Preparation and Diels−Alder Cycloaddition of 2-Acyloxyacroleins. Facile Synthesis of Functionalized Taxol A-Ring Synthons

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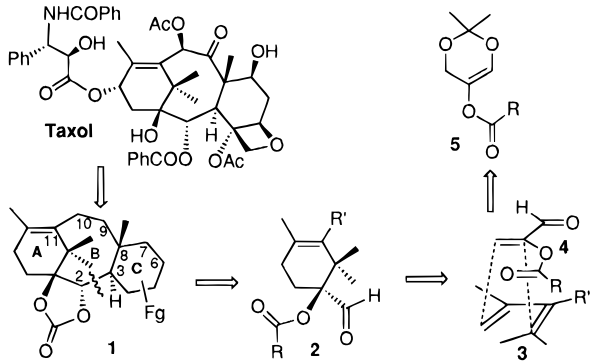
The antimitotic agent taxol has been heralded as a new and exciting lead for the chemotherapeutic treatment of cancer.[1] Indeed, clinical trials for the treatment of breast, melanoma, and lung cancers have been highly encouraging, and taxol has recently been approved for the treatment of ovarian and breast cancer.[1g] Consequently, an enormous amount of effort has been directed toward the total synthesis of taxol.[1d−g] Given the complexity of the molecule, it is unlikely that a synthetic source will be competitive with either the natural one or a semisynthetic source from baccatin III (13-deacyltaxol). Furthermore, the sensitive functionality has permited only minor structural modifications of the natural material to date and, hence, only limited access to structure−activity information.[1b,c,e,g] However, simplified analogs that can only be obtained *via* total synthesis can provide further insight into the structure−activity relationships which underlie taxol's therapeutic activity. These efforts may facilitate the discovery of a structurally simplified, synthetically accessible taxol analog which possesses a comparable or superior biological profile.

Critical to the realization of these goals is the discovery of a concise, stereoselective synthesis of a suitably functionalized taxane carbocyclic framework. Several groups have recognized the benefits of initiating the synthesis with a functionalized A-ring, attaching a C-ring, and then completing the taxane ring system **1** by bond closure at C-10, C-11 (e.g., Heck[2] or Kishi−Nozaki[3] reactions) or C-9, C-10 (e.g., pinacol[4] or vinylogous aldol[5] reactions). In order to investigate our own B-ring annelation strategies, we sought a short synthesis of aldehyde **2** to which functionality appropriate for ring closure could be stereoselectively attached at C-2 in a chelation-controlled process,[6] ideally with the carbamate (R = NEt_2) or carbonate (R = O-*i*-Pr) derivatives of **2**. The most straightforward approach to aldehyde **2** is an intermolecular cycloaddition of diene **3** with a 2-(acyloxy)-acrolein **4**. However, 2-(acyloxy)acroleins **4** had not been



previously employed in Diels−Alder cycloaddition reactions, due to the fact that a mild and versatile synthesis of these valuable dienophiles was lacking.[7] Consequently, as our first goal we planned to investigate the preparation and thermolysis of 5-(acyloxy)-4*H*-1,3-dioxins **5** based upon our previous discovery that the analogous 4-alkyl-4*H*-1,3-dioxins undergo facile retrocycloaddition reactions to provide 3-alkylacroleins and formaldehyde.[8] We describe herein the preparation of 2-(acyloxy)-acroleins by this route and their cycloaddition reactions which constitute an exceptionally brief synthesis of taxol A-ring synthons.[9]

The (acyloxy)dioxins **5** could be readily prepared by O-acylation of ketone **6**[10] with a variety of anhydrides (**5a,b,c,e**: 1.3 equiv of RCO_2COR, 2 equiv of NEt_3, 0.2 equiv DMAP, CH_2Cl_2, reflux) or chloroformate/carbamoyl halides (**5d,f,g**: 1.3 equiv of RCOCl, 2 equiv of NEt_3, 1.3 equiv of DMAP, rt). The outstanding reactivity of ketone **6** is noteworthy (cyclohexanone does not undergo O-acylation with acetic anhydride under these conditions)[11]

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(5) (a) Kuwajima, I.; Furukawa, T.; Horiguchi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8277. (b) Kuwajima, I.; Horiguchi, Y.; Morihira, K.; Seto, M. *J. Org. Chem.* **1994**, *59*, 3165. (c) Kuwajima, I.; Horiguchi, Y.; Tsuruta, K.; Waizumi, N.; Nakamura, T. *Synlett* **1994**, 584.

(6) We, *vide infra*, and others have found that these addition reactions can be highly stereoselective, see refs 2b and 5c.

(7) Only one example of this class of compounds, 2-acetoxyacrolein (**4a**, R = Me), has been reported and was prepared in low yield (10%), accompanied by several byproducts and polymer, by treating (acetoxymercurio)pyruvaldehyde diethyl acetal with acetyl chloride; see: (a) Keiko, N. A.; Musorina, T. N.; Kalikhman, I. D.; Voronkov, M. G. *Zh. Org. Khim.* **1979**, *49*, 170. 2-Alkoxyacroleins are known but were anticipated to be inferior dienophiles based on the relative reactivity of 3-alkoxy- *vs* 3-(acyloxy)-3-buten-2-ones; see: (b) Vogel, P.; Tamariz, J. *Helv. Chim. Acta* **1981**, *64*, 188. For a general preparation of 2-alkoxyacroleins, see: (c) Williams, D. R.; Gaston, R. D.; Hoover, J. F. *Synthesis* **1987**, 909. For the $SnCl_4$-catalyzed [4 + 3] cycloaddition of 2-((trimethylsilyl)oxy)acrolein with butadiene, see: (d) Sasaki, T.; Ishibashi, Y.; Ohno, M. *Tetrahedron Lett.* **1982**, *23*, 1693. For a review of 2-substituted acrolein derivatives, see: (e) Keiko, N. A.; Voronkov, M. G. *Russ. Chem. Rev.* **1993**, *62*, 751.

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(9) For recent syntheses of taxane A-ring synthons, see: (a) Kishi, Y.; Kress, M. H. *Tetrahedron Lett.* **1995**, *36*, 4583. (b) Winkler, J. D.; Bhattacharya, S. K.; Liotta, F.; Batey, R. A.; Heffernan, G. D.; Cladingboel, D. E.; Kelly, R. C. *Ibid.* **1995**, *36*, 2211. (c) Tjepkema, M. W.; Wilson, P. D.; Wong, T.; Romero, M. A.; Audrain, H.; Fallis, A. G. *Ibid.* **1995**, *36*, 6039. (d) Koskinen, A. M. P.; Karvinen, E. K. *Tetrahedron* **1995**, *51*, 7555. (e) Wender, P. A.; Wessjohann, L. A.; Peschke, B.; Rawlins, D. B. *Tetrahedron Lett.* **1995**, *36*, 7181. (f) Taber, D. F.; Sahli, A.; Yu, H.; Meagley, R. P. *J. Org. Chem.* **1995**, *60*, 6571.

(10) This was prepared in two steps from tris(hydroxymethyl)-aminomethane hydrochloride; see: Hoppe, D.; Schmincke, H.; Kleemann, H.-W. *Tetrahedron* **1989**, *45*, 687.

(11) However, aldehydes can be converted to the corresponding enol acetates using these conditions, see: Secrist, J. A., III; Cook, S. L.; Cousineau, T. J. *Synth. Commun.* **1979**, *9*, 157.

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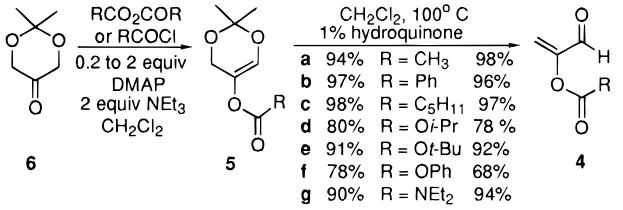
and may reflect a more favorable equilibrium with the enol tautomer and/or a more nucleophilic enol tautomer due to a vinylogous alpha effect.



We were gratified to discover that all of the 5-(acyloxy)-dioxins **5** underwent smooth retrocycloaddition reactions in the presence of 1% hydroquinone upon warming (100 °C) in toluene under an argon atmosphere, or in methylene chloride in a sealed tube, and were complete after 12−24 h as noted by TLC or ^{1}H NMR spectroscopy (toluene-d_8). The resulting 2-(acyloxy)acroleins are reasonably stable compounds and can be purified, if necessary, by column chromatography. However, these compounds polymerize upon standing at room temperature and are best stored at low temperatures (−20 °C).

2-(Acyloxy)acroleins **4** were found to be excellent substrates for Diels−Alder reactions as illustrated by the examples shown in Table 1. Entries a and b demonstrate that these transformations can be conveniently accomplished by generating the dienophile *in situ* from the corresponding acyloxydioxin **5**. Moreover, the stereoselectivity for the reaction of **4b** with cyclopentadiene (entry a) is similar to that observed with methacrolein wherein the methyl group has been found to prefer the *endo* position (76:24, 100 °C).[12] The regioselectivity of the cycloaddition with isoprene is moderate (entry b) but is complete with the silyloxy-substituted dienes shown in entries c and d. The example shown in entry e signifies that (acyloxy)acroleins can also serve as competent heterodienes in cycloadditions with electron rich alkenes under the influence of lanthanide catalysis.[13] Most importantly, optimized conditions for cyclizations with the tetrasubstituted dienes shown in entries f and g were eventually discovered and provide access to highly functionalized taxol A-ring synthons in excellent yields. These cycloadditions were unsuccessful in the absence of Lewis acids at temperatures up to 150 °C. Tin tetrachloride was the most effective of the various Lewis acids examined (e.g., $TiCl_4$, $EtAlCl_2$, BF_3, $MgBr_2$), provided that the presumed bidentate complex generated from the acyloxyacrolein and $SnCl_4$ was soluble at −78 °C. Hence, the more hydrocarbon-rich (acyloxy)acroleins **4c** and **4d** were preferred. Varying amounts (10−15%) of a product derived from heterocycloaddition with the aldehyde moiety of the acycloxyacroleins was observed when CH_2Cl_2 was the solvent, although this side product could be largely suppressed when toluene was employed as a cosolvent.

In summation, we have developed the first general and efficient synthesis of 2-(acyloxy)acroleins and have documented the utility of these valuable reactants in Diels−Alder cycloaddition reactions. Functionalized taxol A-rings are now directly accessible and, moreover, can be further modified by stereoselective addition reactions with organometallic reagents (see the supporting information). Thus, this methodology facilitates the preparation of compounds suitable for the elaboration of the complete taxane framework and related taxol analogs. These possibilities are under active investigation.

Table 1. Cycloadditions of 2-Acyloxyacroleins

entry	diene/hetero-dienophile	acyloxy-acrolein	conditions	adduct	% yield
a	5 equiv	5b[a]	CH_2Cl_2, 120°C, 22 h	+ endo 28	68
b	5 equiv	5b[a]	CH_2Cl_2, 120°C, 20 h	regioisomer 27	71
c	1.5 equiv	4b	CH_2Cl_2, 105°C, 20 h		69
d	2 equiv	4c	C_7H_8, 40°C, 20 h		85
e	10 equiv	4b	CH_2Cl_2, .05 equiv Yb(fod)$_3$, 26°C, 28 h		78
f	.9 equiv[b]	4c	3:1 C_7H_8-CH_2Cl_2, 1.1 equiv $SnCl_4$, -78°C, 3 h		95
g	.9 equiv[c]	4d	3:1 C_7H_8-CH_2Cl_2, 1.1 equiv $SnCl_4$, -78°C, 48 h		90

[a] Dienophile generated *in situ*. [b] Prepared in one-pot from 3-bromo-2,4-dimethyl-1,3-pentadiene:[14] (1) 2 equiv of *t*-BuLi, −78 °C; (2) 1.1 equiv of thienyl-Cu(CN)Li; (3) 0.95 equiv of methyl 4-iodobutyrate, −78 to 0 °C; 88%. [c] Prepared from 3-bromo-2,4-dimethyl-1,3-pentadiene:[14] (1) 2 equiv of *t*-BuLi, −78 °C; 5 equiv of oxirane; 90%; (2) NEt_3, DMAP, $(C_5H_{11}CO)_2O$; 96%.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of compounds **4a**−**g**, **5a**−**g**, the cycloadducts in Table 1, and the product obtained from treatment of cycloadduct **g** with PhMgBr (10 pages).

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