Synthesis and Reactions of 3-(Nosyloxy)-2-keto Esters

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A series of 3-(nosyloxy)-2-keto esters **7a**−**j** were prepared from the corresponding α-keto esters by conversion to the trimethylsilyl enol ether and reaction with *p*-nitrobenzenesulfonyl peroxide. Conversion of these materials to 1,2,3-trifunctionalized compounds is described, and comparison of their properties with isomeric 2-(nosyloxy)-3-keto esters is discussed.

Introduction

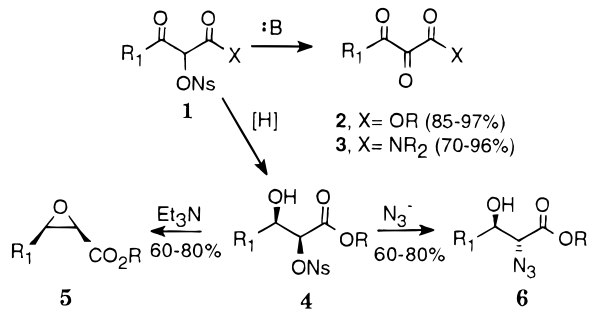
The feasibility and efficiency of selectively transforming polyfunctional compounds by using differential reactivity to distinguish the functional groups (instead of differential protecting groups) has been a major emphasis in our recent work.[1] By independent and orthogonal manipulation of each position of a polyfunctional compound, densely functionalized products can be produced without the need for differential protection schemes. Much greater atom economy, decreased numbers of steps, and, hence, higher yields result.

In this regard, 2-(nosyloxy)-3-keto esters **1**[2] are excellent precursors for the preparation of a variety of densely functionalized products. They have been transformed effectively into 1,2,3-tricarbonyl esters **2**[3] and 1,2,3-tricarbonyl amides **3**, which are functional components of FK-506 and related compounds.[4] Reduction of the ketone function of **1** can be carried out diastereoselectively to give 3-hydroxy-2-(nosyloxy) esters **4** in high yields.[5] Intramolecular cyclization of **4** yields glycidic esters **5**. Alternatively, the nosylate can be replaced by azide to give 3-hydroxy-2-azido esters **6**, which serves as a diastereoselective synthesis of 3-hydroxy-2-amino esters after reduction (Scheme 1).

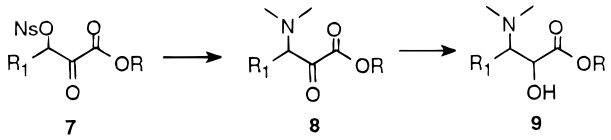
On the basis of the synthetic versatility of **1**, it was envisioned that 3-(nosyloxy)-2-keto esters **7** would also be an attractive functional array for the preparation of 1,2,3-trifunctional compounds. Replacement of the nosyloxy group by amine equivalent nucleophiles would lead to 3-amino-2-keto acid derivatives **8** found in cyclotheonamide B[6] and other proteinase inhibitors of recent interest.[7] Subsequent reduction of the ketone would give 3-amino-2-hydroxy esters **9** (Scheme 2).

This functional grouping is found in the side chain of paclitaxel and has been the focus of a great deal of synthetic attention recently.[8] Other substitution and reduction sequences of **7** could lead to glycidic esters,[9] aziridinyl esters,[10a] and 2,3-diamino esters,[6] among others.

Scheme 1



Scheme 2



Herein, we describe methodology for the preparation of 3-(nosyloxy)-2-keto esters **7** from 2-keto esters and report some aspects of their elaboration into other 1,2,3-trifunctionalized compounds.

Results

Preparation of *β*-(Nosyloxy)-α-keto Esters. The reaction of p-nitrobenzenesulfonyl peroxide (pNBSP) with enol derivatives provides a direct method for the formation of α-(nosyloxy) ketones.[1] This approach was applied to the synthesis of 3-(nosyloxy)-2-keto esters **7** by converting a series of α-keto esters **10a**−**i** to the corresponding TMS ethers, which were reacted with pNBSP to give **7** (Scheme 3).

Slow addition of a triethylamine solution to a mixture of α-keto esters **10a**−**d,h**−**j** and trimethylsilyl chloride in THF produced TMS enol ethers **11a**−**d,h**−**j** in good yields (50−89%).[11] Silyl enol ethers **11a**−**d,h**−**j** were

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(1) Hoffman, R. V. *Tetrahedron* **1991**, *47*, 1109.
(2) Hoffman, R. V.; Wilson, A. L.; Kim, H.-O. *J. Org. Chem.* **1990,** *55*, 1267.
(3) Hoffman, R. V.; Kim, H.-O.; Wilson, A. L. *J. Org. Chem.* **1990**, *55*, 2820.
(4) Hoffman, R. V.; Huizenga, D. *J. Org. Chem.* **1991**, *56*, 6435.
(5) Hoffman, R. V.; Kim, H.-O. *J. Org. Chem.* **1991,** *56*, 6759.
(6) Wipf, P.; Kim, H.-Y. *Tetrahedron Lett.* **1992**, *33*, 4275.
(7) (a) Angelastro, M. R.; Mehdi, S.; Burkhart, J. P.; Peet, N. P.; Bey, P. *J. Med. Chem.* **1990**, *33*, 11. (b) Angelastro, M. R.; Peet, N. P.; Bey, P. *J. Org. Chem.* **1989**, *54*, 3913. (c) Ocain, T. D.; Rich, D. H. *J. Med. Chem.* **1992**, *35*, 451. (d) Burkhart, J. P.; Peet, N. P.; Bey, P. *Tetrahedron Lett.* **1990**, *31*, 1385.
(8) Reviews: (a) Rowinsky, E. K.; Cazenave, L. A.; Donehower, R. C. *J. Natl. Cancer Inst.* **1990**, *82*, 1247. (b) Borman, S. *Chem. Eng. News* ***1991***, *69*(35), 11. (c) Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. *Prog. Chem. Org. Nat. Prod.* **1993**, *61*, 1.
(9) See, for example: Mori, K.; Takikawa, H. *Tetrahedron* **1991**, *47*, 2163 and references therein.
(10) (a) Legters, J.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 1. (b) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **1989**, *54*, 4235.
(11) Creary, X.; Inocencio, P. A.; Underiner, T. L.; Kostromin, R. *J. Org. Chem.* **1985**, *50*, 1932.

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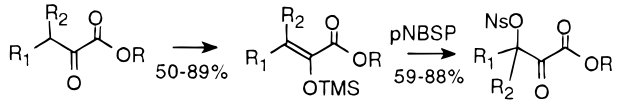
Scheme 3

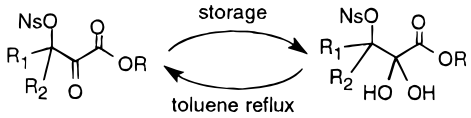


10a, R_1=R_2 = H
10b, R_1=H, R_2=Bn
10c, R_1=H, R_2=*n*-pentyl
10d, R_1=CH_3, R_2=C(O)OEt
10e, R_1=R_2=CH_3
10f, R_1=R_2= -cyclohexyl-
10g, R_1=H, R_2=Ph
10h, R_1=H, R_2=Me
10i, R_1=H, R_2=*i*-Bu
10j, R_1=H, R_2= *i*-Pr

11a-f,h-j

7a-j

Scheme 4



7a-g

found to be stable to hydrolytic workup and silica gel chromatography. The same procedure was not successful for keto esters **10e,f**, which have a tertiary carbon at the β-position. This was attributed to reduced acidity of the β-proton, and thus, a stronger base was needed to produce the enolate.

Potassium hydride was found to convert **10e,f** to their enolates, which could be trapped with TMSCl to give silyl enol ethers **11e,f** in 71% and 72% yields, respectively.[12] Silyl enol ethers **11e,f** were sensitive to hydrolysis and, thus, could not be isolated by aqueous workup or purified by simple silica gel chromatography but were successfully carried on as crude products that contained about 10% of the starting keto ester.

Interestingly, the use of KH with **10c** failed to give silyl enol ether **11c**.[13] Thus, two different procedures are required for the preparation of silyl enol ethers from α-keto esters. When the β-position is unbranched, TEA/ TMSCl is the method of choice, and when the β-position is branched, then KH/ TMSCl can be used successfully. The geometry of **11a−f,h−j** could not be assigned, even by NOE.

Silyl enol ethers **11a−f,h−j** reacted smoothly with pNBSP to give 3-(nosyloxy)-2-keto esters **7a−f,h−j** in good yields (59−88%). The keto esters were purified by recrystallization or chromatography and could be stored for extended periods at 0 °C. Keto ester **10g** contained an appreciable amount of its enol tautomer; thus, it could be reacted directly with pNBSP in the presence of zinc chloride to give **7g** in 67% yield.

Nosylates **7a−j** undergo slow hydration to the *gem*-diol upon storage. This process could be reversed by heating to reflux in toluene (azeotropic distillation) (Scheme 4). The less hindered nosylates **7a,b** hydrate

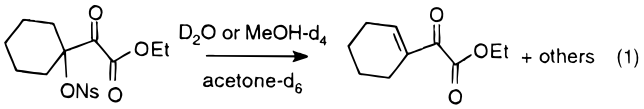
Table 1. Hydration of 3-[(*p*-Nitrobenzenesulfonyl)oxy]-2-keto Esters 7a−g in Acetone-d_6

substrate	time (min)	hydration (%)
7a	15	99
7b	30	96
7c	240	86
7d	120	84
7e	20	60[a]
7f		0[b]
7g	45	97

[a] Decomposition products accompany the hydration product. [b] Only decomposition is detected.

the fastest, while the more hindered examples **7e,f** show very little hydration, even after prolonged storage. The NMR spectra of the crude products revealed that small amounts of the *gem*-diols were present in the isolated products. As expected, the least hindered examples **7a−c,h−j** had greater diol contents (10−24%) than the more hindered examples **7d−g** (0−9%). This trend is consistent with the known influence of steric factors on hydration equilibria.[14]

Since hydration could preclude other carbonyl addition reactions, it was of interest to characterize the hydration equilibrium. This was done for **7a−g** by dissolving each in dry acetone-d_6, adding a few drops of D_2O, and monitoring the formation of the diol by NMR. The data collected in Table 1 reveal that **7a−d,g** are converted nearly completely to the *gem*-diol, whereas tertiary nosyloxy ketones **7e,f** are much less prone to hydration and instead decompose to complex product mixtures, presumably by ionization processes since **12** was detected in the decomposition products of **7f** (eq 1).



(1)

7f **12**- 38%

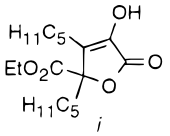
These results defined a protocol for studying the reactions of **7a−j**. The extent of hydration was assayed by NMR, and if necessary, the keto ester was dehydrated by refluxing in toluene to effect azeotropic removal of water. In practice, it was found that stored samples of **7b** required dehydration virtually every time they were used, while samples of **7a,c−g** rarely required dehydration. Moreover, the data clearly establish that solvents must be dry so as to prevent hydration from competing with other carbonyl addition reactions. On the other hand, the data suggest that, as expected, the carbonyl group of **7** is quite electrophilic and easily hydrated[15] and might have a useful pattern of reactivity.

Reactions of β-(Nosyloxy)-α-keto Esters

One attractive mode for the manipulation of 3-(nosyloxy)-2-keto esters is a reduction-substitution sequence. Reduction of the carbonyl group of **7** was first examined

(12) (a) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913; (b) *Ibid.* 1324. (c) Brown, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 982.

(13) Treatment of **10c** with KH led only to aldol dimer *i* in 80% yield.



i

(14) Guthrie, J. P. *Can. J. Chem.* **1975**, *53*, 898.

(15) The hydration of electrophilic ketones has been of recent interest. (a) Krois, D.; Langer, E.; Lehner, H. *Tetrahedron* **1980**, *36*, 1345. (b) Ocain, T. D.; Rich, D. H. *J. Med. Chem.* **1992**, *35*, 451. (c) Yuan, W.; Munoz, B.; Wong, C.-H. *J. Med. Chem.* **1993**, *36*, 211. (d) Peet, N. P.; Burkhart, J. P.; Angelastro, M. R.; Giroux, E. L.; Mehdi, S.; Bey, P.; Kolb, M.; Neises, B.; Schirlin, D. *J. Med. Chem.* **1990**, *33*, 394. (e) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry* **1985**, *24*, 1813. (f) Parisi, M. F.; Abeles, R. H. *Biochemistry* **1992**, *31*, 9429.

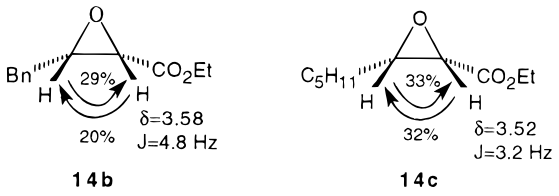
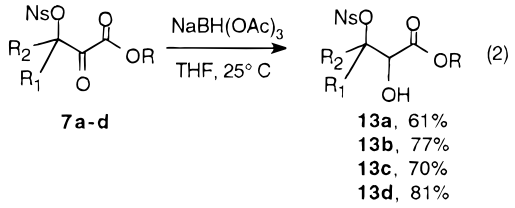


Figure 1.

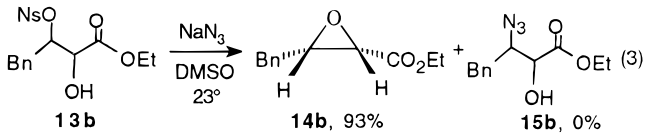
as a method to access 2-hydroxy-3-(nosyloxy) esters **13**. Subsequent substitution for the nosylate group would give 2,3-disubstituted esters. Reaction of **7b** with sodium borohydride in absolute ethanol, used in the reduction of 2-(nosyloxy)-3-keto esters,[5] led only to polymeric products. Change to a mixed solvent system of THF: MeOH (99:1) at −78 °C produced hydroxy product **13b** in good yield (84%). Nosylates **7a,c** gave lower yields, and the products in all cases were difficult to purify.



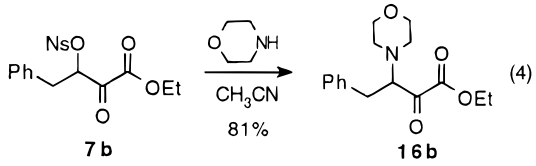
Reduction of **7a**−**d** proceeded smoothly using sodium triacetoxyborohydride[16] in THF at room temperature. Good yields of reduction products **13a**−**d** that were easy to isolate and purify were obtained (eq 2). Only a single diastereomer of **13b,c** was produced, but **13d** was produced as a nearly equimolar mixture of diastereomers. Nosyloxy ketones **7e**−**g**, which have tertiary or benzylic nosylates, appear to undergo reduction, but the products subsequently decompose.[17]

Assignment of the stereochemistry of **13b,c** was accomplished by closure to the glycidic esters **14b,c** by treatment with potassium carbonate in absolute ethanol.[18] The chemical shift and coupling constant of the C-2 protons of **14b** and **14c** were consistent with the chemical shifts and coupling constants of other *cis*-glycidic esters (Figure 1).[5,19] NOE experiments confirmed the structure assignment. The exclusive formation of the *cis*-glycidic ester requires that reduction of **7b,c** occurs stereospecifically to give *syn*-hydroxy nosylates **13b,c**.

The reduction of 3-(nosyloxy)-2-keto esters **7a**−**g** is somewhat problematic, in that the reduction succeeded only for secondary (**7a**−**c**) or deactivated (**7d**) nosylates. When the nosylate is tertiary or benzylic (**7d**−**g**), only decomposition products are observed. Moreover, subsequent displacement reactions of the reduced products by even weakly basic nucleophiles yielded glycidic esters. Thus, treatment of **13b** with sodium azide in DMSO[20] failed to produce azido alcohol **15b** but rather gave glycidic ester **14b** in 93% yield (eq 3). The facile closure of **13b** suggested that a reduction−substitution sequence for the manipulation of 3-(nosyloxy)-2-keto esters was unlikely to be a viable route to 1,2,3-trifunctional displacement products.



An alternate mode of manipulation of 3-(nosyloxy)-2-keto esters is a substitution−reduction sequence wherein a nosylate substitution is followed by a reduction of the ketone group, if necessary. The substitution of 3-(nosyloxy)-2-keto esters **7** by amine nucleophiles was examined first because the reaction of amines with simple α-(nosyloxy) ketones is known to proceed smoothly to give α-amino ketones.[21] Reaction of **7b** with either benzylamine or pyrrolidine gave only complex product mixtures. Reaction of **7b** with morpholine in dry acetonitrile at 0 °C gave adduct **16b** in 81% crude yield (eq 4). While the



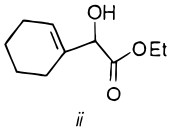
crude product was fairly pure (>90%), attempts to further purify the material led to extensive decomposition. Moreover, reaction of **7a** and **7j** with morpholine under the same conditions gave only complex mixtures.

It appeared that the basicity of amine nucleophiles could be a major contributor to the extensive decomposition observed in the reactions of **7** with amines. This supposition was bolstered by the observation that **7b** and **7d** underwent rapid decomposition when treated with the non-nucleophilic base DBU.[22] To circumvent this base sensitivity, the less basic, amine equivalent nucleophile azide appeared promising.

As a test case, the reaction of **7b** with sodium azide in acetone was examined since this reagent had been used as a mild and effective way to produce α-azido ketones from α-(nosyloxy) ketones.[23] The reaction of **7b** with sodium azide in acetone yielded *gem* diol **17b** as the only isolable product. Apparently, water present in the solvent added to the carbonyl group faster than azide displaced the nosylate group. It was further found that substitution for the nosylate group in **17b** is extremely slow (no reaction after several days), probably because the hydrated nosylate **17b** is structurally analogous to a neopentyl nosylate (eq 5).

(16) (a) Turnbull, M. D.; Hatter, G.; Ledgerwood, D. E. *Tetrahedron Lett.* **1984**, *25*, 5449. (b) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273. (c) Gribble, G. W.; Ferguson, D. C. *J. Chem. Soc., Chem. Commun.* **1975**, 535.

(17) In the case of **7f**, reduction product *ii* was isolated from the reaction mixture.



ii

(18) Fleming, P. R.; Sharpless, K. B. *J. Org. Chem.* **1991**, *56*, 2869.

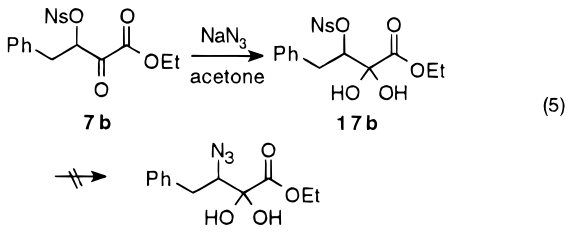
(19) For other examples of *cis*−*trans* assignments of glycidic esters by NMR see: (a) Akita, H.; Matsukura, H.; Oishi, T. *Tetrahedron Lett.* **1986**, *27*, 5397. (b) Petit, Y.; Sanner, C.; Larcheveque, M. *Synthesis* **1988**, 538. (c) Abel-Magid, A.; Pridgen, L. N.; Eggleton, D. S.; Lantos, I. *J. Am. Chem. Soc.* **1986**, *108*, 4595. (d) Denis, J.-M.; Correa, A. Greene, A. E. *J. Org. Chem.* **1990**, *55*, 1957. (e) Denis, J.-M.; Greene, A. E.; Serra, A. A.; Luche, M.-J. *J. Org. Chem.* **1986**, *51*, 46. (f) Caldwell, C. G.; Bondy, S. S. *Synthesis* **1990**, 34.

(20) These conditions had been used previously to convert 2-(nosyloxy)-3-hydroxy esters to 2-azido-3-hydroxy esters in good yield.[5]

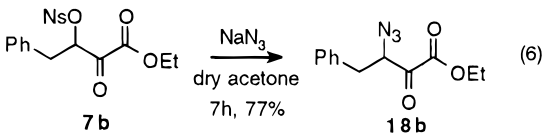
(21) Hoffman, R. V.; Jankowski, B. C.; Carr, C. S.; Duesler, E. N. *J. Org. Chem.* **1986**, *51*, 130.

(22) Upon treatment with DBU in acetonitrile, both **15b** and **15d** turn dark and evolve gas bubbles within 10 min at room temperature.

(23) Patonay, T.; Hoffman, R. V. *J. Org. Chem.* **1995**, *60*, 2368.

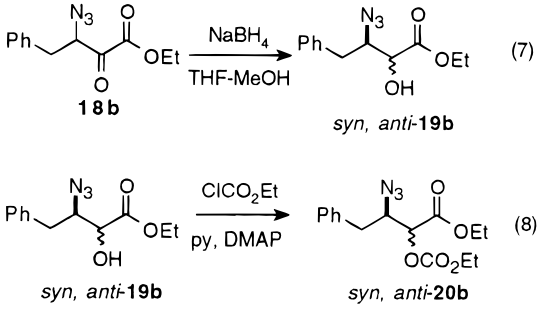


If the acetone solvent was thoroughly dried, reaction of **7b** with sodium azide gave keto azide **18b** in 77% yield (eq 6). Since **18b** is somewhat unstable, the 7 h reaction



time represents a compromise between the extent of conversion to product and decomposition of the product. A reaction time of 4 h gives only 53% conversion, whereas a reaction time of 11 h gives complete loss of starting material but evidence of decomposition products. Nevertheless, **18b** can be used as a synthetic intermediate without further purification.

Treatment of **18b** with sodium borohydride produced a mixture of azido alcohols *syn*- and *anti*-**19b** (eq 7). The

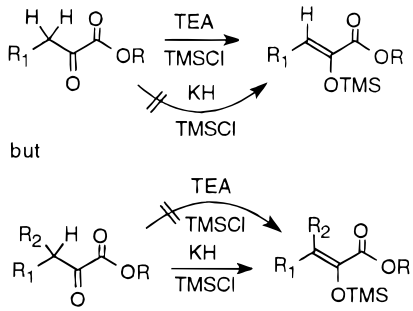


major isomer had a multiplet (1H) at δ 3.72−3.79 and a doublet at δ 4.11 (J = 2 Hz, 1H). These absorptions have previously been assigned to the *syn* isomer of **19b**;[10b] thus, the reduction of **18b** occurs with *syn* diastereoselectivity. The signals were not sufficiently resolved to determine the diastereomeric ratio nor could the diastereomers be separated. The mixture was converted to the carbethoxy derivatives *syn*- and *anti*-**20b** with ethyl chloroformate (eq 8). The diastereomers were not separable, but the ^{1}H NMR of the mixture clearly showed distinct doublets for the C-2 protons at δ 4.89 (major) and δ 5.10 (minor) in a ratio of 76:24; thus, the reduction of **18b** occurs with a 76:24 *syn*-diastereoselectivity. Because of the instability of **18b** and the low diastereoselectivity of its reduction, the substitution−reduction route to 1,2,3-trifunctionalized compounds from **7** is not especially promising.

Discussion

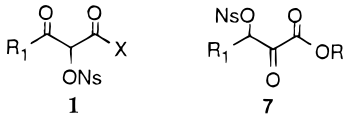
α-Keto esters **10**, the precursors to **7**, have significantly lower enol content than β-keto esters, and they must be converted to enol derivatives for successful reaction with pNBSP. Silyl enol ethers serve this purpose well, but it was found that two different protocols are needed to convert **10** to their corresponding silyl enol ethers. If the β-carbon of **10** is a nonbranched methylene group, then TEA/TMSCl gives the silyl enol ether very effectively. If the β-carbon is branched then KH/TMSCl is required to

Scheme 5



form the silyl enol ether in good yields (Scheme 5). Moreover, the two protocols are not interchangeable. Use of KH with the unbranched α-keto esters gives what appears to be condensation products between the enolate and the electrophilic ketone. Use of TEA with the branched-chain α-keto esters gives no reaction whatsoever, probably due to the steric congestion around the methine proton, which prevents close approach by the TEA. Nevertheless, it is possible to convert most α-keto esters to silyl enol ethers, and these react normally with pNBSP to give **7**.

On the basis of the exceptional synthetic versatility of 2-(nosyloxy)-3-keto esters **1**, it was predicted that their 3-(nosyloxy)-2-keto ester regioisomers **7** would also be very useful for the preparation of 1,2,3-trifunctionalized compounds. The interchange of the ketone and nosylate groups in **7** changes the reactivity patterns significantly from those of **1** and illustrates the sensitivity of chemical reactivity to a polyfunctional environment.



There are two striking reactivity differences between **7** and **1**. Because the ketone group of **7** is sandwiched between the ester and nosylate groups, it is *much* more electrophilic than the ketone group of **1**. For example, the ketone group of **7** hydrates readily and completely in the presence of water. Furthermore, a very mild reducing agent, sodium triacetoxyborohydride, is required to reduce the ketone group of **7** cleanly—sodium borohydride is too reactive and/or basic. (In contrast, the hydration of the ketone in **1** has never been observed, and reduction of **1** proceeds very smoothly with sodium borohydride.) The extreme reactivity of the ketone group in **7** is a vexing problem since spontaneous hydration can thwart carbonyl addition reactions and convert the trigonal ketone group to a tetrahedral center that effectively blocks displacement reactions of the nosylate group.

On the other hand, the nosylate group of **7** is *not* sandwiched between the ester and ketone groups as it is in **1**, and it thus functions much more effectively as a leaving group in eliminations. Consequently, the choice of nucleophiles for displacement reactions is limited to those that are good nucleophiles but very mild bases. Moreover, reduction of the ketone group of **7** is viable only when the β-carbon is unbranched; hence, the resulting secondary nosyloxy alcohol **13** does not decompose rapidly.

Thus, many of the reactions that make **1** such a versatile intermediate are unsuitable for manipulating

7. It is clear from the above results that the electrophilicity of the ketone group dominates the chemistry of **7**, and thus, useful transformations of **7** will have to involve carbonyl addition by nonbasic reagents as the *first* step of the sequence.

Experimental Section

Most chemicals were purchased from Aldrich Chemical Co. and used as received. *p*-Nitrobenzenesulfonyl chloride was purchased from Fluka Chemical Co. and recrystallized from chloroform and hexane. THF was distilled from sodium benzophenone ketyl. Acetone was distilled after being stirred overnight over $CaSO_4$. Acetonitrile, ether, and TEA were dried with CaH_2 and distilled. TMSCl was distilled from magnesium turnings. All other solvents were HPLC-grade solvents.

Melting points are uncorrected. Thin-layer chromatography was performed on silica gel 60 F_{254} plates and visualized by UV irradiation and/or iodine. Analytical HPLC was performed with the indicated solvent systems and flow rates on a 21.4 mm i.d. × 25 cm L Dynamax 60A silica gel column. Flash chromatography was performed using silica gel 60 PF_{254} containing gypsum. Radial chromatography was performed on a radial chromatograph (Harrison) using 1-mm and 2-mm plates of silica gel 60 PF_{254} containing gypsum. Elemental analyses were carried out by M-H-W Laboratories, Phoenix, AZ.

α-Keto esters **10a,b,d,e** were available commercially, and **10c,**[24] **10f,**[25] **10g,**[26] and **10h**−**j**[27] were prepared by a literature procedure. pNBSP was prepared by the literature method.[28]

Ethyl 2-[(Trimethylsilyl)oxy]propenoate, 11a.[11] TEA (5.85 mL, 4.25 g, 42.0 mmol) in THF (40 mL) was added dropwise to a mixture of methyl pyruvate, **10a** (3.17 g, 31.1 mmol), and TMSCl (4.4 mL, 3.77 g, 35.0 mmol) in THF (60 mL) under N_2. After 3.5 h (TLC monitoring, EtOAc:hexane, 1:4), pentane (75 mL) was added, and the reaction mixture was filtered. The filtrate was washed with water (2 × 50 mL) and with brine (1 × 50 mL), dried ($MgSO_4$), and evaporated to give **11a** as a clear liquid (3.63 g, 67%) that was used without further purification: ^{1}H NMR ($CDCl_3$) δ 0.24 (s, 9H), 3.77 (s, 3H), 4.88 (s, 1H), 5.51 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 0.3, 52.4, 104.3, 147.4, 165.2; IR (neat) 2956, 1735, 1627cm^{-1}.

Ethyl 3-Phenyl-2-[(trimethylsilyl)oxy]-2-butenoate, 11b. By the same procedure, **10b** (3.98 g, 19.0 mmol) was reacted with TMSCl (2.9 mL, 2.48 g, 23.0 mmol) and TEA (3.75 mL, 2.72 g, 27.0 mmol). The crude product was separated by radial chromatography (EtOAc:hexane, 1:9) to afford 4.84 g (89%) of **11b**: ^{1}H NMR ($CDCl_3$) δ 0.25 (s, 9H), 1.29 (t, J = 7.2 Hz, 3H), 3.51 (d, J = 7.4 Hz, 2H), 4.20 (q, J = 7.2 Hz, 2H), 6.22 (t, J = 7.4 Hz, 1H), 7.19−7.21 (m, 3H), 7.29−7.27 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 0.6, 14.2, 32.0, 61.0, 121.3, 126.2, 128.5, 128.5, 139.7, 141.0, 164.8; IR (neat) 3028, 1722, 1645, 1603 cm^{-1}.

Ethyl 2-[(Trimethylsilyl)oxy]-2-octenoate, 11c. By the same procedure, **10c** (3.59 g, 19.0 mmol) was reacted with TMSCl (2.9 mL, 2.48 g, 23.0 mmol) and TEA (3.75 mL, 2.72 g, 27.0 mmol). The crude product was separated by radial chromatography using a solvent gradient (EtOAc:hexane 2:98 to 1:9) to afford 2.46 g (49%) of **11c**: ^{1}H NMR ($CDCl_3$) δ 0.22 (s, 9H, 0.90 (t, J = 6.8 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.41 (t, J = 7.2 Hz, 2H), 1.29−1.43 (m, 4H), 2.15 (dt, J = 7.2, J = 7.6 Hz, 2H), 4.21 (q, J = 7.2 Hz, 2H), 6.07 (t, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 0.6, 14.2, 14.4, 22.7, 26.0, 28.6, 31.9, 61.0, 123.9, 140.8, 165.2; IR (neat) 1721, 1647 cm^{-1}.

Ethyl 3-Carbethoxy-3-methyl-1-(trimethylsiloxy)propenoate, 11d. By the same procedure, **10d** (2.95 g, 15.0 mmol) was reacted with TMSCl (2.2 mL, 1.88 g, 17.0 mmol) and TEA (2.90 mL, 2.11 g, 21.0 mmol). Purification by Kugelrohr distillation (0.05−0.06 mmHg) afforded a clear liquid (3.53 g) that contained **11d** (3.00 g, 74% yield) as a nearly equimolar mixture of *E* and *Z* isomers and a small amount of unreacted diethyl oxalpropionate (0.53g, 2.6 mmol). **11d**: ^{1}H NMR ($CDCl_3$) δ 0.26 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H), 1.34 (t, J = 7.2 Hz, 3H), 1.84 (s, 3H), 4.18 (q, J = 7.2 Hz, 2H), 4.25 (q, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 0.7, 12.5, 14.3, 14.5, 61.0, 61.9, 115.4, 148.6, 165.6, 168.6; IR (neat) 1735, 1719, 1638 cm^{-1}. The mixture was used in the next step.

Ethyl 2-[(Trimethylsilyl)oxy]-2-butenoate, 11h. By the same procedure, **10h** (3.77 g, 29.0 mmol) was reacted with TMSCl (4.36 mL, 3.73 g, 34.3 mmol) and TEA (5.76 mL, 4.18 g, 41.3 mmol). The crude silyl enol ether **11h** was obtained as a yellow oil (5.90 g, 100%, 76% purity). This material contained some of the starting ketone and was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 0.23 (s, 9H), 1.31 (t, J = 7.5 Hz, 3H), 1.71 (d, J = 7.5 Hz, 3H), 4.20 (q, J = 7.5 Hz, 2H), 6.15 (q, J = 7.5 Hz, 1H).

Ethyl 5-Methyl-2-[(trimethylsilyl)oxy]-2-hexenoate, 11i. By the same procedure, **10j** 71% purity (7.00 g, 29.0 mmol) was reacted with TMSCl (4.36 mL, 3.73 g, 34.3 mmol) and TEA (5.76 mL, 4.18 g, 41.3 mmol). The crude silyl enol ether **11j** was obtained as yellow oil (9.12 g, 100%, 75% purity). This material was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 0.22 (s, 9H), 0.93 (d, J = 6.6 Hz, 6H), 1.34 (t, J = 7.0 Hz, 3H), 1.68 (m, 1H), 2.08 (t, J = 7.2 Hz, 2H), 4.24 (q, J = 7.1 Hz, 2H), 6.10 (t, J = 7.5 Hz, 1H).

Ethyl 4-Methyl-2-[(trimethylsilyl)oxy]-2-pentenoate, 11j. By the same procedure, **10i** (4.58 g, 29.0 mmol) was reacted with TMSCl (4.36 mL, 3.73 g, 34.3 mmol) and TEA (5.76 mL, 4.18 g, 41.3 mmol) for 24 h. The crude silyl enol ether **11i** was obtained as yellow oil (6.23 g, 67%, 67% purity). This material contained some starting ketone and was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 0.22 (s, 9H), 1.03 (d, J = 6.5 Hz, 6H), 1.32 (t, J = 7.2 Hz, 3H), 1.65−1.77 (m, 1H), 4.20 (q, J = 7.2 Hz, 2H), 5.90 (d, J = 10.0 Hz, 1H).

Ethyl 3-Methyl-2-[(trimethylsilyl)oxy]-2-butenoate, 11e. KH (35% by weight, 1.32 g, 0.46 g actual, 11.5 mmol) was washed with pentane (3 × 5 mL) under N_2. Dry THF (25 mL) was added, and the flask was cooled to 0 °C. Keto ester **10e** (1.55 g, 10.8 mmol) was syringed into the flask, and the reaction was stirred for 30 min. TMSCl (3.0 mL, 2.57 g, 24 mmol) in THF (15 mL) was added dropwise. After 2.5 h, pentane (50 mL) was added, and the reaction mixture was filtered and evaporated to dryness under vacuum (60 mmHg). Kugelrohr distillation of the residue (0.05−0.06 mmHg) afforded a clear liquid (1.81 g) that was a mixture of **11e** (1.64 g, 71% yield) and **10e** (0.17 g, 1.2 mmol). **11e**: ^{1}H NMR ($CDCl_3$) δ 0.19 (s, 9H), 1.33 (t, J = 7.2 Hz, 3H), 1.80 (s , 3H), 2.06 (s, 3H), 4.21 (q, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 0.4, 14.3, 19.7, 20.6, 60.4, 130.6, 135.8, 165.2; IR (neat) 1717, 1637 cm^{-1}.

Ethyl 3-Cyclohexyl-2-[(trimethylsilyl)oxy]propenoate, 11f. By the same procedure, KH (35% by weight, 0.83 g, 0.29 g actual, 7.2 mmol) and **10f** (1.14 g, 6.2 mmol) were reacted and quenched with TMSCl (1.5 mL, 1.28 g, 12.0 mmol). Kugelrohr distillation of the crude product (0.05−0.06 mmHg) afforded **11f** (1.15 g, 72%) that was not completely pure. It was used without further purification: ^{1}H NMR ($CDCl_3$) δ 0.18 (s, 9H), 1.33 (t, J = 7.2 Hz, 3H), 1.57 (m, 6H), 2.28 (m, 2H), 2.64 (m, 2H), 4.20 (q, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 0.5, 14.5, 26.7, 27.7, 28.3, 29.3, 29.4, 60.6, 133.3, 137.2, 165.8; IR (neat) 1716, 1630 cm^{-1}.

Methyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxopropionate, 7a. pNBSP (0.61 g, 1.5 mmol) was added to a cooled solution (0 °C) of **11a** (0.41 g, 2.4 mmol) in EtOAc (40 mL). The mixture was stirred for 4 h at 0 °C and placed in the refrigerator overnight. The pale yellow solution was washed with cold water (2 × 25 mL) and brine (1 × 25 mL). The organic layer was dried ($MgSO_4$) and evaporated until 10 mL of liquid remained. Hexane was added until the solution

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became cloudy, and it was evaporated to afford a pale yellow solid. Recrystallization from EtOAc:hexane gave **7a** as a pale yellow solid (0.375 g, 82%): mp 118−120 °C dec; ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 5.34 (s, 2H), 8.18 and 8.43 (AA′BB′, J = 8.8 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 53.7, 71.2, 124.5, 129.5, 141.5, 151.1, 158.9, 183.8; IR (KBr) 3110, 1764, 1609, 1529 cm^{-1}. Anal. Calcd for $C_{10}H_9NO_8S$: C, 39.61; H, 2.99; N, 4.62. Found: C, 39.76; H, 2.75; N, 4.42.

Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-4-phenylbutanoate, 7b, was prepared by the same procedure from **11b** (0.60g, 2.2 mmol) and pNBSP (0.66 g, 1.6 mmol). Recrystallization from EtOAc:hexane afforded a white solid (0.55 g, 81%): mp 104−105 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, J = 7.2 Hz, 3H), 3.00 (dd, J = 10.0, 14.2 Hz, 1H), 3.27 (dd, J = 3.6, 14.2 Hz, 1H), 4.37 (q, J = 7.2 Hz, 2H), 5.63 (dd, J = 3.6, 10.0 Hz, 1H), 7.05−7.07 (m, 2H), 7.14−7.21 (m, 3H), 7.75 and 8.16 (AA′BB′, J = 8.8 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 12.9, 36.1, 62.4, 81.6, 123.2, 126.5, 127.8, 127.9, 128.3, 132.9, 139.9, 149.5, 158.5, 186.3; IR (KBr) 3027, 1766, 1724, 1603, 1531 cm^{-1}. Anal. Calcd for $C_{18}H_{17}NO_8S$: C, 53.07; H, 4.21; N, 3.44. Found: C, 52.88; H, 4.40; N, 3.24.

Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxooctanoate, 7c, was prepared by the same procedure from **11c** (0.50 g, 1.9 mmol) and pNBSP (0.65 g, 1.6 mmol). The yellow oil was separated by radial chromatography using a solvent gradient of EtOAc:hexane (1:4 to 1:1) to give **7c** as a pale yellow oil (0.55 g, 88%): ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 6.4 Hz, 3H), 1.26 (m, 4H), 1.25−1.27 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H), 1.78−1.87 (m, 1H), 1.91−2.00 (m, 1H), 4.36 (q, J = 7.2 Hz, 2H), 5.65 (dd, J = 4.0, 8.4 Hz, 1H), 8.15 and 8.42 (AA′BB′, J = 8.8 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 13.8, 13.9, 22.2, 24.4, 30.78, 30.81, 63.3, 81.9, 124.4, 129.4, 141.8, 150.9, 159.5, 188.0; IR (neat) 3109, 1756, 1731, 1608, 1535 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_8S$: C, 49.61; H, 5.46; N, 3.62. Found: C, 49.48; H, 5.59; N, 3.59.

Ethyl 3-Carboethoxy-3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxobutanoate, 7d, was prepared by the same procedure from **11d** (0.91 g, 3.3 mmol) and pNBSP (0.63 g, 1.6 mmol) as a pale yellow oil. The oil was dissolved in EtOAc, and hexane was added until cloudy. A pale yellow oil (0.41 g, 65%) was collected by decanting the solvent: ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 1.36 (t, J = 7.2 Hz, 3H), 2.00 (s, 3H), 4.30 (q, 2H, J = 7.2), 4.33−4.39 (m, 2H), 8.16 and 8.42 (AA′BB′, J = 8.8 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 13.8, 13.9, 21.2, 63.4, 63.5, 88.7, 124.4, 129.2, 143.0, 150.9, 159.6, 165.2, 184.4; IR (neat) 3110, 1759, 1737, 1609, 1537 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_{10}S$: C, 44.67; H, 4.25; N, 3.47. Found: C, 44.82; H, 4.02; N, 3.41.

Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-3-methylbutanoate, 7e, was prepared by the same procedure from **11e** (0.36 g, 1.7 mmol) and pNBSP (0.61 g, 1.5 mmol). Recrystallization from EtOAc:hexane gave of an off-white solid (0.32g, 61%): mp 66−68 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.38 (t, J = 7.2 Hz, 3H), 1.83 (s, 6H), 4.36 (q, J = 7.2 Hz, 2H), 8.14 and 8.41 (AA′BB′, J = 8.8 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 14.0, 25.2, 62.9, 91.8, 124.4, 129.0, 143.5, 150.7, 160.5, 191.5; IR (KBr) 3116, 1739, 1607, 1532 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO_8S$: C, 45.22; H, 4.38; N, 4.06. Found: C, 45.12; H, 4.42; N, 4.11.

Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-3-cyclohexylpropionate, 7f, was prepared by the same procedure from **11f** (0.41 g, 1.6 mmol) and pNBSP (0.61 g, 1.5 mmol). Recrystallization from EtOAc:hexane gave a white solid (0.34 g, 59%): mp 103−105 °C; ^{1}H NMR ($CDCl_3$) δ 1.26−1.35 (m, 1H), 1.39 (t, J = 7.2 Hz, 3H), 1.55−1.69 (m, 5H), 1.98 (dt, J = 3.6, 13.2 Hz, 2H), 2.40 (d, J = 14.0 Hz, 2H), 4.36 (q, J = 7.2 Hz, 2H), 8.17 and 8.42 (AA′BB′, J = 8.8 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.9, 24.3, 32.8, 62.8, 94.3, 124.3, 129.1, 143.3, 150.7, 160.3, 191.5; IR (KBr) 3104, 1740, 1605, 1538 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_8S$: C, 49.87; H, 4.97; N, 3.63. Found: C, 49.92; H, 5.11; N, 3.59.

Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxobutanoate, 7h, was prepared by the same procedure from **11h** (0.89 g, 4.4 mmol) and pNBSP (1.3 g, 3.2 mmol). Trituration of the crude product with EtOAc:hexane afforded a clear yellow oil (0.79 g, 75%): ^{1}H NMR ($CDCl_3$) δ 1.38 (t, J = 7.0 Hz, 3H), 1.62 (d, J = 7.5 Hz, 3H), 4.35 (q, J = 7.0 Hz, 2H), 5.77 (q, J = 7.5 Hz, 1H), 8.15 and 8.43 (AA′BB′, J = 10.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 17.1, 63.4, 78.2, 124.4, 129.2, 141.8, 150.9, 159.4, 187.9; IR (neat, hydrate) 3490, 1822, 1735, 1609, 1537 cm^{-1}. Anal. Calcd for $C_{12}H_{13}NO_8S\cdot0.8H_2O$: C, 41.69; H, 4.26; N, 4.05. Found: C, 41.72; H, 4.62; N, 4.25.

Ethyl 5-methyl-3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxohexanoate, 7i, was prepared by the same procedure from **11i** (1.44 g, 75% purity, 4.4 mmol) and pNBSP (1.32 g, 3.20 mmol). Trituration of the crude product with EtOAc:hexane afforded a white solid (0.950 g, 80%): mp 47−49 °C; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 7.7 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H), 1.39 (t, J = 7.0 Hz, 3H), 1.67−1.79 (m, 3H,), 4.36 (q, J = 7.0 Hz, 2H), 5.72 (dd, J = 9.5, 3.3 Hz, 1H), 8.17 and 8.41 (AA′BB′, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 20.8, 23.0, 24.6, 39.2, 63.3, 80.5, 124.4, 129.4, 141.7, 150.9, 159.2, 188.1; IR (KBr, hydrate) 3305, 1716, 1609, 1537 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_8S$: C, 48.25; H, 5.13; N, 3.75. Found: C, 48.25; H, 4.89; N, 3.63.

Ethyl 4-methyl-3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxopentanoate, 7j, was prepared by the same procedure from **11j** (1.51 g, 67% purity, 4.4 mmol) and pNBSP (1.32 g, 3.20 mmol). Trituration of the crude product with EtOAc:hexane afforded a clear yellow oil (0.930 g, 81%): ^{1}H NMR ($CDCl_3$) δ 0.87 (d, J = 6.9 Hz, 3H), 1.04 (d, J = 6.9 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 2.40 (m, 1H), 4.36 (q, J = 7.1 Hz, 2H), 5.53 (d, J = 4.3 Hz, 1H), 8.15 and 8.42 (AA′BB′, J = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 16.3, 18.8, 30.1, 63.3, 85.6, 124.4, 129.4, 141.6, 150.9, 159.8, 188.2; IR (neat) 1750, 1732, 1609, 1537 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_8S$: C, 46.79; H, 4.77; N, 3.90. Found: C, 46.80; H, 4.76; N, 3.97.

Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-3-phenyl-2-oxopropionate, 7g. A mixture of dry zinc chloride (0.21 g, 1.5 mmol) and pNBSP (0.60 g, 1.5 mmol) in EtOAc (50 mL) was stirred at 0 °C until the solution turned clear (20 min). Ethyl 3-phenylpyruvate, **10g** (0.37 g, 1.9 mmol), was added, and the mixture was stirred for 4 h at 0 °C and placed in the refrigerator overnight. The solution was worked up as above and evaporated to dryness after addition of hexane to afford an orange solid. Recrystallization from EtOAc/hexane gave a yellow solid (0.39 g, 67%): mp 105−107 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 4.22 (dq, J = 7.2, 10.6 Hz, 1H), 4.27 (dq, J = 7.2, 10.6 Hz, 1H), 6.71 (s, 1H), 7.26−7.37 (m, 5H), 8.00 and 8.28 (AA′BB′, J = 8.8 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 13.8, 63.3, 83.2, 124.2, 129.1, 129.2, 129.29, 129.33, 130.7, 142.3, 150.7, 159.0, 184.3; IR (KBr) 3109, 1752, 1740, 1609, 1538 cm^{-1}. Anal. Calcd for $C_{17}H_{15}NO_8S$: C, 51.91; H, 3.84; N, 3.56. Found: C, 51.96; H, 4.00; N, 3.50.

Hydration Studies of 3-[(*p*-Nitrobenzenesulfonyl)oxy]-2-keto Esters 7a−g. A sample of **7** (usually 50 mg) was dissolved in dry acetone-d_6, and a drop of D_2O was added. The NMR spectrum was recorded at regular intervals until no further changes in the spectrum were observed. The hydration of **7** was evident by the disappearance of NMR peaks from the keto form and appearance of new peaks from the hydrate. Hydration of the carbonyl group typically caused the chemical shift of the α-protons to move upfield by about 1 ppm. In addition, the ^{13}C chemical shift of the ketone carbon disappeared and a new signal for the *gem* diol carbon grew in at δ 90−95.

Hydration of 7a. After 15 min, the ^{1}H NMR showed **7a** was (99%) hydrated: ^{1}H NMR (acetone-d_6) δ 3.72 (s, 3H), 4.28 (s, 2H), 8.24 and 8.54 (AA′BB′, J = 8.8 Hz, 4H); ^{13}C NMR (acetone-d_6) δ 53.2, 73.3, 92.4, 125.4, 130.4, 141.8, 151.8, 170.6.

Hydration of 7b. After 30 min, the ^{1}H NMR showed **7b** was (96%) hydrated: ^{1}H NMR (acetone-d_6) δ 1.32 (t, J = 7.2 Hz, 3H), 2.92 (dd, J = 10.2, 14.8 Hz, 1H), 3.23 (dd, J = 2.0, 14.8 Hz, 1H), 4.13 (d, J = 4.6 Hz, 2H), 4.21 (dq, J = 4.6, 7.2 Hz, 2H), 5.29 (dd, J = 2.0, 10.2 Hz, 1H), 7.07−7.16 (m, 5H), 7.71 and 8.24 (AA′BB′, J = 8.8 Hz, 4H); ^{13}C NMR (acetone-d_6) δ 14.1, 35.7, 63.0, 88.3, 94.1, 124.9, 127.3, 129.2, 129.4, 130.3, 137.4, 143.7, 151.0, 170.9.

Hydration of 7c. After 240 min, the ^{1}H NMR showed **7c** was (86%) hydrated: ^{1}H NMR (acetone-d_6) δ 0.86 (t, J = 6.8 Hz, 3H), 1.23−1.35 (m, 6H), 1.25 (t, J = 7.2 Hz, 3H), 1.76−1.88 (m, 2H), 4.10 (dq, J = 7.2, 10.8 Hz, 1H), 4.19 (dq, J = 7.2, 10.8 Hz, 1H), 4.98 (dd, J = 3.6, 9.0 Hz, 1H), 8.21 and 8.47

(AA′BB′, J = 8.8 Hz, 4H); ^{13}C NMR (acetone-d_6) δ 14.12, 14.15, 22.9, 25.8, 29.7, 31.9, 62.7, 87.4, 94.2, 124.9, 130.0, 144.2, 151.3, 170.9.

Hydration of 7d. After 120 min, the ^{1}H NMR showed **7d** was (84%) hydrated: ^{1}H NMR (acetone-d_6) δ 1.16 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.95 (s, 3H), 4.14−4.20 (m, 2H), 4.26 (q, 2H, J = 7.2), 8.28 and 8.53 (AA′BB′, J = 8.8 Hz, 4H); ^{13}C NMR (acetone-d_6) δ 14.0, 14.1, 18.2, 63.1, 63.2, 92.2, 95.3, 125.2, 129.7, 144.7, 151.5, 168.5, 170.0.

Hydration of 7e. After 60 min, the ^{1}H NMR showed **7e** was (71%) hydrated; however, what appeared to be an elimination product and other unidentified side products began to grow in after 15 min: ^{1}H NMR (acetone-d_6) δ 1.22 (t, J = 7.2 Hz, 3H), 1.72 (s, 6H), 4.21 (q, J = 7.2 Hz, 2H), 8.21 and 8.50 (AA′BB′, J = 8.8 Hz, 4H); ^{13}C NMR (acetone-d_6) δ 14.2, 22.4, 62.9, 96.1, 97.2, 125.3, 129.6, 145.8, 151.4, 171.4.

Hydration of 7f. After 48 h, the ^{1}H NMR showed **7f** had decomposed, the major product being identified as elimination product **12**: ^{1}H NMR (acetone-d_6) δ 1.33 (t, J = 7.2 Hz, 3H), 1.67 (t, J = 2.8 Hz, 4H), 2.20 (br s, 2H), 2.35 (br s, 2H), 4.33 (q, J = 7.2 Hz), 2H, 6.99 (t, J = 3.6 Hz, 1H); ^{13}C NMR (acetone-d_6) δ 14.3, 22.18, 22.20, 22.6, 27.2, 62.6, 136.6, 150.6, 166.1, 189.8.

Hydration of 7g. After 45 min, the ^{1}H NMR showed **7g** was (97%) hydrated: ^{1}H NMR (acetone-d_6) δ 1.28 (t, J = 7.2 Hz, 3H), 4.18 (q, J = 7.2 Hz, 2H), 5.81 (s, 1H), 7.13−7.22 (m, 3H), 7.33 (d, J = 7.2 Hz, 2H), 7.92 and 8.25 (AA′BB′, J = 8.8 Hz, 4H); ^{13}C NMR (acetone-d_6) δ 14.2, 62.9, 86.6, 94.5, 124.9, 128.3, 129.6, 130.2, 130.5, 133.2, 143.4, 151.3, 170.8.

Methyl 3-[(*p*-Nitrobenzenesulfonyl)oxy]-2-hydroxypropionate, 13a. Sodium triacetoxyborohydride (0.32 g, 1.5 mmol) was added to a solution of **7a** (0.41 g, 1.4 mmol) in THF (40 mL) at 0 °C, and the mixture was stirred for 18 h at room temperature. EtOAc (40 mL) was added, and the reaction mixture was washed with water (3 × 40 mL) and brine (1 × 40 mL). The aqueous layers were extracted with EtOAc, and the combined organic layers were dried ($MgSO_4$), passed through a 1.5 cm pad of silica gel, and evaporated to give a yellow oil. Recrystallization from EtOAc/hexane afforded **13a** as a yellow solid (0.25 g, 61%): mp 80−82 °C; ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H), 4.40 (t, J = 2.8 Hz, 1H), 4.44 (d, J = 2.8 Hz, 2H), 8.12 and 8.41 (AA′BB′, J = 8.4 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 53.4, 69.0, 71.4, 124.4, 129.4, 141.4, 150.9, 171.1; IR (KBr) 3514, 3118, 1735, 1610, 1543 cm^{-1}. Anal. Calcd for $C_{10}H_{11}NO_8S$: C, 39.35; H, 3.63; N, 4.59. Found: C, 39.51; H, 3.75; N, 4.58.

Ethyl 3-[(*p*-Nitrobenzenesulfonyl)oxy]-2-hydroxy-4-phenylbutanoate, 13b. By the same procedure, **7b** (0.35 g, 0.86 mmol) was reacted with sodium triacetoxyborohydride (0.21 g, 0.99 mmol) at room temperature for 11 h to give a yellow oil. Recrystallization from EtOAc/hexane afforded **13b** as a pale, yellow solid (0.27 g, 77%): mp 73−74 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 7.2 Hz, 3H), 3.05 (dd, J = 7.4, 13.8 Hz, 1H), 3.16 (dd, J = 7.4, 13.8 Hz, 1H), 4.19 (dq, J = 7.2, 10.6 Hz, 1H), 4.21 (dd, J = 2.2, 4.2 Hz, 1H), 4.27 (dq, J = 7.2, 10.6 Hz, 1H), 5.23 (ddd, J = 2.2, 7.4, J = 7.4 Hz, 1H), 7.16−7.22 (m, 5H), 7.83 and 8.24 (AA′BB′, J = 8.8 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 14.0, 37.3, 62.9, 70.7, 84.2, 124.2, 127.3, 128.82, 128.84, 129.6, 135.0, 142.2, 150.5, 171.4; IR (KBr) 3491, 3129, 3001, 1743, 1608, 1527 cm^{-1}. Anal. Calcd for $C_{18}H_{19}NO_8S$: C, 52.81; H, 4.68; N, 3.42. Found: C, 52.90; H, 4.69; N, 3.38.

Ethyl 3-[(*p*-Nitrobenzenesulfonyl)oxy]-2-hydroxy-4-octanoate, 13c. By the same procedure, **7c** (0.33 g, 0.85 mmol) was reduced with sodium triacetoxyborohydride (0.20 g, 0.94 mmol) overnight at room temperature to give an orange oil. Purification by radial chromatography (EtOAc:hexane, 1:4) gave **13c** as a yellow oil (0.23 g, 70%): ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 6.4 Hz, 3H), 1.27−1.35 (m, 6H), 1.33 (t, J = 7.2 Hz, 3H), 1.72−1.81 (m, 1H), 1.82−1.91 (m, 1H), 2.99 (br s, 1H), 4.19 (dq, J = 7.2, 10.6 Hz, 1H), 4.26 (d, J = 2.0 Hz, 1H), 4.29 (dq, J = 7.2, 10.6 Hz, 1H), 5.06 (ddd, J = 2.0, 7.4, 7.4 Hz, 1H), 8.09 and 8.39 (AA′BB′, J = 8.8 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.0, 22.4, 24.8, 31.0, 31.3, 62.8, 71.2, 83.7, 124.3, 129.1, 142.7, 150.7, 171.6; IR (neat) 3493, 3109, 1742, 1608, 1535 cm^{-1}. Anal. Calcd for $C_{16}H_{23}NO_8S$: C, 49.35; H, 5.95; N, 3.60. Found: C, 49.15; H, 5.91; N, 3.47.

Ethyl 3-Carbethoxy-3-[(*p*-nitrobenzenesulfonyl)oxy]-2-hydroxybutanoate, 13d. By the same procedure, **7d** (0.42 g, 1.0 mmol) was reduced with sodium triacetoxyborohydride (0.25 g, 1.2 mmol) for 18 h at room temperature to give a clear oil (0.34 g, 81%). Two diastereomers were obtained in a 2:3 ratio that were not separable due to decomposition: ^{1}H NMR ($CDCl_3$) δ 1.16 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.331 (t, J = 7.2 Hz, 3H), 1.335 (t, J = 7.2 Hz, 3H), 1.97 (s, 3H), 1.99 (s, 3H), 3.45 (br s, 1H), 4.17 (q, J = 7.2, 2H), 4.27 (q, J = 7.2, 2H), 4.30 (q, J = 7.2, 2H), 4.31 (q, J = 7.2, 2H), 4.44 (s, 1H), 8.17 and 8.39 (AA′BB′, J = 8.8 Hz, 4H), 8.18 and 8.38 (AA′BB′, J = 8.8 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.0, (14.0), (14.0), 19.3, 20.0, 62.75, 62.80, 62.9, 63.0, 74.6, 75.1, 90.8, 90.9, 124.17, 124.23, 128.9, 129.1, 143.8, 143.9, 150.5, 150.6, 167.7, 168.0, 169.6, 169.9; IR (neat) 3491, 3109, 1745, 1609, 1534 cm^{-1}.

***cis*-Ethyl 4-Phenyl-2,3-oxiranebutanoate 14b.** Anhydrous potassium carbonate (0.31 g, 2.26 mmol) was added to a solution of **13b** (0.26 g, 0.64 mmol) in absolute ethanol (8 mL). The reaction was stirred for 24 h at room temperature. Ether (45 mL) was added, and the organic layer was washed with water (40 mL). The aqueous phase was washed with ether (2 × 30 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), and evaporated to dryness to afford a pale yellow oil (0.11 g, 85%). The crude product was purified by Kugelrohr distillation to afford a pale yellow oil (0.10 g, 77%): ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 7.2 Hz, 3H), 2.90 (dd, J = 6.4, 14.8 Hz, 1H), 3.11 (dd, J = 6.0, 14.8 Hz, 1H), 3.39 (dt, J = 4.8, 6.4 Hz, 1H), 3.57 (d, J = 4.8 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 7.21−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.3, 33.8, 52.8, 57.7, 61.6, 126.9, 128.7, 128.9, 136.6, 168.3; IR (neat) 1749, 1605 cm^{-1}.

Oxirane **14b** was obtained in 93% yield when a solution of *syn*-**13b** in DMSO was treated with sodium azide (2 equiv) at room temperature for 23 h.

***cis*-Ethyl 2,3-Oxiraneoctanoate, 14c**, was prepared by the same procedure from **13c** (0.20 g, 0.51 mmol) to afford a yellow oil (0.043 g, 45%): ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.8 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.50−1.75 (m, 8H), 3.17 (dt, J = 4.8, 5.8 Hz, 1H), 3.51 (d, J = 4.8 Hz, 1H), 4.26 (dq, J = 2.0, 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.2, 22.5, 25.8, 27.2, 31.4, 62.9, 57.7, 61.4, 168.4; IR (neat) 1753 cm^{-1}.

Ethyl 3-Morpholino-2-oxo-4-phenylbutanoate, 16b. Dehydration of **7b** (0.30 g, 0.74 mmol) was effected by refluxing in toluene to effect azeotropic removal of water. After removal of the toluene and dissolution in acetonitrile (50 mL) at 0 °C, morpholine (0.13 mL, 0.13 g, 1.5 mmol) was added, and the reaction mixture was stirred for 4.5 h at 0 °C. CH_2Cl_2 (50 mL) was added, and the organic layers were washed with cold water (2 × 25 mL) and with cold brine (1 × 25 mL). The combined aqueous extracts were combined and washed with CH_2Cl_2 (1 × 50 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to afford a yellow oil. The crude product was dissolved in CH_2Cl_2 and filtered through cotton to remove morpholine salts, and hexane was added until cloudy. A small additional amount of precipitate was collected, and the filtrate was evaporated to yield **16b** (0.17 g, 81%): ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 6.8 Hz, 3H), 2.62 (t, J = 4.2 Hz, 4H), 2.89 (dd, J = 5.6, 13.8 Hz, 1H), 3.05 (dd, J = 8.6, 13.8 Hz, 1H), 3.56−3.64 (m, 4H), 4.16 (dd, J = 5.6, 8.6 Hz, 1H), 4.28 (q, J = 6.8 Hz, 2H), 7.21−7.27 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.1, 28.6, 48.5, 61.0, 66.3, 68.7, 125.4, 127.6, 128.3, 137.1, 162.8, 190.6; IR (neat) 1744, 1728, 1604 cm^{-1}. Product **16b** was not sufficiently stable to obtain elemental analysis.

Ethyl 3-Azido-2-oxo-4-phenylbutanoate, 18b. Sodium azide (0.124 g, 1.91 mmol) was added to **7b** (0.39 g, 0.96 mmol) that was dehydrated by refluxing in toluene and dissolved in dry acetone (30 mL). The reaction was stirred for 7 h at 0 °C. Water (50 mL) was added, and the aqueous layer was washed with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to give a dark yellow oil (0.183 g, 77%). Due to the instability of the product, no further purification was attempted: ^{1}H NMR ($CDCl_3$) δ 1.37 (t, J = 7.2 Hz, 3H), 2.96 (dd, J = 8.8, 13.8 Hz, 1H), 3.23 (dd, J = 5.2, 13.8 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 4.76 (dd, J = 5.2, 8.8 Hz, 1H), 7.25−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.9, 36.3,

63.2, 65.5, 127.4, 128.9, 129.3, 135.4, 160.4, 189.8; IR (neat) 2119, 1732, 1605 cm^{-1}.

Ethyl 3-Azido-2-hydroxy-4-phenylbutanoate, 19b. Sodium borohydride (0.093 g, 2.5 mmol) was slowly added to a cold (−78 °C) mixture of THF:methanol (20 mL:0.5 mL). Ethyl 3-azido-2-oxo-4-phenylbutanoate, **18b** (0.21 g, 0.85 mmol), in THF (25 mL) was added, and the mixture was allowed to stir at −78 °C for 30 min. Water (50 mL) was added, and the pH was adjusted to neutrality with aqueous HCl. The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic layers were dried ($MgSO_4$) and evaporated to give a yellow oil (0.19 g, 90%). The crude product was dissolved in CH_2Cl_2, leaving an insoluble, white solid that was filtered. The filtrate was evaporated to give a yellow oil (0.17 g, 81%): ^1H NMR ($CDCl_3$) major isomer δ 1.28 (t, J = 7.2 Hz, 3H), 3.12 (d, J = 7.8 Hz, 2H), 3.72−3.79 (m, 1H), 4.11 (d, J = 2.0 Hz, 1H), 4.25 (dq, J = 3.6, 7.2 Hz, 1H), 4.29 (dq, J = 3.6, 7.2 Hz, 1H), 7.24−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.1, 35.2, 61.4, 63.3, 70.5, 126.0, 127.8, 128.4, 135.7, 171.7; IR (neat) 3446, 3236, 2112, 1739, 1604 cm^{-1}. The product was a mixture of *syn*- and *anti*-**19b** which could not be separated.

Ethyl 3-Azido-2-carbethoxy-4-phenylbutanoate, 20b. Ethyl chloroformate (0.33 mL, 0.37 g, 3.5 mmol), pyridine (0.075 mL, 0.073 g, 0.93 mmol), and DMAP (0.013 g, 0.11 mmol) in CH_2Cl_2 (15 mL) were stirred at 0 °C for 15 min. Azido alcohol **19b** (0.17 g, 0.68 mmol) in CH_2Cl_2 (15 mL) was added, and the reaction was stirred for 5 h at room temperature. The reaction mixture was washed with water (2 × 30 mL), dried ($MgSO_4$), and filtered through a 1.5 cm pad of silica gel. After evaporation, a yellow oil (0.17 g, 78%) remained. The crude product was purified by preparative TLC using EtOAc:hexane (2:3). A yellow oil (0.15 g, 68%), which consisted of a mixture of diastereomers, *syn* and *anti* (76:24), was collected. The NMR spectra of each isomer could be extracted from the spectrum of the mixture. ***syn*-20b** (major isomer): ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 3.01 (dd, J = 7.4, 13.4 Hz, 1H), 3.08 (dd, J = 8.0, 13.4 Hz, 1H), 4.02 (dt, J = 2.8, 7.4 Hz, 1H), 4.16−4.31 (m, 2H), 4.89 (d, J = 2.8 Hz, 1H), 7.21−7.35 (m, 5H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.1, 14.2, 36.4, 62.2, 62.6, 65.0, 75.5, 127.4, 129.0, 129.1, 135.9, 154.3, 167.5; IR (neat) 2115, 1751, 1604, cm^{-1}. ***anti*-20b** (minor isomer): ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 7.2 Hz, 3H), 2.99 (d, J = 7.4 Hz, 2H, 4.02 (dt, J = 2.8, 7.4 Hz, 1H), 4.16−4.31 (m, 2H), 5.10 (d, J = 3.2 Hz, 1H), 7.21−7.35 (m, 5H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.1, 14.2, 36.0, 62.1, 63.2, 65.0, 76.4, 127.1, 128.7, 129.3, 136.3, 154.1, 166.9.

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Supporting Information Available: ^1H NMR spectra of **11a**−**f**, **13d**, **18b**, and **20b** and ^{13}C spectra of **14b,c**, **16b**, and **19b** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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