mmol), palladium dichloride (0.026 g, 0.14 mmol), 1,3-bis(diphenylphosphino)propane (0.055 g, 0.13 mmol), and anhydrous sodium formate (0.103 g, 1.52 mmol) were loaded into a 20-mL Pyrex sleeve under dry nitrogen. The mixture was then suspended in 10 mL of a degassed 1:1 DMF/toluene mixture, and the atmosphere above the suspension was replaced with CO by repetitively pressurizing the reactor with CO to 200 psig and then releasing pressure in a well-ventilated hood. The reaction vessel was pressurized to 650 psig with CO and heated in an oil bath to 120(± 10) °C for 50 h. After cooling the vessel to ambient temperature, excess CO was vented and 2 mL of 1 N HCl were added to the yellow-orange product mixture. The resultant biphasic mixture was filtered through a 1-cm pad of Celite to remove precipitated salts and palladium black, and the filter cake was rinsed with toluene (3 × 5 mL). The filtrate was washed with water (4 × 25 mL) to remove DMF and then extracted with 1 N KOH (4 × 25 mL). The combined extracts were rinsed with fresh toluene (1 × 10 mL) and then acidified to pH 1 with concentrated HCl. The precipitated acids were extracted into CH_2Cl_2 (3 × 20 mL), and the combined extracts were dried over anhydrous Na_2SO_4 (1 g). The CH_2Cl_2 solution was then filtered and the product acids were isolated by evaporation of solvent under reduced pressure.

Acknowledgment. We thank Professor E. J. Corey and Professor Jeffrey Schwartz for useful discussions and suggestions concerning this work.

Registry No. 1, 22204-53-1; **2a**, 129967-27-7; **2b**, 129967-28-8; **2c**, 129967-29-9; **2d**, 108781-66-4; **2e**, 129967-30-2; **4**, 3453-40-5; **7**, 84194-78-5; **8**, 26159-40-0; **9**, 3243-42-3; **10**, 84194-78-5; **11**, 26159-40-0; **12**, 21658-35-5; **13**, 129967-31-3; **14**, 130060-20-7.

Supplementary Material Available: Characterization data for optically active 1-arylethanols, optically active 1-arylethyl esters, and 2- and 3-arylpropanoic acids, table of aryl methyl ketone asymmetric hydroboration yields, and ^1H NMR spectra of 1-arylethanols (11 pages). Ordering information is given on any current masthead page.

Preparation of 3-Amino-4-(hydroxymethyl)azetidin-2-ones from the Reaction of Glycine Enolates with Imines of a Glycoaldehyde

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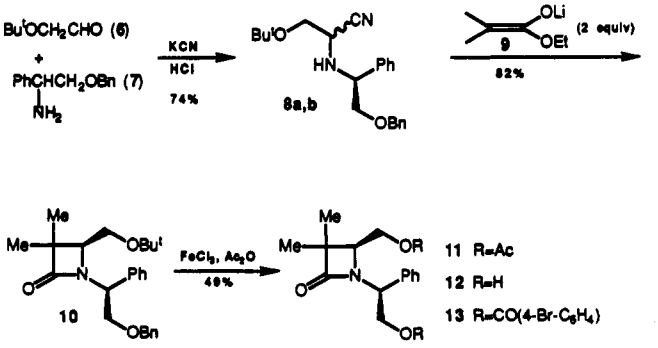
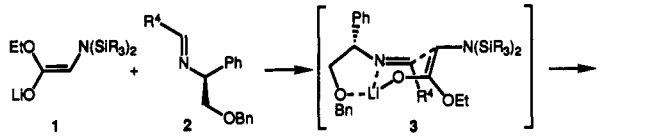
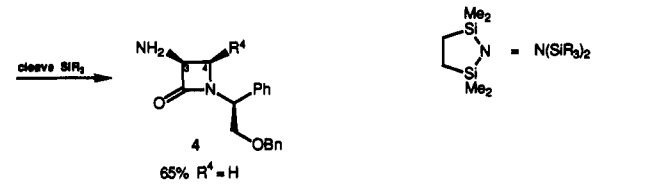
Received March 16, 1990

The preparation of β-lactams from the condensation of imines with metallo enolates (M = Al, B, Li, Mg, Sn, Zn, or Zr) has recently undergone a renaissance.[1] In an earlier disclosure from our laboratories, we reported that a wide variety of 4-unsubstituted β-lactams could be prepared in one step from the reaction of lithium ester enolates with formaldehyde imines, the latter intermediates being generated in situ from cyanomethyl amines.[2] Notably, 1,4-asymmetric induction in forming the C-3 stereogenic center was high (11:1) in condensations of the protected glycine enolate 1[3] with formaldehyde imines of phenylglycinol (e.g. 1, R^4 = H). Condensations of this type result in a useful asymmetric synthesis of 3-aminoazetidin-2-ones.[2] The stereoinduction observed in forming 4 (R^4 = H) was rationalized by a chelated closed transition state (3, R^4 = H).[2,4]

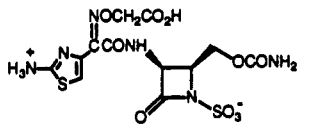
Scheme I







Stimulated by the clinical development of the monocyclic β-lactam carumonam (5),[5] we investigated the possibility of preparing 3-amino-4-(hydroxymethyl)azetidin-2-ones by related condensations of glycoaldehyde-derived imines (eq 1, R^4 = CH_2OR). If these condensations occurred in the sense suggested in transition-state model 3, the desired cis orientation of the β-lactam substituents at C-3 and C-4 would result. In this note we report the first examples of lithium ester enolate condensations of enolizable glycoaldehyde imines.[6,7]



carumonam (5)

Although a few examples of the successful addition of basic metallo ester enolates to enolizable imines have now

(1) For recent reviews, see: Brown, M. J. *Heterocycles* **1989**, *29*, 2225. Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447. Georg, G. I. In *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsvier: Amsterdam; 1989; Vol 4, pp 431-487. Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford; Vol. 2, in press.

(2) Overman, L. E.; Osawa, T. *J. Am. Chem. Soc.* **1985**, *107*, 1698.

(3) Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.* **1981**, *22*, 1787.

(4) For an excellent discussion of the possible transition states of ester enolate–imine condensations, see: Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.

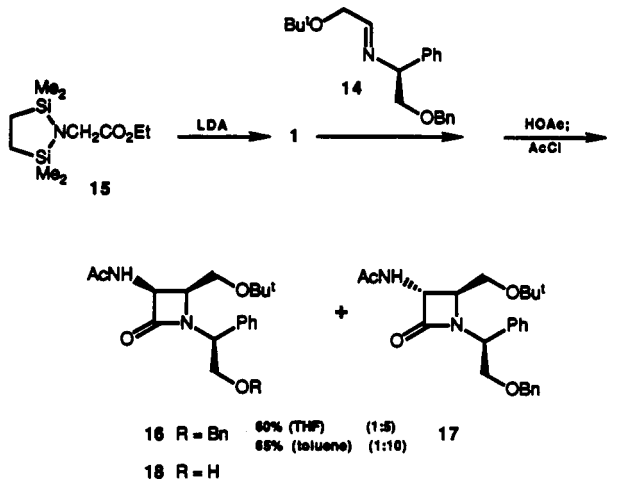
(5) (a) For recent summaries of clinical trials, see: Ashdown, L. R. *Antimicrob. Agents Chemother.* **1988**, *32*, 1435. Edelstein, H.; Oster, S.; Cassano, K.; McCabe, R. *Ibid.* **1988**, *32*, 1031. (b) For syntheses of (3*S*,4*S*)-3-amino-4-(hydroxymethyl)-2-azetidinones, see, inter alia: Thomas, R. C. *Tetrahedron Lett.* **1989**, *30*, 5239. Wei, C. C.; De Bernardo, S.; Tengi, J. P.; Borgese, J.; Weigele, M. *J. Org. Chem.* **1985**, *50*, 3462. Sendai, M.; Hashiguchi, S.; Tomitomo, M.; Kishimoto, S.; Matsuo, T.; Kondo, M.; Ochai, M. *J. Antibiotic.* **1985**, *38*, 346. Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783. Hubschwerlen, C.; Schmid, G. *Helv. Chim. Acta* **1983**, *66*, 2206.

(6) The reaction of lactate-derived imines with lithium ester enolates has been described: Cainell, G.; Panunzio, M.; Giacomini, D.; Martelli, G.; Spunta, G. *J. Am. Chem. Soc.* **1988**, *110*, 6879.

(7) Cinnamaldehyde imines have often been utilized as glycoaldimine equivalents, see, inter alia: Hart, D. J.; Lee, C.-S.; Pirkle, W. H.; Hyon, M. H.; Tsipouras, A. *J. Am. Chem. Soc.* **1986**, *108*, 6054. Georg, G. I.; Kant, J.; Gill, H. S. *Ibid.* **1987**, *109*, 1129.

0022-3263/91/1956-1933$02.50/0

Scheme II



been documented,[1] such additions are not common due to competing α-deprotonation of the imine. Thus, we initially examined the feasibility of employing imines derived from glycoaldehyde ethers in condensations with the lithium salt of ethyl isobutyrate (Scheme I). We have found that imines of this type are best generated in situ from the corresponding α-cyano amines. Conventional Strecker condensation[8] of *tert*-butoxyacetaldehyde (**6**)[9] with *O*-benzylphenylglycinol (**7**)[10,11] provided, in 74% yield, the crystalline cyano amines **8a** and **8b**. These epimers were readily separated by fractional crystallization. Condensation of either cyano amine stereoisomer with 2 equiv of enolate **9** proceeded with high 1,3-asymmetric induction to afford a single β-lactam (**10**) in good yield (82%). The reaction of **9** with the crude imine **14** (prepared from condensation of **6** and **7** at 0 °C) was less efficient with the yield varying widely as a function of imine purity. The stereochemistry of azetidinone **10** was secured by single-crystal X-ray analysis after appropriate derivatization. Treatment of **10** with $FeCl_3$ and acetic anhydride[12] resulted in the cleavage of both ethers to provide diacetate **11**. Deacylation[13] of **11** followed by esterification of diol **12** with *p*-bromobenzoyl chloride provided **13**, which readily yielded crystals suitable for X-ray analysis.[14]

To pursue the preparation of 3-amino-4-(hydroxymethyl)azetidin-2-ones, we examined the reaction of enolate **1** with imine **14** (Scheme II). This latter intermediate was available in crude form from the condensation at 0 °C of glycoaldehyde **6** and amine **7**. Analysis of this intermediate by ^1H NMR indicated that one imine (δ 7.86, CH=N), presumed to be the *E* stereoisomer, predominated to the extent of at least 8:1. β-Lactam formation was carried out by treatment of the silyl-protected glycine ester **15** with lithium diisopropylamide (LDA) at −20 °C in THF to form **1**, followed by addition (at this temperature) of 0.5 equiv of the crude imine **14**.[15] After allowing the reaction to warm to room temperature, 1 equiv of HOAc was added (to cleave the silyl protecting group) and the crude 3-amino-β-lactam products were acetylated to facilitate isolation and chromatographic separation. To our surprise, the major β-lactam **17** produced in this fashion (diastereoselection = 5:1) had the trans stereorelationship of the C-3 and C-4 substituents ($J_{3,4}$ = 2.1 Hz). That the minor isomer **16** ($J_{3,4}$ = 5.2 Hz) was epimeric only at C-3 was readily established by chemical interconversion. Thus, N-silylation of **16** followed by sequential treatment with LDA and HOAc yielded **16** and **17** in a 1:2 ratio, respectively.[16] X-ray analysis[14] of the crystalline alcohol **18**, obtained from **16** by hydrogenolysis, confirmed that **16** and **17** had the same relative orientation of the C-4 stereocenter and the phenylglycinol moiety as that found in the isobutyrate-derived β-lactam **10**. Although the **16**:**17** ratio was somewhat dependant upon solvent (e.g. 1:10 in toluene), we were unsuccessful in finding reaction conditions that favored formation of the cis stereoisomer **16**.[17]

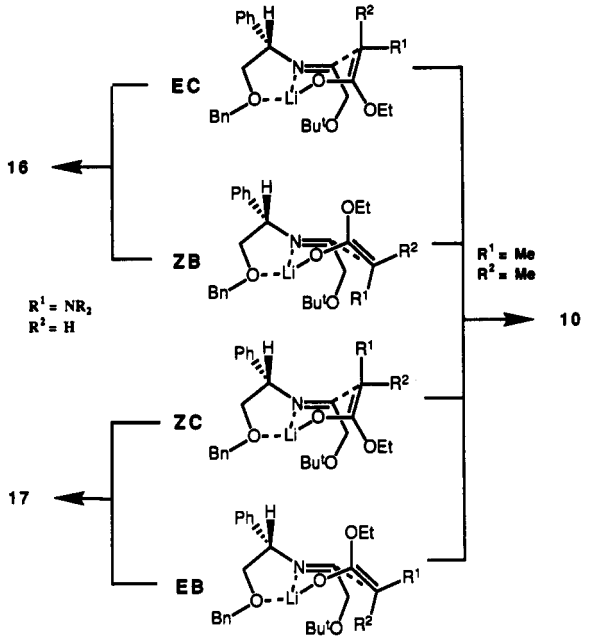


Figure 1. Four "closed" topographies for reaction of the *E* imine chelate.

The preferential formation of β-lactams **10**, **16**, and **17** with the *S**,*S** relative orientation of the C-4 substituent and the phenylglycinol moiety is consistent with the intervention of a chelated form of imine **2** similar to that previously proposed[2] for reactions of the related formaldehyde imine. This stereochemical outcome requires only that the lithium-chelated *E* imine[18] reacts with the enolate nucleophile from the chelate face opposite the phenyl group. Thus, any of the closed transition-state topographies illustrated in Figure 1 would rationalize the formation of the *S**,*S** β-lactam **10** from the reaction of imine **14** with the isobutyrate enolate **9**, as would any related open transition state.

Assuming that the observed β-lactam products result from kinetically controlled enolate–imine addition,[19-23] the

(8) (a) Mowry, D. T. *Chem. Rev.* **1948**, *42*, 189. (b) Kuffner, F.; Koechlin, W. *Monatsh. Chim.* **1962**, *93*, 476.
(9) Hoffmann, H. M. R.; Drischel, W.; Matthei, J. *Synthesis*, in press.
(10) Poindexter, G. S.; Meyers, A. I. *Tetrahedron Lett.* **1977**, 3527.
(11) Racemic phenylglycinol was employed in most of the exploratory studies reported in this note. Both enantiomers of this amine are commercially available.
(12) Ganem, B.; Small, V. R., Jr. *J. Org. Chem.* **1974**, *39*, 3728.
(13) Mori, K.; Tominaga, M.; Takigawa, T.; Matsui, M. *Synthesis* **1973**, 790.
(14) Full X-ray data are provided in the supplementary material.
(15) We anticipate that the yield of this condensation reaction would be improved by employing the cyano amines **8a,b** as in situ precursors of imine **14**.
(16) For an example of a similar epimerization sequence in a penicillin series, see: Vlietinck, A.; Roets, E.; Claes, P.; Janssen, G.; Vanderhaeghe, H. *J. Chem. Soc., Perkin Trans. I* **1973**, 937.
(17) These and other related experiments are described in the Ph.D Dissertation of M. J. Brown, University of California, Irvine, 1989.
(18) There is some evidence to indicate that both stereoisomeric Lewis acid complexes of aldehyde imines can participate in reactions with nucleophiles, see: Keck, G. E.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 146.

predominant formation of the trans β-lactam 17 from the reaction of glycine enolate 1 with 14 demonstrates that a EC transition state is of minor importance only (Figure 1). The preferential formation of 17 by a closed transition state requires either a boat topography (EB, Figure 1) or that the less predominant (by 20:1)[2] *Z*(Li)-enolate[24] is the more reactive (ZC, Figure 1)[25] and accessible from the *E*(Li) stereoisomer. The change in the sense of 1,4 asymmetric induction observed between the formaldehyde imine and glycoaldehyde imine cases would then be rationalized as arising from destabilizing steric interactions between the bulky siylamino and *tert*-butoxymethyl substituents in the closed EC transition state for reaction of the glycoaldimine.[26]

In summary, β-lactams with hydroxymethyl substitution at C-4 are formed in a single step in good yield by lithium ester enolate condensations of the glycoaldehyde-derived imine 14. Significantly, these reactions occur with minimal competing enolization of the glycoaldimine. Imine 14 is most conveniently generated in situ from the corresponding α-cyano secondary amines **8a,b**. Asymmetric induction in forming the C-4 stereocenter of the β-lactam ring is excellent; however, condensations of the silyl glycinate enolate 1 with 14 afford preferentially β-lactams with the trans relationship of the amino and hydroxymethyl substituents.

Experimental Section[27]

***N*-[2-(1,1-Dimethylethoxy)ethylidene]-2-(benzyloxy)-1-phenylethylamine (14).** To a rapidly stirring mixture of 2-(benzyloxy)-1-phenylethylamine (1.1 g, 4.9 mmol),[10] dry Et_2O (50 mL), $MgSO_4$ (2 g), and Na_2SO_4 (2 g) at 0 °C was added (1,1-dimethylethoxy)acetaldehyde (0.57 g, 4.9 mmol).[9] After being stirred for 1 h at 0 °C, the mixture was filtered through a sintered glass funnel and concentrated to give 1.4 g (89%) of crude **14** as a clear oil. Analysis by ^1H NMR showed that this material was ~80% pure. Attempted distillation led to extensive decomposition; repetition of the procedure on other occasions offered less pure imine. Characterization data for crude **14**: ^1H NMR (250 MHz, C_6D_6) δ 7.86 (t, *J* = 4.1 Hz, CH=N), 7.04–7.45 (m, Ph), 4.37 (dd, *J* = 4.2, 8.8 Hz, NC*H*Ph), 4.21–4.33 (m, CH_2Ph), 4.10 (dd, *J* = 4.1, 13.0 Hz, C*H*HOBu^t), 3.99 (dd, *J* = 4.0, 13.0 Hz, CH*H*OBu^t), 3.73 (app t, *J* = 9.5 Hz, C*H*HOBn), 3.59 (dd, *J* = 4.3, 9.6 Hz, CH*H*OBn), 1.02 (s, C$(CH_3)_3$); IR (film) 1675 cm^{-1}; HRMS (EI) *m/z* 325.2028 (325.2042 calcd for $C_{21}H_{27}NO_2$).

2(*R)-[[2-(Benzyloxy)-1(*S**)-phenylethyl]amino]-3-[(1,1-dimethylethoxy)methyl]propanenitrile and 2(*S**)-[[2-(Benzyloxy)-1(*S**)-phenylethyl]amino]-3-[(1,1-dimethylethoxy)methyl]propanenitrile (8a,b).** According to the general method of Kuffner,[8b] 1 N HCl was added to neat 2-(benzyloxy)-1-phenylethylamine (3.18 g, 14.0 mmol)[10] until the mixture was acidic, KCN (0.910 g, 14.0 mmol) dissolved in a minimum amount of H_2O was added at 23 °C, and the resulting mixture was stirred for 5 min. (1,1-Dimethylethoxy)acetaldehyde (1.63 g, 14.0 mmol)[9] was then added, and the reaction was stirred for 3 h at 23 °C. Saturated aqueous K_2CO_3 (5 mL) was then added, and the resulting mixture was stirred for an additional 15 min and then was extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. Crystallization from hexanes gave 1.60 g (32%) of **8a** as a white crystalline solid. Flash chromatography (silica gel, 6:1 hexane–EtOAc) of the mother liquor gave 0.790 g (16%) of **8b** as a white crystalline solid and 1.30 g (26%) of a mxiture of **8a** and **8b**.

8a: mp 92–93 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 7.24–7.38 (m, Ph), 4.57 (AB q, *J* = 11.9 Hz, Δν = 16.1 Hz, CH_2Ph), 4.26 (dd, *J* = 3.9, 5.4 Hz, NC*H*Ph), 3.47–3.61 (m, CH_2OBu^t and CH_2OBn), 3.39 (dt, *J* = 4.0, 12.7 Hz, NCHCN), 2.86 (d, *J* = 12.7 Hz, NH), 1.21 (s, C$(CH_3)_3$); IR (CCl_4) 3330, 3032, 2863, 1455, 1365 cm^{-1}; MS (CI) 326 (MH^+ – CN, 100). Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01; N, 7.95. Found: C, 74.68; H, 7.97; N, 7.80.

8b: mp 56 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 7.28–7.42 (m, Ph), 4.56 (AB q, *J* = 11.9 Hz, Δν = 6.2 Hz, CH_2Ph), 4.17 (dd, *J* = 5.0, 7.6 Hz, NC*H*Ph), 3.88 (app t, *J* = 4.6 Hz, NC*H*CN), 3.47–3.63 (m, CH_2OBu^t and CH_2OBn), 2.68–2.65 (br s, NH), 1.17 (s, C$(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 139.6, 137.9, 128.7, 128.6, 128.4, 128.4, 128.1, 127.7, 127.7, 127.6, 127.6, 127.6, 119.5, 75.4, 73.9, 73.1, 61.5, 60.8, 49.7, 27.3; IR (CCl_4) 3310, 3032, 2978, 1455, 1365 cm^{-1}. Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01. Found: C, 74.79; H, 7.87.

3,3-Dimethyl-1-[2-(benzyloxy)-1(*S)-phenylethyl]-4-(*S**)-[(1,1-dimethylethoxy)methyl]-2-azetidinone (10).** A solution of *n*-BuLi (0.39 mL of a 2.5 M solution in hexane, 0.98 mmol) was added to a solution of diisopropylamine (0.11 g, 1.1 mmol) and THF (4 mL) at –20 °C. After the mixture was stirred at this temperature for 30 min, ethyl isobutyrate (0.10 g, 0.86 mmol) was added dropwise and after 30 min at –20 °C, a solution of cyano amine **8a** (0.15 g, 0.43 mmol) and THF (1 mL) was added dropwise. The cooling bath was removed and the reaction was allowed to warm to 23 °C. After 10 h the reaction was quenched with AcOH (0.5 mL of a 2.2 M solution in THF, 1.1 mmol). The reaction mixture was then diluted with saturated aqueous $KHCO_3$, extracted with EtOAc (3 × 5 mL), and concentrated. Flash chromatography (silica gel, 5:1 hexane–EtOAc) gave 0.14 g (82%) of **10** as a clear oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.26–7.42 (m, Ph), 4.76 (dd, *J* = 5.8, 9.3 Hz, NC*H*Ph), 4.57 (AB q, *J* = 11.8 Hz, Δν = 16.7 Hz, CH_2Ph), 4.21 (app t, *J* = 9.6 Hz, C*H*HOBn), 3.74 (dd, *J* = 5.8, 9.7 Hz, CH*H*OBn), 3.35–3.38 (m, C*H*CH_2OBu^t), 1.25 (s, CH_3), 1.15 (s, CH_3), 1.00 (s, C$(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 174.5, 138.5, 138.3, 128.4, 128.3, 127.9, 127.7, 127.5, 127.4, 73.1, 73.0, 71.2, 64.2, 61.9, 58.8, 51.0, 27.3, 27.2, 22.5, 16.6; IR (CCl_4) 1747 cm^{-1}; MS (CI) *m/z* 396 (MH^+, 100), 340 (3), 218 (49), 91 (28); HRMS (EI) *m/z* 395.2451 (395.2460 calcd for $C_{25}H_{33}NO_3$).

Condensation of cyano amine **8b** (0.14 g, 0.40 mmol) and ethyl isobutyrate (0.10 g, 0.86 mmol) under identical conditions gave 0.13 g (82%) of **10**.

4(*S)-(Acetoxymethyl)-1-[2-acetoxy-1(*S**)-phenylethyl]-3,3-dimethyl-2-azetidinone (11).** According to the method of Ganem,[12] to a solution of **10** (69 mg, 0.17 mmol) and Ac_2O (1 mL) was added a catalytic amount of $FeCl_3$ (~3 mg). After maintaining the reaction at 50 °C for 24 h, H_2O (1 mL) was added and the reaction was extracted with hexane (3 × 1 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated. Flash chromatography (silica gel, 2:1 hexane–EtOAc) of the residue gave 28 mg (49%) of **11** as a colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.33–7.41 (m, Ph), 4.86 (dd, *J* = 5.7, 9.5 Hz, NC*H*Ph), 4.67 (dd, *J* = 9.6, 11.2 Hz, PhCHC*H*HOAc), 4.49 (dd, *J* = 5.7,

(19) Although we consider it unlikely in the case at hand, reversible addition of Reformatsky reagents to imines has been clearly established[20] and retroaldolization is suggested to occur also in some lithium ester enolate–imine condensations.[21] The trans stereoisomer could, in principle, also arise from stereochemical equilibration of the lithium salt of the β-amino ester intermediate prior to cyclization[22] or from epimerization at C-3 of the cis β-lactam stereoisomer.[23] These latter possibilities, although not rigorously excluded, are unlikely on the basis of the control experiments conducted to date[17].

(20) Luche, J. L.; Kagan, H. B. *Bull. Soc. Chim. Fr.* **1971**, 2260. Dardoize, F.; Moreau, J.-L.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1973**, 1668.

(21) Gluchowski, C.; Cooper, L.; Bergbreiter, D. E.; Newcomb, M. *J. Org. Chem.* **1980**, *45*, 3413.

(22) See, e.g.: Georg, G. I.; Kant, J.; Gill, H. S. *J. Am. Chem. Soc.* **1987**, *109*, 1129.

(23) See, e.g.: Burnett, D. A.; Gallucci, J. C.; Hart, D. J. *J. Org. Chem.* **1985**, *50*, 5120.

(24) We use this notation to indicate that Li is assigned higher priority than carbon in specifying enolate stereochemistry, see: Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, p 11.

(25) For a suggestion of this scenario, see: van der Steen, F. H.; Kleijn, H.; Jastrzebski, J. T. B. H.; van Koten, G. *Tetrahedron Lett.* **1989**, *30*, 765.

(26) Alternatively, this destabilizing interaction could result in the glycoaldimine reaction occurring by an open transition state, a mechanistic scenario advocated by a referee. The preferential formation of the trans β-lactam **17** from the reaction of **1** and **14** by an open transition state is certainly not precluded by the experimental evidence on hand. However, such a transition state would place the large bis-silylamino and *tert*-butoxymethyl groups in close proximity. More experiments will obviously be required to unambiguously define the operative transition-state topography.

(27) General experimental details were described recently.[28]

(28) Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 2630.

11.2 Hz, PhCHCH*H*OAc), 4.23 (dd, J = 4.5, 11.8 Hz, C-4 H), 3.96 (dd, J = 8.0, 11.7 Hz, $CMe_2CHCHHOAc$), 3.36 (dd, J = 4.4, 8.0 Hz, $CMe_2CHCHHOAc$), 2.09 (s, $COCH_3$), 2.00 (s, $COCH_3$), 1.30 (s, C-3 CH_3), 1.20 (s, C-3 CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 173.8, 170.6, 170.2, 136.3, 128.9, 128.3, 127.4, 64.0, 63.8, 61.6, 56.7, 51.9, 22.4, 20.7, 20.6, 16.5; IR (CCl_4) 1755, 1752 cm^{-1}; MS (CI) m/z 334 (MH^+, 100), 274 (11), 264 (10), 163 (8), 128 (12).

3,3-Dimethyl-4(*S)-(hydroxymethyl)-1-[2-hydroxy-1-(*S**)-phenylethyl]-2-azetidinone (12).** According to the method of Mori,[13] a solution of diacetate **11** (17 mg, 0.051 mmol), EtOH (1 mL), and a catalytic amount of KCN (~1 mg) was stirred at 23 °C for 7 h. This solution was then diluted with CH_2Cl_2 (5 mL), filtered through Florisil, and concentrated. The residue was purified by flash chromatography (silica gel, 9:1 $CHCl_3$-EtOH) to give 12 mg (92%) of **12** as an oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.40 (m, Ph), 4.61 (dd, J = 3.8, 8.0 Hz, NC*H*Ph), 4.40 (br s, OH), 4.06-4.13 (m, PhCHC*H*HOH), 3.92-3.99 (m, PhCHCH*H*OH), 3.51-3.62 (m, $CMe_2CHCHHOH$), 3.43-3.49 (m, $CMe_2CHCHHOH$), 3.34 (dd, J = 4.6, 5.6 Hz, C-4 H), 2.05 (br s, OH), 1.30 (s, CH_3), 1.26 (s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 175.6, 137.6, 129.0, 128.4, 127.4, 65.6, 64.3, 62.0, 61.4, 51.2, 22.7, 16.6; IR (film) 3387, 1718 cm^{-1}.

1-[2-[(*p*-Bromobenzoyl)oxy]-1(*S)-phenylethyl]-3,3-dimethyl-4(*S**)-[[(*p*-bromobenzoyl)oxy]methyl]-2-azetidinone (13).** A solution of **12** (7 mg, 0.028 mmol), *p*-bromobenzoyl chloride (34 mg, 0.16 mmol), and pyridine (0.5 mL) was stirred at 23 °C for 10 h. The resulting slurry was diluted with H_2O (2 mL) and extracted with Et_2O (3 × 2 mL). The combined organic extracts were washed with 1 M HCl (3 mL), 1 M $KHCO_3$ (3 mL), saturated aqueous $CuSO_4$ (3 mL), and saturated aqueous NaCl (3 mL). After drying (Na_2SO_4) and concentration, the residue was purified by flash chromatography (silica gel, 3:1 hexanes-EtOAc) to give 15 mg (88%) of **13** as a colorless crystalline solid.

An analytical sample of this material prepared from (*R*)-(-)-2-phenylglycine afforded X-ray quality crystals from a mixture of EtOAc-hexane-EtOH: mp 82-83 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 7.54-7.91 (m, 8 H, C_6H_4), 7.27-7.34 (m, Ph), 5.02 (dd, J = 4.8, 10.0 Hz, NC*H*Ph), 4.92 (app t, J = 10.0 Hz, CHC*H*HO), 4.69 (dd, J = 4.9, 10.7 Hz, CHCH*H*O), 4.44 (dd, J = 4.5, 12.0 Hz, CHC*H*HO), 4.22 (dd, J = 7.1, 12.0 Hz, CHCH*H*O), 3.50 (dd, J = 4.5, 7.1 Hz, C-4 H), 1.32 (s, CH_3), 1.25 (s, CH_3); IR (CCl_4) 1730, 1760 cm^{-1}. Anal. Calcd for $C_{28}H_{25}NO_5Br_2$: C, 54.66; H, 4.10; N, 2.28; Br, 25.97. Found: C, 54.58; H, 4.15; N, 2.28; Br, 25.87.

3(*S)-(Acetylamino)-1-[2-(benzyloxy)-1(*S**)-phenylethyl]-4(*S**)-[(1,1-dimethylethoxy)methyl]-2-azetidinone (16) and 3(*R**)-(Acetylamino)-1-[2-(benzyloxy)-1(*S**)-phenylethyl]-4(*S**)-[(1,1-dimethylethoxy)methyl]-2-azetidinone (17).** To a solution of LDA (2.0 mmol, formed as described for the preparation of **10**) were added dropwise at -20 °C a solution of silyl glycinate **15**[3] (0.46 g 1.9 mmol) and 6 mL of THF. After 2 h at -20 °C, a solution of imine **14** (0.56 g, 1.7 mmol) and 2 mL of THF was added dropwise. The reaction mixture was allowed to warm to 23 °C and after 10 h was quenched with AcOH (2 mL of a 1.0 M THF solution), and AcCl (0.60 g, 7.6 mmol) was then added. After 10 h at 23 °C the solvent was removed in vacuo, and the residue was partitioned between saturated $KHCO_3$ (5 mL) and EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give a 1:5 mixture (by GLC analysis) of β-lactams **16** and **17**, respectively. Flash chromatography (silica gel, EtOAc) gave 124 mg (17%) of pure **16** as a clear oil and 305 mg (42%) of pure **17** also as a clear oil.

16: ^1H NMR (250 MHz, $CDCl_3$) δ 7.27-7.42 (m, Ph), 6.58 (br d, J = 8.5 Hz, NH), 5.45 (dd, J = 5.2, 9.5 Hz, C-3 H), 4.52 (AB q, J = 11.7 Hz, $\Delta\nu$ = 28 Hz, CH_2Ph), 4.55-4.59 (m, NC*H*Ph), 4.23 (app t, J = 9.5 Hz, C*H*HOBn), 3.81 (app quintet, J = 2.7 Hz, C-4 H), 3.74 (dd, J = 5.9, 10 Hz, CH*H*OBn), 3.49 (dd, J = 2.2, 10.4 Hz, C*H*HOBu^t), 3.29 (dd, J = 2.9, 10.4 Hz, CH*H*OBu^t), 1.93 (s, $COCH_3$), 1.02 (s, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 169.7, 167.2, 137.9, 137.4, 128.5, 128.4, 127.9, 127.8, 73.3, 70.8, 59.2, 58.5, 58.3, 56.5, 27.2, 27.1, 23.3; IR (CCl_4) 1758, 1740, 1691 cm^{-1}; HRMS (EI) m/z 424.2354 (424.2362 calcd for $C_{25}H_{32}N_2O_4$).

17: ^1H NMR (250 MHz, $CDCl_3$) δ 7.27-7.44 (m, Ph), 6.02 (br d, J = 6.3 Hz, NH), 4.82 (dd, J = 5.9, 9.4 Hz, NC*H*Ph), 4.61 (dd, J = 2.1, 6.3 Hz, C-3 H), 4.59 (s, CH_2Ph), 4.24 (app t, J = 9.6 Hz, C*H*HOBn), 3.80 (dd, J = 5.9, 9.8 Hz, CH*H*OBn), 3.64 (dd, J = 2.5, 9.57 Hz, C*H*HOBu^t), 3.52 (app dt, J ~ 2, 7 Hz, C-4 H), 3.36 (dd, J = 7.3, 9.5 Hz, CH*H*OBu^t), 1.93 (s, $COCH_3$), 1.02 (s, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 170.4, 166.6, 138.1, 137.2, 128.4, 128.3, 127.8, 127.8, 127.6, 73.0, 70.8, 62.6, 62.1, 58.7, 57.2, 27.1, 27.1, 22.7; IR (CCl_4) 1744, 1683 cm^{-1}; HRMS (EI) m/z 424.2384 (424.2364 calcd for $C_{25}H_{32}N_2O_4$).

Alternatively, with toluene as the solvent, **14** (0.56 g, 1.7 mmol) and **15** (0.46 g, 1.9 mmol) gave a 1:10 ratio of **16** and **17**, respectively (determined by GC analysis).

Epimerization of the Cis β-Lactam 16. To a solution of LDA (0.36 mmol, ca. 0.5 M in THF) at -70 °C was added a solution of β-lactam **16** (73 mg, 0.17 mmol) and THF (0.5 mL). After 1 h at -70 °C, Me_3SiCl (~30 μL, 0.24 mmol) was added dropwise, and the reaction was allowed to warm to 0 °C over 1 h. The reaction was then recooled to -70 °C and quenched with AcOH (0.3 mL of a 1.3 M solution in THF, 0.39 mmol). Upon warming to 23 °C, H_2O (2 mL) was added, and the mixture was extracted with EtOAc (3 × 1 mL). The combined organic extracts were washed with saturated aqueous K_2CO_3 (2 mL), dried (Na_2SO_4), and concentrated. The crude residue contained a 2:1 mixture of **17** and **16** as well as two other low boiling products (determined by GC analysis). This crude mixture was dissolved in EtOAc (2 mL) and stirred with 1 M HCl (2 mL) for 1 h. The aqueous layer was removed and washed with EtOAc (2 × 2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give 44 mg (60%) of a 2.2:1 mixture of **17** and **16** as the only products observable by GC and ^1H NMR analysis.

3(*S)-(Acetylamino)-4(*S**)-[(1,1-dimethylethoxy)methyl]-1-(2-hydroxy-1(*S**)-phenylethyl)-2-azetidinone (18).** A mixture of **16** (54 mg, 0.13 mmol), 10% Pd/C (~10 mg), and EtOH (2 mL) was rapidly stirred under an atmosphere of H_2 for 12 h and then filtered through a bed of Celite. Concentration and purification of the residue by flash chromatography (silica gel, 20:1 CH_3Cl-EtOH) gave 28 mg (65%) of **18** as a colorless crystalline solid. An analytical sample was obtained by recrystallization from CH_2Cl_2-hexane: mp 147 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.37 (m, Ph), 6.98 (br d, J = 9.5 Hz, NH), 5.45 (dd, J = 5.3, 9.5 Hz, C-3 H), 4.83 (dd, J = 3.9, 8.6 Hz, NC*H*Ph), 3.97-4.07 (m, C*H*HO*H*), 3.88-3.93 (m, C-4 H and CH*H*OH), 3.57 (dd, J = 2.8, 10.6 Hz, C*H*HOBu^t), 3.43 (dd, J = 2.7, 10.6 Hz, CH*H*OBu^t), 2.00 (s, $COCH_3$), 1.15 (s, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 170.0, 168.5, 136.0, 128.8, 128.2, 127.7, 74.6, 63.4, 60.0, 58.5, 57.5, 56.7, 27.2, 23.1; IR (CCl_4) 3317, 3306, 2875, 1744, 1667 cm^{-1}; MS (CI) m/z 335 (MH^+, 100), 279 (10), 236 (12). Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.58; H, 7.86; N, 8.34.

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Supplementary Material Available: Details of the single-crystal X-ray analyses of **13** and **18** (13 pages). Ordering information is given on any current masthead page.

A Convenient Method for the Synthesis of 3β-Hydroxy 4-En-6-one Steroids

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In view of the synthetic utility of the title compounds and their multistep syntheses,[1] we report a convenient and

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