antifungals obtained in the *n*-butanol fraction was successively chromatographed over columns of Toyopearl HW-40 (Tosoh, 25- × 300-mm i.d.) with MeOH–$H_2O$ (1:1) and Develosil ODS 15/30 (Nomura Chemicals, 10- × 40-mm i.d.) with MeOH–$H_2O$ (1:1), MeOH–$H_2O$ (7:3), and MeOH. The active substance obtained in the methanolic eluate was further purified by HPLC over reversed-phase columns of Develosil ODS-7 (10- × 250-mm i.d.) and Develosil ODS-5 (8- × 250-mm i.d.) with MeCN–$H_2O$ (9:1). Further chromatography of the active fraction on normal-phase Develosil 60-5 (8- × 250-mm i.d.) with $CHCl_3$–MeOH–$H_2O$ (200:10:1) yielded **1**, **2**, and the mixture of **3** and **4**. Each fraction gave a single spot on TLC; silica gel-60 (Merck) was developed with $CHCl_3$–MeOH–$H_2O$ (90:10:1); $R_f$ values for gambieric acid A (**1**), B (**2**), and the mixture of C (**3**) and D (**4**) were 0.32, 0.37, and 0.18, respectively.

**Alkaline Hydrolysis of 3 and 4.** The mixture of **3** and **4** (3.2 mg) was hydrolyzed with 0.8 mg of NaOH in 100 μL of MeOH–$H_2O$ (9:1) at 60 °C for 1 h. The hydrolyzate, after being neutralized with dilute HCl, was extracted with EtOAc. Successive HPLC over Develosil ODS-5 (Nomura Chemicals, 8- × 250-mm i.d.) with MeCN–$H_2O$ (9:1) and Develosil 60-5 (8- × 250-mm i.d.) with $CHCl_3$–MeOH–$H_2O$ (200:10:1) yielded **1** (2.4 mg), **2** (0.5 mg), and 3-methylglutaric acid. Elution of the antifungal substances was monitored by a growth inhibition test against *A. niger*. The final amounts of the compounds used for determining structures were 7.0 mg of **1**, 2.3 mg of **2**, and 5.6 mg of the mixture of **3** and **4**.

**Gambieric acid A (1):** white amorphous solid; $[\alpha]^{20}_D$ +33° (*c* 0.488, MeOH); UV (MeOH) max <210 nm; IR (KBr) 3500, 1735 $cm^{-1}$; HR-FABMS $[M + Na]^+$ *m/z* 1079.6330 (1079.6280 calcd for $[C_{59}H_{92}O_{16}Na]^+$); $^1H$ and $^{13}C$ NMR data are shown in Table I.

**Gambieric acid B (2):** white amorphous solid; UV (MeOH) max <210 nm; HR-FABMS $[M + Na]^+$ *m/z* 1093.6430 (1093.6440 calcd for $[C_{60}H_{94}O_{16}Na]^+$); $^1H$ and $^{13}C$ NMR data are shown in Table I.

**Mixture of gambieric acids C (3) and D (4):** white amorphous solid; UV (MeOH) max <210 nm; HR-FABMS obsd *m/z* 1185.6920 for gambieric acid C (**3**) (calcd for $C_{65}H_{101}O_{19}$ *m/z* 1185.6939); FABMS $[M(3) + H]^+$ 1185, $[M(3) + Na]^+$ 1207, $[M(3) + K]^+$ 1223, $[M(4) + H]^+$ 1199, $[M(4) + K]^+$ 1237.

**Gambieric Acid A Methyl Ester.** The methyl ester of **1** was prepared with use of $CH_2N_2$ diethyl ether solution: white solid; UV (MeOH) max <210 nm; IR (KBr) 3500, 1740 $cm^{-1}$; FABMS $[M + H]^+$ *m/z* 1071, $[M + Na]^+$ *m/z* 1093; $^1H$ NMR (400 MHz, $CD_3OD$–$C_5D_5N$ (1:1)) δ 3.61 (3 H, S, MeO–), 2.31 (1 H, d, 12 Hz, H-2), 1.97 (1 H, dd, 12, 4 Hz, H-2′); $^{13}C$ NMR (100 MHz, $CD_3OD/C_5D_5N$) δ 174.7 (C1), 52.8 (MeO–), 39.9 (C2); the other signals of $^1H$ and $^{13}C$ NMR agreed well with those of gambieric acid A (**1**).

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**Registry No.** Gambieric acid A, 138434-64-7; gambieric acid B, 141363-65-7; gambieric acid C, 138458-89-6; gambieric acid D, 141363-66-8.

**Supplementary Material Available:** ROESY spectrum of gambieric acid A (**1**), HMBC, $^{13}C$ NMR ($^1H$ broad band decoupling), $^1H$–$^1H$ HOHAHA (TOCSY), $^1H$–$^1H$ COSY of gambieric acid B (**2**), and $^1H$–$^1H$ COSY of a mixture of gambieric acid C and D. The other 2D data are available as supplementary material for the previously published communication[1] (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

# Synthesis of Optically Active β-Lactams by the Photolytic Reaction of Imines with Optically Active Chromium Carbene Complexes. 2. Synthesis of 1-Carbacephalothin and 3-ANA Relays

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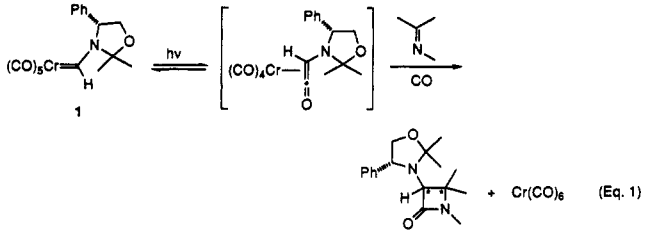
*Received March 31, 1992*

A relay (**3**) to optically active 1-carbacephalothin (**4**) was prepared in modest yield with high stereoselectivity by the photochemical reaction of optically active chromium carbene complex **1** with functionalized imine **2**. In contrast, the photochemical reaction of carbene complex **1** with imine precursors **15a,b** to the nocardicins was much less stereoselective.

## Introduction

Recent studies in these laboratories have dealt with the synthesis of simple optically active β-lactams utilizing photochemical reactions of optically active chromium aminocarbene complexes with imines (eq 1).[1] This reaction proved highly stereoselective (>97% de) for *N*-benzylimines of acetaldehyde, *N*-benzylimidates, thiazolines, oxazines, thiazines, and simple 5- and 6-membered cyclic imines, but less so with (de 70%) symmetrical imines such as those of formaldehyde or acetone. The absolute stereochemistry of the position α to the carbonyl group was determined by the chiral auxiliary on the carbene complex ($R \rightarrow R,S \rightarrow S$) while the relative (cis/trans) stereochemistry was determined by the imine substrate. In marked contrast, reactions of **1** with *N*-benzylimines of benz-




(Eq. 1)

(1) (a) Hegedus, L. S.; Imwinkelried, R.; Alarid-Sargent, M.; Dvorak, D.; Satoh, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1109. (b) For a review on the reactions of chromium aminocarbene complexes see: Schwindt, M. A.; Miller, J. R.; Hegedus, L. S. *J. Organomet. Chem.* **1991**, *413*, 143.

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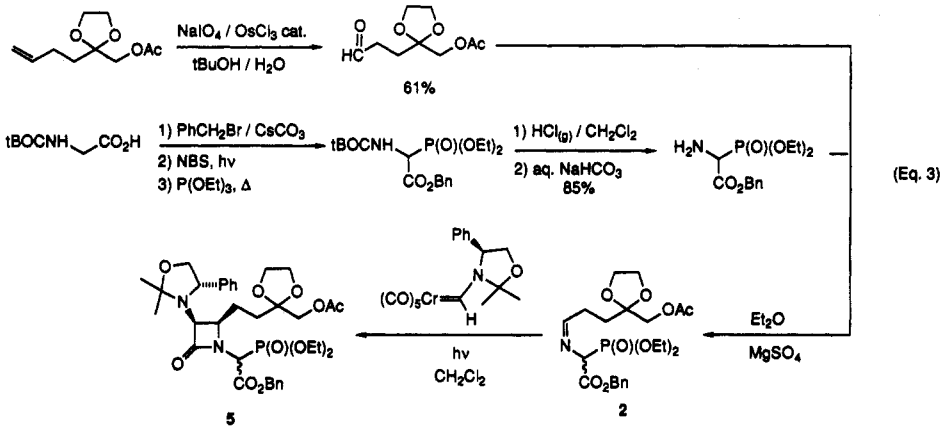
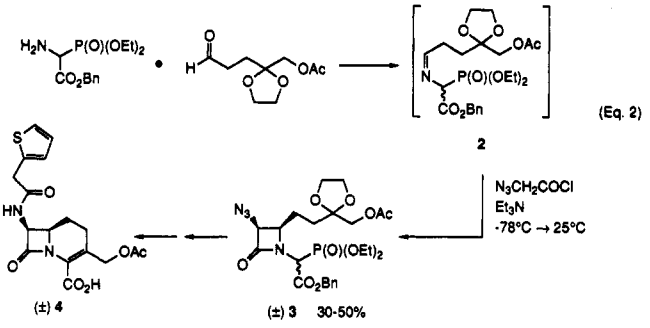



aldehyde and cinnamaldehyde were quite nonselective, with little control of either absolute or relative stereochemistry. A careful study of this system,[2] and comparison with that of the acid chloride derived ketene having an oxazolidinone (rather than oxazolidine) chiral auxiliary,[3] indicated that stereoselectivity was critically dependent upon both the structure of the imine partner and that of the chiral auxiliary. In most cases, chromium carbene derived oxazolidine ketenes were *complimentary* to acid chloride derived oxazolidinone ketenes in their reactions with imines, the best cases for one being the worst for the other. The following studies were carried out to determine the suitability of the chromium carbene methodology to synthesize more highly functionalized β-lactams with high stereoselectivity. The target compounds chosen were relays to 1-carbacephalothin (4) and 3-aminonocardicinic acid (3-ANA) (14).

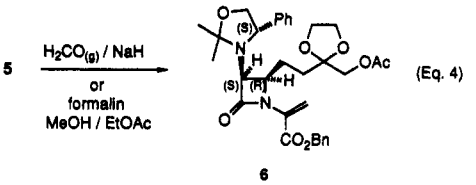
## Results and Discussion

**(a) 1-Carbacephalothin (4).** 1-Carbacephalothin, a carbon analog of the cephalosporins, has previously been synthesized in racemic form[4] using as a key step the reaction of the unstable functionalized imine **2** with acid chloride derived azidoketene (eq 2). In this case, clean



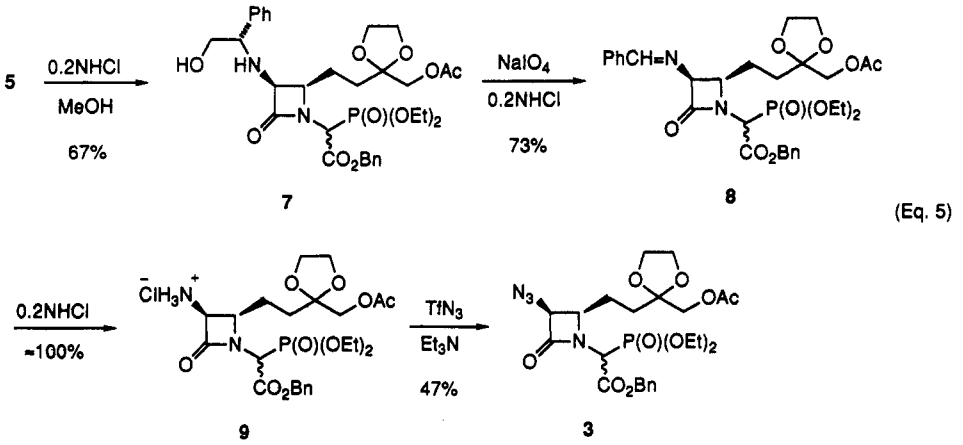

cis stereochemistry was observed and the β-lactam **3** was ultimately converted to 1-carbacephalothin (**4**). Imine **2** appeared to be an ideal substrate to test the stereoselectivity of the chromium carbene reaction chemistry (eq 1) as well as to provide a comparison between two sterically and electronically quite different ketenes. Unfortunately, the original literature procedures[5] for the synthesis of both the amine and aldehyde components lacked specific details and proved inefficient in our hands. The amine component was efficiently synthesized by the method of Kober and Steglich,[6] and the aldehyde component was synthesized by a slight variation of the published[4] procedure (eq 3). These two components were stirred in ether over magnesium sulfate for 40 min at 25 °C, filtered, and concentrated to give the crude imine **2** as a brown oil. This crude material was dissolved in methylene chloride, 1 equiv of (*S*)-carbene complex **1** was added, and the system was flushed with argon and irradiated (400 W, Pyrex) until the carbene had been consumed (44 h). Isolation and purification gave a 32% yield of β-lactam **5** (eq 3). This product consisted of a 1:1 mixture of diastereoisomers ($^1$H NMR) because of the presence of the racemic center α- to the phosphonate. Thus, the reaction appeared to be highly stereoselective, although the relative (cis/trans) stereochemistry could not be assigned at this time because of the complexity of the spectrum. On the basis of previous experience,[1] the absolute stereochemistry at the position α- to the carbonyl group is expected to be (*S*) since the (*S*)-carbene complex **1** was used.

To establish the relative stereochemistry and to demonstrate that the diastereoisomers were indeed due to the racemic phosphonate center, **5** was treated with formaldehyde, converting the racemic sp$^3$ center into an sp$^2$ center. This gave a single compound **6**, indicating that the photoreaction was indeed highly stereoselective. In addition, removal of the phosphonate group exposed the β-lactam C-3 methine signal in the $^1$H NMR spectrum which appeared as a doublet at δ 4.39 with a coupling constant of 5.3 Hz, indicating that the relative stereochemistry was cis (eq 4).




With β-lactam **5** available with high relative and absolute stereoselectivity attention was turned to its conversion to azido β-lactam **3** (eq 5), which has previously been converted to 1-carbacephalothin in the racemic series.[4] The chiral auxiliary was removed under oxidative conditions[1] by hydrolysis of the acetonide, followed by periodate cleavage of amino alcohol **7**, followed by hydrolysis of imine **8** to give amine hydrochloride **9** in good overall yield. (This was N-acylated with phenacetyl chloride, producing **10**, to aid in its characterization.) Treatment of amine hydro-

(2) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784.
(3) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783.
(4) (a) Guthikonda, R. N.; Cama, L. D.; Christensen, B. G. *J. Am. Chem. Soc.* **1974**, *96*, 7584. (b) Firestone, R. A.; Fahey, J. L.; Maciejewicz, N. S.; Patel, G. S.; Christensen, B. G. *J. Med. Chem.* **1977**, *20*, 551.
(5) Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1973**, 4645; 4649; 4653.
(6) Kober, R.; Steglich, W. *Liebigs Ann. Chem.* **1983**, 599.



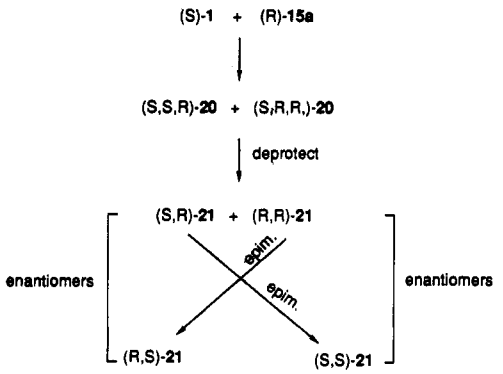
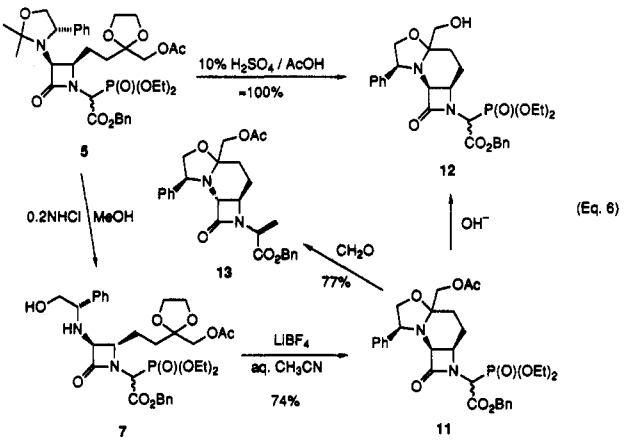




**Figure 1.**

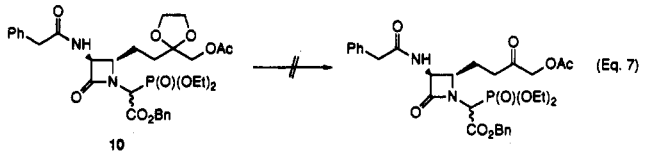
chloride **9** with triflic azide converted it to optically active azido β-lactam **3** with retention of configuration.[7] The physical data for this compound were identical in all respects to those reported for racemic material; it was again a 1:1 mixture of cis diastereoisomers racemic at the phosphonate ester center. This constitutes a formal total synthesis of optically active (*S,R*)-carbacephalothin, since racemic **3** is a synthetic relay to that compound.[4] The (*R,S*)-enantiomer should be available by starting with (*R*)-carbene complex **1**.

The oxidative cleavage **7** → **9** requires comment. In principle, this reaction should proceed in one step since hydrolysis of imine **8** occurs under the conditions required for oxidation. However, when carried out this way the reaction was slow, and the yields were low, primarily because hydrolysis of **8** was slow, and **9** was unstable to long exposure to the oxidant. However, conversion of **7** to **8** was quite rapid (0.5 h), and isolated **8** was hydrolyzed to **9** in the absence of oxidant in excellent yield. A second complication arose in the isolation of **8** from the oxidation product. Use of saturated $NaHCO_3$ in the workup procedure led to production of ≈20% of olefinic material, resulting from the reaction of formaldehyde, produced in the oxidative cleavage, with the phosphonate ylide, similar to eq 4. Use of a phosphate buffer (0.1 M, pH 7) in place of bicarbonate completely suppressed this side reaction.

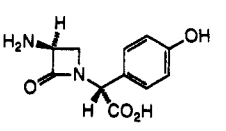
Efforts to bypass azido β-lactam **3** in a direct synthesis of carbacephalothin itself were complicated by functional group incompatibilities. Attempts to remove both the chiral auxilliary and the ketal protecting group from **5** in one step instead resulted in facile side-chain cyclization to give tricyclic compounds **11** or **12**, each a mixture of two diastereoisomers epimeric solely at the racemic phosphonate center, as shown by conversion to a single isomer upon olefination to **13** with formaldehyde (eq 6). Although these are interesting compounds they are of little use in the synthesis of carbacephalothin, and they were not further studied.




Finally, attempts to remove the ketal protecting group from N-protected β-lactam **10** also failed. Either no reaction (*p*-toluenesulfonic acid/acetone or 5% trifluoroacetic acid/5% $H_2O/CH_2Cl_2$) or decomposition ($LiBF_4$/aqueous $CH_3CN$[20] or 10% $H_2SO_4$/acetic acid or 30% trifluoroacetic acid/5% $H_2O/CH_2Cl_2$) resulted.




**(b) 3-Aminonocardicinic Acid (3-ANA) (14).** 3-Aminonocardicinic acid is the parent member of a class of naturally occurring monocyclic β-lactam antibiotics showing chemical and biological similarities to penicillins and cephalosporins.[8] It has been synthesized in a variety of




ways,[9] including the reaction of imines with acid chloride-derived ketenes,[10] and thus was thought to be an in-

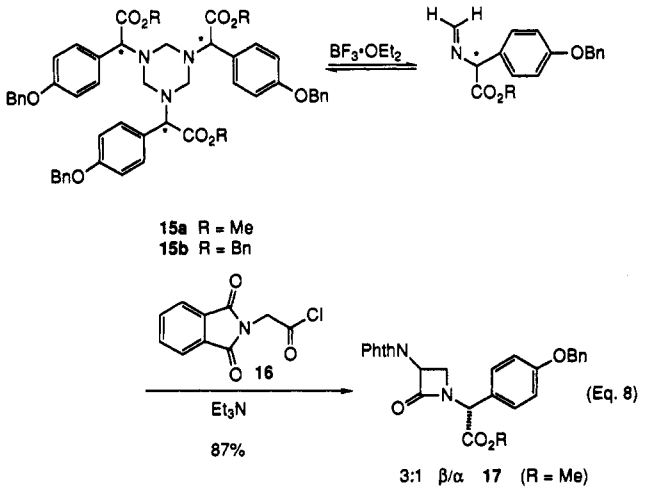
(7) Zaloom, J.; Roberts, D. C. *J. Org. Chem.* **1981**, *46*, 5173.

(8) (a) Hashimoto, M.; Komori, T.; Kamiya, T. *J. Am. Chem. Soc.* **1976**, *98*, 3023. (b) Hashimoto, M.; Komori, T.; Kamiya, T. *J. Antibiot.* **1976**, *29*, 890. (c) Kurita, M.; Jomon, K.; Komori, T.; Miyairi, N.; Aoki, H.; Kuge, S.; Kamiya, T.; Imanaka, H. *J. Antibiot.* **1976**, *29*, 1243.

(9) Salituro, G. M.; Townsend, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 760.

formative target for the chromium carbene based methodology. In addition, the presence of a chiral center in the imine substrate presented the possibility of complications from "double diastereoselection".[11]

The influence of this chiral center depended strongly on the specific reaction in which it participated. Treatment of imine trimer **15** with phthalimido acid chloride **16** led to a 3:1 mixture of diastereoisomers of **17**,[10b,c] indicating the presence of some stereocontrol (eq 8). In

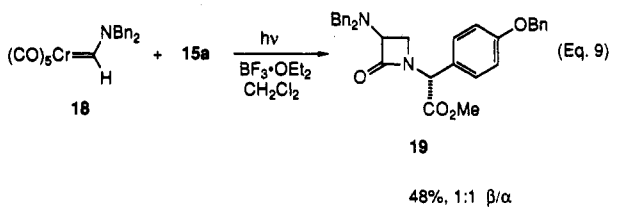


**15a** R = Me
**15b** R = Bn



3:1 β/α **17** (R = Me)

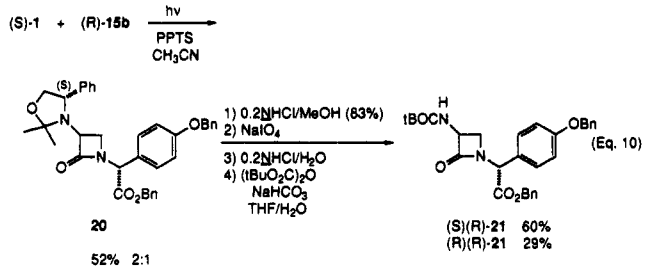
contrast, reaction of the same trimer with (dibenzylamino)carbene complex **18** led to a 1:1 mixture of diastereoisomers of β-lactam **19**,[12] indicating that the structure of the ketene had no influence on the stereochemical outcome of this process (eq 9). This appeared to be an



48%, 1:1 β/α

ideal test substrate to use with optically active chromium carbene complex **1**. However, under a variety of conditions, this system proved remarkably inefficient and nonselective, in light of previous results with simpler systems.[1a] Under the *best* conditions (*hν*, $CH_3CN$, pyridinium tosylate) a 52% isolated yield of a 2:1 mixture of diastereoisomers was obtained. At this stage the absolute stereochemistry of the diastereoisomers could not be assigned, nor could they be separated. Removal of the chiral auxilliary by previously developed oxidation procedures,[1a] followed by protection of the free amino group with the *t*-BOC group, produced the known[13] diastereoisomeric monocyclic β-lactams (*S*,*R*)-**21** and (*R*,*R*)-**21**, which could be separated and were isolated in 60% and 29% yield (from **20**) respectively. As anticipated, (*S*,*R*)-**21** was the major product (eq 10).

The $^1H$ NMR spectrum of (*S*,*R*)-**21** matched exactly that reported[13] for this diastereoisomer and was substantially different from that of the (*R*,*R*). In addition, epimerization



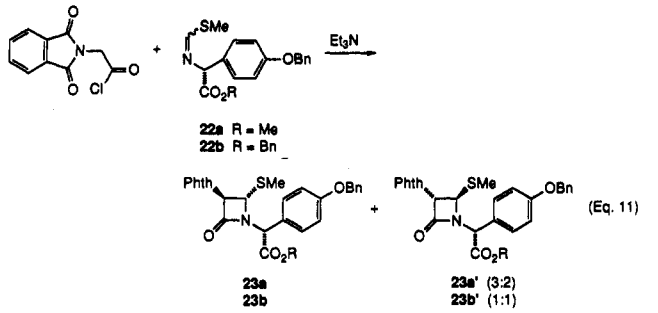
**20**
52% 2:1

(S)(R)-**21** 60%
(R)(R)-**21** 29%

of the (*R*,*R*)-diastereoisomer with triethylamine gave a 4:3 mixture of epimers at the center α to the ester, as previously reported. However, the specific rotation of (*S*,*R*)-**21** was slightly lower than reported $[\alpha]_D$ −63.2° vs −77.8°, indicating an ee of ~82% (confirmed by the use of chiral shift reagents). This loss of stereochemistry is likely to have occurred during the deprotection sequence, which involved several extractions into aqueous sodium bicarbonate. Epimerization of the center α to the ester group of the (*R*,*R*)-diastereoisomer would ultimately lead to (*R*,*S*)-**21**, compromising the stereochemical purity of **21** (Figure 1). Thus, because the initial stereoselectivity is low, and removal of the chiral auxilliary results in some epimerization, this is not an efficient approach to 3-ANA precursors.

Previous experience[2] had shown that, in some instances, when reactions with oxazolidine carbene complex **1** lacked stereoselectivity use of the Evans[2] oxazolidinone acid chloride led to increased stereoselectivity. However, reaction of this acid chloride with **15b** under standard conditions[2] resulted in the production of *no* β-lactam product.

3-ANA precursors have also been made by the reaction of (monomeric) thioimidates with phthalimidoketene (eq 11).[10c] The reaction went in modest yield, and with low

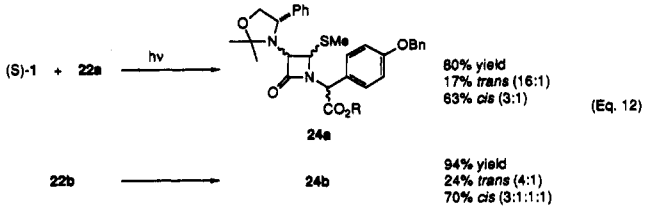


**22a** R = Me
**22b** R = Bn

**23a** **23a'** (3:2)
**23b** **23b'** (1:1)

diastereoselectivity, giving a 3:2 mixture of trans β-lactams **23a**,**a'**. (Since the sulfur is removed in a later step, the *relative* (cis–trans) stereochemistry is unimportant.) When the benzyl ester was used in place of the methyl ester, a 1:1 mixture of trans diastereoisomers was obtained.

The reaction of (*S*)-carbene complex **1** with thioimidate **22b** led to unexpected results (eq 12). Although the



**24a**

**24b**

chemical yield of β-lactam was exceptionally high, cis β-lactams, rather than the expected trans isomer,[14] were the

(10) (a) Curran, W. V.; Sassiver, M. L.; Ross, A. S.; Fields, T. L.; Boothe, J. H. *J. Antibiot.* **1982**, *35*, 329. (b) Nakaguchi, O.; Oku, T.; Takeno, H.; Hashimoto, M.; Kamiya, T. *Chem. Pharm. Bull.* **1987**, *35*, 3985. (c) Kamiya, T.; Hashimoto, M.; Nakaguchi, O.; Oku, T. *Tetrahedron* **1979**, *35*, 323.

(11) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

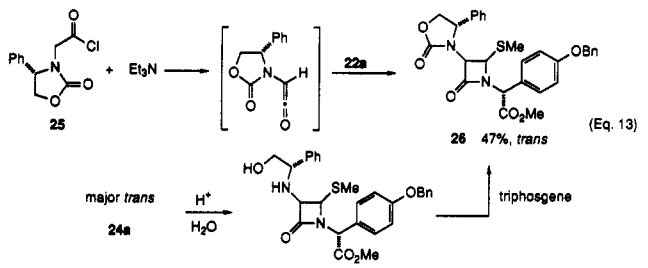
(12) Hegedus, L. S.; D'Andrea, S. *J. Org. Chem.* **1988**, *53*, 3113.

(13) Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1981**, *46*, 1557.

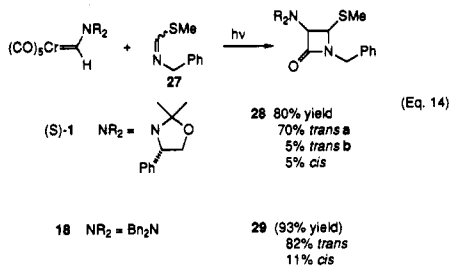
(14) Imines which bear cation-stabilizing groups such as OR or SR on the imine carbon usually give almost exclusively trans β-lactams, since cyclization is slow, and isomerization of the zwitterionic intermediate to give the more stable trans isomer occurs. See ref 2.

major products, and the reaction was virtually nonstereoselective, giving *four* cis isomers and two trans isomers. To form four cis isomers, racemization of the center α to the ester in conjunction with nonstereoselective cyclization must have occurred. Indeed, repeating the reaction with the more configurationally stable methyl ester **23a** led again to good overall yields of β-lactam, and now only two cis and two trans isomers were obtained. Again, the cis isomers predominated, and stereoselectivity in the cis manifold was low.

In contrast, reaction of **22a** with oxazolidinone ketene generated from acid chloride **25** gave a modest yield of a *single* trans isomer which had the same absolute configuration as the major trans isomer of reaction mixture **24a**, as demonstrated by hydrolysis of the oxazolidine in the β-lactam followed by conversion to the oxazolidinone by acylation (eq 13). This is yet another example of remarkable difference in selectivity and reactivity between the oxazolidine and the oxazolidinone ketenes. If the yields of this ketene reaction were improved, it would offer an attractive stereoselective approach to 3-ANA.




The production of cis β-lactams from thioimidates was surprising, since trans β-lactams are normally formed from imines bearing cation-stabilizing substituents on the imine carbon. However, as the bulk of the substituent on nitrogen increases, the steric interaction with the adjacent *S*-methyl group in the zwitterionic intermediate increases, resulting in increased production of the cis product.[15] To see if this was, indeed, the case, reaction of carbene complexes (*S*)-**1**, and **18**, with the simple *N*-benzyl thioimidate **27** were carried out. In both cases, by far the major product was the trans β-lactam (eq 14). With the optically active carbene complex (*S*)-**1** stereoselectivity in the trans manifold was quite high (14:1), indicating again that the oxazolidine chiral auxilliary can be efficient in the asymmetric synthesis of β-lactams.




Attempts to elucidate the role of structural features in the stereochemical outcome of ketene imine reactions continue.

## Experimental Section

**General Procedure.** $^1H$ and $^{13}C$ NMR chemical shifts were reported in ppm relative to TMS using $CDCl_3$ unless otherwise indicated. Ultraviolet irradiation was carried out in a Pyrex test tube or a Pyrex pressure tube placed at a distance of 10 cm from a Conrad-Hanovia 7825 medium-pressure mercury lamp operating at 450 W, which was placed in a water-cooled immersion well. A Conrad-Hanovia 7830-C power supply was used. Reactions run under CO pressure were saturated with CO (three cycles to 80 psi of CO) and were photolyzed under the CO pressure specified.

**Materials.** 1-Acetoxy-5-hexen-2-one ethylene glycol ketal,[4a] benzyl *N*-*t*-Boc bromoglycinate,[6] chromium carbene complex **1**,[16] **18**,[26] triflic azide,[19] ethyl thioformate,[25] and [(*S*)-4-phenyl-2-oxooxazolidin-3-yl]acetyl chloride **25**[3] were prepared according to literature methods.

**Preparation of Imine 2. (a) Oxidative Cleavage of Olefin to Aldehyde.** To a well-stirred mixture of 1-acetoxy-5-hexen-2-one ethylene glycol ketal (0.60 g, 2.98 mmol) in *t*-BuOH (15 mL) and water (25 mL) was added at rt $NaIO_4$ (2.06 g, 9.64 mmol) followed by $OsCl_3$ (21 mg, 0.07 mmol, 2.4 mol %). After being stirred at rt for 0.5 h, the mixture was filtered and the filtrate was extracted with ethyl acetate. The extract was washed with saturated NaCl, dried over $MgSO_4$, and concentrated to give a pale yellow oil which was purified by flash chromatography with hexane–EtOAc (2:1–1:2) as eluent to afford 0.37 g (61% yield) of aldehyde as a colorless oil, which was identical in every respect with that reported previously.[4a]

**(b) Benzyl *N*-*t*-BOC-glycinate.**[18] *N*-*t*-BOC-glycine[17] (1.00 g, 5.70 mmol) was dissolved in MeOH (24 mL) and water (2.4 mL). The solution was titrated to pH 7.0 (pH paper) with a 20% aqueous solution of $Cs_2CO_3$. The mixture was evaporated to dryness and the residue reevaporated twice from DMF (14 mL). The white solid cesium salt was stirred with benzyl bromide (0.74 mL, 6.24 mmol) in DMF (14 mL) for 5 h. The DMF was removed under vacuum to dryness. The solid was triturated in water (40 mL) and collected on a filter paper. The solid was dissolved in EtOAc (60 mL), washed with water (2 × 30 mL), and dried with anhydrous $Na_2SO_4$. The solvent was removed under vacuum to give a white solid in 88% yield (1.33 g): $^1H$ NMR (60 MHz) δ 1.5 (s, 9 H, *t*-$C(CH_3)_3$), 4.0 (d, 2 H, $NCH_2$–), 5.0 (brs, 1 H, NH), 5.2 (s, 2 H, $-CH_2Ph$), 7.3 (s, 5 H, Ph).

**(c) Benzyl *N*-*t*-BOC-2-bromoglycinate.**[6] Benzyl *N*-*t*-BOC-glycinate (1.33 g, 5.00 mmol) was dissolved in $CCl_4$ (17 mL) with *N*-bromosuccinimide (0.89 g, 5.00 mmol) and cooled to 15 °C. The solution was irradiated with a 75-W light bulb until no orange color remained in the solution (~6 h). The solution was decanted into a round-bottom flask and concentrated under vacuum to yield a colorless oil in 100% yield (1.72 g): $^1H$ NMR (270 MHz) δ 1.47 (s, 9 H, $C(CH_3)_3$), 5.24 (s, 2 H, $-CH_2Ph$), 5.9 (br s, 1 H, NH), 6.4 (d, $J$ = 7.6 Hz, 1 H, CHBr), 7.36 (s, 5 H, Ph).

**(d) Benzyl *N*-*t*-BOC-2-(diethoxyphosphoryl)glycinate.** To a solution of freshly prepared benzyl *N*-*t*-BOC-bromoglycinate (9.95 g, 28.90 mmol) in $CH_2Cl_2$ (100 mL) was added at rt a solution of triethyl phosphite (5.2 mL, 30.4 mmol) in $CH_2Cl_2$ (10 mL). This addition caused gentle heat evolution, and this mixture was allowed to stand at rt overnight. After evaporation of the solvent under reduced pressure, the residual yellow oil was chromatographed (silica gel, 125 g; hexane:EtOAc = 4:1–1:2) to give a pale yellow oil (7.07 g, 61%): $^1H$ NMR (270 MHz) δ 1.25 (m, 6 H, $CH_3$), 1.45 (s, 9 H, $CH_3$), 4.1 (m, 4 H, $POCH_2$), 4.9 (dd, $J$ = 7.5, 23.0 Hz, 1 H, $CHP(O)$), 5.2 (d, $J$ = 13.0 Hz, 1 H, $CH_2Ph$), 5.3 (d, $J$ = 13.0 Hz, 1 H, $CH_2Ph$), 5.6 (d, $J$ = 7.5 Hz, 1 H, NH), 7.35 (m, 5 H, $C_6H_5$).

**(e) Benzyl 2-(Diethoxyphosphoryl)glycinate.** Gaseous HCl was bubbled through a solution of benzyl *N*-*t*-BOC phosphorylglycinate (2.43 g, 6.02 mmol) in $CH_2Cl_2$ for 0.5 h, and the mixture was allowed to stand at rt overnight. The solvent was evaporated, and the residue was partitioned between EtOAc and saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the organic layer was washed with saturated $NaHCO_3$ solution and saturated NaCl successively. All of the extracts were combined, dried over $MgSO_4$, and concentrated to give 1.54 g (85% yield) of amine as a pale orange oil, which was identical in every respect with that reported previously:[6] $^1H$ NMR (270 MHz) δ 1.27 (dt, $J$ = 2.1, 7.1 Hz, 6 H, $CH_3$), 1.80 (br, 2 H, $NH_2$), 3.97 (d,

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$J$ = 20.7 Hz, 1 H, C*H*P(O)), 4.1 (m, 4 H, POC$H_2$), 5.20 (d, $J$ = 12.2 Hz, 1 H, C$H_2$Ph), 5.26 (d, $J$ = 12.2 Hz, 1 H, C$H_2$Ph), 7.4 (m, 5 H, C$_6H_5$). This product was used immediately for the imine synthesis.

**(f) Preparation of Imine 2.** To an ice-cooled solution of freshly prepared amine (1.54 g, 5.10 mmol) in $Et_2O$ (30 mL) was added solid $MgSO_4$ (1.33 g) followed by a solution of the aldehyde (1.05 g, 5.20 mmol) in $Et_2O$ (15 mL), and the resultant mixture was stirred at rt for 40 min. The inorganic salt was removed by filtration, and the filtrate was concentrated to give 2.60 g of the crude imine as a brown oil. $^1H$ NMR analysis of the product showed that it contained unreacted excess aldehyde. The ratio of imine/aldehyde was determined to be 3:1 from the integral ratio, and the content of imine was calculated to be 3.9 mmol. This product was used immediately for the next photolytic reaction without further purification, since it rapidly decomposed.

**Photolysis of Chromium Carbene Complex (*S*)-1 with Imine 2 To Produce 5.** In a Pyrex test tube was placed a solution of freshly prepared imine (3.9 mmol) in $CH_2Cl_2$ (65 mL), and chromium carbene complex 1 (1.49 g, 3.90 mmol) was added. The test tube was stoppered with a rubber septum, and the vessel was evacuated and purged with Ar three times. It was then irradiated for 44 h until no more carbene complex was detected by TLC. The clear dark brown mixture was concentrated, and the residue was purified by repeated flash chromatography with EtOAc–acetone (first 9:1–2:1 and then 95:5–85:15) to afford 0.88 g (32% yield) of β-lactam 5 as a pale yellow oil: $^1H$ NMR (270 MHz) δ 1.13–1.32 (m, 6 H, C$H_3$), 1.45 (br s, 6 H, C$H_3$), 1.41–1.68 (m, 4 H, C$H_2$), 2.07 (s, 3 H, AcO), 3.74–4.0 (m, 8 H, C$H_2$O, OC$H_2$CHN, C*H*NCO), 4.07 (m, 4 H, POC$H_2$), 4.28–4.38 (m, 2 H, OC$H_2$CHN, C*H*CON), 4.53 and 4.58 (two dd, 1:1 ratio, $J$ = 4.1, 7.8 Hz, 1 H, OCH$_2$CHN), 4.81 and 4.94 (two d, 1:1 ratio, $J$ = 24.1, 24.4 Hz, 1 H, C*H*P), 5.11 (ABq, $J$ = 12.3 Hz, 1 H, C$H_2$Ph), 5.20 (ABq, $J$ = 15.5 Hz, 1 H, C$H_2$Ph), 7.2–7.4 (m, 10 H, C$_6H_5$); $^{13}C$ NMR (75.5 MHz) δ 16.2 and 16.3 (two d, $J$ = 5, 6 Hz, *C*OP), 20.9 (AcO), 22.0 and 22.1 (*C*CH$_3$), 22.4 and 23.1 (*C*CCO), 27.9 and 28.0 (*C*CH$_3$), 31.4 and 32.1 (*C*CO), 52.8 and 52.9 (two d, $J$ = 148, 153 Hz, P*C*), 62.0 and 62.2 (*C*O, oxazolidine), 62.9 and 63.1 (*C*N, β-lactam), 63.4, 63.5 and 63.7 (three d, $J$ = 6 Hz, *C*OP), 65.3, 65.4 and 65.5 (*C*O ketal, COAc), 67.1 and 67.2 (NCCO, β-lactam), 67.7 and 68.1 (O*C*, benzyl), 72.6 and 72.7 (*C*N, oxazolidine), 96.9 and 97.0 (O*C*N, oxazolidine), 108.3 and 108.4 (O*C*O, ketal), 126.9, 127.2, 128.2, 128.2, 128.3, 128.4, 128.5, 128.5, 128.6, 128.6, 134.7, 135.0, 143.8 (Ar), 165.0 (C=O, ester), 168.8 and 169.4 (C=O, β-lactam), 170.5 (C=O, AcO); IR (film) ν 1746 (C=O) cm$^{-1}$; $[\alpha]_D$ = +17.7° ($c$ = 1.14, $CH_2Cl_2$); MS (FAB) $m/e$ (rel intensity) 703 (37, M + 1), 583 (41), 486 (100, retro[2 + 2], imine part + H), 360 (33), 217 (84 retro[2 + 2], ketene part); exact mass calcd for $C_{35}H_{48}N_2O_{11}P$ (M + H) 703.2996, found 703.2996.

**Reaction of Photolysis Product 5 with Formalin To Give 6.** To a solution of β-lactam 5 (29.4 mg, 0.042 mmol) in EtOAc–MeOH (1 mL each) was added at rt saturated $NaHCO_3$ (1 mL) followed by formalin (37%, 0.2 mL, 20 mmol), and the mixture was stirred at rt for 10 min. The mixture was diluted with saturated $NaHCO_3$ and was extracted three times with EtOAc. The extracts were washed with saturated NaCl, dried over $MgSO_4$, and concentrated to give a pale yellow oil which was purified by chromatography with hexane–EtOAc (2:1–0:1) as eluent to afford 17.8 mg (74%) of 6 as a colorless oil: $^1H$ NMR (270 MHz) δ 1.4–1.65 (m, 4 H, C$H_2$), 1.43 (s, 6 H, C$H_3$), 2.04 (s, 3 H, AcO), 3.75–4.0 (m, 7 H, C$H_2$O, OC$H_2$CHN), 4.17 (q, $J$ = 6.2 Hz, 1 H, C*H*NCO), 4.34 (t, $J$ = 8.5 Hz, 1 H, OC$H_2$CHN), 4.39 (d, $J$ = 5.3 Hz, 1 H, C*H*CON), 4.73 (dd, $J$ = 4.6, 7.8 Hz, 1 H, OCH$_2$C*H*N), 5.16 and 5.17 (ABq, $J$ = 12.5 Hz, 2 H, C$H_2$Ph), 5.76 (s, 1 H, *H*C=C), 5.95 (s, 1 H, *H*C=C), 7.2–7.4 (m, 10 H, C$_6H_5$); $^{13}C$ NMR (75.5 MHz) δ 20.8 (AcO), 21.5 (CCH$_3$), 23.3 (*C*-CCO), 27.9 (*C*CH$_3$), 31.8 (*C*-CO), 61.3 and 61.6 (*C*O, oxazolidine, *C*N, β-lactam), 65.0 (COAc), 65.3 and 65.4 (*C*O ketal), 65.9 and 67.2 (NCCO, β-lactam, O*C*, benzyl), 72.4 (*C*N, oxazolidine), 96.7 (O*C*N, oxazolidine), 108.1 (O*C*O, ketal), 117.4 (C=C), 127.4, 127.7, 128.2, 128.3, 128.5, 128.6 (Ar), 131.1 (C=C), 135.1, 143.4 (Ar), 162.4 (C=O, ester), 166.5 (C=O, β-lactam), 170.3 (C=O, AcO); IR (film) ν 1747 (C=O), 1731 (C=O), 1613 (C=C) cm$^{-1}$; $[\alpha]_D$ = +54.4° ($c$ = 0.270, $CH_2Cl_2$); MS (FAB) $m/e$ (rel intensity) 579 (40, M + 1), 459 (28), 307 (69), 217 (100, retro[2 + 2], ketene part; exact mass calcd for $C_{32}H_{39}N_2O_8$ (M + H) 579.2706, found 579.2707.

**Reaction of 5 with Gaseous Formaldehyde To Give 6.** Under Ar, sodium hydride (50% oil dispersion, 3.4 mg, 0.071 mmol) was added to a solution of β-lactam (14 mg, 0.020 mmol) in dry THF (2 mL) at rt, and the mixture was shaken for ca. 5 min until gas evolution ceased. The flask was then connected with another flask containing paraformaldehyde (0.37 g). Paraformaldehyde was heated to 140 °C, and gaseous formaldehyde was introduced into the solution of β-lactam with a slow stream of argon. The reaction mixture was partitioned between phosphate buffer (pH 7, 0.1 M) and EtOAc, and the aqueous layer was extracted with EtOAc. The extracts were washed with saturated $NaCl_{aq}$, dried over $MgSO_4$, and concentrated to give a colorless oil, which was purified by chromatography with hexane–EtOAc (2:1 to 0:1) as eluent to afford 8.2 mg (71%) of 6 as a colorless oil. The spectroscopic data was identical with that reported above.

**Hydrolysis of 5 to 7.** The starting material 5 (0.12 g, 0.18 mmol) was taken up in MeOH (2 mL), and 0.2 N HCl (2 mL) was added. After being stirred at rt for 1.5 h, the mixture was concentrated to half-volume and was partitioned between EtOAc and saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the organic layers were washed with saturated $NaHCO_3$ and saturated NaCl successively. The organic solution was dried over $MgSO_4$ and was concentrated to give 78 mg (67% yield) of amino alcohol 7 as a colorless oil: $^1H$ NMR (270 MHz) δ 1.24 (m, 6 H, C$H_3$), 1.80 (m, 4 H, C$H_2$), 2.10 (s, 3 H, AcO), 2.98 (br, 2 H, *H*O, N*H*), 3.55 (dd, $J$ = 8.8, 11.0 Hz, 1 H, OC$H_2$CHN), 3.73 (dd, $J$ = 3.7, 11.0 Hz, 1 H, OC$H_2$CHN), 3.8–4.2 (m, 13 H, C$H_2$O, CH), 4.91 and 4.96 (two d, 1:1 ratio, $J$ = 24.0, 24.5 Hz, 1 H, C*H*P), 5.19 and 5.21 (two ABq, 1:1 ratio, $J$ = 12.3, 12.1 Hz, 2 H, C$H_2$Ph), 7.25–7.4 (m, 10 H, C$_6H_5$); $^{13}C$ NMR (67.9 MHz) δ 16.3 (d, $J$ = 6 Hz, *C*COP), 20.8 (AcO), 21.8 and 22.3 (*C*CCO), 31.8 and 32.1 (*C*CO), 52.9 and 52.9 (two d, $J$ = 156, 148 Hz, P*C*), 61.5 and 62.0 (*C*N, β-lactam), 63.5 (d, $J$ = 7 Hz, *C*OP), 63.8, 65.4 (COAc), 65.5, 65.7 (*C*O ketal), 67.0, 68.1 (O*C*, benzyl), 108.7 (O*C*O, ketal), 127.5, 127.6, 127.8, 128.5, 128.6, 128.7, 135.0, 135.1, 140.2 (ArC), 165.1, 165.4, 165.5 (C=O, ester, β-lactam), 170.4 (C=O, AcO); IR (film) ν 3416 (OH, NH), 1747 (C=O) cm$^{-1}$; $[\alpha]_D$ = +8.9° ($c$ = 0.530, $CH_2Cl_2$); MS (FAB) $m/e$ (rel intensity) 663 (98, M + 1), 631 (M – $CH_2$=OH), 589 (13, M – $CH_2OAc$), 486 (77, retro[2 + 2], imine part + H), 304 (89, retro[2 + 2], olefin part – $CH_2$=OH); exact mass calcd for $C_{32}H_{44}N_2O_{11}P$ (M + H) 663.2683, found 663.2677.

**Oxidative Cleavage of Amino Alcohol 7 to Imine 8.** The starting material (28.0 mg, 0.042 mmol) was taken up in 0.2 N HCl (0.5 mL), and solid $NaIO_4$ (20.8 mg, 0.097 mmol) was added to the mixture. After being stirred at rt for 0.5 h, the reaction mixture was diluted with 0.1 M pH 7 phosphate buffer to give a slightly milky solution, which was extracted three times with EtOAc. The extracts were washed with saturated $NaCl_{aq}$, dried over $MgSO_4$, and concentrated to give 19.5 mg (73% yield) of imine 8 as a pale yellow oil: $^1H$ NMR (270 MHz) δ 1.28 (m, 6 H, C$H_3$), 1.6–1.9 (m, 4 H, C$H_2$), 1.97 (s, 3 H, AcO), 3.9–4.2 (m, 11 H, C$H_2$O, CHN), 4.93 and 4.95 (two d, 1:1 ratio, $J$ = 4.9, 5.2 Hz, 1 H, C*H*CO), 5.07 and 5.09 (two d, 1:1 ratio, $J$ = 24.1, 24.3 Hz, 1 H, C*H*P), 5.24 and 5.26 (two ABq, 1:1 ratio, $J$ = 12.0 Hz, 2 H, C$H_2$Ph), 7.3–7.45 (m, 8 H, C$_6H_5$), 7.78 (m, 2 H, C$_6H_5$), 8.50 (m, 1 H, PhCH=N); IR (film) ν 1746 (C=O), 1638 (C=N) cm$^{-1}$.

**Acidic Hydrolysis of Imine 8 to Ammonium Salt 9.** The above imine (19.5 mg, 0.031 mmol) was dissolved in MeOH (2 mL), and 0.2 N HCl (0.4 mL) was added at rt. After being stirred at rt for 70 min, the mixture was concentrated and the residual oil was dried under vacuum to give 19.4 mg (quantitative yield) of ammonium salt 9 as a pale yellow oil. The $^1H$ NMR spectrum gave only broad signals.

**Conversion of 9 to Azide 3.** To an ice-cooled solution of ammonium salt 9 (19.4 mg, 0.031 mmol) in $CH_2Cl_2$ (0.5 mL) was added a solution of freshly prepared triflic azide[19] in $CH_2Cl_2$ (1 M solution, 0.62 mL, 0.62 mmol) followed by triethylamine (0.013 mL, 0.094 mmol). After being stirred with ice-cooling for 15 min, the mixture was allowed to stand at rt overnight. Evaporation of the solvent followed by chromatography of the residual oil, with EtOAc–acetone (1:0–2:1) as elutent, gave 8.2 mg (47% yield) of azide 3 as a colorless oil: $^1H$ NMR (270 MHz) δ 1.28 (m, 6 H, C$H_3$), 1.6–1.9 and 2.1–2.3 (m, 4 H, C$H_2$), 2.10 (s, 3 H, AcO), 4.00 (m,

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7 H, $CH_2O$, CHNCO), 4.12 (m, 4 H, $POCH_2$), 4.70 and 4.71 (two d, 1:1 ratio, $J$ = 5.1, 4.9 Hz, $N_3CH$), 4.99 and 5.00 (two d, 1:1 ratio, $J$ = 24.4, 24.2 Hz, 1 H, CHP), 5.22 and 5.24 (two ABq, 1:1 ratio, $J$ = 12.2, 12.1 Hz, 2 H, $CH_2Ph$), 7.37 (br s, 5 H, $C_6H_5$) (this is identical to the spectrum reported for racemic material);[4a] $^{13}C$ NMR (75.5 MHz) δ 16.2 (CCOP), 20.9 (AcO), 22.1 and 22.7 (CCCO), 30.8 and 31.0 (CCO), 52.2 and 52.7 (two d, $J$ = 154, 147 Hz, PC), 60.0 and 60.3 (CN, β-lactam), 63.5, 63.7, 63.9 and 64.1 (four d, $J$ = 7 Hz, COP), 64.9 and 65.1 (COAc), 65.4, 65.5, 65.6 and 65.6 (CO ketal), 66.3 and 66.3 (CCCO, β-lactam), 68.2 and 68.3 (OC, benzyl), 108.2 (OCO, ketal), 128.5, 128.6, 128.6, 128.7, 128.8, 134.4, 134.6 (ArC), 164.6, 164.7 and 164.8 (C=O, ester, β-lactam), 170.5 (C=O, AcO); IR (film) ν 2109 ($N_3$), 1769 (C=O), 1746 (C=O) $cm^{-1}$; $[\alpha]_D$ = −91.9° ($c$ = 0.335, $CH_2Cl_2$); MS (FAB) $m/e$ (rel intensity) 569 (100, M + 1), 495 (22, M − $CH_2OAc$); exact mass calcd for $C_{24}H_{34}N_4O_{10}P$ (M + H) 569.2013, found 569.1993.

**Amide 10 from Amine Hydrochloride 9.** To an ice-cooled solution of **9** (86 mg, 0.15 mmol) in $CH_2Cl_2$ (8 mL) was added triethylamine (0.063 mL, 0.45 mmol) followed by phenylacetyl chloride (0.040 mL, 0.30 mmol), and the mixture was stirred with ice-cooling for 10 min and at rt for 10 min. After the reaction, saturated $NaHCO_{3aq}$ was added and the mixture was extracted with EtOAc three times. The combined extracts were washed with saturated $NaCl_{aq}$, dried over $MgSO_4$, and concentrated to give a pale yellow oil. Chromatographic separation of this material (silica gel, 5 g; EtOAc to EtOAc–acetone (1:1)) gave 59 mg (60% yield) of the amide as a colorless clear oil: $^1H$ NMR (270 MHz) δ 1.24 (m, 6 H, $CH_3$), 1.56 (m, 4 H, $CH_2$), 2.08 and 2.09 (two s, 3 H, AcO), 3.62 (s, 2 H, $PhCH_2CONH$), 3.87–4.17 (m, 11 H, $CH_2O$, CHCO), 4.92 and 4.97 (two d, 1:1 ratio, $J$ = 24.1, 24.8 Hz, 1 H, CHP), 5.20 and 5.22 (two ABq, 1:1 ratio, $J$ = 12.2 Hz, 2 H, $CH_2Ph$), 5.35 and 5.37 (two dd, 1:1 ratio, $J$ = 5.5, 10.5 Hz and 5.3, 10.2 Hz, 1 H, NCHCO), 5.94 and 5.98 (two br d, $J$ = 10 Hz, 1 H, CONH), 7.25–7.4 (m, 10 H, $C_6H_5$); $^{13}C$ NMR (75.5 MHz) δ 16.1 and 16.2 (two d, $J$ = 5, 6 Hz, CCOP), 20.8 (AcO), 21.5 and 22.2 (CCCO), 30.5 and 30.7 (CCO), 43.3 (PhCCONH), 51.4 and 52.8 (two d, $J$ = 151, 147 Hz, PC), 58.4 (CCO, β-lactam), 60.4 and 60.8 (CN, β-lactam), 63.4, 63.5, 63.6 and 63.9 (four d, $J$ = 7 Hz, COP), 65.2 and 65.3 (COAc), 65.5 (OC, ketal), 68.0 and 68.1 (OC, benzyl), 108.1 and 108.2 (OCO, ketal), 127.4, 128.3, 128.5, 128.6, 129.0, 129.4, 129.5, 134.0, 134.1, 134.5, 134.6 (ArC), 164.6 and 165.1 (C=O, ester), 167.2 (C=O, β-lactam), 170.4 (C=O, AcO), 171.1 (C=O, CONH); IR (film) ν 3286 (NH), 1763 (C=O), 1747 (C=O), 1681 (C=O) $cm^{-1}$; $[\alpha]_D$ = −13.5° ($c$ = 0.051, $CH_2Cl_2$).

**Tricyclic Ketal 11 from Amino Alcohol 7.** To a solution of **7** (0.17 g, 0.26 mmol) in acetonitrile (10 mL)/water (0.2 mL) was added $LiBF_4$ (0.30 g, 3.18 mmol), and the mixture was heated at reflux for 6 h. After addition of $LiBF_4$ (0.13 g, 1.37 mmol), the mixture was again heated at reflux for 6 h. The solvent was removed in vacuo, and the residue was taken up in EtOAc. The solution was washed with saturated NaCl twice, dried over $MgSO_4$, and concentrated to give a brown oil, which was purified by chromatography with EtOAc–acetone (100:0–95:5) as eluent to afford 0.12 g (74% yield) of tricyclic ketal **11** as a colorless oil: $^1H$ NMR (270 MHz) δ 1.2–1.3 (m, 6 H, $CH_3$), 1.7–2.45 (m, 4 H, $CH_2$), 2.08 (s, 3 H, AcO), 3.65 (m, 1 H, $OCH_2CHN$), 3.95 and 3.99 (two d, $J$ = 16.9, 17.1 Hz, 1 H, $CH_2OAc$), 4.0–4.25 (m, 8 H, $CH_2OAc$, $POCH_2$, CHCO, $OCH_2CHN$), 4.38 and 4.46 (two br s, 1 H, CHCON), 5.02 and 5.07 (two d, 1:1 ratio, $J$ = 23.7, 23.9 Hz, 1 H, CHP), 5.18 and 5.23 (two ABq, 1:1 ratio, $J$ = 12.1 Hz, 2 H, $CH_2Ph$), 7.3–7.5 (m, 10 H, $C_6H_5$); $^{13}C$ NMR (67.9 MHz) δ 16.2 (CCOP), 20.0 and 20.5 (CCCO), 20.8 (AcO), 23.7 (CCO) 52.3 and 52.9 (two d, $J$ = 154, 148 Hz, PC), 54.6 and 55.0 (CN, β-lactam), 63.4, 63.5, 63.7 and 63.9 (four d, $J$ = 7 Hz, COP), 67.5, 68.2, 68.9, 69.1, 71.4 (CN, oxazolidine), 93.9 (OCN, oxazolidine), 127.3, 128.2, 128.5, 128.7, 128.9, 134.9, 138.1, 138.2 (ArC), 165.1 and 165.4 (C=O, ester), 169.0 and 169.5 (C=O, β-lactam), 170.5 (C=O, AcO); IR (film) ν 1760 (C=O), 1744 (C=O) $cm^{-1}$; $[\alpha]_D$ = +32.0° ($c$ = 0.30, $CH_2Cl_2$); MS (FAB) $m/e$ (rel intensity) 601 (73, M + 1), 527 (100, M − $CH_2OAc$); exact mass calcd for $C_{30}H_{38}N_2O_9P$ (M + H) 601.2315, found 601.2298.

**Acidic Hydrolysis of 5 to 12.** The starting material (13 mg) was taken up in 10% $H_2SO_4$ (0.8 mL) and AcOH (0.1 mL), and the mixture was heated to 50 °C for 2.5 h. Solid $NaHCO_3$ (480 mg) was added, and after dilution with MeOH insoluble material was removed by filtration. The filtrate was concentrated, and the residue was evaporated with $n$-butanol and with methanol to give a white solid. This material was triturated with acetonitrile, and after filtration, this acetonitrile solution was concentrated to give a pale yellow oil (11 mg, quantitative yield as a crude product): $^1H$ NMR (270 MHz) δ 1.2–1.35 (m, 6 H, $CH_3$), 1.5–2.45 (m, 4 H, $CH_2$), 3.50 (br d, $J$ = 4.9 Hz, 2 H, $CH_2OH$), 3.64 (br t, $J$ = 11.5 Hz, 1 H, $OCH_2CHN$), 4.0–4.25 (m, 7 H, $CH_2OP$, CHCO, $OCH_2CHN$), 4.39 and 4.47 (two br s, 1 H, CHNCO), 5.02 and 5.07 (two d, 1:1 ratio, $J$ = 23.7, 23.8 Hz, 1 H, CHP) 5.19 and 5.21 (two ABq, 1:1 ratio, $J$ = 11.5, 12.1 Hz, 2 H, $CH_2Ph$), 7.3–7.45 (m, 10 H, $C_6H_5$); IR (film) ν 1758, 1745 $cm^{-1}$. These spectroscopic data were identical with those of hydrolysis product from tricyclic β-lactam **11**.

**Reaction of Tricyclic Ketal 11 with Formalin To Give 13.** To a solution of **11** (25.8 mg, 0.043 mmol) in EtOAc–MeOH (1 mL each) was added at rt saturated $NaHCO_3$ (1 mL) followed by formalin (37%, 0.2 ml, 20 mmol), and the mixture was stirred at rt for 10 min. The mixture was diluted with saturated $NaHCO_{3aq}$ and was extracted three times with EtOAc. The extracts were washed with saturated NaCl, dried over $MgSO_4$, and concentrated to give a pale yellow oil which was purified by chromatography with hexane–EtOAc (9:1 to 1:1) as eluent to afford 15.7 mg (77%) of olefin **13** as a colorless oil: $^1H$ NMR (300 MHz) δ 1.68 (dd, $J$ = 8.2, 15.6 Hz, 1 H, $CH_2C$), 1.89 (dt, $J$ = 3.2, 15.6 Hz, 1 H, $CH_2$ C), 2.00 (m, 2 H, $CH_2C$), 2.09 (s, 3 H, AcO), 3.65 (m, 1 H, $OCH_2CHN$), 4.01 (d, $J$ = 11.7 Hz, 1 H, $CH_2OAc$), 4.13 (d, $J$ = 5.2 Hz, 1 H, CHCO), 4.19 (m, 2 H, $OCH_2CHN$) 4.26 (d, $J$ = 11.7 Hz, 1 H, $CH_2OAc$), 4.66 (dt, $J$ = 2.6, 5.2 Hz, 1 H, CHNCO), 5.20 (d, $J$ = 12.2 Hz, 1 H, $CH_2Ph$), 5.25 (d, $J$ = 12.2 Hz, 1 H, $CH_2Ph$), 6.03 (s, 1 H, CH=C), 6.34 (s, 1 H, CH=C), 7.30–7.45 (m, 10 H, $C_6H_5$); $^{13}C$ NMR (75.5 MHz) δ 20.5 and 20.9 (CCCO, AcO), 23.5 (CCO), 54.6 (CN, β-lactam), 63.7 (CO, oxazolidine), 67.0, 67.3, 68.5, 71.3 (CN, oxazolidine), 93.5 (OCN, oxazolidine), 114.6 (C=C), 127.3, 128.2, 128.3, 128.6, 128.7, 128.8 (ArC), 131.7 (C=C), 135.0, 137.5 (ArC), 162.0 (C=O, ester), 167.7 (C=O, β-lactam), 170.7 (C=O, AcO); IR (film) ν 1748 (C=O), 1727 (C=O), 1608 (C=C) $cm^{-1}$; $[\alpha]_D$ = +49.4° ($c$ = 0.235, $CH_2Cl_2$); MS (FAB) $m/e$ (rel intensity) 477 (62, M + 1), 403 (100, M − $CH_2OAc$); exact mass calcd for $C_{27}H_{29}N_2O_6$ (M + H) 477.2026, found 477.2038.

**Synthesis of Hexahydro-1,3,5-triazine 15a.** The trimer **15a** was prepared according to a modification of a method described in the literature.[10b,21] (*R*)-Methyl *p*-(benzyloxy)phenylglycinate hydrochloride[23] (0.50 g, 1.6 mmol) was slurried in EtOAc/$H_2O$ (1:1) (50 mL) and cooled 10 min at 0 °C. Formaldehyde 30% aqueous (0.19 g, 6.4 mmol) was added via syringe, and the reaction mixture was cooled 5 min. $NaHCO_3$ (0.15 g, 1.76 mmol) was added all at once with stirring. Stirring was continued at 0 °C for 2 h and at room temperature overnight. The reaction mixture was partitioned between $Et_2O$ (50 mL) and water (30 mL). The water layer was extracted with $Et_2O$ (2 × 20 mL). The combined ether layers were dried ($MgSO_4$) and the solvent removed under reduced pressure to give a white foam (0.47 g, 99%). The $^1H$ NMR and IR spectra were identical in all respects to those reported in the literature.[12] Compound **15b** was synthesized in an identical manner.

**Synthesis of Nocardicin Precursor 20.** The trimer **15b** (52 mg, 0.048 mmol) and pyridinium *p*-toluenesulfonate (12 mg, 0.04 mmol) were combined as solids and dissolved in MeCN (2 mL) for 5 min. Chromium carbene complex (*S*)-**1** (50 mg, 0.13 mmol) was added in MeCN (2 mL). Normal irradiation (90 h) under argon, oxidation, and purification yielded a mixture of diastereoisomers (2:1) (39 mg, 52%): $^1H$ NMR (300 MHz) δ 1.43 (s, 6 H, Me(b*)), 1.45 (s, 6 H, Me (a*)), 2.41 (dd, $J$ = 2.8, 5.5 Hz, 1 H, $NCH_2$ (a)), 2.98 (m, 2 H, $NCH_2$ (b)), 3.42 (t, $J$ = 5.7 Hz, 1 H, $NCH_2$ (a)), 3.64 (dd, $J$ = 5.4, 8.1 Hz, 1 H, NCHPh (a)), 3.72 (dd, $J$ = 4.6, 7.8 Hz, 1 H, NCHPh (b)), 4.24–4.09 (m, 4 H, $OCH_2Ph$ (a/b)), 4.33 (dd, $J$ = 2.9, 5.9 Hz, 1 H, NCOCH), 5.19–5.00 (m, 8 H, $OCH_2Ph$ (a/b)), 5.42 (s, 1 H, NCHCOOBn (b)), 5.51 (s, 1 H, NCHCOOBn (a)), 7.45–6.82 (m, ArH); IR (film) ν 1741.3 (ester C=O and β-lactam C=O), 1609, 1584, 1511, 1454, 1382, 1333,

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(22) Chiba, K.; Mori, M.; Ban, Y. *Tetrahedron* 1985, *41*, 387.
(23) Miller, M. J.; Mattingly, P. G. *Tetrahedron* 1983, *39*, 2563.

1244, 1177, 1058 cm$^{-1}$; MS (CI(NH$_3$)) $m/e$ 576 (M$^+$). Anal. Calcd. for $C_{36}H_{38}N_2O_5$: C, 74.97; H, 6.29; N, 4.86. Found: C, 74.86; H, 6.34; N, 4.71. (*a major diastereomer and b minor diastereomer).

β-Lactam **20** (75 mg, 0.13 mmol) was dissolved in MeOH (4 mL) with stirring. 0.2 N HCl (4 mL) was added dropwise with some warming. The solution was stirred overnight. The MeOH was removed under reduced pressure. HCl (0.2 N, 2 mL) and $NaIO_4$ (55 mg, 0.25 mmol in 0.5 mL $H_2O$) were added dropwise to the remaining solution and stirred for 2 h. The solution was made basic (pH = 8) with aqueous $NaHCO_3$, extracted with $CH_2Cl_2$ (4 × 7 mL) and EtOAc (2 × 7 mL), and dried ($MgSO_4$). The product was taken up in 0.2 N HCl (5 mL) and water (3 mL) and was made basic (pH = 7–8), and di-*tert*-butyl dicarbonate (61 mg, 0.3 mmol) was added in tetrahydrofuran (THF) (5 mL). The mixture was stirred overnight. The solvent was removed under reduced pressure and the remaining solution partitioned between water/EtOAc (1:2) and extracted with EtOAc (3 × 5 mL). The combined EtOAc layers were washed with saturated NaCl (1 × 5 mL) and dried ($MgSO_4$) to yield a white foam (60 mg, 89%) of **21** as a (2:1) mixture of diastereomers. Separation of the diasteromers by preparative TLC (silica gel, 40:1 methylene chloride/MeOH) gave (*S,R*)-**21** (39.9 mg, 60%) and (*R,R*)-**21** (19.6 mg, 29%) as white solids.

(*S,R*)-**21**[13] (major diastereomer, $R_f$ = 0.55): $^1$H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 9 H, $CMe_3$), 2.98 (br dd, $J$ = 1.9, 5.6 Hz, 1 H, $NCH_2$), 3.87 (t, $J$ = 5.3 Hz, 1 H, $NCH_2$), 4.87 (m, 1 H, NCOC*H*), 4.97 (m, 1 H, NH), 5.05 (s, 2 H, $OCH_2Ph$), 5.17 (dd, $J$ = 12.2, 15.4 Hz, 2 H, $OCH_2Ph$), 5.59 (s, 1 H, NC*H*COOBn), 7.43–6.92 (m, ArH); $^{13}$C NMR (75 MHz) δ 28.23, 48.49, 56.72, 57.08, 67.40, 70.09, 115.37, 125.36, 127.46, 128.12, 128.22, 128.49, 128.59, 128.64, 129.52, 134.98, 136.57, 155.00, 159.14, 167.00; IR (film) ν 3344 (NH), 1765, 1741, 1720 (ester C=O, β-lactam C=O), 1610, 1584, 1512, 1454, 1368, 1330 cm$^{-1}$; MS (CI(NH$_3$)) $m/e$ 516 (M + 1); $[\alpha]_D$ = −63.2° ($c$ 0.62, MeOH).

(*R,R*)-**21** (minor diastereomer, $R_f$ = 0.66): $^1$H NMR (300 MHz) δ 1.42 (s, 9 H, $CMe_3$), 3.38 (t, $J$ = 5.3 Hz, 1 H, $NCH_2$), 3.46 (m, 1 H, $NCH_2$), 4.81 (m, 1 H, NCOC*H*), 5.05 (s, $OCH_2Ph$), 5.10 (m, 1 H, NH), 5.18 (s, 2 H, $OCH_2Ph$), 5.57 (s, 1 H, NC*H*COOBn), 7.43–6.91 (m, ArH); IR (film) ν 3331 (NH), 1760, 1740, 1720 (ester C=O, β-lactam C=O, amide C=O), 1610, 1584, 1512, 1455, 1368, 1335 cm$^{-1}$; $[\alpha]_D$ = +18.1° ($c$ 0.66, MeOH).

**Chiral Shift Experiment.** Eu(hfc)$_3$[24] and (*S,R*)-**21** or (*R,R*)-**21**. (*S,R*)-**21**: no Eu(hfc)$_3$, $^1$H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 9 H, $CMe_3$); 4 mmol % Eu(hfc)$_3$, $^1$H NMR (300 MHz) δ 1.40 (br s, 9 H, $CMe_3$); 8 mmol % Eu(hfc)$_3$, $^1$H NMR (300 MHz) δ 1.40 (br s, 9 H, $CMe_3$); 16 mmol % Eu(hfc)$_3$, $^1$H NMR (300 MHz) δ 1.42 (br s, 9 H, $CMe_3$); 28 mmol % Eu(hfc)$_3$, $^1$H NMR (300 MHz) δ 1.47 (br s, 9 H, $CMe_3$); 42 mmol % Eu(hfc)$_3$, $^1$H NMR (300 MHz) δ 1.57 (br s, 9 H, $CMe_3$).

(*R,R*)-**21**: no Eu(hfc)$_3$, $^1$H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 9 H, $CMe_3$); 2 mmol % Eu(hfc)$_3$, $^1$H NMR (300 MHz) δ 1.48 (br s (with shoulder), 9 H, $CMe_3$); 4 mmol % Eu(hfc)$_3$, $^1$H NMR (300 MHz) δ 1.50 (br s, $CMe_3$), 1.59 (br s, $CMe_3$); 9 mmol % Eu(hfc)$_3$, $^1$H NMR (300 MHz) δ 1.60 (br s, $CMe_3$), 1.69 (br s, $CMe_3$) integration 1:3.

**Synthesis of Nocardicin Precursors 24b.** Chromium carbene complex (*S*)-**1** (51 mg, 0.13 mmol) was dissolved in $CH_2Cl_2$ (1 mL), and methyl thioimidate **22b**[10c] (52 mg, 0.13 mmol) in $CH_2Cl_2$ (0.5 mL) was added via syringe. Glass beads were added to the solution, and the tube was closed with a septum, evacuated, purged with argon (5 x), placed in the 450-W light, and irradiated for 22 h. The $CH_2Cl_2$ was evaporated under reduced pressure. The residue was taken up in ether/EtOAc (10:1) and allowed to air-oxidize in light (3 h). The clear solution with green/brown precipitate was filtered through Celite and the solvent removed under reduced pressure. The residue was purified by preparative TLC plate (silica gel, benzene/EtOAc (9:1), developed 2 x) to yield two trans isomers (18.5 mg, 24%) and four cis isomers (58 mg, 70%). Trans$_a$/trans$_b$ (19%:5%): $^1$H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 3 H, $CMe_2$(a*)), 1.44 (s, 3 H, $CMe_2$(b*)), 1.47 (s, 3 H, $CMe_2$(a)), 1.54 (s, 3 H, S*Me*(b)), 1.74 (s, SMe(a)), 3.65 (dd, $J$ = 3.7, 6.8 Hz, 1 H, NC*H*Ph(a)), 3.76 (d, $J$ = 2.6 Hz, 1 H, NCOC*H*(a)), 3.95 (d, $J$ = 2.5 Hz, 1 H, NCOC*H*(b)), 4.08 (d, $J$ = 2.5 Hz, 1 H, NCOC*H*(b)), 4.15 (d, $J$ = 2.6 Hz, 1 H, NCOC*H*(a)), 4.28–4.23 (m, 4 H, $OCH_2$(a&b)), 5.04 (s, 2 H, $OCH_2Ph$(a)), 5.05 (s, 2 H, $OCH_2Ph$(b)), 5.21–5.11 (m, ~3 H, NC*H*COO$CH_2$Ph(a and b)), 7.42–6.82 (m, ArH); $^{13}$C NMR (75 MHz) δ 14.59, 22.91, 27.65, 57.03, 63.12, 67.43, 67.57, 69.84, 70.03, 71.57, 96.60, 110.80, 114.86, 127.02, 127.43, 128.04, 128.31, 128.45, 128.60, 129.75, 169.00, 177.00; IR (film) ν 1753, 1748 (sh) (ester C=O and β-lactam C=O), 1654, 1593, 1558, 1476, 1411, 1339 cm$^{-1}$; MS (EI) $m/e$) 622 (M$^+$). Anal. Calcd for $C_{37}H_{38}N_2O_5S$: C, 71.35; H, 6.15; N, 4.49. Found: C, 70.97; H, 6.28; N, 4.42.

Two cis isomers (36.9 mg, 44%, 3:1): $^1$H NMR (300 MHz) δ 1.43 (s, 3 H, $CMe_2$(a*)), 1.45 (s, 3 H, $CMe_2$(a)), 1.48 (s, 3 H, $CMe_2$(b)), 1.53 (s, 3 H, S*Me*(a)), 1.91 (s, 3 H, S*Me*(b)), 3.75 (dd, $J$ = 6.5, 8.5 Hz, 1 H, NC*H*Ph(a)), 4.29 (t, $J$ = 8.4 Hz, 1 H, $OCH_2$(a)), 4.47 (d, $J$ = 4.1 Hz, 1 H, NCOC*H*(b)), 4.52 (d, $J$ = 4.5 Hz, 1 H, NCOC*H*(a)), 4.90 (d, $J$ = 4.4 Hz, 1 H, NC*H*S(a)), 5.04 (s, 2 H, $OCH_2Ph$(a)), 5.07 (s, 2 H, $OCH_2Ph$(b)), 5.13 (s, 2 H, $OCH_2Ph$(b)), 5.17 (s, 2 H, $OCH_2Ph$(a)), 5.42 (s, ~1 H, NC*H*COOBn(a and b)), 7.42–6.79 (m, ArH); IR (film) ν 1755, 1748 (sh) (ester C=O and β-lactam C=O), 1645, 1592, 1557, 1478, 1413, 1353 cm$^{-1}$.

Cis a (11.8 mg, 14%): $^1$H NMR (300 MHz) δ 1.45 (s, 3 H, $CMe_2$), 1.48 (s, 3 H, $CMe_2$), 1.64 (s, 3 H, S*Me*), 3.76 (dd, $J$ = 5.7 Hz, 1 H, NC*H*Ph), 4.29 (t, $J$ = 7.5 Hz, 1 H, $OCH_2$), 4.63 (d, $J$ = 4.5 Hz, 1 H, NCOC*H*), 4.70 (m, 1 H, $OCH_2$), 4.92 (d, $J$ = 4.5 Hz, 1 H, NC*H*S), 5.07 (s, 2 H, $OCH_2Ph$), 5.14 (s, 2 H, $OCH_2Ph$), 5.41 (s, 1 H, NC*H*COOBn), 7.40–6.89 (m, ArH); IR (film) ν 1756, 1750 (sh) (ester and β-lactam C=O's), 1636, 1559, 1476, 1411, 1350 cm$^{-1}$.

Cis b (9.8 mg, 12%): $^1$H NMR (300 MHz) δ 1.44 (s, 3 H, $CMe_2$), 1.47 (s, 3 H, $CMe_2$), 1.94 (s, 3 H, S*Me*), 3.80 (dd, $J$ = 4.7, 8.3 Hz, 1 H, NC*H*Ph), 4.30 (d, $J$ = 4.2 Hz, 1 H, NCOC*H*), 4.36 (t, $J$ = 7.0 Hz, 1 H, $OCH_2Ph$), 4.55 (d, $J$ = 4.2 Hz, 1 H, NC*H*S), 4.78 (dd, $J$ = 5.3, 8.1 Hz, 1 H, $OCH_2Ph$), 5.05 (s, 2 H, $OCH_2Ph$), 5.18 (s, 2 H, $OCH_2Ph$), 5.32 (s, 1 H, NC*H*COOBn), 7.43–6.90 (m, ArH); IR (film) ν 1756, 1749 (ester C=O and β-lactam C=O), 1636, 1560, 1475, 1411, 1349 cm$^{-1}$.

**Synthesis of Nocardicin Precursor 24a.** Chromium carbene complex **1** (47 mg, 0.12 mmol) in $Et_2O$ (1.5 mL) was placed in a pressure tube and treated with methyl thioimidate **22a** (39 mg, 0.11 mmol).[10c] The reaction mixture was pressurized to 100 psi of carbon monoxide and irradiated (23 h). After oxidation and preparative TLC (silica gel, PhH/EtOAc (9:1)), **24a** was isolated (52.9 mg, 80%) as two trans isomers (11.2 mg, 17%, 16:1) and two cis isomers (41.7 mg, 63%, 3:1).

Two trans isomers: $^1$H NMR (300 MHz) δ 1.37 (s, 3 H, $CMe_2$(a*)), 1.42 (s, 3 H, $CMe_2$(a)), 1.74 (s, 3 H, S*Me*(a)), 2.10 (s, 3 H, S*Me*(b)), 3.65 (dd, $J$ = 3.9, 7.0 Hz, 1 H, NC*H*Ph(a)), 3.70 (s, 3 H, O*Me*(a and b)), 3.75 (d, $J$ = 2.6 Hz, 1 H, NCOC*H*(a)), 3.95 (d, $J$ = 2.50 Hz, 1 H, NCOC*H*(b)), 4.10 (d, $J$ = 2.2 Hz, 1 H, NC*H*S(b)), 4.17 (d, $J$ = 2.6 Hz, 1 H, NC*H*S(a)), 4.24–4.18 (m, $OCH_2$(a and b)), 4.99 (s, 2 H, $OCH_2Ph$(a and b)), 5.08 (s, 1 H, NC*H*COOMe(a and b), 7.36–6.78 (m, ArH); IR (film) ν 1757, 1747 (sh) (ester C=O and β-lactam C=O), 1611, 1513, 1455, 1369 cm$^{-1}$; MS (EI) $m/e$ 546 (M$^+$).

Two cis isomers: $^1$H NMR (300 MHz) δ 1.38 (s, 3 H, $CMe_2$(a)), 1.40 (s, 3 H, $CMe_2$(a)), 1.53 (s, 3 H, S*Me*(a)), 1.90 (s, 3 H, S*Me*(b)), 3.66 (s, 3 H, O*Me*(a)), 3.71–3.62 (m, NC*H*Ph), 4.26–4.17 (m, $OCH_2$), 4.50 (d, $J$ = 4.4 Hz, 1 H, NCOC*H*(a)), 4.52 (d, $J$ = 4.19 Hz, 1 H, NCOC*H*(b)), 4.83 (t, $J$ = 7.0 Hz, 1 H), 4.89 (d, $J$ = 4.4 Hz, 1 H, NC*H*S(a)), 4.96 (d, $J$ = 4.17 Hz, 1 H, NC*H*S(b)), 4.99 (s, $OCH_2Ph$(a and b)), 5.30 (s, 1 H, NC*H*COOMe), 7.40–6.77 (m, ArH); $^{13}$C NMR (75 MHz) δ 14.65, 22.86, 27.66, 52.47, 57.00, 63.13, 67.55, 69.87, 70.03, 71.53, 96.60, 114.91, 125.24, 127.00, 127.41, 127.71, 128.03, 128.27, 128.60, 129.60, 130.06, 130.41, 142.36, 158.89 (COOMe), 165.66 (NCO); IR (film) ν 1760, 1747 (sh) (ester C=O and β-lactam C=O), 1610, 1512, 1455, 1382 cm$^{-1}$; MS (EI) $m/e$ 546 (M$^+$).

**Synthesis of 2-Azetidinone 26.** A solution of acid chloride **25**[3] (75 mg, 0.33 mmol) in $CH_2Cl_2$ (1 mL) was added dropwise by syringe to a 0 °C solution of thioimidate **22a** (132 mg, 0.40 mmol) and $Et_3N$ (46.7 μL, 0.33 mmol) in $CH_2Cl_2$ (3 mL). The solution was stirred at 0 °C for 2 h under an argon atmosphere. The solution was stirred an additional 2 h at rt and was then filtered through a short pad of silica gel (EtOAc wash) and concentrated. The $^1$H NMR spectrum of the crude product showed a 2.1:1 ratio of the product to the formimide byproduct. The products were separated by flash chromatography (3:2 hexane/EtOAc) to give

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84 mg (0.16 mmol, 47%) of the β-lactam product **26** as a clear oil: $^1$H NMR (300 MHz) δ 1.96 (s, 3 H, $SCH_3$), 3.73 (s, 3 H, $OCH_3$), 4.00 (d, $J$ = 2.4 Hz, 1 H, lactam ring CH), 4.15 (dd, $J$ = 6.6, 8.8 Hz, 1 H, $OCH_2CHN$), 4.66 (t, $J$ = 8.8 Hz, 1 H, $OCH_2CHN$), 4.85 (d, $J$ = 2.4 Hz, 1 H, lactam ring CH), 4.93 (dd, $J$ = 6.6, 8.8 Hz, 1 H, $NCHCH_2O$), 5.07 (s, 2 H, $OCH_2Ph$), 5.21 (s, 1 H, $CHCO_2Me$), 6.90 (m, 2 H, Ph), 7.11 (m, 2 H, Ph), 7.31 (s, 5 H, Ph), 7.39 (m, 4 H, Ph); $^{13}$C NMR (75 MHz) δ 10.7 ($SCH_3$), 52.7 ($CO_2CH_3$), 58.0, 59.0, 62.4, 64.2, 69.9, 70.7, 114.9, 123.9, 127.0, 127.4, 128.1, 128.6, 129.4, 130.5, 136.6, 137.7, 157.1, 159.0 (C=O), 163.2 (C=O), 169.1 (C=O): IR (film) ν 1760 (s, C=O) cm$^{-1}$; MS $m/e$ CI ($NH_3$) (% (% rel intensity) 549 (2.4, M + 17$^+$).

Also isolated by chromatography was 40 mg of the formimide byproduct along with an unidentified impurity: $^1$H NMR (benzene-$d_6$) (300 MHz) δ 3.29 (d, $J$ = 19.7 Hz, 1 H, $NCH_2C(O)N$), 3.35 (s, 3 H, $CO_2CH_3$), 3.57 (t, $J$ = 8.2 Hz, 1 H, $OCH_2CHN$), 4.00 (t, $J$ = 8.7 Hz, 1 H, $OCH_2CHN$), 4.39 (d, $J$ = 19.7 Hz, 1 H, $NCH_2C(O)N$), 4.63 (s, 2 H, $PhCH_2O$), 4.70 (t, $J$ = 82. Hz, 1 H, $OCH_2CHN$), 6.24 (s, 1 H, $CHCO_2Me$), 6.83 (m, 2 H, Ph), 6.88 (m, 2 H, Ph), 7.10 (m, 14 H, Ph), 7.43 (m, 2 H, Ph), 8.25 (s, 1 H, CHO); $^{13}$C NMR (75 MHz) δ 45.8, 52.9, 56.9, 59.7, 59.9, 69.8, 70.0, 70.3, 115.0, 125.9, 127.2, 127.4, 128.4, 128.6, 129.5, 130.8, 136.4, 136.6, 136.8, 158.3 (Ph), 158.5 (Ph), 159.0 (CO), 161.3 (CHO, dept), 168.7 (C=O), 168.8 (C=O); IR (neat) ν 1760 (C=O), 1682 (C=O) cm$^{-1}$; MS CI ($NH_3$) $m/e$ (% rel intensity) 502 (1.7, M$^+$), 519 (2.2, M + 17$^+$).

Addition of $Et_3N$ (1 equiv) to a −78 °C solution of the acid chloride followed by addition of a solution of the imine gave a 37% yield of the β-lactam product **26** as one diastereoisomer and 12% of the formimide byproduct.

**Conversion of 24a (Major Trans) to 26.** A solution of **24a** (40 mg, 0.07 mmol) in 1:1 MeOH/0.2 N HCl was stirred for 48 h. The reaction mixture was concentrated and placed under reduced pressure (0.1 mmHg) overnight. The amino alcohol was then dissolved in 2 mL of $CH_2Cl_2$, cooled to 0 °C, and stirred under an argon atmosphere. Pyridine (30 μL, 0.35 mmol) was added, and then a solution of triphosgene (10.3 mg, 0.035 mmol) in $CH_2Cl_2$ (2 mL) was added via syringe. The solution was warmed slowly to rt and stirred for 16 h. The reaction mixture was filtered through a short pad of silica gel (EtOAc wash) and concentrated to give 37 mg of the crude product **26** as a brown oil. The spectroscopic data was identical with **26** synthesized from **25**.

**Synthesis of Methyl Thioimidate 27.** To a solution of *N*-benzylamine (0.65 g, 6.00 mmol) in $CHCl_3$ (10 mL) was added ethyl thioformate[25] (0.48 g, 5.35 mmol) dropwise and the mixture stirred (22 h) at ambient temperature. The reaction mixture was poured into water (15 mL), extracted with 5% HCl (15 mL) and water (15 mL), and dried ($MgSO_4$) to give an oily solid (0.58 g, 71%): $^1$H NMR (300 MHz) δ 4.70 (d, 2 H, $CH_2Ph$), 7.26–7.24 (m, 5 H, ArH), 8.62 (br s, NH), 8.99 (d, $J$ = 30 Hz, *H*CS), 9.21 (d, $J$ = 14 Hz, 1 H, HCS); $^{13}$C NMR (75 MHz) δ 46.92, 127.88, 128.10, 128.52, 135.33, 188.20; IR (film) ν 3194 (NH), 1698, 1523 (s), 1442 (s), 1284 (s) cm$^{-1}$; MS (EI) $m/e$ 151 (M$^+$). The thioformamide (0.57 g, 3.8 mmol) synthesized above was dissolved in acetone (10 mL) under argon and powdered $K_2CO_3$ (0.78 g, 5.7 mmol) was added. MeI (0.59 g, 4.0 mmol) was added dropwise via syringe and the solution stirred overnight at ambient temperature. A white solid was removed by filtering through Celite. Solvent was removed under reduced pressure and the residue taken up in $CH_2Cl_2$. The $CH_2Cl_2$ solution was extracted with water (1 × 25 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure. The residue was taken up in $Et_2O$ and filtered to give a pale yellow milky oil[27] (0.39 g, 63%): $^1$H NMR (300 MHz) δ 2.28 (s, 3 H, S*Me*(a*)), 2.35 (s, 3 H, S*Me*(b*)), 4.37 (d, $J$ = 2.4 Hz, 2 H, $CH_2Ph$(b)), 4.54 (s, 2 H, $CH_2Ph$(a)), 7.25–7.14 (m, ArH), 8.11 (t, $J$ = 2.4 Hz, 1 H, *H*CS(b)), 8.20 (t, $J$ = 1.1 Hz, 1 H, *H*CS(a)); IR (film) ν 1676 (s), 1638, 1601 (s), 1494, 1452, 1351 cm$^{-1}$.

**Synthesis of 1-Benzyl-3-(2′,2′-dimethyl-5′-phenyl-1′,3′-oxazolidinyl)-4-(thiomethoxy)-3-propane-β-lactam (28).** Chromium carbene complex (*S*)-**1** (78 mg, 0.20 mmol) was dissolved in $Et_2O$ (2 mL) and treated with methyl thioimidate **27** (36 mg, 0.22 mmol) in $Et_2O$ (1 mL) in a pressure tube at 95 psi CO and irradiated (24 h). Oxidation and preparative TLC (silica gel, benzene/EtOAc (9:1)) and a second preparative TLC (silica gel, hexane/EtOAc (2:1)) gave two trans isomers 73% ratio (11:1) and one cis isomer 7%. Two trans isomers (55 mg, 73%). Major trans: $^1$H NMR (300 MHz) δ 1.43 (s, 3 H, C*Me*$_2$), 1.47 (s, 3 H, C*Me*$_2$), 1.74 (s, 3 H, S*Me*), 3.67 (dd, $J$ = 4.4, 7.0 Hz, 1 H, NC*H*Ph), 3.72 (d, $J$ = 2.3 Hz, 1 H, NCOC*H*), 3.85 (d, $J$ = 15 Hz, 1 H, $CH_2Ph$), 4.11 (d, $J$ = 2.0 Hz, 1 H, NC*H*S), 4.32–4.22 (m, 2 H, $OCH_2$), 4.51 (d, $J$ = 15 Hz, 1 H, $CH_2Ph$), 7.28–6.98 (m, ArH). Anal. Calcd for $C_{22}H_{26}N_2O_2S$: C, 69.08; H, 6.85; N, 7.32. Found: C, 69.19; H, 6.96; N, 7.45.

Minor trans: $^1$H NMR (300 MHz) δ 1.41 (s, 3 H, C*Me*$_2$), 1.52 (s, 3 H, C*Me*$_2$), 1.79 (s, 3 H, S*Me*), 3.65 (t, $J$ = 6.6 Hz, 1 H, N*H*Ph), 3.81 (d, $J$ = 15 Hz, 1 H, $CH_2Ph$), 4.17–4.07 (m, 3 H, NOC*H* and $OCH_2$), 4.41 (d, $J$ = 2.0 Hz, 1 H, NC*H*S), 4.53 (d, $J$ = 15 Hz, 1 H, $NCH_2Ph$), 7.35–6.96 (m, ArH); IR (film) ν 1753 (β-lactam C=O), 1674, 1495, 1455, 1386 cm$^{-1}$; MS (EI) $m/e$ 382 (M$^+$).

Cis isomer: $^1$H NMR (300 MHz) δ 1.45 (s, 3 H, C*Me*$_2$), 1.47 (s, 3 H, C*Me*$_2$), 1.92 (s, 3 H, SMe), 3.75 (dd, $J$ = 6.3, 8.6 Hz, 1 H, N*H*Ph), 4.02 (d, $J$ = 15 Hz, 1 H, $NCH_2Ph$), 4.30 (t, $J$ = 8.1 Hz, 1 H, $OCH_2$), 4.40 (d, $J$ = 4.2 Hz, 1 H, NCOC*H*), 4.48 (d, $J$ = 4.2 Hz, 1 H, NC*H*S), 4.49 (d, $J$ = 15 Hz, 1 H, $NCH_2Ph$), 4.89 (t, $J$ = 6.5 Hz, 1 H, $OCH_2$), 7.46–7.08 (m, ArH); IR (film) ν 1755 (β-lactam C=O), 1495, 1454, 1396 cm$^{-1}$.

**Synthesis of 1-Benzyl-3-(dibenzylamino)-4-(thiomethoxy)-3-propane-β-lactam (29).** Pentacarbonyl[(*N*,*N*-dibenzylamino)methylene]chromium carbene complex **18**[26] was dissolved in $Et_2O$ (4 mL) and treated with methyl thioimidate **27** (20 mg, 0.12 mmol) in $Et_2O$ (1 mL) in a similar manner as above. Chromatography (silica gel, hexane/EtOAc (2:1)) yielded a mixed fraction of cis/trans isomers (38.8 mg, 93%) by $^1$H NMR of the trans isomer (82%) and cis isomer (11%): $^1$H NMR (300 MHz) δ (t = trans, c = cis) 1.67 (s, 3 H, S*Me*(t)), 2.03 (s, 3 H, S*Me*(c)), 3.50 (d, $J$ = 13.4 Hz, 2 H, $N(CH_2Ph)_2$(t)), 3.77 (d, $J$ = 13.4 Hz, 2 H, $N(CH_2Ph)_2$(t)), 3.90 (d, $J$ = 15.0 Hz, 1 H, $NCH_2Ph$(t)), 4.10 (d, $J$ = 15.2 Hz, 2 H, $N(CH_2Ph)_2$(c)), 4.14 (d, $J$ = 1.75 Hz, 1 H, NCOC*H*(t)), 4.32 (d, $J$ = 4.6 Hz, 1 H, NCOC*H*(c)), 4.40 (d, $J$ = 2.0 Hz, 1 H, NC*H*S(t)), 4.45 (d, $J$ = 4.6 Hz, 1 H, NC*H*S(c)), 4.68 (d, $J$ = 15 Hz, 1 H, $NCH_2Ph$(t)), 4.69 (d, $J$ = 15.17 Hz, 2 H, $N(CH_2Ph)_2$(c)), 7.32–7.14 (m, ArH); $^{13}$C NMR (75 MHz) δ 10.19, 43.39, 54.98, 59.48, 73.74, 127.35, 127.83, 128.34, 128.47, 128.86, 129.00, 135.54, 138.06, 167.13; IR (film) ν 1755 (β-lactam C=O), 1650, 1495, 1454, 1392 cm$^{-1}$; MS (EI) $m/e$ 402 (M$^+$). Anal. Calcd for $C_{25}H_{26}N_2OS$: C, 74.59; H, 6.51; N, 6.95. Found: C, 74.39; H, 6.48; N, 6.91.

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**Registry No.** (*S*)-**1**, 112044-06-1; (±)-**2**, 142979-99-5; **3** (isomer 1), 143060-54-2; **3** (isomer 2), 143060-55-3; **4**, 63357-47-1; **5** (isomer 1), 142980-00-5; **5** (isomer 2), 143060-56-4; **6**, 142980-01-6; **7** (isomer 1), 142980-02-7; **7** (isomer 2), 143060-57-5; **8** (isomer 1), 142980-03-8; **8** (isomer 2), 143062-02-6; **9** (isomer 1), 142980-04-9; **9** (isomer 2), 143060-58-6; **10** (isomer 1), 142980-05-0; **10** (isomer 2), 143060-59-7; **11**, 143006-17-1; **12**, 143006-18-2; **13**, 143006-19-3; **14**, 67509-41-5; (*R*)-**15a**, 63856-16-6; (*R*)-**15b**, 63856-22-4; **18**, 106502-05-0; **20** (isomer 1), 142980-06-1; **20** (isomer 2), 143060-60-0; (*R*)(*R*)-**21**, 142980-07-2; (*S*)(*R*)-**21**, 76529-92-5; **22a**, 63856-30-4; **22b**, 63854-69-3; *cis*-**24a** (isomer 1), 142980-08-3; *cis*-**24a** (isomer 2), 143060-61-1; *trans*-**24a** (isomer 1), 143060-62-2; *trans*-**24a** (isomer 2), 143060-63-3; *cis*-**24b** (isomer 1), 142980-09-4; *cis*-**24b** (isomer 2), 143060-64-4; *cis*-**24b** (isomer 3), 143060-65-5; *cis*-**24b** (isomer 4), 143060-66-6; *trans*-**24b** (isomer 1), 143060-67-7; *trans*-**24b** (isomer 2), 143060-68-8; **25**, 99333-55-8; **26**, 142980-10-7; **27**, 126789-61-5; **28**, 142980-11-8; *trans*-**28** (isomer 1), 143060-69-9; *trans*-**28** (isomer 2), 143060-70-2; (±)-*cis*-**29**, 142980-12-9; (±)-*trans*-**29**, 142980-13-0; 1-acetoxy-5-hexen-2-one ethylene glycol

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ketal, 54214-74-3; 5-acetoxy-4-oxoopentanal 4-(ethylene glycol ketal, 54214-75-4; *N*-*t*-BOC-glycine, 4530-20-5; benzyl *N*-*t*-BOC-glycinate, 54244-69-8; (±)-benzyl *N*-*t*-BOC-2-bromoglycinate, 142980-14-1; (±)-benzyl *N*-*t*-BOC-2-(diethoxyphosphoryl)-glycinate, 142980-15-2; (±)-benzyl 2-(diethoxyphosphoryl)-glycinate, 142980-16-3; phenylacetyl chloride, 103-80-0; (*R*)-methyl *p*-(benzyloxy)phenylglycinate hydrochloride, 88143-74-2; (*R*)-benzyl *p*-(benzyloxy)phenylglycinate hydrochloride, 67509-34-6; *N*-benzylamine, 100-46-9; ethyl thioformate, 29392-46-9; *N*-benzylthioformamide, 20278-32-4.

**Supplementary Material Available:** NMR spectra of **5**, **6**, **7**, **11**, **13**, and **3** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

# Studies Directed toward the Synthesis of Glycopeptide Antibiotic Teicoplanin: First Synthesis of the N-Terminal 14-Membered Ring†

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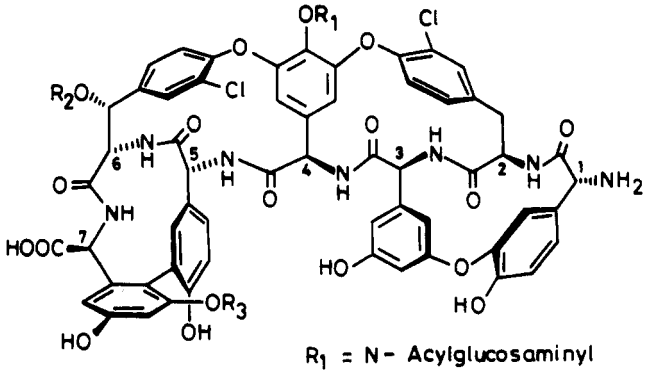
The N-terminal 14-membered ring formed by an ether linkage between the phenyl moieties of amino acids 1 and 3 of glycopeptide antibiotic teicoplanin **1** plays a crucial role in the binding of C-terminal D-Ala-D-Ala residues of the peptidoglycan precursor, thereby inhibiting bacterial cell wall biosynthesis. Herein, the first stereocontrolled synthesis of this very important cyclic peptide **2** is described. The two α-arylglycines present in this segment are constructed in optically pure form by diastereoselective Strecker synthesis using α-phenylglycinol as chiral auxiliary. Finally, the coupling between the acid function of amino acid 1 and the amino function of amino acid 2 leads to the desired macrocyclization. Optical purity of the synthetic product is determined by NMR studies.

## Introduction

Recently, teicoplanin **1** has been introduced in therapeutic use for the parenteral treatment of severe infections caused by Gram-positive bacteria.[1] Teicoplanin, a complex of closely related antibiotics produced by *Actinoplanes teichomyceticus*,[2] belongs to the ristocetin family and is of particular interest because in vitro studies show it to be more active than vancomycin (minimum inhibitory concentrations are 2–8-fold less)[3] against many Gram-positive bacteria and in vivo studies show that effective doses for mice may be more than 1 order of magnitude lower than those of vancomycin. Moreover, teicoplanin is of low toxicity[2a] and exhibits substantially different pharmacokinetic behavior in vivo, having a half-life of 40 h in man.[4] Structurally, teicoplanin is very similar to vancomycin, except that in the former an extra cycle is present which is formed by an ether bond occurring between the phenyl moieties of amino acids 1 and 3.[5]




$R_1$ = N- Acylglucosaminyl
$R_2$ = N-Actyl-β-D-glucosaminyl
$R_3$ = α-D-Mannosyl

**1**

All these compounds express their antibiotic activity by inhibiting bacterial cell wall biosynthesis by selectively binding the C-terminal D-Ala-D-Ala residues of peptidoglycan precursor, muramyl pentapeptide.[6] Though many of these compounds have been known for over 30 years no total synthesis has, so far, been reported[7] due to their complex structures. As part of our recently initiated program on the syntheses of these glycopeptide antibiotics, several steps have been undertaken to overcome the major hurdles still associated in such syntheses. One of these is the presence of a large number of unnatural amino acids in these compounds, in particular α-phenylglycines which are amongst the most difficult amino acids to obtain in optically pure form. This has prompted us to develop an

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