86% yield as a white solid. ***exo*-16:** mp: 165–167°C, $[\alpha]_D^{20}$=+43.5 (c 0.02, $CHCl_3$), $^1$H NMR $\delta$:1.01 (s, 3H, $H_3$-19), 1.25 (s, 3H, $H_3$-17), 1.61 (s, 3H, $H_3$-16), 2.05 (s, 3H, Ac), 2.09 (s, 3H, Ac), 2.11 (s, 3H, Ac), 2.19 (s, 3H, $H_3$-18), 2.67 (s, 3H,

$NCH_3$), 2.68 (d, 1H, *J*=19.8, H-14), 2.96 (d, 1H, *J*=2.0, H-7), 2.98 (d, 1H, *J*=19.8, H-14), 3.19 (d, 1H, *J*=8.6, H-22), 3.21 (d, 1H, *J*=4.5, H-3), 3.29 (d, 1H, *J*=8.6, H-21), 3.47 (d, 1H, *J*=10.2, H-20b), 3.62 (d, 1H, *J*=10.2, H-20a), 5.62 (d, 1H, *J*=4.5, H-2), 5.94 (d, 1H, *J*=11.0, H-9), 6.17 (d, 1H, *J*=11.0 H-10), 6.21 (d, 1H, *J*=7.5, H-5), 6.31 (dd, 1H, *J*=7.5, 2.0, H-6). $^{13}$C NMR $\delta$: 14.1 (q, C-18), 20.1 (q, C-19), 20.7, 21.2, 21.3 (3×q, 3×$CH_3$ of Ac), 24.3 (q, C-16), 30.1 (q, C-17), 38.6 (q, C-25), 39.1 (t, C-14), 41.8 (s, C-15), 43.2 (d, C-3), 47.6 (s, C-8), 51.6 (d, C-22), 51.9 (d, C-21), 52.2 (d, C-7), 54.8 (s, C-4), 61.6 (t, C-20), 71.9 (d, C-2), 72.4 (d, C-10), 75.4 (d, C-9), 76.8 (s, C-1), 130.6 (d, C-6), 131.2 (d, C-5), 140.2 (s, C-12), 149.8 (s, C-11), 169.6, 170.1, 171.4 (3×s, 3×CO of Ac), 177.4 (s, C-23), 177.8 (s, C-24), 199.2 (s, C-13). FAB-MS *m/z* 602 $(MH)^+$, 542 $(MH-AcOH)^+$, 524 $(MH-H_2O-AcOH)^+$, 449 $(MH-H_2O-2AcOH-Me)^+$. HRFABMS *m/z* found 602.2591, calcd for $C_{31}H_{40}O_{11}N$ $(MH)^+$ 602.2599. ***endo*-17:** mp 153–155°C, $[\alpha]_D^{20}$=+32.8 (c 0.006, $CHCl_3$), $^1$H NMR $\delta$: 0.99 (s, 3H, $H_3$-19), 1.31 (s, 3H, $H_3$-17), 1.65 (s, 3H, $H_3$-16), 2.06 (s, 3H, Ac), 2.08 (s, 3H Ac), 2.11 (s, 3H, Ac), 2.21 (s, 3H, $H_3$-18), 2.79 (d, 3H, *J*=4.8, NHC*H*$_3$), 2.74 (d, 1H, *J*=19.6, H-14), 2.98 (dd, 1H, *J*=2.0, 1.6, H-7), 3.01 (d, 1H, *J*=19.6, H-14), 3.17 (dd, 1H, *J*=7.8, 1.6, H-22), 3.31 (d, 1H, *J*=7.8, H-21), 3.50 (d, 1H, *J*=4.6, H-3), 3.89 (d, 1H, *J*=9.6, H-20b), 4.23 (d, 1H, *J*=9.6, H-20a), 5.58 (d, 1H, *J*=4.6, H-2), 5.79 (d, 1H, *J*=7.2, H-5), 5.88 (dd, 1H, *J*=7.2, 2.0, H-6), 5.91 (d, 1H, *J*=10.5, H-9), 6.19 (d, 1H, *J*=10.5, H-10), 6.30 (brs, 1H, NH). $^{13}$C NMR $\delta$: 13.6 (q, C-18), 19.7 (q, C-19), 20.5, 21.1, 21.4 (3×q, 3×$CH_3$ of Ac), 24.1 (q, C-16), 26.2 (q, C-25), 33.2 (q, C-17), 38.9 (t, C-14), 41.5 (s, C-15), 44.6 (d, C-3), 48.2 (s, C-8), 50.9 (d, C-22), 52.7 (d, C-7), 53.4 (d, C-21), 55.8 (s, C-4), 69.5 (t, C-20), 72.3 (d, C-10), 72.6 (d, C-2), 75.8 (d, C-9), 77.2 (s, C-1), 130.3 (d, C-6), 131.4 (d, C-5), 140.7 (s, C-12), 150.2 (s, C-11), 169.4, 169.8, 171.3 (3×s, 3×CO of Ac), 171.4 (s, C-23), 178.5 (s, C-24), 198.8 (s, C-13). FAB-MS *m/z* 602 $(MH)^+$, 542 $(MH-AcOH)^+$, 526 $(MH-H_2O-CONHMe)^+$, 484 $(MH-AcOH-CONHMe)^+$, 482 $(MH-2AcOH)^+$, 464 $(MH-2AcOH-H_2O)^+$. HRFABMS *m/z* found 602.2589, calcd for $C_{31}H_{40}O_{11}N$ $(MH)^+$ 602.2599.

**Compound 18. A dimer derived from 20-hydroxy-4:5,6:7-dienetaxicin-I (12) and (20-hydroxy-5,6-ene-7-oxotaxinine B (7a).** A solution of **12** (10 mg, 0.02 mmol), **7a** (10 mg, 0.02 mmol) and scandium trifluoromethanesulfonate (2 mg, 20 mol%) in $CH_2Cl_2$ (1 mL) was stirred at room temperature for 12 h under nitrogen. The reaction mixture was chromatographed directly by preparative TLC (ethyl acetate–hexane 3:1 v/v) to give **18** in 75% yield (15 mg) as a white solid. mp: 225–227°C, $[\alpha]_D^{20}$=+57.1 (c 0.012, $CHCl_3$), $^1$H NMR $\delta$: 0.98 (s, 3H, $H_3$-19), 0.99 (s, 3H, $H_3$-19′), 1.26 (s, 3H, $H_3$-17′), 1.29 (s, 3H, $H_3$-17), 1.67 (s, 3H. $H_3$-16), 1.70 (s, 3H, $H_3$-16′), 2.05 (s, 3H, Ac), 2.06 (s, 3H, Ac), 2.09 (s, 3H, Ac), 2.09 (s, 3H, Ac), 2.10 (s, 3H, Ac), 2.11 (s, 3H, Ac), 2.18 (s, 3H, $H_3$-18′), 2.15 (dd, 1H, *J*=6.5, 2.4, H-1′), 2.21 (s, 3H, $H_3$-18), 2.45 (m, 1H, H-4′), 2.54 and 2.58 (brs, 2H, 2OH), 2.53 (d, 1H, *J*=19.5, H-14′), 2.69 (d, 1H, *J*=19.8, H-14), 2.78 (dd, 1H, *J*=19.5, 6.5, H-14′), 2.87 (dd, 1H, *J*=8.7, 6.7, H-5′), 2.95 (d, 1H, *J*=2.1, H-7), 3.01 (dd, 1H, *J*=19.8, H-14), 3.17 (dd, 1H, *J*=7.0, 6.0, H-3′), 3.23 (dd, 1H, *J*=10.3, 3.0, H-20′b), 3.25 (d, 1H, *J*=4.5, H-3), 3.35 (d, 1H, *J*=8.7, H-6′), 3.44 (d, 1H, *J*=10.2, H-20b), 3.60 (dd, 1H, *J*=10.3, 2.5, H-20′a), 3.67 (d, 1H, *J*=10.2, H-20a), 5.59 (dd, 1H, *J*=6.0, 2.4, H-2′), 5.68 (d, 1H, *J*=4.5, H-2), 5.89 (d, 1H, *J*=10.5, H-9′), 5.93 (d, 1H, *J*=10.8, H-9), 6.14 (d, 1H, *J*=10.5, H-10′), 6.17 (d, 1H, *J*=10.8, H-10), 6.20 (d, 1H, *J*=7.5, H-5), 6.29 (dd, 1H, *J*=7.5, 2.1, H-6). $^{13}$C NMR $\delta$: 13.9 (q, C-18′), 14.1 (q, C-18), 18.2 (q, C-19′), 19.8 (q, C-19), 20.6, 20.7, 20.9, 20.9, 21.2, 21.3 (6×q, 6×$CH_3$ of Ac and Ac′), 24.6 (q, C-16), 25.1 (q, C-16′), 31.3 (q, C-17), 34.8 (q, C-17′), 38.2 (t, C-14′), 38.9 (s, C-15′), 39.4 (t, C-14), 40.2 (s, C-15), 43.1 (d, C-5′), 43.7 (d, C-3), 44.1 (d, C-3′), 46.8 (d, C-6′), 47.6 (s, C-8), 48.4 (d, C-1′), 48.7 (s, C-8′), 51.4 (d, C-4′), 51.7 (d, C-7), 53.6 (s, C-4), 61.5 (t, C-20), 62.6 (t, C-20′), 69.8 (d, C-2′), 72.1 (d, C-2), 72.6 (d, C-10′) 72.8 (d, C-10), 75.5 (d, C-9), 75.8 (d, C-9′), 77.1 (s, C-1), 130.5 (d, C-6), 131.4 (d, C-5), 140.6 (s, C-12′), 141.2 (s, C-12), 150.8 (s, C-11), 151.2 (s, C-11′), 169.5, 169.6, 169.9, 170.0, 171.4, 171.5 (6×s, 6×CO of Ac and Ac′), 198.6 (s, C-13′), 199.4 (s, C-13), 210.2 (s, C-7′). HRFABMS *m/z* found 1003.4293, calcd for $C_{52}H_{68}O_{18}Na$ $(M+Na)^+$ 1003.4299.

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20. This reaction was performed at room temperature, a 6/8/6/7 ring derivative was also obtained in a small amount in addition to **3**. In the case of **12**, the amount of other two derivatives 6/8/6/7 ring and A-ring contraction was increased at higher temperature. For similar $BF_3$-induced reactions of taxoids see Hosoyama, H.; Shigemori, H.; Kobayashi, J. *Tetrahedron Lett.* **1999**, *40*, 2149–2152 and Ref. 14a.

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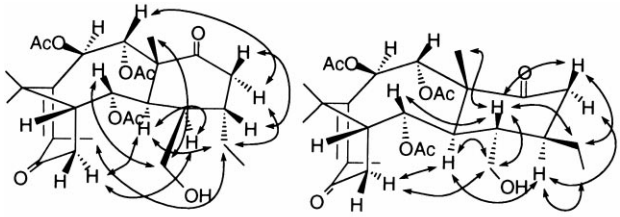
22. It was detected by $^1$H NMR (500 MHz) in a crude mixture. **7a** can be obtained as a pure product by chromatography by preparative TLC twice. The β-orientation of 4-hydroxymethylene in **7a** was suggested from NOE correlations of H-2, $H_3$-19 to $H_2$-20 and H-3, H-14α to H-4. Similarly, the α-orientation of 4-hydroxymethylene in **7b** was suggested from NOE correlation of H-2 and $H_3$-19 to H-4 and H-14α to $H_2$-20 as well as H-3 to H-20b.

23. Key NOE correlations of **8** and **9** are as follows:




Key NOEs of **8** Key NOEs of **9**

24. Calculations were performed on Macintosh using CS Chem 3D Pro. 3.2. in Tohoku University, Japan.

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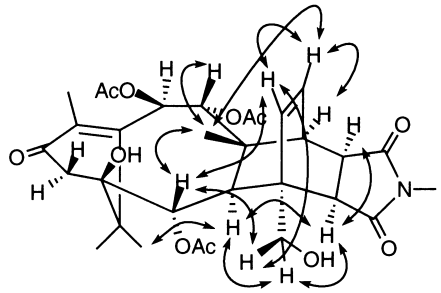
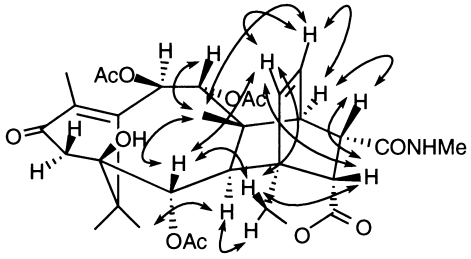
31. The assignment of *exo* or *endo* stereochemistry of the cycloadducts **16** and **17** was carried out on the basis of $^1$H NMR (500 MHz, $CDCl_3$) conducted at 20°C on the cycloadducts **16** and **17**. For assignment of the stereochemistry, our attention focused on the through bond coupling and NOE relationships displayed by the bridgehead proton H-7 and a proton H-22 in the *exo* or *endo* position arising from cycloaddition. It is accepted that in the bicyclo[2.2.2]octene skeleton, generated by cycloaddition, that the bridgehead proton displays a very small coupling to a proton in the *endo* position whereas it displays a large coupling to a proton in the *exo* position. In the case of cycloadduct **16**, no coupling ($J_{7,22}$ 0 Hz) observed in the resonances at δ 2.96 (d) and δ 3.19 (d) could be assigned by $^1$H–$^1$H COSY experiment to coupling between the bridgehead proton H-7 and the *endo* proton (H-22) in the bicyclo[2.2.2]octene skeleton. In contrast, 1.6 Hz coupling ($J_{7,22}$) was observed in the resonances at δ 2.98 (dd) and δ 3.17 (dd) assigned to coupling between the bridgehead proton H-7 and the *exo* proton (H-22) in the bicyclo[2.2.]octene

skeleton of **17**. These observations infer that **16** possesses *exo* stereochemistry whereas **17** possesses *endo* stereochemistry. This tentative assignment was further confirmed by NOE experiments which demonstrated a pattern of NOE which was consistent only with *exo* (H-22) stereochemistry. The key NOESY correlations of *exo*-**16** and *endo*-**17** as follows (500 MHz, CDCl3):




***exo-16***




***endo-17***

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