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Electronically Promoted Payne Rearrangement of 3-CF_3-2,3-Epoxyalcohols

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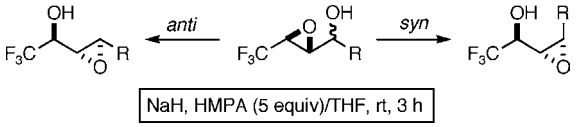
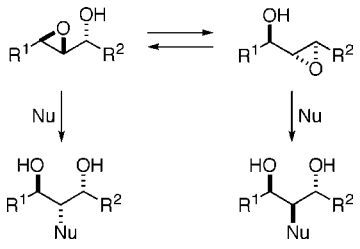
ABSTRACT



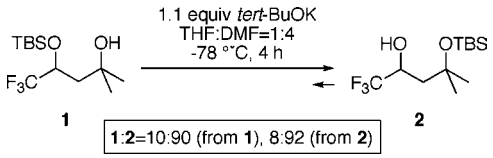
Smooth and selective Payne rearrangement was achieved for the above types of epoxyalcohols with a CF_3 group so as to form thermodynamically more stable alkoxides, where the strongly electron-withdrawing nature of this moiety played a significantly important role and was proved to overcome increased steric instability of epoxides from syn-*E* to anti-*Z* isomers.

Payne rearrangement[1] is known as the base-catalyzed migration of 2,3-epoxyalcohols proceeding with inversion of stereochemistry at the 2 position and is a well-documented and widely used synthetic tool for the construction of target materials.[2] However, formation of an isomeric epoxyalcohol mixture caused a significant problem because, for example, the subsequent oxirane ring opening by appropriate nucleophilic species at the 2 position should furnish epimeric materials. For this reason, it is a crucial issue for synthetic chemists to properly control such a thermodynamic equilibrium.



During the course of our synthetic study of sugars trifluorinated at the 6 position,[3] we have found that the strongly electron-withdrawing CF_3 group promoted the migration of a TBS moiety employed for the hydroxy protection, which effectively facilitated the troublesome and lengthy protection−deprotection processes. Scheme 1 shows a typical example:[4] independent subjection of monosilylated diols **1** and **2** to the described basic condition yielded essentially the same **1**:**2** mixture ratio, which was rationalized as follows. In this sequence, stabilization of the resultant alkoxide directly obtained from **2** should be more pronounced than the one

Scheme 1



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(1) Hanson, R. M. *Org. React.* **2002**, *60*, 1.
(2) (a) Prasit, P.; Robertson, G.; Rokach, J. *Carbohydr. Res.* **1990**, *202*, 93. (b) Wrobel, J. E.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 3761.
(3) (a) Yamazaki, T.; Mizutani, K.; Kitazume, T. *J. Org. Chem.* **1993**, *58*, 4346. (b) Yamazaki, T.; Mizutani, K.; Kitazume, T. *J. Org. Chem.* **1995**, *60*, 6046.
(4) Yamazaki, T.; Oniki, T.; Kitazume, T. *Tetrahedron* **1996**, *52*, 11753.

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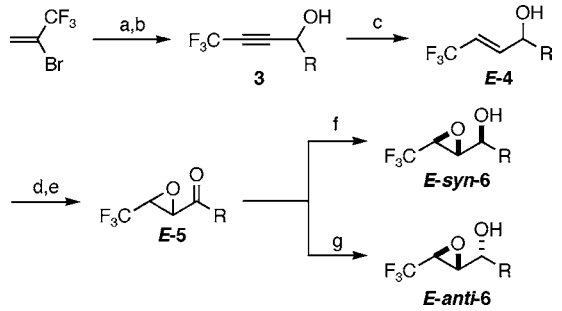
from **1** because of the strongly inductive electron-withdrawal by the CF_3 group, which overwhelmed the undesired steric congestion occurring in **2** and, as a result, moved the equilibrium toward the right to produce the sterically more crowded but electronically more stabilized compound **2**.[5]

This basic information in hand, we have devised a utilization of this anion-stabilizing ability to the Payne rearrangement of 3-CF_3-2,3-epoxyalcohols[6] which led to the anticipation of a single product due to the expected strong equilibrium preference between two isomeric materials. In this communication we describe our preliminary results on this topic, realizing the efficient stereodivergent construction of regioisomeric target epoxyalcohols from a single α,β-unsaturated ketone by way of this unique pathway as the key step.

The requisite diastereomeric starting materials ***E-syn-*** and ***E-anti*-6** were stereoselectively prepared as shown in Scheme 2. Allylic alcohols ***E*-4**, obtained by condensation of in situ

Scheme 2 [a]



[a] Reagents and conditions: (a) 2 equiv LDA/THF, −78 °C, 5 min. (b) RCHO, −78 °C, 30 min. (c) Red-Al/toluene, −78 °C, 3 h. (d) PDC, Ac_2O/CH_2Cl_2, reflux 1 h. (e) Urea-H_2O_2, DBU/THF, −30 °C, 6 h. f) DIBAL-H/THF, −78 °C, 1 h. (g) $NaBH_4$-ZnI_2/CH_2Cl_2, −78 to −10 °C, 6 h. **a**: R = $PhCH_2CH_2$. **b**: R = *n*-C_6H_{13}. **c**: R = Ph. **d**: R = $PhCH_2C(CH_3)_2$.

generated 3,3,3-trifluoropropynyllithium and appropriate aldehydes, followed by the Red-Al reduction,[3b] were transformed into enones that were then reacted with UHP (urea hydrogen peroxide) in the presence of DBU[7] to furnish epoxyketone ***E*-5**. This is the route of choice because the direct electrophilic epoxidation of ***E*-4** was found to be difficult because of the attachment of the strongly electron-withdrawing CF_3 group to the π-system, effectively decreasing the electron density as well as the HOMO energy level[8] which resulted in lower nucleophilicity. Epoxyalcohols ***E*-6** were obtained by the judicious choice of the reducing agents: in the case of R = $PhCH_2CH_2$-, DIBAL-H furnished the syn isomer in a stereoselective fashion by way of an acyclic Felkin−Anh type of transition state (92% syn), whereas intramolecular chelation led to predominant formation of ***E-anti*-6** when the $NaBH_4$−ZnI_2 system[9] was employed (90% anti). The results from four types of substrates (**a**−**d** as shown in Scheme 2) were collected in Table 1. As

Table 1. Preparation of ***E*-4**, ***E*-5**, and ***E*-6**

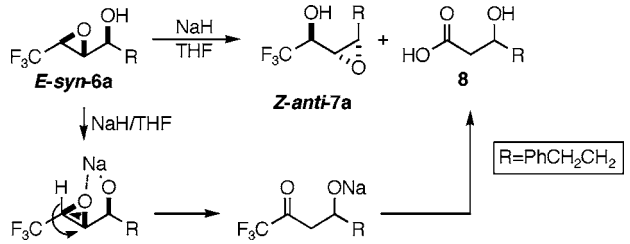
		isolated yield (%)			
	R	**4**[a]	**5**	***E-syn*−6**[b]	***E-anti*−6**[b]
a	$PhCH_2CH_2$	96	61	91 (92:8)	97 (10:90)
b	*n*-C_6H_{13}	84	47	90 (88:12)	83 (11:89)
c	Ph	91	69[c]	90 (46:54)	90 (14:86)
d	$PhCH_2C(CH_3)_2$	88	53[d]	96 (17:83)	67 (5:95)

[a] Total yield from 2-bromo-3,3,3-trifluoropropene. [b] In the parenthesis are shown the syn:anti ratios. [c] Epoxidation was carried out at −30 °C for 2 h. [d] Epoxidation was carried out at −30 °C to rt for 6 h.

reported previously, **4** was obtained in excellent yields, and the two-step sequence to **5** was performed in about 80% for each transformation, resulting in moderate yields.

We next tried to find appropriate reaction conditions for Payne rearrangement using ***E-syn*-6a** as the representative substrate. Treatment of this compound by NaH in THF at 0 °C led to production of the desired rearranged product ***Z-anti*-7a** in only 49% yield along with 50% of the unexpected β-hydroxy carboxylic acid **8** (Scheme 3). The

Scheme 3



latter might be formed by the 1,2-hydride shift of the epoxyalkoxide followed by release of the CF_3 group from the resultant hydroxyketone.[10] Because activation of the intermediate by the intramolecular chelation of sodium cation is assumed to be responsible for the formation of this byproduct, we tried to change this coordination circumstance. It is noteworthy that addition of 5 equiv of HMPA significantly affected the present reaction, leading to completion of isomerization from ***E-syn*-6a** to ***Z-anti*-7a** in only 3 h at ambient temperature in 96% yield.

This rearrangement is quite unique for the following two reasons: (1) in general, Payne rearrangement proceeds

(5) In TBS migration from secondary to secondary hydroxyl groups, perfect regioselectivity was obtained.

(6) Payne rearrangement of the CF_3-containing materials was previously reported: von dem Bussche-Hünnefeld, C.; Seebach, D. *Chem. Ber.* **1992**, *125*, 1273.

(7) Allen, J. V.; Bergeron, S.; Griffiths, M. J.; Mukherjee, S.; Roberts, S. M.; Williamson, N. M.; Wu, L. E. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3171−3180.

(8) Shinohara, N.; Haga, J.; Yamazaki, T.; Kitazume, T.; Nakamura, S. *J. Org. Chem.* **1995**, *60*, 4363.

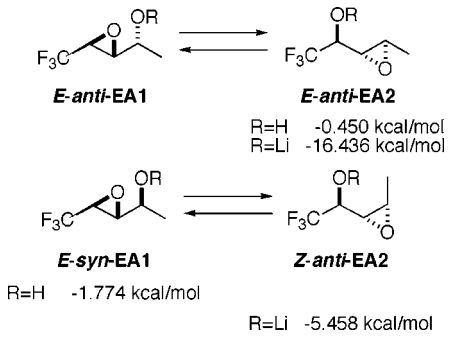
(9) Fustero, S.; Pina, B.; Torre, M. G.; Navarro, A.; Arellano, C. R.; Simon, A. *Org. Lett.* **1999**, *1*, 977.

(10) Hydrolytic removal of a CF_3 group was previously reported: Delgado, A.; Clardy, J. *Tetrahedron Lett.* **1992**, *33*, 2789.

smoothly in an aqueous media and there have been relatively few examples occurring in aprotic solvents, and (2) as is understood readily, ***E-syn*-6a** is a very rare substrate to be exclusively converted to the isomeric ***Z-anti*-7a** with an apparently sterically less stable cis epoxy function. Thus, the energetic difference of sodium alkoxides from ***E-syn*-6a** and ***Z-anti*-7a** would be large enough to compensate for such a steric disadvantage.

Next, ab initio computation (B3LYP/6-31+G*) of the model compounds was carried out[11] to clarify, from the theoretical point of view, if this assumption was the case (Scheme 4). For convenience of calculation, the actual

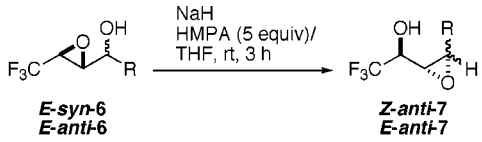
Scheme 4



countercation, sodium, was replaced by lithium. Four isomers with two types of substituents R were compared, whose energy differences wearere shown in Scheme 4.[12] In consideration of equiriburium between ***E-anti*-EA1** and **-EA2**, the energetic preference expects predominance of the latter (R = H) and such tendency is significantly pronounced when R = Li, allowing us to anticipate quite smooth conversion to ***E-anti*-EA2**. On the other hand, epoxyalcohol ***E-syn*-EA1** is 1.8 kcal/mol more stable than its isomer, ***Z-anti*-EA2**, but their alkoxide forms exhibit the opposite trend and ***Z-anti*-EA2** becomes 5.5 kcal/mol more stable despite the sterically less favorable cis epoxide structure. Thus, the energetic preferences obtained by ab initio molecular orbital calculations correctly anticipates the preferred compound in equilibrium, as well as the relative reaction rate.[13]

For confirmation of generality of this electronically promoted Payne rearrangement, other ***E-syn*-** and ***-anti*-6** were employed as substrates. As shown in Table 2, stereospecific

Table 2. Payne Rearrangements of ***E-syn*-** and ***-anti*-6**



a: R=$PhCH_2CH_2$, **b**: R=*n*-C_6H_{13}, **c**: R=Ph, **d**: R=$PhCH_2C(CH_3)_2$

substrate	syn:anti	product	yield[a] (%)	selectivity[b] (%)
***E-syn*-6a**	92:8	***Z-anti*-7a**	96	92
***E-anti*-6a**	10:90	***E-anti*-7a**	91	90
***E-syn*-6b**	88:12	***Z-anti*-7b**	94	91
***E-anti*-6b**	11:89	***E-anti*-7b**	96	89
***E-syn*-6c**[c]	99:1	***Z-anti*-7c**	88[d]	99
***E-anti*-6c**	14:86	***E-anti*-7c**	91[d]	90
***E-syn*-6d**	17:83	***Z-anti*-7d**	29[e]	83
***E-anti*-6d**	5:95	***E-anti*-7d**	81	98

[a] Isolated yield unless otherwise noted. [b] Selectivity of the major isomer. [c] Recrystalized material was used. [d] 3 equiv of EtOH was added. [e] Yield was determined by ^{19}F NMR.

Payne rearrangement was attained with excellent isolated yields irrespective of the original stereochemistry of substrates employed. Epoxyalcohols ***E-syn*-** or ***-anti*-6** were proved to follow extremely smooth rearrangement: facile interconversion of ***E-anti*-6** to ***E-anti*-7** was readily understood by the fact that this process did not require any significant change in steric hindrance, and more importantly, even ***E-syn*-6** was smoothly transformed into the sterically less favorable ***Z-anti*-7**. ***E-syn*-6c** was the special case; subjection of NaH led to formation of a structurally unknown byproduct to some extent, and modulation of the reactivity was realized when NaOEt, generated in situ by use of 1.2 equiv of NaH and 3 equiv of EtOH, was used. The low yield of ***E-syn*-6d** would result from exceeding the steric repulsive interaction between the epoxy moiety and the quaternary center next to the OH-attached carbon atom when the intramolecular S_N2 ring opening was about to occur. The relative stereochemistry was determined by the reductive ring opening of **6** and **7**.[14] For example, ***E-syn*-6a** and its rearranged isomer ***Z-anti*-7a** possessing a $PhCH_2CH_2$ group as R were independently subjected to a THF solution containing Red-Al to exclusively furnish the same 1,3-diol, ***syn*-8a**, in excellent yields without any sign of the regioisomeric 1,2-diol formation. Isolation of the diastereomeric ***anti*-8a** was also attained by application of the same procedure for both ***E-anti*-6a** and ***E-anti*-7a**. These 1,3-diols **8a** were then transformed into the corresponding acetonides ***syn*-** and ***anti*-9a** by the routine method. Close ^1H NMR

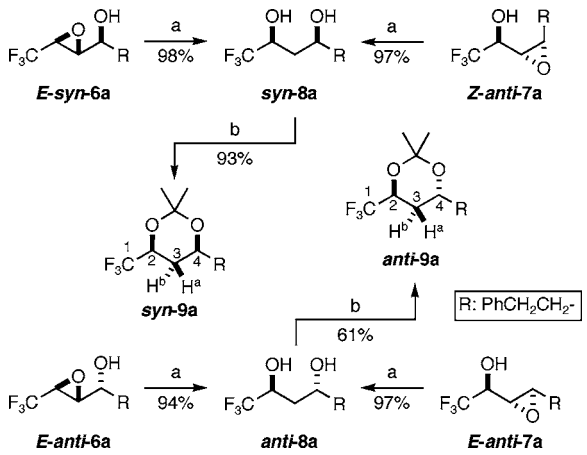
(11) Computation was carried out by Gaussian W03, version 6.0. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian, Inc.: Pittsburgh, PA, 2003.

(12) Interaction between R (H or Li) and epoxy oxygen was found in all the isomers obtained.

(13) When following the reaction by ^{19}F NMR (NaH/THF *in the absence of HMPA*), complete Payne rearrangement was observed for ***E-anti*-6a** in 5 h, but more than 10 h was required for ***E-syn*-6a**.

(14) Málek, J. *Org. React.* **1985**, *34*, 1.

Scheme 5. Reductive Epoxide Ring Opening of **6** and **7** and Acetonide Formation of the Resultant 1,3-Diols **8**[a]



[a] Reagents and conditions: (a) Red-Al/THF, rt, 3 h. (b) 2,2-Dimethoxypropane, cat. *p*-TsOH/PhH, rt, 12 h.

analysis of these materials demonstrated the 1,3-syn relationship for the former on the basis of the coupling constants observed, $J(H^2-H^{3a}) = 11.8$ Hz, $J(H^{3a}-H^4) = 11.5$ Hz, $J(H^2-H^{3b}) = 2.8$ Hz, $J(H^{3b}-H^4) = 2.6$ Hz, which unambiguously proved the axial disposition of H^2, H^{3a}, and $H.^4$ These values for the 1,3-anti isomer were $J(H^2-H^{3a}) = 9.5$ Hz, $J(H^{3a}-H^4) = 5.9$ Hz, $J(H^2-H^{3b}) = 6.6$ Hz, $J(H^{3b}-H^4) = 9.7$ Hz, supporting the anti and syn relationships between H^2-H^{3a} and $H^{3a}-H^4$, respectively. A similar tendency was also found for the acetonides **9b** and **9c**, which led to confirmation of the diastereoselection at the reduction of ***E*-5** as well as the stereostructure of **7** after Payne rearrangement. This assignment was also consistent with the result of ^{13}C NMR on the basis of Rychnovsky's report:[15] chemical shifts of the two methyl groups of acetonides were statistically almost similar (usually <2 ppm) for 1,3-anti forms, but more than 10 ppm difference was noticed for the corresponding 1,3-syn counterparts. In our instance, $\Delta\delta$ values were calculated to be 0.04 and 9.82 ppm for ***anti*-** and ***syn*-9a**, respectively.

In conclusion, we have successfully established the extraordinarily facile electronically controlled Payne rearrangement of 3-CF_3-2,3-epoxyalcohols under basic conditions, which experienced exclusive isomerization to the corresponding 1-CF_3-2,3-epoxyalcohols because the alkoxide of the latter was significantly stabilized by a strongly electron-withdrawing CF_3 group. Because of the electronic property of a CF_3 group, ring opening of these epoxyalcohols would be facilitated in a regiospecific manner so as to afford 2-substituted 1,3-diols,[16] whose verification is now in progress in our laboratory.

Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds (**3**−**9**) and computational details for ***E*-*anti*-EA1**, **-EA2**, ***E*-*syn*-EA1**, and ***Z*-*anti*-EA2**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048229X

(15) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.

(16) It is known that the CF_3-*C*-*O* bond is difficult to cleave because a CF_3 group (1) makes the neighboring bond strong and (2) prevents the approach of incoming nucleophiles by electronically repulsive interaction. See, for example, ref 8.