Asymmetric 1,4-Addition of Higher Order Silylcuprates to Oppolzer's *N*-Enoyl Sultams

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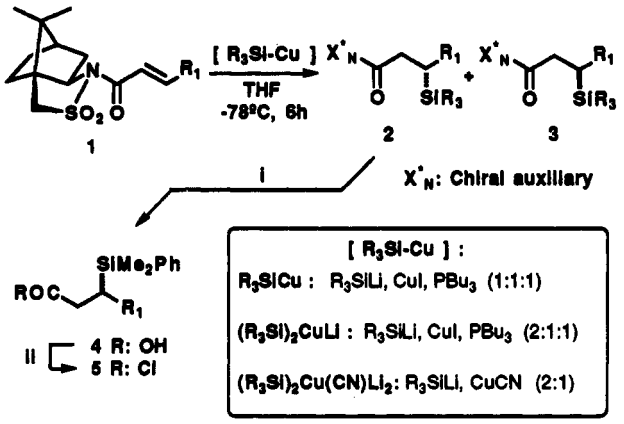
The ability of trialkylsilyl groups to control the stereochemistry in organic reactions has been well established and documented.[1] Among these groups, the dimethylphenylsilyl substituent is particularly atractive in the above context for two reasons: first, it can be removed from the reaction product after the stereochemical control has been effected, and second, it can be converted into a hydroxyl group with retention of configuration.[2] On the basis of these properties, we have recently described the [2 + 2] cycloaddition reaction of β-(dimethylphenylsilyl)-alkyl ketenes to glyoxylic ester derived imines to form racemic β-lactams either as synthetic intermediates of carbapenem antibiotics or as precursors of aspartic acid derivatives.[3] The importance of these compounds in their optically active forms led us to prepare enantiomerically pure β-silylcarboxylic acids and, hence, β-silylketenes to accomplish the asymmetric version of the above cycloaddition reactions.

Organocopper conjugate addition[4] to alkenoic acid derivatives is probably the most suitable general method to obtain β-substituted carboxylic acids, either in their racemic or enantioenriched forms.[5] In this context, several groups have examined the diastereoselective addition of diverse silylcuprate reagents to scalemic α,β-unsaturated esters,[6] *N*-enoyllactams,[6] α-alkylidenelactones,[7] and *N*-enoylsultams,[8] opening convenient synthetic routes to prepare diversely substituted β-trialkylarylsilylalkanoic acids in moderate to good optical purities and in both of their enantiomeric forms. It has been established that the stereocontrol level depends mainly on three factors, the first of which is the structure of the chiral Michael acceptor used. Thus, the study made by Fleming reveals the superiority of more rigid *N*-enoyllactams, like Koga's glutamic acid derived lactam,[9] over sterically crowded but less rigid α,β-unsaturated esters, like those derived from Oppolzer's *N*,*N*-dicyclohexylcamphorsulfonamide alcohol. Confirming this generalization, Oppolzer's[10] *N*-enoylsultams induce greater diastereoselection than the above-mentioned camphor-derived alcohol esters. As a second diastereoselectivity factor, the order in which the substituents are bonded to the newly created stereogenic β-position also plays an important role; for instance, both Fleming and Oppolzer agree that the carbocupration of a chiral β-silyl α,β-unsaturated acyl derivative gives a greater level of diastereoselection than the equivalent silylcupration of a β-carbo-substituted α,β-unsaturated acyl derivative. Finally, the addition of chelating agents, like $EtAlCl_2$ or BF_3-OEt_2, to promote conformational rigidity and, hence, greater stereofacial differentiation, is also a crucial factor. There is, however, another diatereoselection factor that has received little attention in the preceeding studies; that is, the influence of the chemical nature of the silylcuprate used (e.g., monocuprate R_3SiCu, lower order cuprate $(R_3Si)_2CuLi$, or higher order cuprate $(R_3Si)_2Cu(CN)Li_2$).[11] This factor has been almost ignored,[12] and much to our surprise no reports dealing with the addition of higher order silylcyanocuprates to Oppolzer's *N*-enoylsultams have been described. In this paper we report our results concerning the conjugate addition of different silylcuprates to the Oppolzer *N*-enoylsultams, and we demonstrate that the nature of the silylcuprate used can indeed affect the stereoselectivity of the reaction (Scheme 1).

Scheme 1



[a] Reagents and conditions: (i) LiOH, THF, H_2O, *n*-$Bu_4N^+Br^-$ cat., rt, 4 days; (ii) $(COCl)_2$, CH_2Cl_2, 0 °C → rt, 30 min.

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(4) For recent reviews on organocuprate conjugate addition reactions, see: (a) Yamamoto, Y.; Sasaki, N. In *Stereochemical Control, Bonding and Steric Rearrangements*; Bernal, I., Ed.; Elsevier: Amsterdam, 1990; Vol. 4. (b) Chapdelaine, M. J.; Hulce, M. *Org. React.* **1990**, 38, 225. (c) Kozlowski, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon: Oxford, **1991**; vol. 4, p. 169. (d) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Tetrahedron Organic Chemistry Series, No. 9; Pergamon: Oxford, 1992. (e) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.

(5) For reviews dealing directly with organocuprate asymmetric conjugate additions, see: (a) Tomioka, K.; Koga, K. In *Asymmetric Synthesis*; Morrison, J.D., Ed.; Academic: New York, 1983; Vol. 2, p 201. (b) Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 947. (c) Schmalz, H. G., In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 199. (d) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. (e) Ibuka, T.; Yamamoto, Y. *Synlett.* **1992**, 769.

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Table 1. Conjugate Addition of Silylcuprates to *N*-Enoylsultams[a,b]

entry	R^1	cuprate	product 2	yield[c] (%)	molar ratio[d] 2:3	compd 2[e] mp (°C)	compd 2[e] $[\alpha]^{25}_D$ (deg)
1	Me	$PhMe_2SiCu$	a	90	80:20	85–87	−65.8
2		$(PhMe_2Si)_2CuLi$		80	61:39		
3		$(PhMe_2Si)_2CuCNLi_2$		81	99:1		
4		$Ph_2MeSiCu$	b	80	70:30	syrup	−59.6
5		$(Ph_2MeSi)_2CuCNLi_2$		81	82:18		
6		$(Ph_2{}^tBuSi)_2CuCNLi_2$	c	83	87:13	syrup	−50.2
7	Ph	$PhMe_2SiCu$	d	75	86:14	100–102	−55.3
8		$PhMe_2SiCu$			90:10[f]		
9		$(PhMe_2Si)_2CuLi$		65	54:46		
10		$(PhMe_2Si)_2CuCNLi_2$		72	98:2		
11		$Ph_2MeSiCu$	e	75	58:42	syrup	−4.3
12		$(Ph_2MeSi)_2CuCNLi_2$		97	79:21		
13		$Ph_2{}^tBuSiCu$	f	48	72:28	190–192	−47.3
14		$(Ph_2{}^tBuSi)_2CuCNLi_2$		85	95:5		
15	4-MePh	$PhMe_2SiCu$	g	92	64:36	123–125	−64.2
16		$(PhMe_2Si)_2CuCNLi_2$		96	98:2		
17		$(Ph_2MeSi)_2CuCNLi_2$	h	95	85:15	188–190	−12.8
18	4-MeOPh	$PhMe_2SiCu$	i	95	53:47	100–102	−59.5
19		$(PhMe_2Si)_2CuCNLi_2$		89	93:7		
20	4-ClPh	$PhMe_2SiCu$	j	96	59:41	168–170	−66.2
21		$(PhMe_2Si)_2CuCNLi_2$		87	96:4		
22	2-Furyl	$PhMe_2SiCu$	k	58	51:49	syrup	−69.4
23		$(PhMe_2Si)_2CuCNLi_2$		64	81:19		

[a] *N*-Alkenoylsultam: silylcuprate molar ratios used were 1:10 for R_3SiCu, 1:5 for $(R_3Si)_2CuLi$, and for $(R_3Si)_2Cu(CN)Li_2$ 1:1.5 with cinnamates and 1:1 with crotonates. [b] Conditions: reaction tempeature −78 °C; reaction time 6 h. [c] Yield of isolated products after flash column chromatography (silica gel; eluent hexane/ethyl acetate (10:1 to 15:1)). [d] Diastereomeric ratio determined by 300-MHz ^{1}H-NMR analysis of the crude reaction mixture. [e] Physical data referred to crystallized products or purified by HPLC (de > 99%). [f] $EtAlCl_2$ added (10 equiv referred to *N*-enoylsultam) yield not determined, see ref 8.

The operational conditions chosen to prepare the different cuprates were the following: for the R_3SiCu reagent, 1 equiv of silyllithium[13] prepared from the corresponding chlorosilane and lithium sand in THF were added at −78 °C to a mixture of CuI (1 equiv) and tri-*n*-butylphosphine[14] (1 equiv) in diethyl ether. The mixture was stirred for 30 min at −78 °C and then warmed at −30 °C (darkening resulted) and recooled to −78 °C, giving the reagent solution ready for use. For the $(R_3Si)_2CuLi$ reagent, the preparation was identical to that of the prior reagent, but 2 equiv of silyllithium was added. The higher order reagent $(R_3Si)_2Cu(CN)Li_2$ was prepared[15] by reacting 2 equiv of silyllithium with 1 equiv of CuCN in THF at 0 °C for 20 min. All the conjugate additions studied were performed by adding THF solutions of the corresponding *N*-enoylsultams to the above silylcuprates. The progress of the reactions was monitored by TLC analysis of aliquots, and it was established that 6 h were needed in most cases until completion, operating at −78 °C.

The diastereomeric ratio could be easily determined (^{1}H-NMR analysis after flash chromatography of the reaction crude) by integrating for both **2** and **3** isomers the singlet signals assigned to the geminal methyl groups bonded to the norbornane bridgehead. As a rule, these methyl groups resonate at lower fields in isomers **2** than in isomers **3** (typically δ = 0.9 and 1.1 ppm for the former and near δ = 0.8 ppm for the latter in all the β-aryl-β-silyl *N*-propanoylsultams studied). This rule was inverted, however, for β-alkyl-β-silyl *N*-acylsultams that showed the aforementioned methyl groups at slightly higher fields in isomers **2** than in isomer **3** (R^1 = Me). As shown in the Table 1, the reaction yields were similarly high for lower and higher order silylcuprates, but most interestingly, the level of diastereoselection of the reaction was strongly dependent on the nature of silylcuprate used and invariably increased when higher order silylcyanocuprates were used. This behavior is clearly illustrated in entries 1–3, 9, 10, and 15–23, which show a general stereofacial discrimination ability given by the sequence: $(R_3Si)_2Cu(CN)Li_2 > R_3SiCu >> (R_3Si)_2CuLi$.

In spite of the virtual absence of stereoselection observed for any silyl group substituents in lower order reagents, the diastereoselection levels were uniformly good (from 93 to 99%) for crotonates and cinnamates when higher (dimethylphenylsilyl)cyanocuprates were used as reagents. Other more hindered silyl groups like the diphenylmethylsilyl group or the *tert*-butyldiphenylsilyl group showed somewhat lower diastereoselection levels, although surprisingly, the (*tert*-butyldiphenylsilyl)cyanocuprate reagent was more selective (entries 6 and 14) than the diphenylmethylsilyl partner (entries 5 and 12). The stereochemical assignment of the products obtained was primarily determined by cleavage of the sultam auxiliary (LiOH, aqueous THF),[16] conversion of the resulting β-silyl carboxylic acids, Table 2, to their methyl esters, and stereospecific transformation into the corresponding β-hydroxy esters following Fleming's protocol. For instance, when this sequence was applied to compound **2d** (R^1 = Ph), a $[\alpha]^{25}_D$ +19.2° (*c* 2.0, EtOH) was found for the corresponding methyl β-hydroxy ester, indicating the R absolute configuration at the newly created stereogenic β-center.[17] The stereochemistry of the other adducts was established by analogy, and the results are in good

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(14) The use of tri-*n*-butylphosphine was imperative for the formation of homocuprates, since the reaction of 1:1 and 2:1 mixtures of silyllithium and CuI with *N*-crotonyl- or *N*-cinnamoylsultam resulted in complete recovery of the starting *N*-enoyl derivative either at −78 °C or at 0 °C.

(15) Cuadrado, P.; Gonzalez, A. M.; Pulido, F. J. *Synth. Commun.* 1989, 275.

(16) Oppolzer, W.; Poli, G.; Kingma, A. J.; Starkemann, C.; Bernardinelli, G. *Helv. Chim. Acta* 1987, *70*, 2201.

(17) Literature value for (*S*)-methyl 3-hydroxy-3-phenylpropanoate $[\alpha]^{25}_D$ −17.9° (*c* 2.09, EtOH), see: Helmchen, G.; Leikauf, U.; Taufer-Knopfel, I., *Angew. Chem., Int. Ed. Engl.* 1985, *24*, 874.

Table 2. β-(Dimethylphenylsilyl)propanoic Acids 4 Prepared[a]

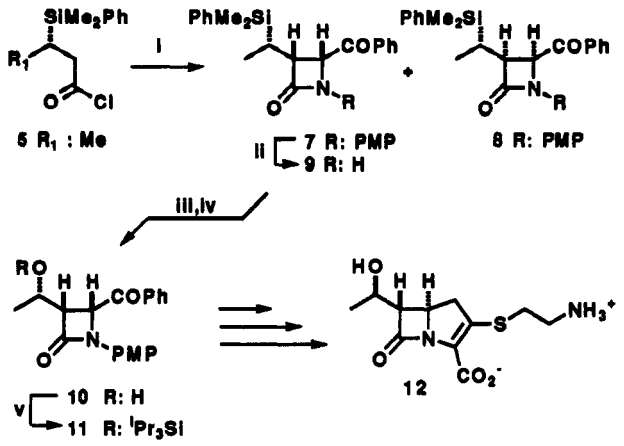
compd	R^1	yield[b] (%)	mp (°C)	$[\alpha]^{25}_D$[c] (deg)
4a	Me	62	106/0.01[d]	+5.8
4b	Ph	90	99–100[e]	+3.0
4c	4-MeC_6H_4	71	oil	−5.8
4d	4-$MeOC_6H_4$	82	oil	−6.8
4e	4-ClC_6H_4	74	oil	−5.3

[a] Reactions conducted on a 10 mmol scale. [b] Isolated yield of pure compounds. [c] Measured in CH_2Cl_2 at c = 1.0. Oil products were purified by preparative HPLC. [d] Boiling point (°C/mmHg). [e] Crystallization solvent: hexanes.

agreement with Oppolzer's observations. Thus, the stereochemical outcome of these addition reactions can be accounted for by invoking a preferential SO_2/C=O *syn*-disposition combined with a *s-cis* C=O/C=C conformation followed by a silylcuprate attack from the less hindered alkene bottom face.[8] Therefore, it follows that higher order silylcuprates are more effective than monocuprates and lower order silylcuprates to achieve efficient complexation with Oppolzer's *N*-enoylsultams.[18] In contrast, and most notably, we found that (*S*)-phenyloxazolidinone crotonate, which has recently proved to be very effective for organocuprate additions[19] when reacted with higher order silylcuprates under the same conditions employed for Oppolzer's *N*-enoylsultams, exerted a very poor level of reaction diastereoselection, typically 50% de. Similarly, (*S*)-benzyloxazolidinone crotonates led to the corresponding adducts with de in the range 15%–20%.

Further evidence for the absolute stereochemical course of the above reactions was provided by the synthesis of the β-lactam 11 which has been used to prepare the potent antibiotic (+)-thienamycin (12)[20] (Scheme 2). Namely, reaction of the β-(dimethylphenylsilyl)butanoyl chloride (5) (R^1 = Me) with the imine 6[21] in the presence of triethylamine led to the formation of the β-lactam 7 together with its *syn*-diastereomer 8 in a ratio of 75:25. Both compounds were readily separated from the reaction crude by crystallization from methanol, affording 7 in 60% and 8 in 15% isolated yields. The *cis* relationship of the C_3-H and C_4-H in 7 and 8 was established by their ^1H NMR coupling constants of 5.4 Hz, consistent with the assigned *cis* configuration.[20] In addition, no traces of the corresponding *trans* isomers were detected by ^1H NMR analysis of the crude reaction mixture. This latter aspect contrasts with the result obtained from the parent cycloaddition reaction developed in this laboratory[3b] using the *N*-(*p*-methoxyphenyl)imine of methyl glyoxalate,

Scheme 2



[a] Reagents and conditions: (i) PMPN=CHCOPh, (6), NEt_3, CH_2Cl_2, 40 °C, 20–24 h; (ii) $(NH_4)_2Ce(NO_3)_6$, CH_3CN/H_2O, −5 °C, 15 min; (iii) HBF_4, Et_2O, CH_2Cl_2, 0 °C → rt, 2 h; (iv) AcOOH, AcOH, NEt_3, CH_2Cl_2, 0 °C → rt, 3 h; (v) F_3CSO_3Si-*i*-Pr_3, 2,6-lutidine, CH_2Cl_2, rt; (h) PMP group: 4-$MeOC_6H_4$.

which produced a mixture of the four possible diastereomers.[22] Finally, compound 7 was N-dearylated[23] to give 9 in 75% yield. Although attempts to transform the silyl group in 9 into the corresponding hydroxyl group were not extremely successful, the N-protected β-lactam 7 could be cleanly converted into the desired hydroxy derivative 10 in 80% overall yield. Subsequent protection of the hydroxy group in 10, using triisopropylsilyl triflate and 2,6-lutidine as base,[24] led to the β-lactam 11 identical to that previously reported by a Merck group.[25] This result corroborated the assigned stereochemistry for adducts 2 and provided a further entry for the synthesis of optically active 3-alkyl β-lactams via [2 + 2] cycloaddition reaction for which only a few examples have been described to date.[26]

In conclusion, it has been demonstrated that the silylcupration of Oppolzer's *N*-enoylsultams by means of higher order silylcuprates is comparable to the carbocupration of β-silyl-substituted *N*-enoylsultams in terms of diastereofacial selectivity, and provides an efficient process for the preparation of enantiomerically pure β-silyl carboxylic acids for use in asymmetric synthesis.[1,2]

Experimental Section

Melting points were determined on a Büchi SMP-20 instrument and are uncorrected. Proton nuclear magnetic resonance spectra

(18) The fact that nonchelating controlled reactions that occur only at the C_β-position of *N*-enoylsultams often show both low stereoselectivity and opposite sense of induction supports the proposed transition model for silylcuprate additions. For an excellent discussion of nonchelation as well as chelation-controlled asymmetric reactions with Oppolzer's camphor sultam, see: Kim, B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293.

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(22) For an explanation of the observed stereochemical outcome, see: (a) ref 20b. For theoretical studies on this subject, see: (b) Sordo, J. A.; Gonzalez, J.; Sordo, T. *J. Am. Chem. Soc.* **1992**, *114*, 6249. (c) Yamabe, S.; Minato, T.; Osamura, Y. *J. Chem. Soc., Chem. Commun.* **1993**, 450. (d) Cossio, F. P.; Ugalde, J. M.; Lopez, X.; Lecea, B.; Palomo, C. *J. Am. Chem. Soc.* **1993**, *115*, 995.

(23) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

(24) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

(25) (a) Tschaen, D. M.; Fuentes, L. M.; Lynch, J. E.; Laswell, W. L.; Volante, R. P.; Shinkai, I., *Tetrahedron Lett.* **1988**, *29*, 2779. We were unable to reproduce the literature data for the enantiomer of compound 11 $[\alpha]^{25}_D$ −141.48° (c 5.40, $CHCl_3$). This value seems to correspond to the rotation observed instead of the specific rotation; see: (b) Lynch, J. E.; Riseman, S. M.; Laswell, W. L.; Tschaen, D.M.; Volante, R. P.; Smith, G. B.; Shinkai, I. *J. Org. Chem.* **1989**, *54*, 3792.

(26) All of these cases are based on the use of optically active 3-hydroxybutyric acid chloride derivatives; see: (a) ref. 25. (b) Lombardi, P.; Colombo, M.; Crugnola, A.; Franceschi, G. GB 2144419A, 1985 *Chem. Abstr.* **1985**, *103*, 53864m. (c) Ernest, B.; Bellus, D. D. E. 3620467, 1987 *Chem. Abstr.* **1987**, *106*, 176045g. For some solutions to the problems associated with the preparation of 3-alkylazetidin-2-ones via cycloaddition reaction, see ref 20b.

and ^{13}C spectra were recorded on a Varian VXR 300 spectrometer. All chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane. Infrared (IR) spectra were recorded on a Shimadzu IR-435 spectrometer. Mass spectra were obtained using a Shimadzu GCMS QP-200 spectrometer operated at 70 eV. HPLC analyses were performed on a Shimadzu apparatus, using a SPD-6AV UV detector and Lichrosorb Si 60 (7 μm) preparative 25-cm column (Merck). Microanalytical data were obtained on a Perkin-Elmer 240-C instrument. Commercially available compounds were used in this work without further purification or were prepared following literature procedures. Acetonitrile and hexane were dried and purified by distillation. Tetrahydrofuran was distilled over sodium and benzophenone (indicator). Methylene chloride was shaken with concentrated sulfuric acid, dried over potassium carbonate, and distilled.

General Procedure for the Asymmetric Conjugate Addition of Higher Order (Cyanodimethylphenylsilyl)cuprate Reagent to Chiral α,β-Unsaturated *N*-Acylsultams. Preparation of Compounds 2. A solution of (dimethylphenylsilyl)-lithium (6 mL, 1 M, 6.00 mmol) in tetrahydrofuran was added dropwise at 0 °C over copper(I) cyanide (0.27 g, 3.00 mmol), and the resulting suspension was stirred at the same temperature for 20 min. Then, the dark solution was cooled at −78 °C and a solution of the corresponding α,β-unsaturated acylsultam 1 (2.00 mmol) was added dropwise while the mixture was stirred at the same temperature during 6 h. Then, the reaction mixture was poured into methylene chloride (30 mL) and aqueous saturated ammonium cloride solution (25 mL), and it was stirred for 15 min at 0 °C. The mixture was filtered over Celite, and the organic layer was dried over magnesium sulfate. After evaporation, the reaction crude was purified either by flash chromatography (silica gel; eluent: hexane/ethyl acetate (10:1) or by direct crystallization from hexane. **2a** (0.71 g, 85%): mp 85 - 87 °C (hexane). ^1H NMR ($CDCl_3$): δ 7.52–7.49 (m, 2H, arom.), 7.36–7.33 (m, 2H, arom), 3.85 (t, 1H, J = 6.3 Hz, CHN), 3.43 (dd, 2H, J = 13.7Hz, J = 19.5 Hz, CH_2SO_2), 2.83 (dd, 1H, J = 4.2 Hz, J' = 15.9 Hz, CH_2CO), 2.44 (dd, 1H, J = 10.4, 15.9 Hz, CH_2CO), 2.02 (m, 2 H, CH_2CH_2), 1.88 (m, 3 H,CH_2CH_2CH), 1.61 (m, 1H, CHSi), 1.35 (m, 2 H, CH_2CH), 1.12 (s, 3H, CH_3C), 0.95 (d, 3H, J = 7.3 Hz, CH_3CHSi), 0.95 (s, 3H, CH_3C), 0.29 (s, 3H, CH_3Si), 0.06 (s, 3H, CH_3Si).^{13}C NMR ($CDCl_3$): δ 172.2, 137.3, 134.0, 129.0, 127.7, 65.1, 52.9, 48.2, 47.7, 44.5, 38.5, 38.42, 32.8, 26.4, 20.8, 19.9, 15.9, 14.4, -4.9, -5.2. MS: m/e 420 (M^+). $[\alpha]^{25}_D$: −65.8° (c 1.0, CH_2Cl_2).

General Procedure for the Preparation of β-Dimethylphenylsilyl Carboxylic Acids 4. Lithium hydroxide monohydrate (3.78 g, 90 mmol) was added to a solution of *N*-[β-(dimethylphenylsilyl)alkanoyl]sultam (10 mmol) and tetra-*n*-butylammonium bromide (cat., 0.3 mmol) in tetrahydrofuran/water (100 mL/60 mL), and the mixture was stirred for 4 days at room temperature. After this time, the reaction mixture was acidified with 1 M HCl, saturated with sodium chloride, and extracted with diethyl ether (4 × 40 mL). The combined organic solutions were dried over $MgSO_4$ and evaporated under reduced pressure, and the pure acids were separated from the sultam by column chromatography (silica gel, eluant: CH_2Cl_2/hexanes (1:20)). As an example, hydrolysis of adduct **2a** (R_1 = Me) gave (3*S*)-3-(dimethylphenylsilyl)butanoic acid (**4a**) (62%), purified by preparative HPLC (AcOEt/hexane (1:3) as eluant, 8 mL/min, rt 16.8 min). Bp: 106 °C/0.01 mmHg. ^1H NMR ($CDCl_3$): δ 7.49 (m, 2H, arom), 7.36 (m, 3H, arom), 2.42 (dd, 1H, J = 3.7, 15.3 Hz, CH_2CO), 2.06 (dd, 1H, J = 11.4, 15.3 Hz, CH_2CO), 1.42 (m, 1H, CHSi), 1.00 (d, 3H, J = 7.5 Hz, CH_3), 0.29 (s, 6H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$). ^{13}C NMR ($CDCl_3$): δ 180.3, 137.0, 133.8, 129.1, 127.8, 36.6, 16.3, 14.4, −5.1, −5.4. MS: m/e 207 (M^+ − 15). $[\alpha]^{25}_D$: +5.8 (c 1.0, CH_2Cl_2).

(3*S*,4*R*)-4-Benzoyl-3-[1(*S*)-(dimethylphenylsilyl)ethyl]-1-(*p*-methoxyphenyl)azetidin-2-one (7). A solution of 3(*S*)-(dimethylphenylsilyl)butanoyl chloride (2.38 g, 9.9 mmol) in dry benzene (25 mL) was added dropwise to a cooled (0 °C) mixture of imine **6** (2.15 g, 9.0 mmol) and triethylamine (2.10 mL, 15 mmol) in the same solvent (40 mL) during 10 min. After the ice bath was removed, the reaction mixture was stirred at room temperature for 15 h and then diluted in methylene chloride (100 mL) and washed successively with H_2O (50 mL), 1 M HCl (50 mL), saturated $NaHCO_3$ (50 mL), and H_2O (50 mL). Drying over $MgSO_4$ and evaporation of solvents yielded the corresponding crude β-lactams as a mixture of *anti,cis*- and *syn,cis*-isomers, from which **7** was separated by crystallization in methanol (2.40g, 60%), mp 140–142 °C (MeOH). ^1H NMR ($CDCl_3$): δ 7.99 (d, 2H, arom), 7.63–7.27 (m, 8H, arom), 7.10 (d, 2H, arom), 6.71 (d, 2H, arom), 5.53 (d, 1H, J = 5.4 Hz, CHCOPh), 3.66 (s, 3H, OCH_3), 3.48 (dd, 1H, J = 5.4, 12.3 Hz, CHCO), 0.98–0.92 (m, 1H, $CHCH_3$), 0.54 (d, 3H, J = 7.2 Hz, CH_3CH), 0.53 (s, 3H, CH_3Si), 0.40 (s, 3H, CH_3Si). ^{13}C NMR ($CDCl_3$): δ 195.3, 165.0, 156.1, 137.2, 136.5, 134.4, 134.2, 133.9, 130.9, 129.3, 129.1, 129.0, 128.4, 128.1, 127.9, 127.6, 118.3, 114.3, 114.1, 60.7, 56.4, 55.4, 16.9, 15.9, 1.9, −2.8, −4.0. $[\alpha]^{25}_D$: +44.5 (c 1.0, CH_2Cl_2). Anal. Calcd for $C_{27}H_{29}NO_3Si$: C, 73.09; H, 6.60; N, 3.16. Found: C, 73.05; H, 6.58; N, 3.16.

(3*S*,4*R*)-4-Benzoyl-3-[1(*S*)-(dimethylphenylsilyl)ethyl]-azetidin-2-one (9). A solution of ammonium cerium(IV) nitrate (8.28 g, 15 mmol) in water (60 mL) was added dropwise to a cooled (0 °C) solution of the β-lactam **7** (1.33 g, 3 mmol) in acetonitrile (50 mL) within 15 min. Then, the reaction mixture was stirred at 0 °C for 30 min. On completion, the reaction mixture was taken up over water (150 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layer was washed succesively with saturated sodium hydrogen carbonate (50 mL), sodium hydrogen sulfite (4 × 40 mL), sodium hydrogen carbonate (40 mL), and brine (40 mL). After drying and evaporation of the solvents, the resulting crude product was purified by column chromatography (silica gel; eluent: hexane–methylene chloride (1:1)), yielding compound **9** (0.76 g, 75%), mp 150–152 °C (MeOH). ^1H NMR ($CDCl_3$): δ 7.99–7.97 (m, 2H, arom), 7.62–7.31 (m, 8H, arom), 5.30 (d, 1H, J = 5.4 Hz, CHCOPh), 3.53 (dd 1H, J = 5.4, 12.3 Hz, CHCO), 1.28–1.22 (m, 1H, $CHCH_3$), 0.47 (d, 3H, J = 7.2 Hz, CH_3CH), 0.45 (s, 3H, CH_3Si), 0.35 (s, 3H, CH_3Si). ^{13}C NMR ($CDCl_3$): δ 197.4 169.4, 137.4, 137.2, 136.5, 134.3, 134.0, 129.0, 128.9, 128.1, 127.5, 63.5, 53.8, 17.3, 15.9, −2.9, −4.2. $[\alpha]^{25}_D$: +2.5 (c 1.0, CH_2Cl_2). Anal. Calcd for $C_{20}H_{23}NO_2Si$: C, 71.17; H, 6.88; N, 4.15. Found: C, 71.38; H, 6.58; N, 4.16.

(3*S*,4*R*)-4-Benzoyl-3-(1(*S*)-hydroxyethyl)-1-(*p*-methoxyphenyl)azetidin-2-one (10). $HBF_4{\cdot}2Et_2O$ (0.63 mL, 3.6 mmol) was added to a cooled (0 °C) solution of azetidinone **7** (1.3 g, 3.0 mmol) in methylene chloride (25 mL), and the mixture was stirred at room temperature for 15 h. After this time, the reaction mixture was washed with cold water (10 mL) and brine (20 mL). The organic solvent was dried and evaporated to yield the corresponding dimethylfluorosilane. The crude product was dissolved in cold (0 °C) 32% peracetic acid in acetic acid (15 mL), and triethylamine (0.45 mL, 3.2 mmol) was added dropwise within 5 min at the same temperature. The mixture was stirred at room temperature for 3.5 h, then methylene chloride (50 mL) was added and the resulting solution was successively washed with 1 M HCl (30 mL), 40% $NaHSO_3$ (30 mL), $NaHCO_3$ (30 mL), and water (30 mL). Drying and evaporation afforded the crude (3*S*,4*R*)-4-benzoyl-3(*S*)-(1-hydroxyethyl)-1-(*p*-methoxyphenyl)-azetidin-2-one that was purified by column chromatography (silica gel, eluent: methylene chloride/hexane (1:3)) to afford pure **10** (0.80 g, 80%), mp 152 °C. ^1H NMR ($CDCl_3$): δ 7.99–7.97 (m, 2H, arom), 7.62–7.31 (m, 8H, arom), 5.30 (d, 1H, = 5.4 Hz, CHCOPh), 3.53 (dd, 1H, J = 5.4, 12.3 Hz, CHCO), 1.28–1.22 (m, 1H, $CHCH_3$), 0.47 (d, 3H, J = 7.2 Hz, CH_3CH), 0.45 (s, 3H, CH_3Si), 0.35 (s, 3H, CH_3Si). ^{13}C NMR ($CDCl_3$): δ 197.4, 169.4, 137.4, 136.5, 134.3, 134.0, 128.9, 129.0, 128.1, 127.5, 63.5, 53.8, 17.3, 15.9, −2.9, −4.2. MS: m/e 325 (M^+). $[\alpha]^{25}_D$ +16.2 (c 1.0, CH_2Cl_2). Anal. Calcd for $C_{20}H_{23}NO_2Si$: C, 71.17; H, 6.88; N, 4.15. Found: C, 71.38; H, 6.88; N, 4.05.

(3*S*,4*R*)-4-Benzoyl-3-[1(*S*)-[(triisopropylsilyl)oxy]ethyl]-1-(*p*-methoxyphenyl)azetidin-2-one (11). A solution of (3*S*,4*R*)-4-benzoyl-3-(1(*S*)-hydroxyethyl)-1-(*p*-methoxyphenyl)azetidin-2-one (**10**) (0.68 g, 2 mmol) in dry methylene chloride (5 mL) was added to a solution of trisisopropylsilyl triflate (0.61 g, 2 mmol) in dry methylene chloride (10 mL). 2,6-Lutidine (0.52 mL, 4.5 mmol) was added to the mixture cooled at 0 °C and stirred at room temperature for 15 h. After this time, the reaction mixture was successively washed with 0.1 M HCl (15 mL) and saturaded $NaHCO_3$ (15 mL). Drying over $MgSO_4$ and evaporation of the solvent yielded the corresponding crude compound which was purified by column chromatography (silica gel, eluent: methylene chloride/hexane (1:10)) to afford pure **11** (0.29 g, 30%, not

optimized). ^{1}H NMR ($CDCl_3$): δ 8.02–7.99 (m, 2H, arom), 7.62–7.51 (m, 3H, arom), 7.25 (d, 2H, arom), 6.81 (d, 2H, arom), 5.40 (d, 1H, J = 6.3 Hz, CHN), 4.38–4.30 (m, 1H, CHOSi), 3.92 (dd, 1H, J = 3.7, 6.3 Hz, CHCO), 3.76 (s, 3H, OCH_3), 1.34 (d, 3H, J = 6.4 Hz, CH_3CH), 0.96–0.90 (m, 18H, CH_3CH), 0.86–0.82 (m, 3H, CHSi). ^{13}C NMR ($CDCl_3$): δ 192.4, 163.8, 156.1, 135.2, 134.4, 131.4, 128.8, 128.6, 118.3, 114.3, 65.7, 62.4, 58.4, 55.4, 21.9, 17.9, 18.0, 13.0. Anal. Calcd for $C_{28}H_{39}NO_4Si$: C, 69.80; H, 8.18; N, 2.91. Found: C, 69.84; H, 8.24; N, 2.92. $[\alpha]^{25}_D$ +26.1° (*c* 1.0, $CHCl_3$).[25b]

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Supplementary Material Available: Spectral and analytical data (^{1}H NMR, ^{13}C NMR, IR, MS, $[\alpha]^{25}_D$) for compounds **2b-k** and **4b-e** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.