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Hetero Diels-Alder Cyclocondensation of *F*-Alkyl Aldehydes with the Danishefsky diene.

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Abstract: *The heterocyclocondensation of F-alkylated aldehydes $R_F(CH_2)_nCHO$ with Danishefsky's diene depends on the mutual vicinity of the carbonyl and the F-alkyl chain: when n=4 it leads to 4-oxo pyr-2-ene 4, but when n=0 the trimethylsilyloxypyrene* **3** *without methoxy elimination only results.*
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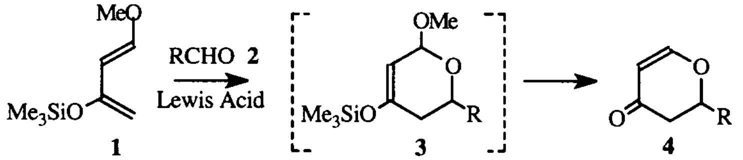
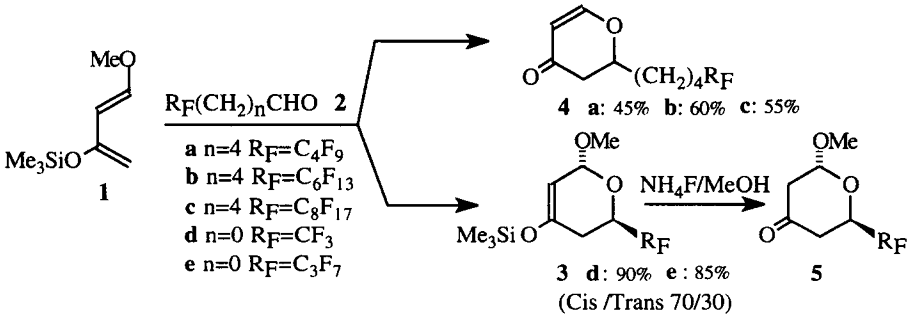
Since it's description by Danishefsky[1], the Lewis Acid Catalyzed Diene Aldehyde Cyclocondensation (LACDAC) has proven to be one of the most reliable reactions for the preparation of pyranosic synthons. The reaction of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) **1** and an appropriate aldehyde **2** in the presence of a Lewis acid provides a general route to the pyrenones **4** without isolation of the acid-labile intermediate 4-trimethylsilyloxy-2-methoxypyr-3-ene **3**[2].



If this cyclocondensation has been widely used in hydrocarbon series, we found only few examples reporting the preparation of a *F*-alkyl pyrenone, but without using Lewis acids[3].

The following scheme describes the behavior of some *F*-alkylated aldehydes in the hetero Diels-Alder cyclocondensation with Danishefsky's diene.



The 5-*F*-alkylpentanals $R_F(CH_2)_4CHO$ **2a-c** were prepared in three steps: a free-radical addition of *F*-alkyliodides on 4-penten-1-ol followed by the HCl/Zn reduction of the adduct leads to 5-*F*-alkylpentanols[4],

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which are then submitted to the Swern's oxidation[5].

Under Danishefsky's standard conditions (with $BF_3.Et_2O$ at -78 °C in CH_2Cl_2), these aldehydes reacted with **1** to give directly 6-(-4-*F*-alkylpropyl) 4-oxopyr-2-ene **4** [6,7].

When this cyclocondensation method was applied to *F*-aldehydes (R_FCHO) **2d-e**, we found a remarkable difference: it runs at room temperature, needs no catalytic activation and gives only the intermediate 6-*F*-alkyl-2-methoxy-4-trimethylsilyloxypyr-3-ene **3** as a cis/trans (70/30) mixture[8].

The ammonium fluoride desilylation[9] of **3** gives the 6-*F*-alkyl 2-methoxy pyr-4-one **5** resulting from the regeneration of the carbonyl fonction without methoxy group elimination, instead of the corresponding pyrenone **4**.

These results illustrate the strong inductive effect induced by the *F*-alkyl chain: - it polarizes the aldehydic carbonyl function so strongly that the heterocyclisation does not need Lewis acid activation. - on carbon 6 of the pyranosic ring, the inductive effect can even be observed at a longer distance through the intracyclic oxygen, precluding the elimination of the methoxy group.

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7 - **Typical procedure:** At -78 °C, under nitrogen, to a solution of 1.25 eq. of diene **1** and 1 eq. of aldehyde **2 (a, b** or **c)** in anhydrous CH_2Cl_2, was added 1 eq. of $BF_3.OEt_2$. After one hour on stirring the mixture was allowed to warm up to room temperature over 5 hours and then quenched with saturated $NaHCO_3$. The organic layer was extracted by diethylether, washed by lime saturated water, dried over Na_2SO_4 and concentrated under reduced pressure. The residual liquid was purified by chromatography on silica gel (eluent pentane/Et_2O 1/1). **4a** $R_F = C_4F_9$ mp = 42 °C yield = 45%; **4b** $R_F = C_6F_{13}$ mp = 49 °C yield = 60%; **4c** $R_F = C_8F_{17}$ mp = 54 °C yield = 55%. IR (cm^{-1}, KBr film) 1678 (νC=0), 1602 (νC=C), 1300-1100 (νCF). RMN ^1H (200 MHz, $CDCl_3$): 1.8 (m, 8H), 2.4 (m, 2H), 4.35 (m, 1H), 5.35 (d, J = 8.7 Hz, 1H), 7.3 (d, J = 8.7 Hz, 1H). ^{13}C: 192.3, 163.0, 107.1, 79.0, 41.8, 34.0, 30.7 (t), 24.4, 20.0. ^{19}F: -81.3 (CF_3), -114.8, -122.4/-123.3 (CF_2x 1,2 or 3: **4a**, **4b**, **4c**), -124, -126.6.

8 - **Typical procedure**: In a Schlenk tube fitted with a liquid nitrogen cooler, to a solution of 1.25 eq. of diene **1** in anhydrous CH_2Cl_2, was bubbled 1 eq. of aldehyde **2 (d** or **e)** distilled over P_2O_5. The mixture was stirred at room temperature for one hour and after solvent evaporation under reduced pressure we obtained **3** (yield 90%). for **3e** Cis/Trans: 70/30 IR (cm^{-1}, KBr film) 1300-1100 (νCF). RMN ^1H: 0.1 (s, 9H), 1.9 (m, 1H), 2.4 (m, 1H), 3.3 (s, 3H, cis), 3.4 (s, 3H, trans), 4.2 (m, 1H, cis), 4.5 (m, 1H, trans), 4.7 (m, 1H), 5.0 (m, 1H). ^{13}C: 151.1, 102.7 (trans), 101.1 (trans), 99.7 (cis), 97.4 (cis), 69.0 (trans, dd, J = 21.2 Hz, J = 31.1 Hz), 65.0 (cis, dd, J = 21.2 Hz, J = 31.1 Hz), 57.9 (trans, d, J = 18.7 Hz), 55.3 (cis, d, J = 18.7 Hz), 27.6, 0.0. ^{19}F: 81,3 (CF_3), AB syst.: -123.00 ($F_{\alpha A}$), −127.5 ($F_{\alpha B}$), $^2J_{FF}$ = 294 Hz ($CF_{2\alpha}$), AB syst.: -125.83 ($F_{\beta A}$), -127.0 ($F_{\beta B}$), $^2J_{FF}$ = 294 Hz ($CF_{2\beta}$).

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10 - **5d** $R_F = CF_3$ yield = 60%; **5e** $R_F = C_3F_7$ yield = 57%; for **5e** cis/trans: 90/10 IR (cm^{-1}, KBr film) 1652 (νC=O), 1300-1100 (νCF). RMN ^1H: 2.65 (m, 4H), 3.3 (s, 3H, trans), 3.4 (s, 3H, cis), 4.6 (m, 1H), 5.2 (m, 1H). ^{13}C: 200.5, 100.0, 65.9 (dd, J = 22.8 Hz, J = 32.5 Hz), 55.6, 46.3, 38.5. ^{19}F: -81.1 (CF_3), AB syst.: -122.93 ($F_{\alpha A}$), -127.77 ($F_{\alpha B}$), $^2J_{FF}$ = 281 Hz ($CF_{2\alpha}$), AB syst: -125.83 ($F_{\beta A}$), -126.88 ($F_{\beta B}$), $^2J_{FF}$ = 291 Hz ($CF_{2\beta}$).

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