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Selective monofluorination of diols using DFMBBA

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Selective monofluorination of 1,2- or 1,3-diols was achieved by the reaction with DFMBBA. The method is applicable for the synthesis of optically active fluorohydrin derivatives.

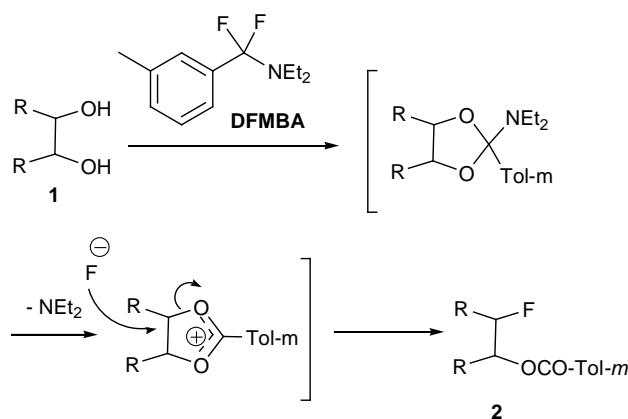
Selective monofluorination of 1,2- or 1,3-diols is useful methodology for the synthesis of fluorinated sugars,¹ nucleosides,² or optically active fluorohydrins.³ However, it is difficult to selectively convert one hydroxy group of the diols to fluoride and leave another one unchanged, because prevention of the second deoxyfluorination reaction is usually difficult. Moreover, when 1,2- or 1,3-diols were treated with diethylaminosulfur trifluoride (DAST), the most typical deoxyfluorination reagents, or deoxyfluor™, its analog, side reactions such as rearrangement⁴ or cyclic sulfonate formation⁵ competitively took place, and the expected fluorination products could not be obtained in good yields. Recently, we reported that primary and anomeric hydroxy groups in sugars can be selectively converted to fluoride by *N,N*-diethyl- α,α -difluoro(*m*-methylbenzyl)amine (DFMBBA).⁶ We wish to report here the selective monofluorination of diols using DFMBBA and its application for the synthesis of optically active fluorohydrin derivatives.

When ethylene glycol (**1a**) was subjected to the reaction with 2.4 eq of DFMBBA in heptane at 98 °C for 1 h, *m*-methylbenzoyl ester of 2-fluoroethanol (**2a**) was obtained in 79 % yield. Only one hydroxy group of **1a** was fluorinated and the other hydroxy group was esterified by DFMBBA. When the reaction was carried out under irradiation of microwave, the reaction was completed in 10 min and **2a** was obtained in 73 % yield.

Under similar conditions, various 1,2-diols (**1a,c,d**) and 1,3-diols (**1b,e,f**) could be converted to the corresponding fluorohydrin derivatives in good yields as shown in Table 1. When an unsymmetrical diol (**1f**) was used, a mixture of two regioisomers was obtained nonselectively. On the other hand, the reaction of 1,12-dodecanediol (**1g**), in which the hydroxy groups are separated by many methylene groups, gave a difluorinated product in good yield.

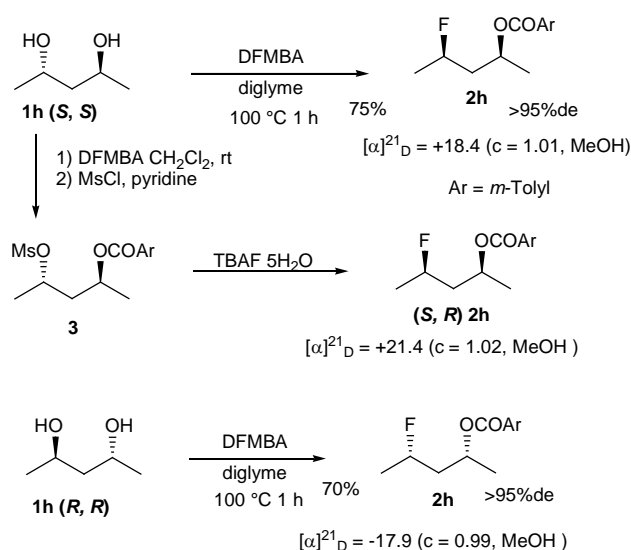
Any special care is not necessary to terminate the reaction at monofluorinated step. Therefore, the reaction seems to be proceeding through a cyclic intermediate, and after monofluorination reaction, the remained hydroxy group was changed to the ester group which is inert to DFMBBA (Scheme 1).

When an optically active (2*S*,4*S*)-2,4-pentandiol (**1h**) was subjected to the reaction with DFMBBA, a monofluorinated product (**2h**) was obtained in 75 % yield with high diastereoselectivity. In order to examine the stereochemistry of the reaction, **1h** was converted to the monomesylate **3**. Monofluorination of **3** was carried out with



Scheme 1

the inversion of stereochemistry by TBAF 5H₂O⁷ to give (2*S*,4*R*)-4-fluoro-2-pentanol *m*-methylbenzoyl ester. As its ¹H and ¹⁹F NMR spectra, and optical rotation⁸ coincided with those of **2h**, fluorination of alcohols by DFMBBA was found to proceed with inversion of stereochemistry. From (2*R*,4*R*)-**1h**, (2*R*,4*S*)-**2h** was obtained selectively (Scheme 2).



Scheme 2

In a similar manner, optically active fluorohydrin derivatives could be obtained from commercially available optically active 2,3-pentandiol (**1i**), 1,2-diphenylethanediol (**1j**) with high diastereoselectivity. In nature, many compounds such as sugars have optically active diol functions. When a manitol derivative

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See <http://www.rsc.org/suppdata/xx/b0/b000000x/>

* xxx@aaa.bbb.ccc

(**1k**) was subjected to the reaction with DFMBFA, a monofluorinated product (**2k**) was obtained with high diastereoselectivity.

Table 1 Reaction of diols with DFMBFA

Diol	Solvent	Condition	Product	Yield (%) ^a
$\text{HO}-(\text{CH}_2)_n-\text{OH}$ 1a : $n = 2$ 1b : $n = 3$	heptane diglyme	98 °C 1 h 100 °C 1 h	$\text{F}-(\text{CH}_2)_n-\text{OCOTol-}m$ 2a : $n = 2$ 2b : $n = 3$	79 75
 1c $n = 1$ 1d $n = 7$	heptane heptane	MW 10 min MW 10 min	 2c $n = 1$ 2d $n = 7$	82 75
 1e	heptane	MW 2 min	 2e	88
 1f	diglyme	100 °C 1 h	 2f-1 38 : 62 ^b 2f-2	78
$\text{HO}-(\text{CH}_2)_{12}-\text{OH}$ 1g	heptane	MW 10 min	$\text{F}-(\text{CH}_2)_{12}-\text{F}$ 2g	91
 1i : $\text{R} = \text{CH}_3$ 1j : $\text{R} = \text{Ph}$ 1k : $\text{R} = \text{O} \begin{array}{c} \diagup \text{CH}_2 \diagdown \\ \quad \\ \text{C} \quad \text{C} \\ \quad \\ \text{CH}_2 \text{CH}_2 \end{array}$	diglyme — nonane	140 °C 1.5 h 140 °C 1 h MW 10 min	 2i 2j 2k	74 (>95) 83 (>95) 55 (>95)

^a Isolated yields based on diols used. In parentheses, diastereoselectivities. ^b Determined by ¹⁹FNMR.

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Notes and references

† **General procedure of mono-fluorination of diols using DFMBFA:** A mixture of diol (1 mmol), DFMBFA (2.2 mmol), and solvent (1 ml) in a Teflon PFA™ vessel was heated by microwave⁶ or oil bath at the temperature and for the time shown in Table 1. After the reaction, the mixture was poured into aq NaHCO₃ and extracted with ether three times. The combined organic phases were dried over MgSO₄, concentrated under reduced pressure, and purified by column chromatography (silica gel/hexane-ether) to give monofluoride **2**.

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- (2*R*, 4*S*)-**2h**, prepared by the reaction with TBAF-5H₂O, was contaminated by about 10 % of olefinic by-products which were difficult to separate from **2h**, and it must be the reason why it had a larger value in optical rotation than that of **2h** prepared from **1h** and DFMBFA.