JOC Article

Stereoselective Synthesis of 3-Hydroxyproline Benzyl Esters from *N*-Protected *β*-Aminoaldehydes and Benzyl Diazoacetate

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The synthesis of a series of 3-hydroxyproline benzyl esters from α-alkyl and α-alkoxy *N*-protected aminoaldehydes with benzyl diazoacetate is described. Aldehydes with α-alkyl substituents afforded prolines as a single diastereomer with a *trans-cis* relative configuration in 14−77%. An α-*tert*-butyldimethylsilyloxy aminoaldehyde afforded a proline as a single diastereomer with a *trans-trans* relative configuration in 37% yield.

Prolines are common structural elements found in natural products with important biological activity that have been targets of syntheses.[1,2] A variety of methods for the stereoselective synthesis of substituted prolines have been reported.[2−6] Despite these previous synthetic efforts, there is still a need for a new, efficient, stereoselective route to these compounds.

We have previously reported a novel method for the stereoselective synthesis of tetrahydrofurans **2a** from silyloxy aldehydes **1a** and benzyl diazoacetate.[7−9] Given the importance of prolines, we hoped that our tetrahydrofuran methodology could be adapted for the synthesis of substituted proline benzyl esters (**2b**, Scheme 1).

Our working hypothesis for the mechanism of the THF synthesis, and presumably what would also be the mechanism for the proline synthesis, is one in which the diazoester acts as a nucleophile[10] toward the aldehyde to afford intermediate **4** or participates in a 1,3-dipolar cycloaddition[11] to afford **5** (Scheme 1). Both **4** and **5** could then afford either the cyclized heterocycle **2** (pathway a) or *β*-ketoester **3** (pathway b).

For the proline synthesis to be effective, the protecting group on nitrogen must be selected, such that nitrogen is still a viable nucleophile in the presence of a Lewis acid to effect closure of the proline ring. *N*-Protected *β*-amino aldehydes were easily prepared using known methods including imino,[12] benzylamino,[13] dibenzylamino,[13] amide, carbamate, and sulfonamide, and several different amine protecting groups were also screened. We report here the successful extension of our methodology to the synthesis

* To whom correspondence should be addressed. Fax: (909) 787-4713.

(1) For current examples and leading references to the synthesis of substituted biologically active proline natural products, see: (a) Stapon, A.; Li, R.; Townsend, C. A. *J. Am. Chem. Soc.* **2003**, *125*, 8486−8493. (b) Makino, K.; Kondoh, A.; Hamada, Y. *Tetrahedron Lett.* **2002**, *43*, 4695−4698. (c) Decicco, C. P.; Grover, P. *J. Org. Chem*. **1996**, *61*, 3534−3541. (d) Nakao, Y.; Maki, T.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N. *Tetrahedron* **2000**, *56*, 8977−8987. (e) Wipf, P.; Methot, J.-L. *Org. Lett.* **2000**, *2*, 4213−4216. (f) Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003**, *5*, 1467−1470.

(2) For the synthesis of a substituted, nonnatural biologically active proline, see: Hanessian, S.; Bayrakdarian, M.; Luo, X. H. *J. Am. Chem. Soc.* **2002**, *124*, 4716−4721.

(3) For current examples and leading references to the synthesis of substituted prolines using nucleophilic displacement or addition reactions, see: (a) Flamant-Robin, C.; Wang, Q.; Chiaroni, A.; Sasaki, N. A. *Tetrahedron* **2002**, *58*, 10475−10484. (b) Pellegrini, N.; Schmitt, M.; Guery, S.; Bourguignon, J.-J. *Tetrahedron Lett.* **2002**, *43*, 3243−3246. (c) Taylor, C. M.; Barker, W. D.; Weir, C. A.; Park, J. H. *J. Org. Chem.* **2002**, *67*, 4466−4474. (d) Qiu, X.; Qing, F. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2052−2057. (e) Jacobsen, M. F.; Turks, M.; Hazell, R.; Skrydstrup, T. *J. Org. Chem.* **2002**, *67*, 2411−2417. (f) Lee, J. H.; Kang, J. E.; Yang, M. S.; Kang, K. Y.; Park, K. H. *Tetrahedron* **2001**, *57*, 10071−10076. (g) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2874−2883. (h) Wang, Q.; Dau, M.-E. T. H.; Sasaki, N. A.; Potier, P. *Tetrahedron* **2001**, *57*, 6455−6462. (i) Khalaf, J. K.; Datta, A. *J. Org. Chem.* **2004**, *69*, 387−390.

(4) For current examples and leading references to the synthesis of substituted prolines using [3 + 2] cycloadditions, see: (a) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236−4238. (b) Gu, Y. G.; Xu, Y.; Krueger, A. C.; Madigan, D.; Sham, H. L. *Tetrahedron Lett.* **2002**, *43*, 955−957. (c) Merino, I.; Laxmi, S.; Florez, J.; Barluenga, J.; Ezquerra, J.; Pedregal, C. *J. Org. Chem.* **2002**, *67*, 648−655. (d) Chinchilla, R.; Falvello, L. R.; Galindo, N.; Najeria, C. *Eur. J. Org. Chem.* **2001**, 3133−3140. (e) Casas, J.; Grigg, R.; Najera, C.; Sansano, J. M. *Eur. J. Org. Chem.* **2002**, 1971−1982.

(5) For current examples and leading references to the synthesis of substituted prolines using amino-zinc-enolate carbometalation reactions, see: (a) Karoyan, P.; Quancard, J.; Vaissermann, J.; Chassaing, G. *J. Org. Chem.* **2003**, *68*, 2256−2265. (b) Karoyan, P.; Chassaing, G. *Tetrahedron Lett.* **2002**, *43*, 1221−1223. (c) Karoyan, P.; Chassaing, G. *Tetrahedron Lett.* **2002**, *43*, 253−255. For current examples and leading references to the synthesis of substituted prolines using Rh-catalysts, see: (d) Davis, F. A.; Fang, T.; Goswami, R. *Org. Lett.* **2002**, *4*, 1599−1602. (e) Li, G.-Y.; Chen, J.; Yu, W.-Y. Hong, W.; Che, C.-M. *Org. Lett.* **2003**, *5*, 2153-2156.

(6) For a current example and leading references to the synthesis of substituted prolines using radical cyclizations, see: Agami, C.; Comesse, S.; Guesne, S.; Kadouri-Puchot, C.; Martinon, L. *Synlett* **2003**, *7*, 1058−1060.

(7) Angle, S. R.; Bernier, D. S.; ElSaid, N. A.; Jones, D. E.; Shaw, S. Z. *Tetrahedron Lett.* **1998**, *39*, 3919−3922.

(8) Angle, S. R.; Wei, G. P.; Ko, Y. K.; Kubo, K. *J. Am. Chem. Soc.* **1995**, *117*, 8041−8042.

(9) Angle, S. R.; Bernier, D. S.; Chann, K.; Jones, D. E.; Kim, M.; Neitzel, M. L.; White, S. L. *Tetrahedron Lett.* **1998**, *39*, 8195−8198.

(10) López-Herrera, F. J.; Valpuesta-Fernández, M.; García-Claros, S. *Tetrahedron* **1990**, *46*, 7165−7174.

(11) Zhu, Z.; Espenson, J. H. *J. Org. Chem.* **1995**, *60*, 7090−7091.

(12) Angle, S. R.; Kubo, K. Unpublished results from our laboratories.

(13) Shaw, S. Z. Ph.D. Dissertation, University of California, Riverside, 2001.

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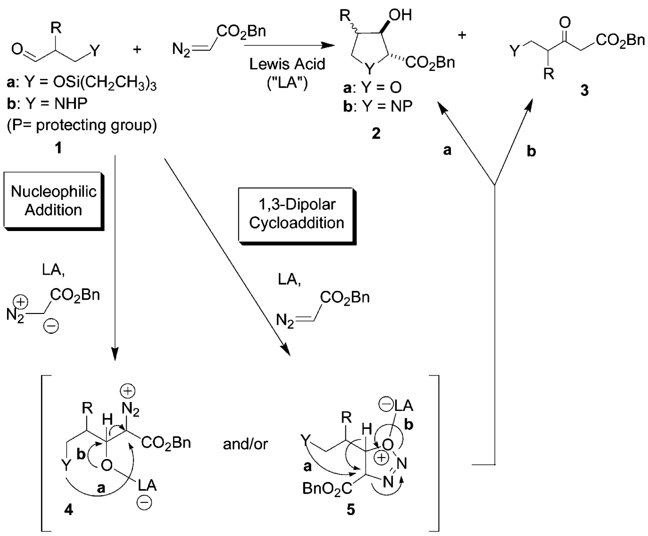
SCHEME 1. Proposed Proline Annulation Reaction



of 3-hydroxyprolines **2b** from β-(*N*-tosyl)amino aldehydes **1b** (P = $SO_2C_6H_6p$-CH_3, Scheme 1).

Results and Discussion

Synthesis of α-Alkyl Aminoaldehydes. Several *N*-protected aminoaldehydes were synthesized to study the scope and limitations of the proline synthesis. Scheme 2 shows the synthesis of aminoaldehydes **12a**−**e.** Diols **6a**−**c** were monoprotected with TES−Cl and treated with MsCl[14] to give mesylates **7a**−**c** (Scheme 2). Crude mesylates **7a**−**c** were heated with NaN_3 to give azides **8a**−**c**.[14] The TES protecting group was partially removed in the case of the isopropyl and methyl substrates (**7b** and **7c**) to afford a mixture of silyloxy azides (**8b**,**c**) and compounds tentatively identified (^{1}H NMR) as azidoalcohols (**9b**,**c**). These compounds were separated by flash chromatography. Azides **8a**−**c** were reduced with $LiAlH_4$ to give amino alcohols **10a**−**c**. Amino alcohols **10a**−**e**[15] were protected with TsCl using modified Schotten−Baumann reaction conditions[16] to give tosylamides **11a**−**e**, which were then oxidized with Dess−Martin periodinane (DMP)[17] to give aldehydes **12a**−**e**. Aldehyde **13** was prepared from amino alcohol **10b** as shown in Scheme 3.

Synthesis of α-Silyloxy Aldehyde 15. The synthesis of α-silyloxy aldehyde **15** was nontrivial. Several different approaches were investigated, all of which involved the oxidation of an alcohol to an aldehyde as the final step. During these studies it became apparent that aldehyde **15** is unstable and decomposes rapidly.[18] Therefore, we devised a new route that did not require the oxidation of an alcohol or purification after the final step (Scheme 4). Amino alcohol **14** (prepared from crotonaldehyde using Evans' procedure)[19] was protected as the sulfonamide and *tert*-butyldimethylsilyl ether. The resulting alkene underwent ozonolysis to give α-silyloxy aldehyde **15** in 43% yield (3 steps). It should be noted that aldehyde **15** decomposed rapidly and was therefore used immediately without purification.

Synthesis of Proline Benzyl Esters. Aldehyde **12a** was reacted with benzyl diazoacetate to give proline **16** (Table 1, entries 1 and 2). When 1.1 equiv of benzyl diazoacetate was used, proline **16** was isolated in 64% (Table 1, entry 1). When 3 equiv of benzyl diazoacetate was used, proline **16** was isolated in 77% yield (Table 1, entry 2). In both cases, proline **16** was formed as a single diastereomer, and the corresponding β-ketoester was not detected in either case. Reaction of aldehyde **13** (P = Cbz) with benzyl diazoacetate failed to afford any proline product (Table 1, entry 3). All subsequent studies used a tosyl protecting group on nitrogen.

Aldehyde **12b** was reacted with 3 equiv of benzyl diazoacetate to give proline **17** in 54% yield (Table 1, entry 4). When the amount of benzyl diazoacetate was decreased to 1.1 equiv (Table 1, entry 5) the reaction afforded proline **17** and what appeared to be β-keto ester **18** (^{1}H NMR analysis) as an inseparable 1:1 mixture in 12% yield.

Reaction of α-silyloxy aldehyde **15** with benzyl diazoacetate (3.0 equiv) gave proline ester **19** in 37% yield (Table 1, entry 6). The yield may be lower as a result of the rapid decomposition of unstable aldehyde **15**, which was made and used immediately. No β-keto ester was isolated.

When aldehyde **12c** was reacted with benzyl diazoacetate (3.0 equiv), proline **20** was formed in 56% yield as an inseparable 2:1 mixture (^{1}H NMR) of proline **20** and a compound tentatively assigned as β-keto ester **21** (Table 1, entry 7). HPLC purification afforded an analytical sample of **20** for characterization; however, β-keto ester **21** could not be isolated.

Aldehyde **12d** was reacted with benzyl diazoacetate (3.0 equiv) to afford proline **22** and β-keto ester **23** in 71% as a 1:4 mixture (Table 1, entry 8). Unlike proline **20**, proline **22** was readily purified by flash chromatography (3:1 hexanes/ethyl acetate) to afford **22** in 14% isolated yield. Homogeneous β-keto ester **23** could not be isolated.

When aldehyde **12e** was reacted with benzyl diazoacetate (3.0 equiv) no proline was isolated, and only β-keto ester was observed (^{1}H NMR analysis). In the case of the α,α-dihydrogen aldehyde used in the THF synthesis with benzyl diazoacetate[7] and diazosulfones,[20] the same observation was made: the α,α-dihydrogen aldehyde gave the lowest yield of product.

Stereochemistry of Prolines. X-ray quality crystals of proline **17** were obtained by recrystallization from hexanes/ethyl acetate. The X-ray[21] clearly shows that proline **17** possesses a *trans* orientation between the ester and the hydroxyl group and a *cis* orientation between the hydroxyl and the isopropyl substituent. It should be noted that proline **17** has the same *trans-cis* relative configu-

(14) Banfi, L.; Guanti, G.; Riva, R. *Tetrahedron: Asymmetry* **1999**, *10*, 3571−3592.
(15) Amino alcohol **10d** is commercially available from Lancaster, Windham, NH. Amino alcohol **10e** is commercially available from Aldrich, Milwaukee, WI.
(16) Maurer, P. J.; Knudsen, C. G.; Palkowitz, A. D.; Rapaport, H. J. *J. Org. Chem.* **1985**, *50*, 325−332.
(17) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *43*, 4155−4156.
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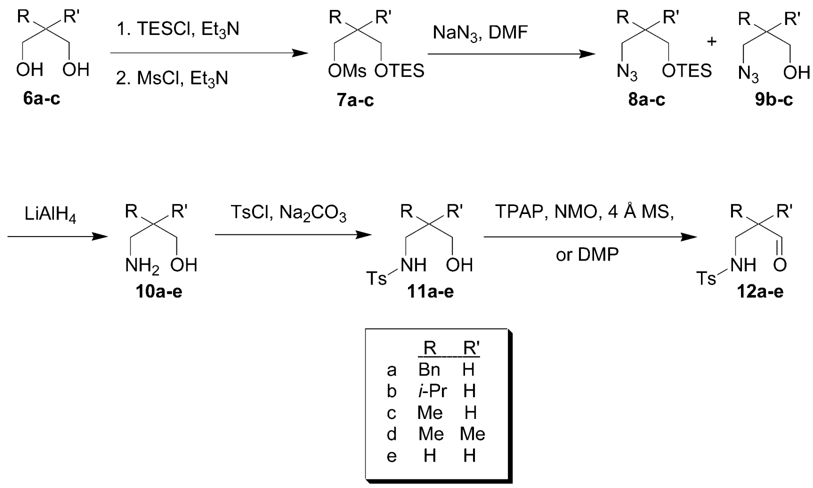
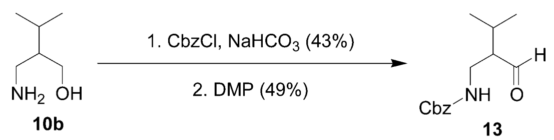
(19) Evans, D. A.; Carroll, G. L.; Truesdale, L. *J. Org. Chem.* **1974**, *39*, 914−917.
(20) Angle, S. R.; Shaw, S. Z. *Tetrahedron* **2001**, *57*, 5227−5232.
(21) See Supporting Information for the ORTEP diagram of proline **17**.

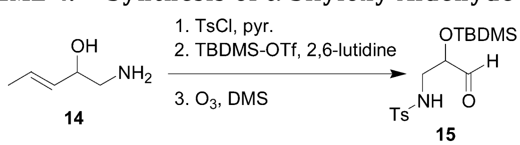
SCHEME 2. Synthesis of Aminoaldehydes 12a−e



SCHEME 3. Synthesis of Carbamate 13



SCHEME 4. Synthesis of α-Silyloxy Aldehyde 15



ration as that of the 4-alkyl-substituted THFs synthesized in our laboratory.[7−9]

X-ray quality crystals of proline **19** were obtained by recrystallization from hexanes/ethyl acetate. The X-ray[22] clearly shows that proline **19** possesses a *trans* orientation between the ester and hydroxyl substituents. The hydroxyl group and the silyl ether are also in a *trans* orientation to each other. Here, too, it is interesting to note that proline **19** has the same *trans-trans* relative configuration as the 4-alkoxy-substituted tetrahydrofurans synthesized in our laboratory.[23]

The stereochemistry of prolines **16** and **20** was assigned by correlation of the H^3-H^4 coupling constant to that of proline **17** (J_{H3-H4} was determined to be 3.6 Hz; Table 2, entry 1). The J_{H3-H4} coupling constant for prolines **16** and **20** was 3.8 and 4.2 Hz, respectively (Table 2, entries 2 and 3); thus the relative stereochemistry was assigned as also being the same as **17** with the substituents arranged with a *cis-trans* orientation about the ring. In proline **19** the substituents are arranged with a *cis-trans* orientation around the ring, and J_{H3-H4} was determined to be 0 Hz.

The relative orientation of the ester and hydroxyl substituents was assigned to be *trans*, the same as for our tetrahydrofuran work, on the basis of the X-ray structures of **17** and **19** and the consistency of and J_{H2-H3} to each other and to the tetrahydrofurans with similar substitution.[7,8]

In conclusion, we have found the reaction of *β*-amido aldehydes with benzyl diazoacetate affords proline benzyl esters in fair to good yields. The mechanism of the reaction and the origin of the stereoselectivity are currently under investigation.

Experimental Section

General Information. All HPLCs were done on a high-performance silica Si 83-121-c column (21.4 × 250 mm). Unless otherwise stated, the following parameters were used: flow rate = 9.9 mL/min; the appropriate mixture of hexanes/ethyl acetate was used. In all cases, solvents were removed in vacuo.

Methanesulfonic Acid 2-Phenylmethyl-3-(triethylsilyloxy)propyl Ester (7a). To a solution of known diol **6a**[14] (2.30 g, 13.8 mmol) and Et_3N (2.12 mL, 15.2 mmol) in CH_2Cl_2 (55 mL) at 0 °C was added TES−Cl (2.31 mL, 13.8 mmol) dropwise. The ice bath was removed, and the reaction mixture was stirred for 2 h. The reaction mixture was diluted with water (25 mL). The organic layer was washed with a saturated aqueous solution of NH_4Cl, a saturated aqueous solution of $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (9:1 hexanes/ethyl acetate) gave the known[9] silyl ether (3.23 g, 83%) as a clear, colorless oil.

Using the procedure of Banfi and co-workers,[14] a solution of the above silyl ether (2.00 g, 7.13 mmol) in CH_2Cl_2 (17.8 mL) at −30 °C was treated with Et_3N (1.29 mL, 9.27 mmol), followed by MsCl (0.66 mL, 8.6 mmol). The reaction mixture was stirred for 5 h, and then saturated aqueous NH_4Cl (10 mL) was added. The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with a saturated aqueous solution of $CuSO_4$ (15 mL) and brine, dried ($MgSO_4$), and concentrated to give the mesylate **7a** (2.57 g, 100%). The product was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.17 (m, 5H), 4.22 (m, 2H), 3.64 (dd, J = 10.3, 4.6 Hz, 1H), 3.56 (dd, J = 10.3 6.2 Hz, 1H), 2.97 (s, 3H), 2.69 (m, 2H), 2.18 (m, 1H), 0.95 (t, J = 8.0 Hz, 9H), 0.59 (q, J = 8.0 Hz, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 138.9, 129.0, 128.5, 126.4, 69.5, 61.1, 42.8, 36.9, 33.7, 6.8, 4.3.

Methanesulfonic Acid 3-Methyl-2[(triethylsilyloxy)-methyl]butyl Ester (7b). The procedure given previously for the preparation of **7a** was carried out using known diol **6b**[24,25] (1.40 g, 11.8 mmol), Et_3N (1.83 mL, 13.0 mmol) in CH_2Cl_2 (59 mL), and TES−Cl (1.99 mL, 11.8 mmol). Flash chromatography (9:1 hexanes/ethyl acetate) gave the known[9] silyl ether

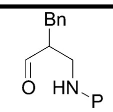
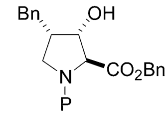
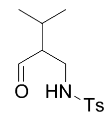
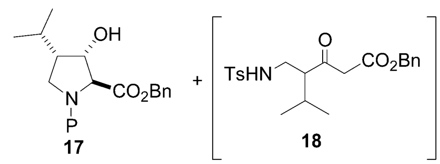
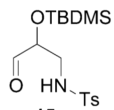
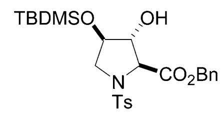
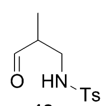
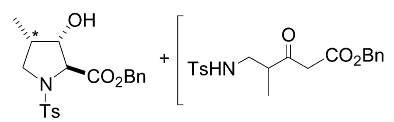
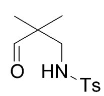
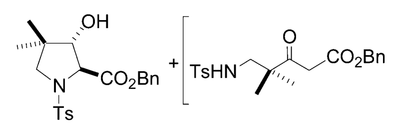
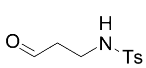
(22) See Supporting Information for the ORTEP diagram of proline **19**.

(23) Bernier, D. S. Ph.D. Dissertation, University of California, Riverside, 2001.

(24) Neitzel, M. L. Ph.D. Dissertation, University of California, Riverside, 2000.

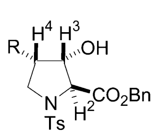
(25) Ohta, H.; Tetsukawa, H.; Noto, N. *J. Org. Chem.* **1982**, *47*, 2400−2404.

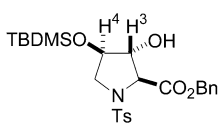
TABLE 1. Synthesis of *N*-Protected Substituted Prolines

	Aldehyde	$N_2=CHCO_2Bn$ (equiv.)	Time (h)	Product	(yield)
1		1.1	2.5		(64%)[a]
2	**12a**, P=Ts	3.0	1.5	**16**	(77%)[a]
3	**13**, P = Cbz	3.0	3.0		No product
4		3.0	14.25		(54%)[a]
5	**12b**	1.1	8.0	**17** + **18**	(12%)
6	 **15**	3.0	2	 **19**	(37%)[a]
7	 **12c**	3.0	16	 **20** + **21** 2:1[b]	(56%)[c]
8	 **12d**	3.0	13	 **22** + **23** 1:4[b]	(71%)[d]
9	 **12e**	3.0	17	No product[e]	

[a] The only product detected by ^{1}H NMR was proline. [b] Ratio of proline to β-keto ester. [c] Yield is for proline and β-keto ester product mixture. [d] Proline **22** was isolated in 14% yield. [e] Only β-keto ester was isolated.

TABLE 2. Stereochemistry of Prolines





19: J_{H3-H4} = 0 Hz

	proline	R	J_{H3-H4} (Hz)
1	**17**	*i*Pr	3.6
2	**16**	Bn	3.8
3	**20**	Me	4.2
4	**19**	OTBS	0

(2.37 g, 86%). The above silyl ether (2.00 g, 8.60 mmol) in CH_2Cl_2 (22 mL), Et_3N (1.56 mL, 11.2 mmol), and MsCl (0.80 mL, 7.0 mmol) gave mesylate **7b** (2.76 g, quantitative) as a clear, colorless oil. The product was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (dd, J = 9.5, 4.9 Hz, 1H), 4.30 (dd, J = 10.0, 6.7 Hz, 1H), 3.73 (dd, J = 10.3, 4.6 Hz, 1H), 3.58 (dd, J = 10.3, 7.2 Hz, 1H), 2.99 (s, 3H), 1.80 (m, 1H), 1.64 (m, 1H), 0.95 (s, 15H), 0.59 (q, J = 7.7 Hz, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 68.8, 60.0, 46.7, 36.9, 26.0, 20.1, 6.8, 4.3; IR (neat) 2958, 2912, 2877, 1466, 1415, 1352, 1239, 1175, 842 cm^{-1}.

Methanesulfonic Acid (2-Methyl-3-triethylsilyloxy)-propyl Ester (7c). The procedure given previously for the preparation of **7a** was carried out using commercially available 2-methyl-1,3-propanediol **6c**[26] (5.00 mL, 56.3 mmol) in CH_2Cl_2 (225 mL), Et_3N (8.63 mL, 62.0 mmol), and TES−Cl (9.45 mL, 56.3 mmol). Flash chromatography (9:1 hexanes/ethyl acetate) gave the known silyl ether (8.74 g, 76%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.74 (dd, J = 9.8, 4.5 Hz, 1H), 3.61 (dd, J = 10.6, 3.5 Hz, 2H), 3.54 (dd, J = 9.8, 8.2 Hz, 1H), 2.95 (br s, 1H), 1.96 (m, 1H), 0.96 (t, J = 7.84 Hz, 9H), 0.83 (d, J = 6.9 Hz, 3H), 0.61 (q, J = 7.9 Hz, 6H); IR (neat) 3355, 2957, 2940, 2909, 2876, 2735, 1458, 1415, 1239, 1088, 1039, 1016 cm^{-1}. The above silyl ether (4.88 g, 23.9 mmol) gave mesylate **7c** (6.71 g, 100%), which was used without further purification in the next reaction: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.24 (dd, J = 5.9, 9.5 Hz, 1H,), 4.16 (dd, J =

(26) Commercially Available from Aldrich, Milwaukee, WI.

5.7, 9.2 Hz, 1H), 3.60 (dd, $J = 4.9$, 10.0, 1H), 3.50 (dd, $J = 6.7$, 10.3 Hz, 1H), 3.00 (s, 3H), 2.05 (m, 1H), 0.98 (d, $J = 6.7$ Hz, 3H), 0.95 (t, $J = 8.4$ Hz, 9H), 0.59 (q, $J = 8.4$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 71.8, 63.5, 37.0, 35.8, 13.2, 6.7, 4.3; IR (neat) 2957, 2877, 1467, 1357, 1178, 1098 cm^{-1}.

[(3-Azido-2-phenylmethyl)propyloxy]triethylsilane (8a). To a solution of mesylate **7a** (1.00 g, 2.77 mmol) in DMF (11.1 mL) was added sodium azide (541 mg, 8.32 mmol). The reaction was heated at 50 °C for 24 h. Water (20 mL) was added, and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography (9:1 to 7:3 pet. ether/diethyl ether) gave the silyloxy azide **8a** (707 mg, 83%) as a clear, colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.19 (m, 3H), 3.59 (dd, $J = 10.0$, 4.9 Hz, 1H), 3.52 (dd, $J = 10.3$, 6.2 Hz, 1H) 3.38 (dd, $J = 11.8$, 5.1 Hz, 1H), 3.39 (dd, $J = 11.8$, 6.2 Hz, 1H), 2.69 (dd, $J = 13.3$, 7.2 Hz, 1H), 2.59 (dd, $J = 13.3$, 7.4 Hz, 1H), 1.99 (m, 1H), 0.96 (t, $J = 7.9$ Hz, 9H), 0.50 (q, $J = 7.9$ Hz, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 139.6, 129.1, 128.4, 126.1, 62.1, 51.7, 43.1, 34.8, 6.8, 4.3; IR (neat) 2956, 2911, 2876, 2099, 1239, 742 cm^{-1}; MS (CI/NH_3) *m/z* 306 (3, MH^+), 278 (6), 146 (3), 132 (100); HRMS (CI/NH_3) *m/z* calcd for $C_{16}H_{28}N_3OSi$ 306.2002, found 306.1999.

[(2-Azidomethyl-3-methyl)but-1-oxy]-triethylsilylane (8b) and 2-Azidomethyl-3-methylbutan-1-ol (9b). The procedure previously given for the preparation of **8a** was carried out using mesylate **8b** (5.10 g, 16.4 mmol), DMF (66 mL), and sodium azide (3.20 mg, 49.3 mmol). Flash chromatography (pet. ether, then 9:1 pet. ether/diethyl ether) gave silyloxy azide **8b** (3.33 mg, 79%) as a clear, colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (dd, $J = 10.0$, 4.0 Hz, 1H), 3.56 (dd, $J = 10.0$, 6.7 Hz, 1H), 3.41 (m, 2H), 1.78 (sextet, $J = 6.7$ Hz, 1H), 1.48 (m, 1H), 0.98 (m, 15H), 0.60 (q, $J = 7.7$ Hz, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 61.0, 50.6, 46.9, 26.6, 20.1, 20.0, 6.8, 4.3; IR (neat) 2959, 2912, 2877, 1459, 1414, 1389, 1369, 1104, 1016, 817, 777, 743, 675 cm^{-1}; MS (CI/NH_3) *m/z* 258 (MH^+, 75), 230 (100), 200 (36), 170 (10), 132 (47); HRMS (CI/NH_3) *m/z* calcd for $C_{12}H_{28}N_3OSi$ (MH^+) 258.2002, found 258.1995. In some cases the TES group was removed during the reaction to give alcohol **9b** as a clear, colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.73 (dd, $J = 4.4$, 11.0 Hz, 1H), 3.63 (dd, $J = 6.9$, 11.0 Hz, 1H), 3.53 (dd, $J = 5.1$, 12.3 Hz, 1H), 3.41 (dd, $J = 7.2$, 12.3 Hz, 1H), 1.78 (m, 2H,), 1.53 (m, 1H), 0.93 (d, $J = 6.7$ Hz, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 62.1, 51.3, 46.5, 26.8, 19.9, 19.9; IR (neat) 3356, 2962, 2876, 2099, 1466, 1370, 1269 cm^{-1}; MS (CI/NH_3) *m/z* 144 (MH^+, 5), 116 (100), 98 (12); HRMS (CI/NH_3) *m/z* calcd for $C_6H_{14}N_3O$ (MH^+) 144.1137, found 144.1139.

[(3-Azido-2-methyl)propyloxy]triethylsilane (8c) and 3-Azido-2-methyl-propan-1-ol (9c). The procedure given previously for the preparation of **8a** was carried out using mesylate **7c** (10.0 g, 35.4 mmol), DMF (71 mL), and sodium azide (6.90 g, 106 mmol). Flash chromatography (50:1 to 3:1 hexanes/ethyl acetate) gave silyloxy azide **8c** (1.96 g, 24%) and alcohol **9c** (2.01 g, 49%) as clear, colorless oils. **[(3-Azido-2-methyl)propyloxy)triethylsilane (8c):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.54 (dd, $J = 5.1$, 10.3 Hz, 1H), 3.46 (dd, $J = 6.7$, 10.3 Hz, 1H), 3.37 (dd, $J = 5.9$, 12.0 Hz, 1H), 3.22 (dd, $J = 6.7$, 11.8 Hz, 1H), 1.88 (m, 1H), 0.96 (t, $J = 7.7$ Hz, 9H), 0.94 (d, $J = 7.2$ Hz, 3H), 0.60 (q, $J = 8.0$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.7, 54.3, 36.2, 14.5, 6.7, 4.3; IR (neat) 2955, 2912, 2878, 2099, 1458, 1281, 1240 cm^{-1}; MS (CI/NH_3) *m/z* 230 (MH^+, 63), 202 (100), 132 (89); HRMS (CI/NH_3) *m/z* calcd for $C_{10}H_{24}N_3OSi$ (MH^+) 230.1689, found 230.1681. **3-Azido-2-methyl-propan-1-ol (9c):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.57 (m, 2H), 3.34 (m, 2H), 1.93 (m, 1H), 1.66 (br s, 1H), 0.97 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 65.4, 54.6, 35.8, 14.4.

3-Amino-2-(phenylmethyl)propan-1-ol (10a).[14] To a solution of $LiAlH_4$ (93.0 mg, 2.45 mmol) in ether (2.0 mL) at 0 °C was added silyl ether **8a** (250 mg 0.818 mmol) in ether (2.0 mL). The reaction mixture was stirred 3 h, and then NaF (412 mg, 9.80 mmol) and water (0.135 mL, 7.35 mmol) were added sequentially. The resulting suspension was stirred overnight, filtered, and concentrated to give amino alcohol **10a**[14] (133 mg, 99%) as a clear, colorless oil. The product was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.15 (m, 5H), 3.80 (dd, $J = 11.3$, 3.1 Hz, 1H), 3.64 (dd, $J = 10.8$, 8.2 Hz, 1H), 3.07 (broad m, 3H), 2.79 (dd, $J = 11.8$, 9.2 Hz, 1H), 2.58 (dd, $J = 7.2$, 13.9 Hz, 1H), 2.48 (dd, $J = 7.2$, 13.9 Hz, 1H), 2.03 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 128.9, 128.4, 126.2, 67.6, 46.0, 42.3, 35.9; IR (CCl_4) 3295, 3260, 3000, 2923, 1453, 1031, 760 cm^{-1}.

2-Aminomethyl-3-methylbutan-1-ol (10b). To a solution of $LiAlH_4$ (92.0 mg, 24.1 mmol) in ether (35 mL) was added silyloxy azide **8b** in ether (12 mL) at 0 °C. The reaction mixture was stirred for 4 h, and then water (0.92 mL), a solution of 15% aqueous NaOH (0.92 mL), and water (2.76 mL) were sequentially added. The resulting suspension was stirred overnight. The reaction mixture was filtered, and the filter cake was washed with ether (100 mL) and concentrated to give amino alcohol **10b** (1.05 g, 97%) as a clear, colorless oil. The product was used without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.74 (s, 2H), 3.80 (ddd, $J = 1.5$, 3.6, 10.8 Hz, 1H), 3.73 (dd, $J = 10.3$, 8.2 Hz, 1H), 3.08 (apparent dt, $J = 1.5$, 12.3 Hz, 1H), 2.81 (dd, $J = 12.3$, 9.2 Hz, 1H), 2.68−1.80 (broad s, 1H), 1.65 (m, 1H), 1.42 (m, 1H), 0.90 (d, $J = 1.0$ Hz, 3H), 0.87 (d, $J = 1.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.7, 47.0, 44.9, 27.5, 20.1, 20.0.

3-Amino-2-(methyl)propan-1-ol (10c). The procedure given previously for the preparation of **10a** was carried out using $LiAlH_4$ (861 mg, 22.7 mmol) in ether (44 mL), azide **10c** (2.01 g, 8.72 mmol) in ether (10 mL), NaF (3.81 g, 90.7 mmol), water (1.23 mL, 68.0 mmol), and $Na_2SO_4\cdot10H_2O$ (2.00 g) to give amino alcohol **10c** (704 mg, 91%) as a clear, yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.84 (br s, 1H), 3.67 (ddd, $J = 1.5$, 4.1, 10.8 Hz, 1H), 3.55 (dd, $J = 8.2$, 10.8 Hz, 1H), 2.95 (dd, $J = 4.1$, 12.3 Hz, 1H), 2.66 (dd, $J = 8.7$, 12.3 Hz, 1H), 1.79 (m, 1H), 0.81 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.6, 48.4, 36.5, 14.6.

***N*-[(3-Hydroxy-2-phenylmethyl)propyl]-4-methylbenzenesulfonamide (11a).** To a solution of amino alcohol **10a** (250 mg, 1.51 mmol) in water (2.25 mL) was added Na_2CO_3 (481 mg, 4.54 mmol). The mixture was stirred until all Na_2CO_3 dissolved, and then TsCl (433 mg, 4.54 mmol) was added. The reaction mixture was stirred for 6.5 h and then diluted with water (10 mL) and ethyl acetate (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 4 mL). The combined organic layers were washed with brine, dried (K_2CO_3), and concentrated. Flash chromatography (1:3 hexanes/ethyl acetate) gave amide **11a** (428 mg, 89%) as a white solid: mp 92−94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, $J = 8.2$ Hz, 2H), 7.30 _ 7.19 (m, 5H), 7.09 (d, $J = 6.7$ Hz, 2H), 3.73 (dd, $J = 11.0$, 3.9 Hz, 1H), 3.56 (dd, $J = 10.8$, 6.7 Hz, 1H), 3.06 (dd, $J = 4.4$, 13.1 Hz, 1H), 2.95 (dd, $J = 6.9$, 13.1 Hz, 1H), 2.56 (m, 2H), 2.43 (s, 3H), 1.97 (m, 1H), 1.70 (broad s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 139.2, 136.9, 129.7, 128.9, 128.6, 127.0, 126.3, 63.6, 44.6, 42.1, 35.1, 21.5; IR (neat) 3566 1616, 1623, 1419 cm^{-1}; MS (CI/NH_3) *m/z* 320 (MH^+, 100), 260 (7), 184 (3), 166 (12), 155 (4), 118 (5), 91 (12); HRMS (CI/NH_3) *m/z* calcd for $C_{17}H_{22}NO_3S$ (MH^+) 320.1320, found 320.1307.

***N*-[(3-Hydroxy-2-methylethyl)propyl]-4-methylbenzenesulfonamide (11b).** The procedure given previously for the preparation of **11a** was carried out using amino alcohol **11b** (1.56 g, 13.3 mmol) in water (22 mL), Na_2CO_3 (4.23 g, 39.9 mmol), and TsCl (3.81 g, 20.0 mmol). Flash chromatography (1:1 hexanes/ethyl acetate) gave amide **11b** (1.55 g, 43%) as a clear, colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, $J = 8.2$ Hz, 2H), 7.30 (d, $J = 8.2$ Hz, 2H), 5.45 (t, $J = 6.2$ Hz, 1H), 3.76 (dt, $J = 10.8$, 3.9 Hz, 1H), 3.61 (m, 1H), 3.09 (ddd, $J = 3.9$, 6.9, 12.6 Hz, 1H), 2.95 (ddd, $J = 5.4$, 7.7, 12.8 Hz, 1H), 2.42 (s, 3H), 2.22 (t, $J = 4.4$ Hz, 1H), 1.66 (m, 1H), 1.42 (m, 1H), 0.85 (d, $J = 5.1$ Hz, 3H), 0.83 (d, $J = 5.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 136.8, 129.7, 127.0, 63.4, 45.9, 43.8, 27.0, 21.5, 20.0; IR (neat) 3523, 3323, 2881, 1599, 1495, 1469, 1336, 1184, 1153 cm^{-1}; MS (CI/NH$_3$) *m/z* 289 (MNH$_4^+$, 7), 272 (MH$^+$, 100), 189 (2), 118 (10), 98 (40); HRMS (CI/NH$_3$) *m/z* calcd for $C_{13}H_{22}NO_3S$ (MH$^+$) 272.1320, found 272.1318.

***N*-[(3-Hydroxy-2-methyl)propyl]-4-methylbenzenesulfonamide (11c).** The procedure given previously for the preparation of **11a** was carried out using **10c** (300 mg, 3.36 mmol) in water (6 mL), Na_2CO_3 (1.07 g, 10.1 mmol), and TsCl (962 mg, 5.05 mmol). Flash chromatography (1:1 hexanes/ethyl acetate) gave amide **11c** (420 mg, 51%) as a clear, colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 5.09 (broad s, 1H), 3.67 (m, 1H), 3.47 (m, 1H), 3.02 (m, 1H), 2.88 (m, 1H), 2.43 (s, 3H), 1.85 (m, 1H), 1.61 (broad s, 1H), 0.86 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 143.4, 136.9, 129.7, 127.0, 66.1, 46.8, 35.2, 21.5, 14.3; IR (neat) 3530, 3286, 2930, 2926, 2880, 1598, 1455, 1326, 1159 cm^{-1}; MS (CI/NH$_3$) *m/z* 261 (MNH$_4^+$, 17), 244 (MH$^+$, 100), 226 (5); HRMS (CI/NH$_3$) *m/z* calcd for $C_{11}H_{18}NO_3S$ (MH$^+$) 244.1007, found 244.1005.

***N*-[(2,2-Dimethyl-3-hydroxy)propyl]-4-methylbenzenesulfonamide (11d).** The procedure given previously for the preparation of **11a** was carried out using commercially available amino alcohol **10d**[15] (110 mg, 1.07 mmol) in water (1.6 mL), Na_2CO_3 (509 mg, 4.80 mmol), and TsCl (305 mg, 1.60 mmol). Flash chromatography (1:1 hexanes/ethyl acetate) gave amide **11d** (127 mg, 47%) as a white solid: mp 101−105 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 5.15 (t, *J* = 6.0 Hz, 1H), 3.40 (s, 2H), 2.77 (d, *J* = 6.2 Hz, 2H), 2.42 (s, 3H), 2.15−1.85 (broad s, 1H), 0.85 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 143.4, 136.9, 129.7, 127.0, 69.3, 50.5, 36.0, 22.2, 21.5; IR (neat) 3488, 3159, 2964, 1596, 1456, 1327, 1154 cm^{-1}; MS (CI/NH$_3$) *m/z* 258 (MH$^+$, 100), 223 (4), 104 (11), 91 (2); HRMS (CI/NH$_3$) *m/z* calcd for $C_{12}H_{20}NO_3S$ (MH$^+$) 258.1164, found 258.1161.

***N*-[(3-Hydroxy)propyl]-4-methylbenzenesufonamide (11e).** The procedure given previously for the preparation of **11a** was carried out using commercially available 3-amino propanol **10e**[15] (0.305 mL, 3.99 mmol) in water (6.0 mL), Na_2CO_3 (1.27 g, 12.0 mmol), and TsCl (1.14 g, 5.99 mmol). Flash chromatography (1:1 hexanes/ethyl acetate) gave amide **11e** (776 mg, 84%) as a clear, colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 5.24 (broad s, 1H), 3.71 (t, *J* = 5.6 Hz, 2H), 3.10 (q, *J* = 5.9, 11.8 Hz, 2H), 2.42 (s, 3H), 2.17 (broad s, 1H), 1.69 (pentuplet, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 143.4, 136.8, 129.7, 127.0, 60.5, 40.9, 31.4, 21.5; IR (neat) 3495, 3293, 2946, 2880, 1598, 1495, 1327, 1159 cm^{-1}; MS (CI/NH$_3$) *m/z* 230 (MH$^+$, 100), 155 (3), 76 (12); HRMS (CI/NH$_3$) *m/z* calcd for $C_{10}H_{16}NO_3S$ (MH$^+$) 230.0851, found 230.0846.

***N*-(2-Phenylmethyl)-3-(4-methyl)phenylsulfonylamidopropanal (12a).** To a solution of amide **11a** (420 mg, 1.31 mmol) in CH_2Cl_2 (6.6 mL) at 0 °C was added Dess−Martin periodinane[17] (836 mg, 1.97 mmol). The reaction mixture was stirred for 5 h and then filtered through SiO_2. The filter cake was washed (ethyl acetate) and concentrated. Flash chromatography (1:1 hexanes/ethyl acetate) gave aldehyde **12a** (341 mg, 82%) as a white solid: mp 82.7−84.7 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.67 (s, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.27 (m, 5H), 7.15 (d, *J* = 8.2 Hz, 2H), 5.00 (t, *J* = 6.7 Hz, 1H), 3.07 (m, 2H), 3.01 (dd, *J* = 6.2, 13.3 Hz, 1H), 2.87 (m, 1H), 2.77 (dd, *J* = 8.0, 13.1 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 203.2, 143.5, 137.2, 136.5, 129.7, 128.8, 128.8, 127.0, 126.9, 52.9, 41.2, 32.6, 21.5; IR (neat) 3255, 1727, 1458, 1328, 1162, 1152 cm^{-1}; MS (CI/NH$_3$) *m/z* 335 (MNH$_4^+$, 100), 318 (MH$^+$, 47), 301 (3), 189 (74), 164 (18), 146 (10), 118 (8), 108 (11), 91 (5); HRMS (CI/NH$_3$) *m/z* calcd for $C_{17}H_{20}NO_3S$ (MH$^+$) 318.1164, found 318.1152.

***N*-(Methylethyl-3-(4-methyl)phenylsulfonylamido-propanal (12b).** To a solution of amide **11b** (1.54 g, 5.67 mmol) in CH_2Cl_2 (28 mL) was added powdered 4Å MS (2.90 g), NMO (997 mg, 8.51 mmol) and then TPAP[27] (99 mg, 0.28 mmol). The reaction mixture was stirred 1 h and then filtered through SiO_2. The filter cake was washed (1:1 hexanes/ethyl acetate) and concentrated. Flash chromatography (4:1 to 3:1 hexanes/ethyl acetate) gave aldehyde **12b** (752 mg, 49%) as a clear, colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.69 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 4.87 (t, *J* = 6.0 Hz, 1H), 3.10 (m, 2H), 2.48 (m, 1H), 2.40 (s, 3H), 2.14 (m, 1H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 204.7, 143.5, 136.9, 129.8, 127.0, 57.6, 39.5, 27.2, 21.5, 20.1, 19.7; IR (neat) 3526, 3290, 2964, 1714, 1598, 1464, 1334, 1154, 1092 cm^{-1}; MS (CI/NH$_3$) *m/z* 287 (MNH$_4^+$, 33), 270 (MH$^+$, 90), 189 (100), 155 (18), 124 (14), 108 (46), 91 (40); HRMS (CI/NH$_3$) *m/z* calcd for $C_{13}H_{20}NO_3S$ (MH$^+$) 270.1164, found 270.1174.

***N*-(2-Methyl-3-(4-methyl)phenylsulfonylamido-propanal (12c).** The procedure given previously for the preparation of **12a** was carried out using **11c** (200 mg, 0.822 mmol) in CH_2Cl_2 (4.1 mL) and DMP[17] (523 mg, 1.23 mmol) to give aldehyde **12c** (135 mg, 68%) as a clear, colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.60 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 2H), 4.92 (broad t, *J* = 6.0 Hz, 1H), 3.08 (dt, *J* = 2.9, 6.3 Hz, 2H), 2.66 (m, 1H), 2.43 (s, 2H), 1.60 (broad s, 1H), 1.17 (d, *J* = 7.7 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 203.6, 143.5, 136.7, 129.8, 127.0, 46.3, 43.2, 21.5, 11.4; IR (neat) 3529, 3290, 3266, 2968, 2924, 1715, 1598, 1455, 1327, 1160, 1093 cm^{-1}; MS (CI/NH$_3$) *m/z* 259 (MNH$_4^+$, 100), 242 (MH$^+$, 91), 229 (4), 189 (25), 108 (26), 91 (17); HRMS (CI/NH$_3$) *m/z* calcd for $C_{11}H_{16}NO_3S$ (MH$^+$) 242.0851, found 242.0848.

***N*-(2,2-Dimethyl-3-(4-methyl)phenylsulfonylamido-propanal (12d).** The procedure given previously for the preparation of **12a** was carried out using amide **11d** (95.0 mg, 0.369 mmol) in CH_2Cl_2 (1.8 mL) and DMP[17] (235 mg, 0.554 mmol). Flash chromatography (3:2 hexanes/ethyl acetate) gave aldehyde **12d**(56 mg, 60%) as a white solid: mp 68−71 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.35 (s, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 7.7 Hz, 2H), 4.90 (t, *J* = 5.9 Hz, 1H), 2.94 (d, *J* = 6.7 Hz, 2H), 2.43 (s, 3H), 1.12 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 205.0, 143.5, 136.9, 129.8, 127.0, 48.3, 46.7, 21.5, 19.8; IR (neat) 3551, 3288, 1723, 1329, 1160, 1094 cm^{-1}; MS (CI/NH$_3$) *m/z* 273 (MNH$_4^+$, 43), 256 (MH$^+$, 100), 226 (11), 184 (29), 155 (13), 118 (24), 91 (11); HRMS (CI/NH$_3$) *m/z* calcd for $C_{12}H_{18}NO_3S$ (MH$^+$) 256.1007, found 256.1012.

***N*-3-(4-Methyl)phenylsulfonylamido-propanal (12e).** The procedure given previously for the preparation of **12a** was carried out using amide **11e** (400 mg, 1.74 mmol) in CH_2Cl_2 (9 mL) and DMP[17] (1.11 g, 2.61 mmol). Flash chromatography (1:1 hexanes/ethyl acetate) gave aldehyde **12e** (310 mg, 78%) as a clear, colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.74 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 4.89 (broad s, 1H), 3.21 (dd, *J* = 5.6, 12.3 Hz, 2H), 2.75 (t, *J* = 5.9 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 200.8, 143.6, 136.7, 129.8, 127.0, 43.6, 36.8, 21.5; IR (neat) 3283, 2927, 2877, 1721, 1598, 1327, 1158 cm^{-1}; MS (CI/NH$_3$) *m/z* 245 (MNH$_4^+$, 57), 228 (MH$^+$, 100), 184 (13), 155 (12), 91 (13); HRMS (CI/NH$_3$) *m/z* calcd for $C_{10}H_{14}NO_3S$ (MH$^+$) 228.0694, found 228.0697.

[(2-Formyl-3-methyl)butyl]carbamic Acid Phenylmethyl Ester (13). To a solution of amino alcohol **10b** (1.00 g, 8.53 mmol) in CH_2Cl_2 (17.0 mL) was added a saturated aqueous solution of $NaHCO_3$ (8.53 mL). The two-phase solution was cooled to 0 °C. CbzCl (1.83 mL, 12.8 mmol) was added, and the reaction was stirred for 8 h. The reaction was diluted with water (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine, dried (K_2CO_3), and concentrated. Flash chromatography (3:1, then 1:1 hexanes/ethyl acetate) gave the carbamate (1.50 g, 70%) as a clear, colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.28 (m, 5H), 5.11 (s, 2H), 3.74−3.67 (m, 1H), 3.60−3.51 (m, 1H), 3.44 (ddd, *J* = 4.1, 10.7, 14.4 Hz, 1H), 3.26 (dd, *J* = 14.1, 6.9 Hz, 1H), 2.76 (t, *J* = 5.9 Hz, 1H), 1.70−1.60 (m, 2H), 1.40−1.34 (m, 1H), 0.95 (s, 3H), 0.93 (s, 3H); ^{13}C (75 MHz, CDCl$_3$) δ 157.6, 136.4, 128.5, 128.2, 128.1, 66.9, 62.0,

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47.4, 40.4, 27.1, 20.5, 20.4; IR (neat) 3399, 2958, 1693, 1455, 1254, 1137 cm^{-1}; MS (CI/NH$_3$) *m/z* 252 (100, MH$^+$), 234 (4), 208 (85), 144 (55), 108 (24), 91 (58); HRMS (CI/NH$_3$) *m/z* calcd for $C_{14}H_{22}NO_3$ (MH$^+$) 252.1600, found 252.1608.

The procedure given previously for the preparation of **12a** was carried using the above amide (150 mg, 0.593 mmol) in CH_2Cl_2 (3.00 mL) and DMP[17] (377 mg, 0.890 mmol) to give aldehyde **13** (137 mg, 92%) as white solid: mp 68.6−70.8 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.75 (s, 1H), 7.34 (m, 5H), 5.08 (ABq, J = 13.2 Hz, $\Delta\upsilon$ = 15.3 Hz, 3H), 3.46 (m, 1H), 3.36 (ddd, J = 5.1, 9.2, 13.9 Hz, 1H), 2.47 (m, 1H), 2.14 (m, 1H), 1.07 (d, J = 6.7 Hz, 3H), 1.01 (d, J = 6.7 Hz, 3H); ^{13}C (75 MHz, CDCl$_3$) δ 204.9, 156.3, 136.4, 128.5, 128.1, 128.1, 66.7, 58.2, 37.4, 27.2, 20.1, 19.8; IR (neat) 3315, 2973, 1718, 1685, 1541, 1276 cm^{-1}; MS (CI/NH$_3$) *m/z* 250 (MH$^+$, 100), 206 (8), 144 (12), 120 (6), 108 (33), 91 (46); HRMS (CI/NH$_3$) *m/z* calcd for $C_{14}H_{20}NO_3$ (MH$^+$) 250.1443, found 250.1435.

(*E*)-*N*-(2-*tert*-Butyldimethylsilyloxy)3(4-methyl)phenylsulfonylamido-propanal (15). To a solution of known amino alcohol **14**[19] (500 mg, 4.94 mmol) in CH_2Cl_2 (55 mL) at 0 °C was added pyridine (1.20 mL, 14.8 mmol) and then TsCl (942 mg, 4.90 mmol). The reaction mixture was stirred 24 h, and the solvent removed in vacuo. The residue was dissolved in ethyl acetate (25 mL) and water (25 mL), and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried (MgSO$_4$), and concentrated. Flash chromatography (2:1 hexanes/ethyl acetate) gave the protected amide (766 mg, 61%) as a clear, colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.74 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 5.72 (m, 1H), 5.38 (ddd, J = 15.4, 6.9, 1.8 Hz, 1H), 4.77 (m, 1H), 4.15 (m, 1H), 3.09 (broad d, J = 12.3 Hz, 1H), 2.87 (dd, J = 12.3, 7.7 Hz, 1H), 2.43 (s, 3H), 1.68 (dd, J = 5.6, 1.0 Hz, 3H), 1.63 (d, J = 1.5 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 143.5, 136.7, 130.0, 129.7, 129.4, 127.1, 71.1, 48.4, 21.5, 17.7; IR (neat) 3493, 3283, 3033, 2920, 2883, 1598, 1447, 1324 cm^{-1}; MS (CI/NH$_3$) *m/z* 273 (MNH$_4^+$, 13), 255 (1), 238 (100), 189 (8), 116 (7); HRMS (CI/NH$_3$) *m/z* calcd for $C_{12}H_{21}N_2O_3S$ (MNH$_4^+$) 273.1273, found 273.1264.

To a solution of the above amide (500 mg, 1.96 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added 2,6-lutidine (0.456 mL, 3.92 mmol) and then TBDMS−OTf (0.675 mL, 2.94 mmol). The reaction mixture was stirred 1 h, and then water (3 mL) was added. The organic layer was washed sequentially with a saturated aqueous solution of NaHCO$_3$ (5 mL), a saturated aqueous solution of NH$_4$Cl (5 mL), and brine, dried (MgSO$_4$), and concentrated. Flash chromatography (9:1 hexanes/ethyl acetate) gave the silyl ether (551 mg, 76%) as a clear, colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.72 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 5.58 (partially overlapping dq, J = 15.4, 6.7 Hz, 1H), 5.25 (ddd, J = 1.5, 7.2, 15.4 Hz, 1H), 4.59 (t, J = 5.9 Hz, 1H), 4.09 (apparent q, J = 5.9 Hz, 1H), 2.95 (collapsed dd, J = 4.6, 6.8 Hz, 1H), 2.85 (overlapping dd, J = 5.6, 6.7 Hz, 1H), 2.42 (s, 3H), 1.63 (dd, J = 6.4, 1.3 Hz, 3H), 0.83 (s, 9H), −0.02 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 143.3, 136.9, 130.9, 129.7, 128.4, 127.1, 72.0, 49.1, 25.8, 21.5, 18.1, 17.6, −4.3, −4.9; IR (neat) 3292, 2951, 2927, 2856, 1599, 1462, 1406, 1361, 1331, 1254, 1163 cm^{-1}; MS (CI/NH$_3$) *m/z* 370 (MH$^+$), 312 (3), 255 (4), 238 (100); HRMS (CI/NH$_3$) *m/z* calcd for $C_{18}H_{32}NO_3SiS$ (MH$^+$) 370.1872, found 370.1859.

A solution of the above amide (200 mg, 0.78 mmol) in CH_2Cl_2 (10 mL) at −78 °C was cleaved with ozone. Dimethyl sulfide was added, and the reaction mixture was stirred for 2 h and concentrated. The residue was dissolved in CH_2Cl_2 (5 mL), washed with water (3 × 10 mL) and brine, dried (K$_2$CO$_3$), and concentrated to give aldehyde **15** (184 mg, 93%) as a clear, colorless oil. This compound rapidly decomposed and was used immediately in the next reaction: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.56 (s, 1H), 7.73 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 4.90 (t, J = 6.2 Hz, 1H), 4.08 (t, J = 5.4 Hz, 1H), 3.18 (m, 2H,), 2.63 (solvent, DMSO-d_6), 2.43 (s, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 202.0, 143.8, 136.4, 129.8, 127.2, 75.7, 44.7, 40.9, 25.6, 21.5, 18.1, −4.8, −5.0; MS (CI/NH$_3$) *m/z* 375 (MNH$_4^+$, 58), 358 (MH$^+$, 80), 340 (9), 328 (17), 286 (28), 271 (100), 226 (23), 184 (64), 155 (45), 129 (65), 91 (21); HRMS (CI/NH$_3$) *m/z* calcd for $C_{16}H_{28}NO_4SiS$ (MH$^+$) 358.1508, found 358.1500.

General Experimental Procedure for Proline Synthesis. To a solution of aldehyde (1.0 equiv) in CH_2Cl_2 (0.2 M) at −78 °C was added benzyl diazoacetate (3.0 equiv). The reaction mixture was stirred 10 min, and BF$_3$·OEt$_2$ (1.0 equiv) was added dropwise over 20−50 min. The reaction mixture was stirred and then poured into a stirring saturated aqueous solution of NaHCO$_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), and concentrated. Flash chromatography (hexanes/ethyl acetate) gave the proline.

(±)-(2*S,3*R**,4*R**)-3-Hydroxy-1-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)-pyrrolidine-2-carboxylic Acid Phenylmethyl Ester (16).** Using the general experimental procedure, aldehyde **12a** (50 mg, 0.16 mmol) afforded proline ester **16** (56 mg, 77%) as a clear, colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.74 (d, J = 8.2 Hz, 2H), 7.37−7.18 (m, 10H), 7.09 (d, J = 6.7 Hz, 2H), 5.14 (ABq, $\Delta\nu$ = 15.9 Hz, J = 12.3 Hz, 2H), 4.34 (broad s, 1H), 4.13 (s, 1H), 3.53 (apparent t, J = 8.0 Hz, 1H), 3.15 (apparent t J = 9.5 Hz, 1H), 2.76 (dd, J = 8.2, 13.3 Hz, 1H), 2.65 (dd, J = 7.2, 13.8 Hz, 1H), 2.56 (m, 1H), 2.42 (s, 3H), 1.74 (d, J = 3.2 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.6, 143.7, 139.1, 135.3, 135.0, 129.6, 128.6, 128.5, 125.5, 128.1, 127.6, 126.4, 75.0, 69.8, 67.3, 50.5, 44.8, 32.0, 21.6; IR (neat) 3506, 3067, 3031, 2962, 1731, 1599, 1496, 1337 cm^{-1}; MS (CI/NH$_3$) *m/z* 483 (MNH$_4^+$, 2), 466 (MH$^+$, 31), 448 (12), 332 (25), 310 (22), 294 (42), 242 (19), 204 (24), 160 (58), 139 (64), 108 (89), 91 (100); HRMS (CI/NH$_3$) *m/z* calcd for $C_{26}H_{28}NO_5S$ (MH$^+$) 466.1688, found 466.1704.

(±)-(2*S,3*R**,4*R**)-3-Hydroxy-4-methylethyl-1-[(4-methylphenyl)sulfonyl]-pyrrolidine-2-carboxylic Acid Phenylmethyl Ester (17).** Using the general experimental procedure, aldehyde **12b** (500 mg, 1.86 mmol) afforded proline ester **17** (404 mg, 54%) as a white solid: mp 152.4−154.9 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.75 (d, J = 8.2 Hz, 2H), 7.36 (s, 5H), 7.27 (d, J = 7.7 Hz, 2H), 5.18 (s, 2H), 4.37 (s, 1H), 4.26 (t, J = 3.6 Hz, 1H), 3.61 (t, J = 8.2 Hz, 1H), 3.06 (dd, J = 8.5, 11.0 Hz, 1H), 2.41 (s, 4H), 1.86 (m, 1H), 1.71 (m, 1H), 1.61 (s, 1H), 0.86 (apparent t, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.7, 143.6, 135.3, 135.0, 129.6, 128.6, 128.5, 128.2, 127.6, 74.7, 70.2, 67.3, 50.6, 50.1, 25.8, 21.5, 21.4, 20.9; IR (neat) 3488, 2959, 1746, 1336, 1289, 1163 cm^{-1}; MS (CI/NH$_3$) *m/z* 435 (MNH$_4^+$, 100), 418 (MH$^+$, 57), 401 (6), 282 (25), 262 (6); HRMS (CI/NH$_3$) *m/z* calcd for $C_{22}H_{28}NO_5S$ (MH$^+$) 418.1688, found 418.1674. Proline **17** was recrystallized from hexanes/ethyl acetate as a white solid (X-ray quality).

(±)-(2*S,3*R**,4*S**)-4-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-1-[(4-methylphenyl)-sulfonyl]-pyrrolidine-2-carboxylic Acid Phenylmethyl Ester (19).** Using the general experimental procedure, aldehyde **15** (40 mg, 0.11 mmol) afforded proline ester **19** (21 mg, 37%) as a white solid: mp = 103−104 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.79 (d, J = 8.2 Hz, 2H), 7.36 (s, 5H), 7.24 (d, J = 9.8 Hz, 2H), 5.16 (ABq, $\Delta\nu$ = 10.9 Hz, J = 12.3 Hz, 2H), 4.38 (d, J = 2.05 Hz, 1H), 4.35 (s, 1H), 4.02 (overlapping dt, J = 2.6, 5.1 Hz, 1H), 3.61 (dd, J = 5.1, 10.3 Hz, 1H), 3.23 (dd, J = 2.6, 10.3 Hz, 1H), 2.40 (s, 3H), 1.92 (broad s, 1H), 0.81 (s, 9H), −0.01 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.0, 143.7, 135.3, 135.3, 129.5, 128.5, 128.3, 128.1, 127.8, 67.3, 67.1, 53.7, 25.5, 21.5, 17.9, −5.0; IR (neat) 3486, 2947, 2928, 2893, 2857, 1759, 1462, 1341, 1252, 1158 cm^{-1}; MS (CI/NH$_3$) *m/z* 523 (MNH$_4^+$, 5), 506 (MH$^+$, 100), 350 (67), 260 (13), 216 (41), 139 (23), 108 (44), 91 (73); HRMS (CI/NH$_3$) *m/z* calcd for $C_{25}H_{36}NO_6SiS$ (MH$^+$) 506.2033, found 506.2026.

(±)-(2*S,3*R**,4*R**)-3-Hydroxy-4-methyl-1-[(4-methylphenyl)sulfonyl]-pyrrolidine-2-carboxylic Acid Phenylmethyl Ester (20).** Using the general experimental procedure, aldehyde **12c** (51 mg, 0.21 mmol) afforded an inseparable 2:1 mixture (^{1}H NMR) of proline ester **20** and a compound believed to be β-keto ester **21** (45 mg, 56%) as a clear oil. An analytical sample of proline ester **20** was obtained by HPLC (3:1 hexanes/ethyl acetate): t_R 53.4 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 8.2 Hz, 2H), 7.36 (s, 5H), 7.27 (d, J = 8.2 Hz, 2H), 5.18 (s, 2H), 4.31 (s, 1H), 4.16 (d, J = 4.1 Hz, 1H), 3.56 (t, J = 8.0 Hz, 1H), 3.00 (t, J = 9.0 Hz, 1H), 2.41 (s, 3H), 2.37 (m, 1H), 1.76 (s, 1H), 0.95 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 143.6, 135.3, 134.9, 129.6, 128.6, 128.4, 128.2, 127.6, 69.5, 67.4, 51.9, 37.5, 29.7, 21.6, 10.3; IR (neat) 3504, 2963, 2924, 2885, 1746, 1598, 1340, 1306, 1162 cm^{-1}; MS (CI/NH_3) m/z 407 (MNH_4^+, 100), 390 (MH^+, 87), 254 (21), 236 (20), 234 (34), 218 (4), 108 (20), 100 (19), 91 (10); HRMS (CI/NH_3) m/z calcd for $C_{20}H_{24}NO_5S$ (MH^+) 390.1375, found 390.1363.

4-Methyl-3-oxo-5-[(4-methylphenyl)sulfonylamino)-pentanoic Acid Benzyl Ester (21). To a solution of $SnCl_2$ (5.0 mg, 0.03 mmol) in CH_2Cl_2 (0.8 mL) was added benzyl diazoacetate (54 mg, 0.31 mmol), and the mixture was cooled to −78 °C. Aldehyde **12c** (70.0 mg, 0.290 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and added to the reaction mixture. The reaction mixture was stirred for 6 h and diluted with ether (5.0 mL) and brine (5.0 mL). The aqueous layer was extracted with ether (3 × 2.0 mL), washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography (2:1 hexanes/ethyl acetate) gave β-keto ester **21** as a clear, colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 8.2 Hz, 2H), 7.38 (m, 5H), 7.29 (d, J = 7.7 Hz, 2H), 5.16 (s, 2H), 5.07 (t, J = 6.4 Hz, 1H), 3.51 (s, 1H), 3.05 (m, 2H), 2.92 (m, 1H), 2.41 (s, 3H), 1.11 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.4, 166.7, 143.4, 136.8, 135.1, 129.7, 128.6, 128.5, 128.4, 126.9, 67.2, 47.5, 46.5, 44.6, 21.4, 14.1.

(±)-(2*S,3*R**)-3-Hydroxy-4,4-dimethyl-1-[(4-methylphenyl)sulfonyl]pyrrolidine-2-carboxylic Acid Phenylmethyl Ester (22).** Using the general experimental procedure, aldehyde **12d** (50 mg, 0.20 mmol) afforded proline ester **22** (11 mg, 14%) and β-keto ester **23** (45 mg, 57%) as clear, colorless oils: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 8.2 Hz, 2H), 7.38 (m, 5H), 7.35 (d, J = 7.7 Hz, 2H), 5.24 (ABq, J = 12.1 Hz, $\Delta\nu$ = 12.9, 2H), 4.09 (d, J = 6.2 Hz, 1H), 3.94 (d, J = 6.7 Hz, 1H), 3.25 (d, J = 10.3 Hz, 1H), 3.15 (d, J = 10.3 Hz, 1H), 2.42 (s, 3H), 1.95 (s, 1H), 1.00 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 143.7, 135.4, 134.9, 129.6, 128.6, 128.4, 128.3, 127.7, 81.4, 67.4, 66.5, 58.4, 41.6, 23.5, 21.6, 18.7; IR (neat) 3481, 2963, 2929, 1746, 1598, 1339, 1160 cm^{-1}; MS (CI/NH_3) m/z 404 (MH^+, 2), 218 (82), 201 (100), 155 (4), 128 (4); HRMS (CI/NH_3) m/z calcd for $C_{21}H_{26}NO_5S$ (MH^+) 404.1532, found 404.1530.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra and X-rays (where applicable) for compounds **7a**−**c**, **8a**−**c**, **9b,c**, **10a**−**c**, **11a**−**e**, **12a**−**e**, **13**, **15**, **16**, **17**, **19**, and **20**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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