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Regiospecific Preparation and Allylation of Fluoromethyl Ketone Enol Ethers via Fluoro-olefination of 1,2,3-Triol Derivatives

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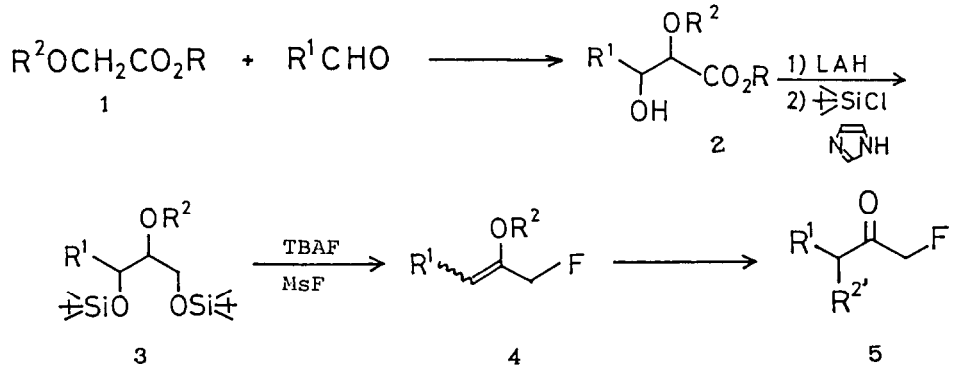
Summary: Fluoromethyl ketone enol ethers are regiospecifically prepared in good yields by treatment of 2-alkoxy-1,3-bis(*t*-butyldimethylsiloxy)alkane with TBAF-MsF, and subsequent thermal [3,3]-sigmatropic rearrangement on the 2-alkenyl enol ethers gives α-allylated products.

A fluoromethyl ketone bearing an α-branched alkenyl group has large potentials as the most convenient synthon for construction of mono-fluorinated mimics of bioactive natural compounds as prototype, in particular, of the isoprenoid unit structure. However, all the available methods deal with either fluorinated material from initial step[1], or chloro- or bromomethyl-carbonyl compounds for nucleophilic fluorination in a final step[2], whose freedom in variety as associated with accessible synthons, or chemoselectivity in syntheses is rather insufficient to date[3].

We now describe herein an efficient and regiospecific transformation of 1,2,3-triols into fluromethyl ketone enol ethers using fluoro-olefination reaction with tetrabutylammonium fluoride(TBAF) and methanesulfonyl fluoride(MsF)[4], and a subsequent allylation by thermal [3,3]-sigmatropic rearrangement. In the present method alkoxyacetic acid ester 1 can be employed in order to give a ready access to a fluoroacetyl synthon.



The key intermediate, 2-alkoxy-1,3-bis(*t*-butyldimethylsiloxy)-alkane **3** is readily prepared in good overall yield (80-100 %) via aldol type addition of 1 with an aldehyde followed by reduction with LAH and silylation with *t*-butyldimetylsilyl chloride/imidazole in DMF. Treatment of 1,3-bis(*t*-butyldimethylsiloxy) ether **3** with TBAF, and MsF gave **4** exclusively as a mixture of *E*-and *Z*-isomers. Examples of fluoro-olefination are listed in Table 1.

Table 1: Preparation of Fluoromethyl Ketone Enol Ether[a]

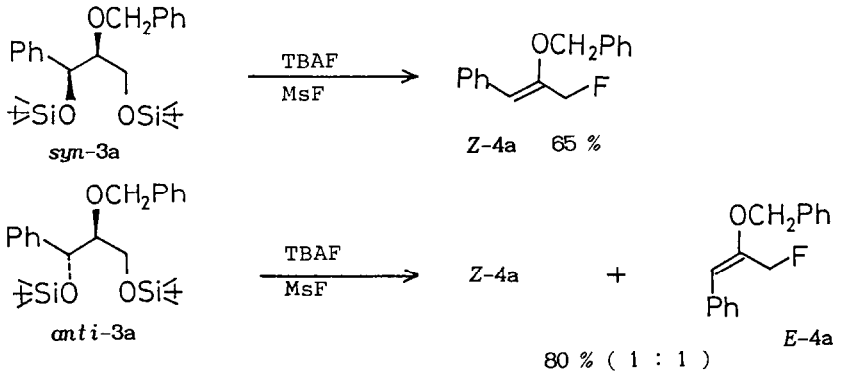
entry	R^1	R^2	4 yield (%)[b]
a	Ph	$PhCH_2$	85
b	$PhCH{=}CH$	$PhCH_2$	76
c	$PhCH_2CH_2$	$PhCH_2$	49
d	Ph	β-Np	73
e	$PhCH{=}CH$	β-Np	80
f	Ph	$PhCH{=}CHCH_2$	74

[a] The reaction was carried out with 3:TBAF:MsF=1:5.0:3.5 in THF at 50-55 °C for 12-36 hr.

[b] Isolated yield. All compounds gave satisfactory spectral data.

As shown in Table 1 most of the bis(siloxy)ethers gave the fluoromethyl ketone enol ethers in good yields, and no regioisomers were obtained. When R^2=alkyl, the fluorination reaction proceeded slowly to give the desired product in moderate yield.

Stereochemical outcome of the fluoro-olefination was examined by using **3a** as model. The *syn*-isomer gave *Z*-**4a** exclusivly, whereas the *anti*-isomer afforded a mixture of *Z*- and *E*-isomers in a 1:1 ratio[5].



This result may be explained as follows: the *anti*-elimination of MsOH is facilitated with *syn*-**3a** where leaving 3-MsO and 2-proton can occupy the *anti* position. However, the *anti* disposition of 3-MsO and H appears to be hindered in the *anti*-**3a** due to a gauche interaction between Ph and CH_2, giving a 3-mesyloxy-1-alkene or a mixture of mesyloxy-1- and 2-alkenes as intermediate, which is then fluorinated to afford a mixture of *E*- and *Z*-olefins[6].

Regiospecfic allylation of the resultant enol ethers could be accomplished with allyl enol ether derivatives via [3,3]-sigmatropic rearrangement. Results are shown in Table 2.

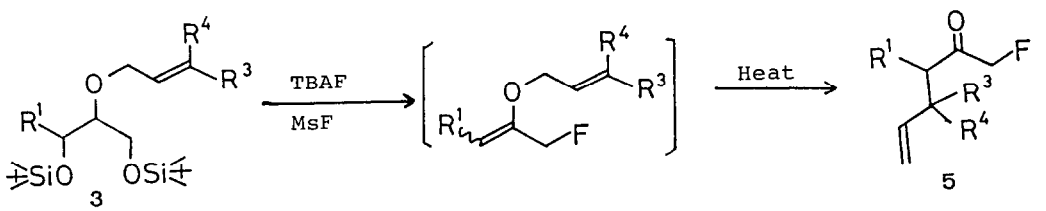


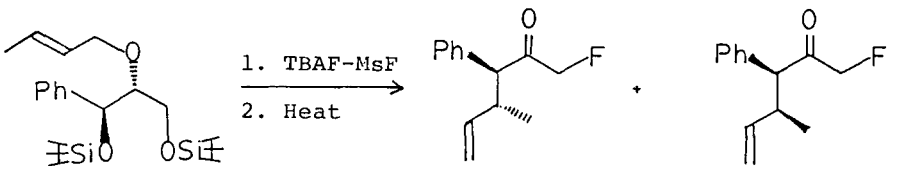
Table 2: Preparation of 3-Allyl-1-fluoroalkan-2-one via [3,3]-Sigmatropic Rearrangement[a]

entry	R^3	R^4	5 yield (%)[b]
g	H	H	95
h	CH_3	H	89
i	CH_3	CH_3	53

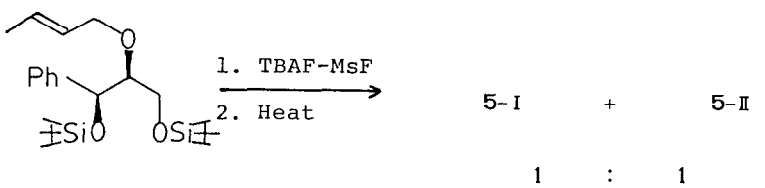
[a] The reaction was carried out with 3:TBAF:MsF=1:5.0:3.5 in THF at 50-55 °C for 12-36 hr and then in $PhCH_3$ at reflux for 2 hr.

[b] Isolated overall yield from 3. All compounds gave satisfactory spectral data.

As shown, allyl substituents were regiospecifically introduced in good yields. In the cases with 3h and 3i the rearrangement proceeded under fluoro-olefination conditions (THF, 50 °C), while more forced conditions ($PhCH_3$, reflux) were needed for 3g. Furthermore, the stereochemistry of the introduced methallyl group was examined particularly with 3h. The *anti*-3h gave a 3:1 mixture of 5-I and 5-II, whereas the *syn*-3h gave a 1:1 mixture of the isomers[7]. We are currently studying the effects of substituents in this reaction.



anti-3h　　5-I　　5-II



syn-3h

In addition, the 1,3-bis(siloxy)alk-2-yl ethers 4, the essential intermediates of the present procedure, can be also derived from 1,2,3-triols through selective protection/deprotection methods[8]. This methodology provides us with an important pathway leading to a wide variety of fluoromethyl ketones most suitable for synthesis of monofluorinated mimics of bioactive natural products.

The following example represents a typical experimental procedure: a solution of TBAF·$3H_2O$ (397 mg, 1.26 mmole) in 5 ml of THF was stirred with molecular sieves 4A(1.5 g) at room temp for 1 hr. To it was added successively solutions of the bis(siloxy)ether 3a(122 mg, 0.252 mmole, a mixt. of *anti*- and *syn*-isomers) in 2 ml of THF and MsF(86 mg, 0.878 mmole) in 2 ml of THF at room temp. After being stirred at 50-55 °C for 36 hr, the reaction mixture was filtered through a pad of SiO_2. Concentration of the filtrate gave an oil, which was separated on TLC(eluent:n-Hexane/EtOAc=4/1) to give 4a(51.6 mg, 85 %) as a mixture of *E*- and Z-isomers.

References and Notes

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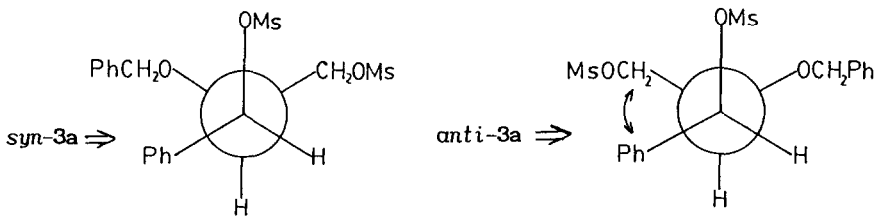
5. *Syn*- and *anti*-**3a** were readily separated by flash column chromatography of the corresponding 1,3-acetonides. *Z*-**4a** and *E*-**4a** exhibit the following NMR spectra; *Z*-**4a**:($CDCl_3$) δ 4.99 (d, 2 H, J = 48.2 Hz), 5.10 (s, 2 H), 5.78 (d, 1 H, J = 5.5 Hz), 7.2~7.8 (m, 10 H). *E*-**4a**:($CDCl_3$) δ 4.96 (d, 2 H, J = 48.3 Hz), 4.98 (s, 2 H), 6.06 (d, 1 H, J = 3.94 Hz), 7.2 ~ 7.5 (m, 10 H). Stereochemistry of **4a** was determined based on chemical shifts of olefinic protons. (higher for *Z*-**4a** than that for *E*-**4a**)
6. The bis-mesylated intermediates are depicted below:



7. The following NMR spectra were obtained for **5**-I and **5**-II, respectively. **5**-I :($CDCl_3$) δ 1.09 (d, 3 H, J = 6.37 Hz), 2.8 ~ 3.3 (m, 1 H), 3.74 (dd, 1 H, J = 10.23 and 3.30 Hz), 4.76 (d, 2 H, J = 47.47 Hz), 4.7 ~ 5.0 (m, 2 H), 5.49 (ddd, 1 H, J = 7.47, 9.89 and 17.14 Hz), 7.2 ~ 7.3 (m, 5 H). **5**-II :($CDCl_3$) δ 0.79 (d, 3 H, J = 6.81 Hz), 2.8 ~ 3.3 (m, 1 H), 3.75 (dd, 1 H, J = 3.52 and 10.77 Hz), 4.72 (d, 2 H, J = 47.68 Hz), 4.9 ~ 5.2 (m, 2 H), 5.79 (ddd, 1 H, J = 17.36, 10.11 and 7.47 Hz), 7.3 (s, 5 H). Stereochemistry of **5**-I and **5**-II was determined by examining chemical shifts of CH_3 and olefinic protons. (CH_3: higher for **5**-II ,olefinic: higher for **5**-I); related examples, see, D. E. McGreer and J. W. McKinley, *Can. J. Chem.*, 49, 105 (1971); W. Sucrow and W. Richter, *Chem. Ber.*, 104, 3679 (1971).
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