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A NOVEL REAGENT FOR REGIOSELECTIVE CLEAVAGE OF 2,3-EPOXYALCOHOLS BY FLUORIDE - A SYNTHESIS OF 3-FLUORO-2,3-DIDEOXY-D-*ERYTHRO*-PENTOSE.

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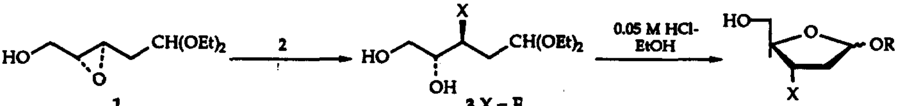
Key Words: Regioselective epoxide cleavage; bis(isopropoxy)titanium difluoride; tri(isopropoxy)titanium fluoride; 2,3-epoxy alcohols; 3-fluoro-2,3-dideoxy-D-*erythro*-pentose.

ABSTRACT: **The cleavage of the oxirane ring of 3,4-anhydro-2-deoxy-D-*threo*-pentose diethyl acetal by (isopropoxy)-titanium fluorides is discussed. The high regioselectivity found with bis(isopropoxy)titanium difluoride is the basis for an enantioselective synthesis of 3-fluoro-2,3-deoxy-D-*erythro*-pentose from a non-carbohydrate precursor.**

The excellent anti-HIV[1] activity of 3'-fluoro-3'-deoxythymidine (FLT) has generated much attention to the preparative synthesis of 3-fluoro-2,3-dideoxy-D-ribose from carbohydrate[2] and non-carbohydrate precursors.[3] Conceptually, an expedient synthesis of **7** by fluoride cleavage of epoxy acetal **1** would be desirable, but reactions with the traditional fluorinating reagents, *e.g.* potassium bifluoride in refluxing ethylene glycol[4] (<5%) or hydrogen fluoride in dioxane (<5%),[5] afforded low yields of fluoroacetal **3** in addition to poor regioselectivity. We have previously reported that substituted tri(isopropoxy)titanium reagents, $(i\text{-PrO})_3TiX$ (X = Cl, RCO_2 and RCOS),[6] are effective in cleaving 2,3-epoxyalcohols, *e.g.* **1**, with high regioselectivity and this procedure is the cornerstone for a general synthesis of 2,3-dideoxypentoses.[7] We will communicate in this report an extension of the above methodology for the synthesis of ethyl 3-fluoro-2,3-dideoxy-D-ribosides (**5**) from 3,4-anhydro-2-deoxy-D-*threo*-pentose diethyl acetal (**1**) *via* a regioselective epoxide cleavage with titanium-based fluorinating agents.



1

3 X = F
4 X = $i\text{-}C_3H_7O$

5 X = F; R = Et
6 X = $i\text{-}C_3H_7O$; R = Et
7 X = F; R = H

$$Ti(O\text{-}i\text{-}Pr)_4 + n\,RCOF \longrightarrow (i\text{-}PrO)_{4-n}TiF_n + RCO_2\text{-}i\text{-}Pr$$

R = CH_3 or C_6H_5

2a n = 1
2b n = 2.2
2c n = 2.7

In contrast to the earlier described titanium reagents, the reaction of tri(isopropoxy)titanium fluoride [$(i\text{-PrO})_3TiF$

(2a)], obtained from titanium (IV) isopropoxide and acetyl fluoride (or benzoyl fluoride),[8] with epoxy alcohol **(1)** afforded predominantly (>95%) the 3-isopropoxy acetal **(4)** with small amounts of the 3-fluoroacetal **(3)**. The preference for **4** is a consequence of the intrinsic low nucleophilicity of fluoride *vs.* isopropoxide. We thus considered, the more Lewis acidic higher-order alkoxyfluorotitaniums, *e.g.* $(i\text{-PrO})_2TiF_2$ and $(i\text{-PrO})TiF_3$, which are obtained by reacting titanium (IV) isopropoxide with benzoyl fluoride (2 or 3 equiv.). Interestingly, elemental and spectroscopic analyses of the higher order alkoxytitanium fluorides showed that they are mixtures of dialkoxytitanium difluoride and monoalkoxytitanium trifluoride. Thus, the fluorine-titanium ratios of the so-call di(isopropoxy)titanium difluoride **(2b)** and mono(isopropoxy)titanium trifluoride **(2c)** were 2.2 and 2.7, respectively.

Indeed, increasing the fluoride-titanium ratio from 1 to 2.2, "$(i\text{-PrO})_{1.8}TiF_{2.2}$", resulted in increased amounts of the acetal **(3)** (5 to 20%), but further increases in the fluoride-titanium ratios were not effective. As shown in Table 1, significant enhancements in the ratio of acetal **3** to acetal **4** were obtained at higher temperatures and not with variations in reaction solvents or times. However, at higher temperatures, concommitant formation of the deoxyribosides **(5-6)** occurred. Since, we were interested in the acid labile **5**, mild acid catalyzed cyclization (0.05M HCl - CH_2Cl_2) of **3** afforded high yields (>85%) of the α,β-anomers.

Table 1. Ring Cleavage of 3,4-Anhydro-2-deoxy-D-*threo*-pentose Diethyl Acetal (1) with Di(isopropoxy)titanium difluoride

Reaction Conditions				**Product Yield, %**			
Solvent	**T°C**	**time (hr)**	**Conversion,%**	**3** (X = F)	**5** (X = F)	**4** (X = *i*-PrO)	**6** (X = *i*-PrO)
chloroform	0	10	90	5	-	95	-
chloroform	20	1.5	>98	20	-	80	-
hexane	20	2.0	>98	18	-	82	-
benzene	20	1.5	>98	23	-	77	-
hexane	69	0.5	>98	33	3	5	59
benzene	80	0.1	>98	47	5	≤2	≥46
heptane	98	0.1	>98	38	10	-	52
toluene	112	0.1	>98	40	12	-	48

In summary, we have described a) the synthesis of a series of higher order alkoxytitanium fluorides and b) their use in a regioselective cleavage of 2,3-epoxy alcohols. Further refinements of these reagents will be described in a later communication.

References and Notes

1. a) Hartmann, H.; Vogt, M. W.; Durno, A. G.; Hirach, M. S.; Hunsmann, G.; Eckstein, F. *AIDS Res. Hum. Retroviruses*, **1988**, *4*, 457. b) Koshida, R.; Cox, S.; Harmenberg, Y.; Gilljam, G.; Wakren, B. *Antimicrob. Agents Chemother.*, **1989**, *33*, 2083-2088. c) Balzarini, J.; Baba, M.; Pawels, R.; Herdewijn, P.; De Clercq, E. *Biochemical Pharmacology* **1988**, *37*, 2847. d) Herdewijn, G.; Balzarini, J.; De Clercq, E.; Pauwels, R.; Baba, M.; Broder, S.; Vanderhaeghe, H. *J. Med. Chem.* **1987**, *30*, 1270. e) Huang, J.-T.; Chen, L.-C.; Wang, L.; Kim, M.-H.; Warshaw, J. A.; Armstrong, D.; Thu, Q.-Y.; Chou, T.-C.; Watanabe, K. A.; Matulic-Adamic, J.; Su. T.-L.; Fox, J. J.; Polsky, B.; Baron, P. A.; Gold, J. W. M.; Hardy, W. D.; Zuckerman, E. *J. Med. Chem.*, **1991**, *34*, 1640-1646.
2. a) Fleet, G. W. J.; Son, J. C.; Derome, A. E., *Tetrahedron*, **1988**, *44*, 625-636. b) Fleet, G. W. J.; Son, J. C. *Tetrahedron*, **1987**, *28*, 3615-3618.
3. Bravo, P.; Piovosi, E.; Resnati, G.; Fronza, G. *J. Org. Chem.*, **1989**, *54*, 5171-5176.
4. Welch, J. T. *Tetrahedron*, **1987**, *43*, 3123-3197.
5. Kowollik, G.; Landen, P. Z. *Chem.*, **1975**, *15*, 147-148.
6. Raifeld, Yu. E.; Nikitenko, A. A.; Arshava, B. M. *Tetrahedron Asymmetry*, **1991**, *2*, 1083-84..
7. a) Makin, S.M.; Raifeld, Y.E.; Zilberg, L.L.; Arshava, B.M. *Zh. Org. Khim.*, **1984**, *20*, 210-211. b) Raifeld, Yu. E.; Zil'berg, L. L.; Arshava, B. M.; Makkin, S. M. *Zh. Org. Khim.*, **1984**, *20*, 1330-2. c) Arshava, B. M.; Raifeld, Yu. E.; Makin, S. M. *Zh. Org. Khim.*, **1990**, **26**, 1664-71. d) Raifeld, Yu. E.; Vid, G. Ya; Mikerin, I. E.; Arshava, B. M.; Nikitenko, A. A. *Carbohydrate Research*, **1991**, in press.
8. Bruker, A. B.; Frenkel, R. I.; Soborovski, L. Z. *Zh. Obshch. Khim.*, **1958**, *28*, 2413-2415.

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