Synthesis of (*Z*)-2-Acyl-2-enals via Retrocycloadditions of 5-Acyl-4-alkyl-4*H*-1,3-dioxins: Application in the Total Synthesis of the Cytotoxin (±)-Euplotin A

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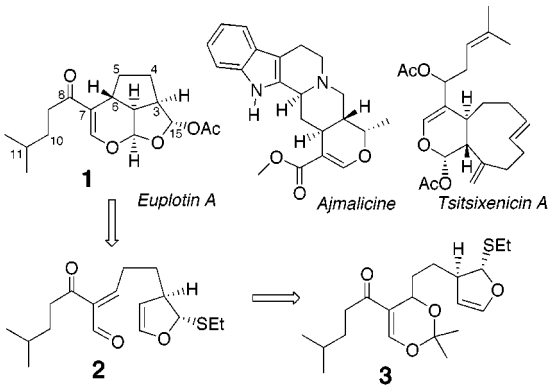
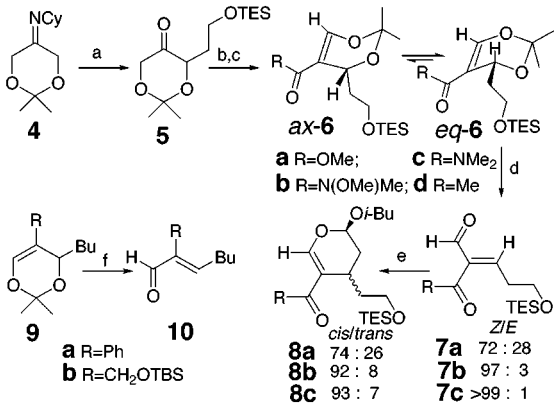
The 5-acyl-3,4-dihydro-2*H*-pyran substructure and its reduced analogue are common to a variety of natural products which possess a diverse array of biological properties (Scheme 1). A well-established strategy for the construction of this key structural unit is via the heterocycloaddition reaction of an unsaturated carbonyl compound,[1] preferably as an activated 3-*acyl*-1-oxadiene, with an alkene. Many conceivable implementations of this viable approach require the stereocontrolled syntheses of (*Z*)-2-acyl-2-enals. For example, a projected synthesis of the cytotoxin euplotin A (**1**)[2] might proceed through an *exo* cycloaddition (vide infra) of the dihydrofuran moiety with the (*Z*)-2-acyl-2-enal **2**. Unfortunately, methodology for the stereoselective generation of 2-acylenals under the requisite mild conditions is unavailable.[3] We have recently demonstrated that 5-acyl-4*H*-1,3-dioxins are viable precursors to 2-acyl*propenals* via facile retrocycloaddition reactions.[4a] The extension of this protocol to the stereoselective preparation of the more highly functionalized (*Z*)-2-acylenals and its application in the first total synthesis of (±)-euplotin A are reported herein.

Scheme 1



Our initial objective was to examine the stereoselectivity of the retrocycloaddition as a function of the acyl substituent of the 1,3-dioxin **6** (Scheme 2). To that end, the cyclohexyl imine derivative of commercially available 4*H*-1,3-dioxin-5-one was metalated and alkylated to provide the 6-alkyldioxinone **5**. Regioselective conversion of ketone **5** to the corresponding less-substituted enol triflate was accomplished by kinetic deprotonation with NaHMDS in the presence of *N*-phenyltrifluoromethanesulfonimide. This enol triflate was then subjected to a variety of palladium-catalyzed carbon monoxide insertion reactions (**6a**,**b**,**c**) as well as a Heck reaction with ethyl vinyl ether (**6d**) to deliver the desired 5-acyl-4-alkyl-4*H*-1,3-dioxins.

Scheme 2[a]



[a] Reagents: (a) $LiNEt_2$; ICH_2CH_2OTES, −78 °C to rt, 2 h, 87%; (b) NaHMDS, $PhNTf_2$, −78 °C to rt, 2 h, 93%; (c) $Pd(OAc)_2$, dppp, *i*-Pr_2NEt, K_2CO_3, CO, THF, MeOH, 86% for **6a**; $Pd(OAc)_2$, dppp, *i*-Pr_2NEt, DMF, HN(OMe)Me/$HNMe_2$, 81 and 90% for **6b** and **6c**, respectively; $Pd(OAc)_2$, ethyl vinyl ether, DMSO, 48 h, H_3O^+, 93% for **6d**; (d) $CDCl_3$, 50 °C, 36 h, 99% for **7a**; toluene, 90 °C, 2 h, 93% for **7b**; toluene, 100 °C, 1 h, 85% for **7c**; (e) 5 equiv *iso*-butyl vinyl ether, CH_2Cl_2, rt, 24 h, 81% for **8a**; 12 kbar, 18 h (71 and 85% for **8b** and **8c**, respectively; (f) toluene, 110 °C, 8 h, 99% for **9a**; toluene, 95 °C, 2 h, 95% for **9b**.

On the basis of previous retrocycloadditions of dioxins analogous to **6** which lacked the 5-acyl substituent,[4b] we anticipated that the retrocycloaddition of **6** would proceed preferentially through the boat conformer *eq*-**6** rather than the boat conformer *ax*-**6** which suffers from a flagpole−flagpole interaction with the O(3) axial lone pair. However, in this case, the preference for *eq*-**6** might be attenuated by an $A^{1,2}$ interaction between the acyl substituent and the C(4) equatorial substituent. Indeed, we were pleased to discover that the amides **6b** and **6c** afforded the desired (*Z*)-2-acyl-2-enal with high or complete stereoselectivity, respectively, although the more facile (50 °C) retrocycloaddition of ester **6a** was less stereoselective. Moreover, each of the acylenals could be converted by subsequent treatment with *iso*-butyl vinyl ether to an *endo*/*exo* mixture of the targeted 5-acyl-3,4-dihydro-2*H*-pyrans **8**. However, further experimentation revealed that the *Z*/*E* stereoisomeric ratios for enals **7** are likely the result of thermodynamically controlled isomerizations. Thus, the amide **7b** was photoisomerized (Hanovia 500 W, toluene, 3 h) to a mixture of isomers (*Z*:*E* = 80:20) which upon heating (toluene, 1 h) afforded a ratio of isomers (*Z*:*E* = 96:4) nearly identical to that initially obtained.[5] It would appear that 2-acylenals are particularly prone to thermal isomerization[6] since the dioxins **9** all afforded a single stereoisomer of enals **10** and photoisomerized stereoisomeric mixtures of enals **10** remained

(1) For reviews, see: (a) Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (c) Waldmann, H. *Synthesis* **1994**, 535. (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (e) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1. (f) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304.

(2) In addition to euplotin A, two additional cytotoxic natural products, euplotin B ($\Delta^{10,11}$) and euplotin C (C-8 CO = CH_2), were isolated from the ciliated protist *Euplotes crassus* and were shown to inhibit the cell division of or kill the related marine ciliates *E. vannus* and *E. minuta* via cell-to-cell encounters, thereby imparting a competitive advantage to the former ciliate, see: (a) Dini, F.; Guella, G.; Giubbilini, P.; Mancini, I.; Pietra, F. *Naturwissenschaften* **1993**, *80*, 84. (b) Guella, G.; Dini, F.; Tomei, A.; Pietra, F. *J. Chem. Soc. P. T. 1* **1994**, *17*, 161. (c) Guella, G.; Dini, F.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 710.

(3) For the preparation of alkylidenemalonaldehydes, see: (a) Tietze, L.-F.; Glusenkamp, K.-H.; Holla, W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 793. (b) Arnold, Z.; Kryshtal, G. V.; Kral, V.; Dvorak, D.; Yanovskaya, L. A. *Tetrahedron Lett.* **1988**, *29*, 2861. For the in situ generation 2-(trichloroacetyl)-2-enals, presumably as a mixture of stereoisomers, see: (c) Tietze, L. F.; Meier, H.; Nutt, H. *Chem. Ber.* **1989**, *122*, 643. (d) Tietze, L. F.; Meier, H.; Nutt, H. *Liebigs Ann. Chem*. **1990**, 253.

(4) (a) Funk, R. L.; Fearnley, S. P.; Gregg, R. *Tetrahedron* **2000**, *56*, 10275. (b) Funk, R. L.; Bolton, G. L. *J. Am. Chem. Soc.* **1988**, *110*, 1290.

(5) In addition, oxidation (Dess−Martin, rt, 1 h) of the known methyl *E*-2-(hydroxymethyl)-2-pentenoate (Charette, A. B.; Côté, B.; Monroc, S.; Prescott, S. *J. Org. Chem.* **1995**, *60*, 6888) gave rise to a mixture of stereoisomers (*Z*:*E* = 70:30) of methyl 2-formyl-2-pentenoate.

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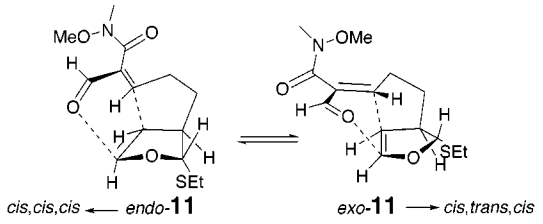
Scheme 3

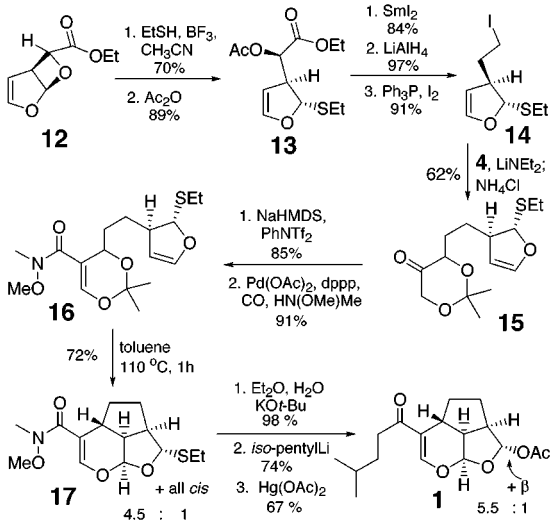


unchanged upon heating in toluene. Finally, it should be noted that the ketoenal (**7**, R = Me) derived from thermolysis of dioxin **6d** could not be isolated and led to a complex mixture of dimerization and enolization products. Moreover, a mixture of four products derived from *endo*/*exo* cycloaddition with both the enal as well as the enone heterodiene moieties was obtained upon in situ trapping with *iso*-butyl vinyl ether.

Having completed our preliminary studies, we turned to the application of this methodology in the total synthesis of euplotin A. It was now clear that the keto acylenal **2** would be an unsuitable cycloaddition substrate, and hence, we focused on the preparation/generation of the 2-(*N*-methoxy-*N*-methylamido)enal **11** (Scheme 3). Although the (*Z*)-2-acyl-2-enal stereochemistry of **11** was now assured, the stereoselectivity of the subsequent heterocycloadditon reaction was not. Thus, an *endo* transition state would lead to the significantly less strained all-*cis* isomer rather than the stereochemistry found in euplotin A which would be derived from an *exo* transition state. Molecular mechanics calculations predict an energy difference for these two cycloaddition products of 6.4 kcal/mol, and the strain present in euplotin A is reflected, in part, by calculated angles for C(5−6−7) and C(4−3−15) of 126° and 118°, respectively.[7] Nonetheless, it was hoped that an early, highly asynchronous transition state[8] as well as the *cis*-enol ether moiety[1] would combine to favor the *exo* transition state.

The synthesis of the precursor to the acylenal **11**, dioxin **16**, was initiated with the preparation of the known Paterno−Buchi photocycloadduct **12**[9] (Scheme 4). Stereoselective Lewis acid-catalyzed ring opening of the acetal moiety of **12** followed by acylation of the resulting hydroxyl gave the dihyrofuran **13**. Samarium diiodide-mediated reductive removal of the acetoxy functionality followed by reduction (LAH) of the remaining ester moiety gave an alcohol which was converted to iodide **14**. The aza-enolate derivative of imine **4** was alkylated with iodide **14** to afford the dioxinone **15** which was converted to the pivotal acyldioxin **16** using the previously established protocol. We were

Scheme 4



pleased to discover that the acyl dioxin **16** underwent a smooth retrocycloaddition, cycloaddition[10] to deliver a 4.5:1 mixture of 5-acyldihyropyrans, the major isomer of which possesses the desired stereochemical relationship as indicated by the diagnostic ^{1}H NMR proton coupling constants and NOE experiments. This assignment was confirmed upon single-crystal X-ray analysis of the major isomer. Indeed, the angles for C(5−6−7) and C(4−3−15), 126.4° and 117.6°, respectively, were similar to those calculated (vide supra).

It was with some trepidation that we examined the remaining two functional group transformations upon the potentially labile, strained acetal **17**, namely, introduction of the isopentyl ketone and acetal functionalities. While the amide **17** could be directly converted to the isopentyl ketone upon treatment with isopentyllithium, the yield (39%) was significantly reduced due to a competing conjugate addition reaction. Consequently, the amide was hydrolyzed to the corresponding carboxylic acid which could be cleanly converted to the desired ketone. Fortunately, the thioacetal moiety[11] of this product could be selectively activated for exchange with an acetoxy substituent by treatment with mercuric acetate to afford racemic euplotin A (**1**) as well as the β-anomer (5.5:1). The spectral properties of the synthetic material were identical to those found for authentic euplotin A.

In summary, we have developed a mild and versatile protocol for the preparation of (*Z*)-2-acyl-2-enals via retrocycloaddition reactions of the easily available 5-acyl-4-alkyl-4*H*-1,3-dioxins. This methodology facilitated a concise total synthesis of the strained cytotoxin euplotin A. The exploitation of this strategy in the total syntheses of other natural products which also embody 5-acyl-3,4-dihydro-2*H*-pyran substructures or close relatives thereof is now underway.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Thermolysis of dioxin **6b** in the presence of an equivalent amount of an analogous dioxin possessing a 1,1-dideuteriohexyl substituent instead of the 2-(triethylsilyloxy)ethyl substituent gave enal **7b** without incorporation of deuterium and an enal derived from the deuterated dioxin which was fully deuterated in the allylic position, thereby ruling out an enolization pathway for the *Z*/*E* isomerization.

(7) Indeed, it has been suggested that this strain accounts for the biological properties of this natural product by facilitating the ring opening to aldehyde containing mono- or bicyclic compounds (see ref 2).

(8) This prediction was tenuous, at best, based upon calculations using PCMODEL (v 6.0). We employed bond order parameters of 0.1 and 0.9 for the forming C−O and C−C bonds, respectively, and calculated an energy difference of 0.9 kcal/mol favoring the *exo* transition state. However, if the bond orders used by Tietze (based upon preliminary AM1 calculations: 0.1 C−O, 0.7 C−C; Tietze, L. F.; Geissler, H.; Fennen, J.; Brumby, T.; Brand, S.; Schulz, G. *J. Org. Chem.* **1994**, *59*, 182) for a more synchronous heterocycloaddition were used, then the *exo* transition state preference was reduced to 0.5 kcal/mol. Even more disconcerting was the calculation of the *exo* transition structure for the stereoisomeric *E*-2-acyl-2-enal heterodiene (2.8 kcal/mol *lower* than *exo*-*Z*, C−O 0.1, C−C 0.9). This alternative pathway to the undesired all-*cis* cycloadduct was an especially serious concern if the rate of *Z*/*E* isomerization is faster than that of the cycloaddition.

(9) Zamojski, A.; Kozluk, T. *J. Org. Chem.* **1977**, *42*, 1089. Initial attempts in our laboratory to identify a chiral auxiliary for the photocycloaddition of furan with the derivatized chiral glyoxylate have been unrewarding (8-phenylmenthol; 57:43), see also: Inoue, Y. *Chem. Rev.* **1992**, *92*, 741.

(10) The intermediate acylenal **11** was not detected during the course of the reaction using either TLC or ^{1}H NMR spectroscopic analysis.

(11) However, the analogous methyl ether gave rise to ring-opened products in several attempts to effect a similar exchange.