An Enantioselective Approach to (+)-Thienamycin from Dimethyl 1,3-Acetonedicarboxylate and (+)-α-Methylbenzylamine[1]

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A practical, high-yielding synthesis of chiral amino acid **3b**, a precursor to (+)-thienamycin and its derivatives, has been achieved. The key element in the synthesis is the reduction of the enamino ketone **9** which establishes the three asymmetric centers. Two reduction procedures, one utilizing a borane–borohydride tandem combination and the other a catalytic hydrogenation, are described. The latter procedure allowed the design of a process that required the isolation of only a single intermediate, the lactone diastereomer **15**.

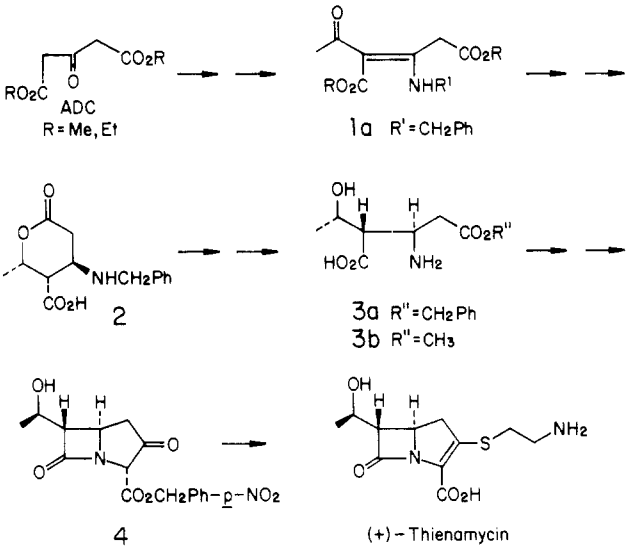
Introduction

Several years ago we reported[2] the synthesis of the racemic amino acid **3a** and demonstrated an efficient conversion of it to (±)-thienamycin. The enormous commercial potential of thienamycin derivatives and other potent carbapenem antibiotics coupled with the challenging structural features has resulted in intense and varied synthetic effort.[3] The simplicity of the conversion of **3** to the bicyclic carbapenem **4** made the acetonedicarboxylate (ADC) route a desirable process when considering large-scale synthesis. A serious drawback to this route was that it produced racemic intermediates. Subsequent to our disclosure, G. Gal, D. G. Reinhold, and R. M. Purick of these labs developed a resolution of the lactone **2** which afforded chiral **3b** and ultimately (+)-thienamycin. Although the resolution of **2** provided usable quantities of **3b** and fueled the development[4] of the chemistry from **3b** to (+)-thienamycin, it nonetheless did not constitute a commercially sound process due to the number of manipulations and the limiting theoretical yield of 50%. An asymmetric synthesis of **3b** could in theory eliminate both of these drawbacks, and in this report we describe a simple accomplishment of this goal (see Scheme I).

Strategy for an Asymmetric Synthesis

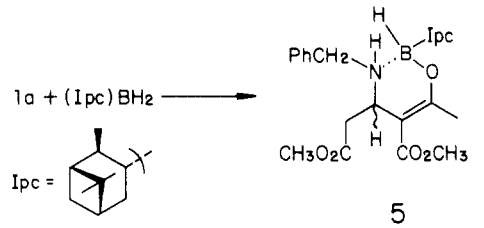
Two conceptually different approaches were considered to make the ADC route enantioselective: (1) reduction of achiral enamino ketone **1** with a chiral reducing agent or

Scheme I



(2) reduction of a chiral variant of **1** with achiral reducing agents.[5]

The hydrogenation of achiral **1a** over Raney nickel modified with (+)-tartaric acid[6] or chiral rhodium catalysts failed due to the inertness of the substrate. More successful results were obtained from the reduction of **1a** with chiral boranes. For example, the reduction of **1a** (R = CH_3) with monoisopinocampheylborane[7] gave a 50% diastereomeric excess (by NMR) of boron enolates **5**. However, as with the boron chelates that will be described below, a subsequent reduction using a borohydride is required to reduce the enolate bond of **5**.



(1) Presented in part at the 18th Middle Atlantic Regional Meeting, Newark, NJ, May 21, 1984.

(2) (a) Melillo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Tetrahedron Lett.* **1980**, *21*, 2783. (b) *Ibid* **1981**, *22*, 913.

(3) (a) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161. (b) Bouffard, F. A.; Christensen, B. G. *J. Org. Chem.* **1981**, *46*, 2208. (c) Karady, S.; Amato, J. S.; Reamer, R. A.; Weinstock, L. M. *J. Am. Chem. Soc.* **1981**, *103*, 6765. (d) Shiozaki, M.; Ishida, N.; Hiraoka, T.; Yanagisawa, H. *Tetrahedron Lett.* **1981**, *22*, 5205. (e) Kametani, T.; Huang, S.-P.; Nagahara, T.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2282. (f) Kametani, T.; Nagahara, T. D.; Ihara, M. *Ibid.* **1981**, 3048. (g) Durette, P. *Carbohydr. Res.* **1982**, *100*, C27. (h) Hanessian, S.; Desilets, D.; Rancourt, G.; Fortin, R. *Can. J. Chem.* **1982**, *60*, 2292. (i) Ikota, N.; Yoshino, O.; Koga, K. *Chem. Pharm. Bull.* **1982**, *30*, 1929. (j) Reider, P. J.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 2293. (k) Stevens, R. V.; Albizati. K. *J. Chem. Soc., Chem. Commun.* **1982**, 104. (l) Kametani, T.; Huang, S.-P.; Nakayama, A.; Honda, T. *J. Org. Chem.* **1982**, *47*, 2328. (m) Aratani, M.; Sawada, K.; Hashimoto, M. *Tetrahedron Lett.* **1982**, *23*, 3921. (n) Okano, K.; Izawa, T.; Ohno, M. *Ibid* **1983**, *24*, 217. (o) Shibasaki, M.; Nishida, A.; Ikegami, S. *Heterocycles* **1983**, *20*, 136. (p) Grieco, P. A.; Flynn, D. L.; Zelle, R. E. *J. Am. Chem. Soc.* **1984**, 106. 6414.

(4) This was the result of the labors of numerous individuals in this department and was reported on by S. H. Pines. See: Pines, S. H. "Organic Synthesis Today and Tomorrow", Trost, Barry M., Hutchinson, C. Richard, Eds.; Pergamon Press: Oxford, NY. 1981.

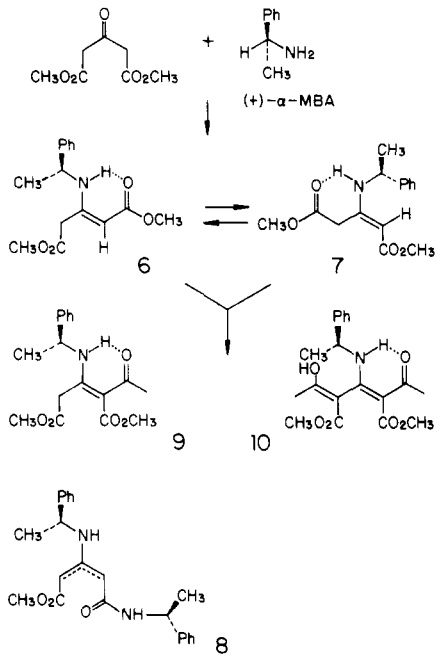
(5) A basic difference between these two approaches, which is not immediately obvious, is that the first gives the reduction product as an enriched pair of *enantiomers* and the second as *diastereomers*. We expected that purification of the desired optical isomer in the latter case would be simpler and more efficient.

(6) Harada, T.; Izumi, Y. *Chem. Lett.* **1978**, 1195 and references therein.

(7) Pelter, A.; Ryder, D. J.; Sheppard, J. H.; Subrahmanyam, C.; Brown, H. C.; Mandal, A. K. *Tetrahedron Lett.* **1979**, 4777.

0022-3263/86/1951-1498$01.50/0

Scheme II



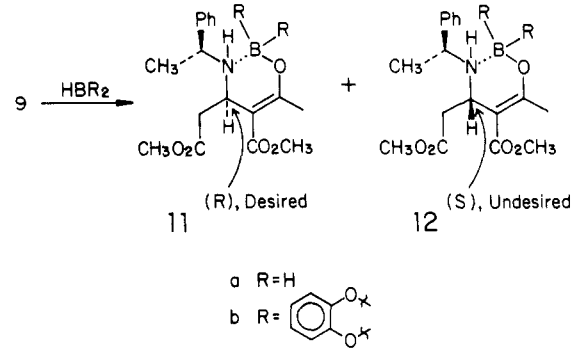
Our attention then turned to the second conceptual approach, the incorporation of a chiral auxiliary onto substrate **1** at one of three suitable sites: either of the ester groups or on the nitrogen. We anticipated that either ester group would be too far removed from the asymmetric centers being established to be effective. Having the chiral group attached to the nitrogen was more appealing in light of the results of our chemical reductions on the enamino ketone system which proceeded via initial reduction of the carbon, C-3, attached to the nitrogen (e.g., see **5**). A significant degree of asymmetric induction might be obtained by virtue of the proximity of the chiral center. The substitution of α-methylbenzylamine for benzylamine in **1a** was particularly attractive because of the price and availability of both enantiomers and also its use would not require extensive alteration of the chemistry that we had demonstrated for the racemic series.[8]

Results and Discussion

(A) Preparation of the Chiral Enamino Ketone 9. The condensation of dimethyl acetonedicarboxylate with (R)-(+)-α-methylbenzylamine[9] proceeds smoothly in toluene as well as in a number of other solvents such as diethyl ether, ethyl acetate, and methylene chloride. This condensation to form **6** and **7**, vinylogous urethanes, does not require the removal of water and, in fact, can even be performed in aqueous medium. The use of toluene as the solvent allows the eventual removal of water by azeotropic distillation leaving a dry solution of **6** and **7** in nearly quantitative yield. Purification or isolation is unnecessary.

In solution, the enamine formed exists as an equilibrium mixture of **6** and **7** (see Scheme II) (in $CDCl_3$ the ratio of **6**/**7** is approximately 85/15).[10] However, crystallization

Scheme III



of these equilibrating isomers gives only isomer **7**. This equilibrium becomes subtly important to the success of the subsequent acetylation reaction with ketene.

The presence of a small amount of acetic acid (6 mol %) in the condensation reaction is recommended because it (a) doubles the rate of enamine formation, (b) lowers the amount of the major byproduct, amide **8**, to less than 1%, and (c) greatly increases the solubility of **7** in toluene.

The acylation of the mixture of enamines **6** and **7** can be accomplished by using either acetic anhydride or ketene.[11,12] Acylation in acetic anhydride requires heating at 95 °C for 20–30 h and gives **9** in 80% overall yield from α-methylbenzylamine. Ketene gas, on the other hand, reacts instantaneously with the enamines **6** and **7** in toluene at 25 °C. The overall yield of **9** from α-methylbenzylamine exceeds 95% as long as precautions are taken to establish the equilibrium between isomers **6** and **7** prior to the introduction of ketene. To illustrate this point, if freshly dissolved crystalline isomer **7** is immediately treated with ketene, enamino ketone **9** is formed along with an equal amount of the diacetylated product **10**. In contrast, an equilibrated solution of **6** and **7** produces **9** in >95% yield.[13] The unique properties of the diacetyl compound **10** and the dichotomy of mechanisms for the two enamine isomers **6** and **7** will be the subject of a future communication.

Since the enamino ketone was produced in high yield and with few impurities, it was used without purification.

(B) Reduction of the Enamino Ketone 9 Using Boron Reagents. Upon initiation of this project, only borohydrides under acidic conditions had been used to successfully reduce the enamino ketone moiety of **1**. Applying such conditions—$NaCNBH_3/HOAc$[2]—to the chiral enamino ketone **9** resulted in very poor stereochemical control, and a complex array of many, if not all, of the eight theoretically possible diastereomers was obtained.

As mentioned earlier, our further investigation revealed another class of reagents, the boranes, that reduced the

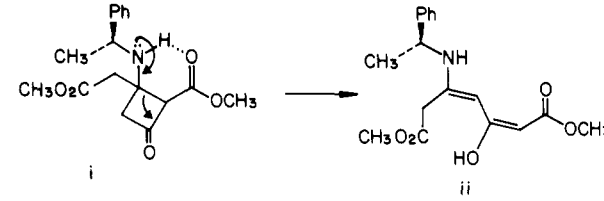
(8) Chiral amino alcohols, phenylglycinates, and other chiral amino acids were considered. Although similar stereochemical results were obtained, there were no advantages over α-methylbenzylamine.

(9) The *S* enantiomer reacts analogously to give the other stereochemical series. However, the (*R*)-amine leads to the (+)-amino acid **3b**, which is the enantiomer needed to produce (+)-thienamycin. Therefore, the ensuing discussion will be limited to the stereochemical series derived from (*R*)-α-methylbenzylamine.

(10) A similar isomerization was recently described for the benzyl enamine of ethyl acetoacetate, see: Shieh, T.-L.; Lin, C.-T.; McKenzie, A. T.; Byrn, S. R. *J. Org. Chem.* **1983**, *48*, 3103.

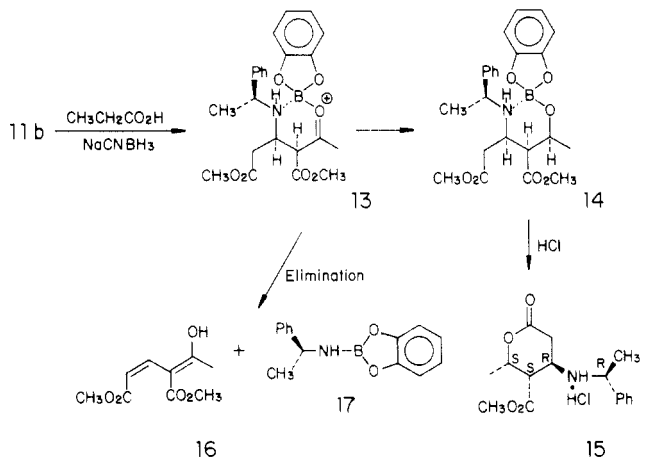
(11) Another reagent combination, acetyl chloride and triethylamine, acylates the enamine **6** but an entire mole of nonvolatile amine hydrochloride is produced. This would necessitate a workup step.

(12) We believe that both reagents directly acylate the carbon β to the enamine nitrogen as opposed to an initial 2 + 2 cycloaddition to give the cyclobutanone intermediate i. The opening of i would almost certainly give predominantly the unobserved product ii.



(13) The overreaction of **9** with ketene to form the diacetylated product **10** is relatively slow.

Scheme IV

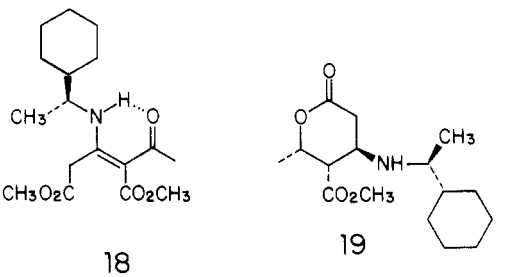


enamino ketone moiety in an exploitable fashion.[14] In contrast to the borohydrides, the boranes introduce only the first asymmetric center (see structures **11** and **12**). For example, reaction of the enamino ketone **9** with borane THF at 0 °C cleanly produced[15] amine boranes **11a** and **12a** in a 4/1 ratio determined by ^1H and ^{13}C NMR spectroscopy. Likewise,[16] catechol borane reacted smoothly with **9** at 0 °C to give a 5/1 mixture of the diastereomers **11b**/**12b** (see Scheme III). Furthermore, the amount of minor diastereomer **12b** became undetectable (<5%) by NMR when the reaction temperature was lowered to −78 °C.

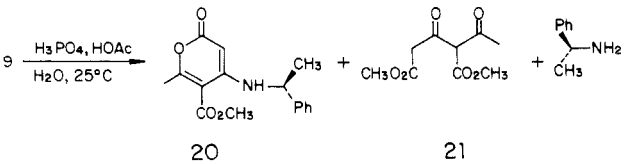
Reduction of the chelates **11a** and **12a** with $NaCNBH_3$ in acetic acid proved to be slow (days) and produced very little desired product. On the other hand, the substituted chelate **11b** was readily reduced with $NaCNBH_3$ in acetic acid or propionic acid. This increased rate may be due to the increased charge stabilization of the intermediate **13**.[17] A consequence of the increased reactivity of intermediate **13** is elimination to **16** and **17** (see Scheme IV). In fact, if **11b** is allowed to age in the acidic medium in the absence of hydride reducing agent, **16** and **17** are the sole products. Therefore the hydride reduciton of **13** must quickly follow its formation, the result of which is decreased stereoselectivity. For example, both protonation of the chelate **11b** and the hydride reduction of the oxonium intermediate **13** can occur from the opposite face of the molecule as that drawn in the scheme resulting in diastereomers. In spite of these problems, a 49% overall yield of pure lactone **15**[18] was isolated by lactonization in a fashion similar to that reported for the racemic synthesis.[2]

While this approach did not meet all our needs for a large-scale synthesis, this chemical reduction sequence did demonstrate two important facts: (1) the chirality of the α-methylbenzyl group of the enamino ketone **9** was capable of effectively guiding a reducing agent in from a specific side of the molecule, and (2) the lactone **15** possessed physical properties that are exploitable for an isolation/purification. With these encouraging leads, a catalytic hydrogenation method was explored and developed.

(C) Catalytic Hydrogenation of the Enamino Ketone 9. Our initial attempts to reduce the keto enamine system of **9** revealed that this would not be a trivial undertaking. The substrate **9** was inert to typical hydrogenation conditions using palladium, Raney nickel, and Wilkinson-type catalysts, whereas rhodium or ruthenium-on-carbon catalysis led to selective aromatic ring reduction producing the cyclohexyl derivative **18**. Platinum catalysts provided the only source of encouragement. Although **9** was inert to platinum catalysts in neutral or basic solvents, in acidic solvents such as acetic acid a low yield (10%) of the desired **15** was obtained. Hydrogenation of the aromatic ring of both **9** and **15** was the major competitive reaction resulting in **19** as the major product after lactonization. Further investigation revealed that various

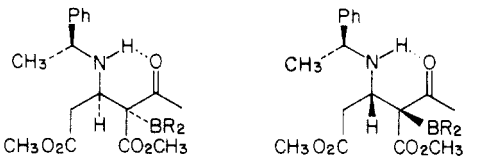


acidic activators influenced the selectivity of the catalytic system. Lewis acids such as $BF_3{\cdot}OEt_2$ and $AlCl_3$ and various Brönstead acids such as HCl, trichloroacetic, H_2SO_4, methane or *p*-toluenesulfonic acids, trifluoroacetic, oxalic, and phosphoric acid all served to activate the substrate **9** towards catalytic reduction. Phosphoric acid and oxalic acid gave the best enamino ketone versus aromatic ring reduction selectivity and minimized other side product formation. A typical reduction using phosphoric acid gives less than 4%[19] of the acid-catalyzed decomposition to the pyrone **20**, diketone **21**, and α-methylbenzylamine. Several of the other activators including



(14) Many other types of reducing agents were probed without success. The stability of the keto enamine system necessitated the use of pressing conditions for any reaction to occur. Basic reagents such as $LiAlH_4$, the alcohol-modified aluminates, and borohydrides such as the Selectrides (Aldrich) resulted in proton abstraction from the acidic methylene group. More vigorous reaction conditions on the resulting enolate resulted in side reactions such as reduction of the ester groups. On the other hand, strongly acidic conditions, like those required for ionic silane reductions, caused hydrolysis of the enamine and/or cyclization to the pyrone derivative **20**. Finally, reductions done under nucleophilic conditions caused solvolytic side reactions such as deacetylation or decarboalkoxylation.

(15) It is uncertain whether the borane reagents react with **9** in a 1,4-addition to give the chelates **11** and **12** directly or in a 1,2 mode to give the adducts iii which then undergo rapid C to O boron migration.



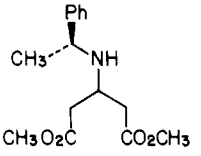
(16) Thus far, every borane reagent we have tried reacted with **9** to give the reduced chelates **11** and **12**.

(17) We believe a manifestation of this protonation of **11b** to **13** is the change in the chemical shift for the enol methyl group from δ 2.13 to 2.35 upon addition of acetic acid to the $CDCl_3$ solution of **11b**. A similar shift does not occur with **11a**.

(18) This is the required lactone diastereomer, the so-called *SSR-R* diasteromer. The order of the descriptors is listed as drawn in figure **15**. That this was the desired diastereomer was determined by converting it, using the chemistry to be described, to the amino acid **3b** which had already been converted to natural (+)-thienamycin.[4] Of course, the use of (*S*)-α-methylbenzylamine for making **9** leads to the "unnatural" thienamycin intermediate, that is the *RRS-S* lactone which is the mirror image of **15**.

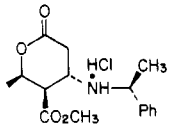
(19) This estimate is based on the ratio of the half-life of **9** in a typical reduction (1.5 h) to the half-life of **9** in the same medium without hydrogen present (38 h).

HCl, trichloroacetic, and the sulfonic acids caused competing deacetylation of the substrate **9** leading to varying amounts of the amine **22**.

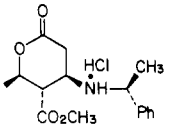


22

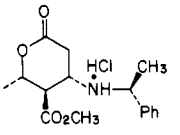
Significantly, with phosphoric acid, the amount of aromatic saturation that occurs is from the reduction of **9** to **18** and not the result of overreduction of **15** to **19**. This enables the reduction to be run until the hydrogen uptake ceases and obviates the problem of stoichiometry, which could result from the use of crude **9**. The phosphoric acid procedure was chosen for optimization. Ideally, hydrogenations of the enamino ketone **9** are performed in acetic acid containing 2 mol equiv of H_3PO_4 at 20 °C and 90–1000 psi H_2 in a well-stirred autoclave.[20] By HPLC assay, the yield of the desired product **15** (or **29**) was approximately 60%. The major byproducts are the *RRS-R* diastereomer **23** (15–18%),[21] dienol **16**, α-methylbenzylamine (10%), and cyclohexyl lactone **19** (5–10%). A low but detectable (HPLC, <2%) level of another minor isomer, (*RSR-R*)-**24**, is also produced[22] presumably accompanied by an even smaller amount of its diastereomer, (*SRS-R*)-**25**.



23 RRS-R



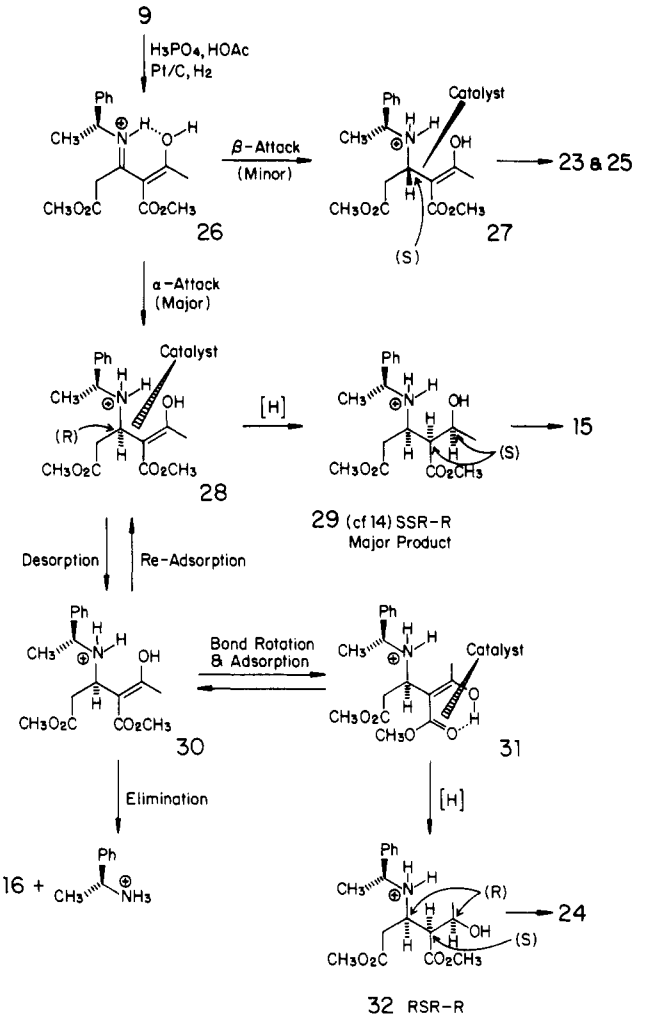
24 RSR-R



25 SRS-R

(D) Mechanism of the Catalytic Reduction. A basic understanding of the reduction mechanism has been constructed from the stereochemical and regiochemical results as well as from how these results change as a function of reaction conditions. Because no hydrogenation occurs in the absence of acid and because the rate of reduction increases as the pKa of the acid decreases (trifluoroacetic > oxalic $\simeq$ H_3PO_4 > HOAc), a protonated intermediate **26** (see Scheme V) is inferred in the proposed mechanistic scheme.[23] No such intermediate could be directly observed (^1H and ^{13}C NMR) in solution, but its intermediacy is also implied in the formation of pyrone **20** and diketone **21**. While it is not certain whether this protonation occurs before or after adsorption on the catalyst surface, the predominant mode of approach of the catalyst is from the α-face (pro-*R* face) of the substrate in the conformation drawn which maximizes hydrogen bonding and minimizes steric interactions between the C-2 ester and the benzylic groups. Rotation of the benzylic carbon–nitrogen bond is sterically restricted resulting in a planar molecule with the α-face shielded predominantly by a methyl group and the β-face shielded by the larger phenyl group. Hydrogenation

Scheme V



of the iminium group produces **27** and **28**.[24] These intermediates are very reactive[25] and have not been directly observed. Higher hydrogenation temperatures lead to increased formation of α-methylbenzylamine and dienol **16** presumably due to accelerated thermal instability of **27** and **28**. Lower hydrogenation temperatures likewise result in increased amounts of α-methylbenzylamine and dienol **16**, due to a deceleration of the second reduction step to give the stable amino alcohols **29** and **32**. Low hydrogen pressure and poor agitation, which lead to a "hydrogen-poor" catalyst surface, also result in larger amounts of α-methylbenzylamine and dienol **16**, again reflecting the need to quickly hydrogenate intermediates **27** and **28**.

The reduction of the intermediate **28** produces the all-syn reduced amino alcohol **29**. Likewise, the minor intermediate **27** gives the all-β-syn diastereomer of **29**. Minor amounts of isomer **32** have been identified by HPLC and even smaller amounts of other diastereomers are assumed to be formed in the reduction as a result of bond rotation of intermediates either adsorbed on the catalyst or after desorption (see intermediate **31** in Scheme V).

(E) Isolation of the Reduction Product 15. The catalytic reduction of the enamino ketone **9** as described

(20) Higher pressure and better agitation both have a beneficial effect on the yield by providing a more hydrogen-rich catalyst surface.

(21) This translates to a 60% diasteromeric excess of the desired isomer **15**.

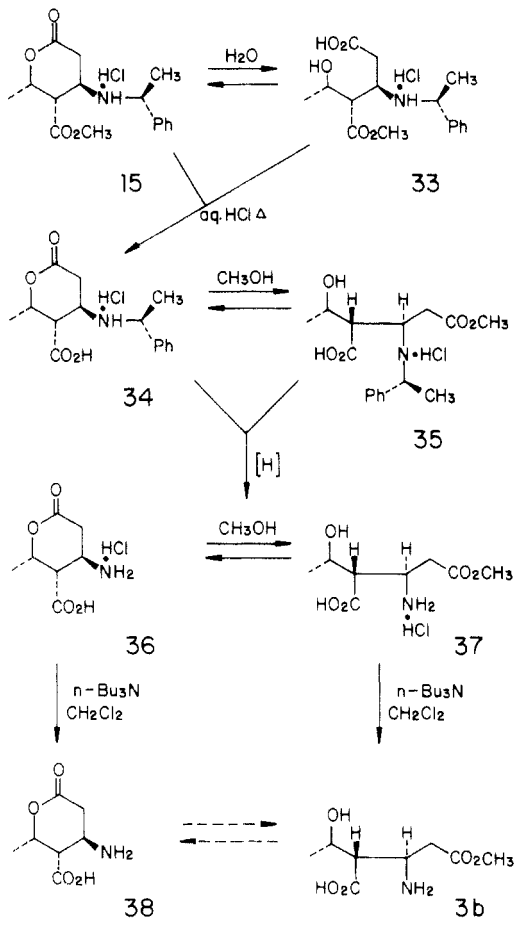
(22) An authentic sample of **24** was prepared from **15** using the inversion procedure described for the racemic *N*-benzyl series, see ref 1b. The HPLC retention time of the authentic sample was identical with that of the minor isomer.

(23) Protonation on oxygen is expected, see: Greenhill, J. V. *Chem. Soc. Rev.* **1977**, 277.

(24) Since the ratio of diastereomers **15**/**23** is 3.5/1, the ratio of **28**/**27** presumably is approximately the same.

(25) Elimination of α-methylbenzylamine was an expected side reaction. Forewarning of the ease of this reaction was offered by the fragmentation of the boron enolate **13** to **16** and **17**.

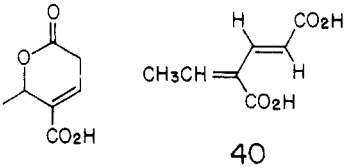
Scheme VI



above produces an assay yield of greater than 60% of the *SSR-R* diastereomer **29**. Amino alcohol **29** coexists in the reduction solution with its corresponding lactone and with time (3–6 days at room temperature) it will convert completely to the lactone, as do the minor diastereomers present. However, treatment with a stronger acid, such as hydrochloric, affects rapid lactonization of **29** to produce **15**. For the purpose of isolation, after filtration of the catalyst most of the acetic acid is removed by vacuum distillation. The residue is diluted with a nonpolar, aprotic solvent such as ethyl acetate or diethyl ether and then treated with HCl gas. The lactone **15** crystallizes efficiently (80–90%) and with high purity (>96%). The minor diastereomer, (*RRS-R*)-**23**, which would lead to the undesired enantiomer of **3b**, is completely removed.

(F) Conversion of the Lactone 15 to the Amino Acid 3b. The conversion of the lactone **15** to the target amino acid **3b** includes the following operations: hydrolysis of the ester, hydrogenolysis of the α-methylbenzyl group, methanolysis of the lactone ring, and isolation. After considerable planning and experimentation we decided that the most streamlined process would result from doing the operations in that order (see Scheme VI). In particular, this would set up the possibility of a simultaneous solvolysis/hydrogenolysis procedure simply by performing the reduction in methanol solution. As indicated in Scheme VI, the proposed route involves a number of equilibria between lactone intermediates (on the left-hand side of the scheme) and acylcic intermediates (on the right). Control of these equilibria is essential to achieve a high overall yield of amino acid **3b**.

Hydrolysis of the ester **15** by heating at reflux in constant-boiling 6 N aqueous HCl gave an 85–90% HPLC assay yield of the desired acid **34**. The major byproducts were α-methylbenzylamine, lactone **39**, and diacid **40**, all resulting from thermal elimination reactions. Because it was shown that the acid **34** was stable to the hydrolysis conditions, the formation of **39** and **40** due to overreaction was ruled out. Instead, they must arise from side reaction of the ester **15**. This suggested that if the rate of hydrolysis were accelerated, perhaps the yield of acid **34** could be increased at the expense of the byproducts **39** and **40**.



Indeed, by performing the reaction in concentrated aqueous HCl the rate of hydrolysis was significantly increased and allowed the reaction to be done at lower temperature (75–85 °C vs. 109 °C). This lower temperature disfavored the pyrolytic side reactions. Thus, heating the ester **15** in concentrated aqueous HCl for 4–6 h at 85 °C under pressure gave approximately a 98% yield of the acid **34**. Slightly lower yields were obtained if the hydrolysis were done in an open system which allows loss of HCl gas during the hydrolysis.

With such a high reaction yield for the hydrolysis, purification of **34** is not necessary for the hydrogenolysis/solvolysis sequence, but removal of the H_2O and HCl is necessary. This is readily accompished by vacuum concentration to a crystalline residue. Alternatively, the acid **34** can be crystallized from the cooled hydrolysis solution, but only with moderate efficiency. These losses can be minimized to a few percent if the suspension is partially concentrated before filtration.

The hydrogenolysis reaction is performed in methanol at 60 °C using a palladium-on-carbon catalyst at 40 psi H_2 and a reaction time of 10 h. These conditions ensure enough time for complete reduction and solvolytic ring opening to occur. With excellent product stability, underreaction is the major detriment to a high-yielding sequence (98%). The hydrogenolysis reaction is quantitative, but because the solvolysis is an equilibrium reaction a 2% yield of lactone **36** remains. Ideally, isolation of the amino acid **3b** would involve neutralization of the amino acid hydrochloride **37** with a base that gives a soluble hydrochloride in a solvent system that **3b** would be insoluble.[26] This was not possible in methanol solution due to the high solubility of **3b**. However, concentration of the methanol solution of the hydrochloride **37**, dilution of the oil with an aprotic solvent, and addition of one equivalent of an amine[27] such as n-Bu_3N or Et_3N resulted in the crystallization of the desired product **3b** in high yield (>90% from **15**) and excellent purity (>97%).

In summary, this enantioselective process enables the large-scale preparation of the highly functionalized, chiral amino acid **3b** which has been converted to (+)-thienamycin.[4] The process affords **3b** in approximately 50% overall yield with only one intermediate purification required.

(26) A similar approach was demonstrated for the *d*-10-camphorsulfonate salt of **3b** by Zambito, A. J.; Shukis, W. F.; Grabowski, E. J. J. (see ref 4).

(27) Alternatively, propylene oxide or epichlorohydrin can be added to the methanol concentrate. These reagents react with the amine hydrochloride **37** giving chlorohydrins and the free amino acid **3b** which crystallizes as it is formed. The yield is usually the same as that obtained using the amine neutralization procedure; therefore, in light of the toxicity of these epoxide reagents, we do not recommend their use.

Experimental Section

The (*R*)-(+)-α-methylbenzylamine, $[\alpha]^{25}_D$ +37° (neat), was purchased from Aldrich or Hexcel, stored under N_2, and used without purification. Dimethyl acetonedicarboxylate was obtained from either Aldrich or Lonza AG and normally used without purification as long as low levels of methyl acetoacetate were present. Catechol borane and sodium cyanoborohydride were purchased from Aldrich. The platinum and palladium catalysts were prepared by Engelhard Industries. Ketene gas was generated by pyrolysis of acetone vapors over a heated filament in an apparatus similar to the one available from Ace Glass, Inc. Ketene is a poisonous gas and methane is produced as a byproduct, and *both must be adequately vented.* Reagent grade solvents were used without purification. Melting points were determined on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The following spectrometers were used to record spectral data: IR, Perkin-Elmer 237B, polystyrene used as a reference; UV, Beckman ACTA-III; ^{1}H NMR, Hitachi Perkin-Elmer R-24A 60 MHz or Bruker WM-250. Elemental analyses were performed by J. Wu of our Analytical Research Department.

(*R*)-3-[(1-Phenylethyl)amino]-2-pentenedioic Acid Dimethyl Esters (6 and 7). To a stirred solution of 35.1 g (0.202 mol) of dimethyl acetonedicarboxylate[28] and 0.72 g (0.012 mol) of acetic acid in 175 mL of toluene was added dropwise 24.2 g (0.20 mol) of (+)-α-methylbenzylamine. The solution was heated to 60 °C and aged for 4 h. The flask was fitted with a Dean–Stark apparatus and vacuum (70–100 mm) applied to the heated system to achieve reflux. After no further water separated in the distillate, the solution was cooled to room temperature and used, as is, in the following acylation procedures.

A sample of the crystalline isomer **7** was prepared by concentration of the toluene solution in vacuo and crystallization of the residue from diethyl ether to give colorless prisms: mp 97–99 °C, dependent on heating rate; IR ($CHCl_3$) 3400, 1740, 1650, and 1610 cm^{-1}; $[\alpha]^{25}_D$ = +135.6° (*c* 0.5%, MeOH) changes on standing due to isomerization to **6**; UV λmax (MeOH) 274 nm (ε 23,000) changing to 282 nm (ε 17,100) at equilibrium; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.45 (d, 3 H, *J* = 6 Hz, $-CHPhCH_3$), 3.48 (s, 3 H, $-CO_2CH_3$), 3.67 (s, 3 H, $-CO_2CH_3$), 3.88 (s, 2 H, $-CH_2-$), 4.1–4.8 (m including singlet at 4.49, 2 H, benzylic and vinylic H), 5.2 (b, 1 H, –NH), and 7.2 (s, 5 H, Ph). Upon standing, new peaks for isomer **6** appear at δ 1.48 (d, 3 H, *J* = 6 Hz, $-CHPhCH_3$), 3.01 (s, 2 H, $-CH_2-$), 3.55 (s, 3 H, $-CO_2CH_3$), 3.63 (s, 3 H, $-CO_2CH_3$), and 8.87 (b, 1 H, NH). Equilibrium is reached after approximately 4 h at probe temperature.

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.91; H, 7.15; N, 4.99.

[*R*-(*E*)]-2-Acetyl-3-[(1-phenylethyl)amino]-2-pentenedioic Acid Dimethyl Ester (9). Method A: Ketene. The toluene solution as described above containing approximately 63 g (0.20 mol) of the enamines 6 and 7 and 0.12 g (1.0 mmole of 85% H_3PO_4[29] was treated (subsurface introduction) at 25 °C with ketene gas generated by pyrolysis of acetone. CAUTION: Ketene is a poisonous gas. The progress of the reaction was followed by HPLC (DuPont Zorbax-Sil, 25 cm × 4.6 mm, hexane:$CHCl_3$:EtOH:HOAc (50:50:0.5:0.5), flow rate 2.2 mL/min, detector 295 nm, retention times: 3.1 min for **6** and **7**, 5.5 min for **9**). When 1–2% of the starting material remained, the introduciton of ketene gas was stopped and the toluene was removed in vacuo to give 70.1 g of a yellow oil that contained 61.2 g of **9** (96% yield from α-methylbenzylamine) by HPLC assay. This crude product was used without purification in the catalytic hydrogenation. For the borane procedure, and to obtain an analytical sample, the crude product was crystallized from MeOH–H_2O (60:40) at 0 °C to give colorless needles: mp 48–49.5 °C; IR ($CHCl_3$) 1740, 1685, and 1590 cm^{-1}; $[\alpha]^{25}_D$ = −243° (*c* 0.7%, MeOH); UV max (MeOH) 244 nm (ε 7,600) and 309 (16,400); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.55 (d, 3 H, *J* = 6 Hz, $-CHPhCH_3$), 2.30 (s, 3 H, $-COCH_3$), 3.46 (s, 2 H, $-CH_2-$), 3.58 (s, 3 H, saturated $-CO_2CH_3$), 3.62 (s, 3 H, unsaturated $-CO_2CH_3$), 4.69 (m, 1 H, benzylic H), 7.15 (s, 5 H, Ph), and 13.02 (b 1 H, NH).

Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.93; H, 6.63; N, 4.39. Found: C, 64.12; H, 6.77; N, 4.25.

Method B. Acetic Anhydride. A toluene solution of **6/7**, prepared as described above from 388 g of dimethyl acetonedicarboxylate and 244 g of (+)-α-methylbenzylamine, was concentrated in vacuo to an oil weighing 631 g. This residue was dissolved in 2 L of acetic anhydride and heated at 95 °C for 30 h at which point 1% of enamines **6/7** remained (HPLC). The solvents were removed under reduced pressure to give a red-amber oil containing 484 g (80% yield from α-methylbenzylamine) of the enamino ketone **9** by HPLC assay.

[2*S*-[2α,3α,4β(*R)]]-Tetrahydro-2-methyl-6-oxo-4-[(1-phenylethyl)amino]-2*H*-pyran-3-carboxylic Acid Methyl Ester Hydrochloride (15). Method A. Borane/Borohydride Reduction.** A solution of 0.62 g (5.17 mmol) of catecholborane in 8 mL of tetrahydrofuran, dried over 4-Å molecular sieves, was added dropwise over 20 min to a solution of 1.50 g (4.70 mmol) of the purified enamino ketone **9** in 9 mL of dry tetrahydrofuran at −78 °C. After it was stirred at −78 °C for 1 h, the solution was warmed to room temperature and concentrated under vacuum to a gum.[30] This residue was dissolved in 10 mL of dry propionic acid, cooled to 0 °C, and immediately treated by rapid addition of 0.44 g (7.0 mmol) of sodium cyanoborohydride in 10 mL of propionic acid. The resulting solution was warmed to room temperature, aged for 2 h, and then concentrated in vacuo. An ethyl acetate solution of this residue was washed with three portions of saturated aqueous $NaHCO_3$, and the organic layer was dried with Na_2SO_4, and concentrated to a yellow oil (2.25 g). Lactonization was affected by dissolving the oil into 20 mL of CH_2Cl_2 that had been saturated with HCL gas.[31] The lactone was crystallized by dilution with 20 mL of diethyl ether. After aging overnight at 5 °C the white solid was filtered and washed with cold 60% ethyl ether/CH_2Cl_2 to give 0.76 g (49% yield) of **15**. Physical properties of **15** are described below.

Method B. Catalytic Hydrogenation. A solution of the crude[32] enamino ketone [66.8 g of the crude containing 47.9 g (0.15 mol) of **9**] in 250 mL of acetic acid was charged in a 1-L stirred autoclave. To this solution was added 4.8 g of 5% platinum-on-carbon catalyst[33] and 43.2 g (0.375 mol) of 85% aqueous H_3PO_4. The vessel was cooled to 15 °C, purged with nitrogen, and pressurized to 1000 psi with hydrogen. The suspension was stirred at that pressure while maintaining a temperature of 15–20 °C for 20 h. The vessel was vented, purged with nitrogen, and filtered, and the catalyst was washed twice with acetic acid. Assay of the combined filtrates by HPLC[34] indicated a 63% yield of the desired

(28) The ketone used in this experiment was purified by crystallization from diethyl ether–hexane at 0 °C. Two impurities that have been identified (VPC or HPLC) in some lots of ketone are the methyl enol ether derivative, which is inert to the reaction conditions and is harmless, and methyl acetoacetate, which consumes α-methylbenzylamine and subsequently reacts with acetylating agent. Vacuum distillation removes the latter impurity, whereas fractional crystallization removes both. Normally, good quality samples of ADC are used without purification with the same results.

(29) A trace impurity of a basic nature which catalyzes ketene polymerization and causes yield variations is neutralized by the H_3PO_4. Alternatively, extraction of the toluene solution of **6** and **7** with water will remove this impurity. Addition of <1 mol % of a trialkylamine such as NEt_3 to the enamine solution exaggerates the polymerization and yield loss.

(30) An analytical sample of this intermediate could not be prepared. The ^{1}H NMR spectrum ($CDCl_3$, 60 MHz) of the crude revealed that several changes in chemical shifts had occurred as a result of the reduction. For example, the benzylic multiplet now appears at δ 4.51, the methyl ester singlets are at δ 3.61 and 3.33, the benzyl methyl doublet at δ 1.71, and most importantly the enol methyl singlet appears at δ 2.13. When the borane reduction is performed at a higher temperature, the presence of the other diastereomer **12b** can clearly be detected by an accompanying singlet at δ 2.24.

(31) HPLC assay (described under Method B) at this stage revealed several interesting features. The yield of the desired lactone isomer **15** was 56%. The ratio of diastereomers **15/23**, which is a reflection on the ratio of the boron enolates **11b** and **12b**, was approximately 30/1. Although excellent control of the absolute stereochemistry was achieved, several decomposition products (e.g., **16** and **17**) and lactone epimers (e.g. **25**) were evident. The catalytic reduction, Method B, offered much better control over these types of byproducts.

(32) The sample used in this experiment was produced by the ketene method A. Crude enamino ketone produced by the acetic anhydride method B works as well, after removal of residual Ac_2O.

(33) The reduction is sensitive to the amount and activity of the platinum catalyst.

lactone **15**. The filtrate was concentrated under reduced pressure (<25 mmHg) and the residue (90 mL) was dissolved in 950 mL of ethyl acetate containing 8.25 g HCl. The suspension was aged at 20–25 °C for 1 h and then at 0–5 °C for 1 h. The white solid was filtered, washed twice with 15-mL portions of cold ethyl acetate, and vacuum-dried to give 28.0 g of the lactone **15** (55% yield from α-methylbenzylamine, 57% from **9**); HPLC assay indicated that the purity was >98% and that none of the diastereomer **23** was present.

An analytical sample of **15** was prepared by recrystallization from MeCN to give colorless needles: mp 175.5–177.0 °C; IR (nujol) 1765 and 1735 cm^{-1}; $[\alpha]^{25}_D = -60.2°$ (*c* 0.65%, HOAc); ^1H NMR (D_2O, 250 MHz) δ 1.40 (d, 3 H, *J* = 6.6 Hz, CH_3–C_2), 1.71 (d, 3 H, *J* = 6.8 Hz, –CHPh*CH*$_3$), centered at 2.99 (*ABX*, 2 H, *J* = 7.4, 9.8, and 15.6 Hz, H_5 and H_5'), 3.47 (dd, 1 H, *J* = 3.3 and 3.6 Hz, H_3), 3.73 (s, 3 H, $-CO_2CH_3$), 3.82 (AB*X*, 1 H, *J* = 3.3, 7.4, and 9.8 Hz, H_4), 4.64 (q, 1 H, *J* = 6.8 Hz, benzylic H), 4.98 (dq, 1 H, *J* = 3.6 and 6.5 Hz, H_2), and 7.4–7.6 (m, 5 H, Ph).

Anal. Calcd for $C_{16}H_{22}ClNO_4$: C, 58.62; H, 6.77; N, 4.27; Cl, 10.82. Found: C, 58.69; H, 6.78; N, 4.24; Cl, 10.80.

The diastereomer **23** was isolated from the filtrate of **15** by concentrating in vacuo, partitioning the residue between EtOAc and aqueous $NaHCO_3$, and chromatographing the material in the organic layer on silica gel. The fractions eluted with 40% hexane–EtOAc were concentrated to give the free amine of **23**. Recrystallization from diethyl ether–hexane provided a pure sample of **23** (free base): mp 67–68 °C. The hydrochloride, **23**, was prepared by treating a diethyl ether–CH_2Cl_2 solution of the amine with HCl gas. The filtered solid was recrystallized from MeCN to give pure **23** as colorless needles: mp 167.0–169.5 °C; IR (nujol) 1765 and 1735 cm^{-1}; $[\alpha]^{25}_D = +130.1°$ (*c* 1.0%, HOAc); ^1H NMR (D_2O, 250 MHz) δ 1.30 (d, 3 H, *J* = 6.6 Hz, CH_3–C_2), 1.71 (d, 3 H, *J* = 6.8 Hz, –CHPhCH_3), centered at 3.14 (*ABX*, 2 H, *J* = 7.5, 9.1, and 16.3 Hz, H_5 and H_5'), 3.15 (dd, 1 H, *J* = 3.9 and 4.7 Hz, H_3), 3.68 (s, 3 H, $-CO_2CH_3$), 3.86 (AB*X*, 1 H, *J* = 4.7, 7.5, and 9.1 Hz, H_4), 4.58 (q, 1 H, *J* = 6.8 Hz, benzylic H), 4.97 (dq, 1 H, *J* = 3.9 and 6.6 Hz, H_2), and 7.4–7.6 (m, 5 H, Ph).

Anal. Calcd for $C_{16}H_{22}ClNO_4$: C, 58.62; H, 6.77; N, 4.27; Cl, 10.82. Found: C, 58.76; H, 6.78; N, 4.03; Cl, 10.65.

[2*S*-[2α,3α,4β(*R)]]-Tetrahydro-2-methyl-6-oxo-4-[(1-cyclohexylethyl)amino]-2*H*-pyran-3-carboxylic Acid Methyl Ester Hydrochloride (19).** A mixture of 12.0 g (0.037 mol) of the lactone **15**, 5.0 g of 5% platinum-on-carbon catalyst, and 10 mL of trifluoroacetic acid in 150 mL of acetic acid was stirred at room temperature in an autoclave under 150 psi hydrogen for 30 h. The vented and purged (N_2) suspension was filtered. The filtrate was concentrated under reduced pressure to an oil which was crystallized from CH_2Cl_2–diethyl ether to give 9.87 g (81% yield) of the cyclohexyl lactone **19** as a white powder. Recrystallization from CH_3CN provided a pure sample of **19** as colorless needles: mp 168.5–169.5 °C; IR (nujol) 1760 and 1735 cm^{-1}; $[\alpha]^{25}_D = -95.3°$ (*c* 1.0%, HOAc); ^1H NMR (Me_2SO-d_6), δ 0.8–1.9 (m, 11 H, cyclohexyl), 1.15 (d, 3 H, *J* = 6.6 Hz, –NCHCH_3), 1.30 (d, 3 H, *J* = 6.5 Hz, CH_3–C_2), 3.0–3.5 (m, 3 H, H_4, H_5, and H_5'), 3.72 (s, 3 H, $-CO_2CH_3$), 3.95 (b, 1 H, –N*CH*CH_3), and 5.19 (m, 1 H, H_2).

Anal. Calcd for $C_{16}H_{28}ClNO_4$: C, 57.56; H, 8.45; N, 4.19; Cl, 10.62. Found: C, 57.75; H, 8.33; N, 3.96; Cl, 10.54.

[2*S*-[2α,3α,4β(*R)]]-Tetrahydro-2-methyl-6-oxo-4-[(1-phenylethyl)amino]-2*H*-pyran-3-carboxylic Acid Hydrochloride (34).** A suspension of 14.71 g (4.49 mmol) of the ester **15** in 75 mL of 12 N aqueous HCl was stirred at 75–80 °C in a glass pressure bottle for 15 h. Considerable pressure is generated upon heating so appropriate care must be exercised. If this hydrolysis is done in an open vessel, a slightly lower yield is obtained. The reaction mixture was concentrated in vacuo to half its original volume and cooled at −10 °C for 2 h. The dense white prisms are filtered and vacuum-dried to give 13.17 g (93.5% yield) of the acid **34**. A methanol solution of this material can be substituted in the procedure described below.

An analytical sample of **34** was prepared by recrystallization from 6 N aqueous HCl: mp 188 °C dec; IR (nujol) 3250, 1765, 1740, and 1700 cm^{-1}; $[\alpha]^{25}_D = -60.1°$ (*c* 0.6%, HOAc); UV λmax (MeOH) 215 nm (ε, 1,150) and 256 (455); ^1H NMR (D_2O, 250 MHz) δ 1.47 (d, 3 H, *J* = 6.6 Hz, CH_3–C_2), 1.74 (d, 3 H, *J* = 6.8 Hz, –CHPh*CH*$_3$), centered at 2.98 (*ABX*), 2 H, *J* = 7.5, 9.5, and 16.0 Hz, H_5 and H_5'), 3.35 (dd, 1 H, *J* = 3.4 and 3.6 Hz, H_3), 3.82 (AB*X*, 1 H, *J* = 3.4, 7.5, and 9.5 Hz, H_4), 4.66 (q, 1 H, *J* = 6.8 Hz, benzylic H), 5.01 (dq, 1 H, *J* = 3.6 and 6.6 Hz, H_2), and 7.5 (s, 5 H, Ph).

Anal. Calcd for $C_{15}H_{23}ClNO_4$: C, 57.41; H, 6.42; N, 4.46; Cl, 11.30. Found: C, 57.34; H, 6.52; N, 4.22; Cl, 11.10.

[2*S*-[2*R,(*R**),3*S**]]-3-Amino-2-(1-hydroxyethyl)pentanedioic Acid 5-Methyl Ester (3b).** A suspension of 8.00 g (98% pure, 0.024 mol) of the ester lactone **15** in 40 mL of concentratd aqueous HCl was heated in a glass-lined rocker bomb at 85 °C for 6 h. The resulting suspension was concentrated in vacuo to constant weight. Assay of the solid by HPLC indicated a yield of **34** of 97–98%.

A methanol solution (40 mL) of the crude acid **34** was transferred to a Parr bottle, 0.75 g of 5% palladium-on-carbon catalyst was added, and the suspension was shaken under 40 psi hydrogen at 60 °C for 10 h. The suspension was cooled, vented, and filtered. The filtrate was concentrated at reduced pressure rapidly to avoid equilibration to the lactone **36**. The pale yellow oil, which weighed 9.53 g and contained approximately 30 wt % MeOH, was diluted with 60 mL of CH_2Cl_2 and treated with 4.42 g (0.024 mol) of tri-*n*-butylamine over a few minutes at room temperature. The resulting suspension was aged at room temperature for 6 h and then the product was filtered, washed several times with $CHCl_2$ to remove amine hydrochloride, and vacuum-dried to afford the amino acid **3b** as a white powder, 4.58 g (93.5% from **15**). This material was 98% pure by HPLC assay.[35]

Recrystallization from MeOH[36] provided pure **3b** as very small, colorless needles: mp 133 °C dec; IR (nujol) 1735 cm^{-1}; $[\alpha]^{25}_D = +32.2°$ (*c* 0.5%, MeOH, recorded immediately after dissolution); ^1H NMR (D_2O, 250 MHz) δ 1.12 (d, 3 H, *J* = 6.3 Hz, CH_3CH), 2.13 (dd, 1 H, *J*'s ≃ 5.0 Hz, H_2), centered at 2.72 (*ABX*, 2 H, *J* = 5.8, 7.4, 16.9 Hz, H_4), 3.54 (m, 1 H, H_3), 3.62 (s, 3 H, $-CO_2CH_3$), and 3.95 (m, 1 H, CH_3CH).

Anal. Calcd for $C_8H_{15}NO_5$: C, 46.82; H, 7.37; N, 6.83. Found: C, 46.52; H, 7.25; N, 6.71.

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Registry No. 3b, 79814-47-4; **6**, 101142-84-1; **7**, 101142-83-0; **9**, 101142-85-2; **11b**, 101142-86-3; **14**, 101032-71-7; **15**, 81972-25-0; **19**·HCl, 101032-74-0; **23**, 101032-73-9; **23** (free base), 101032-72-8; **34**, 84935-21-7; **36**, 79814-46-3; ADC (R=Me), 1830-54-2; (+)-α-MBA, 3886-69-9; ketene, 463-51-4; (+)-thienamycin, 59995-64-1.

(34) The weighed sample was first lactonized by treatment with 5% HCl in acetic acid, then it was diluted with MeCN and assayed on a DuPont C8-SP150, 25 cm × 4.6 mm reverse-phase column, mobile phase H_2O:CH_3CN:85% H_3PO_4 (70:10:4), flow rate 1.3 mL/min, detector 210 nm, retention times: 21 min for **15**, 19 min for the diastereomer **23**.

(35) DuPont C8-SP150, 25 cm × 4.6 mm reverse-phase column, mobile phase H_2O:CH_3CN:H_3PO_4 (99:1:0.1) containing 0.005 M sodium 1-hexanesulfonate, flow rate 2.0 mL/min, detector 210 nm, retention times: 6.8 min for **3b**, 2.6 min for the major impurity, **38**.

(36) The filtered solid must be washed immediately with CH_2Cl_2 to remove surface MeOH to prevent lactonization to **38** during drying.