H-9), 6.60–6.35 (m, 5 H, H-10, -11, -12, -23, -36), 6.19 (d, J = 7.0 Hz, 1 H, H-5), 5.95 (m, 3 H, H-13, -22, -37), 5.89 (s, 1 H, 29-OH), 5.70–5.44 (m, 4 H, H-24, -35, -38, NH), 4.90 (s, 1 H, H-1″), 4.64 (d, $J_{1',2'}$ = 7.5 Hz, 1 H, H-1′), 4.38 (m, 2 H, H-15, -16), 4.30 (d, J = 7.0 Hz, 1 H, H-33), 4.20 (br s, 2 H, H-14, OH), 4.00–3.30 (series of multiplets, 2 H, H-17, -25, -30, -31, -2′, -3′, -4′, -5′, -2″, -3″, -5″), 3.62, 3.60 and 3.54 (singlets, 3H each, OMe), 3.48 (s, 3 H, NMe), 3.22 (d, J = 9.5 Hz, 1 H, H-20), 3.20 (s, 3 H, 20-OMe), 3.01 (t, J = 8.5 Hz, 1 H, H-4″), 2.90 (d, J = 7.5 Hz, 1 H, OH), 2.64 (dd, J = 10.0, 3.5 Hz, 1 H, H-28), 2.54 (s, 1 H, OH), 2.40 and 2.34 (doublets, J = 7.0 Hz, 1 H each, OH), 2.15 (s, 3 H, OAc), 2.15 (m, 1 H, H-19), 2.02 (s, 3 H, 8-Me), 1.76 (dd, J = 7.0, 1.5 Hz, 3 H, H-39), 1.75 (m, 2 H, H-45), 1.68 (s, 3 H, 21-Me), 1.32 and 1.23 (doublets, J = 6.0 Hz, 3 H each, H-6′ and H-6″), 0.90 and 0.96 (singlets, 3 H each, 32-Me), 0.96 (obscured, 3 H, H-46), 0.88 (d, J = 7.5 Hz, 3 H, 19-Me). Anal. ($C_{61}H_{91}N_2O_{21}$) C,H,N.

Coupling of Advanced Intermediate I and Allylamine. Preparation of Compound 5. Allylamine (0.08 mL, 1.10 mmol) in dry methylene chloride (2 mL) was treated with trimethylaluminum (0.50 mL of a 2 M solution in toluene; 1.0 mmol) at room temperature. The solution was stirred for 15 min and then slowly added to a solution of lactone I (113 mg, 0.18 mmol) at 0 °C. The reaction mixture was brought to room temperature and stirred at that temperature overnight, whereupon it was poured into ethyl acetate (10 mL) and saturated sodium potassium tartrate (5 mL). The aqueous layer was separated and extracted with ethyl acetate (2 × 10 mL). Combining the extracts, drying over $MgSO_4$, removing the solvents under reduced pressure, and recrystallizing the residue (ether–hexane) afforded compound **5** (81 mg, 67%). **5**: mp 156–158 °C (from ether–hexane); R_f = 0.46 (silica, 5% methanol in ether); $[\alpha]^{24}_D$ -54.90° (c 1.13, $CHCl_3$); IR ($CHCl_3$ film) ν_{max} 3560 and 3440 (NH, OH), 3000, 2960, 1640 (amide), 1525, 1450, 1370, 1080, 1020 cm^{-1}; ^1H NMR 4.29 6.45 (dd, J = 15.0, 11.0 Hz, 1 H, H-2′), 6.00 (m, 3 H, H-4′, 3-OH, NH), 5.80 (m, 1 H, H-2″), 5.60 (dd, J = 15.0, 7.0 Hz, 1 H, H-1′), 5.46 (dd, J = 11.0, 7.5 Hz, 1 H, H-3′), 5.24 (dd, J = 17.0 0.2 Hz, 1 H, H-3″), 5.10 (dd, J = 10.0, 0.2 Hz, 1 H, H-3a″), 4.90 (d, J = 0.1 Hz, 1 H, H-1‴), 4.65 (d, J = 7.5 Hz, 1 H, H-1‴), 4.28 (d, J = 7.0 Hz, 1 H, H-6), 4.00–3.45 (multiplets, 10 H, H-1″, -3,-4,-2‴,-3‴,-5‴,-2⁗,-3⁗, -5⁗), 4.60, 4.56 and 4.29 (singlets, 3 H each, OMe), 3.40 (dd, J = 10.0, 2.0 Hz, 1 H, H-4‴), 3.02 (t, J = 9.0 Hz, 1 H, H-4⁗), 2.65 (dd, J = 10.0, 4.0 Hz, 1 H, $CHCH_2CH_3$), 2.58 (s, 1 H, OH), 2.50 and 2.38 (doublets, J = 8.0Hz each, 1 H each, OH), 1.75 (dd, J = 7.0, 1.5 Hz, 3 H, H-5′), 1.75 (obscured, 2 H, $CHCH_2CH_3$), 1.32 (d, J = 7.0 Hz, 3 H, H-6⁗), 1.21 (d, J = 7.0 Hz, 3 H, H-6‴), 0.98 and 0.91 (singlets, 3 H each, 5-Me), 0.89 (t, J = 5.0 Hz, 3 H, $CHCH_2CH_3$); HRMS calculated for $C_{34}H_{57}NO_{13}$ (M^+) 671.3877, found 671.3876.

Acknowledgment. We wish to express our many thanks to Drs. Huber Maehr, Hoffmann-La Roche, Nutley, New Jersey, and Dr. Georg Albers-Shonberg of Merck, Sharp + Dohme for generous samples of aurodox and efrotomycin, respectively, and for many helpful discussions on the chemistry of these natural products. Our thanks are also due to Drs. George Furst and Patrick Carroll and Margaret Davis of this department for their superb NMR and Mass spectroscopic and X-ray crystallographic assistance and useful comments. Finally, we acknowledge generous financial support of our programs by Merck, Sharp + Dohme, Smith, Kline + French, the Camille and Henry Dreyfus Foundation, the J. S. Guggenheim Foundation, and the National Institutes of Health.

A Convenient Synthesis of 4-Unsubstituted β-Lactams

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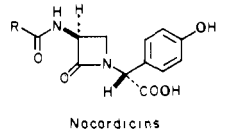
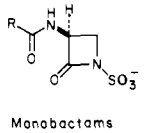
Abstract: The reaction of lithium ester enolates with *N*-(cyanomethyl)amines affords 4-unsubstituted β-lactams in good yields, see eq 1. The N-1 substituent can be varied widely, as can the C-3 substituents, which can be H, alkyl, SPh, NH_2, or NHCOR. The preparation of 3-amino-substituted β-lactams (**8–10**, **12**, **14–17**) in one step from *N*-(cyanomethyl)amines and esters of α-amino acids is a particularly significant feature of this new β-lactam synthesis. Enantiomerically pure 3-amino-substituted β-lactams, with either the 3*R* (**19** and **21**) or 3*S* (**23** and **24**) configuration, can also be prepared from the chiral, nonracemic, *N*-(cyanomethyl)amines. The asymmetric induction observed in the reactions of these latter *N*-(cyanomethyl)amines with the lithium enolate of **14** is rationalized by a chelated transition state **26**.

The powerful antibiotic activity of the nocardicins and monobactams[1] against Gram negative organisms has highlighted the importance of developing new efficient procedures for preparing monocyclic 4-unsubstituted β-lactams.[2] Gilman was the first to



Nocardicins



Monobactams

describe the formation of β-lactams from the reaction of ester enolates with imines.[3] Although this reaction has proven to be a useful method for preparing substituted β-lactams,[4,5] in particular β-lactams containing aryl substituents at *N*-1 and C-4, it has not been utilized to prepare 4-unsubstituted β-lactams[6] due to the inaccessibility of monomeric formaldehyde imines.[7] We recently disclosed that unstable formaldehyde imines could be generated

(1) For recent reviews, see the following. (a) Nocardicins: Kamiya, T.; Aoki, H.; Mine, Y. In "Chemistry and Biology of β-Lactam Antibiotics"; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vol. II, Chapter 3. (b) Monobactams: Koster, W. H.; Cimarusti, C. M.; Sykes, R. B. *Ibid.*, Vol. III, Chapter 7.

(2) For a recent comprehensive review of β-lactam synthesis, see: Koppel, G. A. In "Small Ring Heterocycles—Azetidines, β-Lactams, Diazetidines, and Diaziridines"; Hassner, A., Ed.; Wiley: New York, 1983; Chapter 2.

(3) Specifically Reformatksy reagents: Gilman, H.; Speeter, M. *J. Am. Chem. Soc.* **1943**, *65*, 2255.

(4) For reviews, see: (a) ref 2, pp 337–359. (b) Gaudemar, M. *Organomet. Chem. Rev. A* **1972**, *8*, 183.

(5) For recent examples, see: (a) Gluchowski, C.; Cooper, L.; Bergbreiter, D. E.; Newcomb, M. *J. Org. Chem.* **1980**, *45*, 3413. (b) Bose, A. K.; Khajavi, M. S.; Manhas, M. S. *Synthesis* **1982**, 407. (c) Barrett, A. G. M.; Quayle, P. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2193. (d) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T.-K. *J. Org. Chem.* **1983**, *48*, 289. (e) Bose, A. K.; Gupta, K.; Manhas, M. S. *J. Chem. Soc., Chem. Commun.* **1984**, 86. (f) Ikeda, K.; Yoshinaga, Y.; Achiwa, K.; Sekiya, M. *Chem. Lett.* **1984**, 369. (g) Liebeskind, L. S.; Welker, M. E.; Goedken, V. *J. Am. Chem. Soc.* **1984**, *106*, 441. (h) Georg, G. I. *Tetrahedron Lett.* **1984**, *25*, 3779. (i) Ha, D.-C.; Hart, D. J.; Yang, T.-K. *J. Am. Chem. Soc.* **1984**, *106*, 4819.

(6) 4-Unsubstituted β-Lactams have been prepared from hexahydrotriazines by reaction with a Lewis acid followed by treatment with an acid chloride and pyridine,[6a] or from the reaction of the derived *N*-(chloromethyl)carbamates with silyl ketene acetals[6b]: (a) Kamiya, T.; Oku, T.; Nakaguchi, O.; Takeno, H.; Hashimoto, M. *Tetrahedron Lett.* **1978**, 5119. (b) Ikeda, K.; Terao, Y.; Sekiya, M. *Chem. Pharm. Bull.* **1981**, *29*, 1747.

(7) For recent methods for generating these intermediates in situ, see: (a) Overman, L. E.; Burk, R. M. *Tetrahedron Lett.* **1984**, *25*, 1635. (b) Barleunga, J.; Bayon, A. M.; Asensio, G. *J. Chem. Soc., Chem. Commun.* **1983**, 1109; **1984**, 427.

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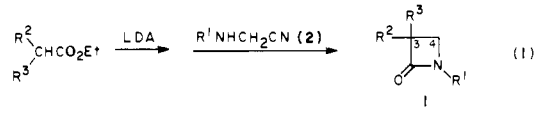
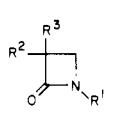
in situ from the reaction of secondary *N*-(cyanomethyl)amines with organolithium or Grignard reagents.[7a] In this short article we report that a wide variety of 4-unsubstituted β-lactams **1** can be prepared in *one step* from the reaction of lithium ester enolates and secondary *N*-(cyanomethyl)amines (**2**, eq 1). Biologically



important β-lactams **1** with nitrogen substituents at C-3 can be readily assembled in this way from amino acid precursors, and optically active β-lactams can be prepared from *N*-(cyanomethyl)amines derived from certain enantiomerically pure primary amines.

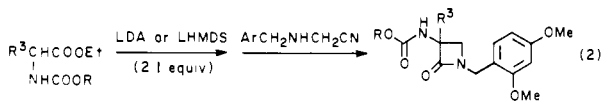
The general method is illustrated by the preparation of the known[8] β-lactam **3**. The lithium enolate of ethyl isobutyrate (0.2

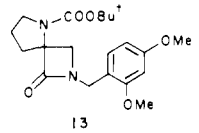


3, $R^1 = CH_2Ph$, $R^2 = R^3 = Me$ 66%
4, $R^1 = Ph$, $R^2 = R^3 = Me$ 77%
5, $R^1 =$  , $R^2 = R^3 = Me$ 66%
6, $R^1 = CH_2Ph$, $R^2, R^3 = -(CH_2)_5$ 65%
7, $R^1 = CH_2Ph$, $R^2 = Me$, $R^3 = SPh$ 62%

M in 10:1 THF–hexane) was generated at −70 °C with lithium diisopropylamide (LDA)[9] and treated at this temperature with 0.48 equiv of (benzylamino)acetonitrile (**2**, $R^1 = CH_2Ph$).[10] After 1 h at −70 °C, the reaction was allowed to warm to room temperature, and after 20 h, it was quenched with aqueous NH_4Cl. Purification on silica gel gave 1-benzyl-3,3-dimethyl-2-azetidinone (**3**)[8] in 66% yield based on **2**. Quenching this reaction after ~1 h at −40 °C afforded substantial amounts of ethyl 3-(benzylamino)-2,2-(dimethyl)propionate in addition to β-lactam **3**. Many other β-lactams can be prepared in a similar fashion, and **4**–**7**[11,12] are representative.

Similar reaction of the dianion[13] of a *N*-BOC- or *N*-Cbz-protected α-amino ester affords 3-(acylamino)-4-unsubstituted β-lactams in good yields (eq 2). For example, β-lactams **8**–**11**[12]



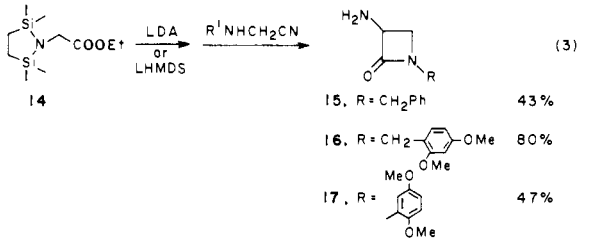


13

8, $R = CH_2Ph$, $R^3 = Me$ 74%
9, $R = Bu^t$, $R^3 = Me$ 60%
10, $R = Bu^t$, $R^3 = CHMe_2$ 45%
11, $R = CH_2Ph$, $R^3 = H$ 63%

were prepared from [(2,4-dimethoxybenzyl)amino]acetonitrile (**12**)[10,12] and N-protected esters of alanine, valine, and glycine, respectively. The related reaction of the lithium enolate of ethyl *N*-(*tert*-butoxycarbonyl)-L-prolinate with **12** provided the unusual spirocyclic β-lactam **13**[12] in 64% yield. For these reactions, it was advantageous to use lithium bis(trimethylsilyl)amide (LHMDS) as the base and quench the reaction after 3 h at −20 to −25 °C with acetic acid. Removal of the 2,4-dimethoxybenzyl group from **11** by treatment with ceric ammonium nitrate[14] gave 3-(benzyloxycarbonyl)-2-azetitinone (78% yield), an intermediate which has been previously utilized to prepare monobactams.[15]

An alternate method for preparing 3-amino-substituted β-lactams having a hydrogen substituent at C-3 is to utilize the lithium enolate (from LHMDS or LDA) of the silyl-protected[16] glycine ester **14** (eq 3). Quenching the reaction of eq 3 at room

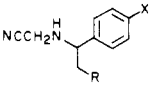


14

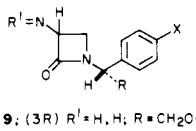
15, $R = CH_2Ph$ 43%
16, $R = CH_2$ 80%
17, $R =$ 47%

temperature with aqueous NH_4Cl followed by purification on silica gel[17] provided directly the 3-amino β-lactams **15**–**17**.[12]

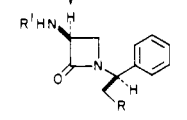
Enantiomerically pure 4-unsubstituted β-lactams also can be prepared by this method. Reaction of the (*R*)-cyanoamine **18** (>95% ee)[18a,19] with 2.1 equiv of the lithium salt of **14** (−70 → 23 °C in THF) gave the (*R*),(*R*)-β-lactam **19**[12] [$[\alpha]^{25}_D$ −31.6° (*c* 1.05, $CHCl_3$); >95% ee[19]] in 72% yield and 11:1 diastereoselectivity. The stereochemical assignment for **19** is based on the chemical shift of the C-4 hydrogens (α C-4 *H*: δ 3.06, dd, J = 2.3, 5.6 Hz; β C-4 *H*: δ 3.45, app t, $J \sim 5.5$ Hz) which differ from those of the (*S*),(*R*)-diastereomer (δ 2.89, dd, J = 2.3, 5.5 Hz; δ 3.54, app t, $J \sim 5.5$ Hz) in the same diagnostic way as the diastereomers of 3-aminonocardicinic acid precursors.[6a,20] Asymmetric induction was similar with the methoxymethyl ether



18, (R) R = X = OCH_2Ph
20, (R) R = OCH_2OMe, X = OCH_2Ph
22, (S) R = OCH_2Ph, X = H



19; (3R) R^1 = H, H; R = CH_2OCH_2Ph, X = OCH_2Ph
21; (3R) R^1 = H, H; R = CH_2OCH_2OMe, X = OCH_2Ph
24; (3S) R^1 = H, $COOBu^t$; R = CH_2OCH_2Ph, X = OCH_2Ph
25; (3S) R^1 = Ft; R = COOH; X = OH



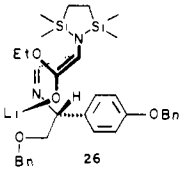
23, R^1 = H, R = OCH_2Ph

derivative **20**, which gave **21**[12] and its C-3 diastereomer in a 11:1 ratio (54% yield). β-Lactams with the natural 3*S* configuration could be prepared in a similar fashion from (*S*)-cyanoamine **22**

(8) Okawara, T.; Matsuda, T.; Furukawa, M. *Chem. Pharm. Bull.* **1982**, *30*, 1225.
(9) Rathke, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3222.
(10) Baker, W.; Ollis, W. D.; Poole, V. D. *J. Chem. Soc.* **1949**, 307. New secondary *N*-(cyanomethyl)amines were prepared from the corresponding primary amine by standard procedures, see footnote 5 of ref 7.
(11) B-Lactam **4** was prepared from *N*-(benzotriazolmethyl)aniline,[7] rather than from the corresponding cyanomethyl derivative.
(12) New β-lactams showed IR, 250-MHz, ^1H NMR, ^{13}C NMR, and mass spectra consistent with their assigned structures.
(13) (a) For previous reactions of dianions of this general type, see, inter alia: Krapcho, A. P.; Dundulis, E. A. *Tetrahedron Lett.* **1976**, 2205. Shanzer, A.; Somekh, L.; Butina, D. *J. Org.* Chem. **1979**, *44*, 3967. (b) Bartlett, P. A.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3933. (c) For the related preparation of 4-aryl β-lactams, see ref 5b.
(14) Huffman, W. F.; Holden, K. G.; Buckley, T. F., III; Gleason, J. G.; Wu, L. *J. Am. Chem. Soc.* **1977**, *99*, 2352.
(15) Cimarusti, C. M.; Applegate, H. E.; Chang, H. W.; Floyd, D. M.; Koster, W. H.; Slusarchyk, W. A.; Young, M. G. *J. Org. Chem.* **1982**, *47*, 179.
(16) Djaric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.* **1981**, *22*, 1787.
(17) Rapid flash chromatography of these free amines was not complicated by dimerization to form diketopiperazines.
(18) Prepared by standard methods from (a) (*R*)-(−)-4-hydroxyphenylglycine [$[\alpha]^{23}_D$ −156° (*c* 1, 1 N HCl)] or (b) (*S*)-(+)-α-phenylglycine [$[\alpha]^{20}_D$ +156° (*c* 1, 1 N HCl)]. See: Koppel, G. A.; McShane, L.; Jose, F.; Cooper, R. D. G. *J. Am. Chem. Soc.* **1978**, *100*, 3933. Poindexter, G. S.; Meyers, A. I. *Tetrahedron Lett.* **1977**, 3527.
(19) The enantiomeric purity of this intermediate was determined by the method of Mosher: Mosher, H. S.; Dale, J. A.; Dull, D. L. *J. Org. Chem.* **1969**, *34*, 2543. The Mosher ester of the racemic amine precursor of **18**, as well as racemic β-lactam **19**, showed clearly separated signals for the diastereomers in the 250-MHz ^1H NMR spectrum. When none of the minor diastereomer could be detected, we estimate the enantiomeric purity to be >95%.
(20) See: (a) Kamiyo, T.; Hashimoto, M.; Nakaguchi, O.; Oku, T. *Tetrahedron* **1979**, *35*, 323. (b) Wasserman, H. H.; Hlasta, D. J.; Tremper, A. W.; Wu, J. S. *Ibid.* **1981**, *46*, 2999, ref 6a.

(>95% ee).[12,18b,19] Thus, the reaction of **22** with the lithium salt of **14** proceeded with 10:1 selectivity to give the (*S*),(*S*)-β-lactam **23**[12] [$[\alpha]^{25}_D$ + 28.5° (*c* 1.02, $CHCl_3$); ^1H NMR δ 3.07 (dd, *J* = 5.2, 2.4 Hz), 3.51 (app t, *J* ~ 5.3 Hz); >95% ee[19]] in 65% yield. We have not yet succeeded in obtaining similarly high diastereoselectivities in the reaction of lithium dianions[13,21] of α-(acylamino) esters with (*R*)-cyanoamine **18**. Reaction (−70 → 23 °C, THF, 51%) of the dilithium salt of ethyl *N*-(*tert*-butoxycarbonyl)glycinate with **18** did provide the (*S*),(*R*)-β-lactam **24** [^1H NMR δ 3.06 (dd, *J* = 5.5, 2.3 Hz), 3.59 (m)] as the major product; however, the stereoselectivity was only 2:1.[21] Nonetheless, this mixture was useful in confirming stereochemical assignments in this series, since the β-lactam products could be correlated in four steps[22a] with N-(phthalamido)nocardicinic acid (**25**), and C-3 *epi*-**25**.[20a,22b]

The stereoselectivity[23] observed in the reaction of the lithium enolate of **14** with the formaldehyde imines generated from **18**, **20**, and **22** is consistent with the chelated transition state **26**. That kinetic enolization of **14** proceeded with high selectivity to yield the (*Z*)-enolate[26] was confirmed by trapping this intermediate with Me_3SiCl.[27]



26

In summary, the β-lactam synthesis we have developed allows a variety of 3-amino- and 3-acylamino-substituted monocyclic β-lactams to be conveniently prepared in optically active form from α-amino acid precursors. The preparation of monocyclic β-lactams with substituents at C-4 and the preparation of optically active β-lactams from nonracemic chiral metal enolates[28] is currently under investigation.

Representative Experimental Procedures[29]

1-Benzyl-3,3-dimethyl-2-azetidinone (3). To a solution of diisopropylamine (0.81 mL, 5.80 mmol) and THF (20 mL) cooled to −70 °C was added *n*-BuLi (2.4 mL of a 2.2 M solution in hexane, 5.3 mmol). The resulting solution was stirred for 30 min at −70 °C, and then a solution of ethyl isobutyrate (614 mg, 5.29 mmol) and THF (5 mL) was added dropwise. The resulting solution was stirred for 1 h at −70 °C, and then a solution of (benzylamino)acetonitrile[10] (370 mg, 2.53 mmol) and THF (5 mL) was added dropwise. After 1 h at −70 °C, the reaction mixture was allowed to warm up to room temperature, and after 20 h it was quenched by adding excess solid NH_4Cl and H_2O. The quenched reaction mixture was extracted with $CHCl_3$, and the organic extract was washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography (silica gel, 96:4 hexane–acetone) afforded 317 mg (66%) of the known[8] β-lactam **3** as a colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.20–7.40 (m, NCH_2Ph), 4.34 (s, NCH_2Ph), 2.91 (s, C-4 CH_2), 1.30 (s, C-3 Me); ^{13}C NMR (63 MHz, $CDCl_3$) δ 174.1, 136.2, 129.0, 128.3, 127.8, 54.1, 51.1, 45.8, 21.3; IR ($CHCl_3$) 1738 cm^{-1}; MS (CI) *m/e* 190 (MH).

3-[(Benzyloxycarbonyl)amino]-1-(2,4-dimethoxybenzyl)-2-azetidinone (11). A solution of $(Me_3Si)_2NLi$ [prepared from Me_3SiNH (0.58 mL, 2.74 mmol) and *n*-BuLi (0.99 mL of a 2.5 M solution in hexane, 2.5 mmol) in THF (12 mL) at −70 °C] was added at −70 °C to a solution of ethyl *N*-(benzyloxycarbonyl)glycinate (294 mg, 1.24 mmol) and THF (3 mL). After 1 h at −70 °C, a solution of [2,4-dimethoxybenzyl)-amino]acetonitrile[10] (122 mg, 0.59 mmol) and THF (3 mL) was added at −70 °C and the resulting solution maintained at this temperature for 1 h and then at −20 to −25 °C for 3 h. After neutralizing the solution with HOAc in THF, it was poured into ice water and extracted with $CHCl_3$. The organic extract was washed with brine, dried (Na_2SO_4), and concentrated, and the residue was purified by flash chromatography (silica gel, $CHCl_3$) to give 138 mg (63%) of **11** as a colorless solid. Recrystallization from ethyl acetate–hexane gave an analytical specimen of fine needles: mp 102–104 °C; ^1H NMR ($CDCl_3$) δ 7.33 (br s, OCH_2Ph), 7.12 (br d, *J* = 8.9 Hz, C-6 Ar*H*), 6.43 (m, 2H, Ar*H*), 5.62 (m, NH), 5.09 (s, CH_2Ph), 4.79 (m, C-3 H), 4.33 (m, NCH_2Ph), 3.80 (s, two OMe), 4.43 (m, C-4 H), 3.08 (m, C-4 H); IR ($CHCl_3$) 3443, 1760, 1727 cm^{-1}; MS(CI) *m/e* 371 (MH), 263, 261, 151.

Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.95; H, 6.02; N, 7.55.

3-Amino-1-(2,4-dimethoxybenzyl)-2-azetidinone (16). *n*-BuLi (1.98 mL of a 2.5 M solution in hexane, 5.0 mmol) was added to the solution of hexamethyldisilazane (1.15 mL, 5.48 mmol) and THF (24 mL) at −70 °C. After the solution was stirred at this temperature for 30 min, a solution of ethyl 2-(2,2,4,4-tetramethyl-2,5-disilylazacyclopentyl)-glycinate (**14**)[16] (1.21 g, 4.96 mmol) and THF (6 mL) was added dropwise. After an additional 1 h of stirring at −70 °C, a solution of [(2,4-dimethoxybenzyl)amino]acetonitrile[10] (486 mg, 2.36 mmol) and THF (6 mL) was added dropwise. The resulting solution was maintained at −70 °C for 2 h, allowed to warm to room temperature, and after 20 h quenched with solid NH_4Cl and H_2O. The reaction mixture was then poured into ice water, and the product was isolated with $CHCl_3$. The $CHCl_3$ extract was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (silica gel, 99:1 $CHCl_3$/MeOH)[17] to give 449 mg (80%) of **16** as a pale yellow oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.9 Hz, C-6 ArH), 6.46 (d, *J* = 2.5 Hz, C-3 ArH), 6.44 (dd, *J* = 8.9, 2.5 Hz, C-5 ArH), 4.31 (app br s, NCH_2Ph), 4.10 (m, C-3 H), 3.80 (s, OMe), 3.81 (s, OMe), 3.40 (app t, *J* = 5.3 Hz, C-4 H), 2.87 (dd, *J* = 5.3, 2.2 Hz; C-4 H), 1.72 (br s, NH_2); IR ($CHCl_3$) 1747 cm^{-1}; MS (CI) *m/e* 237 (MH), 193, 151. Acylation of this material with benzyloxycarbonyl chloride gave **11**, mp 102–104 °C.

3(*R*)-Amino-1-[2-benzyloxy-1(*R*)-(4-benzyloxy)phenylethyl]-2-azetidinone (19). A solution of ethyl 2-(2,2,4,4-tetramethyl-2,5-disilylazacyclopentyl)glycinate[16] (**14**) (607 mg, 2.40 mmol) and THF (3 mL) was treated at −70 °C with $(Me_3Si)_2NLi$ [prepared from $(Me_3Si)_2NH$ (0.58 mL, 2.76 mmol) and *n*-BuLi (0.99 mL of a 2.5 M solution in hexane, 2.5 mmol) in THF (12 mL) at −70 °C]. After 1 h at −70 °C, a solution of [(2-benzyloxy)-1(*R*)-(4-benyloxy)phenyl)ethyl]aminoacetonitrile[10,18] (440 mg, 1.18 mmol) and THF (3 mL) was added and the resulting solution maintained at −70 °C for 2 h and then at room temperature for 20 h. The reaction was quenched with solid NH_4Cl and extracted with $CHCl_3$. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated, and the residue was purified by flash chromatography (silica gel, 98:2 $CHCl_3$–MeOH)[17] to give 342 mg (72%) of the product azetidinone as a pale yellow oil. The 250-MHz ^1H NMR spectrum showed that this sample was contaminated with 9% of the C-3 diastereoisomer.

An analytical sample of **19** was obtained by acylating a 1.07-g (2.6 mmol) sample of comparable material with di-*tert*-butyl dicarbonate (648 mg, 2.86 mmol) in CH_2Cl_2 (5 mL, 0 °C, 48 h). Concentration, followed by purification of the residue on silica gel (70:30:1 hexane–ethyl acetate–triethylamine), gave 1.21 g (91%) of the crystalline *N*-(*tert*-butoxycarbonyl) derivative. Two recrystallizations from ethyl acetate–hexane gave an isomerically pure sample (470 mg)[30] of this derivative: mp 131–132 °C; MS (CI) *m/e* 503 (MH), 447, 403, 375, 149.

(21) The stereoselective formation of enolates of this type (the enolate oxygen and the anionic acylamido substituent are cis) has been described.[13b] The low diastereoselectivities we observe may result from partial epimerization of the β-lactam products, or β-amino ester intermediates, under the strongly basic reaction conditions.

(22) (a) CF_3COOH, anisole (75%); *N*-(carboethoxy)phthalimide (85%); 10% Pd–C/MeOH/$CHCl_3$; Jones reagent (~40%). (b) ^1H NMR (Me_2SO-d_6),[20a] **25**: 3.40 (dd), 3.98 (t). 3-*epi*-**25**: 4.04 (dd), 3.67 (t); chemical shifts were concentration dependent. Unfortunately, we were unsuccessful in obtaining comparison samples of **25** or 3-ANA.

(23) Diastereoselectivities lower than those we observe were seen in a previous study of the reaction of optically active imines with Reformatsky reagents.[24] Excellent diastereoselectivities have been reported for the acid-catalyzed reaction of chiral imines with silyl ketene acetals.[25]

(24) Furukawa, M.; Okawara, T.; Noguchi, Y.; Terawaki, Y. *Chem. Pharm. Bull.* **1978**, *26*, 260.

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(26) This would be expected if the (tetramethyldisilyl)azacyclopentyl substituent behaves as a typical large substituent: Heathcock, C. H. In "Comprehensive Carbanion Chemistry"; Durst, T., Buncel, E., Eds.; Elsevier: New York, 1981; Chapter 4.

(27) The major ketene silyl acetal showed diagnostic ^1H NMR signals at δ 4.67 (s, =CH) and 3.81 (q, *J* = 7.1 Hz, OCH_2). A small (~5%) quartet signal for what could be the (*E*)-stereoisomer was also observed at δ 4.13. Irradiation of the vinyl singlet at δ 4.67 resulted in nuclear Overhauser enhancement of the Me_2Si and Me_3Si signals at 0.21 and 0.08 ppm; the OCH_2 absorption was unchanged.

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(29) General experimental details can be found: Overman, L. S.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192. Overman, L. E.; Lesuisse, D.; Hashimoto, M. *Ibid.* **1983**, *105*, 5373.

(30) No attempt was made to optimize the yield of this recrystallization.

Anal. Calcd for $C_{30}H_{34}N_2O_5$: C, 71.69; H, 6.82; N, 5.57. Found: C, 71.77; H, 6.87; N, 5.51.

Deprotection of a 388-mg sample of this pure *N*-(*tert*-butoxy)carbonyl derivative of **19** by treatment at 0 °C with a solution of CF_3COOH (3 mL), CH_2Cl_2 (3 mL), and anisole (500 mg) gave, after purification on silica gel (99:1 $CHCl_3$–MeOH), 297 mg of pure **19** as a colorless powder: ^1H NMR (250 MHz, $CDCl_3$) δ 7.17–7.42 (m, 12 H, ArH), 6.19–6.96 (m, 2 H, ArH), 5.03 (s, OCH_2Ph), 4.89 (dd, J = 5.0, 8.5 Hz, NC*H*ArH), 4.57 (AB quartet, OCH_2Ph), 4.08 (dd, J = 2.3, 5.4 Hz, C*H*NH_2), 3.95 (dd, J = 10.1, 8.5 Hz, C*H*HOBn), 3.76 (dd, J = 10.1, 5.0 Hz, CH*H*OBn), 3.45 (app t, J = 5.5 Hz, β C-4 H), 3.06 (dd, J = 2.3, 5.6 Hz, α C-4 H), 1.92 (br s, NH_2); IR ($CHCl_3$) 1761 cm^{-1}; MS (CI) m/e 403 (MH), 375.

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Registry No. 2 (R^1 = CH_2Ph), 3010-05-7; **2** (R^1 = Ph), 3009-97-0; **2** (R^1 = cyclohexyl), 1074-58-4; **2** (R^1 = 2,5-$(MeO)_2C_6H_3$), 94459-25-3; **3**, 77564-97-7; **4**, 27983-93-3; **5**, 28002-72-4; **6**, 94459-04-8; (±)-**7**, 87568-29-4; (±)-**8**, 94459-05-9; (±)-**9**, 94459-06-0; (±)-**10**, 94459-07-1; (±)-**11**, 94459-08-2; (±)-**11** (1-debenzylated derivative), 87637-98-7; **12**, 94459-09-3; **13**, 94459-10-6; **14**, 78605-23-9; (±)-**15**, 94459-11-7; (±)-**16**, 94459-12-8; (±)-**17**, 94459-13-9; **18**, 94459-14-0; **19**, 94459-15-1; **19** (R^1 = H, COOBu-*t*), 94459-21-9; **20**, 94459-16-2; **21**, 94459-17-3; **22**, 94459-18-4; **23**, 94459-19-5; **24**, 94459-20-8; (3*R*)-**24**, 94459-21-9; **29**, 71336-86-2; (3*R*)-**25**, 94459-22-0; Me_2CHCO_2Et, 97-62-1; (±)-MeCH(SPh)CO_2Et, 94535-33-8; DL-CbzNHCH(Me)CO_2Et, 72604-33-2; DL-BOCNHCH(Me)CO_2Et, 72604-32-1; DL-DOCNHCH($CHMe_2$)CO_2Et, 94459-23-1; $CbzNHCH_2CO_2Et$, 1145-81-9; $BOCN^-CH^-CO_2Et{\cdot}2Li^+$, 94459-26-4; ethyl cyclohexanecarboxylate, 3289-28-9; ethyl *N*-(*tert*-butoxycarbonyl)prolinate lithium enolate, 94459-24-2; (*R*)-(−)-4-hydroxyphenylglycine, 22509-74-6; (*S*)-(+)-α-phenylglycine, 2935-35-5; *N*-(carboethoxy)phthalimide, 22818-40-2.

Stable Simple Enols. 9.[1] Solid State Structures and Conformations of Several Simple Enols and Their Keto Tautomers

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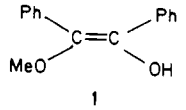
Abstract: The structures of the enols trimesitylethenol (**2**), (*Z*)-1,2-dimesityl-2-phenylethenol (**4**), their keto isomers **5** and **6**, the ethanolate of 1-(9-anthryl)-2,2-dimesitylethenol (**3**), and trimesitylethylene (**7**) were determined by X-ray crystallography. The structures of **2–4** are the first ones determined for *simple* enols, and the structural effects of crowding on bond lengths and angles are discussed. The main features of the solid-state conformations are consistent with and reinforce those found in solution as follows: (a) Compounds **2–7** have propeller structures where all the rings are twisted from the reference plane in the same direction, corroborating static and dynamic NMR data in solution. The torsional angles of the rings in the vinyl propellers which were compared with literature values can be correlated with the rotational barriers for the enantiomerization in solution. (b) The OH group of **2** is in a syn-periplanar conformation in the direction of the cis-β-mesityl group, while that of **3** is in anti-periplanar conformation due to hydrogen bonding to an ethanol of crystallization. This is in line with the conformational dependence of the enolic OH geometry in solution on hydrogen bonding to the solvent or to the β-mesityl group. (c) The HCCO torsional angles in **5** and **6** are 177.4° and −157.8°, in agreement with the conformation suggested from UV spectra for bulky ketones in solution. (d) The α-ArCO torsional angle in **5** is 47.7°, a value lower than for formally less bulky α-aryl ketones, but in line with UV data in solution.

Remarkable progress in the preparation and reactions, especially ketonization, of simple ions (i.e., enols substituted only by hydrogens, alkyl, or aryl groups, but not by strongly electron-withdrawing substituents such as CO, CN, SO_2R, etc.) has been achieved in recent years.[2–4] Structural data are available for vinyl alcohol in the gas phase from microwave[5a] and infrared spectra[5b] or from MM and MO calculations[6] and for its radical ion from photoelectron spectroscopy.[7] The conformation of the OH group in solution in relation to the double bond was deduced from ^3J(HCOH) and ^4J(HC=COH) coupling constants[2c,d,8,9] or from IR studies.[9,10] Only four structures of aryl-substituted enols were determined in the solid state by X-ray crystallography[11] but all the compounds were substituted by electron-withdrawing (e.g., C=N, C=O) groups. Even the "simplest" one, i.e., **1**,[11d] is not



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"simple" by the definition above, due to the electron-withdrawing MeO group and to the strong intramolecular hydrogen bonding, which increase the enol stability and enable its isolation.

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