Regioselective β-Functionalizations of *syn*-2,3-Dihydroxy Esters

Jung Nam Park and Soo Y. Ko*

Department of Chemistry and Division of Molecular Life Sciences, Ewha Womans University, Seoul 120-750, Korea
Received October 9, 2001

Keywords : Regioselection, *syn*-2,3-Dihydroxy esters, Asymmetric dihydroxylation.

The view that epoxides correspond to "one of the main muscles" in organic synthesis[1] helps the reader understand why Sharpless's asymmetric epoxidation process has become widely accepted since its discovery.[2] Indeed, synthetic utilities of an asymmetric process will depend on, among other things, how easily the initial product of the asymmetric reaction can be converted to other enantio-enriched compounds. Accordingly, Sharpless's asymmetric dihydroxylation (AD) has rekindled the interests in diol chemistry, which in return have expanded the synthetic utilities of the AD process beyond the preparation of enantio-enriched dihydroxy compounds.[3]

The regiochemistry is among the issues that need to be considered in the chemistry of *vic*-diols. While a unique strength of the AD process is its wide scope in the substrate generality (*i.e.*, functional group tolerance), if one wishes to convert the AD products to other compounds, only certain *vic*-diols are going to allow regioselective transformations. Of these, *syn*-2,3-dihydroxy esters are perhaps among the most useful AD products as the presence of the ester substituent renders some of the diol chemistry regioselective.

Of the two hydroxyl groups in *syn*-2,3-dihydroxy esters, most of the literature examples seem to favor reactions at the α-hydroxyl site. This regioselection was achieved either via α-selective S_N2-displacements of the fully activated diols (usually in cyclic forms),[4] or *via* α-selective sulfonylations under basic conditions.[5] Therefore, β-hydroxyl-selective transformation protocol of *syn*-2,3-dihydroxy esters would complement with existing methodologies, and expand synthetic utility of the AD process.[6]

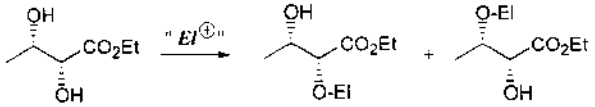
The α-regioselection observed from the sulfonylations under basic conditions was attributed to the higher acidity of the α-hydroxyl group than of the β-OH. We envisaged that the very effect that caused the α-hydroxyl group to be more acidic in 2,3-dihydroxy esters would make the non-bonding electrons of that α-hydroxyl oxygen *less* nucleophilic. Therefore, under suitable reaction conditions in which the nucleophilicities of the non-bonding electrons are determining factor for the regiochemical outcomes, electrophiles would react selectively with the β-hydroxyl group. For such reaction conditions, we investigated two sets: the *O*-stannylene ketal activating conditions[7] and acidic conditions. The regiochemical outcomes observed from each set of reaction conditions were then compared against the related results observed under basic conditions in which the acidities of the hydroxyl groups are the determining factors. The crotonate ester diol **1** was chosen as a model substrate devoid of any strong steric bias for this study (Table 1).

As reported in the literature,[5] we confirmed that this substrate exhibited a complete regioselection for the α-hydroxyl group when tosylated under basic conditions (entry 1). Benzoylation (Bz-Cl) in the presence of pyridine produced a somewhat diminished, but still synthetically useful (7 : 1) selection for the α-hydroxyl group (79% combined yield, entry 3).

These transformations were then repeated under Sn-activating conditions. While the regioselectivity for the β-hydroxyl group had been noted earlier under Sn-conditions,[6b] we repeated these reactions in the present work, specifically to find out whether the *reversal* of the regioselectivity would be realized, going from the basic to Sn-conditions as we had envisaged. For this purpose, we consciously limited ourselves in this study to using the same electrophilic reagents that had been investigated under the basic conditions.

Thus, the diol **1** was treated with Bu_2SnO in dichloroethane (reflux under a Dean-Stark, 4 hr). The mixture was then cooled to room temp and treated with tosyl chloride *without* any added base. The product thus obtained was

Table 1. Regioselective Esterifications/Etherifications of *syn*-2,3-Dihydroxy Esters



1 α-regioisomer β-regioisomer

Entry	"El"	Conditions	Reagents	Regio-selectivity (α:β)	Yield[a]
1	Ts	basic	TsCl, Et_3N[b]	α only	72%
2	Ts	Sn-activation	Bu_2SnO, TsCl[c]	1 : 1.7	83%
3	Bz	basic	BzCl, pyridine[d]	7 : 1	79%
4	Bz	Sn-activation	Bu_2SnO, BzCl[e]	1 : 34	98%
5	Bn	basic	BnBr, NaH[f]	3 : 1	67%
6	Bn	acidic	$BnOC(=NH)CCl_3$, TfOH[g]	1 : 3	60%
7	MOM	basic	MOM-Cl, NaH[h]	3 : 1	66%
8	THP	acidic	DHP, PPTS[i]	1 : 5	68%

[a]combined yield of the regioisomers. [b]TsCl (1 eq.), Et_3N (1.2 eq.) in dichloromethane. [c]Bu_2SnO (1.2 eq.) in dichloroethane, Dean-Stark reflux; TsCl (1 eq.). [d]BzCl (1 eq.), pyridine (1.3 eq.) in dichloromethane. [e]Bu_2SnO (1.2 eq.) in dichloroethane, Dean-Stark reflux; BzCl (1 eq.). [f]BnBr (1 eq.), NaH (1.2 eq.) in THF. [g]$BnO(=NH)CCl_3$ (1 eq.), TfOH (catalytic) in cyclohexane-dichloromethane (2:1). [h]MOM-Cl (1 eq.), NaH (1.2 eq.) in THF. [i]DHP (1 eq.), PPTS (catalytic) in dichloromethane.

characterized to be a 1 : 1.7 mixture of α-and β-tosylate regioisomers (83% combined yield, entry 2).[8] While the regioselectivity itself wasn't high, it was still remarkable that the same reagent (Ts-Cl) that had showed a complete regioselection for the α-hydroxyl group in the presence of Et_3N, would now display a slight, but clear preference for the β-hydroxyl group under the Sn-activation conditions. Encouraged by these results, the Sn-ketal was similarly treated with benzoyl chloride at room temp *without* any added base. The 7 : 1 α-selection under the basic conditions was now reversed to a nearly complete (34 : 1) β-preference under these Sn-conditions (98% combined yield, entry 4).

While these esterifications proceeded rapidly under the Sn-ketal activating conditions using acid chlorides, ether formation reactions using alkyl halides were too slow to be synthetically practical. The ether formations were therefore studied under acidic conditions.

To begin with usual basic conditions first, benzylation and methoxymethylation were performed using BnBr/NaH and MOM-Cl/NaH, respectively. Both produced 3 : 1 mixtures of the corresponding α-protected and the β-protected regioisomers (entries 5 and 7). While the regioselectivities for the ether forming reactions were lower than those for the esterifications under basic conditions, the direction of the regioselection was consistently for the more acidic α-hydroxyl group. It may be pointed out that the reactions studied above in the presence of bases proceed under kinetic (*i.e.*, non-equilibrating) conditions and it is arguable that the acidity, a thermodynamic term, alone should determine the regiochemical outcome. Still, the acidity factor provides a working guideline to predict the direction of the regioselections in reactions performed under basic conditions.

These ether formations could not be repeated under acidic conditions employing the same reagents (Bn-Br and MOM-Cl, respectively) as used under basic conditions. Instead, benzylation was performed employing benzyl 2,2,2-trichloroacetimidate in the presence of triflic acid.[9] Under these conditions, a 3 : 1 mixture of the β-OBn and the α-OBn regioisomers was obtained (entry 6). Clearly, a modest (3 : 1) preference for the more acidic α-hydroxyl group under basic conditions (entry 5) was reversed to a leaning (to the same extent) toward the more nucleophilic β-hydroxyl group under non-deprotonating conditions.

The methoxymethylation reaction needed further adjustments in order to be studied under acidic conditions. Neither MOM-Cl nor any other methoxymethylating agents could be used as all the usual reagents are to be employed under basic conditions.[10] Instead of the MOM-protection, therefore, we opted to study a THP-ether formation, another ketal-type protection reaction. The ester diol **1** was treated with DHP in the presence of a catalytic amount of pyridinium tosylate. The product thus obtained, being a mixture of not only the regioisomers but the diastereomers, showed too complex NMR signals to be fully analyzed. The crude product was therefore derivatized first by tosylating the remaining free hydroxyl group, then deprotecting the THP ether. The hydroxy tosylate thus obtained was characterized to be a 5 : 1 mixture of the α-OTs and the β-OTs regioisomers. This then confirmed that the original mono-THP ether product had been a 5 : 1 mixture of the β-THP and the α-THP regioisomers and that the diastereomerism had been solely due to the stereocenter on the THP ring (entry 8). Once again, a modest β-regioselection was realized in the reaction of the ester diol **1** under acidic conditions.

In conclusion, either of the two hydroxyl groups in *syn*-2,3-dihydroxy esters can now be made to react regioselectively with electrophiles. Under basic conditions, the α-hydroxyl group reacts selectively, while the preference is reversed for the β-OH under Sn-ketal activating or acidic conditions. With these complementary regioselections in the reactions of *syn*-2,3-dihydroxy ester substrates, the AD process will find further use in the syntheses of enantioenriched synthetic intermediates.

Acknowledgment. This work was supported by the MOST (00-B-WB-06-A-07). J.N.P. is grateful to the Brain Korea 21 project for a graduate fellowship.

References

1. Seebach, D.; Weidmann, B.; Wilder, L. In *Modern Synthetic Methods 1983*; Scheffold, R., Ed.; Otto Salle Verlag: Frankfurt, 1983; p 323.
2. (a) Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; vol. 7, chap 3.2. (b) Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; vol. 5, chap. 7. (c) Pfenninger, A. *Synthesis* **1986**, 89. (d) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, 2nd Ed; Ojima, I., Ed.; Wiley-VCH: New York, 2000; chap. 6A.
3. (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, 2nd Ed; Ojima, I., Ed.; Wiley-VCH: New York, 2000; chap. 6D. (c) Markó, I. E.; Svendsen, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; vol. II, chap. 20.
4. (a) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538. (b) Byun, H. S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051. (c) Lohray, B. B. *Synthesis* **1992**, 1035. (d) Kang, S. K.; Park, H. S.; Rho, H. S.; Yoon, S. H.; Shin, J. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3513. (e) Ko, S. Y. *J. Org. Chem.* **1995**, *60*, 6250. (f) Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515.
5. Fleming, P. R.; Sharpless, K. B. *J. Org. Chem.* **1991**, *56*, 2869.
6. Rare examples of the β-hydroxyl-selective transformation protocol of *syn*-2,3-dihydroxy esters: (a) Oikawa, M.; Wada, A.; Okazaki, F.; Kusumoto, S. *J. Org. Chem.* **1996**, *61*, 4469. (b) Kirschning, A.; Kreimeyer, M.; Blanke, H.-P. *Tetrahedron* **1993**, *4*, 2347. (c) We have recently observed that the Mitsunobu reactions of *syn*-2,3-dihydroxy esters are completely regioselective for the β-hydroxyl group. These results will be published elsewhere.
7. David, S.; Hanessian, S. *Tetrahedron* **1984**, *40*, 643.
8. The regioselectivity was determined by the NMR spectroscopy of the regioisomeric mixture.
9. (a) Eckenberg, P.; Groth, U.; Huhn, T.; Richter, N.; Schmeck, C. *Tetrahedron* **1993**, *49*, 1619. (b) Wessel, H. P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247.
10. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd Ed.; Wiley-Interscience: New York, 1999.