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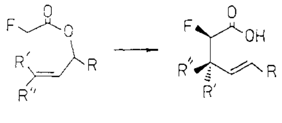
Facile Diastereoselective Ester Enolate Claisen Rearrangements of Allyl Fluoroacetates

Summary: The diastereoselective ester enolate Claisen rearrangement of allyl fluoroacetate esters results from stereoselective deprotonation of the ester to form the *E* enolate.

Sir: The power and the utility of the Claisen rearrangement has led to its popular use in synthesis.[1] The Ireland ester enolate Claisen rearrangement has extended the applicability of the rearrangement by facilitating its employment in convergent approaches.[2] It is well established that the reaction is tolerant of α substitution.[3] The effect of fluorination on sigmatropic rearrangement has been reported in only a few cases, and the effect of fluorination on the Claisen rearrangement in particular has not previously been described. We were therefore pleased to find that allyl fluoroacetates undergo a facile and diastereoselective ester enolate Claisen rearrangement which may have general synthetic utility.



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In our studies of the synthetic utility of the ester enolates of fluoroacetic acid, we were frustrated by the poor diastereoselectivity of these reagents in directed aldol reactions.[4] In the Claisen rearrangement, we observed that excellent diastereoselectivity was possible, as high as 20:1, as determined by both ^{13}C and ^{19}F NMR, in good overall yield. This diastereoselectivity requires the stereoselective deprotonation of the ester to form only one enolate. Control experiments where the rearrangement was conducted with excess base demonstrated that the product trimethylsilyl esters are readily epimerized to a thermodynamic mixture. Previously generation of the enolate of ethyl fluoroacetate with excess lithium hexamethyldisilazide (LHMDS) followed by trapping experiments with chlorotrimethylsilane indicated that both the *E* and *Z* enolates were being formed.[4a]

The best diastereoselectivity and yields were obtained when lithium diisopropylamide (LDA) was used to generate the enolate.[5] When formation of the enolate of allyl fluoroacetates with LHMDS under comparable conditions was attempted, the yields of rearranged products were consistently low. Excess LDA masked the diastereoselectivity of the rearrangement by epimerizing the products. The well-documented effect of hexamethylphosphoramide (HMPA) on the enolate geometry,[6] promotion of the formation of *Z* enolates,[7] was not observed. The addition of HMPA did degrade the diastereoselectivity of the rearrangement slightly (See Table I).

The facile rearrangement of fluorinated substrates predicted by a number of different criteria was confirmed by these experiments. The thermodynamic analysis of the Cope rearrangement of 1,1-difluoro-1,5-hexadiene to 3,3-difluoro-1,5-hexadiene suggests the energy of activation is lowered 2.5 kcal/mol relative to the unfluorinated diene,[8] with the result of the equilibrium being shifted to favor formation of 3,3-difluoro-1,5-hexadiene exclusively. Quantitative observations of NMR spectra of monofluorobullvalene, which undergoes Cope rearrangements,[9] suggest the equilibria have also been displaced by fluorination.

Carpenter's resonance energy model, based upon the calculated difference in Hückel π-electron energy for suitable reactant and transition-state models, predicts π donors would lower the difference in reaction enthalpy.[10] Fluorine, a π donor, would therefore result in an increase in resonance energy in preceding from the reactant to the transition-state model, and the rearrangement would be accelerated.

Comparison of the half-lives of fluoroacetate allyl esters with published half-lives and rate constants from the literature demonstrate there is a slight but definite acceleration of the rearrangement upon fluorination. The

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[5] Typical procedure: To a magnetically stirred, three-necked round-bottomed flask containing 20 mL of anhydrous THF and 0.0044 mol of lithium diisopropylamide (prepared in the usual manner at 0 °C), under an inert atomosphere at −100 °C, was added dropwise over 2 min 0.0037 mol of an allyl fluoroacetate dissolved in 5 mL of THF. After 3 min, 0.0044 mol of chlorotrimethylsilane was rapidly added. The mixture was allowed to warm to 0 °C and then was stirred at 40 °C for 2–4 h. The reaction mixture was quenched with methanol and was exhaustively extracted with 5% sodium hydroxide. The combined basic extract was washed twice with 10 mL of ether and then was acidified with concentrated HCl. The product acids were extracted with dichloromethane, were washed with brine, and were dried over anhydrous magnesium sulfate. The crude product was isolated by rotary evaporation of the solvent.

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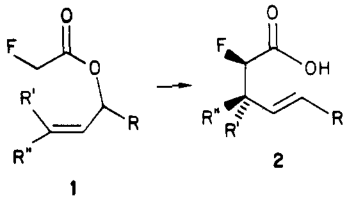
Table I. Claisen Rearrangement of Fluoroacetate Allyl Ester Enolates

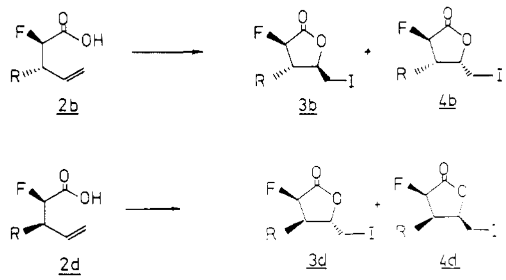


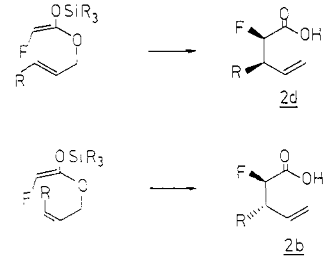
ester	R	R′	R″	diastereoselectivity	base	temp, °C	% yield
1a	CH_3	H	H		3 × LDA	−78	88
1a	CH_3	H	H		0.9 × LDA	−100	23
1b	H	CH_3	H	1:1	3 × LDA	−100	81
1b	H	CH_3	H	1:20	1.1 × LDA	−100	43
1c	H	H	H		3 × LDA	−78	72
1d	H	H	CH_3	1:1	3 × LHMDS	−78	43
1d	H	H	CH_3	2:1	4 × LTMP	−78	82
1d	H	H	CH_3	2:1	4 × LTMP[a]	−78	76
1d	H	H	CH_3	2:1	4 × LTMP[b]	−78	
1d	H	H	CH_3	2:1	3 × LDA	−100	97
1d	H	H	CH_3	2:1	1.1 × LDA[a]	−100	
1d	H	H	CH_3	2:1	1.1 × LDA[b]	−100	
1d	H	H	CH_3	4:1	1.2 × LDA	−100	65
1d	H	H	CH_3	9:1	0.9 × LDA	−100	15

[a] $^1/_2$ equiv of HMPA. [b] 23% by volume HMPA.

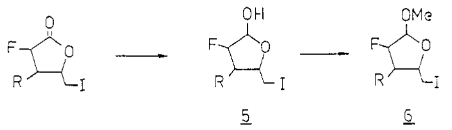
half-life for the rearrangement of **1d** at 40 °C was 40 min. Certainly the observed effect is less than that which would be expected in comparison with the effect of difluorination on the Cope rearrangement. Apparently the π-donating and σ-withdrawing influence on the π orbital nearly cancel one and another[11a] in the ester enolate Claisen. More complete studies of the rate of rearrangement are under way.

Although determination of the diastereoselectivity by ^{13}C and ^{19}F NMR was straightforward, direct determination of which acid diastereomer was being preferentially formed was not possible. Our attempts to isolate the *tert*-butyldimethylsilyl ether after trapping with chloro-*tert*-butyldimethylsilane or *tert*-butyldimethylsilyl triflate, failed. The olefinic acids were subjected to iodolactonization under the conditions of thermodynamic control.[12] Iodolactonization of **2b** yielded a 4:1 mixture of **3b** to **4b**, whereas **2d** preferentially formed only **3d** as determined by ^1H NMR. The configuration of the lactones was determined by 2D *J*-resolved spectroscopy in conjunction with ^{13}C chemical shift data and ^{19}F–^1H coupling constants. As expected, the ^1H resonance assigned to the methyl in **3b** showed a γ coupling to fluorine of 2.4 Hz, whereas in **3d** no γ coupling was observed. In **3b** $J_{H_aH_b}$ = 7.33 Hz and in **3d** $J_{H_aH_b}$ = 9.74 Hz in agreement for the anti and syn relationship of H_a and H_b in **3b** and **3d** respectively. The remainder of the observed proton coupling constants were in agreement with the structures shown. In the ^{13}C spectra of **3d** the methyl chemical shift, 6.54 ppm, was at higher field than the methyl resonance of **3b**, 15.08 ppm, where the methyl and the fluorine have an anti relationship. Assignment of the structures of **2d** and **2b** formed by rearrangement of the *E* and *Z* esters require the rearrangement to proceed from only the *E* enolate. Formation of the *E* enolates would be in agreement with reported ester enolate geometry resulting from deprotonation propionate esters with LDA under similar conditions.[13]





The iodolactones **3b** and **3d** have been reduced with lithium diisobutylaluminum hydride to the lactols **5**. The lactols have been cleanly converted to the methyl acetals **6** without epimerization of the carbon bearing fluorine. Out studies in this area are part of an ongoing investigation into new fluoro carbohydrate and fluoro sugar nucleoside syntheses, the details of which will be reported in the future.



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Supplementary Material Available: Complete spectral and analytical data for all new compounds (5 pages). Ordering information is given on any current masthead page.

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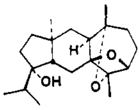
Dictyoxetane, a Novel Diterpene from the Brown Alga *Dictyota dichotoma* from the Indian Ocean

Summary: A specimen of *Dictyota dichotoma* from the Indian Ocean contained dictyoxetane (1), the first example of a new tricyclic diterpene carbon skeleton.

Sir: A study of the brown alga *Dictyota dichotoma* (Hudson) Lamouroux[1] was undertaken as part of a survey of marine organisms from the coast of India. Previous chemical investigations of *Dictyota* species have yielded diterpenes belonging to several different structural classes.[2] Some representative examples are dictyodial from *Dictyota crenulata* and *D. flabellata*,[3] sanadaol from *D. crenulata*,[4] dictyolene from *D. acutiloba*,[5] the dictyols from *D. dichotoma*,[6] the dolabellanes from *D. dichotoma*[6] and *Dictyota* sp.,[7] and the dolastanes from *Dictyota* sp.[8] The Indian Ocean sample of *Dicytota dichotoma* contains at least 20 new diterpenes, most of which belong to the familiar dolabellane class. In this communication we report the structural determination of dictyoxetane (1), the first example of a new tricarbocyclic diterpene skeletal class.



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The sample of *Dictyota dichotoma* was collected by hand at Krusadai Island, Gulf of Mannar, India. The combined chloroform and methanol extracts of *D. dichotoma* were subjected to repeated silica gel chromatography, and the final purification of dictyoxetane (1, 7 × 10^{-4}% dry weight) was achieved by LC on μ-Porasil using 8:1 hexane–ethyl acetate as eluant.

Dictyoxetane (1), $[\alpha]_D$ +35.0° (*c* 3.0, $CHCl_3$) is a colorless crystalline solid, mp 87–90 °C, that has the molecular formula $C_{20}H_{32}O_3$. The IR spectrum contained a weak hydroxyl band at 3600 cm^{-1} but no carbonyl bands. Five signals at δ 80.1 (s), 80.6 (s), 81.3 (d), 82.7 (s), and 97.2 (s) in the ^{13}C NMR spectrum were assigned to carbon atoms bearing oxygen. Since there were no signals at δ >100 in the ^{13}C NMR spectrum, we concluded that dictyoxetane (1) must be a tricarbocyclic diterpene with two ether rings. The ^1H NMR spectrum contained signals at δ 0.91 (d, 3 H, J = 6.5 Hz) and 0.97 (d, 3 H, J = 6.5 Hz), assigned to an isopropyl residue, three methyl signals at δ 1.10 (s, 3 H), 1.30 (s, 3 H), 1.37 (s, 3 H), and a C*H*OR signal at δ 4.40 (br d, 1 H, J = 3 Hz). Even assuming that the structure of dictyoxetane could be derived by further cyclization of the dolabellane ring system, there were too many possibilities for the compound to be identified by analysis of spectral data alone. The structure of dictyoxetane (1) was therefore determined by a single-crystal X-ray analysis.

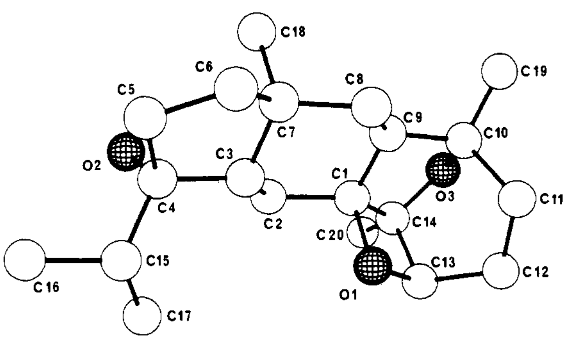

Figure 1. A computer-generated perspective drawing of the final X-ray model of dictyoxetane (1). Hydrogens are omitted for clarity, and no absolute configuration is implied.

Crystals of dictyoxetane (1) belonged to the monoclinic crystal class with a = 7.842 (2) Å, b = 16.320 (4) Å, c = 8.242 (1) Å, and β = 115.86 (2)°. Systematic extinctions indicated space group $P2_1$ with one molecule of $C_{20}H_{32}O_3$ forming the asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were collected on a computer-controlled four-circle diffractometer using variable speed, 1° ω-scans, and graphite monochromated Cu K$\bar{\alpha}$ radiation (1.54178 Å). Of the 1331 reflections measured in this way, 981 (74%) were judged observed ($F_o \geq 3\sigma(F_o)$) after correction for Lorentz, polarization, and background effects.[9] A phasing model was found by using the MULTAN series of programs,[9] and the first E synthesis revealed most of the non-hydrogen atoms. The remaining non-hydrogen atoms were located with tangent formula recycling,[10] and hydrogen atoms were located on a subsequent ΔF synthesis. Block diagonal least-squares refinements with anisotropic non-hydrogen atoms and isotropic hydrogens have converged to a conventional crystallographic residual of 0.074 for the observed reflections. Additional crystallographic details can be found in the supplementary material.

Figure 1 is a computer-generated perspective drawing of the final X-ray model less hydrogens. The absolute configuration shown is an arbitrary choice. The five-membered ring has an envelope conformation with C7 serving as the flap. The six-membered ring is in a chair conformation as is the seven-membered ring. The oxetane ring is only slightly folded with all of the torsional angles roughly ±6°. The C–O interatomic distances are 1.50 (1)

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[1] A voucher specimen (Herbarium #M.A.-64) was deposited in the Central Marine Fisheries Research Institute, Mandapan Camp, India.

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