Unusual Regioselection in the Mitsunobu Reactions of *syn*-2,3-Dihydroxy Esters: Synthesis of Statine and Its Diastereomer

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Abstract: Mitsunobu reactions of *syn*-2,3-dihydroxy esters exhibit a complete regioselection for the *β*-hydroxyl group. Benzoylation, azidation, and tosylation have been performed under these conditions. *β*-Functionalizations of *syn*-2,3-dihydroxy esters are uncommon, and the Mitsunobu reactions are complementary to other diol chemistries in the regioselection. In addition, the configurational inversion accompanying the Mitsunobu protocol offers a means for diastereochemical diversity, as exemplified by a synthesis of statine and its anti diastereomer. These findings will further expand the synthetic utilities of the Sharpless AD process.

The advent of the Sharpless asymmetric dihydroxylation (AD) process has provided easy access to enantiopure vicinal-diols.[1] Selective transformations of diols further expand the synthetic utilities of the AD. Their discoveries, therefore, are much sought after. Of various AD products, *syn*-2,3-dihydroxy esters are the most common, perhaps because reliable methods exist for the construction of the substrates, (*E*)-α,*β*-unsaturated esters, with their geometry being well established.[2] As for selective transformations of AD products, *syn*-2,3-dihydroxy esters again provide a fertile ground as the presence of the ester group renders some of the alcohol chemistry regioselective.

Most of the previous works in this area result in regioselective reactions at the α-hydroxyl group of *syn*-2,3-dihydroxy esters, employing one of the following two strategies. One approach takes advantage of the higher acidity of the α-hydroxyl group (induced by the adjacent ester group).[3] Under basic reaction conditions, the more acidic α-hydroxyl group gets selectively deprotonated (if only partially), and the resulting α-alkoxide (or $R-O^{\delta-}\cdots H^{\delta+}$) regioselectively reacts with electrophiles. Sulfonylations (RSO_2Cl with pyridine or Et_3N) have been reported to produce a complete regioselection for the α-hydroxyl group. The monosulfonates thus produced are useful intermediates for synthesis of various compounds with the general structure of *anti*-α-Nu-*β*-hydroxy esters.[4]

In the second approach, both hydroxyls are activated, usually in the form of cyclic intermediates; then, only one of them gets selectively displaced by nucleophiles. The regiodifferentiation takes place in the S_N2 step, wherein the adjacent ester group favors the reaction at the C-2 to produce, once again, *anti*-α-Nu-*β*-hydroxy ester-type compounds. The cyclic activating groups studied in this approach include cyclic sulfates,[5] sulfites,[6] carbonates,[7] and thionocarbonates[8] as well as cyclic acetoxonium ions.[9] The cyclic thionocarbonates[8] and more recent cyclic iminocarbonates[10] are unique in that they can undergo rearrangements to protected hydroxy thiol and amino alcohol functionalities, respectively, with net retention of configurations at both carbinol carbons. The sulfur or nitrogen in these rearrangements is still directed at C-2 to produce, after suitable deprotections, *syn*-α-sufhydryl (or amino)-*β*-hydroxy esters.[11]

This leaves the *β*-hydroxyl-selective functionalizations of *syn*-2,3-dihydroxy esters a very much undeveloped area. A rare case of *β*-hydroxyl-selective acylation has been reported in acidic hydrolysis of the cyclic ortho esters.[12]

In addition to the regioselection, the inability of the AD process to produce anti diols means that the question of diastereochemical diversity (syn/anti) is always an important issue in this field.[13]

We postulated that while the electron-withdrawing inductive effect of the ester group made the α-hydroxyl group more acidic in 2,3-dihydroxy esters, the same effect would make the nonbonding electrons of the *β*-hydroxyl oxygen more nucleophilic. Therefore, under suitable reaction conditions in which the hydroxyls are not even partially deprotonated, electrophiles would react selectively with the *β*-hydroxyl group. A similar case of unequal nucleophilicities is well-known in amino acid chemistry where α-amino groups are far less reactive than *ω*-amino groups.[14] Of the various alcohol chemistries usually performed under nonbasic reaction conditions, Mitsunobu reactions seemed paticularly interesting to investigate as they would offer a means of addressing not only regiodiversity but also diastereodiversity issues as well (vide infra).[15]

Using the crotonate ester diol **1** as a model substrate devoid of any strong steric bias, we performed Mitsunobu reactions with triphenylphosphine-DEAD in the presence

(1) Review: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(2) (a) Wadsworth, W. S. *Org. React.* **1992**, *25*, 73. (b) Beatmann, H. J.; Vostrowsky, O. *Top. Curr. Chem.* **1983**, *109*, 85.
(3) Fleming, P. R.; Sharpless, K. B. *J. Org. Chem.* **1991**, *56*, 2869.
(4) (a) Hoffman, R. V. *Tetrahedron* **1991**, *47*, 1109. (b) Hoffman, R. V.; Kim, H. O. *Tetrahedron* **1992**, *48*, 3007. (c) Rao, A. V. R.; Rao, S. P.; Bhanu, M. N. *J. Chem. Soc., Chem. Commun.* **1992**, 859.
(5) (a) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538. (b) Lohray, B. B. *Synthesis* **1992**, 1035. (c) Byun, H. S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051.
(6) (a) Gao, Y.; Zepp, C. M. *Tetrahedron Lett.* **1991**, *32*, 3155.
(7) (a) Kang, S. K.; Park, H. S.; Rho, H. S.; Yoon, S. H.; Shin, J. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3513. (b) Chang, H.-T.; Sharpless, K. B. *Tetrahedron Lett.* **1996**, *37*, 3219.
(8) Ko, S. Y. *J. Org. Chem.* **1995**, *60*, 6250.
(9) (a) Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515. (b) Golding, B. T.; Hall, D. R.; Sakriker, S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1214.
(10) Cho, G. Y.; Ko, S. Y. *J. Org. Chem.* **1999**, *64*, 8745.
(11) cf.: (a) Cho, G. Y.; Park, J. N.; Ko, S. Y. *Tetrahedron Lett.* **2000**, *41*, 1789. (b) Park, J. N.; Ko, S. Y.; Koh, H. Y. *Tetrahedron Lett.* **2000**, *41*, 5553. (c) Cho, G. Y.; An, K. M.; Ko, S. Y. *Bull. Korean Chem. Soc.* **2001**, *22*, 432.
(12) Oikawa, M.; Wada, A.; Okazaki, F.; Kusumoto, S. *J. Org. Chem.* **1996**, *61*, 4469.
(13) cf.: (a) Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568. (b) Ko, S. Y.; Malik, M.; Dickinson, A. F. *J. Org. Chem.* **1994**, *59*, 2570.
(14) Bodanszky, M. *Principles of Peptide Synthesis*; Springer-Verlag: Berlin, 1984.
(15) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Organic Reactions*; John Wiley & Sons: New York, 1992; Vol. 42, pp 235−657.

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Scheme 1

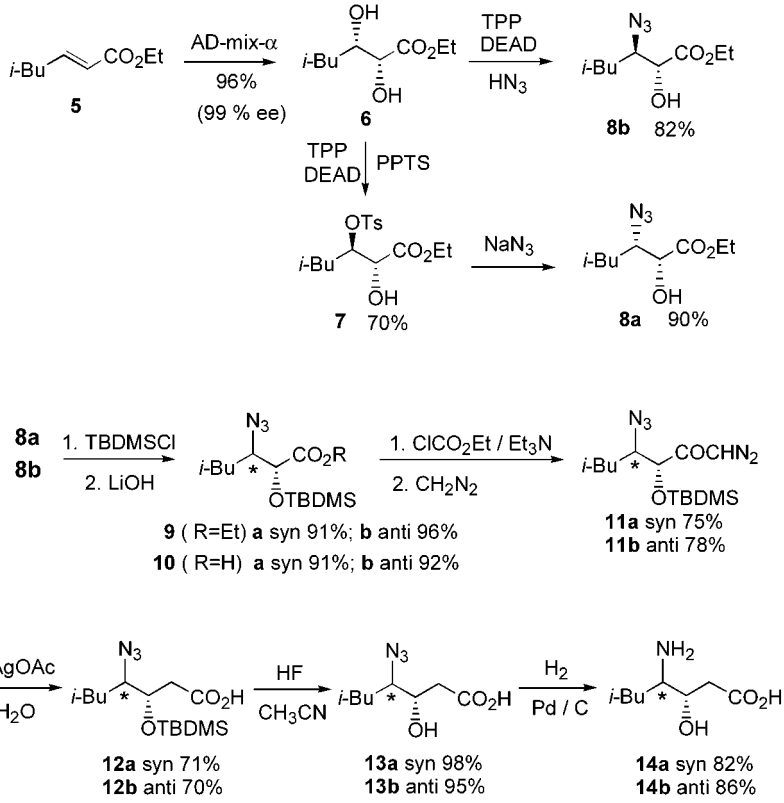
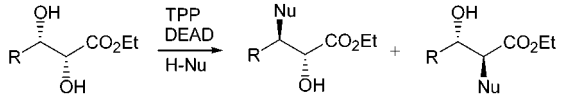


Table 1.



entry	R	H−Nu	α:β[a]	yield[b]
1	Me(**1**)	$PhCO_2H$	β only	57%
2	Me(**1**)	HN_3	β only	78%
3	Me(**1**)	Pyr·HOTs	β only	55%
4	Ph(**2**)	HN_3	β only	82%
5	*p*-MeO−Ph(**3**)	HN_3	β only	67%[c]
6	H(**4**)[d]	$PhCO_2H$	β only	88%

[a] Determined by NMR spectroscopy of the crude product. [b] Isolated yields of the β-regioisomers. Unreacted starting materials and some β-elimination products (for entries 1 and 3) make up the rest. [c] A mixture of diastereomers (anti:syn =3:1, both β-regioisomers) was obtained. [d] Butyl ester was used.

of benzoic acid, HN_3,[16] or pyridinium tosylate as the nucleophile (entries 1−3, Table 1). The reactions took place at the β-hydroxyl group with a complete regioselection, as judged by NMR spectroscopy of the crude products.[17] In cases of benzoylation and tosylation, some β-eliminations accompanied the regioselective Mitsunobu reactions, resulting in lower yields of the desired β-benzoate or β-tosylate. In no case, however, were the α-substitution products observed.[17] Cinnamate ester diol **2** and its *p*-methoxy analogue **3** also showed a complete regioselection for the β-hydroxyl group when reacted with HN_3 under Mitsunobu conditions (entries 4 and 5[18]). Acrylate diol **4** proved to be no exception in β-hydroxyl-selective Mitsunobu benzoylation (entry 6). This last example is an interesting case and points to the importance of electronic factors in the regioselective Mitsunobu reactions of 2,3-dihydroxy esters.[19]

When alkyl- or aryl-substituted glycols such as propylene diol or styrene diol are subjected to Mitsunobu conditions, the reactions are reported to take place selectively at the more substituted carbinol carbon.[19] A cyclic intermediate has been proposed for these reactions wherein steric effects are thought to determine the regiochemical outcomes. The results with acrylate diol (entry 6), on the other hand, suggest that the electronic effects overshadow the steric ones in Mitsunobu reactions of carboxyl-substituted glycol substrates. A model study shows that a cyclic intermediate may not necessarily be involved in these regioselective Mitsunobu reactions of 2,3-dihydroxy esters.[20]

In addition to the unique regioselection, Mitsunobu reactions of 2,3-dihydroxy esters also provide a means of realizing diastereochemical diversity (syn/anti), as demonstrated in the following synthesis of statine and its anti diastereomer (Scheme 1).[21] The key steps include the AD of an appropriate (*E*)-α,β-unsaturated ester followed either by β-regioselective Mitsunobu azidation (for the anti diastereomer) or by β-regioselective Mitsunobu tosylation and a subsequent substitution of an amino function (for the natural *syn*-statine).

The required substrate (**5**) for the AD was constructed with a high selectivity (*E*:*Z* = 98:2) via a Horner−Emmons reaction. The AD of the (*E*)-isomer **5** (using AD-

(16) Loibner, H.; Zbral, E. *Helv. Chim. Acta* **1976**, *59*, 2000.

(17) Some of the α-regioisomeric products (*anti*-α-azido-β-hydroxyl and *anti*-α-benzoyloxy-β-hydroxyl compounds) and the syn diastereomers (α- or β-monotosylates, α- or β-monobenzoates, and β-azide) were separately prepared (see refs 8 and 9a), and their absence in the crude Mitsunobu reaction product was vigorously established.

(18) See Table 1, footnote c.

(19) (a) Pautard, A. M.; Evans, S. A., Jr. *J. Org. Chem.* **1988**, *53*, 2300. (b) Pautard-Cooper, A.; Evans, S. A., Jr. *J. Org. Chem.* **1989**, *54*, 2485.

(20) See Supporting Information for details.

mix-α) yielded the (2*R*,3*S*)-*syn*-2,3-dihydroxy ester **6** in 96% yield and 99% ee.[22] Mitsunobu azidation (TPP, DEAD, HN_3) provided the *anti*-α-hydroxy-*β*-azido ester **8b** in 82% yield. The synthesis of the corresponding syn diastereomer required two steps: Mitsunobu tosylation (TPP, DEAD, TPPS) to give *anti*-α-hydroxy-*β*-tosylate ester **7** in 70% yield, followed by a displacement of the *β*-tosylate by azide to give *syn*-α-hydroxy-*β*-azido ester **8a** in 90% yield. The subsequent transformations ran in parallel for each diastereomer. The α-hydroxyl group was TBDMS-protected (**9**) and the ester function hydrolyzed (**10**). The required one-carbon extension was achieved via Arndt−Eistert reaction to give **12**.[23] Desilylation followed by azide reduction yielded natural *syn*-statine (**14a**) and its anti diastereomer (**14b**) in parallel.

In conclusion, Mitsunobu reactions of *syn*-2,3-dihydroxy esters exhibit a complete regioselection for the *β*-hydroxyl group to give the *anti*-α-hydroxy-*β*-Nu ester-type compounds (Nu = OBz, OTs, N_3). In addition, Mitsunobu tosylation products (*anti*-*β*-tosylates) can be converted to various *syn*-α-hydroxy-*β*-Nu ester-type compounds. Thus, the Mitsunobu protocol allows not only a unique *β*-hydroxyl regioselection but also syn/anti diastereochemical diversity with *syn*-2,3-dihydroxy ester substrates. With these additions to the repertoire, the synthetic utilities of the AD process will be further expanded.

Experimental Section

General Procedure for Regioselective Mitsunobu Reactions of *syn*-2,3-Dihydroxy Esters. The *syn*-2,3-dihydroxy ester substrate was dissolved in THF (4 mL/mmol diol), and the solution was cooled in an ice bath. Triphenylphosphine (1.2 equiv) and H−Nu (2 equiv) were added. DEAD (1.3 equiv) was added dropwise as a THF solution (2 mL). The mixture was warmed to room temperature and stirred. When the reaction was judged to be complete (TLC), the mixture was partitioned between ethyl acetate and 10% $NaHCO_3$ aqueous solution. The aqueous phase was extracted with portions of ethyl acetate. The combined organic phases were washed with brine and dried with Na_2SO_4. Following filtration and concentration, the crude product was first analyzed by NMR for the regioselectivity. It was then purified by flash silica column chromatography.

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Supporting Information Available: The model study,[20] experimental procedure, and spectral data for the synthetic intermediates described in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) For recent syntheses, see: (a) Alemany, C.; Bach, J.; Farras, J.; Garcia, J. *Org. Lett*. **1999**, *1*, 1831. (b) Sengupta, S.; Sensarma, D. *Tetrahedron: Asymmetry* **1999**, *10*, 4633. (c) Bonin, B. F.; Franchini, C. M.; Fochi, M.; Laboroi, F.; Mazzanti, G.; Ricci, A.; Varchi, G. *J. Org. Chem*. **1999**, *64*, 8008. (d) Hoffman, R. V.; Tao, J. *J. Org. Chem*. **1997**, *62*, 2292. (e) Reddy, G. V.; Rao, G. V.; Lyenga, D. S. *Tetrahedron Lett*. **1999**, 40, 775. (f) Veeresha, G.; Datta, A. *Tetrahedron Lett*. **1997**, *38*, 5223. (g) Bravo, P.; Corradi, E.; Pesenti, C.; Vergani, B.; Viani, F.; Volonterio, A.; Zanda, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3731. (h) Meunier, N.; Veith, U.; Jager, V. *Chem. Commun*. **1996**, 331. (i) Ender, D.; Reinhold, U. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 1219. (j) Neibois, P.; Greene, A. E. *J. Org. Chem*. **1996**, *61*, 5210. (k) Gennari, C.; Pain, G.; Moresca, D. *J. Org. Chem*. **1995**, *60*, 6248.

(22) The optical purity was determined using chiral HPLC (Pirkle column).

(23) (a) Godemann, K.; Ernest, M.; Hoyer, D.; Seebach, D. *Angew. Chem., Int. Ed*. **1999**, *38*, 1223. (b) Seebach, D.; Overhand, M.; Kunhnle, N. M.; Martinoni, B. *Helv. Chim. Acta* **1996**, *79*, 913. (c) Podlech, J.; Seebach, D. *Liebigs Ann*. **1995**, 1217.