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Synthesis of New α,α-Difluoro-γ-lactones through Intramolecular Radical Cyclization as a Key Reaction

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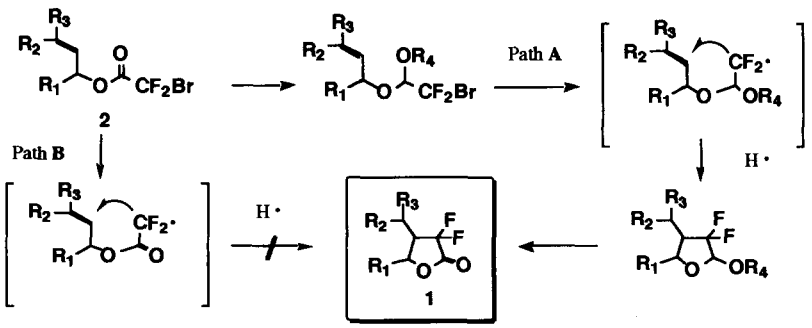
Abstract: Carbon radicals from allyl o-trimethylsilyl-α-bromo-α,α-difluoro-acetals can cyclize onto olefines regiospecifically to give γ-lactols in good yield. These lactols have been converted to the corresponding α,α-difluoro-γ-lactones. The first synthesis of three new α,α-difluoro-γ-lactones has been accomplished.

Partially fluorinated analogs of biologically important compounds demonstrated dramatic changes and distinctive modifications in their biological activities.[1] This makes efficient methods for the synthesis of selectively fluorinated compounds ever more necessary. We were attracted by difluoromethylene compounds among partially fluorinated compounds because of their biological activity. They have been applied to analogs of widely varied types of compounds such as amino acids,[2] vitamin D_3,[3] nucleotides,[4] prostaglandines,[5] fatty acids,[6] and insect pheromones.[7] One of the most striking means to construct difluoromethylene moiety in a compound is begin the synthesis from a proper building block that possesses a diofluoromethylene group.[8] Since many biologically active compounds possess γ- or δ-lactone moiety, we attempted preparation of α,α-difluoro-γ-lactones **1** as a synthetic building block for difluoromethylene compounds.[9] Free radical cyclization of olefines has been used for the construction of 5- or 6-membered rings.[10] We wish to report the first systematic synthesis of α,α-difluoro-γ-lactones using intramolecular cyclization of α,α-difluoro acetal radicals onto olefine as a key reaction (Path A in the Scheme 1).

Initially we attempted to cyclize allyl α-bromo-α,α-difluoroacetates **2** using Bu_3SnH in the presence of



Scheme 1

various radical initiators. The only product obtained was a reduction product.[11,12] We then attempted electro-reductive intramolecular cyclization of esters **2**, but no cyclized compound **1** was obtained under these reaction conditions (Path B in the Scheme 1).[13]

Esters of α-radical species have reportedly been considered unsuitable for C-C bond formation because of their stable nature.[14] Radical cyclization of the α-bromo acetal method was developed as an indirect efficient route to γ-lactones by Ueno et al.[15a] and Stork et al.[15b] We found that the intramolecular radical addition of α-bromo-α,α-difluoroacetals **3** onto olefine was regiospecific and gave only the corresponding 5-membered lactols **4**. The lactols **4** were then converted to the desired α,α-difluoro-γ-lactones **1** by PDC oxidation (Eq. 1). Typical procedure of the present reaction is carried out as follows: To a solution of cinnamyl (1-bromo-1,1-difluoro)acetate **1a** (R_1=H, R_2=Ph; 698 mg, 2.40 mmol) in CH_2Cl_2 (12 mL) was added DIBAL solution (1.9 mL, 1.5 M in toluene) at -78°C over a 20 min period. After the reaction mixture was stirred for 1h at the same temperature, a CH_2Cl_2 (2 mL) solution of TMSOTf (853mg, 3.84 mmol) and pyridine (569 mg, 7.19 mmol) was added. After further stirring at room temperature for 1 h, the reaction was quenched by addition of water (157mg, 8.7 mmol) and NaF (483 mg, 11.5 mmol). Vigorous stirring was continued for 0.5 h, then the mixture was filtered through a short florisil column, eluted with ether and evaporated. Silica gel flash column chromatography using hexane-ethyl acetate (50:1 to 20:1) as eluent gave the TMS acetal **3a** (R_1=H, R_2=Ph; 796 mg, 2.18 mmol) in 87% yield. To a benzene (4 mL) solution of the acetal **3a** (700mg, 1.92 mmol) and AIBN (18 mg, 0.11 mmol) was slowly added a benzene (33 mL) solution of tributyltinhydride (863 mg, 2.97 mmol) over 5 h under reflux conditions. The reaction mixture was heated to reflux for an additional 4 hours, then cooled to room temperature. After evaporation, silica gel flash column chromatography using hexane-ethyl acetate (200:1 to 50:1) as eluent gave the cyclized product **4a** (340 mg, 1.19 mmol) in 62% yield. This step finished regiospecifically to provide only 5-membered lactol and no 6-membered lactol was obtained. TMS lactol **4a** (308mg, 1.08 mmol) was then treated with tetrabutylammoniumfluoride (1.3 mmol, 1.0 M in THF solution) at room temperature for 21 h to provide the deprotected lactol (218 mg) which was used immediately for oxidation without further purification. PDC (1.172 g, 3.05 mmol) oxidation of the lactol in CH_2Cl_2 (7.1 mL) in the presence of molecular sieves 4Å powder (814 mg) at room temperature for 6 h, and subsequent purification using silica gel flash column gave the desired γ-lactone **1a** (219 mg, 1.03 mmol) in 95% yield. Three types of new α,α-difluoro-γ-lactones **1a**(R_1=H, R_2=Ph), **1b**(R_1=H, R_2=H), and **1c**(R_1=$PhCH_2CH_2$, R_2=H) were obtained by the same sequence, and the results are summarized in Table 1.

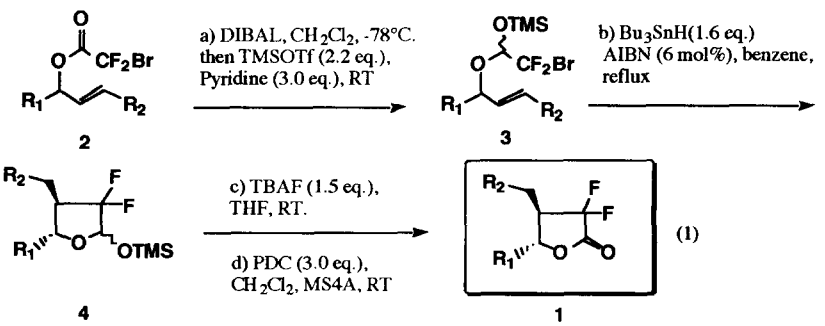


Table 1. Synthesis of α,α-difluorolactones *via* intramolecular radical cyclization of TMS acetal **3**

Entry	R_1	R_2	Yield of **3**	Yield of **4**	Yield of **1**
1	H	Ph	87	62	95
2	H	H	65[a]	57[a]	47[a]
3	$PhCH_2CH_2$	H	77	62	57 (*trans*: *cis*=92:8)[b]

a) Since this compound is very volatile, a significant loss of amount was observed during the purification process. b) The ratio was determined by ^1H NMR (500 MHz) analysis. Stereoconfiguration was assigned by results of NOE experiment of *trans*-**1c**. Strong NOE (11%) was observed at C-4 methyne proton with C-3 methyl group.

The most important point of the present reaction is that radical cyclization occurred regiospecifically. Neither 6-membered lactol nor intermolecular coupling products formed. In addition, *trans*-lactone **1c** was obtained as a sole product, as shown in Table 1. Therefore, *the radical cyclization gave cyclized products with excellent stereochemical control.* It should be noted that the reaction was completed smoothly, though isolated yields of lactols **4** were moderate. Significant losses due to volatility were observed during the purification process using silica gel flash column chromatography. All new lactols **4** and lactones **1** are stable compounds and easily handled, except for the volatility.[16]

In conclusion, the present reaction provides an efficient general method for the synthesis of a variety of new α,α-difluoro-γ-lactones.[17] Further study of the scope and limitation and mechanistic details concerning the radical cyclization is ongoing.

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11) We obtained allyl α,α-difluoroacetate in 60 ~ 80% yield. It has been reported that only the starting material was recovered when allyl α,α-difluoro-α-iode acetate was reated with hexabutylditin under irradiation conditions of a sunlamp; Barth, F.; O-Yang, C. *Tetrahedron Lett.* **1990**, *31*, 1121.

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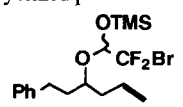
16) Satisfactory spectral data were obtained for all new compounds. Selected physical data are shown below:

Lactone **1a**: ^{1}H NMR(200MHz, δ, $CDCl_3$) 1.85(1H,dd,J=13.5Hz,9.6Hz), 1.97-2.22(1H,m), 2.28 (1H,dd, J=13.5Hz,5.4Hz), 3.23(1H, dd,J=9.3Hz,8.1Hz), 3.36(1H,dd,J=9.4Hz,7.5Hz), 6.29-6.50(5H,m); ^{13}C NMR(50MHz, ppm, $CDCl_3$) 30.17(d,J_{C-F}=6.2Hz), 43.50(t,J_{C-F}=20.3Hz), 68.58(d,J_{C-F}=7.3Hz), 114.60 (dd,J_{C-F}=256.9Hz,251.8Hz), 127.25, 128.53, 128.98, 135.85, 165.35(t,J_{C-F}=32.8Hz); ^{19}F NMR(188MHz, ppm, $CDCl_3$, C_6F_6) 41.51(1F, dd, J=276.0Hz, 17.1Hz) 47.88(1F,dd,J=276.0Hz, 12.6Hz); IR(neat) 3010, 2905, 1800(CO), 1495, 1230, 1195, 1100, 980, 750, and 725 cm^{-1}; Bp 65°C/7 torr (Kugelrohr); Rf 0.44, hexane/ethyl acetate (4:1).

Lactone **1b**: ^{1}H NMR(200MHz, δ, $CDCl_3$) 1.23(3H,dd,J=7.0Hz,1.3Hz), 2.65-2.95(1H,m), 4.00(1H,t,J=8.5Hz) 4.52(1H,t,J=8.5Hz); ^{13}C NMR(50MHz, ppm, $CDCl_3$) 8.46(d,J=7.0Hz) 37.04(t,J $_{C-F}$=21.4Hz) 70.13(d,J=7.6Hz) 114.95(t, J_{C-F}=253.3Hz) 165.5; ^{19}F NMR(188MHz, ppm, $CDCl_3$, C_6F_6) 39.46(1F, dd, J=274.9Hz, 17.0Hz) 46.41(1F, dd, J=275.0Hz, 13.1Hz); IR(neat) 2995, 1810(CO), 1220, 1005, 840 and735 cm^{-1} ; Bp120°C/760 torr (Kugelrohr); Rf 0.33, hexane/ethyl acetate (4:1).

Lactone **1c**(*trans*): ^{1}H NMR(200MHz, δ, $CDCl_3$) 1.12(3H,d,J=7.0Hz), 1.78-2.12(2H,m), 2.18-2.42(1H,m), 2.61-2.94(2H,m), 4.06(1H,dt,J=9.0Hz,3.3Hz), 7.11-7.29(5H,m); ^{13}C NMR(50MHz, ppm, $CDCl_3$) 7.59(d,J_{C-F}=7.6Hz) 31.21, 35.17, 42.94(t,J_{C-F}=20.5Hz), 81.71(d,J_{C-F}=8.1Hz), 115.46 (t,J_{C-F}= 258.0Hz) 126.46, 128.36, 128.69, 139.91, 165.24; ^{19}F NMR(188MHz, ppm, $CDCl_3$, C_6F_6) 41.07 (1F,dd, J=274.8Hz,20.6Hz), 47.22(1F,dd,J=274.8Hz, 12.5Hz); IR(neat) 2825, 1800(CO), 1210, 1010, 745, and 695 cm^{-1}; Bp125°C/4.5 torr (Kugelrohr); Rf 0.44, hexane/ethyl acetate (4:1).

17) Radical cyclization of TMS acetal **5** gave unsatisfactory results. The radical reaction progressed very slowly and afforded cyclized product **6** in 11% yield with a complex mixture of byproducts.



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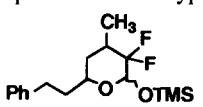

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