Reaction of 1-Substituted 2,2-Difluorostyrene with Dianions of β-Enamino Ketones

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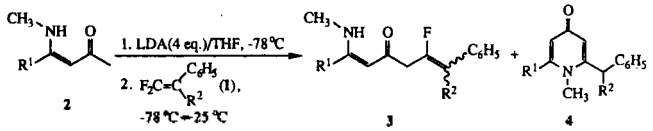
Since *gem*-difluoroolefins have a unique reactivity with nucleophiles, their synthetic utilities as building blocks for fluorinated and nonfluorinated compounds have recently been greatly explored.[1] Most of these works have focused on the stereochemical aspects of the addition-elimination products,[2] proton exchange reaction of carbanion generated *via* nucleophilic addition pathway in alcoholic media,[3] and ease of β-defluorination of resultant carbanion,[4] and only limited work has been directed to the synthetic application of *gem*-difluoroolefins.[5] For example, the reaction of 2,2-difluorovinyl ketones with carbon or heteroatom nucleophiles afforded α,β-unsaturated ketones or α-oxoketene acetals *via* successive replacements of the two fluorines[5a] and the reaction of *gem*-difluorinated ketene dithioacetals with a bidendate sulfur nucleophile has been reported.[5b] Recently, we reported an efficient method for the synthesis of 1-phenylthio-2,2-difluorostyrene (**1a**), as a new type of *gem*-difluoroolefin, from 2,2,2-trifluoro-1,1-bis(phenylthio)ethylbenzene[6] and the synthetic application of this compound for the preparation of various types of heterocyclic ketene acetals[7] and 4*H*-pyran-4-one derivatives[8] *via* exocyclization of **1a** with bidendate nuclophiles. In our continuing studies on the chemistry of **1a** toward bidendate nucleophiles, we found that **1a** reacted with dianions of β-enamino ketones to give monosubstituted products or pyridinone derivatives, depending on the type of β-enamino ketone. Especially, this reaction provides a new methodology for the formation of pyridinone derivatives which are very important framework for the antibacterial agents.[9] In this communication, we wish to report a preliminary result of this reaction.

When the reaction of 1-phenylthio-2,2-difluorostyrene (**1a**) with dianion of 4-(N-methylamino)pent-3-en-2-one (**2a**), generated by the treatment of **2** with 4 equiv. of LDA at −78 °C,[10] was carried out at −78 °C, only monosubstituted product **3a** (E:Z=78:22) was obtained in 76% isolated yield. No pyridinone derivative was detected. However, the reaction of **1a** with dianion of **2** at −78 °C, followed by warming to 25 °C, provided the monosubstituted product **3a**[11] and pyridinone derivative **4a**[12] in 74% and 6% isolated yields, respectively. This result indicates that the monosubstituted product **3a** does not easily undergo exocyclization under the employed reaction conditions, which is quite contrast to the case of the reaction of **1a** with dianion of 1,3-diketone.[8] The use of 2 or 3 equiv. of LDA to generate the dianion of **2** did not complete this reaction, while the starting material was always recovered. The reactions of other types of 1-substituted 2,2-difluorostyrenes **1b-f** with **2** under the same reaction condition afforded only monosubstituted products **3**. The results of these reactions were summarized in Table 1. The assignments for isomers of **3a** were based on the chemical shift for vinyl fluorine in ^{19}F NMR and allylic protons in ^{1}H NMR. Generally, the allylic protons which are arranged to the same side of phenylthio group (E-isomer) are more deshielded than those of Z-isomer.[13]

Table 1. Reaction of 1-Substituted 2,2-Difluorostyrenes **1** with Dianion of **2**



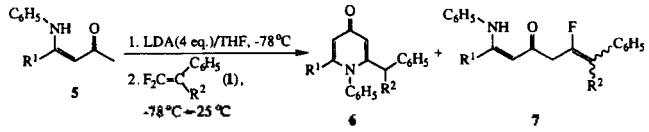
2 3 4

Compound No.	R^1	R^2	Yield (%)[a]	
			3[b]	**4**
3a, 4a	CH_3	SC_6H_5	74	6
3b	CH_3	C_6H_5	68	0
3c	CH_3	CH_3	45	0
3d	CH_3	H	32	0
3e	CH_3	CF_3	24	0
3f	C_6H_5	SC_6H_5	70	0

[a] Isolated yields. [b] All products are *E*- and *Z*- isomeric mixtures.

In contrast to the reaction of **1a** with dianion of **2**, the reaction of **1a** with dianion of 4-(N-phenylamino)pent-3-en-2-one (**5**), which was generated by the treatment of **5** with 4 equiv. of LDA at −78 °C, under the same reaction condition afforded pyridinone derivative **6a** and the monosubstituted product **7a** in 43% and 28% isolated yields, respectively. The similar reactions of dianion of **5** with several types of 1-substituted 2,2-difluorostyrenes **1b-d** also provided a mixtures of **6b-d** and **7b-d** in moderate yields. When dianion of **5** was reacted with **1e** under the same reaction condition, however, pyridinone derivative **6e** was isolated in 18% yield. This reaction gave a complex reaction mixture and other product **7e** could not be isolated. The results of these reactions were summarized in Table 2. A plausible mechanism for the formation of **6** can be proposed as shown in Figure 1. Initial attack of more nucleophilic carbon atom in the dianion[I] on the starting material **1** resulted in the formation of intermediate[II] *via* addition and β-defluorination. Exocyclization *via* nucleophilic attack of nitrogen on fluorovinyl carbon atom in intermediate[II], followed by β-defluorination to provide intermediate[III] which gave the final adduct **6** *via* 1,3-hydrogen shift. This 1,3-hydrogen shift can be rationalized by generation of enolate *via* a reaction of intermediate[III] with fluoride, followed by allylic rearrangement which is favorable for the formation of resonance hybrided 4-pyridinone.

Table 2. Reaction of 1-Substituted 2,2-Difluorostyrenes **1** with Dianion of **5**



Compound No.	R^1	R^2	Yield (%)[a]	
			6	**7**[b]
6a, 7a	CH_3	SC_6H_5	43	28
6b, 7b	CH_3	C_6H_5	38	23
6c, 7c	CH_3	CH_3	32	12
6d, 7d	CH_3	H	36	8
6e, 7e	CH_3	CF_3	18	–[c]

[a] Isolated yields. [b] All products are *E*- and *Z*-isomeric mixtures. [c] Product could not be isolated from a complex reaction mixture.

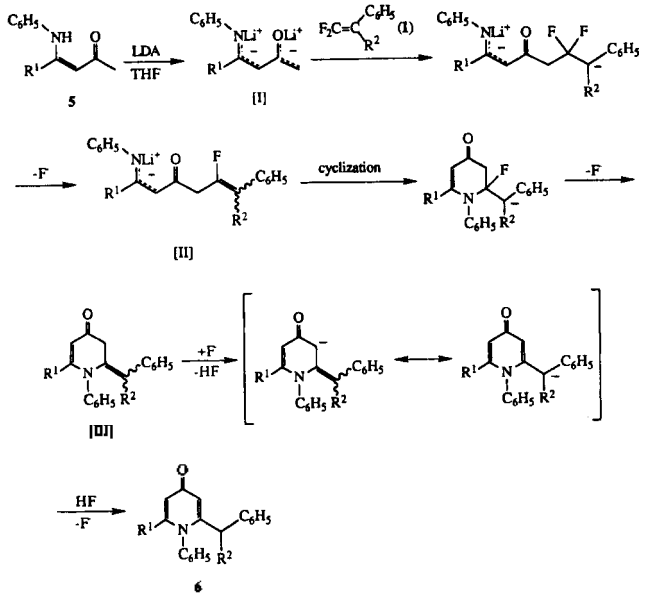


Figure 1. A plausible mechanism for the formation of **6** from the reaction of **1** with **5**.

A typical reaction procedure is as follows. To a tetrahydrofuran (10 mL) solution of 4-(N-phenylamino)pent-3-en-2-one (0.175 g, 1.0 mmol) was added LDA (4.0 mmol) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. under argon atmosphere. 1-Phenylthio-2,2-difluorostyrene (0.248 g, 1.0 mmol) was added dropwise at −78 °C and the reaction mixture was stirred at −78 °C for 2 hours, followed by warming to room temperature. The reaction mixture was poured on ice water and extracted with ethyl acetate. The ethyl acetate solution was dried, concentrated in vacuo and the residue was chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate (1 : 2) provided N-phenyl-2-methyl-6-(1-phenylthiobenzyl)-4*H*-pyridinone (**6a**) (0.165 g, 43%). **6a**: mp 198-199 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 1H), 7.88 (m, 1H), 7.60 (m, 1H), 7.48 (m, 1H), 7.32-7.20 (m, 8H), 7.05 (m, 2H), 6.86 (d, *J*=1.2 Hz, 1H), 6.79 (d, *J*=1.1 Hz), 5.06 (s, 1H), 2.11 (s, 3H); MS, m/z (relative intensity) 383 (M^+, 13), 274 (100), 246 (36), 109 (10), 77 (29); IR(KBr) 3400, 1650, 1560, 1480, 1360, 750, 690 cm^{-1}.

E- and *Z*- mixture of 2-fluoro-1-phenyl-6-phenylamino-1-phenylthiohept-1,5-dien-4-one (**7a**) (0.113 g, 28%) was obtained as a minor product. **7a**: *E*-isomer: yellowish oil; ^{1}H NMR ($CDCl_3$) δ 7.65 (bs, 1H), 7.40-7.00 (m, 15H), 5.60 (s, 1H), 3.92 (d, *J*=21.9 Hz, 2H), 2.04 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −86.0 (t, *J*=23.2 Hz, 1F); MS, m/z (relative intensity) 403 (M^+, 1), 383 (1), 274 (8), 246 (4), 160 (100), 118 (11), 109 (5); IR (neat) 3000, 1590, 1560, 1480, 1530, 1320, 1260, 740, 680 cm^{-1}. *Z*-isomer: yellowish oil; ^{1}H NMR ($CDCl_3$) δ 7.62 (bs, 1H), 7.42-7.05 (m, 15H), 5.56 (s, 1H), 3.34 (d, *J*=21.9 Hz, 2H), 2.08 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −85.5 (t, *J*=23.2 Hz, 1F); MS, m/z (relative intensity) 403 (M^+, 1), 383 (1), 274 (8), 246 (4), 160 (100), 118 (11), 109 (5); IR (neat) 3000, 1590, 1560, 1480, 1530, 1320, 1260, 740, 680 cm^{-1}.

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11. Spectroscopic data of **3a** is as follows. *E*-isomer: yellowish oil; ^{1}H NMR ($CDCl_3$) δ 7.67 (bs, 1H), 7.43-7.08 (m, 10H), 5.11 (s, 1H), 3.82 (d, *J*=20.1 Hz, 2H), 3.10 (d, *J*=5.1 Hz, 3H), 2.02 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −93.3 (t, *J*=19.8 Hz, 1F); MS, m/z (relative intensity) 341 (M^+, 2), 294 (23), 264 (100), 244 (83), 232 (21); IR (neat) 3000, 1600, 1560, 1470, 1530, 1330, 1250, 730, 680 cm^{-1}. *Z*-isomer: yellowish oil; ^{1}H NMR

($CDCl_3$) δ 7.67 (bs, 1H), 7.43-7.08 (m, 10H), 5.11 (s, 1H), 3.27 (d, *J*=20.1 Hz, 2H), 3.10 (d, *J*=5.1 Hz, 3H), 2.02 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −92.2 (t, *J*=19.8 Hz, 1F); MS, m/z (relative intensity) 341 (M^+, 2), 294 (23), 264 (100), 244 (83), 232 (21); IR (neat) 3000, 1600, 1560, 1470, 1530, 1330, 1250, 730, 680 cm^{-1}.

12. Spectroscopic data of **4a** is as follows. **4a**: mp 124-125 °C; ^1H NMR ($CDCl_3$) δ 7.41-7.17 (m, 10H), 6.67 (d, *J*= 1.1 Hz, 1H), 6.24 (d, *J*=1.0 Hz, 1H), 5.35 (s, 1H), 3.43 (s, 3H), 2.11 (s, 3H); MS, m/z (relative intensity) 321 (M^+, 18), 212 (100), 184 (75), 109 (47); IR (KBr) 3350, 1620, 1520, 1380, 1170, 750, 690 cm^{-1}.
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Enantioselective Synthesis of a *trans*-Hydrindane System for the Preparation of Vitamin D Metabolites§

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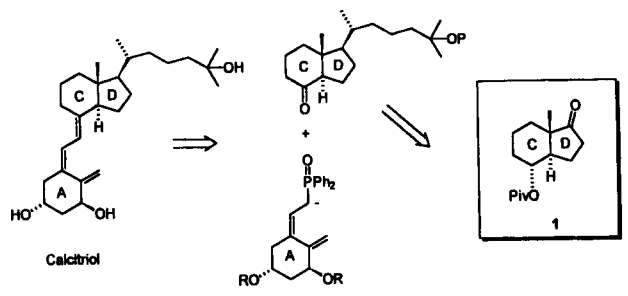
Vitamin D metabolites and their analogs are receiving an intense attention due to their medicinal and therapeutic importances.[1] *trans*-Hydrindane system constitutes the C/D ring synthon of these vitamin D compounds and continuous efforts have been made to develop new methods for constructing this structure. Approaches based on Lythgoe's methodology[2] *via* a convergent Wittig coupling of the A-ring fragments and this bicyclic C/D-ring system remain particularly attractive in the synthesis of various vitamin D related analogs. Hoffmann-LaRoche group's synthesis[3] of 1α, 25-dihydroxycholecalciferol (calcitriol), a medicinally active vitamin D_3 metabolite, is the classical example employing this strategy (Scheme 1).

Control of vicinal stereochemistry is very important in constructing this *trans* "angularly methylated" hydrindane and much effort has been directed to this area. For the enantioselective synthesis of angularly methylated hydrindanes, various routes have been devised including intramolecular Diels-Alder methodology,[4] *o*-quinodimethane strategy,[5] chiral auxiliary induced asymmetric polyene cyclization,[6] Mukaiyama-Michael conjugate addition,[7] use of β-sulfonyl vinyl ketone,[8] in addition to Uskokovic approach[3] using a known asymmetric ketoacid.[9]

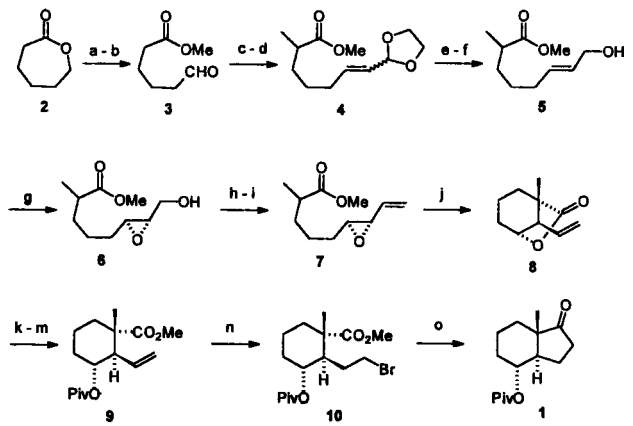


Scheme 1.

§This paper is dedicated to the 60th birthday of Professor Sang Chul Shim at KAIST.

Here we report a new enantioselective synthesis of functionalized *trans*-hydridanone **1**[10] based on the highly stereoselective epoxide cyclization reaction with carbanions.[11] Our synthetic plan is highlighted in Scheme 2.

The preparation of **7**, which served as the substrate for the intramolecular allylic epoxide cyclization was made starting from ε-caprolactone **2**. Saponification of ε-caprolactone followed by Swern oxidation[12] of the resulting ester alcohol afforded ester aldehyde **3** (77%). Two-carbon homologation to aldehyde functionality by Wittig reagent[13] gave **4** (79%) as a mixture of two isomers ((*Z*)-**4**:(*E*)-**4**=85:15). Methylation of this ketal ester **4** (61%) and subsequent ketal hy-



Scheme 2. (a) NaOMe, MeOH. (b) Swern oxidation. (c) (1,3-dioxolan-2-yl)methylenetriphenylphosphorane in DMSO, boiling THF. (d) LDA, THF; CH_3I, −78 °C. (e) 1 N HCl, THF. (f) $NaBH_4$, MeOH, 0 °C. (g) (−)-DET, $Ti(O\text{-}iPr)_4$, TBHP, 4 A° sieves, CH_2Cl_2, −23 °C. (h) Swern oxidation. (i) Ph_3PCH_3I, KHMDS, THF, −78 °C. (j) LDA, HMPA (0.3 eq.), THF, −78 °C to r.t.. (k) 1 N NaOH, MeOH. (l) CH_2N_2, ether. (m) pivaloyl chloride, DMAP (3 eq.), CH_2Cl_2. (n) HBr(g), 300 nm, *n*-pentane. (o) *t*-BuLi, THF, −78 °C.