Synthesis and Reactions of 3-Hydroxy-2-nosyloxy Esters Produced by the Stereoselective Reduction of 2-Nosyloxy-3-keto Esters

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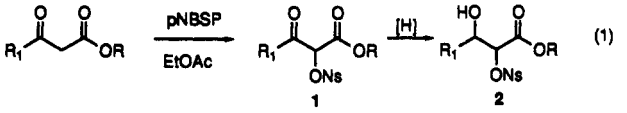
The reduction of 2-nosyloxy-3-keto esters is an effective method for the preparation of 3-hydroxy-2-nosyloxy esters. The reduction is stereoselective for the syn isomer. The anti isomer can be produced as the major product by the addition of *p*-nitrobenzenesulfonyl peroxide to ketene bis-silyl acetal derivatives of 3-hydroxy esters. The diastereomers are separable chromatographically and can be converted stereospecifically to glycidic esters and 2-azido-3-hydroxy esters. As such they appear to have excellent potential as versatile synthetic intermediates for the synthesis of 1,2,3-trifunctional substances.

Introduction

2-Nosyloxy-3-keto esters **1** are readily available from the reaction of β-keto esters with *p*-nitrobenzenesulfonyl peroxide (pNBSP, $(NsO)_2$).[1] These compounds are 1,2,3-trifunctional molecules with greatly differentiated reactivity; thus, they could serve as useful intermediates for the synthesis of other densely functionalized compounds.[2] For example, they are very readily converted by reductive elimination to 1,2,3-tricarbonyl esters.[3] Another transformation of interest is their reduction to 3-hydroxy-2-nosyloxy esters **2** (eq 1). These products are

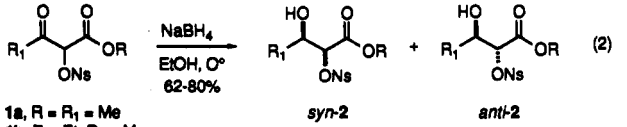


1 2 (1)

themselves very useful synthetic intermediates for 1,2,3-trifunctional compounds. We reported, in preliminary form,[2] that 3-hydroxy-2-nosyloxy esters **2** can be converted to α,β-epoxy esters with high stereoselectivity and that the nosyloxy group of **2** can be replaced by azide to yield 2-azido-3-hydroxy esters with good stereoselectivity.[2] A recent report by Sharpless concerns the preparation of chiral 3-hydroxy-2-nosyloxy esters **2** by the selective sulfonylation of chiral 2,3-dihydroxy esters and also describes their conversion to α,β-epoxy esters and 3-hydroxy-2-azido esters.[4] Herein we detail our results on the synthesis and reactions of this very useful class of synthetic intermediates.

Results and Discussion

Reaction of a series of 2-nosyloxy-3-keto esters **1a–g** with sodium borohydride in absolute ethanol at 0 °C led to the smooth reduction of the ketone to give 3-hydroxy-2-nosyloxy esters **2a–g** as a mixture of syn and anti diastereomers in good yields (eq 2). The diastereomers could



syn-2 anti-2 (2)

1a, R = R_1 = Me
1b, R = Et, R_1 = Me
1c, R = *t*-Bu, R_1 = Me
1d, R = Et, R_1 = *n*-Pr
1e, R = Et, R_1 = Ph
1f, R = Et, R_1 = *i*-Pr
1g, R = *t*-Bu, R_1 = *i*-Pr

Table I. NMR Data for the C-2 Protons of Epoxy Esters 3 Obtained from the Base-Catalyzed Ring Closure of 2

entry	substrates	δ of cis (*J*, Hz)	δ of trans (*J*, Hz)
1	**3a**, R = Me, R_1 = Me	3.53 (4.6)	3.21 (2.0)
2	**3b**, R = Et, R_1 = Me	3.50 (4.4)	3.18 (1.6)
3	**3c**, R = *t*-Bu, R_1 = Me	3.40 (4.6)	3.07 (1.8)
4	**3d**, R = Et, R_1 = *n*-Pr	3.52 (4.6)	3.22 (1.8)
5	**3e**, R = Et, R_1 = Ph	3.72 (4.6)	3.50 (1.8)
6	**3f**, R = Et, R_1 = *i*-Pr	3.54 (4.6)	3.26 (1.8)
7	**3g**, R = *t*-Bu, R_1 = *i*-Pr	3.44 (4.6)	

Table II. Preparation of Epoxy Esters 3 from Hydroxynosylate Esters 2 by TEA in MeCN

entry	starting ester 2	syn:anti	yield[a] (%)	cis:trans[b]
1	R = Me, R_1 = Me (**2a**)	100:0	88	100:0
2	R = Me, R_1 = Me (**2a**)	0:100	91	0:100
3	R = Et, R_1 = Me (**2b**)	100:0	91	100:0
4	R = Et, R_1 = Me (**2b**)	60:40	87	55:45
5	R = *t*-Bu, R_1 = Me (**2c**)	66:34	75	70:30
6	R = Et, R_1 = *n*-Pr (**2d**)	67:33	85	65:35
7	R = Et, R_1 = Ph (**2e**)	100:0	52[c]	66:34
8	R = Et, R_1 = *i*-Pr (**2f**)	92:8	82	75:25
9	R = *t*-Bu, R_1 = *i*-Pr (**2g**)	100:0	91	100:0

[a] The yields refer pure isomers or isomer mixtures after purification by bulb to bulb distillation. [b] The ratio was determined by integration of ^{1}H NMR signals and/or by GC. [c] Comparable results were also obtained using NaH in THF or K_2CO_3 in DMF.

be separated by preparative HPLC to furnish pure samples of each diastereomer. The ^{1}H NMR spectrum of the crude product showed that one diastereomer was favored by a ≈2:1 ratio over the other. However, assignment of syn or anti stereochemistry to the diastereomers of **2** was not possible from either the chemical shifts or coupling constants of the methine protons, which were found to vary in an unsystematic fashion.

The assignment of the ^{1}H NMR spectra for *syn*- and *anti*-**2a–g** was accomplished by converting them to the corresponding epoxides **3** by treatment with triethylamine in acetonitrile (eq 3). The cis and trans epoxides have

syn,anti-2 cis,trans-3 (3)

distinct chemical shifts and coupling constants of the C-2 protons, and thus they were easily distinguishable. In all cases the C-2 protons of the cis isomers were at lower field and had larger coupling constants than the C-2 protons of the trans isomers. This is consistent with data reported in the literature for *cis*- and *trans*-**3a**[5,6] and *cis*-**3b**[6] as well

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(2) Hoffman, R. V. *Tetrahedron* **1991**, *47*, 1109.
(3) Hoffman, R. V.; Kim, H.-O.; Wilson, A. L. *J. Org. Chem.* **1990**, *55*, 2820.
(4) Fleming, P. R.; Sharpless, K. B. *J. Org. Chem.* **1991**, *56*, 2869.

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Table III. Stereochemical Results for the Reduction of 3-Keto-2-nosyloxy Esters 1 with Hydride Reducing Agents

		syn:anti ratio[a]		
entry	substrate	$NaBH_4$	$Zn(BH_4)_2$	L-Selectride
1	**1a**	76:24		43:57
2	**1b**	62:38	66:34	56:44
3	**1c**	66:34	60:40	<5:>95
4	**1d**	65:35		38:62
5	**1e**	100:0		100:0
6	**1f**	93:7	63:37	100:0
7	**1g**	100:0		100:0
8	yield[b] (%)	62–80	>70	50–75

[a] The ratio was determined by integration of ^1H NMR signals and/or by analytical HPLC. [b] The yields are isolated yields of pure products obtained after chromatography.

as for other related cis,trans glycidic esters.[7] The chemical shifts and coupling constants for the C-2 protons of cis and trans epoxides **3** are presented in Table I.

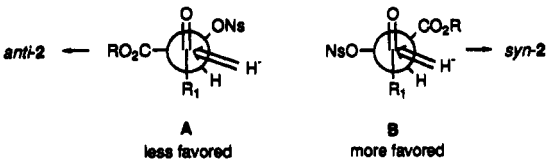
It was found that hydroxy nosylates **2** were converted to epoxides **3** in high yields with generally high stereoselectivity. As seen in Table II, pure diastereomers gave a single epoxide isomer (*syn*-**2** gives *cis*-**3** and *anti*-**2** gives *trans*-**3**) (entries 1–3, 9). Diastereomeric mixtures of **2** gave mixtures of isomeric epoxides **3** with cis–trans isomer ratios that were substantially the same as the syn–anti ratios of the starting diastereomers (entries 4–6). Hydroxynosylates **2e** and **2f** produced epoxides **3e** and **3f** which were epimerized to the extent of 33% and 25%, respectively, but this did not preclude the straightforward syn and anti assignment of the starting materials.

While the stereoselectivity of the closure of **2a–g** to epoxides **3a–g** using triethylamine in refluxing acetonitrile is sufficiently high to make confident stereochemical assignments (>95% except for **2e**, **2f**), Sharpless reported that potassium carbonate in ethanol can be used to give the epoxides **3** stereospecifically (one example),[4] and Greene employed an aqueous potassium carbonate–DMF mixture to accomplish a similar transformation stereospecifically.[7b] We employed Greene's conditions for **2e** and still obtained only 75:25 diastereoselectivity. Thus, while potassium carbonate in a protic solvent appears to be the reagent of choice for producing glycidic esters **3** stereospecifically from 3-hydroxy-2-nosyloxy esters **2**, some isomerization is still possible for certain substrate types.

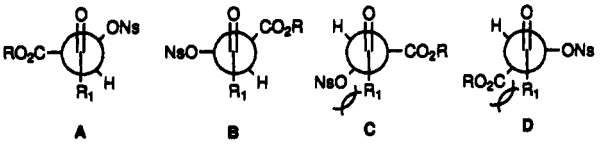
Having identified the ^1H NMR signals for the syn and anti isomers of **2a–g**, the diastereoselectivity of the reduction of nosyloxyketo esters **1** by sodium borohydride could be determined accurately (Table III). The syn isomer was the major product in all cases and, in some, was formed with very high diastereoselectivity (entries 5–7). To determine the stereochemical effect of the metal counterion on the reduction, zinc borohydride and L-Selectride (Aldrich) (lithium tri-*sec*-butylborohydride) in THF were used in place of sodium borohydride. Comparable yields of reduction products were obtained. The results of these reductions are also collected in Table III.

The Felkin–Anh model[8] provides a suitable model for explaining the observed stereoselectivity. Based on the requirements of this model, several reactive conformers

Scheme I



are possible. Conformers A and B should be favored over C and D due to increased steric repulsions between the nosylate or ester groups with the R_1 group in the latter.



Addition of borohydride to A gives *anti*-**2**, and addition of borohydride to B gives *syn*-**2** (Scheme I). The reactive conformer appears to be determined by competing steric and stereoelectronic effects. Since the ester group is sterically larger than the nosylate group,[9] it would preferentially occupy the position antiperiplanar to the carbonyl group as in A. The nosylate group would preferentially occupy the position antiperiplanar to the carbonyl group as in B due to its electron withdrawing properties.[8b] The results presented in Table III indicate that when R_1 is relatively small (Me, *n*-propyl), addition to B is favored (entries 1–4). Thus, the electronic effect of the nosylate group appears to be more important than the steric effect of the ester group. However, the reaction stereochemistry is sensitive to structural effects in the reactant.

If R_1 is larger (*i*-Pr, Ph), increased steric interactions between R_1 and the ester function in A reduce its importance further so that B becomes the reactive conformer and nearly exclusive formation of *syn*-**2** results (entries 5–7). Interestingly, changing the ester group from ethyl to *tert*-butyl does not change the distereoselectivity (cf. entries 1, 3). Thus, the major factor influencing the stereoselection is the size of R_1.

Using the more bulky reducing agent L-Selectride gives increased amounts of *anti*-**2** (entries 1–4). One possible explanation for this trend is that increased steric interactions between the bulkier reducing agent and the ester function in B slow the rate of addition to B and thus decrease the proportion of *syn*-**2** that is produced. Support for this interpretation is found in entry 3, which shows that while the size of the ester group in **1c** does not influence the diastereoselectivity for small reducing agents, use of L-Selectride gives *anti*-**2c** as the major product. However, the steric bulk of R_1 still retains greater influence on the diastereoselectivity than either the size of the ester group or bulkiness of the reducing agent (entries 5–7). As seen in entry 7 reduction of **1g**, which has a larger isopropyl group as the ketonic substituent, gives only *syn*-**2g**, irrespective of the reducing agent or the size of the ester group.

The use of zinc borohydride gives the same stereochemical results as sodium borohydride, indicating that chelation is an unimportant factor in the diastereoselection. (Unchanged diastereoselectivity was also observed for the reduction of **1b** with $(Me)_4NBH_4$.) In this respect, the reductions of 3-keto esters with electronegative substituents at the 2-position are quite different than the reductions of 2-alkyl-3-keto esters. For example, reductions of

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(6) Petit, Y.; Sanner, C.; Larcheveque, M. *Synthesis* **1988**, 538.
(7) (a) Abel-Magid, A.; Pridgen, L. N.; Eggleton, D. S.; Lantos, I. *J. Am. Chem. Soc.* **1986**, *108*, 4595. (b) Denis, J.-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1990**, *55*, 1957. (c) Denis, J.-N.; Greene, A. E.; Serra, A. A.; Luche, M.-J. *J. Org. Chem.* **1986**, *51*, 46. (d) Caldwell, C. G.; Bondy, S. S. *Synthesis* **1990**, *34*.
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(9) The *A* value for the tosylate group (and by interference the nosylate group) is 0.52 while that of the carbomethoxy group is 1.3. Jensen, F. R.; Bushweller, C. H. *Adv. Alicycl Chem.* **1971**, *3*, 139.

Table IV. Preparation of 2-Azido-3-hydroxy Esters 6 from 3-Hydroxy-2-nosyl Esters 2 and Sodium Azide

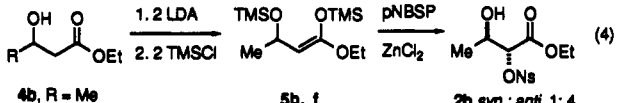
entry	nosylate (syn:anti)	yield[a] (%)	ratio (syn:anti)[b]
1	**2a** (75:25)	56	38:62
2	**2b** (62:38)	53	36:64
3	**2f** (syn only)	49	25:75
4	**2f** (92:8)	63[c]	25:75

[a] Reported yields are for purified products for two steps from nosylates 1. [b] Ratio determined by integration of the signals of the C-2 protons in 6. [c] 1,1,3,3-Tetramethylguanidinium azide was used as the azide source.

2-alkyl-3-keto esters with borohydride reagents with poorly coordinating counterions (K^+,[10] or Me_4N^+[11]) are anti selective by about 3:1. Changing to a lithium counterion (LAH) gives a syn selectivity of about 9:1. Using zinc as counterion ($Zn(BH_4)_2$) gives an increase in syn selectivity to >98:2. Zinc is particularly effective as a chelating metal as similar trends were found for reductions of 3-keto-amides.[12]

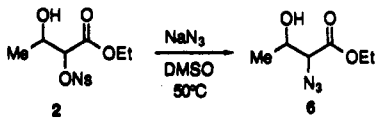
In contrast no chelation effect is found for the reductions of 2-nosyloxy-3-keto esters 1. Similar lack of metal ion effects have been reported for reductions of 2-fluoro-2-methyl-3-keto esters.[13] Electron-withdrawing groups might decrease the coordinating ability of the ketone and ester groups to the extent that chelation is ineffective in dictating the reactive conformation.

Since reduction of 1 gives predominantly *syn*-**2**, an alternate synthesis of **2** was sought which could provide the anti diastereomer as the major product. Ethyl 3-hydroxybutanoate, **4b**, was converted to its bis-silylketene acetal derivative **5**[14] and reacted with pNBSP in the presence of $ZnCl_2$.[15] Compound **2b** was obtained in 40% yield after purification by chromatography in a syn/anti ratio of 1:4 (eq 4). In a similar fashion **2f** was obtained



from **4f** in 17% yield with a syn/anti ratio of 1:3. Work is underway to understand why reduced yields occur for these substrates, but the preference for the anti diastereomer is clear. Since separation of diastereomers is straightforward, the two methods are complementary for securing either isomer in pure form.

Replacement of the nosylate group in **2** by amine-equivalent nucleophiles provides a route to physiologically important 2-amino-3-hydroxy acid derivatives.[16] Based on the ease of epoxide formation observed with triethylamine, only weakly basic nucleophiles are appropriate for the substitution. We found that sodium azide in DMSO effected substitution to give 2-azido-3-hydroxy esters in moderate (49–63%) yields (eq 5). Under these conditions 25% epimerization at C-2 was found (Table III). Sharpless found substitutions by azide in **2** occur in similar yields but with no epimerization using DMF as solvent.[4]



In summary, we have shown that the reduction of 2-(nosyloxy)-3-keto esters is an effective method for the preparation of 3-hydroxy-2-nosyloxy esters. The reduction is stereoselective for the syn isomer. The anti isomer can be produced as the major product by the addition of *p*-nitrobenzenesulfonyl peroxide to ketene bis-silyl acetal derivatives of 3-hydroxy esters. The diastereomers are separable chromatographically and can be converted stereospecifically to glycidic esters and 2-azido-3-hydroxy esters. As such they appear to have excellent potential as versatile synthetic intermediates for the synthesis of 1,2,3-trifunctional substances.

Experimental Section

^1H NMR and ^{13}C NMR spectra were recorded at 200 and 100 MHz, respectively, on Varian instruments. 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 Rainin chromatograph equipped with a 8 mm × 25 cm silica gel column and UV detector (254 nm). Flash chromatography was performed using silica gel 60 (230–400 mesh). Radial chromatography was performed on a radial chromatograph (Harrison) using a 2-mm layer of silica gel 60 PF_{254} containing gypsum. Gas chromatographic (GC) analyses were performed on a HP-5890 chromatograph using either a phenylmethylsilicone or polyethylene glycol glass capillary column (0.32-μm film thickness) and a thermal conductivity detector. GC/MS analyses were performed by phenylmethylsilicone or polyethylene glycol glass capillary column (0.32-μm thickness) connected to a quadruple mass detector. The column temperature was from 50 to 300 °C at 5 °C/min with 3 mL/min of helium gas flow rate. Elemental analyses were carried out by M-H-W Laboratories, Phoenix, AZ.

Ethyl 4-Methyl-2-[(*p*-nitrobenzenesulfonyl)oxy]-3-hydroxypentanoate (2f). $NaBH_4$ method: $NaBH_4$ (40 mg, 1.1 mmol) was added in one portion to a stirred solution of ethyl 4-methyl-2-[(*p*-nitrobenzenesulfonyl)oxy]-3-oxopentanoate (**1f**) (360 mg, 1.0 mmol) in ethanol (15 mL) at 0 °C. The reaction wsa stirred at the same temperature for 1 h, and 1 N HCl (5 mL) was added slowly. Most of the ethanol was removed by rotary evaporation, and the aqueous phase was extracted with ethyl acetate (50 mL). The ethyl acetate extract was washed with brine (50 mL), passed through the short pad of $MgSO_4$ and silica gel 60, and concentrated to provide **2f** as a white solid (260 mg, 72%) after purification by flash chromatography (hexane/ethyl acetate (80:20)): mp 101–102 °C; ^1H NMR ($CDCl_3$) δ 0.97 and 1.04 (two d, 6 H, J = 7 Hz, $CH(CH_3)_2$), 1.23 (t, 3 H, J = 6.6 Hz, OCH_2CH_3), 1.83 (m, 1 H, $CH(CH_3)_2$), 2.30 (br s, 1 H, OH), 3.70 (dd, 1 H, J = 2.8, 2.6 Hz, CHOH), 4.17 (q, 2 H, J = 6.6 Hz, OCH_2CH_3), 5.19 (d, 1 H, J = 2.8 Hz, CHONs), 8.19 and 8.39 (ABq, 4 H, aromatic CH); the ^1H NMR spectrum was consistent with 93:7 ratio of syn/anti isomers; IR (CH_2Cl_2) 3550, 3100, 2960, 1725, 1530 cm^{-1}. HPLC analysis (ethyl acetate/hexane (50:50); 1.0 mL/min) revealed that there were two components at t_R 4.32 and 4.61 min in the ratio of 93:7 for the syn and anti isomers. Anal. Calcd for $C_{14}H_{17}NO_8S$: C, 46.54; H, 5.26; N, 3.88. Found: C, 46.64; H, 5.52; N, 3.68.

L-Selectride method: L-Selectride (3.0 mL of 1 M solution in THF, 3 mmol) was added to a stirred solution of ethyl 4-methyl-2-[(*p*-nitrobenzenesulfonyl)oxy]-3-oxopentanoate (**1f**) (650 mg, 1.8 mmol) in THF (30 mL) at −78 °C. After the resulting solution was stirred at −78 °C for 2 h, 30% H_2O_2 (20 mL) was added, and the mixture was stirred at room temperature for 2 h. The solution was extracted with ethyl acetate (70 mL). The ethyl acetate extract was washed with brine (100 mL), passed through the short pad of $MgSO_4$ and silica gel 60, and concentrated to provide **2f** (520 mg, 80%) after purification by flash chromatography (hexane/ethyl acetate (80:20)). The ^1H NMR spectrum and HPLC analysis of the product were in good agreement with

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those of an authentic sample, and only the syn isomer was detected.

$Zn(BH_4)_2$ method: A solution of $Zn(BH_4)_2$ (prepared from a 1 M solution of $ZnCl_2$ (1 mL) and $NaBH_4$ (760 mg) in THF[17] was added dropwise to a stirred solution of ethyl 4-methyl-2-[(*p*-nitrobenzenesulfonyl)oxy]-3-oxopentanoate (**1f**) (360 mg, 1.0 mmol) in THF (20 mL) at −78 °C. After stirring the resulting solution at −78 °C for 2 h, H_2O (20 mL) was added, followed by 1 N HCl (20 mL), and the mixture was stirred at room temperature for 2 h. The solution was extracted with ethyl acetate (2 × 30 mL). The ethyl acetate extracts were passed through the short pad of $MgSO_4$ and silica gel 60 and concentrated to provide **2f** (270 mg, 75%) after purification by flash chromatography (hexane/ethyl acetate (80:20)). The ^1H NMR spectrum was in good agreement with those of an authentic sample and was determined to be a 63:37 mixture of syn and anti isomers.

Methyl 2-[(*p*-nitrobenzenesulfonyl)oxy]-3-hydroxybutanoate (2a) was prepared from **1a** by reduction with $NaBH_4$ in 67% yield: ^1H NMR ($CDCl_3$) δ 1.28 (d, 3 H, J = 6.8 Hz, $CHCH_3$), 2.70 (br, 1 H, OH), 3.71 (s, 3 H, OCH_3), 4.29 (m, 1 H, $CHCH_3$), 4.93 (d, 0.8 H, J = 3.6 Hz, CHONs), 5.05 (d, 0.2 Hz, J = 3.8 Hz, CHONs), 8.21 and 8.41 (ABq, 4 H, aromatic CH); the ^1H NMR spectrum was consistent with a 78:22 mixture of syn/anti isomers in the product; IR (neat) 3520 (br), 3100, 2970, 1740, 1520 cm^{-1}. HPLC analysis (hexane/ethyl acetate 50:50, 2.0 mL/min) showed two peaks at t_R 3.80 and 4.35 min in the ratio of 76:24 for the syn and anti isomers. Anal. Calcd for $C_{11}H_{13}NO_8S$: C, 41.37; H, 4.08; N, 4.39. Found: C, 41.65; H, 4.14; N, 4.30.

Reduction of **1a** with L-Selectride gave **2a** in 86% yield; HPLC analysis showed a 43:57 ratio of syn and anti isomers in the product.

Ethyl 2-[(*p*-nitrobenzenesulfonyl)oxy]-3-hydroxybutanoate (2b) was prepared from **1b** by reduction with $NaBH_4$ in 81% yield: mp 96–98 °C; ^1H NMR ($CDCl_3$) δ 1.23 (t, 3 H, J = 7.2 Hz, OCH_2CH_3), 1.24 and 1.30 (two d, 3 H, $CHCH_3$), 2.60 (brs, 1 H, OH), 4.17 (q, 2 H, J = 7.2 Hz, OCH_2CH_3), 4.29 (m, 1 H, $CHCH_3$), 4.90 and 5.04 (two d, 1 H, J = 3.6, 3.8 Hz, CHONs), 8.19 and 8.41 (ABq, 4 H, aromatic CH). The ^1H NMR spectrum of the product was consistent with a 63:37 mixture of syn and anti isomer; IR (neat) 3500 (br), 3100, 2980, 1740, 1525 cm^{-1}. HPLC analysis (hexane/ethyl acetate (50:50), 1 mL/min) showed two peaks at t_R 6.67 and 7.15 min in the ratio of 62:38 for the syn and anti isomers. Anal. Calcd for $C_{12}H_{15}NO_8S$: C, 43.24; H, 4.50; N, 4.20. Found: C, 43.40; H, 4.51; N, 4.08.

Reduction of **1b** with L-Selectride gave **2b** in 84% yield; HPLC analysis showed a 56:44 ratio of the syn and anti isomers in the product.

Reduction of **1b** with $Zn(BH_4)_2$ gave **2b** in 71% yield; HPLC analysis showed a 66:34 ratio of the syn and anti isomers in the product.

$Me_4NB(OAc)_3H$ method: $Me_4NB(OAc)_3H$ (1.3 g, 5 mmol)[18] was added to a stirred solution of **1b** (330 mg, 1.0 mmol) in acetic acid (5 mL) and acetonitrile (10 mL) at 0 °C. After the resulting solution was stirred at 0 °C for 3 h and at room temperature for 16 h, NaOAc buffer (pH 6, 20 mL) was added and the mixture was poured into saturated $NaHCO_3$ (30 mL). The solution was extracted with ethyl acetate (3 × 50 mL). The ethyl acetate extracts were passed through the short pad of $MgSO_4$ and silica gel 60 and concentrated to provide **2b** in quantitative yield. The ^1H NMR spectrum of the product showed it to be a 70:30 mixture of syn and anti isomers by comparison with authentic samples.

Reduction of **1b** with Me_4NBH_4[18] also gave **2b** in quantitative yield. HPLC analysis showed a 65:35 ratio of the syn and anti isomers in the product.

***tert*-Butyl 2-[(*p*-nitrobenzenesulfonyl)oxy]-3-hydroxybutanoate (2c)** was prepared by the reduction of **1c** with $NaBH_4$ in 78% yield: mp 99–102 °C; ^1H NMR ($CDCl_3$) δ 1.27 (two d, 3 H, J = 6.4 Hz, $CHCH_3$), 1.42 (two s, 9 H, $C(CH_3)_3$), 4.24 (m, 1 H, CHOH), 4.77 (d, 0.7 H, J = 3.8 Hz, CHONs), 4.94 (d, 0.3 Hz, J = 3.8 Hz, CHONs), 8.20 and 8.42 (ABq, 4 H, aromatic CH); the ^1H NMR spectrum was consistent with a 68:32 ratio of syn/anti isomers in the product; IR (CH_2Cl_2) 3560 (br), 2970, 1750, 1535 cm^{-1}. HPLC analysis (hexane/ethyl acetate (50:50), 1 mL/min) showed two peaks at t_R 4.70 and 5.23 in the ratio of 66:34 for the syn and anti isomers. Anal. Calcd for $C_{14}H_{19}NO_8S \cdot {}^1/_4\ H_2O$: C, 45.96; H, H, 5.34; N, 3.83. Found: C, 45.80; H, 5.33; N, 3.66.

Reduction of **1c** with L-Selectride gave **2c** in 58% yield; HPLC analysis showed only the anti isomer to be present in the product.

Ethyl 2-[(*p*-nitrobenzenesulfonyl)oxy]-3-hydroxyhexanoate (2d) was prepared from **1d** by reduction with $NaBH_4$ in 52% yield: ^1H NMR ($CDCl_3$) δ 0.92 (m, 3 H, $CH_3CH_2CH_2$–), 1.23 (dt, 3 H, OCH_2CH_3), 1.45 (m, 4 H, $CH_3CH_2CH_2$–), 4.10 (m, 1 H, CHOH), 4.17 (q, 2 H, OCH_2CH_3), 4.99 (d, 0.7 H, J = 3.2 Hz, CHONs), 5.06 (d, 0.3 H, J = 3.8 Hz, CHONs), 8.20 and 8.42 (ABq, 4 H, aromatic CH). The ^1H NMR spectrum was consistent with a 70:30 ratio of syn/anti isomers in the product; IR ($CDCl_3$) 3500, 3100, 2950, 1750, 1525, 1345, 1180 cm^{-1}. HPLC analysis (hexane/ethyl acetate (50:50), 2 mL/min) showed two peaks at t_R 2.16 and 2.27 in the ratio of 65:35 for the syn/anti isomers. Anal. Calcd for $C_{14}H_{19}NO_8S$: C, 46.53; H, H, 5.30; N, 3.88. Found: C, 46.47; H, 5.63; N, 3.77.

Reduction of **1d** with L-Selectride gave **2d** in 48% yield. HPLC analysis gave a 38:62 ratio of the syn/anti isomers in the product.

Reductino of **1d** with $Zn(BH_4)_2$ gave **2d** in 75% yield. HPLC analysis gave a 60:40 ratio of the syn/anti isomers in the product.

Ethyl 2-[(*p*-nitrobenzenesulfonyl)oxy]-3-phenyl-3-hydroxypropanoate (2e) was prepared from **1e** by reduction with $NaBH_4$ in 68% yield (from ethylbenzoyl acetate): mp 115–118 °C; ^1H NMR ($CDCl_3$) δ 1.18 (t, 3 H, OCH_2CH_3), 4.17 (q, 2 H, OCH_2CH_3), 5.01 (d, 1 H, J = 4.0 Hz, CHONs), 5.21 (br, 1 H, CHOH), 7.23 (m, 5 H, phenyl), 7.80 and 8.19 (ABq, 4 H, aromatic CH); FTIR ($CDCl_3$) 3601 (br), 3106, 2985, 1740, 1535, 1350, 1189 cm^{-1}. HPLC (hexane/ethyl acetate (50:50), 2 mL/min) showed a single peak at t_R 2.17 min which was due to the syn isomer. Determination of the stereochemistry of this compound was carried out by transformation to a known epoxide.[19]

Reduction of **1e** with L-Selectride gave **2e** in 48% yield (for two steps). HPLC analysis showed only the syn isomer to be present in the product.

***tert*-Butyl 4-methyl-2-[(*p*-nitrobenzenesulfonyl)oxy]-3-hydroxypentanoate (2g)** was prepared from **1g** by reduction with $NaBH_4$ in 62% yield: ^1H NMR ($CDCl_3$) δ 0.95 and 1.04 (two d, 6 H, J = 6.6 Hz, $CH(CH_3)_2$), 1.42 (s, 9 H, $C(CH_3)_3$), 1.70 (m, 1 H, $CH(CH_3)_2$), 3.65 (dd, 1 H, J = 2.8, 8.6 Hz, CHOH), 5.05 (d, 1 H, J = 2.8 Hz, CHONs), 8.18 and 8.40 (ABq, 4 H, aromatic CH); the ^1H NMR spectrum showed only the syn isomer to be present; IR (neat) 3530, 3100, 2950, 1750, 1710, 1520, 1340, 1185 cm^{-1}. HPLC (hexane/ethyl acetate (50:50), 2.0 mL/min) showed a single peak at t_R 1.99 min corresponding to the syn isomer. Anal. Calcd for $C_{16}H_{23}NO_8S$: C, 49.35; H, 5.95; N, 3.60. Found: C, 49.92; H, 6.16; N, 3.50.

Reduction of **1g** with L-Selectride gave **2g** in 85% yield. HPLC showed only the syn isomer to be present in the product.

Ethyl 2-[(*p*-Nitrobenzenesulfonyl)oxy]-3-hydroxybutanoate (2b) from 1,3-Bis[(trimethylsilyl)oxy]-1-ethoxybutene (5b). A solution of 1,3-bis[(trimethylsilyl)oxy]-1-ethoxybutene (830 mg)[14] in ethyl acetate (20 mL) was added dropwise to a stirred suspension of $ZnCl_2$ (1.37 g, 10 mmol) and pNBSP (810 mg, 2.0 mmol) in ethyl acetate (80 mL) at −78 °C. After completion of the addition, the resulting solution was warmed to room temperature and stirred overnight. The solution was washed with H_2O (100 mL), passed through the short pad of $MgSO_4$ and silica gel 60 to provide a pale yellow oil (260 mg, 40%) after purification by flash chromatography (hexane/ethyl acetate (80:20)). The ^1H NMR spectrum and TLC of the product, which was a 1:4 ratio of syn/anti isomers, were in good agreement with an authentic sample of **2b**.

Ethyl 4-Methyl-2-[(*p*-nitrobenzenesulfonyl)oxy]-3-hydroxypentanoate (2f) from 4-Methyl-1,3-bis[(trimethylsilyl)oxy]-1-ethoxy-1-pentene (5f). To a −78 °C solution of LDA (32 mmol) in THF (30 mL) was added ethyl 3-hydroxy-4-methylpentanoate (**4f**) (2.45 g, 15.3 mmol). After the solution was stirred for 1 h, TMSCl (5 mL) was added and the mixture was stirred at room temperature for 1 h. The solvent was removed

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by rotary evaporation, and the white residue was taken up in pentane (150 mL) and filtered. The pentane was removed by rotary evaporation, and the product was distilled by bulb to bulb distillation (90–100 °C, 0.1 mmHg) to give **5f** as a colorless oil (4.15 g, 89%): ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 9 H, $-SiMe_3$), 0.23 (s, 9 H, $-SiMe_3$), 0.87 (two d, 6 H, J = 6.6 Hz, $CH(CH_3)_2$), 1.30 (t, 3 H, J = 7.0 Hz, OCH_2CH_3), 1.62 (m, 1 H, $CH(CH_3)_2$), 3.52 (d, 1 H, J = 9.2 Hz, =CH), 3.75 (q, 2 H, J = 7 Hz, OCH_2CH_3), 4.15 (dd, 1 H, J = 7, 9.2 Hz, $CHOSiMe_3$). Compound **5f** (1.52 g, 5 mmol) was added to a 0 °C, stirred suspension of pNBSP (1.21 g, 3 mmol) in ethyl acetate (60 mL). Sodium methoxide (440 mg, 8 mmol) was then added, and the resulting mixture was stirred at 0 °C for 3 h and at room temperature overnight. The reaction mixture was washed with 1 N HCl (100 mL), passed through a short pad of silica gel and $MgSO_4$, concentrated by rotary evaporation, and purified by flash chromatography (hexane/ethyl acetate (95:5 to 9:1) to give **2f** (180 mg, 17%) as a colorless oil. The ^{1}H NMR spectra confirmed the presence of **2f** as a 1:3 mixture of syn and anti isomers.

Other additives such as $ZnCl_2$ or 2,6-di-*tert*-butyl-4-methylpyridine did not give significant improvement in yield, purity, or stereoselectivity.

Ethyl 3-methyloxiranecarboxylate (3b) was prepared by a typical procedure for the formation of epoxides **3** from 2-(nosyloxy)-3-hydroxy esters **2**. A mixture of ethyl 2-[(*p*-nitrobenzenesulfonyl)oxy]-3-hydroxybutanoate (**2b**) (1.0 g, 3.0 mmol, syn:anti = 60:40) and triethylamine (0.8 mL, 6 mmol) in acetonitrile (50 mL) was heated at reflux overnight. After concentration by rotary evaporation (bath temperature 35 °C), residue was taken up into dichloromethane (100 mL), washed with 1 N HCl (50 mL), dried ($MgSO_4$), concentrated by rotary evaporation (bath temperature <30 °C), and distilled by bulb to bulb distillation (bath temperature 80–85 °C (38 mmHg)) to provide **3b** as a colorless oil (170 mg, 87%): ^{1}H NMR ($CDCl_3$) δ 1.31 (two t, 3 H, J = 7.2 Hz, OCH_2CH_3), 1.41 (two d, 3 H, J = 5.4 Hz, $OCHCH_3$), 3.18 (d, 0.5 H, J = 1.6 Hz, trans $OCHCO_2Et$), 3.27 (m, 1 H, $OCHCH_3$), 3.50 (d, 0.5 H, J = 4.4 Hz, cis $OCHCO_2Et$), 4.26 (two q, 2 H, J = 7.2 Hz, OCH_2CH_3);[6] the ^{1}H NMR spectrum was consistent with a 55:45 ratio of cis/trans isomers in the product; FTIR (neat) 2980, 2934, 1750, 1422, 1287, 1194, 1036 cm^{-1}. GC analysis was consistent with 54:46 ratio of cis/trans isomers: GC/MS (t_R 3.10 min) m/z 130 (0.5), 102 (100), 87 (12), 85 (32), 84 (23), 74 (52), 73 (37), 69 (16), 58 (44), 57 (99), 55 (16). (t_R 3.32 min) m/z 130 (0.4), 102 (100), 87 (4), 85 (21), 74 (48), 73 (34), 69 (5), 58 (36), 57 (80), 55 (15).

syn-**2b**, which was separated by preparative HPLC (hexane/ethyl acetate (50:50), 12 mL/min, more polar component), gave **3b** in 91% yield. ^{1}H NMR analysis showed only cis isomer present in the product.

Methyl 3-methyloxiranecarboxylate (3a) was prepared from *anti*-**2a** (210 mg, 0.66 mmol) which was separated by preparative HPLC (hexane/ethyl acetate (50:50), 12 mL/min, less polar component) and triethylamine (0.2 mL) as a colorless oil (70 mg, 91%) after bulb to bulb distillation (bath temperature 80–85 °C (38 mmHg)): ^{1}H NMR (400 MHz)($CDCl_3$) δ 1.41 (d, 3 H, J = 5.2 Hz, $CHCH_3$), 3.21 (d, 1 H, J = 2.0 Hz by decoupling experiment, trans C-2), 3.23 (dq, 1 H, J = 5.2, 2.0 Hz, trans C-3), 3.78 (s, 3 H, OCH_3). The ^{1}H NMR spectrum of **3a** was in good agreement with the literature spectrum[6] and was consistent with only trans isomer being present in the product.

From *syn*-**2a** (the molar polar component in preparative HPLC), *cis*-**3a** was obtained in 88% yield: ^{1}H NMR ($CDCl_3$) δ 1.39 (d, 3 H, J = 5.4 Hz, $CHCH_3$), 3.30 (m, 1 H, J = 4.8 Hz, $CHCH_3$), 3.53 (d, 1 H, J = 4.6 Hz, cis C-2), 3.81 (s, 3 H, OCH_3); ^{1}H NMR spectrum was in good agreement with literature[6] and was consistent with the cis isomer as the only product; ^{13}C NMR ($CDCl_3$) δ 12.96, 52.31, 52.96, 53.50, 168.75.

***tert*-Butyl 3-methyloxiranecarboxylate (3c)** was prepared from **2c** (1.38 g, 3.8 mmol, syn:anti = 66:34) and triethylamine (1.2 mL) as a colorless oil (450 mg, 75%) after bulb to bulb distillation (bath temperature 80–90 °C (40 mmHg)): ^{1}H NMR ($CDCl_3$) δ 1.38 (d, 3 H, J = 5.4 Hz, $CHCH_3$), 1.49 and 1.50 (two s, 9 H, ratio 67:33, $C(CH_3)_3$), 3.07 (d, 0.3 H, J = 1.8 Hz, trans C-2), 3.24 (m, 1 H, C-3H), 3.40 (d, 0.7 H, J = 4.6 Hz, cis C-2); ^{1}H NMR was consistent with a 66:34 ratio of cis/trans isomers; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 27.9 (27.85), 53.4 (53.1), 54.6 (54.2), 82.3, 168.3; FTIR ($CDCl_3$) 2980, 1739, 1370, 1255, 1162 cm^{-1}. GC analysis was consistent with a 70:30 ratio of cis/trans isomers: GC/MS (t_R 6.72) m/z 102 (5, $M^+ - t$-Bu), 59 (21), 57 (100), 56 (97), 55 (44), 53 (15), 51 (13), 50 (17); (t_R 7.52) m/z 102 (8, $M^+ - t$-Bu), 59 (19), 57 (100), 56 (74), 55 (35), 53 (11), 51 (9), 50 (13). Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.90; H, 8.82.

Ethyl 3-*n*-propyloxiranecarboxylate (3d) was prepared from **2d** (240 mg, 0.67 mmol, syn:anti = 2:1) and triethylamine (0.2 mL) as a colorless oil (90 mg, 85%) after purification by bulb to bulb distillation (bath temperature 85–95 °C (40 mmHg)): ^{1}H NMR ($CDCl_3$) δ 0.98 (m, 3 H, $CH_2CH_2CH_3$), 1.31 (t, 3 H, J = 7 Hz, OCH_2CH_3), 1.60 (set of m, 4 H, $CH_2CH_2CH_3$), 3.17 (m, 1 H, C-3), 3.22 (d, 0.4 H, J = 1.8 Hz, trans C-2), 3.52 (d, 0.6 H, J = 4.6 Hz, cis C-2), 4.27 (dq, 2 H, OCH_2CH_3); FTIR ($CDCl_3$) 2964, 2875, 1747, 1466, 1381, 1202 cm^{-1}. GC analysis showed a 65:35 ratio of cis/trans isomers. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.59; H, 8.80.

Ethyl 3-phenyloxiranecarboxylate (3e) was prepared from *syn*-**2e** (870 mg, 2.19 mmol) and triethylamine (0.7 mL, 5 mmol) as a pale yellow oil (220 mg, 52%) after purification by preparative TLC (hexane:ethyl acetate = 95:5): ^{1}H NMR ($CDCl_3$) major isomer (cis) δ 0.91 (t, 3 H, OCH_2CH_3), 3.72 (d, 1 H, J = 4.6 Hz), 3.89 (q, 2 H, OCH_2CH_3), 4.16 (d, 1 H, J = 4.8 Hz), 7.21 (m, 5 H, phenyl), minor isomer (trans) δ 1.32 (t, 3 H, OCH_2CH_3), 3.50 (d, 1 H, J = 1.8 Hz), 4.00 (q, 2 H, OCH_2CH_3), 4.09 (d, J = 1.8 Hz), 7.34 (m, 5 H, phenyl); ^{1}H NMR showed a 66:34 ratio of cis/trans isomers; FTIR ($CDCl_3$) 3066, 2982, 1750, 1456, 1204 cm^{-1}; GC/MS (t_R 20.80 min) m/z 192 (M^+, 8), 135 (93), 119 (15), 118 (34), 107 (69), 106 (17), 105 (59), 91 (100), 90 (44), 89 (41), 79 (58), 77 (54), 65 (26), 64 (11), 63 (21), 51 (36), 50 (18); (t_R 22.16 min) m/z 192 (M^+, 7), 135 (100), 119 (15), 118 (31), 107 (74), 106 (18), 105 (59), 91 (92), 90 (41), 89 (40), 79 (58), 77 (57), 65 (24), 64 (10), 63 (20), 51 (39), 50 (17). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.66; H, 6.22.

Alternative methods for the preparation of **3e** were examined. Potassium carbonate (1.17 g, 8.5 mmol) was added to a stirred solution of *syn*-**2e** (1.10 g, 2.78 mmol) in DMF (17 mL) and H_2O (0.25 mL, 17 mmol) at room temperature.[7b] The resulting suspension was stirred at room temperature for 23 h. Additional water (50 mL) was added, and the solution was extracted with ether (3 × 50 mL). The combined etheral extracts were dried ($MgSO_4$) and concentrated to provide **3e** as a colorless oil (220 mg, 42%) after purification by radial chromatography (hexane/ethyl acetate (95:5)). The ^{1}H NMR showed a 75:25 ratio of cis/trans isomers in the product.

In another experiment, a solution of *syn*-**2e** (360 mg, 0.9 mmol) in THF (20 mL) was added dropwise to a 0 °C suspension of NaH (48 mg, 50% in mineral oil) in THF (15 mL). After stirring at room temperature for 2 h, water (30 mL) was added and most of the THF was removed by rotary evaporation. The remaining aqueous mixture was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with brine (100 mL), passed through a short pad of $MgSO_4$ and silica gel 60, and concentrated to provide **3e** as a pale yellow oil (75 mg, 43%) after purification by preparative TLC (hexane/ethyl acetate (90:10)). The ^{1}H NMR showed **3e** to be a 67:33 mixture of cis/trans isomers.

Ethyl 3-isopropyloxiranecarboxylate (3f) was prepared from **2f** (360 mg, 1.0 mmol, syn:anti = 92:8) and triethylamine (0.28 mL, 4.0 mmol) as a colorless oil (130 mg, 82%) after purification by bulb to bulb distillation (bath temperature 85–90 °C (38 mmHg)): ^{1}H NMR ($CDCl_3$) major isomer (cis) δ 0.92 (d, 3 H, J = 7.0 Hz, $CH(CH_3)_2$), 1.15 (d, 3 H, J = 6.6 Hz, $CH(CH_3)_2$), 1.31 (t, 3 H, J = 7.2 Hz, OCH_2CH_3), 1.70 (m, 1 H, $CH(CH_3)_2$), 2.86 (dd, 1 H, J = 9.2, 4.6 Hz, $OCHCH(CH_3)_2$), 3.54 (d, 1 H, J = 4.6 Hz, EtO_2CCH), 4.27 (q, 2 H, J = 7.0 Hz, OCH_2CH_3); minor isomer (trans) δ 1.00 (d, 3 H, J = 7.0 Hz, $CH(CH_3)_2$), 1.04 (d, 3 H, J = 6.6 Hz, $CH(CH_3)_2$), 1.70 (m, 1 H, $CH(CH_3)_2$), 2.98 (dd, 1 H, J = 6.6, 2.0 Hz, $OCHCH(CH_3)_2$), 3.26 (d, 1 H, J = 1.8 Hz, $OCHCH(CH_3)_2$), 4.27 (q, 2 H, J = 7.0 Hz, OCH_2CH_3). The ^{1}H NMR was consistent with a 75:25 ratio of cis/trans isomers in the product. GC analysis also gave a 75:25 ratio of cis/trans isomers: GC/MS (t_R 3.94) m/z 130 ($M^+ - Et$, 5), 115 (6), 101 (17), 87 (8), 85 (100), 75 (8), 73 (20), 69 (8), 57 (18), 56 (97), 55 (47); (t_R 4.20) m/z 130 ($M^+ - Et$, 4), 115 (20), 101 (18), 87 (19), 85 (67), 75 (10), 73 (22), 69 (10), 57 (20), 56 (100), 55 (41); FTIR ($CDCl_3$) 2968, 2873, 1752,

1468, 1380, 1202 cm^{-1}. Further structure proof of **3f** was carried out by saponification to the known 3-isopropyloxiranecarboxylic acid.

Ethyl 3-isopropyloxiranecarboxylate (**3f**) in ether (50 mL) was treated with 10% NaOH. The resulting biphasic mixture was stirred at room temperature overnight. The aqueous phase was then separated, acidified with 6 N HCl (pH 3), and extracted with ethyl acetate (2 × 50 mL). The combined ethyl acetate extracts were dried ($MgSO_4$) and concentrated to provide an oil (64%) after purification by flash chromatography (hexane/ethyl acetate (50:50)): ^{1}H NMR ($CDCl_3$) δ 0.97 (d, 3 H, J = 6.8 Hz, $CH(CH_3)_2$), 1.14 (d, 3 H, J = 6.6 Hz, $CH(CH_3)_2$), 1.67 (m, 1 H, $CH(CH_3)_2$), 2.94 (dd, 1 H, J = 9.2, 4.8 Hz, $OCHCH(CH_3)_2$), 3.60 (d, 1 H, J = 4.4 Hz, HO_2CCH), 10.3 (br, 1 H, COOH); FTIR(neat) 3687-2218 (br), 2967, 1727, 1468, 1204 cm^{-1}. Spectral data were in good agreement with literature data for 3-isopropyloxiranecarboxylic acid.[7d]

***tert*-Butyl 3-isopropyloxiranecarboxylate (3g)** was prepared from *syn*-**2g** (390 mg, 1.0 mmol) and triethylamine (0.3 mL) as a colorless oil (170 mg, 91%) after bulb to bulb distillation (bath temperature 85-95 °C (38 mmHg)): ^{1}H NMR ($CDCl_3$) δ 0.94 and 1.14 (two d, 6 H, J = 6.8 Hz, $CH(CH_3)_2$), 1.50 (s, 9 H, $C(CH_3)_3$), 1.60 (m, 1 H, $CH(CH_3)_2$), 2.81 (dd, 1 H, J = 4.6, 9.2 Hz, C-3), 3.44 (d, J = 4.6 Hz, cis C-2). ^{1}H NMR was consistent with the cis isomer. GC analysis also showed only a single component: GC/MS (t_R 9.68) m/z 130 (M^+ - *t*-Bu, 11), 85 (20), 59 (17), 57 (100), 56 (88), 55 (46), 53 (14), 51 (10), 50 (13); ^{13}C NMR (100 MHz) δ 18.34, 20.18, 26.99, 28.05, 53.64, 62.92, 82.29, 167.36; FTIR (neat) 2970, 1747, 1472, 1369, 1251, 1159 cm^{-1}. Further structure proof of this compound was confirmed by transformation to 3-isopropyloxiranecarboxylic acid.

tert-Butyl 3-isopropyloxiranecarboxylate (**3g**, 250 mg, 1.35 mmol), was treated with trifluoroacetic acid (2 mL) at room temperature for 2 h. After dilution with ether (100 mL), the solution was washed with H_2O (2 × 100 mL), dried ($MgSO_4$), and purified by bulb to bulb distillation to provide 3-isopropyloxiranecarboxylic acid (170 mg, 97%) as a colorless oil. Spectral data were in good agreement with the literature data.[7d]

Methyl 2-azido-3-hydroxybutanoate (6a) was prepared by a typical procedure for the formation of 2-azido-3-hydroxy esters **6** from 3-hydroxy-2-nosyloxy esters **2**. Nosylate **2a** (2.25 g, syn:anti = 75:25) was prepared from methyl 2-[(*p*-nitrobenzenesulfonyl)oxy]-3-oxobutanoate (**1a**) (10 mmol) and $NaBH_4$ and used without purification. This material was dissolved in DMSO (20 mL) at room temperature and NaN_3 (1.30 g, 20 mmol) was added. The resulting solution was heated at 50 °C for 20 h. After the mixture was cooled to room temperature, H_2O (100 mL) was added, and the solution was extracted with ether (4 × 100 mL), dried ($MgSO_4$), and concentrated to provide a pale yellow oil (850 mg, 56% for two steps from **1a**) after purification by flash chromatography (hexane/ethyl acetate (90:10 to 80:20)): ^{1}H NMR ($CDCl_3$) δ 1.28 (d, 3 H, J = 6.4 Hz, $CHCH_3$), 2.60 (br, 1 H, OH), 3.84 (s, 3 H, OCH_3), 3.98 (d, 1 H, J = 5.6 Hz, anti CHN_3), 4.14 (m, 1 H, J = 6.0 Hz, CHOH); the ^{1}H NMR spectrum was consistent with 38:62 ratio of syn/anti isomers in the product; IR (neat) 3340 (br), 2970, 2100, 1735 cm^{-1}. Anal. Calcd for $C_6H_9N_3O_3$: C, 33.74; H, 5.70; N, 26.40. Found: C, 37.56; H, 5.63; N, 26.19.

Ethyl 2-azido-3-hydroxybutanoate (6b) was prepared from **2b** (3.3 g, 10 mmol, syn:anti = 62:38) and NaN_3 (1.3 g, 20 mmol) as a colorless oil (900 mg, 53% after two steps from **1b**) after purification by flash chromatography (hexane/ethyl acetate (90:10)): ^{1}H NMR ($CDCl_3$) δ 1.34 (set of m, 6 H, OCH_2CH_3 and $CHCH_3$), 2.57 and 2.74 (br, 1 H, OH for two isomers), 3.80 (d, 0.4 H, J = 3.8 Hz, syn CHN_3), 3.96 (d, 0.6 H, J = 5.6 Hz, anti CHN_3), 4.15 (q, 1 H, CHOH), 4.30 (dt, 2 H, OCH_2CH_3); FTIR-(neat) 3442 (br), 2983, 2111, 1731, 1480, 1266, 1196 cm^{-1}. Spectral data were in good agreement with literature data,[20] and the ^{1}H NMR spectrum was consistent with a 36:64 ratio of syn/anti isomers in the product.

Ethyl 2-azido-3-hydroxy-4-methylpentanoate (6f) was prepared from *syn*-**2f** (1.03 g, 2.9 mmol) and NaN_3 (390 mg, 6 mmol) as a colorless oil (280 mg, 49%) after purification by flash chromatography (hexane/ethyl acetate (90:10)): ^{1}H NMR ($CDCl_3$) δ 0.99 (two d, 6 H, J = 4.6, 4.8 Hz, $CH(CH_3)_2$), 1.34 (t, 3 H, OCH_2CH_3), 1.93 (m, 1 H, J = 5.4 Hz, $CH(CH_3)_2$), 1.90 (br, 1 H, OH), 3.69 (dd, 1 H, J = 4.6 Hz, CHOH), 3.90 (d, 0.8 H, J = 6.4 Hz, anti CHN_3), 4.04 (d, 0.2 H, J = 4 Hz, syn CHN_3), 4.49 (q, 2 H, OCH_2CH_3); the ^{1}H NMR spectrum was consistent with a 25:75 ratio of syn/anti isomers in the product; FTIR(neat) 3496 (br), 2965, 2109, 1736, 1372 cm^{-1}. Anal. Calcd for $C_8H_{15}N_3O_3$: C, 47.75; H, 7.51; N, 20.88. Found: C, 47.69; H, 7.44; N, 20.67.

Azido ester **6f** was also prepared from **2f** (syn:anti = 92:8) and 1,1,3,3-tetramethylguanidinium azide[20] (3 equiv) in 63% yield after purification by flash chromatography (hexane:ethyl acetate = 90:10). The ^{1}H NMR spectrum was consistent with a 25:75 ratio of syn/anti isomers in the product.

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Functional Group Hybrids. Reactivity of α'-Nucleofuge α,β-Unsaturated Ketones. 1. Reactions with Organocopper Reagents

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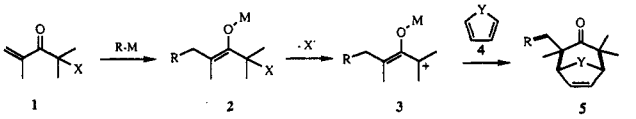
A series of α-nucleofuge α',β'-unsaturated ketones encompassing a variety of structural types and nucleofuges was prepared. Treatment of these compounds with lithium dimethylcuprate or methylcopper leads primarily to either reductive cleavage of the α-nucleofuge or conjugate addition. Good α-nucleofuges favored the reduction pathway while poorer nucleofuges favored conjugate addition.

Introduction

In recent years, a variety of chemical processes involving sequential C-C bond-forming reactions have been described and were the topic of a recent review by Posner.[1] Most of these multireaction processes involve either sequential pericyclic reactions or sequential conjugate additions and lead to a large increase in molecular complexity[2] in a single step. In an effort to develop efficient polycyclic synthesis methodology, we considered the

Scheme I. Sequential Conjugate Addition-Cycloaddition Process



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