Thienamycin Total Synthesis: Stereocontrolled Introduction of the Hydroxyethyl Side Chain

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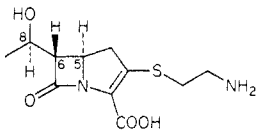
The *trans*-(*R*)-hydroxyethyl side chain of thienamycin has been introduced in a stereocontrolled manner via stereoselective reduction of a thermodynamically favored *trans*-acetylazetidinone precursor (III) using potassium tri-*sec*-butylborohydride in diethyl ether. The acetylazetidinones are prepared via acetylation of the lactam enolate (I → III). Experimental results suggest that the stereoselective generation of the 8*R* carbinol (III → IV) occurs via hydride attack on the least hindered face of a complex (VII) formed between the metal cation and the carbonyls. Conversion of **2** → **9** → **3a** as described herein constitutes a formal stereocontrolled synthesis of racemic thienamycin.

Thienamycin (I) is an exceptionally potent, broad-spectrum β-lactam antibiotic whose isolation,[1] structure determination,[2] and total synthesis[3] have been the subjects of recent communications from these laboratories. In our original synthesis of (±)-thienamycin,[3a] the hydroxyethyl



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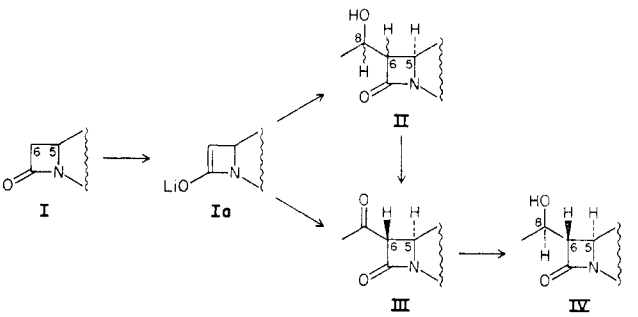
5*R*, 6*S*, 8*R*

side chain was introduced in a nonstereocontrolled manner to obtain most readily the C(6)–C(8) epithienamycins for structure–activity studies, as well as thienamycin itself. The condensation of a β-lactam enolate intermediate (i.e., Ia in Scheme I) with acetaldehyde provided each of the four possible diastereomeric carbinols II. A stereocontrolled synthesis of (+)-thienamycin from an appropriate chiral precursor was next undertaken. To maintain flexibility regarding the introduction of C(6) substituents, it seemed worthwhile to retain a β-lactam enolate in the new synthetic scheme. Stereocontrolled hydroxyethylation of an azetidinone intermediate possessing the correct chirality at that carbon atom corresponding to C(5) of thienamycin would provide a fully functionalized azetidinone of correct absolute stereochemistry for elaboration to thienamycin. This paper describes the generation of the (8*R*)-hydroxyethyl side chain IV via stereoselective reduction of a thermodynamically favored *trans*-acetylazetidinone precursor III. The acetylazetidinone can be prepared by direct acylation of the lactam enolate (I → III). This sequence was developed by using the readily available racemic azetidinones **2** and **5** while efforts were simultaneously underway to prepare a suitable chiral azetidinone intermediate compatible with this hydroxyethylation methodology. A further reason for the inclusion of **5** in this work was to be certain that the stereoselectivity achieved with bicyclic azetidinone **2** was also attainable on a monocyclic substrate as it was anticipated that the chiral hydroxyethylation template would be a monocyclic azetidinone.

Scheme I



Scheme II[4]

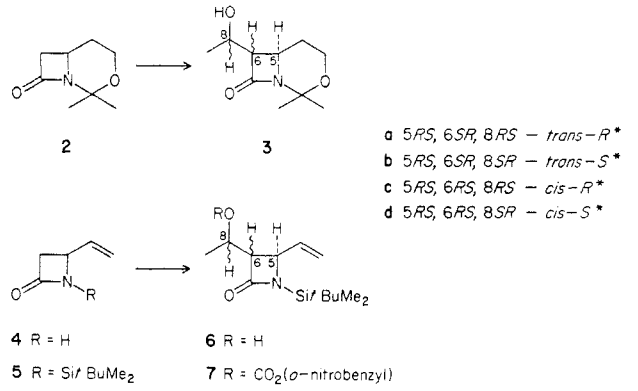


Table I. 300-MHz ^{1}H NMR Data[a] [δH_6 ($J_{5,6}$, Hz)] for Diastereomers 3a–d, 6a–d, and 7a,b

trans-(*R**)	*trans*-(*S**)	*cis*-(*R**)	*cis*-(*S**)
3a 2.83 (1.5)	**3b** 2.85 (1.5)	**3c** 3.14 (5)	**3d** 3.18 (5)
6a 2.99 (2.9)	**6b** 2.94 (2.9)	**6c** 3.33 (6)	**6d** 3.41 (6)
7a 3.13 (2.7)	**7b** 3.20 (2.7)		

[a] Spectra were recorded in chloroform-*d* using tetramethylsilane as internal standard.

Results

Identification of Stereoisomers. To use model compound **5** in these studies, the stereoisomeric identity of carbinols **6a–d** derived from **5** first had to be established conclusively as had been done for carbinols **3a–d** derived from **2**[3b] (Scheme II). The lactam nitrogen of vinylazetidinone **4**[5] was protected by conversion to the *tert*-

(1) J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, H. B. Woodruff, and J. Birnbaum, *J. Antibiot.*, **32**, 1 (1979), and references cited therein.

(2) G. Albers-Schonberg, B. H. Arison, O. D. Hensens, J. Hirshfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin, and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 6491 (1978).

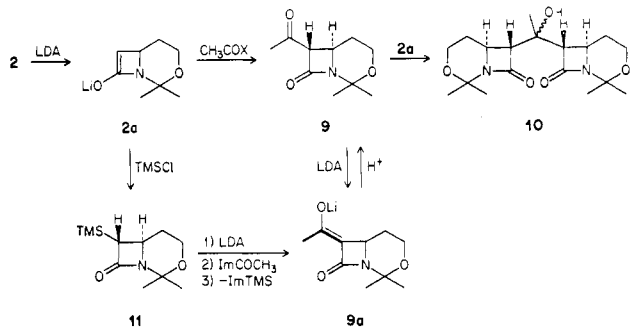
(3) (a) D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 313 (1978); (b) F. A. Bouffard, D. B. R. Johnston, and B. G. Christensen, *J. Org. Chem.*, **45**, 1130 (1980); (c) S. M. Schmitt, D. B. R. Johnston, and B. G. Christensen, *ibid.*, **45**, 1135, 1142 (1980).

(4) Numbering corresponds to that of thienamycin.

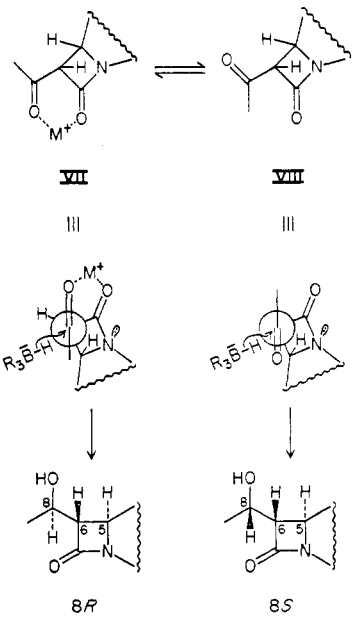
(5) E. J. Moriconi and W. C. Meyer, *Tetrahedron Lett.*, 3823 (1968).

0022-3263/81/1946-2208$01.25/0

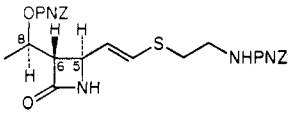
Scheme III



Scheme IV



butyldimethylsilyl derivative **5**, using *tert*-butyldimethylchlorosilane and triethylamine in *N,N*-dimethylformamide.[6] Hydroxyethylation of monocyclic azetidinone **5**, as previously described for bicyclic azetidinone **2**,[3b] gave aldol mixture **6a–d** in 92% overall yield. Examination of the product mixture by 300-MHz ^{1}H NMR revealed a **6a:6b:6c:6d** ratio of 46:37:14:2, respectively, based on integration of H_6. The two major diastereomers (**6a,b**) were separated from the two minor diastereomers (**6c,d**) by silica gel chromatography and assigned the trans β-lactam stereochemistry based on their smaller β-lactam proton coupling constants ($J_{5,6}$) and the upfield positions of H_6 (see Table I). Analogous to the stereochemical assignment of **3c**,[3b] the major cis diastereomer **6c** was also assigned the *R** side-chain configuration. The NMR correlation previously noted[3b] which relates the side chain C(8) configuration for a given pair of trans diastereomers to δH_6 [δH_6 (8*R*) upfield from δH_6 (8*S*)] was ambiguous in this instance. This became evident when *trans*-(*R**,*S**)-carbinol mixture **6a,b** was converted to *o*-nitrobenzyl carbonates **7a,b** which were separable on silica gel. Photolytic reversion of carbonate **7b** (whose H_6 appears *downfield* relative to that of **7a**) gave carbinol **6b** (whose H_6 appears *upfield* relative to that of **6a**). The side-chain configuration of **6a** was definitively established by multistep conversion of it to thioenol ether **8** and correlation



8 (8*R**)

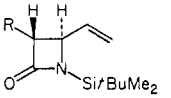
PNZ = *para*-nitrobenzyloxycarbonyl

with authentic *trans*-(*R**) material.[7] It thus follows that carbinol **6a** has the *R** side-chain configuration and **6b** the *S** configuration.

Since the most direct introduction of the hydroxyethyl side chain is via the aldol reaction, attempts were initially made to improve its stereoselectivity. The sensitivity of the reaction to substrate structure, solvent polarity, temperature, and metal cation was investigated; however, no significant maximization of the desired *trans*-(*R**) stereoisomer resulted.

Acylation. Next, the two-step acylation–reduction sequence was studied. The introduction, by direct acylation, of an acetyl group α to the β-lactam carbonyl was complicated by the high reactivity of the product. Treatment of a tetrahydrofuran solution of enolate **2a** with acetyl chloride (Scheme III, X = Cl) at −78 °C gave a mixture of products including the *trans*-acetylazetidinone **9**, recovered starting material **2**, and dilactam **10**. The dilactam arises from attack of enolate **2a** at the ketone carbonyl of the product.[8] Experimental modifications such as inverse addition or the use of an additional equivalent of base to convert **9**, as it is formed, into the less reactive β-keto lactam enolate **9a** did not significantly improve the net conversion to **9**. Yields ranged from 10–30% while up to 60% of the dilactam was isolated. However, substituting acetyl imidazole as the acylating agent, **9** (and **13**) can be prepared directly in yields of 43–60%.

The dilactam product can be eliminated by directly generating the β-keto lactam enolate **9a**, thus delaying formation of **9** prior to quench. This procedure, analogous to the ester enolate acylation of Hartzell and Rathke,[9] involves silylation of lactam enolate **2a** to give *trans*-trimethylsilylazetidinone **11** which is enolized and treated with acetylimidazole. Loss of (trimethylsilyl)imidazole leads initially to **9a** which gives **9** upon protic workup. The trimethylsilyl intermediate **11** was isolated and characterized; however, the entire sequence can most conveniently be done in one pot to give **9** in yields of 50–63%. Analogously, vinylazetidinone **5** was converted to **13** via **12**.[10]



12 R = TMS
13 R = $COCH_3$

Stereoselective Reduction. Although the selective reduction of the ketone carbonyl of a β-keto lactam system such as III (Scheme I) was not expected to be a problem,[12]

(6) R. W. Ratcliffe, T. N. Salzmann, and B. G. Christensen, *Tetrahedron Lett.*, 31 (1980).

(7) (a) Merck & Co., German Offenlegungsschrift 2 751 597 (1978). (b) Thioenol ether **8** prepared from **6a** was identical, by 300-MHz ^{1}H NMR, with *trans*-(*R**)-thioenol ether prepared as described in ref 3c.

(8) An analogous dilactam product has been previously observed in the acylation of a β-lactam enolate with methyl benzoate: T. Durst and M. J. LeBelle, *Can. J. Chem.*, **50**, 3196 (1972).

(9) S. L. Hartzell and M. W. Rathke, *Tetrahedron Lett.*, 2757 (1976).

(10) Swern oxidation[11] of cis/trans aldol mixtures **3a–d** and **6a–d** gave exclusively the trans ketones **9** and **13**, respectively, indicating the facile epimerization of the cis ketone to the thermodynamically favored trans form.

(11) S. L. Huang, K. Omura, and D. Swern, *Synthesis*, 297 (1978).

Table II. Borohydride Reduction of β-Keto Lactam 9. Product Ratio as a Function of Reaction Conditions[a]

entry	reducing agent	molar equiv	solvent[b]	temp, °C	additive[c]	8R*/8S* product ratio (3a/3b)[d]	overall % yield[e]
1	$NaBH_4$	4	*i*-PrOH	0		40:60	54
2	$LiBH_4$	4	Et_2O	25		32:68	60
3	L-Selectride in THF	1.2	THF	−78		8:92	71
4	L-Selectride in THF	1.2	THF	25		29:71	45
5	L-Selectride in THF	1.2	Et_2O	25		43:57	38
6	L-Selectride in THF	1.2	Et_2O	25	12-crown-4	21:79	*f*
7	K-Selectride in THF	1.2	THF	−78		53:47	70
8	K-Selectride in THF	1.2	THF	0		66:34	77
9	K-Selectride in THF	1.2	THF	25		73:27	62
10	K-Selectride in THF	1.2	THF	25	HMPA	42:58	72
11	K-Selectride in THF	1.2	DME	25		64:36	68
12	K-Selectride in THF	1.2	Et_2O	25		79:21	64
13	K-Selectride in THF	1.2	Et_2O	25	18-crown-6	24:76	60
14	K-Selectride in THF	1.2	Et_2O	25	$MgBr_2$	83:17	29
15	K-Selectride in THF	2.4	Et_2O	25		86:14	66
16	K-Selectride in Et_2O	2.4	Et_2O	25		88:12	46
17	K-Selectride in THF	2.4	Et_2O	25	KI	88:12	81

[a] Reductions were run on a 0.2–0.3-mmol scale. The reducing agent was added to a 0.1–0.2 M solution of the ketone under a nitrogen atmosphere and the reaction mixture stirred for 90 min. See the Experimental Section for workup details. [b] THF = tetrahydrofuran; DME = 1,2-dimethoxyethane. [c] 1–1.2 molar equiv; 12-crown-4 = 1,4,7,10-tetraoxacyclooctadecane; HMPA = hexamethylphosphoric triamide; 18-crown-6 = 1,4,7,10,13,16-hexaoxacyclooctadecane. [d] Determined by 300-MHz ^1H NMR (H_6) of the product mixture after chromatography. [e] Not corrected for conversion. Unreacted starting material was not recovered by PLC as it is sensitive to silica gel. [f] Chromatographed product still contaminated with crown ether.

achieving the desired stereoselectivity did present a challenge.[13] The possibility of inducing some constraint on the conformationally mobile side chain via internal metal ion complexation of the 1,3-disposed carbonyl groups of the ketone and lactam encouraged us to study the reduction.[14,15] We have found that, when using a sterically demanding complex borohydride reducing agent, the stereoselectivity of the reduction is highly sensitive to the reaction conditions, including temperature, solvent, and borohydride counterion. The 8R*/8S* product ratio can be varied from 8:92 to 88:12, with the experimental evidence suggesting that the desired 8R* epimer is formed via a directed borohydride attack on a chelated reaction intermediate as represented by VII in Scheme IV.

Table II presents the results of the reduction of β-keto lactam **9** by the simple borohydride reducing agents $M^+BH_4^-$ (M = Na, Li) and the bulky tri-*sec*-butylborohydrides $M^+(sec\text{-}Bu)_3BH_4^-$ (M = Li, K); the latter two are known as L-Selectride[16a] and K-Selectride.[16b] Although the temperature (compare entry 3 vs. 4 and 7 vs. 8 and 9) and coordinating power of the solvent (entry 4 vs. 5) affect the product ratio, the most striking role is that played by the Selectride counterion. Comparison of entry 4 (Li^+) with entry 9 (K^+) shows a reversal in the product ratio favoring, in the latter case, the desired 8R* isomer (29:71 vs. 73:27). Changing the solvent to Et_2O and using excess K-Selectride further improves the product ratio to 86:14 (entry 9 vs. 15). Completely eliminating THF has little additional effect on the stereoselectivity (entry 16).[16c] The more highly hindered potassium trisiamylborohydride (K-Super Selectride)[17] worked poorly, providing only a small amount of carbinol product which was difficult to purify and analyze. Running the reduction in the presence of $MgBr_2$ or KI did not significantly improve the product ratio (entry 12 vs. 14 and 15 vs. 17); however, the best overall yield (80–85%) was most consistently achieved in the presence of KI (entry 17). These optimized conditions on β-keto lactam **13** provided 8R* carbinol **6a** with comparably high stereoselectivity.

Discussion

Mechanism of Reduction. The observed dependence of the product ratio on the nature of the cation is consistent with the involvement of a syn-chelated conformer VII as depicted in Scheme IV.[18] Preferred attack of the borohydride anion on the β-face of the ketone carbonyl of VII generates the desired 8R* carbinol. Further support for this mechanism is provided by experiments in which ionizing additives are shown to alter the product ratio, consistently producing relatively more of the 8S* carbinol (Table II: compare entry 5 vs. 6, 9 vs. 10, and 12 vs. 13). The effect of these additives is thought to be that of displacing the conformational equilibrium VII ⇌ VIII toward the latter in which β-face attack of the borohydride anion on the ketone carbonyl of anti conformer VIII generates the 8S* carbinol. Examination of CPK space-filling molecular models of VII and VIII indicates that the preferred β-face attack of the bulky $(sec\text{-}Bu)_3BH_4^-$ is a result of both steric and electrostatic interactions. Attack on the face of the ketone carbonyl opposite to that indicated in the Newman projections of VII and VIII is disfavored in both

(12) For recent reviews of complex metal hydride reducing agents, see H. C. Brown and S. Krishnamurthy, *Tetrahedron*, **35**, 567 (1979); E. R. Walker, *Chem. Soc. Rev.*, **5**, 23 (1976).

(13) For an alternate synthesis of **9** and its reduction by $NaBH_4$, see R. J. Ponsford and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 846 (1979).

(14) Complexation of the carbonyl group by a metal cation in the reduction of ketones by complex metal hydrides has been demonstrated to influence the stereochemical outcome of the reaction: E. C. Ashby, J. R. Boone, and J. P. Oliver, *J. Am. Chem. Soc.*, **95**, 5427 (1973).

(15) For recent examples of heteroatom-assisted stereoselective carbonyl reductions using simple and complex metal hydride reducing agents, see R. S. Glass, D. R. Deardorff, and K. Henegar, *Tetrahedron Lett.*, 2467 (1980); H. Handel and J. L. Pierre, *Tetrahedron*, **31**, 997 (1975); D. C. Wigfield and S. Feiner, *Can. J. Chem.*, **56**, 789 (1978); W. G. Dauben and J. W. Ashmore, *Tetrahedron Lett.*, 4487 (1978).

(16) (a) H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94**, 7159 (1972). (b) C. A. Brown, *ibid.*, **95**, 4100 (1973). (c) The Selectrides are supplied by Aldrich as THF solutions. K-Selectride in Et_2O was obtained by special order.

(17) S. Krishnamurthy and H. C. Brown, *J. Am. Chem. Soc.*, **98**, 3383 (1976).

(18) Subsequent to the completion of this work, erythro-selective reduction of β-keto esters with zinc borohydride was reported to occur via a similar mechanism involving association of the zinc ion with the carbonyls: T. Nakata and T. Oishi, *Tetrahedron Lett.*, 1641 (1980).

instances by steric interference due to H_5 and electrostatic repulsion between the negatively charged borohydride anion and the lone-pair electrons of the lactam nitrogen.

Effect of Solvent, Temperature, and Cation. Both the coordinating power of the solvent and the reaction temperature were found to influence the product ratio. With regard to producing more of the desired 8*R** carbinol, the preferred solvent is Et_2O. Consistent with the above mechanism, the poorer cationic solvating ability of Et_2O relative to THF would be expected to shift the substrate equilibrium toward syn-chelated conformer VII. Increasing the reaction temperature also favors the 8*R** carbinol. this temperature effect may be a reflection of the entropy requirement for the complexation of the metal cation by the substrate. Finally, the preferred cation ($K^+ > Li^+$) is consistent with the recently reported chelating effectiveness of alkali metal ions by neutral imides ($K^+ > Li^+$) vs. enolate anions ($Li^+ > K^+$).[19]

Conclusions

The *trans*-(*R*)-hydroxyethyl side chain of thienamycin can be introduced in a stereocontrolled manner via the stereoselective reduction of a thermodynamically favored *trans*-acetylazetidinone precursor. The reductive generation of the 8*R* carbinol using K-Selectride/THF in Et_2O at room temperature can best be explained by a mechanism involving syn-chelated conformer VII (Scheme IV).

Since *trans*-(*R**)-carbinol **3a**, derived from the aldol condensation, has been converted to racemic thienamycin,[3] the preparation of **3a** as described in this paper renders our original thienamycin synthesis stereoselective. In addition, this work provided the needed hydroxyethylation methodology for the recently completed stereocontrolled synthesis of natural thienamycin.[20,21]

Experimental Section

General Procedures. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Dimethylformamide (DMF) was distilled under reduced pressure and stored over 4-Å molecular sieves. Hexamethylphosphoramide (HMPA), triethylamine, and diisopropylamine were distilled from calcium hydride. Acetaldehyde and acetyl chloride were distilled prior to use. Silylation-grade trimethylchlorosilane (Pierce) was used as supplied. Commercial *N*-acetylimidazole was recrystallized from benzene and stored at −10 °C.

All enolate anion reactions were run under an inert atmosphere of nitrogen, using freshly prepared lithium diisopropylamide (LDA). Routine workup of reaction mixtures is represented as follows: extraction solvent, washing solutions, drying agent. Filtration to remove the drying agent and concentration of the filtrate on a rotary evaporator under house vacuum at a water-bath temperature of 30–40 °C are implied. Plate-layer chromatography (PLC) was done on Analtech silica gel GF plates and EtOAc was routinely used as the eluting solvent. Column chromatography was done with Baker silica gel (60–200 mesh). High-pressure liquid chromatography (HPLC) was done on a Waters Associates Prep LC/System 500 instrument using PrepPAK-500/silica cartridges which contain 325 g of packing per cartridge.

Melting points are uncorrected. All reported elemental analyses are within ±0.3% of the calculated value. All NMR spectra were recorded on a 60-MHz instrument unless otherwise noted, using tetramethylsilane as internal standard.

1-(*tert*-Butyldimethylsilyl)-4-vinylazetidin-2-one (5). Triethylamine (5.20 mL, 37.4 mmol) was added to a solution of **4** (3.30 g, 34.0 mmol) and *tert*-butyldimethylchlorosilane (5.39 g, 35.7 mmol) in 30 mL of anhydrous DMF at 0 °C, resulting in the immediate appearance of a heavy white precipitate. The ice bath was removed and the reaction mixture was stirred for a period of 1 h. Workup (Et_2O (100 mL), H_2O (4 × 50 mL), brine, $MgSO_4$) gave 7.2 g of a straw-colored liquid. Distillation provided 5.6 g of **5** (78%): bp 69 °C (0.5 mm); NMR ($CDCl_3$) δ 0.18 and 0.23 (2 s, $Si(CH_3)_2$), 0.98 (s, *t*-BuSi), 2.73 (dd, J_{gem} = 15, J_{trans} = 3 Hz, H_3), 3.35 (dd, J_{gem} = 15, J_{cis} = 6 Hz, H_3), 4.07 (ddd (apparent 7-line m), J_{vinyl} = 8, J_{cis} = 6, J_{trans} = 3 Hz, H_4), 5.1–6.2 (m, $CH{=}CH_2$). Anal. ($C_{11}H_{21}NOSi$) C, H, N.

1-(*tert*-Butyldimethylsilyl)-3-(1-hydroxyethyl)-4-vinylazetidin-2-ones (6a–d). A 0.4 M solution of **5** in THF was added to a freshly prepared 0.2 M solution of LDA (1.1 equiv) in THF made from equimolar amounts of *n*-BuLi and diisopropylamine at −78 °C. The resulting enolate solution was aged for a period of 10 min and then treated with neat CH_3CHO (3 equiv). After being stirred for an additional 10 min, the reaction was quenched by the addition of saturated NH_4Cl solution and the cooling bath was removed. Workup (EtOAc, brine, $MgSO_4$) gave the crude diastereomeric carbinols as a pale yellow oil. Purification of the mixture was done on silica gel either by PLC (20% EtOAc/$CHCl_3$) or column chromatography (10% EtOAc/$CHCl_3$). Partial separation of the less polar *cis*-(*R**) carbinol from the trans pair was achieved. See text for overall yield and isomer distribution. The minor *cis*-(*S**) carbinol was observed only in the 300-MHz ^1H NMR spectrum of the total product mixture (see Table I).

***trans*-(*R**,*S**)-Carbinols 6a,b**: IR (CH_2Cl_2) 5.79 μm; NMR ($CDCl_3$) δ 0.17 and 0.23 (2 s, $Si(CH_3)_2$), 0.98 (s, *t*-BuSi), 1.23 and 1.30 (2 d, J = 6 Hz, CH_3CH of **6a** and **6b**, respectively), 2.93 (m, H_6 and OH), 3.8–4.4 (m, H_5 and CH_3CH), 5.1–6.3 (m, $CH{=}CH_2$).

***cis*-(*R**)-Carbinol 6c**: IR (CH_2Cl_2) 5.79 μm; NMR ($CDCl_3$) δ 0.17 and 0.23 (2 s, $Si(CH_3)_2$), 0.97 (s, *t*-BuSi), 1.20 (d, J = 6 Hz, CH_3CH), 2.70 (br s, OH), 3.27 (dd, J = 6, 7 Hz, H_6), 4.10 (dd on m, J = 6, 8 Hz, H_5 on CH_3CH), 5.1–6.3 (m, $CH{=}CH_2$).

1-(*tert*-Butyldimethylsilyl)-3-(1-[[[(*o*-nitrobenzyl)oxy]carbonyl]oxy]ethyl)-4-vinylazetidin-2-one (7a,b). A mixture of carbinols **6a,b** was converted to *o*-nitrobenzyl carbonates **7a,b** by either of the two previously described methods.[3b] The two trans diastereomers were separated by PLC (5% EtOAc/$CHCl_3$).

***trans*-(*R**)-Carbonate 7a**: R_f 0.28–0.39; IR (CH_2Cl_2) 5.75, 6.57 μm; NMR ($CDCl_3$) δ 0.17 and 0.25 (2 s, $Si(CH_3)_2$), 0.97 (s, *t*-BuSi), 1.43 (d, J = 6 Hz, CH_3CH), 3.13 (dd, J = 5.7 2.7 Hz, H_6), 4.13 (dd, J = 7.2, 2.7 Hz, H_5), 5.1–6.3 (m, H_8 and $CH{=}CH_2$), 5.62 (s, CH_2Ar), 7.4–8.3 (m, Ar H); mass spectrum, m/e 434 (M^+), 419, 377.

trans*-S-Carbonate 7b**: R_f 0.41–0.51; IR (CH_2Cl_2) 5.76, 6.57 μm; NMR ($CDCl_3$) δ 0.17 and 0.27 (2 s, $Si(CH_3)_2$), 1.00 (s, *t*-BuSi), 1.50 (d, J = 6 Hz, CH_3CH), 3.20 (dd, J = 2.7, 4 Hz, H_6), 3.90 (dd, J = 2.7, 7.1 Hz, H_5), 5.1–6.2 (m, H_8 and $CH{=}CH_2$), 5.63 (s, CH_2Ar), 7.4–8.3 (m, Ar H); mass spectrum, m/e 434 (M^+), 419, 377.

Photolytic Reversion of Carbonate 7b to Carbinol 6b. A degassed solution of **7b** (7 mg, 0.016 mmol) in 7 mL of 1:1 H_2O–dioxane in a cold-finger-cooled vessel was irradiated at 350 nm in a Rayonet reactor for a period of 90 min. Lyophilization of the resulting yellow solution and chromatography of the lyophilizate (PLC, 20% EtOAc/$CHCl_3$) gave 4 mg of recovered **7b** (51%; R_f 0.55–0.66) and 2 mg of unmasked carbinol (49%; R_f 0.18–0.24) whose 300-MHz ^1H NMR spectrum was identical with that of **6b**.

Reaction of Lactam Enolate 2a with Acetyl Chloride. To a stirred solution of freshly prepared LDA (0.718 mmol) in THF (4 mL) at −78 °C was added a solution of **2** (55.6 mg, 0.359 mmol) in THF (1.5 mL) at −78 °C. The resulting enolate solution was stirred for 2 min and neat acetyl chloride (26 μL, 0.359 mmol) was added. The mixture was stirred for 5 min at −78 °C and poured into 0.2 M pH 7 phosphate buffer (5 mL). Solid NaCl was added to saturation. The mixture was extracted with CH_2Cl_2 (10 mL, 2 × 5 mL). The combined CH_2Cl_2 solutions were dried ($MgSO_4$) and evaporated under vacuum. PLC of the residual oil (82 mg), using Et_2O as the developing solvent (2×), afforded dilactam **10** (56%) as a ca. 1:1 mixture of isomers:[22] R_f 0.08–0.15;

(19) M. Raban, R. A. Keintz, and E. A. Noe, *Tetrahedron Lett.*, 1633 (1979).

(20) (a) T. N. Salzmann, R. W. Ratcliffe, F. A. Bouffard, and B. G. Christensen, *Philos. Trans. R. Soc. London, Ser. B*, **289**, 191 (1980); (b) T. N. Salzmann, R. W. Ratcliffe, B. G. Christensen, and F. A. Bouffard, *J. Am. Chem. Soc.*, **102**, 6161 (1980).

(21) Alternate routes to thienamycin in which the hydroxyethyl moiety is incorporated prior to construction of the β-lactam ring include D. G. Melillo, I. Shinkai, T. Liu, K. Ryan, and M. Sletzinger, *Tetrahedron Lett.*, 2783 (1980); T. Kametani, T. Nagahara, Y. Suzuki, S. Yokohama, S.-P. Huang, and M. Ihara, *Heterocycles*, **12**, 403 (1980).

IR (CH_2Cl_2) 5.71 μm; NMR ($CDCl_3$) δ 1.46 (m, CH_3COH and one of the two *gem*-dimethyl groups), 1.77 (s, *gem*-dimethyl), 1.96 (m, $CHCH_2CH_2O$), 2.60 (br s, OH), 2.97 and 3.06 (2 d, J = 2 Hz, isomeric $CHCHCH_2$), 3.78 (m, CH_2O and $CHCHCH_2$); mass spectrum, m/e 352 (M^+), 337.

Reaction of Lactam Enolate 2a with *N*-Acetylimidazole. (6*R,7*S**)-2,2-Dimethyl-7-acetyl-1-aza-3-oxabicyclo[4.2.0]-octen-8-one (9).** To a stirred solution of freshly prepared LDA (2.72 mmol) in THF (12 mL) at −78 °C was added a solution of **2** (211 mg, 1.36 mmol) in THF (2 mL). The resulting enolate solution was stirred for 3 min. The solution was transferred, under positive nitrogen pressure, to a cold[23] solution of *N*-acetylimidazole (299 mg, 2.72 mmol) in THF (10 mL). The transfer was completed in ca. 3 min, producing a white precipitate. The cooling bath was removed and stirring was continued for 9 min during which time the mixture became homogeneous. Saturated aqueous ammonium chloride solution (8 mL) was added. Workup (Et_2O (25 mL), H_2O (8 mL, 3 × 15 mL), brine, $MgSO_4$) gave 116 mg (43%) of acetylazetidinone **9** which was identical, by NMR, with authentic material prepared via aldol oxidation as described below.

(3*R,4*S**)-1-(*tert*-Butyldimethylsilyl)-3-acetyl-4-vinylazetidin-2-one (13).** Following the procedure described above for the preparation of **9** from **2** using *N*-acetylimidazole, **5** was converted to **13**. The colorless oil obtained after workup was dissolved in 1:9 Et_2O/petroleum ether. The solution was filtered through a bed of Baker silica gel, washing with additional Et_2O/petroleum ether. Evaporation of the filtrate under vacuum afforded acetylazetidinone **13** (60%) as an oil: IR (CH_2Cl_2) 5.73, 5.83 μm; NMR ($CDCl_3$) δ 0.17 and 0.23 (2 s, $Si(CH_3)_2$), 0.97 (s, *t*-BuSi), 2.30 (s, CH_3CO), 3.98 (d, J = 2.5 Hz, CH_3COCH), 4.43 (dd, J = 2.5, 8 Hz, $CHCH{=}CH_2$), 5.10–5.50 (m, $CH{=}CH_2$), 5.62–6.18 (m, $CH{=}CH_2$); mass spectrum, m/e 196.

Acetyl Introduction via a Trimethylsilyl Intermediate. A. Isolation of Trimethylsilyl Intermediate. (6*R,7*R**)-2,2-Dimethyl-7-(trimethylsilyl)-1-aza-3-oxabicyclo[4.2.0]octen-8-one (11).** To a stirred solution of freshly prepared LDA (1.34 mmol) in THF (4 mL) at −78 °C was added a solution of **2** (197 mg, 1.27 mmol) in THF (1.0 mL). The resulting enolate solution was stirred for 5 min and neat Me_3SiCl (170 μL, 1.34 mmol) was added. This mixture was stirred for 14 min at −78 °C. Saturated aqueous NH_4Cl solution (4 mL) was added. Workup (Et_2O (10 mL, 5 mL), brine, $MgSO_4$) gave 278 mg of white, crystalline product. Recrystallization from pentane (5 mL) required cooling in dry ice to obtain a low recovery (15 mg) of analytically pure **11** (mp 60–62 °C). The crystallization liquor was concentrated. PLC of the recovered material (30% EtOAc/C_6H_{12}) provided an additional 222 mg of **11** (R_f 0.34–0.53). The combined yield was 82%: IR (CH_2Cl_2) 5.75 μm; NMR ($CDCl_3$) δ 0.13 (s, $Si(CH_3)_2$), 1.37 and 1.77 (2 s, *gem*-dimethyl), 1.8 (m, $H_{5\alpha}$ and $H_{5\beta}$), 2.37 (d, J = 1.6 Hz, H_7), 3.35 (ddd, J = 10.3, 5.4, and 1.6 Hz, H_6), 3.86 (4-line m, $H_{4\alpha}$ and $H_{4\beta}$); mass spectrum, m/e 212. Anal. ($C_{11}H_{21}NO_2Si$) C, H, N.

(3*R,4*R**)-1-(*tert*-Butyldimethylsilyl)-3-(trimethylsilyl)-4-vinylazetidin-2-one (12).** Following the procedure described above for oxazoline–azetidinone **2**, vinylazetidinone **5** was enolized and silylated to give **12**, obtained as a colorless liquid in 89% yield: IR (CH_2Cl_2) 5.79 μm; NMR ($CDCl_3$) δ 0.10–0.20 (multiple s, $Si(CH_3)_3$ and $Si(CH_3)_2$), 0.95 (s, *t*-BuSi), 2.60 (d, J = 2.5 Hz, H_3), 3.73 (dd, J = 8, 2.5 Hz, H_4), 4.87–6.13 (m, $CH{=}CH_2$); mass spectrum, m/e 283 (M^+), 268, 226, 210.

B. One-Pot Procedure. As described in part A, vinylazetidinone **5** (102 mg, 483 mmol) was treated with freshly prepared LDA (0.508 mmol) followed by neat Me_3SiCl (0.508 mmol). After the mixture was stirred for 19 min at −78 °C, a second addition of LDA (0.508 mmol) was made. The yellow solution was stirred for 2.25 h. A solution of *N*-acetylimidazole (56 mg, 0.508 mmol) in THF (1 mL) was added. Stirring was continued for 25 min at −78 °C. The cooling bath was removed and the solution was stirred for an additional 35 min. Saturated NH_4Cl solution (4 mL) was added. Workup (Et_2O (10 mL, 5 mL), H_2O (3 × 5 mL), brine, $MgSO_4$) provided 115 mg of a yellow oil. PLC (10% EtOAc/C_6H_{12}) afforded 11 mg (8%) of a ca. 1:1 mixture of **12** and its cis isomer (R_f 0.45–0.51) and 77 mg (63%) of *trans*-acetylazetidinone **13** (R_f 0.17–0.33). The NMR spectrum of recovered (trimethylsilyl)azetidinone showed the following signals assignable to the cis isomer: ($CDCl_3$) δ 3.13 (d, J = 5 Hz, H_3), 4.17 (dd, J = 9, 5 Hz, H_4).

Similarly via a one-pot procedure, **2** was converted to **9**.

Aldol Oxidation. Preparation of 9 from 3a–d. The oxidation was done according to the method of Swern[11] (procedure A). Workup (H_2O (3×), brine, $MgSO_4$) provided crude ketone as an oil. This material was dissolved in a minimum amount of 5% EtOAc/CH_2Cl_2. The solution was filtered through a bed of Baker silica gel, washing with additional EtOAc/CH_2Cl_2. The material recovered by evaporation of the filtrate under vacuum was purified by HPLC on silica. Elution was 4% EtOAc/CH_2Cl_2 provided crystalline **9** in 85% yield. Recrystallization from ca. 1:1 hot Et_2O/pentane afforded analytically pure material: mp 73–74 °C; IR (Nujol mull) 5.72 5.86 μm; NMR ($CDCl_3$) δ 1.42 and 1.72 (2 s, *gem*-dimethyls), 1.7–1.9 (m, $CHCH_2$), 2.30 (s, CH_3CO), 3.8–4.1 (m, $CHCHCH_2CH_2$). Anal. ($C_{10}H_{16}NO_3$) C, H, N.

Similarly, aldol mixture **6a–d** was oxidized to *trans*-acetylazetidinone **13**. The product was isolated by PLC (10% EtOAc/C_6H_{12}; R_f 0.14–0.28).

General Procedure for the K-Selectride Reduction. A 0.5 M solution of K-Selectride (2.4 equiv) in THF was added to a 0.1–0.2 M solution of the β-keto lactam (i.e., **9** or **13**) in anhydrous Et_2O at 25 °C under a nitrogen atmosphere. The resulting solution was stirred for a minimum of 30 min. Prolonged reaction time does not increase the conversion of ketone to carbinol. The reaction was quenched by the addition of glacial acetic acid (2–4 equiv).[24] The mixture was diluted three- to fourfold with EtOAc and filtered through a packed bed of Supercel. The filter cake was washed with additional EtOAc. The filtrate was evaporated under vacuum to give crude carbinol which was purified by PLC or column chromatography as described above. The yields typically ranged from 65–85% of a ca. 9:1 mixture of diastereomers, with the major diastereomer being the desired 8*R** carbinol.

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Registry No. (±)-**1**, 65750-57-4; (±)-**2**, 65750-48-3; **3a**, 65794-45-8; **3b**, 65794-44-7; **3c**, 72690-81-4; **3d**, 72690-80-3; (±)-**4**, 45468-20-0; (±)-**5**, 67245-86-7; **6a**, 77122-80-6; **6b**, 77122-81-7; **6c**, 77122-82-8; **6d**, 77122-83-9; **7a**, 77097-58-6; **7b**, 77122-84-0; **9**, 77097-59-7; **10** (isomer 1), 77097-60-0; **10** (isomer 2), 77122-85-1; **11**, 77097-61-1; (±)-*cis*-**12**, 77097-62-2; (±)-*trans*-**12**, 77097-63-3; **13**, 77097-64-4.

(22) Acetylazetidinone **9**, a minor product in this reaction observed in the NMR of the crude product, was not isolated by PLC as it is sensitive to silica gel. However, **9** can, on large scale, be purified by preparative HPLC, a more rapid chromatographic method in which the silica gel contact time is decreased.

(23) The solution of *N*-acetylimidazole in THF is placed in a −78 °C cooling bath just prior to initiating the enolate transfer. More efficient cooling results in precipitation of the *N*-acetylimidazole.

(24) An aqueous workup was avoided due to the water solubility of **3**.