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Preparation of 2-Alkyl- and 2-Acylpropenals from 5-(Trifluoromethanesulfonyloxy)-4*H*-1,3-dioxin: A Versatile Acrolein α-Cation Synthon

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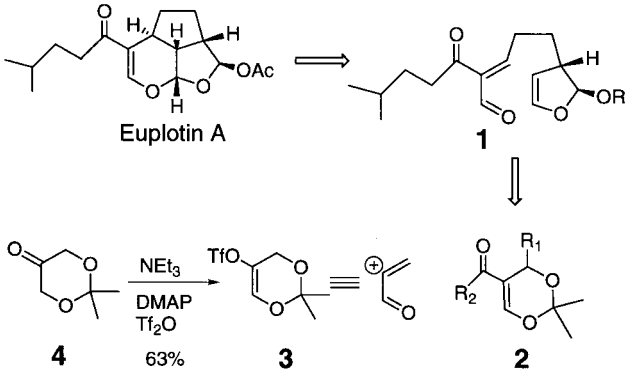
Abstract—5-(Trifluoromethanesulfonyloxy)-4*H*-1,3-dioxin (**3**) participates in a variety of nucleophilic substitution reactions with cuprate reagents or in palladium catalyzed cross-coupling reactions to provide 5-substituted-4*H*-1,3-dioxins **5**. Upon thermolysis, these compounds undergo facile retrocycloaddition reactions to generate the corresponding 2-substituted acroleins which, if necessary, can be trapped in situ with dienes or heterodienophiles. In particular, the heretofore unknown 2-acylacroleins can be generated using this methodology and trapped with enol ethers to afford 5-acyl-3,4-dihydro-2*H*-pyrans (**6g**,**h**), a substructural unit common to many natural products. © 2000 Elsevier Science Ltd. All rights reserved.

The Diels–Alder reaction is arguably the premier reaction for the construction of six-membered carbocycles and heterocycles. Nevertheless, Diels–Alder chemistry is not without restrictions, particularly in matching frontier orbitals of the reacting partners to achieve acceptable stereo- and regioselectivity. Thus, the further development of this reaction rests, in part, on the discovery of new dienes/dienophiles which is often stimulated by natural product total synthesis endeavors. For example, a hypothetical approach to the cytotoxic agent euplotin A, one of many natural products which embodies an 5-acyl-3,4-dihydro-2*H*-pyran substructural unit,[1] might proceed quite efficiently through an intramolecular cycloaddition of the activated heterodiene moiety of **1** with the cyclic enol ether.[2] However, methodology capable of stereoselectively generating the labile 2-acyl-β-substituted acrolein heterodiene unit of **1** under the mild conditions most likely required for the successful execution of this plan is lacking.[3] Since we have previously demonstrated that 4-alkyl[4a] and 5-(acyloxy)[4b] substituted 4*H*-1,3-dioxins undergo smooth retrocycloaddition at 90–100°C to the corresponding 3-alkyl- and 2-(acyloxy)acroleins, respectively, we considered the preparation of the 5-acyl-dioxin **2** and its thermal transformation to **1** as well as additional substrates for similar applications of this type of intramolecular heterocycloaddition reaction.[5] As a first step toward this goal, we report herein the preparation of the triflate **3**, document its utility as a novel acrolein α-cation synthon, and demonstrate that 5-acyl-4*H*-1,3-dioxins are viable precursors to the heretofore unknown 2-acylacroleins.[6]



The triflate **3** was prepared from ketone **4**[7] following a procedure similar to the one previously reported for the preparation of 2-(acyloxy)-4*H*-1,3-dioxins.[4b] Thus, addition of triflic anhydride to a mixture of ketone **4**, triethylamine (1 equiv.), and DMAP (1 equiv.) in CH_2Cl_2 (0°C to −23°C, 24 h), followed by evaporation of the solvent and purification of the residue by flash chromatography afforded pure triflate **3**. Triflate **3** is stable for extended periods of time if kept below 0°C, but does undergo a quantitative and especially facile cycloreversion upon refluxing in benzene-d_6 (1.5 h, NMR analysis) to afford 2-(trifluoromethanesulfonyloxy)-2-propenal.

The triflate **3** was subjected to a variety of nucleophilic substitution reactions which commonly employ vinyl or aryl triflates[8] as starting materials. As shown in Table 1, triflate **3** is no exception and participates in cuprate reactions

Keywords: hetero Diels–Alder reaction; retrocycloaddition; 2-substituted acroleins.

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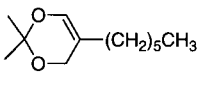
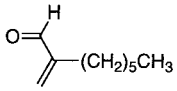
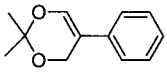
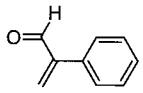
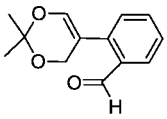
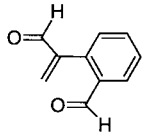
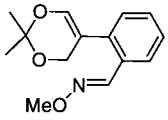
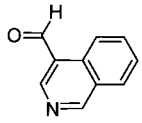
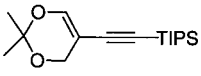
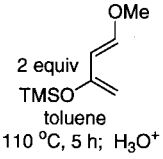
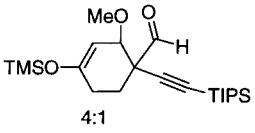
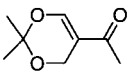
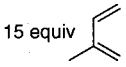
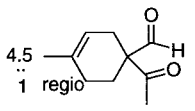
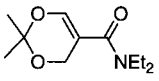
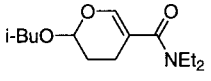
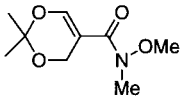
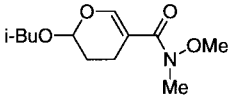
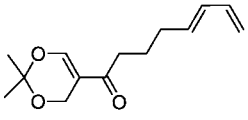
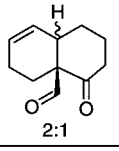
Table 1. Preparation of 5-substituted 4*H*-1,3-dioxins from triflate **3** and retrocycloaddition/cycloaddition reactions

Entry	Coupling Conditions	Product **5**	% Yield	Thermolysis Conditions	Product **6**	% Yield
a	2.5 equiv Hex_2CuLi THF, -20 °C, 20 h		76	$CDCl_3$ 115 °C, 3 h		79
b	.01 equiv $Pd_2(dba)_3$ .08 equiv $AsPh_3$ 1.2 equiv $PhSnBu_3$ NMP, rt, 60 h		60	C_7D_8 130 °C, 1.2 h		97 (dimer)
c	.05 equiv $Pd(PhCN)_2Cl_2$ .1 equiv $AsPh_3$ 1.8 equiv Cs_2CO_3 1.5 equiv $ArB(OH)_2$ DMFTHF/H_2O, rt, 14 h		88	$CDCl_3$ 130 °C, 48 h		88
d	product of entry *c* $MeONH_3Cl$, pyridine 4 A sieves		89	*o*-dichlorobenzene 130 °C, 1 h		96
e	.03 equiv $Pd(PPh_3)_4$ .05 equiv CuI 2 equiv TIPS acetylene Et_2NH, rt, 36 h		82	 2 equiv toluene 110 °C, 5 h; H_3O^+	 4:1	100
f	5 equiv ethyl vinyl ether 2 equiv NEt_3 .03 equiv $Pd(OAc)_2$ DMSO, rt, 24 h; H_3O^+		67	 15 equiv C_6H_6, 78 °C, 48 h	 4.5 : 1 regio	
g	.075 equiv $Pd(OAc)_2$ .15 equiv PPh_3 1 atm CO, 2 equiv NEt_3 5:1 DMF/Et_2NH, rt, 24 h		60	 80 °C, 48 h		92
h	.075 equiv $Pd(OAc)_2$ .075 equiv dppp 1 atm CO, 2 equiv NEt_3 4:1 DMF/MeONHMe, rt, 4 h		50	 80 °C, 48 h		70
i	product of entry *h* 7-lithio-1,3-hexadiene Et_2O, 0 °C, 1h		60	C_6D_6, 70 °C, 14 h	 2:1	80

(entry a) as well as palladium catalyzed cross-coupling reactions with aryl stannanes (entry b), aryl boronic acids (entry c), terminal acetylenes (entry e), enol ethers (entry f) and carbon monoxide insertions (entries g and h). Moreover, the products of some of these reactions were shown to be useful for the preparation of additional substrates for subsequent retrocycloaddition reactions, for example, the conversions of aldehyde **5c** to oxime ether **5d** and Weinreb-type amide **5h** to ketone **5i**.

The retrocycloaddition reaction for each of the dioxins **5** was first examined in the absence of any diene or heterodienophile trapping agent. Thus, the thermolyses of dioxins **5a**,**b**,**c** were uneventful and cleanly transformed (NMR analysis) to the corresponding 2-substituted acroleins **6a**,**b**,**c**, respectively. However, concentration of the retrocycloaddition product **6b** afforded the corresponding known dimer.[9b] It was gratifying to observe that oxime ether **5d** was directly converted to the desired quinoline carbaldehyde **6d** upon heating in *ortho*-dichlorobenzene. An electrocyclization of the intermediate 2-arylacrolein and concomitant elimination of methanol may be the operative pathway. Not unexpectedly, thermolysis of **5e** gave the corresponding dimer derived from a hetero Diels–Alder reaction.[9] However, the intermediate 2-alkynylacrolein could be efficiently intercepted with Danishefsky's diene to afford the adduct **6e** as a 4:1 mixture of stereoisomers. Surprisingly, the 2-acylacrolein derived from the thermolysis of diethylamide **5g** was stable and showed no tendency to dimerize, although similar treatment of ketone **5f** and amide **5h** afforded polymer. However, each of the intermediate 2-acylacroleins of entries f, g, h could be

trapped, either as the Diels–Alder adduct **6f** derived from cyclization with isoprene or, more importantly, the products **6g** and **6h** produced from heterocycloaddition with isobutyl vinyl ether. Finally, the feasibility of performing a retrocycloaddition–intramolecular cycloaddition sequence is documented in entry i, although the stereoselectivity of the reaction is poor and presumably reflects the competition by each of the carbonyl groups for secondary orbital interaction with the diene.[10]

In summation, the synthetic equivalency of (trifluoromethanesulfonyloxy)dioxin **3** with an acrolein α-cation synthon has been demonstrated in several two-step alkylation, retrocycloaddition processes. A valuable aspect of this methodology is that the sensitive acrolein functionality can be slowly generated under mild and neutral conditions which are advantageous for cycloaddition reactions employing reactive/labile dienophiles. Indeed, a new class of 1,1-diactivated alkenes, 2-acylacroleins, is now available for synthesis applications. These possibilities as well as those enumerated above are under active investigation.

Experimental

All non-aqueous reactions were carried out under argon using standard techniques for the exclusion of air and moisture. All solvents used were obtained anhydrous, either by appropriate distillation or by direct purchase. Where necessary, reagents were dried and purified according to the recommended methods. Thin layer chromatography was carried out on Analtech Uniplate Silica Gel HLF 250 μM glass plates. Flash chromatography was performed over ICN Siliech 32–36D 6A silica. Melting points were determined on an electrothermal apparatus and are uncorrected. Infra-red absorption spectra were recorded on a Perkin–Elmer FT-1600 instrument, as thin films, $CHCl_3$ solutions, or KBr discs. Both ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 instrument at 200 and 50 MHz respectively, referenced to the appropriate deuterium lock. *J* values are given in Hz. Mass spectra were measured on Kratos MS-25 (CI, isobutane) and Kratos MS9/50 (EI, 70 eV; +FAB, xenon) instruments. Percentile figures refer to relative intensity as a proportion of the base peak.

2,2-Dimethyl-5-trifluoromethanesulfonyloxy-4*H*-1,3-dioxin (3). To a stirred solution of ketone **4** (1.00 g, 7.68 mmol), triethylamine (1.07 mL, 7.68 mmol) and DMAP (0.939 g, 7.68 mmol) in CH_2Cl_2 (15 mL) cooled to 0°C was added dropwise neat triflic anhydride (1.29 mL, 7.68 mmol). After 24 h at −23°C, the dark brown solution was partially reduced in vacuo to yield a mobile black residue. Immediate further purification by flash chromatography (silica ratio 20:1 of total reagent mass, pentane/CH_2Cl_2 gradient elution 9:1 to 4:1) yielded a colorless oil (1.27 g, 63%). R_f: 0.18 (pentane/CH_2Cl_2 7:1); ^1H NMR: (200 MHz, $CDCl_3$) δ 6.76 (t, *J*=1.3 Hz, 1H), 4.31 (d, *J*=1.4 Hz, 2H), 1.45 (s, 6H); ^{13}C NMR: (50 MHz, $CDCl_3$) δ 137.8, 129.1, 115.7, 100.9, 58.6, 23.0; IR: (neat) ν_{max} 3001.1, 1688.2, 1425.8, 1215.6, 1140.3, 1118.6 cm^{-1}; MS: (EI) *m/z* 262 $[M]^+$ 8.1%; HRMS: (EI) *m/z* 262.0130 (262.0123 calcd for $C_7H_9O_5F_3S$).

2,2-Dimethyl-5-hexyl-4*H*-1,3-dioxin (5a). To a stirred suspension of CuI (370 mg, 1.94 mmol) in dry THF (4 mL), cooled to 0°C, was added dropwise a 2.0 M solution of *n*hexyl lithium in hexanes (1.40 mL, 2.80 mmol). After 20 min, the black suspension was cooled to −15°C and a solution of triflate **3** (150 mg, 0.57 mmol) in dry THF (2 mL) added dropwise. After 20 h, the mixture was filtered over Florisil with hexanes and reduced in vacuo to yield a pale yellow oil. Further purification by flash chromatography (silica ratio 50:1, pentane/Et_2O 50:1) yielded a colorless oil (86.5 mg, 76%). R_f: 0.31 (pentane/Et_2O 40:1); ^1H NMR: (200 MHz, $CDCl_3$) δ 6.18 (s, 1H), 4.06 (s, 2H), 1.82 (bt, *J*=6.8 Hz, 1H), 1.38 (s, 6H), 1.30–1.15 (bm, 8H), 0.82 (t, *J*=6.5 Hz, 3H); ^{13}C NMR: (50 MHz, $CDCl_3$) δ 135.8, 111.4, 98.0, 61.3, 31.3, 28.9, 28.5, 27.5, 23.8, 22.2, 13.5; IR: (neat) ν_{max} 2926.4, 1675.8, 1233.5, 1125.0 cm^{-1}; MS: (CI) *m/z* 199 $[M+H]^+$ 52%; HRMS: (EI) *m/z* 198.1634 (198.1620 calcd for $C_{12}H_{22}O_2$).

2,2-Dimethyl-5-phenyl-4*H*-1,3-dioxin (5b). To a stirred solution of triflate **3** (550.5 mg, 2.10 mmol) in *N*-methyl pyrrolidinone (10 mL), previously purged with a stream of argon, was added triphenylarsine (32 mg, 0.168 mmol) and $Pd_2(dba)_3{\cdot}CHCl_3$ (22 mg, 0.021 mmol) at rt. After 10 min, Bu_3SnPh (680 μL, 2.10 mmol) was added. After 45 h, further Bu_3SnPh (170 μL, 0.525 mmol) and $Pd_2(dba)_3.CHCl_3$ (5 mg, 0.005 mmol) were added. After 50 h total, water (25 mL) was added and the resultant mixture extracted with hexanes (2×25 mL). The combined organic fractions were washed with water (25 mL), stirred over sat. KF (50 mL) for 30 min, washed with brine (25 mL), dried ($MgSO_4$), filtered and reduced in vacuo to yield a black oil. Further purification by flash chromatography (silica ratio 30:1, benzene/Et_20 97:3) yielded a colorless solid (100 mg, 75%). R_f: 0.64 (hexane/EtOAc 19:1); ^1H NMR: (200 MHz, $CDCl_3$) δ 7.3–7.1 (m, 5H), 6.82 (bs, 1H), 4.46 (d, *J*=1.5 Hz, 2H), 1.40 (s, 6H); ^{13}C NMR: (50 MHz, $CDCl_3$) δ 138.8, 136.0, 129.0, 126.8, 124.0, 111.6, 98.9, 60.1, 23.9; IR: (neat) ν_{max} 2993.2, 2844.4, 1645.5, 1211.4, 1135.3 cm^{-1}; MS: (EI) *m/z* 190 $[M]^+$ 16.3%; HRMS: (EI) *m/z* 190.0998 (190.0994 calcd for $C_{12}H_{14}O_2$).

2,2-Dimethyl-5-(2-formylphenyl)-4*H*-1,3-dioxin (5c). To a solution of triflate **3** (200 mg, 0.763 mmol), 2-formylphenyl boronic acid (172 mg, 1.144 mmol), triphenylarsine (23.4 mg, 0.076 mmol) and Cs_2CO_3 (447 mg, 1.373 mmol) in dimethylformamide/THF/H_2O 1:1:1 (9 mL), was added, in one portion, bis(benzonitrile) palladium (II) chloride (14.6 mg, 0.0381 mmol) with stirring at rt. After 14 h, water (20 mL) was added and the resultant mixture extracted with Et_2O (4×20 mL). The combined organic fractions were dried ($MgSO_4$), filtered and reduced in vacuo to yield a pale brown oil. Further purification by flash chromatography (silica ratio 75:1, hexane/EtOAc gradient elution 19:1 to 9:1) yielded a colorless oil, (147.1 mg, 88%). R_f: 0.32 (hexane/EtOAc 6:1); ^1H NMR: (200 MHz, $CDCl_3$) δ 10.32 (s,1H), 7.94 (dd, *J*=7.7, 0.6 Hz, 1H), 7.57 (tdd, *J*=7.6, 1.4, 0.9 Hz, 1H), 7.37 (m, 2H), 6.38 (m, 1H), 4.48 (m, 2H), 1.54 (s, 6H); ^{13}C NMR: (50 MHz, $CDCl_3$) δ 192.2, 142.3, 139.8, 135.2, 134.0, 130.2, 129.1, 127.9, 109.2, 99.2, 62.0, 24.1; IR: (neat) ν_{max} 2993.4, 1689.4, 1211.9, 1133.9 cm^{-1}; MS: (EI) *m/z* 218 $[M]^+$ 2.5%; HRMS: (EI) *m/z* 218.0952 (218.0943 calcd for $C_{13}H_{14}O_3$).

2,2-Dimethyl-5-[2-(methoxyiminyl)phenyl]-*4H*-1,3-dioxin (5d). To a suspension of aldehyde **5c** (21.8 mg, 0.10 mmol) and 4 Å mol. sieves (35 mg) in pyridine (0.5 mL), was added methoxyamine hydrochloride (9.6 mg, 0.115 mmol) with stirring at rt. After 80 min, the solvent was removed in vacuo, the residue taken up in CH_2Cl_2, filtered through a plug of silica, and evaporated. Further purification by flash chromatography (silica ratio 60:1, hexane/EtOAc 19:1) yielded a colorless oil (21.9 mg, 89%). R_f: 0.38 (hexane/EtOAc 9:1); ^{1}H NMR: (200 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.84 (dd, J=7.6, 2.0 Hz, 1H), 7.4–7.15 (m, 3H), 6.37 (s, 1H), 4.35 (d, J=1.5 Hz, 2H), 3.96 (s, 3H), 1.52 (s, 6H); ^{13}C NMR: (50 MHz, $CDCl_3$) δ 147.9, 141.0, 136.2, 131.1, 130.0, 129.9, 127.9, 126.9, 110.5, 98.8, 62.0, 61.8, 24.0; IR: (neat) ν_{max} 2993.0, 2938.4, 1657.0, 1052.6 cm^{-1}; MS: (EI) m/z 247 $[M]^+$ 5.5%; HRMS: (EI) m/z 247.1204 (247.1208 calcd for $C_{14}H_{17}NO_3$).

2,2-Dimethyl-5-(triisopropylsilylethynyl)-4*H*-1,3-dioxin (5e). To a stirred solution of triflate **3** (166.2 mg, 0.634 mmol) in diethylamine (3 mL), previously purged with a stream of argon, was added triisopropylsilylacetylene (284 μL, 1.27 mmol), CuI (6.0 mg, 0.032 mmol) and $Pd(PPh_3)_4$ (22 mg, 0.019 mmol) at rt. After 32 h, water (20 mL) was added and the resultant mixture extracted with Et_2O (4×20 mL). The combined organic fractions were dried ($MgSO_4$), filtered and reduced in vacuo to yield a black oil. Further purification by flash chromatography (silica ratio 100:1, hexane/EtOAc 50:1) yielded a colorless oil (152.4 mg, 82%). R_f: 0.60 (hexane/EtOAc 19:1); ^{1}H NMR: (200 MHz, $CDCl_3$) δ 6.82 (s, 1H), 4.18 (s, 2H), 1.43 (s, 6H), 1.03 (bs, 21H); ^{13}C NMR: (50 MHz, $CDCl_3$) δ 148.2, 101.9, 99.5, 96.4, 91.4, 60.8, 24.1, 18.2, 10.8; IR: (neat) ν_{max} 2942.8, 2865.3, 2140.5, 1632.8, 1232.8 cm^{-1}; MS: (CI) m/z 295 $[M+H]^+$ 47.7%; HRMS: (EI) m/z 294.2003 (294.2015 calcd for $C_{17}H_{30}O_2Si$).

5-Acetyl-2,2-dimethyl-*4H*-1,3-dioxin (5f). To a solution of triflate **3** (525 mg, 2.0 mmol) in dimethyl sulfoxide (15 mL), was added sequentially ethyl vinyl ether (957 μL, 10.0 mmol), triethylamine (558 μL, 4.0 mmol) and $Pd(OAc)_2$ (13.5 mg, 0.06 mmol) with stirring at rt. After 24 h, the mixture was cooled to 0°C, ice water (75 mL) was added and the resultant mixture extracted with Et_2O (4×50 mL). The combined organic fractions were dried ($MgSO_4$), filtered and reduced in vacuo to yield a brown oil, the intermediate enol ether (^{1}H NMR: (200 MHz, $CDCl_3$) δ 6.93 (bs, 1H), 4.27 (d, J=1.4 Hz, 2H), 3.86 (d, J=2.7 Hz, 1H), 3.76 (q, J=7.0 Hz, 2H), 3.66 (d, J=2.8 Hz, 1H), 1.41 (s, 6H), 1.27 (t, J=7.0 Hz, 3H). The residue was taken up in $CHCl_3$ (15 mL), water was added (5 drops), and the resultant mixture stirred at rt. After 24 h, solvent was removed in vacuo to yield a brown oil. Further purification by flash chromatography (silica ratio 30:1, pentane/Et_2O 3:1) yielded a colorless oil (210.5 mg, 67%). R_f: 0.18 (pentane/Et_2O 3:1); ^{1}H NMR: (200 MHz, $CDCl_3$) δ 7.50 (s, 1H), 4.37 (s, 2H), 2.13 (s, 3H), 1.41 (s, 6H); ^{13}C NMR: (50 MHz, $CDCl_3$) δ 195.1, 154.3, 115.3, 101.3, 77.2, 58.0, 23.9; IR: (neat) ν_{max} 2995, 1656, 1629, 1242 cm^{-1}; MS: (EI) m/z 156 $[M]^+$ 10.5%; HRMS: (EI) m/z 156.0787 (156.0786 calcd for $C_8H_{12}O_3$).

5-(Diethylaminocarbonyl)-2,2-dimethyl-*4H*-1,3-dioxin (5g). To a stirred solution of triflate **3** (262 mg, 1.00 mmol) and triphenylphosphine (39.3 mg, 0.15 mmol) in dimethylformamide/diethylamine 5:1 (18 mL), previously purged with a stream of CO, was added triethylamine (280 μL, 2.00 mmol) and $Pd(OAc)_2$ (16.8 mg, 0.075 mmol), with stirring under an atmosphere of CO at rt. After 24 h, water (50 mL) was added and the resultant mixture extracted with Et_2O (4×25 mL). The combined organic fractions were dried ($MgSO_4$), filtered and reduced in vacuo to yield a black oil. Further purification by flash chromatography (silica ratio 50:1, hexane/EtOAc 4:1) yielded a colorless oil, (127 mg, 60%). R_f: 0.22 (hexane/EtOAc 4:1); ^{1}H NMR: (200 MHz, $CDCl_3$) δ 6.52 (s, 1H), 4.33 (s, 2H), 3.35 (q, J=7.0 Hz, 4H), 1.41 (s, 6H), 1.08 (t, J=7.0 Hz, 6H); ^{13}C NMR: (50 MHz, $CDCl_3$) δ 168.1, 143.2, 108.4, 99.7, 59.3, 41.0, 23.9, 13.1; IR: (neat) ν_{max} 2989.9, 1648.4, 1610.6, 1232.5 cm^{-1}; MS: (CI) m/z 214 $[M+H]^+$ 8.2%; HRMS: (EI) m/z 213.1368 (213.1365 calcd for $C_{11}H_{19}NO_3$).

2,2-Dimethyl-5-(*N*,*O*-dimethylhydroxyaminocarbonyl)-*4H*-1,3-dioxin (5h). To a solution of triflate **3** (390.6 mg, 1.489 mmol) and dppp (46.2 mg, 0.112 mmol) in dimethylformamide/*N*,*O*-dimethylhydroxylamine 4:1 (10 mL), previously purged with a stream of CO, was added triethylamine (418 μL, 2.98 mmol) and $Pd(OAc)_2$ (25.1 mg, 0.112 mmol) with stirring under an atmosphere of CO at rt. After 4 h, ice water (50 mL) was added and the resultant mixture extracted with Et_2O (4×25 mL). The combined organic fractions were dried ($MgSO_4$), filtered and reduced in vacuo to yield a black oil. Further purification by flash chromatography (silica ratio 30:1, hexane/EtOAc 2:1) yielded a colorless oil (150.0 mg, 50%). R_f: 0.20 (hexane/EtOAc 2:1); ^{1}H NMR: (200 MHz, $CDCl_3$) δ 7.60 (bs, 1H), 4.44 (d, J=1.4 Hz, 2H), 3.62 (s, 3H), 3.18 (s, 3H), 1.44 (s, 6H); ^{13}C NMR: (50 MHz, $CDCl_3$) δ 167.0, 151.8, 105.9, 100.2, 60.7, 59.2, 32.9, 23.9; IR: (neat) ν_{max} 2993.7, 1652.3, 1603.0, 1231.7 cm^{-1}; MS: (EI) m/z 201 $[M]^+$ 4.6%; HRMS: (EI) m/z 201.0999 (201.1001 calcd for $C_9H_{15}NO_4$).

2,2-Dimethyl-5-(5,7-octadienoyl)-*4H*-1,3-dioxin (5i). To a stirred solution of 7-iodohepta-1,3-diene (111 mg, 0.50 mmol[11]) in Et_2O (3.5 mL), cooled to −78°C, was added dropwise a solution of *t*-BuLi in pentane (1.5 M, 0.60 mL, 0.90 mmol). After 2 h, this solution was added, via cannula, to a stirred solution of amide **5h** (40.2 mg, 0.20 mmol) in Et_20 (1 mL) cooled to 0°C, and then allowed to warm to rt. After 75 min, sat. NH_4Cl (10 mL) and water (10 mL) were added and the resultant mixture extracted with Et_2O (4×20 mL). The combined organic fractions were dried ($MgSO_4$), filtered and reduced in vacuo to yield a yellow oil. Further purification by flash chromatography (silica ratio 150:1, hexane/EtOAc/1% NEt_3 gradient elution 12:1 to 9:1) yielded a colorless oil (26.6 mg, 0.113 mmol, 56%). R_f: 0.18 (hexane/EtOAc 9:1); ^{1}H NMR: (200 MHz, $CDCl_3$) δ 7.54 (s, 1H), 6.29 (dt, J=16.9, 2×1.3 Hz, 1H), 6.04 (dd, J=15.1, 10.5 Hz, 1H), 5.64 (~p, J=7.3 Hz, 1H), 5.00 (m, 2H), 4.40 (d, J=1.2 Hz, 2H), 2.44 (t, J=7.5 Hz, 2H), 2.06 (q, J=7.2 Hz, 2H), 1.69 (q, J=7.3 Hz, 2H), 1.42 (s, 6H); ^{13}C NMR: (50 MHz, $CDCl_3$) δ 198.3, 154.0, 137.6, 134.7, 132.3, 115.6, 115.0, 101.5, 58.1, 35.0, 31.5, 23.8, 23.6; IR: (neat) ν_{max} 2941.0, 1628.0, 1251.1, 1125.4 cm^{-1}; MS: (+ve FAB) m/z 237

$[M+H]^+$ 23%; HRMS: (EI) *m/z* 221.1185 $[M-CH_3]^+$ (221.1178 calcd for $C_{13}H_{17}O_3$).

Representative procedure for retrocycloaddition

A solution of dioxin (5–10 mg) in an appropriate deuterated solvent (~0.7 mL) was transferred to a resealable NMR tube and purged with a stream of argon for 20 min. A trace of hydroquinone was added, the tube sealed and a preliminary NMR recorded. The tube was placed in a sand bath, the temperature increased until a reasonable rate of retrocycloaddition was evident by NMR, and then maintained until completion of the reaction.

2-Trifluoromethanesulfonyloxy-2-propenal. Dioxin **3** was heated in d_6-benzene for 1.5 h at 80°C. ^{1}H NMR: (200 MHz, C_6D_6) δ 8.26 (s, 1H), 5.06 (d, J=4.0 Hz, 1H), 4.52 (d, J=4.0 Hz, 1H).

2-Hexyl-2-propenal (6a). Dioxin **5a** was heated in $CDCl_3$ for 3 h at 115°C with omission of dihydroquinone. Careful evaporation of the solvent afforded a colorless oil (7.5 mg, 0.0535 mmol, 79%) ^{1}H NMR: (200 MHz, CD_2Cl_2) δ 9.54 (s, 1H), 6.23 (m, 1H), 5.98 (s, 1H), 2.24 (t, J=6.8 Hz, 2H), 1.5–1.2 (bm, 8H), 0.88 (t, J=6.7 Hz, 3H).

2-Phenyl-2-propenal (6b). Dioxin **5b** was heated in d_8-toluene for 70 min at 120–140°C. ^{1}H NMR: (200 MHz, C_7D_8) δ 9.42 (s, 1H), 7.37 (m, 2H), 7.12 (m, 3H), 5.95 (s, 1H), 5.36 (s, 1H). Extended reaction times and/or evaporation of the solvent afforded the dimer as a colorless oil (7.4 mg, 0.028 mmol, 97%). ^{1}H NMR: (200 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.5–7.1 (m, 11H), 2.6–2.1 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.7, 140.6, 138.8, 136.9, 129.2, 128.9, 126.9, 126.0, 124.8, 115.2, 84.4, 27.5, 19.8; IR (neat) ν_{max} 2918.9, 1734.7, 1638.9, 1166.1 cm^{-1}.

2-(1-Formylethenyl)benzaldehyde (6c). Dioxin **5c** was heated in $CDCl_3$ for 48 h at 130°C with omission of dihydroquinone. Evaporation of the solvent afforded a colorless oil. (6.6 mg, 0.041 mmol, 88%). ^{1}H NMR: (200 MHz, $CDCl_3$) δ 9.94 (s, 1H), 9.83 (s, 1H), 7.94 (dd, J=7.1, 2.0 Hz, 1H), 7.61 (m, 2H), 7.26 (m, 2H), 6.48 (s, 1H), 6.43 (s, 1H); ^{13}C NMR: (50 MHz, $CDCl_3$) δ 193.0, 192.4, 149.6, 136.6, 136.1, 134.9, 134.5, 131.7, 131.5, 129.7; IR: (neat) ν_{max} 2923.4, 2850.0, 1692.6, 1198.0 cm^{-1}; MS: (EI) *m/z* 160 $[M]^+$ 60%; HRMS: (EI) *m/z* 160.0521 (160.0524 calcd for $C_{12}H_{22}O_2$).

Isoquinoline-4-carbaldehyde (6d). Heating dioxin **5d** in d_4-*o*-dichlorobenzene for 70 min at 130°C resulted in clean retrocycloaddition, electrocyclization and aromatization. ^{1}H NMR: (200 MHz, d_4-*o*-dcb) δ 10.32 (d, J=1.7 Hz, 1H), 9.28 (d, J=0.7 Hz, 1H), 9.16 (d, J=8.8 Hz, 1H), 8.83 (d, J=1.5 Hz, 1H), 7.81 (d, J=8.1 Hz, 1H), 7.71 (~tm, J=~7.7 Hz, 1H), 7.52 (bt, J=7.5 Hz, 1H), 7.01 (s, 1H). Evaporation, followed by flash chromatography (silica ratio 150:1, hexane/EtOAc 1:1) afforded an off-white solid (4.9 mg, 97%). Mp: 100–101°C (lit.[12] 101–103°C.).

Bis-2,5-(trimethylsilylethynyl)-3,4-dihydro-2*H*-pyran-2-carbaldehyde (entry e, no diene). Dioxin **5e** was heated in d_8-toluene at 100°C. Resonances attributable to the initial retrocycloaddition product were evident in the reaction mixture. ^{1}H NMR: (200 MHz, C_7D_8) δ 8.97 (s, 1H), 5.94 (s, 1H), 4.43 (s, 1H), 1.1 (bm, 21H). Additional heating for 12 h afforded the dimer: δ 9.19 (s, 1H), 6.78 (s, 1H), 2.32 (m, 1H), 1.92 (dm, J=16.4 Hz, 1H), 1.71 (m, 1H), 1.50 (m, 1H), 1.1–0.9 (m, 42H). IR: (neat) ν_{max} 2941.9, 2861.7, 2141.5, 1749.0, 1625.9, 1167.4 cm^{-1}; MS: (EI) *m/z* 472 $[M+H]^+$ 79%; HRMS: (EI) *m/z* 472.3184 (472.3193 calcd for $C_{28}H_{48}O_2Si_2$).

2-Methoxy-1-triisopropylsilylethynyl-4-trimethylsilyloxy-3-cyclohexene-1-carboxaldehyde (6e). To a stirred solution of dioxin **5e** (51.0 mg, 0.173 mmol) in toluene (3 mL), was added neat Danishefsky's diene (67 μL, 0.346 mmol), and the mixture brought to reflux. After 5 h, solvent was removed in vacuo to yield a pale yellow oil as a 4:1 mixture of diastereoisomers (78.9 mg, 100%). ^{1}H NMR: (200 MHz, $CDCl_3$) δ 9.64 (minor) and 9.51 (major) (2×s, 1H total), 5.06 (major) (dd, J=5.3, 1 Hz) and 4.92 (minor) (dm, J=4.4 Hz) (1H total), 4.12 (m, 1H), 3.34 (minor) and 3.27 (major) (2×s, 3H total), 2.4–1.8 (m, 4H), 0.98 (m, 21H), 0.14 (m, 9H). This initial adduct mix was further characterized as the corresponding 4-formyl-4-triisopropylethynyl-2-cyclohexen-1one by mild acid hydrolysis. The residue was taken up in THF (2 mL), THF-0.005 M HCl 2:1 (3 mL) added, and the resultant mixture stirred at rt. After 5 h, water (10 mL) was added and the resultant mixture extracted with Et_2O (4×10 mL). The combined organic fractions were dried ($MgSO_4$), filtered and reduced in vacuo to yield a pale yellow oil. Further purification by flash chromatography (silica ratio 100:1, pentane/Et_2O 4:1) proved problematic, due to co-elution of the corresponding β-methoxyketones. However, preparative tlc. (20×20 cm analytical plate, pentane/Et_2O 4:1, 3 elutions) yielded a sample of pure enone as a colorless oil (14.0 mg, 0.046 mmol, 27% isolated). R_f: 0.14 (pentane/Et_2O 4:1); ^{1}H NMR: (200 MHz, $CDCl_3$) δ 9.57 (s, 1H), 6.89 (d, J=10.1 Hz, 1H), 6.12 (d, J=10.1 Hz, 1H), 2.8–2.2 (m, 4H), 0.98 (s and m, 21H); ^{13}C NMR: (50 MHz, $CDCl_3$) δ 198.5, 194.3, 144.7, 131.0, 101.3, 90.4, 49.1, 33.5, 29.7, 17.9, 10.3; IR: ($CHCl_3$) ν_{max} 2945.1, 2162.2, 1736.2, 1688.6 cm^{-1}; MS: (EI) *m/z* 304 $[M]^+$ 5.2%; HRMS: (EI) *m/z* 304.1856 (304.1858 calcd for $C_{18}H_{28}O_2Si$).

3-Formyl-3-butenone (entry f, no diene). Heating dioxin **5f** in d_8-toluene for 2 h at 85°C resulted in extensive decomposition and/or polymerization, although signals attributable to the initial retrocycloaddition product were evident in the reaction mixture. ^{1}H NMR: (200 MHz, C_7D_8) δ 9.51 (s, 1H), 5.82 (s, 1H), 5.63 (s, 1H), 1.84 (s. 3H).

1-Acetyl-3-methyl-3-cyclohexene-1-carboxaldehyde and 1-acetyl-4-methyl-3-cyclohexene-1-carboxaldehyde (6f). To a stirred solution of ketone **5f** (50 mg, 0.32 mmol) in benzene (3 mL), previously purged with a stream of argon, was added isoprene (320 μL, 3.20 mmol) and the mixture heated to reflux. After 7 h, additional isoprene (160 μL, 1.60 mmol) was added and heating was continued for 40 h. The solvent was removed in vacuo to yield a brown oil. Further purification by flash chromatography (silica ratio 100:1, hexane/EtOAc 6:1) yielded a colorless oil (25.6 mg, 48%) which ^{1}H NMR analysis revealed to be a 4.5:1 mixture of the inseparable regioisomers. R_f: 0.36 (hexane/EtOAc 4:1); ^{1}H NMR: (200 MHz, $CDCl_3$) δ 9.52

(s, 1H), 5.42 (major) and 5.11 (minor) (2×bm, 1H total), 2.6–2.2 (m, 2H), 2.12 (s, 3H), 2.2–1.9 (m, 4H), 1.70 (minor) and 1.60 (major) (2×bs, 3H total); ^{13}C NMR: (50 MHz, $CDCl_3$) δ 207.2, 201.6, 135.0, 121.3, 117.7, 63.9, 31.4, 27.2, 26.7, 26.3, 25.2, 24.8, 23.3, 22.9, 21.8; IR: (neat) ν_{max} 2925.6, 1703.6, 1440.5, 1355.8 cm^{-1}; MS: (CI) *m/z* 167 $[M+H]^+$ 84.5%; HRMS: (EI) *m/z* 166.0979 (166.0994 calcd for $C_{10}H_{14}O_2$).

***N*,*N*-Diethyl-2-formylpropenamide (entry g, no diene).** Heating dioxin **5g** in d_8-toluene for 2.75 h at 100°C resulted in clean retrocycloaddition. ^{1}H NMR: (200 MHz, C_7D_8) δ 9.04 (s, 1H), 5.77 (s, 1H), 5.32 (s, 1H), 3.21 (q, *J*=7.2 Hz, 2H), 2.56 (q, *J*=7.2 Hz, 2H), 0.97 (t, *J*=7.1 Hz, 3H), 0.68 (t, *J*=7.1 Hz, 3H).

***N*,*N*-Diethyl-2-isobutoxy-*4H*-2,3-dihydropyran-4-carboxamide (6g).** A stirred solution of dioxin **5g** (12.0 mg, 0.056 mmol) in isobutyl vinyl ether (2 mL), previously purged with a stream of argon for 15 min, was heated to reflux. After 48 h the solvent was removed in vacuo to yield a brown oil. Further purification by flash chromatography (silica ratio 65:1, hexane/EtOAc 3:1) yielded a colorless oil (13.1 mg, 92%). R_f: 0.29 (hexane/EtOAc 1:1); ^{1}H NMR: (200 MHz, $CDCl_3$) δ 6.53 (s, 1H), 5.01 (t, *J*=2.9 Hz, 1H), 3.51 (dd, *J*=9.3, 7.0 Hz, 1H), 3.36 (q, *J*=7.0 Hz, 4H), 3.27 (dd, *J*=9.3, 6.3 Hz, 1H), 2.25 (m, 2H), 1.82 (m, 3H), 1.54 (s, 6H), 1.09 (t, *J*=7.2 Hz, 6H), 0.85 (d, *J*=6.8 Hz, 6H); ^{13}C NMR: (50 MHz, $CDCl_3$) 171.4, 142.0, 111.3, 97.0, 75.0, 40.9, 28.1, 25.6, 18.7, 17.3, 13.2; IR: (neat) ν_{max} 2961.8, 1651.4, 1622.0, 1058.9 cm^{-1}; MS: (CI) *m/z* 256 $[M+H]^+$ 100%; HRMS: (EI) *m/z* 255.1817 (255.1834 calcd for $C_{14}H_{25}NO_3$).

***N*-Methoxy-*N*-methyl-2-isobutoxy-*4H*-2,3-dihydropyran-4-carboxamide (6h).** A stirred solution dioxin **5h** (11.2 mg, 0.0556 mmol) in isobutyl vinyl ether (2 mL), previously purged with a stream of argon for 15 min, was heated to reflux. After 26 h, solvent was removed in vacuo to yield a brown oil. Further purification by flash chromatography (silica ratio 100:1, hexane/EtOAc gradient elution 3:1 to 2:1) yielded a colorless oil (9.4 mg, 70%). R_f: 0.40 (hexane/EtOAc 1:1); ^{1}H NMR: (200 MHz, $CDCl_3$) δ 7.30 (s, 1H), 5.05 (t, *J*=3.1 Hz, 1H), 3.60 (s, 3H), 3.51 (dd, *J*=9.3, 6.9 Hz, 1H), 3.29 (dd, *J*=9.4, 6.3 Hz, 1H), 3.19 (s, 3H), 2.55–2.2 (m, 2H), 1.95–1.65 (m, 3H), 0.847 and 0.842 (2×d, *J*=6.7 Hz, 2×3H); ^{13}C NMR: (50 MHz, $CDCl_3$) δ 170.5, 149.9, 109.1, 97.7, 75.2, 60.5, 33.4, 28.1, 25.8, 18.8 (×2), 16.8; IR: (neat) ν_{max} 2958.3, 1649.8, 1100.2, 1051.8 cm^{-1}; MS: (CI) *m/z* 244 $[M+H]^+$ 100%.

***cis*- and *trans*-1-Decalones 6i.** Dioxin **5i** was heated in d_6-benzene for 14 h at 70°C. ^{1}H NMR: (200 MHz, C_6D_6) δ 9.63 (minor) and 9.06 (major) (2×s, 1H total), 5.5–5.3 (m, 1H), 5.23 (minor) (dm, *J*=9.9 Hz) and 5.08 (major) (dm, *J*=10.0 Hz) (1H total), 2.54 (major) and 2.37 (minor) (2×m, 1H total), 2.2–1.8 (m, 4H), 1.8–1.0 (m, 6H). Evaporation of the solvent and filtration through silica gel yielded a colorless oil (3.7 mg, 80%), as a 2:1 mixture of inseparable stereoisomers. R_f: 0.47 (hexane/EtOAc 4:1); IR: ($CHCl_3$) ν_{max} 2932, 1727, 1701, 1120 cm^{-1}; MS: (EI) *m/z* 178 $[M]^+$ 16%; HRMS: (EI) *m/z* 178.0998 (178.0994 calcd for $C_{11}H_{14}O_2$).

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