Preparation of a C-1 Oxygenated Taxane A Ring *via* a Highly Efficient Diels−Alder Strategy Utilizing an α-(Aroyloxy) Enone Captodative Dienophile

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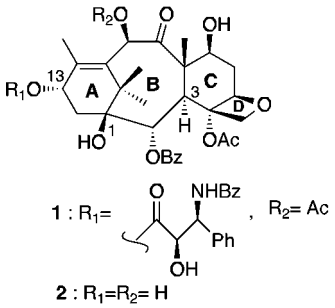
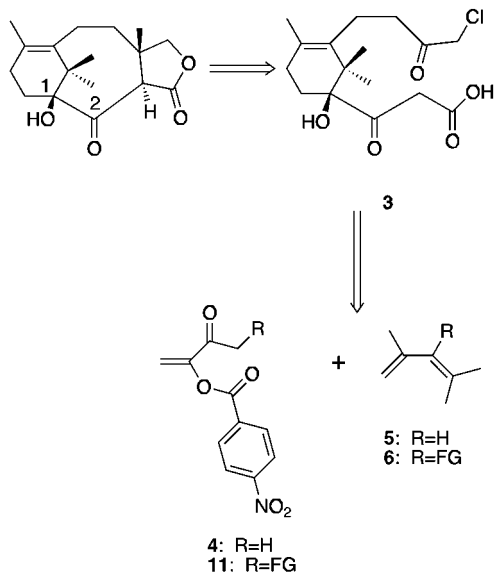
Paclitaxel (**1**), a tetracyclic diterpene alkaloid isolated from the Pacific yew *Taxus brevifolia*, has recently attracted considerable attention from the scientific community owing to its remarkable cytotoxicity against various human neoplasms.[1] Initially, its natural scarcity and the ecologically inefficient methods available for its isolation made paclitaxel a prime target for total synthesis.[2] Although the supply problem has been adequately addressed *via* semisynthesis from 10-deacetylbaccatin III (**2**),[1d] a renewable resource isolated from the European yew *Taxus baccata*, the synthesis of structural analogs which might exhibit similar or improved biological activity is still an area of intense research.[1]



Previously, our group has shown the viability of a macrolactonization/transannular aldol condensation approach for construction of the taxane AB ring system.[3] In extending this strategy to the synthesis of a taxane AB ring system that is fully functionalized along the "southern" periphery, we required access to a chloro keto acid intermediate such as **3** that contains the taxane A ring and which bears both a C-1 hydroxyl group and C-2 oxygenation (taxane numbering, see Scheme 1). In this paper, we establish the feasibility of employing a Diels−Alder strategy for constructing the requisite taxane A ring that establishes both the C-1 hydroxyl group and C-2 oxygenation *directly* in the cycloaddition step. Our strategy is predicated on the use of the captodative dienophile **4**, which exploits the powerfully electron-withdrawing *p*-nitrobenzoyl (PNB) group in order to attenuate the electron-donating ability of the vinyl oxygen substituent. While the Diels−Alder reaction has been widely exploited for construction of the taxane A ring,[4] few approaches have involved the direct incorporation of C-1 functionality *via* the use of captodative dienophiles.[5] Furthermore, at the time we initiated these studies, no examples existed where C-1 oxygenation was incorporated *directly* in the cycloaddition step.[6]

Scheme 1



Previous work by Tamariz *et al.*[7] has shown that dienophile **4** undergoes Diels−Alder reactions with uncrowded dienes, however, until now no studies had been reported with the kinds of highly substituted dienes needed for construction of the taxane A ring. Therefore, we have examined the reaction of dienophile **4** with highly crowded 2,4-dimethyl-1,3-pentadiene (**5**), a commercially available diene that was expected to serve as a good model for the C-3 substituted dienes (e.g. **6**) required in the synthesis of the taxane AB ring system.

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(1) For several recent general reviews, see: (a) Kingston, D. G. I.; Molinero, A .D.; Rinaldi, J. M. In *Progress in the Chemistry of Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, Ch., Eds.; Springer-Verlag: Vienna, 1993; Vol. 61, pp 1−206. (b) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15. (c) Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. *Contemp. Org. Synth.* **1994**, 47. (d) *Taxane Anticancer Agents*; Georg, G. I., Chen, T. T., Ojima, I., Vyasi, D. M., Eds.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995. (e) *The Chemistry and Pharmacology of Taxol® and its Derivatives*; Farina, V., Ed.; Elsevier: Amsterdam, Holland, 1995.

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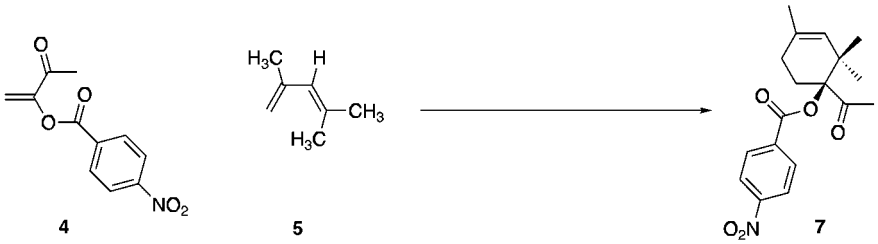
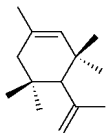
Table 1. Diels–Alder Cycloaddition Reactions



entry	5:4	proton scavenger (equiv)	Lewis acid (equiv)	solvent	*T* (°C)	time (h)	isolated yield[a] (%)
1	5:1		$BF_3{\cdot}OEt_2$ (5)	CH_2Cl_2	−78	15	30[b]
2	5:1		$BF_3{\cdot}OEt_2$ (cat.)	CH_2Cl_2	−78	1	30[b]
3	5:1		$ZnCl_2$ (3)	CH_2Cl_2	−78	22	(10)[b]
4	5:1		Et_2AlCl (3)	CH_2Cl_2	−78	1	0[b,c]
5	5:1	4 Å mol sieves (10% w/v)	$BF_3{\cdot}OEt_2$ (3)	CH_2Cl_2	−78 → rt	18	(20)[b]
6	5:1			H_2O	rt	48	(0)[d]
7	5:1		5 M $LiClO_4$	Et_2O	rt	3	(16)[b]
8	5:1	Proton Sponge (4.2)	$BF_3{\cdot}OEt_2$ (5)	CH_2Cl_2	−78 → rt	48	(13)[b]
9	1.2:1	2,6-DtBP (0.25)	$BF_3{\cdot}OEt_2$ (1.1)	C_6H_6	rt	2	88[e]
10	1.2:1		$BF_3{\cdot}OEt_2$ (1.1)	C_6H_6	rt	2	40[b]
11	1.2:1	2,6-DtBP (0.25)	$BF_3{\cdot}OEt_2$ (1.1)	CH_2Cl_2	rt	2	99
12	2:1			xylenes	120	72	60[e]

[a] Yields in parentheses were determined by GC analysis. [b] Most of the diene underwent oligomerization side reactions. [c] See footnote 15. [d] No volatile products were detected by GC analysis. [e] The reaction was performed in the presence of 9 mol % hydroquinone in a sealed tube.

Initial studies were performed under $BF_3{\cdot}OEt_2$ catalysis, conditions that Tamariz had successfully employed using much less crowded and more reactive dienes (Table 1, entry 1);[7c] however, using 5 equiv of $BF_3{\cdot}OEt_2$ and a large excess of diene **5**, the desired cycloadduct **7** was obtained in only 30% isolated yield. Most of the diene underwent oligomerization side reactions, presumably mediated by adventitious protic acid impurities in the Lewis acid. The major byproduct was found to be the diene dimer **8**. This was confirmed by a control experiment in which the reaction was repeated without added dienophile.[8] This reaction yielded a relatively clean sample of **8**, identified by ^{1}H NMR spectroscopy.[8a]



8

Attempts to remove protic acid impurities by using base-treated glassware or *via* very careful distillation of the $BF_3{\cdot}OEt_2$ from CaH_2 failed to improve the yield of cycloadduct **7**. Similarly, the use of catalytic $BF_3{\cdot}OEt_2$ (entry 2), different Lewis acids (e.g. entries 3 and 4),[9] 4 Å molecular sieves heterogeneously dispersed in the reaction solvent (entry 5),[10] or different media well-known to accelerate Diels–Alder reactions (e.g. entries 6 and 7)[11] also all failed to afford **7** in synthetically useful quantities.

Our attention was next focused on the removal of adventitious proton impurities using the proton scavengers, Proton Sponge (1,8-bis(dimethylamino)naphthalene, Aldrich) and 2,6-di-*tert*-butylpyridine (2,6-DtBP), sterically crowded nitrogen bases which are known to slowly react with protons but do not effectively interact with Lewis acids such as BF_3.[12] Although initial attempts using Proton Sponge (entry 8) failed to give acceptable yields of the desired cycloadduct **7**, success was finally achieved using 2,6-DtBP with only a slight excess of diene **5** (entry 9). A control experiment conducted in the absence of 2,6-DtBP (entry 10) confirmed the importance of having this proton scavenger present.[13]

Prior to pursuing these studies, we were aware that Hersh *et al.* had observed decreased catalytic activity of $BF_3{\cdot}OEt_2$ in Diels–Alder reactions using dichloromethane as solvent when 2,6-DtBP was used as a proton scavenger.[13c] They attributed the fall off in the reaction efficiency to proton abstraction from the dichloromethane solvent by 2,6-DtBP with concomitant chloride ion transfer to the BF_3 catalyst, rendering it ineffective. It was for this reason that benzene, a less acidic and poorly coordinating medium, was initially chosen as the reaction solvent (entry 9). Interestingly, however, when the reaction was repeated using dichloromethane as the solvent (entry 11), the expected fall off in the catalytic

(8) For other reports of the dimerization of diene **5**, see: (a) Giguere, R. J.; von Ilsemann, G.; Hoffman, H. M. R. *J. Org. Chem.* **1982**, *47*, 4948. (b) Takemoto, K.; Miyata, M. *Mol. Cryst. Liq. Cryst.* **1990**, *186*, 189. (c) Gassman, P. G.; Singleton, D. A.; Kagechika, H. *J. Am. Chem. Soc.* **1991**, *113*, 6271.

(9) For a review suggesting the use of alkyl aluminum species as both Lewis acids and proton scavengers, see: Snider, B. B.; Rodini, D. J.; Karras, M.; Kirk, T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron* **1981**, *37*, 3927.

(10) For an example of the use of molecular sieves in a Diels–Alder reaction, see: (a) Ketter, A.; Glahsl, G.; Herrmann, R. *J. Chem. Res. Synop.* **1990**, 278; *J. Chem. Res. Miniprint* **1990**, 2118.

(11) (a) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159. (b) Grieco, P. *Aldrichimica Acta* **1991**, *24*, 59.

(12) 2,6 DtBP: Brown, H. C.; Kanner, B. *J. Am. Chem. Soc.* **1966**, *88*, 986. Proton Sponge: (a) Kennedy, J. P.; *et al. J. Macromol. Sci., Chem.* **1982**, *A18*, 3–152. (b) Staab, H. A.; Saupe, T. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 865. (c) Alder, R. W. *Chem. Rev.* **1989**, *89*, 1215. (d) Brzezinski, B.; Grech, E.; Malarski, Z.; Sobezyk, L. *J. Chem. Soc., Perkin Trans. 2* **1991**, 857. (e) Platts, J. A.; Howard, S. T.; Wozniak, K. *J. Org. Chem.* **1994**, *59*, 4647.

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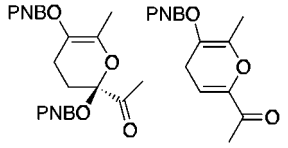
activity of the $BF_3{\cdot}OEt_2$ was not observed. On the contrary and, much to our delight, we found that the reaction proceeded in almost quantitative yield.

Given the successful thermally mediated Diels−Alder reactions of captodative dienophiles described by Tamariz[7a] and Nicolaou,[2b,c] we also studied the cycloaddition reaction between **4** and **5** under thermally mediated conditions. We found that modest success could be achieved by performing the reaction in a sealed tube at 120 °C for 3 days (entry 12); 60% of the desired cycloadduct was obtained when employing a 2:1 ratio of diene to dienophile. Performing a control experiment in the absence of added diene allowed us to establish that the major byproducts in these reactions were the dienophile−dienophile hetero-Diels−Alder cycloadduct **9** and its thermal elimination adduct **10**. Interestingly, the amount of byproducts formed in these thermal reactions was found to vary (between 6 and 30% by GC analysis) with both the pressure at which the reaction tube was sealed and with the diene to dienophile ratio. Byproduct formation increased as the pressure at which the tube was sealed increased (∼0.2 mmHg up to ∼760 mmHg) and/or as the diene to dienophile ratio decreased.



9 **10**

In conclusion, we have shown the viability of a novel and efficient Diels−Alder approach to the taxane A ring using an α-(aroyloxy) enone captodative dienophile whereby the C-1 oxygen functionality is incorporated *directly* in the cycloaddition step. This approach is attractive both because of its efficiency and its potential versatility (e.g. asymmetric variants may be possible[14]). Further studies directed toward the use of C-3 substituted dienes (e.g. **6**) and more highly functionalized α-(aroyloxy) enone dienophiles (e.g. **11**) in such Diels−Alder chemistry (performed in an inter- as well as an intramolecular fashion), as well as the use of the resulting cycloadducts in our macrolactonization/transannulation approach to the taxane B ring, are currently underway in our laboratory. The results of these studies will be reported in due course.

Experimental Section

CH_2Cl_2, C_6H_6, and $BF_3{\cdot}OEt_2$ were purified by distillation under N_2 from CaH_2, and xylenes were distilled from P_2O_5. 2,4-Dimethyl-1,3-pentadiene (**5**) (Aldrich) was distilled from CaH_2 and stored on activated 5 Å molecular sieves before use. Where noted glassware was base-treated by soaking in a 1:1 solution of concentrated NH_4OH and H_2O for at least 1 h. All reactions were performed in oven-dried (125 °C) glassware under N_2 using standard inert atmosphere techniques and were monitored by GC. Only major diagnostic IR spectral absorption bands are reported. Mass spectra were obtained by GC/MS with electron impact ionization; only selected ions are reported. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 300 and 75 MHz, respectively. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA.

1′-Acetyl-2′,2′,4′-trimethyl-3′-cyclohexenyl 4-nitrobenzoate (7). 3-[(4-(Nitrobenzoyl)oxy]-3-buten-2-one (**4**) (100 mg, 0.43 mmol) was added to a base-treated, flame-dried round bottom flask along with anhydrous CH_2Cl_2 (2.2 mL) at room temperature. Then, in 15 min intervals, $BF_3{\cdot}OEt_2$ (0.060 mL, 0.47 mmol), 2,6-di-*tert*-butylpyridine (0.020 mL, 0.11 mmol), and 2,4-dimethyl-1,3-pentadiene (**5**) (0.070 mL, 0.52 mmol) were added sequentially with stirring. After 2 h, the crude reaction mixture was partitioned between 5% aqueous HCl and ethyl acetate. The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4. After filtration and concentration *in vacuo*, the crude product was purified by flash column chromatography (5:1 hexanes:ethyl acetate) to yield the desired cycloadduct **7** (145 mg, 99%): IR (Nujol, cm^{-1}) 3077, 1724, 1713, 1608; ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J = 9 Hz, 2H), 8.15 (d, J = 9 Hz, 2H), 5.10 (br s, 1H), 2.66 (ddd, J = 14.4, 5.3, 1.3 Hz, 1H), 2.35 (ddd, J = 14.3, 12.1, 6.0 Hz, 1H), 2.28 (s, 3H), 1.94 (dd, J = 17.7, 5.7 Hz, 1H), 1.80−1.70 (m, 1H), 1.68 (s, 3H), 1.26 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 163.8, 150.7, 135.4, 130.8, 130.7, 129.9, 123.7, 89.3, 38.8, 28.2, 26.8, 26.5, 24.2, 23.9, 23.0. Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.34; H, 6.39; N, 4.23. Found: C, 65.69; H, 6.67; N, 3.89.

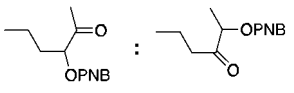
Dienophile−Dienophile Cycloaddition Adducts 9 and 10. A stirred solution of 3-[(4-nitrobenzoyl)oxy]-3-buten-2-one (**4**) (250 mg, 1.1 mmol) and hydroquinone (12.1 mg, 0.11 mmol) in anhydrous xylenes (7.7 mL) was heated at 130 °C for 7d. Then, the solvent was removed *in vacuo*, and the sample was diluted with 3:1 hexanes:ethyl acetate (5 mL) and vacuum filtered. The filtrate was concentrated *in vacuo*, and the residue was purified *via* flash column chromatography (3:1 hexanes:ethyl acetate) to afford cycloadduct **9** (50 mg, 20%). The filtered solid (98 mg) was dissolved in ethyl acetate (50 mL), extracted with excess saturated aqueous $NaHCO_3$, washed with brine, and dried on anhydrous Na_2SO_4. The solution was filtered and concentrated *in vacuo* to give **10** (29 mg as a 5:1 mixture with *p*-nitrobenzoic acid). This material was purified by flash column chromatography (3:1 hexanes:ethyl acetate) to yield **9** (20 mg, >90% pure, 8%). Analytical data for **9**: IR (Nujol, cm^{-1}) 3117, 1732, 1607; ^1H NMR (300 MHz, $CDCl_3$) δ 8.332 (d, J = 9.0 Hz, 2H), 8.329 (d, J = 9 Hz, 2H), 8.27 (d, J = 9 Hz, 2H), 8.25 (d, J = 9 Hz, 2H), 2.89 (dddq, J = 21, 14.4, 6.6, 2.3 Hz, 1H), 2.52 (s, 3H), 2.50−2.35 (m, 2H), 2.08 (ddd, J = 13.9, 12.4, 6.8 Hz, 1H), 1.83 (t, J = 1.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 163.1, 162.6, 150.9, 140.7, 134.4, 134.3, 131.2, 131.1, 131.0, 127.5, 123.7, 98.3, 27.3, 25.4, 19.9, 14.0; EIMS *m*/*z* (rel intensity) 303 (0.8), 260 (6), 150 (100), 120 (8), 104 (21). Anal. Calcd for $C_{22}H_{18}N_2O_{10}$: C, 56.18; H, 3.86; N, 5.96. Found: C, 56.30; H, 3.91; N, 6.05.

Analytical data for **10**: IR (Nujol, cm^{-1}) 3108, 1720, 1698, 1606, 1525; ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, J = 9 Hz, 2H), 8.27 (d, J = 9 Hz, 2H), 6.06 (t, J = 4.1 Hz, 1H), 3.20 (dq, J = 3.9, 1.5 Hz, 2H), 2.32 (s, 3H), 1.88 (t, J = 1.5 Hz, 3H); $^1H-^1H$ COSY data: diagnostic crosspeaks were observed between δ 1.88/3.20 and 3.20/6.06; ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.2, 162.5, 150.9, 147.8, 141.6, 134.4, 131.2, 125.5, 123.7, 108.4, 25.7, 24.4, 13.6; EIMS *m*/*z* (rel intensity) 303 (M^+, 5), 260 (5), 150 (100), 120 (8), 104 (18). Anal. Calcd for $C_{15}H_{13}NO_6$: C, 59.41; H, 4.32; N, 4.62. Found: C, 59.80; H, 3.97; N, 5.01.

Addition Adducts 12 and 13. A solution of 3-[(4-nitrobenzoyl)oxy]-3-buten-2-one (**4**) (75 mg, 0.32 mmol) in anhydrous CH_2Cl_2 (2 mL) was cooled to −78 °C, and a 1 M Et_2AlCl solution in hexanes (0.96 mL, 0.96 mmol) was added dropwise. After 20 min, a solution of diene **5** (0.21 mL, 1.60 mmol) in anhydrous CH_2Cl_2 (1 mL) was added slowly by syringe. After 1 h the reaction mixture was allowed to warm to room temperature and was subsequently partitioned between H_2O and ether. The ether layer was washed with saturated aqueous $NaHCO_3$ and brine and stored on anhydrous Na_2SO_4. After filtration and concentration *in vacuo*, the crude product was purified by flash column chromatography (5:1 hexanes:ethyl acetate) to yield a 2:1 mixture of **12:13** (39 mg, 46%): IR (of the mixture, neat, cm^{-1}) 3077, 1735, 1713, 1605; EIMS (of the mixture) *m*/*z* (rel intensity) 265 (M^+, 0.2), 222 (9), 150 (100), 134 (9), 120 (7), 104 (25); ^1H NMR (300 MHz, $CDCl_3$) (**12**): δ 8.30 (d, J = 9 Hz, 2H), 8.24 (d,

(14) Dienes, Z.; Vogel, P. *J. Org. Chem.* **1996**, *61*, 6958.

(15) The dienophile was precomplexed with the Lewis acid, and the following addition adducts were obtained in a 2:1 ratio:



12 **13**

J = 9.2 Hz, 2H), 5.28 (t, J = 6.3 Hz, 1H), 2.24 (s, 3H), 1.95−1.87 (m, 2H), 1.65 (sextet, J = 7.3 Hz, 2H), 1.00 (t, J = 7.3 Hz, 3H); (**13**): δ 8.30 (d, J = 9 Hz, 2H), 8.24 (d, J = 9.2 Hz, 2H), 5.36 (q, J = 7.1 Hz, 1H), 2.57 (dt, J = 17.4, 7.2 Hz, 1H), 2.47 (dt, J = 17.4, 7.2 Hz, 1H), 1.56 (d, J = 6.9 Hz, 3H), 1.53 (sextet, J = 7.4 Hz, 2H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) (**12**): δ 204.0, 164.2, 150.7, 134.8/128.8, 130.9, 123.6, 79.7; (**13**): δ 206.5, 164.0, 150.7, 134.8/128.8, 130.9, 123.6, 75.9. The following ^{13}C NMR resonances upfield of 70 ppm could not be unambiguously assigned to **12** or **13**: δ 40.2, 32.2, 26.2, 18.6, 16.7, 16.1, 13.7.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of the mixture containing adducts **12** and **13** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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