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THE TOTAL SYNTHESIS OF (±) KAWAIN VIA A HETERO-DIELS-ALDER CYCLOADDITION

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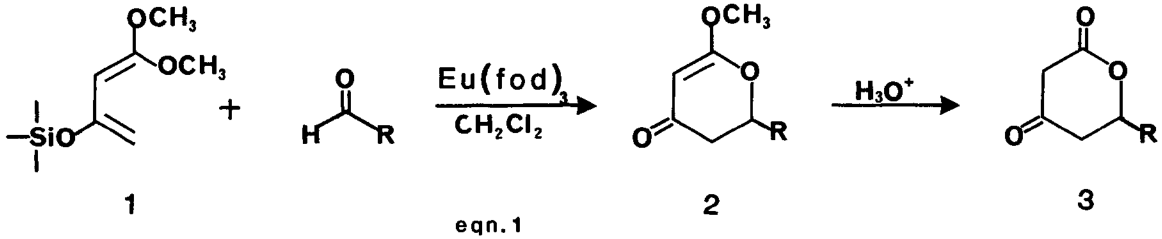
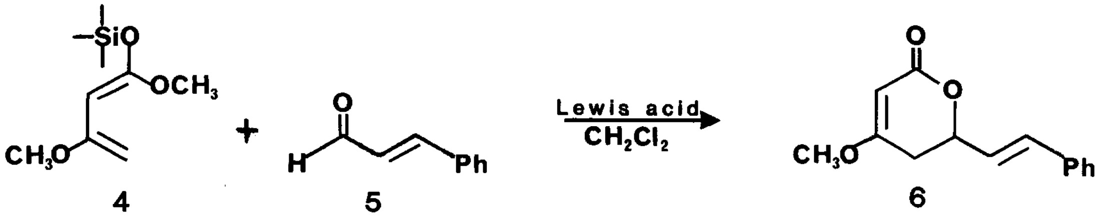
Abstract: The hetero-Diels-Alder reaction between 1,3-dimethoxy-1-trimethylsilyloxybutadiene 4, and cinnamaldehyde 5, produces (±) kawain in 75% and 84% yield respectively when catalyzed by Eu(fod)$_3$ or Yb(fod)$_3$. When Ag(fod) is employed as the catalyst a unique condensation reaction occurs which produces two acyclic diastereomers in 72% yield.

In a recent communication [1,2] we demonstrated that 1,1-dimethoxy-3-trimethylsiloxy-1,3-butadiene 1 and various aldehydes undergo cyclization in the presence of catalytic amounts of Eu(fod)$_3$ to produce β-oxo-cyclic ketene acetals 2, which can be isolated and hydrolyzed to β-oxo-γ-lactones 3, (Eqn. 1). We also noted that an activated α-β unsaturated aldehyde shows exclusive carbon-oxygen addition in the presence of the Eu(fod)$_3$ catalyst while the uncatalyzed reaction shows little differentiation between the two dienophilic sites and nets a poor combined yield.

Kawain 6, is one of several α-pyrones isolated from the kava plant, Piper methysticum. Constituents isolated from this plant have demonstrated physiological activity[3]. In this communication, we wish to detail the results of the cycloaddition reaction between 1,3-dimethoxy-1-trimethylsilyloxybutadiene[4] 4, and cinnamaldehyde 5, which provides a convenient and efficient synthesis of (±) kawain 6[5], (Eqn. 2).

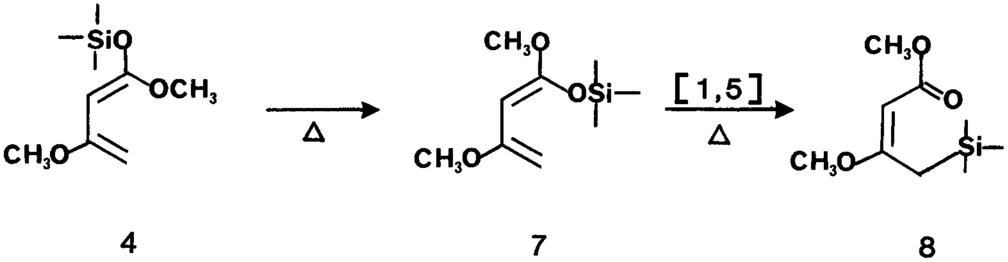


eqn.1



eqn2.

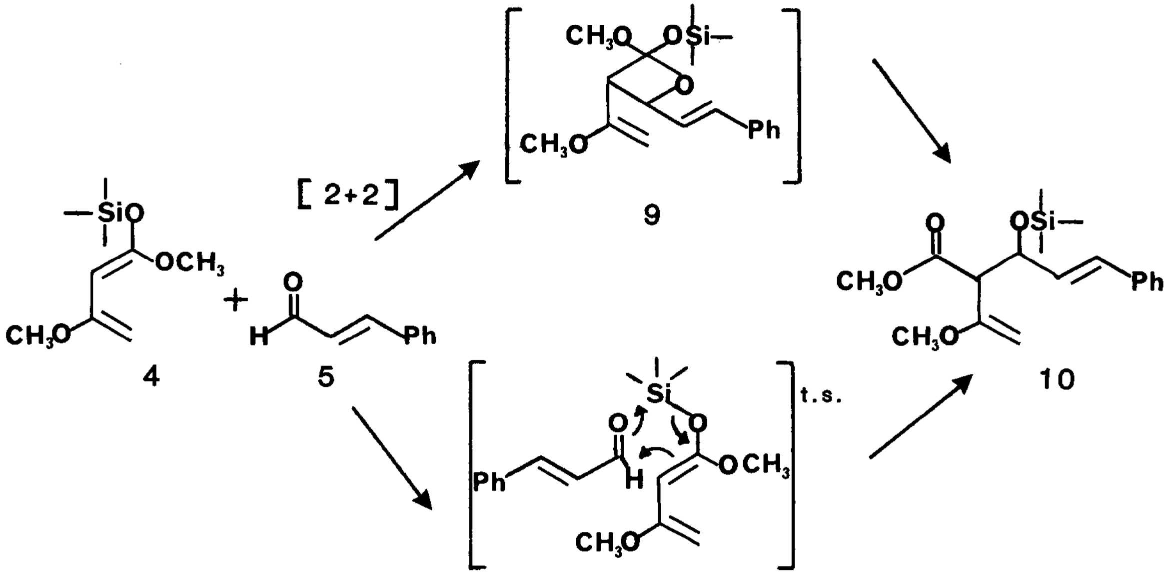
The diene 4 is prepared by the method described by Brassard and Savard[4]. Based on an NOE experiment[6] compound 4 is assigned the E-stereochemistry. Upon heating (100°C, 1 hr), the diene 4, is completely isomerized to 8[7]. It was previously noted that Z 1-siloxydienes readily undergo a thermal 1,5-migration of the silyl group from oxygen to carbon[8]. Presumably, the diene 4, isomerizes to the Z-isomer 7, which then undergoes a rapid 1,5 migration of the silyl group to produce compound 8, (Scheme 1). Attempts to detect the Z-isomer 7, by ^{1}H-NMR during thermal isomerization were not successful.



Scheme 1

The synthesis is completed by adding cinnamaldehyde 5, to a stirring solution of the diene 4, and Eu(fod)$_3$[9] (1.7 mole%) in CH_2Cl_2 under N_2. The reaction is allowed to stir at room temperature for 48 hrs. before the reaction product is purified by vacuum flash chromatography[10]. Crystalline (±) kawain 6, is obtained in a 75% isolated yield (based on diene), as the sole product[11]. Under identical reaction conditions, the stronger Lewis acid Yb(fod)$_3$[9] catalyses the cycloaddition of 4 and 5 to produce (±) kawain in 84% yield. The use of a stoichiometric amount of anhydrous $ZnCl_2$ in the reaction of 4 and 5 produces 6 in 78% yield.

In order to evaluate the selectivity of the Lewis acid catalyst in the cycloaddition reaction Ag(fod)[9] (4.7 mole %), was employed in the reaction between the diene 4 and cinnamaldehyde, 5. Reaction conditions were identical to those previously used with the added precaution of protecting the reaction from light. Upon work up, two diastereomers (60:40 by gc) of compound 10 are isolated in 72% yield[12]. Formation of 10 is consistent with either a [2+2] cycloaddition to produce an oxetane 9[13] which undergoes a subsequent ring opening and silyl transfer[14] or a direct formation of the acyclic adduct 10 through a six membered ring transition state[14], (Scheme 2). While the exact role of the Ag(fod) in this reaction is not clear, a Mukaiyama type condensation[15] is considered unlikely since the attempted reaction of diene 1, and cinnamaldehyde in the presence of Ag(fod) affords no condensation products; only starting materials are isolated.



Scheme 2

In summary, the cycloaddition reaction of activated dienes with aldehydes can provide a convenient and direct access to natural products as well as synthetically useful intermediates in high yields. The nature of the catalyst used in the reaction can have a dramatic effect on the product distribution. In general, the Lewis acid mediated cyclocondensation between oxygenated dienes and aldehydes produces pyrone ring systems[1,2]. The Ag(fod) catalyzed reaction described herein is unique. We are continuing to examine the selectivity of various Lewis acids and plan to incorporate this methodology into the total synthesis of natural products.

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6. NOE difference spectrum: irradiation at 0.23 δ (TMS): enhancement observed at 4.31 δ (vinyl H).

7. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.01(s,9H), 2.42(s,2H), 3.58(s,3H), 3.61(s,3H), and 4.89(s,1H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ -1.34(q), 24.08(t), 50.35(q), 54.95(q), 87.35(d), 168.57(s), and 176.66(s).
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11. Mp. 142-143°C. ^{1}H-NMR: (300 MHz, $CDCl_3$) δ 2.59(dd,J=17 and 4.5 Hz, 1H), 2.71(ddd, J=17, 10.6, and 1 Hz, 1H), 3.80(s,3H), 5.10(dddd, J=10.6, 4.5, 6.3 and 1 Hz, 1H), 5.24(d, J=1 Hz, 1H), 6.30(dd, J=16 and 6.3 Hz, 1H), 6.78(dd, J=16 and 1 Hz, 1H), and 7.3-7.45(m, 5H). ^{13}C-NMR: (50 MHz, $d_6$acetone) δ 33.65(t), 56.59(q), 76.40(d), 90.90(d), 127.47(d), 127.69(d), 128.89(d), 129.45(d), 133.23(d), 137.08(s), 166.4(s), and 173.3(s). IR: (CH_2Cl_2) νcm^{-1} 1715 and 1633. EIMS: M/Z 230.094(M+).
12. Major diastereomer, ^{1}H-NMR: (200 MHz, $CDCl_3$) δ 0.15(s, 9H), 3.24(dd, J=10 and 1 Hz, 1H), 3.48(s, 3H), 3.72(s, 3H), 4.05(dd, J=2.5 and 1 Hz, 1H), 4.18(d, J=2.5 Hz, 1H), 4.83 (ddd, J=10, 7, and 1 Hz, 1H), 6.15(dd, J=16 and 7 Hz, 1H) 6.58(dd, J=16 and 1 Hz, 1H), and 7.42-7.24(m, 5H). ^{13}C-NMR: (50 MHz, $CDCl_3$) δ 0.30(q), 51.93(q), 55.03(q), 59.47(d), 73.63(d), 84.97(t), 126.50(d), 127.50(d), 128.49(d), 129.85(d), 130.84(d), 136.94(s), 157.76(s), and 171.17(s). IR: (CCl_4) νcm^{-1} 1750, 1666, and 1625. EIMS: M/Z 334.160 (M+). The diastereomers were separated by hplc.
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