Thienamycin

16.1 Introduction

In the late 1970s, scientists at Merck disclosed the potent antibacterial properties\(^1\) and the structure\(^2\) of the \(\beta\)-lactam antibiotic thienamycin (1). This compound is a constituent of fermentation broths of the soil microorganism, \textit{Streptomyces cattleya}, and it displays activity against \textit{Pseudomonas} and \(\beta\)-lactamase-producing species. Thienamycin is a zwitterionic compound, and its novel carbapenem structure, including absolute stereochemistry, was deduced on the basis of chemical, spectroscopic, and X-ray crystallographic studies.

In this chapter, we address the Merck synthesis of (+)-thienamycin (1).\(^3\) The development of this elegant synthesis was guided by the following realizations: (a) it is necessary to defer construction of thienamycin's carbapenem framework to a late stage in the synthesis by virtue of its rather unstable and reactive nature; (b) it would be advantageous to append the cysteamine and hydroxyethyl side chains at carbons 2 and 6, respectively, to a preformed ring system so that analogs could be readily prepared; and (c) it is desirable to develop an enantiospecific synthesis of thienamycin from a readily available, enantiomerically pure starting material. With these objectives in mind, the Merck group developed a highly efficient, novel, and enantiospecific synthesis of thienamycin. We begin with a discussion of the general strategy outlined retrosynthetically below.
16.2 Retrosynthetic Analysis and Strategy

The strained bicyclic carbapenem framework of thienamycin is the host of three contiguous stereocenters and several heteroatoms (Scheme 1). Removal of the cysteamine side chain affixed to C-2 furnishes β-keto ester 2 as a possible precursor. The intermolecular attack upon the keto function in 2 by a suitable thiol nucleophile could result in the formation of the natural product after dehydration of the initial tetrahedral adduct. In a most interesting and productive retrosynthetic maneuver, intermediate 2 could be traced in one step to α-diazo keto ester 4. It is important to recognize that diazo compounds, such as 4, are viable precursors to electron-deficient carbenes. In the synthetic direction, transition metal catalyzed decomposition of diazo keto ester 4 could conceivably furnish electron-deficient carbene 3; the intermediacy of 3 is expected to be brief, for it should readily insert into the proximal N–H bond to

![Scheme 1. Retrosynthetic analysis of thienamycin (1).](image-url)
give 2. This approach to the bicyclic nucleus of thienamycin is novel, and is strategically very different from Merck's first-generation synthesis of thienamycin which relied on the creation of a bond between C-2 and C-3 to achieve bicycle formation.\textsuperscript{4} It is instructive to draw attention to the $\beta$-hydroxy carbonyl moiety in intermediate 5, the projected precursor of diazo keto ester 4. This functional group relationship constitutes the retron for the aldol condensation transform.\textsuperscript{5} Thus, cleavage of the indicated bond in 5 furnishes monosubstituted $\beta$-lactam 7 and acetaldehyde (6) as potential precursors. In the synthetic direction, deprotonation of 7 at the site adjacent to the electron- withdrawing lactam carbonyl with a suitable base would furnish a lactam enolate which could be employed in an intermolecular aldol condensation with acetaldehyde (6). This event would result in the formation of the C6–C8 bond and would accomplish the introduction of the remaining two contiguous stereocenters.

The trimethylsilyl dithiane moiety is a conspicuous feature of intermediate 7. In addition to its role as a stable surrogate for a carboxyl function, this group provides a convenient opportunity for molecular simplification. Retrosynthetic cleavage of the indicated carbon–carbon bond in 7 furnishes intermediates 8 and 9 as potential precursors. The anion-stabilizing properties of the dithiane group in 9 should permit the formation of the corresponding carb-anion, the conjugate base of 9. The carbanion formed by deprotonation of 9 could then be used as a nucleophile in a coupling reaction with alkyl iodide 8, a suitable electrophile. The convergent union of intermediates 8 and 9, in this manner, would result in the formation of the C1–C2 bond of thienamycin. Through some straightforward functional group manipulations, iodide 8 could be formed from lactam ester 10. Amino diester 11 is derived retrosynthetically from 10 and could conceivably be elaborated in short order from inexpensive and readily available L-aspartic acid (12).

### 16.3 Total Synthesis

Merck's thienamycin synthesis commences with mono $N$-silylation of dibenzyl aspartate (13, Scheme 2), the bis(benzyl) ester of aspartic acid (12). Thus, treatment of a cooled (0\(^\circ\)C) solution of 13 in ether with trimethylsilyl chloride and triethylamine, followed by filtration to remove the triethylamine hydrochloride by-product, provides 11. When 11 is exposed to the action of one equivalent of tert-butyllithium chloride, the active hydrogen attached to nitrogen is removed, and the resultant anion spontaneously condenses with the electrophilic ester carbonyl four atoms away. After hydrolysis of the reaction mixture with 2 \(\times\) HCl saturated with ammonium chloride, enantiomerically pure azetidinone ester 10 is formed in 65–70\% yield from 13. Although it is conceivable that
Scheme 2. Synthesis of intermediate 16.
racemization at C-5 could have occurred during the course of the conversion of 11 to 10, it was found by chemical correlation that no such event takes place during this transformation.

Intermediate 10 must now be molded into a form suitable for coupling with the anion derived from dithiane 9. To this end, a chemoselective reduction of the benzyl ester grouping in 10 with excess sodium borohydride in methanol takes place smoothly and provides primary alcohol 14. Treatment of 14 with methanesulfonyl chloride and triethylamine affords a primary mesylate which is subsequently converted into iodide 15 with sodium iodide in acetone. Exposure of 15 to tert-butyldimethylsilyl chloride and triethylamine accomplishes protection of the β-lactam nitrogen and leads to the formation of 8. Starting from L-aspartic acid (12), the overall yield of 8 is approximately 50%, and it is noteworthy that this reaction sequence can be performed on a molar scale.

The dithiane moiety is a familiar protecting group for the carbonyl function. When it is used to mask the carbonyl group of an aldehyde, the dithiane function can actually alter the reactivity potential of the molecule. The sulfur atoms of a dithiane confer lability to the hydrogen atom that was formerly aldehydic; in the presence of a strong base (e.g., n-butyllithium), this hydrogen can be removed as a proton leaving behind a carbanion which is stabilized by the polarizable sulfur atoms. Dithiane-stabilized carbanions are valuable carbon nucleophiles in organic synthesis, and are synthetically equivalent to acyl anions because the carbonyl group can be easily regenerated from the dithiane after the key bond-forming event. The use of an aldehyde-derived dithiane as a precursor for a carbanion permits a reactivity umpolung; the formerly electrophilic aldehyde carbonyl carbon is converted into a competent nucleophile through the intermediacy of a dithiane. It is as if the inherent polarization of the aldehyde carbonyl has been reversed.

When 2-lithio-2-(trimethylsilyl)-1,3-dithiane, formed by deprotonation of 9 with an alkyl lithium base, is combined with iodide 8, the desired carbon–carbon bond forming reaction takes place smoothly and gives intermediate 7 in 70–80% yield (Scheme 2). Treatment of 7 with lithium diisopropylamide (LDA) results in the formation of a lactam enolate which is subsequently employed in an intermolecular aldol condensation with acetaldehyde (6). The union of intermediates 6 and 7 in this manner provides a 1:1 mixture of diastereomeric trans aldol adducts 16 and 17, epimeric at C-8, in 97% total yield. Although stereochemical assignments could be made for both aldol isomers, the development of an alternative, more stereoselective route for the synthesis of the desired aldol adduct (16) was pursued. Thus, enolization of β-lactam 7 with LDA, as before, followed by acylation of the lactam enolate carbon atom with N-acetylimidazole, provides intermediate 18 in 82% yield. Alternatively, intermediate 18 could be prepared in 88% yield, through oxidation of the 1:1 mixture of diastereomeric aldol adducts 16 and 17 with trifluoroacetic anhydride (TFAA) in
DMSO/triethylamine.\textsuperscript{10} It was recognized that a potential solution to the problem of establishing the (R) configuration at C-8 of thienamycin would be the diastereoselective reduction of a trigonal carbonyl group at C-8. Gratifyingly, the action of excess potassium tri-sec-butylborohydride (K-Selectride) and potassium iodide on intermediate 18 results in the formation of a 9:1 mixture of C-8 epimers in favor of the desired C-8 β-OH isomer 16. The undesired C-8 epimer 17 could be recovered and converted back to 18 by oxidation. This two-step reaction sequence (7 → 18 → 16) provides an adequate and simple solution to the challenge presented by the C-6 side chain of thienamycin, and the contiguous stereocenters at C-6 and C-8. It should be noted at this point that the task of securing the correct absolute configurations at positions 5, 6, and 8 of thienamycin has been accomplished.

We are now in a position to address the elaboration of the C-5 side chain in 16 into a form suitable for the crucial cyclization event. Exposure of intermediate 16 to HgCl\textsubscript{2} and HgO in aqueous methanol results in hydrolysis of the dithiane moiety and furnishes acyl silane 19 in 93% yield (see Scheme 3). On warming in the presence of a slight excess of hydrogen peroxide in aqueous methanol, intermediate 19 is converted into carboxylic acid 5 in 76% yield after crystallization. To achieve the synthesis of thienamycin, it is obvious that a two-carbon chain must be appended to C-2 at some stage. Although the C-2 carboxyl group in 5 could conceivably be used to acylate a reactive organic nucleophile, its inherent acylating potential is low. It is, therefore, necessary to convert the carboxyl group of intermediate 5 into a more reactive carboxylic acid derivative. By way of a modification of Masamune’s protocol,\textsuperscript{11} 5 can be converted into imidazolidine 20 with 1,1’-carbonyldiimidazole in THF at 25°C. Imidazolidine 20 is not isolated; it is treated directly with the magnesium salt of the mono para-nitrobenzyl ester of malonic acid (21), and is converted into β-keto ester 22 in 86% yield after decarboxylation. Removal of the tert-butyldiemethylsilyl protecting group from the lactam nitrogen atom in 22 with methanolic HCl (90% yield), followed by introduction of the diazo functionality with para-carboxybenzenesulfonyl azide (90% yield) affords the requisite cyclization substrate, intermediate 4.

The diazo function in compound 4 can be regarded as a latent carbene. Transition metal catalyzed decomposition of a diazo keto ester, such as 4, could conceivably lead to the formation of an electron-deficient carbene (see intermediate 3) which could then insert into the proximal N–H bond. If successful, this attractive transition metal induced ring closure would accomplish the formation of the targeted carbapenem bicyclic nucleus. Support for this idea came from a model study\textsuperscript{12} in which the Merck group found that rhodium(II) acetate is particularly well suited as a catalyst for the carbamoid-mediated cyclization of a diazo azetidinone closely related to 4. Indeed, when a solution of intermediate 4 in either benzene or toluene is heated to 80°C in the presence of a catalytic amount of rhodium(II) acetate (substrate : catalyst, ca. 1000 : 1), the processes
Scheme 3. Synthesis of (+)-thienamycin (1).
just outlined occur smoothly, and culminate in the formation of bicyclic \(\beta\)-lactam 2. Although the bicyclic framework of intermediate 2 is highly strained, it is formed in quantitative yield from \(\alpha\)-diazoketo ester 4!

The \(\beta\)-keto ester moiety is a prominent structural feature of intermediate 2. *A priori*, the keto function in 2 could suffer an attack by a thiol nucleophile to give, under dehydrating conditions, a vinyl sulfide. \(\beta\)-Keto esters can, however, exhibit a strong tendency to enolize, an event that would effectively attenuate the electrophilic character of the keto group. One might expect the \(\beta\)-keto ester moiety in 2 to exist largely in its enolic form, and it may be a simple matter to derivatize the enolic form of 2 in a manner that affords a more reactive electrophile. As it turns out, a bicyclic keto ester analogous in structure to compound 2 was found to exist exclusively in the keto ester tautomeric form.\(^{12}\) Nevertheless, treatment of 2 with diphenyl phosphorochloridate, Hüning’s base (\(i\)-Pr\(_2\)NEt), and a catalytic amount of 4-dimethylaminopyridine smoothly produces vinyl phosphate 42 which subsequently undergoes conversion to vinyl sulfide 23 upon exposure to N-\([(\text{para-nitrobenzyl})\text{-oxycarbonyl}]\) cysteamine (70% overall yield). The attack of the thiol nucleophile on the vinyl phosphate can be formulated as a Michael addition/elimination reaction.

The reactions that accomplished the conversion of intermediate 16 into intermediate 23 have taken place very smoothly. It is worth acknowledging that the \(\beta\)-hydroxy lactam moiety did not, at any stage, participate in any undesirable side reaction processes. The stability of the \(\beta\)-hydroxy lactam substructure in the presence of basic reagents is particularly noteworthy since a destructive retroaldol cleavage reaction could have conceivably occurred on several occasions. The stability of this potentially labile moiety permits all of the desired transformations leading from 16 to 23 to be conducted without prior protection of the C-8 hydroxyl group.

To complete the synthesis of thienamycin, it only remains to cleave the carbamate and ester functions in 23. Catalytic hydrogenation of 23 accomplishes both of these objectives, and furnishes (+)-thienamycin (1). Synthetic (+)-thienamycin, prepared in this manner, was identical in all respects with natural thienamycin.

In 1980, a Merck group disclosed the results of a model study which amply demonstrated the efficiency with which the strained bicyclic ring system of thienamycin can be constructed by the carbene insertion cyclization strategy.\(^{12}\) Armed with this important precedent, Merck’s process division developed and reported, in the same year, an alternative route to carbene precursor 4.\(^{13}\) Although this alternative approach suffers from the fact that it provides key intermediate 4, and ultimately thienamycin, in racemic form, it is very practical and is amenable to commercial scale production. The details of this interesting route are presented in Schemes 4-6.

The starting material for this synthesis is diethyl 1,3-acetonedicarboxylate (24, Scheme 4), an inexpensive and commercially
available substance. Treatment of a solution of 24 in toluene with benzylamine and molecular sieves results in the formation of enamine 25. After filtration of the reaction mixture, treatment of the toluene filtrate with ketene gas accomplishes a smooth mono-C-acetylation of the nucleophilic enamine function in 25, and provides keto enamine 26. A salient and important feature of intermediate 26 is its intramolecular hydrogen bond. It was anticipated that this hydrogen bond would, by conferring conformational rigidity to 26, permit the execution of a highly stereoselective reduction process. Indeed, exposure of 26 to sodium cyanoborohydride results in the diastereoselective reduction of both keto and enamine functions, and provides racemic 27 in an overall yield of 61% from diethyl acetenedicarboxylate (24). For clarity, only the desired enantiomer is shown in Scheme 4. This simple reduction protocol creates three contiguous stereocenters from an achiral molecule. Although intermediate 27 can be purified by chromatography on silica gel, it is more convenient to lactonize it, and then purify the carboxylic acid that forms upon acid-induced hydrolysis of the ethyl ester function. Interestingly, the action of concentrated HCl on 27 at reflux accomplishes both of these objectives, and furnishes, after cooling of the reaction mixture, crystalline, diastereomerically pure lactone ammonium salt 28 in 40% yield from 24.

It is important to note that the one-step conversion of 27 to 28 (Scheme 4) not only facilitates purification, but also allows differentiation of the two carbonyl groups. After hydrogenolysis of the N-benzyl group (see 28 → 29), solvolysis of the δ-lactone ring in 29 with benzyl alcohol and a catalytic amount of acetic acid at 70°C provides a 3:1 equilibrium mixture of acyclic ester 30 and starting lactone 29. Compound 30 can be obtained in pure form simply by washing the solid mixture with isopropanol; the material in the filtrate can be resubjected to the solvolysis reaction.

Intermediate 30 is depicted in a manner suggestive of a key transformation in this synthesis. Treatment of a solution of 30 in acetonitrile at 60°C with 1,3-dicyclohexylcarbodiimide (DCC) and triethylamine results in the formation of crystalline β-lactam 31 (92% yield). In this step, DCC reacts with the free carboxyl group in 30 to give an activated ester which subsequently suffers an intramolecular attack by the primary amino group four atoms removed. Gratifyingly, β-lactam 31 can be obtained from this reaction in a form that is sufficiently pure for further advance. Thus, silylation of the β-lactam ring nitrogen atom and the C-8 hydroxyl group with tert-butyldimethylsilyl chloride, followed by hydrogenolysis of the benzyl ester, provides protected carboxylic acid 32.

To set the stage for the crucial carbene insertion reaction, the acetic acid side chain in 32 must be homologated. To this end, treatment of 32 with 1,1′-carbonyldimidazole furnishes imidazole 33, a competent acylating agent, which subsequently reacts with the conjugate base of Meldrum’s acid (34) to give 35. Solvolysis of this substance with para-nitrobenzyl alcohol in acetonitrile at reflux provides β-keto ester 36 after loss of one molecule of ace-
tone and one molecule of carbon dioxide (see Scheme 4). This method for achieving the desired homologation is based on a known procedure. \( \beta \)-Keto ester 36 is easily purified by crystallization from isopropanol, and is obtained in 60–72% yield from 31.

You will note that the relative stereochemical relationships between the three contiguous stereocenters in 36 do not match exactly those found in thienamycin. Although the trans disposition of the two side-chain appendages at carbons 5 and 6 in \( \beta \)-lactam 36 (Scheme 5) is correct, the configuration of the chirality center at C-8, relative to the other two, is incorrect. To secure correct relative stereochemical relationships, the errant configuration at C-8 must be inverted at some stage in the synthesis. When faced with the challenge of inverting the configuration of a hydroxyl-bearing stereocenter, one process that immediately comes to mind is the Mitsunobu reaction.\(^{15}\) After removal of the silyl protecting groups from 36 with HCl in aqueous methanol (see Scheme 5), subjection of the resultant secondary alcohol to a variant of the Mitsunobu reaction\(^{16}\) using triphenylphosphine, diisopropyl azodicarboxylate (DIAD), and formic acid results in the formation of secondary alcohol 37 after acid-induced hydrolysis of the inverted C-8 formate ester. It will be noted that the relative stereochemical relationships found in 37 now agree with those found in thienamycin.

As an alternative to the intermolecular Mitsunobu inversion strategy illustrated in Scheme 5, the Merck group subsequently described the use of an intramolecular Mitsunobu reaction to correct, earlier in the synthesis, the configuration of the C-8 hydroxyl-bearing stereocenter\(^{17}\) (see Scheme 6). Treatment of a solution of compound 27 in CH\(_2\)Cl\(_2\) with anhydrous HCl at 25 °C induces lactonization and provides \( \delta \)-lactone ester 38. In contrast to the rather vigorous conditions employed to accomplish the conversion of 27 to 28 in Scheme 4, the action of HCl on 27 under anhydrous conditions at room temperature permits lactone ring formation without concomitant hydrolysis of the ethyl ester function. In spite of the presence of two potentially reactive carbonyl groups in compound 38, selective hydrolysis of the newly formed lactone ring with one equivalent of sodium bicarbonate in water produces acyclic hydroxy acid 39, and sets the stage for the key intramolecular Mitsunobu reaction. Interestingly, exposure of 39 to 1.3 equivalents each of triphenylphosphine and diethyl azodicarboxylate (DEAD) results in the formation of a new lactone, compound 40, presumably through the processes illustrated in Scheme 6. During the course of the conversion of 39 to 40, the configuration of the hydroxyl-bearing stereocenter is cleanly inverted. Although compound 40 can be purified by column chromatography, it is more convenient to hydrolyze the ethyl ester function with aqueous acid, and then to purify the resultant carboxylic acid ammonium salt 41 by crystallization from acetone (53% overall yield from 38). Intermediate 41, a diastereoisomer of 28, can be transformed into 37 through a sequence of reactions that closely parallels the one illustrated in Scheme 4.\(^{17}\)
Scheme 5. Synthesis of (±)-thienamycin [(±)-1].
Scheme 6. Intramolecular Mitsunobu strategy for the inversion of the C-8 stereocenter (39 → 41).
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Intermediate 37 can be transformed into (±) thienamycin [(±)-1] through a sequence of reactions nearly identical to that presented in Scheme 3 (see 22 → 1). Thus, exposure of β-keto ester 37 to tosyl azide and triethylamine results in the facile formation of pure, crystalline diazo keto ester 4 in 65% yield from 36 (see Scheme 5). Rhodium(II) acetate catalyzed decomposition of 4, followed by intramolecular insertion of the resultant carbene 3 into the proximal N–H bond, affords [3.2.0] bicyclic keto ester 2. Without purification, 2 is converted into enol phosphate 42 and thence into vinyl sulfide 23 (76% yield from 4).18 Finally, catalytic hydrogenation of 23 proceeds smoothly (90%) to afford (±)-thienamycin [(±)-1].

16.4 Conclusion

The unprecedented structure and potent antibiotic properties of thienamycin (1) motivated the development of many interesting synthetic strategies.19,20 In this chapter, we have witnessed two variants of a most elegant and conceptually novel approach to the synthesis of thienamycin. Both variants were developed by Merck scientists, and both feature the use of an intramolecular carbene insertion reaction21 to construct the strained bicyclic nucleus of the natural product. The development of this novel cyclization strategy can be traced to some earlier work at Merck which culminated in the synthesis of (±)-1-oxabispenicillin G, a biologically active penicillin G analog.22 The synthesis of the latter substance has historical significance since it provides the first example of an intramolecular insertion of a carbenoid species into the N–H bond of a β-lactam.

The noteworthy successes of a relevant model study12 provided the foundation for Merck’s thienamycin syntheses. In the first approach (see Schemes 2 and 3), the journey to the natural product commences from a readily available derivative of aspartic acid; this route furnishes thienamycin in its naturally occurring enantiomeric form, and is noted for its convergency. During the course of this elegant synthesis, an equally impressive path to thienamycin was under parallel development (see Schemes 4 and 5). This operationally simple route is very efficient (>10% overall yield), and is well suited for the production of racemic thienamycin on a commercial scale.
References


