Palladium(II)-Assisted Difunctionalization of Monoolefins: Total Synthesis of (+)-Negamycin and (−)-5-*epi*-Negamycin

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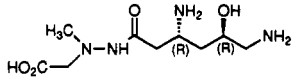
(+)-Negamycin and (−)-5-*epi*-negamycin were synthesized by a process involving the palladium(II)-assisted alkylation of an optically active ene carbamate followed by carbonylative coupling to a trialkylvinyltin. The synthesis of (+)-negamycin was completed in 15 steps with an overall yield of 13%. The synthesis of (−)-5-*epi*-negamycin was completed in 12 steps with an overall yield of 20%. In preparing these compounds, a highly diastereoselective reduction of an unsaturated ketone and an efficient intramolecular Mitsunobu reaction were also carried out.

Introduction

Negamycin (1) is an unusual antibiotic which contains a hydrazine peptide linkage. It was first isolated by Umezawa et al. in 1970 from the culture filtrate of three strains related to *Streptomyces purpeofuscus*.[1] The structure of negamycin was elucidated by Umezawa et al. in 1971 via degradation studies[2] and confirmed by total synthesis from D-galacturonic acid in 1972.[3] The absolute stereochemistry of the natural product was assigned as shown below, being *R,R*.

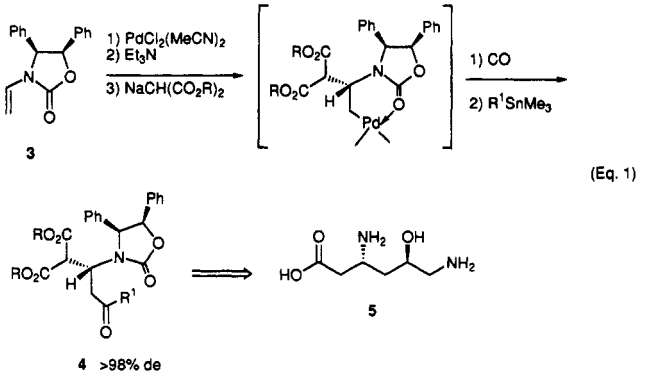


1 (+)-negamycin
2 (-)-5(S)-*epi*-negamycin

Negamycin exhibits very low acute toxicity (LD_{50} ~400–500 mg/kg) and has considerable activity toward multiple-drug resistant enteric Gram-positive and Gram-negative bacteria including *Pseudomonas aerginosa*.[1] *In vitro*, negamycin also exhibits genetic miscoding activity on bacterial ribosome systems[4] and is a specific inhibitor of protein synthesis in *Escherichia coli* K12.[5]

A variety of derivatives and diastereoisomers of (+)-negamycin have also been examined for biological activity.[3,6–10] Most of the diastereoisomers displayed significant activity, with (−)-5-*epi*-negamycin (2) being the most active of the three possible diastereoisomers.

Several syntheses of negamycin in both racemic[6,7,11] and optically active[12–18] form have been accomplished. One total synthesis of (−)-5-*epi*-negamycin[19] and several syntheses of the racemic material[6,7,19] have also been achieved. All of these syntheses have relied upon the construction of a 3,6-diamino-5-hydroxyhexanoic acid fragment 5 of appropriate stereochemistry, followed by peptide formation with the 1-methylhydrazineacetic acid. We have recently reported the development of an efficient palladium(II)-assisted tandem alkylation/carbonylative coupling procedure of optically active ene carbamates which is potentially applicable to the asymmetric synthesis of this fragment (eq 1).[20] Herein we describe the use of this methodology for the total synthesis of (−)-5-*epi*-negamycin and (+)-negamycin.



3

(Eq. 1)

4 >98% de

Results and Discussion

Central to the success of the proposed syntheses was the choice of reagents which would permit the stereoselective introduction and adjustment of the necessary functional group array in the presence of a number of

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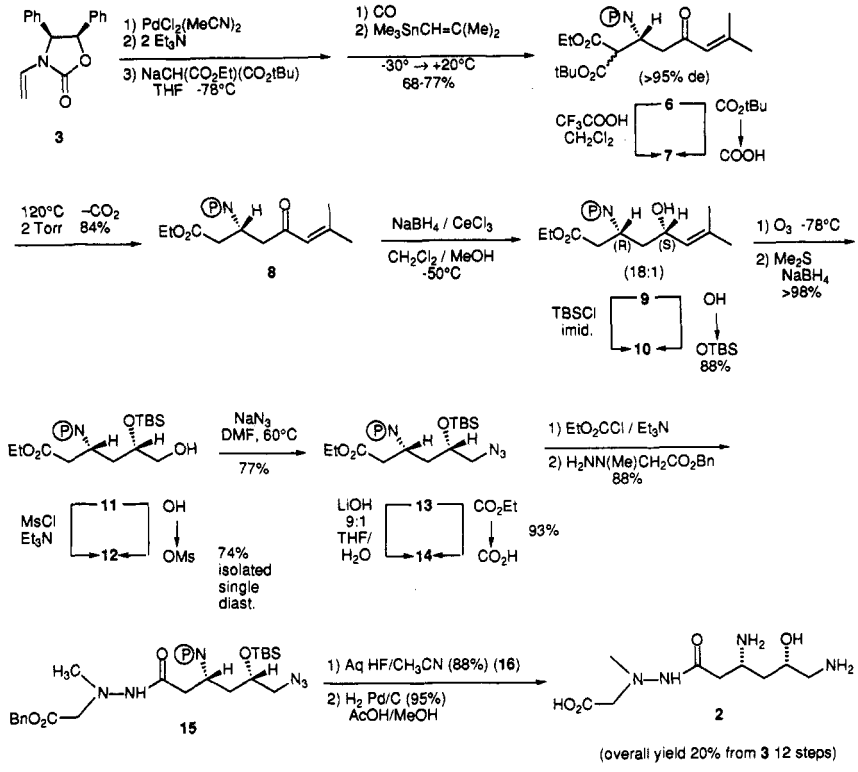
Scheme I. Total Synthesis of (−)-5-*epi*-Negamycin (2)



(overall yield 20% from 3 12 steps)

sensitive groups. Preliminary studies[20] had shown that use of the dimethyl carbonylative coupling agent, produced 4 (R = Me, R^1 = isobutenyl) in 76% yield with ≥98% de. However all attempts to decarbalkoxylate this dimethyl malonate led, instead, to elimination of the oxazolidinone group.

To circumvent this problem, the mixed *tert*-butyl ethyl malonate was used as the carbanion, with the intent of subsequent selective, mild hydrolysis of the *tert*-butyl ester. Treatment of ene carbamate **3** with $PdCl_2(MeCN)_2$, triethylamine, and the sodium anion of *tert*-butyl ethyl malonate at −78 °C, followed by exposure to 1 atm of carbon monoxide, followed by addition of isobutenyltrimethylstannane afforded good yields (68–77%) of the desired difunctionalized product **6**, as a 1:1 mixture of diastereoisomers about the malonate carbon but isomerically pure at the amine carbon (Scheme I). Hydrolysis of the *tert*-butyl ester with trifluoroacetic acid led cleanly to mono acid **7**, which was decarboxylated by heating the crude material, neat, at 120 °C for 1 h under vacuum to give monoester **8** in 84% yield over the two steps.

The next step, a diastereoselective reduction of the 5-keto group, was central to the success of the desired syntheses, since it set the stereochemistry of the second stereogenic center. After substantial experimentation, it was found that treatment of enone **8** with 1 equiv each of cerium trichloride and sodium borohydride in 3:7 CH_2Cl_2/MeOH (the CH_2Cl_2 was required to dissolve **8**) at −50 °C resulted in clean 1,2-reduction of the keto group in high yield and with high diastereoselectivity (>89% de).[21] It was necessary to carry out the acidic hydrolysis of the borate esters rapidly (<10 min) and at low temperatures (<0 °C) to prevent isomerization of the allylic alcohol. Since the allylic alcohol **9** was somewhat unstable to chromatography on silica gel, it was used without further purification. At this juncture it was not possible to assign the absolute configuration of the newly generated stereogenic center, but completion of this synthesis showed it to be *S*, putting compound **9** in the 5-*epi*-negamycin series.

Conversion of the isobutenyl group to a terminal amino group *via* ozonolysis/reductive amination was undertaken next. The allylic alcohol was protected as the *tert*-butyldimethylsilyl ether (TBS) **10**[22] in preparation for the ozonolysis step. Attempted direct ozonolysis/reductive amination using benzylamine hydrochloride and sodium cyanoborohydride led, instead, to complete decomposition of starting material, an indication of the instability of the aldehyde resulting from ozonolysis of **10**. To circumvent this problem, the ozonolysis was carried out at low temperature, and the reaction mixture was subjected directly to a reductive workup, giving crude alcohol **11** in virtually quantitative yield. Conversion of this alcohol to the mesylate gave a separable mixture of diastereoisomers, from which 74% of the desired (*R*,*S*)-**12** was isolated. Treatment with sodium azide in DMF gave the azide **13** in 77% yield, as a single diastereoisomer, completing the synthesis of a masked form of the desired 3,6-diamino-5-hydroxyhexanoic acid fragment. Completion of the total synthesis of (−)-5-*epi*-negamycin only required peptide bond formation and deprotection.

Mild saponification of **13** gave excellent yields of the free acid **14**. Attempts to couple this to the requisite 2-(*N*-methylhydrazino)acetic acid ester using DCC were complicated by the inability to separate the desired product from dicyclohexyl urea. Instead, a mixed anhydride procedure[23] involving ethyl chloroformate proved efficient, giving the protected product **15** in excellent yield. Removal of the silyl protecting group with aqueous hydrogen

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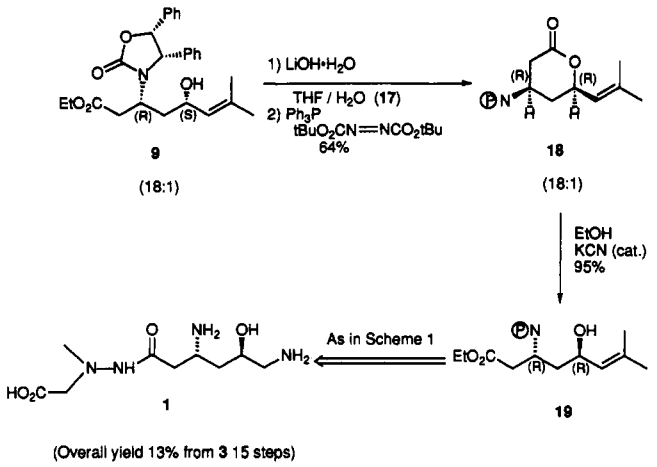
Scheme II. Total Synthesis of (+)-Negamycin



fluoride in acetonitrile[24] (the use of TBAF led to some elimination of the oxazolidinone) followed by hydrogenolytic cleavage of the benzyl ester and the diphenyloxazolidinone as well as reduction of the azide produced the acetate salt of (−)-5-*epi*-negamycin (**2**). Purification by ion-exchange chromatography (Amberlite GC 50, NH_4^+ form)[1] afforded pure **2** having spectroscopic and physical data identical in all respects to that reported for **2**.[7,19] This was further converted to the bis *N*-Cbz methyl ester derivative,[7] and the physical data for this derivative were identical to that previously reported.[7] The chemistry reported in Scheme I constitutes a total synthesis of (−)-5-*epi*-negamycin in 12 steps and overall 20% yield from the limiting reagent, palladium(II) chloride–bis(benzonitrile) complex.

This same approach could be directly applied to the total synthesis of (+)-negamycin (**1**) if it were possible to invert the stereochemistry at C-5 in intermediate **9**. The traditional way to achieve this with alcohols is the Mitsunobu reaction.[25] However the Mitsunobu reaction of allylic alcohols, particularly sterically hindered ones such as compound **9**, is complicated by competing S_N1, S_N2, and elimination reactions. Indeed, subjecting[9] to classic Mitsunobu conditions (Ph_3P, diethyl azodicarboxylate) with benzoic acid, *p*-nitrobenzoic acid, and chloroacetic acid resulted in only modest yields of the inverted ester, with substantial loss of stereochemistry (from 18:1 in **9** to ~10-3:1 in the product ester), accompanied by varying amounts of the diene resulting from elimination.

Recently, intramolecular Mitsunobu inversions of allylic alcohols have met with greater success,[26] and this approach was examined next (Scheme II). Mild saponification of ester **9** followed by the Mitsunobu cyclization using di-*tert*-butyl azodicarboxylate to facilitate separation of the byproducts resulted in a fair yield of lactone **18** with inverted stereochemistry at C-5 and *without* loss of stereochemistry in the conversion of **9** to **18**. Heating lactone **18** in ethanol with a catalytic amount of potassium cyanide produced the *R,R* "inverted" allylic alcohol **19** in excellent yield.

With this allylic alcohol in hand, the preparation of (+)-negamycin was completed as in Scheme I. Treatment of **19** with *tert*-butyldimethylsilyl chloride and imidazole in *N,N*-dimethylformamide afforded the TBS ether **20** in 81% yield. Ozonolysis followed by *in situ* reduction with sodium borohydride produced the primary alcohol **21** (99%), which was converted to the mesylate **22** by treatment with methanesulfonyl chloride and triethylamine in dichloromethane. The diastereoisomers were readily separated using silica gel chromatography, affording the enantiomerically pure *R,R* compound in 87% yield. Displacement of the mesylate with sodium azide in *N,N*-dimethylformamide afforded the azide **23** in 83% yield.

Mild saponification of **23** afforded the carboxylic acid **24** in 99% yield. Peptide bond formation using ethyl chloroformate produced the acid hydrazide **25** in 84% yield. Deprotection of the TBS ether afforded **26** (79% yield), which after hydrogenation produced the ammonium acetate salt of (+)-negamycin in quantitative yield. Purification by ion-exchange chromatography [Amberlite CG-50 (NH_4^+ form)] afforded (+)-negamycin (**1**) in excellent yield (91%) as a white powder (mp = 103–118 °C dec; lit.[1,27] mp = 110–120 °C dec).

This asymmetric synthesis of (+)-negamycin was completed in 15 steps with an overall yield of 13% based on the amount of initial palladium(II) chloride salt used. This total synthesis is comparable to the other asymmetric syntheses of (+)-negamycin reported (11 steps, 16% overall,[12] 8 steps, 14% overall,[14] 10 steps, 32% overall[17]), as well as those which began with optically active materials (14 steps, 18% overall,[15] 9 steps, 7% overall,[16] 20 steps, 19% overall[18]).

In summary, an efficient asymmetric total synthesis of (+)-negamycin and (−)-5-*epi*-negamycin was carried out. This was accomplished using the highly functionalized, optically active products obtained from the previously developed[20] alkylation/acylation procedure with optically active ene carbamates. In addition, a highly diastereoselective 1,3-induction in a hydride reduction of an unsaturated ketone and an efficient intramolecular Mitsunobu reaction were also carried out.

Experimental Section

General. General experimental information is identical to that previously reported.[20] Chemical shifts for ^1H NMR spectra are given in ppm relative to the solvent as an internal reference. Chemical shifts for ^{13}C NMR spectra recorded in $CDCl_3$ are given in ppm relative to the solvent as an internal reference. Chemical shifts for ^{13}C NMR spectra recorded in D_2O are given in ppm relative to 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt, which was used as an external reference. Ion-exchange chromatography was performed using Amberlite CG-50 (NH_4^+ form) ion-exchange resin and standard techniques. The ion-exchange resin was obtained from Amberlite CG-50 (H^+ form) (Aldrich) by treatment with 10% aqueous NH_4OH followed by neutralization with H_2O.

Preparation of Isobutenyltrimethylstannane. A solution of 1-bromo-3-methylpropene (2.84 g, 21.0 mmol) in 30 mL of 4:1:1 THF/diethyl ether/pentane at −120 °C was treated dropwise over 0.2 h with a solution of *tert*-butyllithium (1.70 M in pentane, 25.0 mL, 42.5 mmol) and was stirred at −120 °C for 0.75 h. The mixture was transferred *via* cannula to a solution of trimethyltin chloride (4.38 g, 22.0 mmol) in 25 mL of THF at room temperature and was stirred for 4 h. The mixture was added to H_2O (75 mL) and diethyl ether (100 mL). The organic extract was washed

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(27) Spectroscopic data were identical to that of the racemic material (kindly provided by Dr. P. Siret of ICI Pharma, France).

with H_2O (3 × 75 mL) and brine (1 × 50 mL) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue purified by distillation (bp = 70–86 °C, 40 mmHg), affording 5.09 g (56%) of the title compound (clear oil).

^1H NMR (300 MHz): δ 5.45 (s, 1H, Me_3SnCH=), 1.87 (d, 3H, J = 1.0 Hz, CH=C(CH_3)$_2$), 1.77 (s, 3H, CH=C(CH_3)$_2$), 0.11 (s, 9H, Me_3Sn).

Preparation of Ene Carbamate 3. A solution of methoxymethylpentacarbonylchromium(0) carbene (4.45 g, 17.8 mmol) in 15 mL of DMF was treated with (−)-(1*R*,2*S*)-diphenylethanolamine (3.79 g, 17.8 mmol) and was stirred at room temperature for 0.5 h. The mixture was poured into H_2O (100 mL) and diethyl ether (100 mL). The aqueous phase was washed with diethyl ether (3 × 50 mL), and the organic extracts were combined, washed with H_2O (1 × 50 mL) and brine (1 × 50 mL), and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was taken up in 50 mL of THF and treated with NaH (50% in oil, 864 mg, 18.0 mmol). After H_2(g) evolution, the dark red solution was transferred *via* cannula to a solution of NaH (50% in oil, 864 mg, 18.0 mmol) and diphenyl carbonate (4.28 g, 20.0 mmol) and was stirred for 6 h. The resulting solution was saturated with air (1 h) and filtered through SiO_2 using EtOAc as eluent. The solvent was removed *in vacuo* and the residue was taken up in 700 mL of 1:1 EtOAc/hexane and placed in a light box (36 h) equipped with six 20-W Vitalite fluorescent lamps. Filtration of the resulting mixture through SiO_2 followed by removal of solvent *in vacuo* afforded the crude reaction mixture. The mixture was taken up in EtOAc (350 mL) and washed with 2.0 N NaOH (4 × 100 mL) and H_2O (1 × 100 mL) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was dissolved in diethyl ether (500 mL) and hexane (150 mL). Removal of solvent *in vacuo* (cold, 1 h) afforded a white precipitate. The precipitate was collected by filtration and washed with hexanes (200 mL) to afford 3.85 g (82%) of (−)-**3** (white solid; mp = 161–163 °C). Physical and spectroscopic data were identical to that previously reported.[28]

Preparation of 6. A solution of Pd(PhCN)$_2$Cl$_2$ (1.34 g, 3.50 mmol) and ene carbamate **3** (994 mg, 3.75 mmol) in 80 mL of THF at −78 °C was treated dropwise with a solution of triethylamine (708 mg, 7.00 mmol) in 5 mL of THF over a period of 0.25 h. A −78 °C THF solution of the sodium anion of *tert*-butyl ethyl malonate (0.20 M solution in THF, 20 mL, 4.0 mmol) was then added rapidly. The solution was cooled to −85 °C and was stirred for 15 h. The mixture was placed in a −30 °C bath, the reaction vessel was evacuated (2×), the atmosphere was replaced with carbon monoxide (1 atm), and the solution was stirred for 1.5 h. The resulting black slurry was treated with isobutenyltrimethylstannane (1.75 g, 8.00 mmol), slowly allowed to warm to room temperature, and stirred for 4 h. The mixture was filtered through a pad of silica gel using ethyl acetate as the eluent. Removal of solvent *in vacuo* and purification of the residue by flash chromatography (SiO_2, 3:2 CH_2Cl_2/hexane to 4:1 hexane/EtOAc, R_f = 0.22) afforded 1.27 g (68%) of **6** (colorless oil) as a 1:1 mixture of diastereoisomers at the malonate carbon.

[Starting with 77 mg (0.20 mmol) of Pd(PhCN)$_2$Cl$_2$, 64 mg (0.24 mmol) of **3**, 60 μL (0.40 mmol) of Et_3N, the sodium anion of *tert*-butyl ethyl malonate (0.20 M solution in THF, 1.4 mL, 0.28 mmol), carbon monoxide, and 77 mg (0.35 mmol) of isobutenyltrimethylstannane afforded 82 mg (77%) of **6** using the procedure described above.]

^1H NMR (300 MHz, mixture of diastereoisomers): δ 7.02 (m, 6H, 2*Ph*), 6.95 (m, 4H, 2*Ph*), 5.87, 5.84 (s, 1H, C*H*=C(CH_3)$_2$), 5.75, 5.74 (d, 1H, J = 8.1 Hz, OC*H*Ph), 5.23, 5.22 (d, 1H, J = 8.1 Hz, NC*H*Ph), 4.46 (dt, 1H, J = 6.1, 8.7 Hz, C*H*N$_{oxa}$), 4.20, 4.00 (m, 2H, $CO_2CH_2CH_3$), 3.94, 3.89 (d, 1H, J = 8.9 Hz, C*H*(ester)$_2$), 3.12 (m, 1H, CH_2CO), 2.92, 2.86 (dd, 1H, J = 5.8, 11.8 Hz, CH_2-CO), 1.91, 1.90 (s, 3H, CH=C(CH_3)$_2$), 1.77 (s, 3H, CH=C(CH_3)$_2$), 1.48, 1.36 (s, 9H, CO_2-*t*-*Bu*), 1.27, 1.16 (t, 3H, J = 6.9 Hz, $CO_2CH_2CH_3$). ^{13}C NMR (75.5 MHz): δ 195.8, 195.6 (*C*O), 167.9, 167.4, 166.7, 166.2 (CO_2R), 157.2, 157.1, 156.5, 156.4 (*C*O$_{oxa}$) 166.7, 166.2, 135.01, 134.97, 134.53, 134.48, 129.20, 128.16, 128.11, 128.07, 128.03, 127.7, 127.53, 127.50, 125.7, 122.9, 122.8 (*Ar*), 82.5, 82.4 (*C*(CH_3)$_3$), 80.1 (*C*H), 67.01, 66.97 (*C*H), 61.53, 61.45 (CH_2), 55.6, 55.4 (*C*H), 49.5, 49.3 (*C*H), 45.6, 45.5 (CH_2), 27.8, 27.64, 27.59 (C(*C*H$_3$)$_3$), 20.69, 20.66 (CH_3), 14.0, 13.8 (CH_3). IR (neat): ν 1755, 1687 (CO), 1619 (C=C) cm^{-1}.

Preparation of 7. A solution of **6** (1.12 g, 2.09 mmol) in 10 mL of CH_2Cl_2 at room temperature was treated with 10 mL of trifluoroacetic acid. After the solution was stirred for 1 h, the volatile components were removed *in vacuo* to afford 1.00 g (100%) of **7** (yellow oil) as a 1:1 mixture of diastereoisomers at the malonate carbon. This material was decarboxylated without further purification.

^1H NMR (300 MHz, mixture of diastereoisomers): δ 9.5 (br s, CO_2H), 7.04 (m, 6H, 2*Ph*), 6.93 (m, 4H, 2*Ph*), 5.92 (m, 1.5H, C*H*=C(CH_3)$_2$, OC*H*Ph), 5.87 (d, 0.5H, J = 8.3 Hz, OC*H*Ph), 5.39, 5.25 (d, 1H, J = 8.3 Hz, NC*H*Ph), 4.45 (m, 1H, C*H*N$_{oxa}$), 4.27 (q, 0.5H, J = 7.2 Hz, $CO_2CH_2CH_3$), 4.13 (m, 0.5H, $CO_2CH_2CH_3$), 4.04 (d, 1H, J = 7.4 Hz, C*H*(CO_2H)(CO_2Et)), 3.93 (d, 1H, J = 6.4 Hz, C*H*(CO_2H)(CO_2Et)), 3.48 (dd, 0.5H, J = 8.0, 17.8 Hz, CH_2-CO), 3.39 (dd, 0.5H, J = 7.8, 18.3 Hz, CH_2CO), 2.85 (m, 1H, CH_2CO), 1.98, 1.97 (s, 3H, CH=C(CH_3)$_2$), 1.83 (s, 3H, CH=C-(CH_3)$_2$), 1.31, 1.23 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$). ^{13}C NMR (75.5 MHz): δ 197.7, 197.2 (*C*O), 171.1, 170.8, 167.9, 167.5 (*C*O$_2$R), 159.7, 159.4, 159.2, 158.9 (*C*O$_{oxa}$), 133.9, 133.6, 128.8, 128.73, 128.69, 128.6, 128.4, 127.90, 127.87, 125.7, 122.71, 122.66 (*Ar*), 81.2, 81.1 (*C*H), 67.1, 66.9 (*C*H), 62.7, 62.5 (CH_2), 54.0, 53.9 (*C*H), 50.2, 50.0 (*C*H), 45.1, 44.9 (CH_2), 30.2, 28.3, 27.7, 21.0 (=C(*C*H$_3$)$_2$), 13.63, 13.59 (CH_3). IR (neat): 3700–3000 (CO_2H), 1750, 1688 (CO), 1617 (C=C) cm^{-1}.

Decarboxylation of 7 To Give 8. A 50-mL round-bottomed flask containing **7** (1.00 g, 2.09 mmol) was heated at 120 °C for 0.75 h under high vacuum (0.2 mmHg) using a bulb-to-bulb distillation apparatus. The residue in the distillation flask was dissolved in 5 mL of CH_2Cl_2 and was slowly added dropwise to a stirred solution of hexanes (250 mL). After 2 h, the resulting precipitate was collected by filtration and washed with 10 mL of diethyl ether at 0 °C, affording 0.77 g (84%; $[\alpha]_D$ = 5.6° (c = 0.9, CH_2Cl_2)) of **8** (white solid, mp = 146–147 °C) as a single diastereoisomer.

^1H NMR (300 MHz): δ 7.05 (m, 6H, 2*Ph*), 6.94 (m, 4H, 2*Ph*), 5.94 (m, 1H, C*H*=), 5.80 (d, 1H, J = 8.3 Hz, OC*H*Ph), 5.25 (d, 1H, J = 8.3 Hz, NC*H*Ph), 4.15 (m, 1H, C*H*N$_{oxa}$), 4.13 (q, 2H, J = 7.1 Hz, $CO_2CH_2CH_3$), 3.26 (dd, 1H, J = 9.0, 16.9 Hz, CH_2CO), 2.99 (dd, 1H, J = 9.4, 16.9 Hz, CH_2CO), 2.56 (dd, 1H, J = 5.0, 16.9 Hz, CH_2CO_2Et), 2.43 (dd, 1H, J = 4.6, 16.9 Hz, CH_2CO_2Et), 2.04 (d, 3H, J = 0.7 Hz, =C(CH_3)$_2$), 1.83 (d, 3H, J = 0.8 Hz, =C(CH_3)$_2$), 1.25 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$). ^{13}C NMR (75.5 MHz): δ 197.4 (*C*O), 171.6 (CO_2Et), 157.2, 157.1 (*C*O$_{oxa}$), 135.3, 134.6, 128.4, 128.2, 127.8, 127.6, 125.8, 123.1 (*Ar*), 80.0 (*C*H), 66.6 (*C*H), 60.7 (CH_2), 48.1 (*C*H), 46.4 (CH_2), 36.7 (CH_2), 27.7 (CH_3), 20.8 (CH_3), 14.1 (CH_3). IR (neat): 1738, 1682 (CO), 1619 (C=C) cm^{-1}. Anal. Calcd for $C_{26}H_{29}NO_5$: C, 71.70; H, 6.71; N, 3.22. Found: C, 71.64; H, 6.53; N, 3.19.

1,2-Reduction of Enone 8 to Allyl Alcohol 9; Diastereoisomer-(3*R*,5*S*). A solution of **8** (520 mg, 1.19 mmol) and $CeCl_3$ (295 mg, 1.20 mmol) in 65 mL of 3:7 CH_2Cl_2/MeOH at −50 °C was treated with $NaBH_4$ (45 mg, 1.2 mmol). After 0.25 h, the reaction was quenched by the addition of 0.2 N HCl (20 mL, 4.0 mmol), H_2O (50 mL), and EtOAc (50 mL). The aqueous phase was washed with EtOAc (2 × 50 mL), and the organic extracts were combined, washed with H_2O (1 × 50 mL) and brine (1 × 50 mL), and dried (Na_2SO_4). Removal of solvent *in vacuo* afforded 520 mg (99%) of **9** (clear oil) as a greater than 18:1 mixture of diastereoisomers (>89% de). This material was carried on without further purification.

^1H NMR (300 MHz, major diastereoisomer-(3*R*,5*S*)): δ 7.04 (m, 6H, 2*Ph*), 6.95 (m, 4H, 2*Ph*), 5.83 (d, 1H, J = 8.3 Hz, OC*H*Ph), 5.18 (d, 1H, J = 8.3 Hz, NC*H*Ph), 5.07 (dm, 1H, J = 8.6 Hz, C*H*=), 4.38 (dt, 1H, J = 4.6, 8.5 Hz, C*H*OH), 4.14 (m, 1H, C*H*N$_{oxa}$), 4.05 (q, 2H, J = 7.2 Hz, $CO_2CH_2CH_3$), 2.73 (dd, 1H, J = 8.1, 16.6 Hz, CH_2CO_2Et), 2.23 (dd, 1H, J = 6.3, 16.6 Hz, CH_2CO_2Et), 2.08 (m, 1H, CH_2OH), 1.92 (ddd, 1H, J = 4.6, 6.8, 14.2 Hz, CH_2CHOH), 1.83 (m, 1H, CH_2CHOH), 1.65 (d, 3H, J = 1.0 Hz, CH=C(CH_3)$_2$), 1.60 (d, 3H, J = 1.1 Hz, CH=C(CH_3)$_2$), 1.19 (t, 3H, J = 7.2 Hz, $CO_2CH_2CH_3$). ^{13}C NMR (75.5 MHz): δ 171.4 (CO_2Et), 157.6 (*C*O$_{oxa}$), 135.7, 134.7, 128.32, 128.30, 128.1, 127.8, 127.5, 127.2, 125.8 (*Ar*), 79.9 (*C*H), 66.5 (*C*H), 65.1 (*C*H), 60.6 (CH_2), 49.6

(28) Montgomery, J.; Wieber, G. M.; Hegedus, L. S. *J. Am. Chem. Soc.* 1990, *112*, 6255.

(CH), 39.5 (CH_2), 37.4 (CH_2), 25.7 (CH_3), 18.1 (CH_3), 14.1 (CH_3). IR (neat): 3434, 3242 (OH), 1732 (CO), 1620 (C=C) cm^{-1}.

Protection of 9 To Produce 10. A solution of **9** (310 mg, 0.709 mmol) in 15 mL of DMF at room temperature was treated with TBDMSCl (301 mg, 2.00 mmol) and imidazole (95 mg, 1.4 mmol) and was stirred for 40 h. The mixture was poured into CH_2Cl_2 (50 mL) and H_2O (50 mL). The aqueous phase was washed with CH_2Cl_2 (2 × 30 mL), and the organic extracts were combined, washed with H_2O (2 × 30 mL) and brine (1 × 30 mL), and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2; 9:1 hexane/EtOAc; R_f = 0.16), affording 345 mg (88%) of **10** (clear oil).

^1H NMR (300 MHz, major diastereoisomer-(3*R*,5*S*)): δ 7.03 (m, 6H, 2*Ph*), 6.95 (m, 4H, 2*Ph*), 5.76 (d, 1H, *J* = 8.4 Hz, OC*H*Ph), 5.18 (d, 1H, *J* = 8.4 Hz, NC*H*Ph), 4.89 (dt, 1H, *J* = 1.3, 8.5 Hz, C*H*=), 4.19 (m, 1H, C*H*N_{oxa}), 4.12 (q, 2H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 3.77 (m, 1H, C*H*OTBS), 3.03 (dd, 1H, *J* = 10.0, 16.6 Hz, CH_2CO_2Et), 2.44 (dd, 1H, *J* = 4.0, 16.6 Hz, CH_2CO_2Et), 2.16 (ddd, 1H, *J* = 4.3, 9.8, 13.9 Hz, CH_2CHOTBS), 1.60 (ddd, 1H, *J* = 4.3, 8.6, 13.9 Hz, CH_2CHOTBS), 1.56 (d, 3H, *J* = 1.1 Hz, CH=C(CH_3)$_2$), 1.48 (d, 3H, *J* = 1.1 Hz, CH=C(CH_3)$_2$, 1.24 (t, 3H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 0.66 (s, 9H, Si(*t-Bu*)), −0.13 (s, 3H, Si(*Me*)$_2$), −0.18 (s, 3H, Si(*Me*)$_2$). ^{13}C NMR (75.5 MHz): δ 171.9 (CO_2Et), 156.9 (CO_{oxa}), 135.1, 134.9, 132.1, 128.3, 128.2, 128.1, 128.0, 127.7, 127.4, 125.7 (*Ar*), 79.6 (CH), 67.0 (CH), 66.8 (CH), 60.5 (CH_2), 48.8 (CH), 40.6 (CH_2), 35.8 (CH_2), 25.6, 25.4 (Si(*t-Bu*)), 17.9 (CH_3), 17.7 (C_{quat}), 14.1 (CH_3), −4.3 (Si(*Me*)$_2$), −5.2 (Si(*Me*)$_2$). IR (neat): 1757 (CO), 1676 (C=C) cm^{-1}. Anal. Calcd for $C_{32}H_{45}NO_6Si$: C, 69.65; H, 8.22; N, 2.53. Found: C, 69.49; H, 7.98; N, 2.47.

Ozonolysis/Reduction of 10 To Give Alcohol 11. A solution of **10** (930 mg, 1.68 mmol) in 150 mL of 2:8 MeOH/CH_2Cl_2 at −78 °C was treated with ozone. After a light blue solution resulted, the mixture was treated with Me_2S (300 μL) followed by $NaBH_4$ (65 mg, 1.7 mmol). The mixture was slowly warmed to room temperature, and treated with 0.2 N HCl (15 mL), H_2O (40 mL), and CH_2Cl_2 (50 mL). The aqueous phase was washed with CH_2Cl_2 (2 × 30 mL), and the organic extracts were combined, washed with H_2O (1 × 30 mL) and brine (1 × 30 mL), and dried (Na_2SO_4). Removal of solvent *in vacuo* afforded 840 mg (95%) of **11** (clear oil), which was used without further purification.

^1H NMR (300 MHz, major diastereoisomer-(3*R*,5*S*)): δ 7.00 (m, 6H, 2*Ph*), 6.92 (m, 4H, 2*Ph*), 5.76 (d, 1H, *J* = 8.5 Hz, OC*H*Ph), 5.18 (d, 1H, *J* = 8.5 Hz, NC*H*Ph), 4.10 (q, 2H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 3.72 (m, 1H, C*H*N_{oxa}), 3.55 (m, 1H, C*H*OTBS), 3.25 (m, 2H, CH_2OH), 2.99 (dd, 1H, *J* = 9.9; 16.8 Hz, CH_2CO_2Et), 2.39 (dd, 1H, *J* = 3.9, 16.8 Hz, CH_2CO_2Et), 2.17 (ddd, 1H, *J* = 5.1, 8.9, 14.1 Hz, CHCH_2CH), 2.02 (m, 1H, CH_2OH), 1.81 (ddd, 1H, *J* = 5.6, 7.5, 14.0 Hz, CHCH_2CH), 1.20 (t, 3H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 0.68 (s, 9H, OSi(*t-Bu*)), −0.05 (s, 3H, Si(*Me*)$_2$), −0.08 (s, 3H, Si(*Me*)$_2$). ^{13}C NMR (75.5 MHz): δ 171.7 (CO_2Et), 156.9 (CO_{oxa}), 134.9, 134.6, 128.31, 128.29, 128.0, 127.6, 127.4, 125.6 (*Ar*), 79.5 (CH), 69.8 (CH), 66.6 (CH), 65.5 (CH_2), 60.5 (CH_2), 48.7 (CH), 36.4 (CH_2), 36.1 (CH_2), 25.5 (Si(*t-Bu*)), 17.6 (C_{quat}), 14.0 (CH_3), −4.6 (Si(*Me*)$_2$), −5.1 (Si(*Me*)$_2$). IR (neat): 3448 (OH), 1740 (CO) cm^{-1}.

Preparation of Mesylate 12. A solution of **11** (832 mg, 1.57 mmol) in 25 mL of CH_2Cl_2 at room temperature was treated with methanesulfonyl chloride (163 μL, 2.10 mmol) followed by triethylamine (237 μL, 1.70 mmol). After the solution was stirred for 20 h, the solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2, 7:3 hexane/EtOAc), affording 704 mg (74%; $[\alpha]_D$ = 10.7°; *c* = 1.2, CH_2Cl_2) of **12** (clear oil) as a single diastereoisomer and 162 mg (17%) of a mixture of diastereoisomers.

^1H NMR (300 MHz): δ 7.06 (m, 6H, 2*Ph*), 6.95 (m, 4H, 2*Ph*), 5.80 (d, 1H, *J* = 8.4 Hz, OC*H*Ph), 5.19 (d, 1H, *J* = 8.4 Hz, NC*H*Ph), 4.16, 4.15 (q, 2H, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 3.85-3.70 (m, 4H, CH_2OMs, C*H*N_{oxa}, C*H*OTBS), 3.07 (dd, 1H, *J* = 10.0; 16.9 Hz, CH_2CO_2Et), 2.92 (s, 3H, OSO_2CH_3), 2.42 (dd, 1H, *J* = 3.9, 16.9 Hz, CH_2CO_2Et), 2.27 (ddd, 1H, *J* = 4.5, 9.1, 14.0 Hz, CHCH_2CH), 1.78 (ddd, 1H, *J* = 5.4, 7.5, 14.2 Hz, CHCH_2CH), 1.26 (t, 3H, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 0.70 (s, 9H, Si(*t-Bu*)), 0.00 (s, 3H, Si(*Me*)$_2$), −0.05 (s, 3H, Si(*Me*)$_2$). ^{13}C NMR (75.5 MHz): δ 171.6 (CO_2Et), 156.9 (CO_{oxa}), 135.0, 134.7, 128.6, 128.5, 128.3, 127.9, 127.7, 125.7 (*Ar*), 79.8 (CH), 71.8 (CH_2), 67.6 (CH), 66.9 (CH), 60.8 (CH_2), 48.6 (CH), 37.3 (SO_2CH_3), 36.7 (CH_2), 36.1 (CH_2), 25.6 (Si(*t-Bu*)), 17.8 (C_{quat}), 14.2 (CH_3), −4.5 (Si(*Me*)$_2$), −5.0 (Si(*Me*)$_2$). IR (neat): 1753 (CO), 1359, 1176 (OSO_2CH_3) cm^{-1}.

Preparation of Azide 13. A solution of **12** (704 mg, 1.16 mmol) in 23 mL of DMF was treated with sodium azide (130 mg, 2.00 mmol) and was heated at 55 °C for 22 h. The reaction mixture was poured into H_2O (75 mL) and EtOAc (50 mL). The aqueous phase was washed with EtOAc (3 × 50 mL), and the organic extracts were combined, washed with H_2O (2 × 50 mL) and brine (1 × 50 mL), and dried (Na_2SO_4). Removal of solvent *in vacuo* and purification of the residue by flash chromatography (SiO_2, 4:1 hexane/EtOAc, R_f = 0.30) afforded 493 mg (77%) of **13** (clear oil) and 103 mg (13%) of unreacted **12**.

^1H NMR (300 MHz): δ 7.07 (m, 6H, 2*Ph*), 6.96 (m, 4H, 2*Ph*), 5.79 (d, 1H, *J* = 8.5 Hz, OC*H*Ph), 5.18 (d, 1H, *J* = 8.5 Hz, NC*H*Ph), 4.15 (q, 2H *J* = 7.1 Hz, $CO_2CH_2CH_3$), 3.67 (m, 2H, C*H*N_{oxa}, C*H*OTBS), 3.07 (m, 2H, CH_2CO_2Et, CH_2N_3), 2.83 (dd, 1H, *J* = 4.8, 12.7 Hz, CH_2N_3), 2.40 (dd, 1H, *J* = 3.9, 16.8 Hz, CH_2CO_2Et), 2.18 (ddd, 1H, *J* = 5.2, 8.7, 14.3 Hz, CHCH_2CH), 1.87 (m, 1H, CHCH_2CH), 1.27 (t, 3H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 0.73 (s, 9H, Si(*t-Bu*)), 0.01 (s, 3H, Si(*Me*)$_2$), −0.03 (s, 3H, Si(*Me*)$_2$). ^{13}C NMR (75.5 MHz): δ 171.7 (CO_2Et), 156.9 (CO_{oxa}), 135.0, 134.7, 128.6, 128.5, 128.2, 127.8, 127.6, 125.7 (*Ar*), 79.7 (CH), 68.8 (CH), 66.9 (CH), 60.8 (CH_2), 55.9 (CH_2), 48.8 (CH), 37.4 (CH_2), 36.3 (CH_2), 25.6 (Si(*t-Bu*)), 17.7 (C_{quat}), 14.1 (CH_3), −4.5 (Si(*Me*)$_2$), −5.0 (Si(*Me*)$_2$). IR (neat): 2102 (N_3), 1755, 1679 (CO) cm^{-1}. Anal. Calcd for $C_{29}H_{40}O_5N_4Si$: C, 63.02; H, 7.29; N, 10.14. Found: C, 62.98; H, 7.42; N, 10.07.

Preparation of Benzyl 2-(*N*-Methylhydrazino)acetate. A solution of *N*-methylhydrazine (230 mg, 5.00 mmol) and triethylamine (708 mg, 7.00 mmol) in 15 mL of CH_2Cl_2 at 0 °C was treated dropwise with a solution of benzyl 2-bromoacetate (1.0 M solution in CH_2Cl_2, 5.0 mL, 5.0 mmol) and was stirred at 0 °C for 0.5 h and room temperature for 4 h. The solvent was removed *in vacuo* and the residue purified by flash chromatography (SiO_2, 95:5 EtOAc/MeOH, R_f = 0.19), affording 952 mg (98%) of the title compound (clear oil).

A solution of the product (66 mg, 0.34 mmol) in 0.5 mL of THF was treated with *p*-toluenesulfonic acid (65 mg, 0.34 mmol) and was stirred at room temperature for 0.5 h. The mixture was then added dropwise to a stirred solution of diethyl ether. After 4 h, the resulting precipitate was collected by filtration and washed with diethyl ether (100 mL) to afford 127 mg (97%) of the *p*-toluenesulfonic acid salt (white solid; mp = 96–99 °C). Spectroscopic data were identical to that reported in the literature.[9]

^1H NMR (300 MHz): δ 7.33 (m, 5H, *Ph*), 5.15 (s, 2H, CO_2CH_2Ph), 3.43 (s, 2H, NCH_2), 3.38 (br s, 2H, NH_2), 2.61 (s, 3H, NCH_3). ^{13}C NMR (75.5 MHz): δ 170.1 (CO_2Bn), 135.5, 128.5, 128.3 (*Ar*), 66.3 (CH_2), 62.3 (CH_2), 48.7 (NCH_3). IR (neat): 3344 (NH), 1737 (CO) cm^{-1}.

Saponification of Ester 13 To Give Free Acid 14. A solution of **13** (125 mg, 0.226 mmol) in 15 mL of 9:1 THF/H_2O was treated with LiOH·H_2O (19 mg, 0.45 mmol) and was stirred at room temperature for 22 h. The reaction was quenched by the addition of 0.2 N HCl (10 mL), H_2O (25 mL), and EtOAc (25 mL). The aqueous phase was washed with EtOAc (3 × 25 mL), and the organic extracts were combined, washed with H_2O (2 × 25 mL) and brine (1 × 25 mL), and dried (Na_2SO_4). Removal of solvent *in vacuo* afforded 110 mg (93%, $[\alpha]_D$ = 25.0° (*c* = 0.9, CH_2Cl_2)) of **14** (white solid: mp = 140–142 °C). This material was used without further purification.

^1H NMR (300 MHz): δ 10.28 (br s, 1H, CO_2H), 7.07 (m, 6H, 2*Ph*), 6.97 (m, 4H, 2*Ph*), 5.85 (d, 1H, *J* = 8.5 Hz, OC*H*Ph), 5.21 (d, 1H, *J* = 8.5 Hz, NC*H*Ph), 3.75 and 3.66 (m, 2H, C*H*N_{oxa}, C*H*OTBS), 3.12 (m, 2H, CH_2CO_2Et, CH_2N_3), 2.87 (dd, 1H, *J* = 4.8, 12.7 Hz, CH_2N_3), 2.51 (dd, 1H, *J* = 4.0, 16.9 Hz, CH_2CO_2Et), 2.21 (ddd, 1H, *J* = 5.2, 8.6, 14.2 Hz, CHCH_2CH), 1.90 (m, 1H, CHCH_2CH), 0.74 (s, 9H, Si(*t-Bu*)), 0.03 (s, 3H, Si(*Me*)$_2$), −0.01 (s, 3H, Si(*Me*)$_2$). ^{13}C NMR (75.5 MHz): δ 176.2 (CO_2H), 157.4 (CO_{oxa}), 134.7, 134.5, 128.6, 128.5, 128.2, 127.8, 127.7, 125.7 (*Ar*), 79.8 (CH), 68.7 (CH), 66.8 (CH), 55.8 (CH_2), 48.7 (CH), 37.3 (CH_2), 36.2 (CH_2), 25.6 (Si(*t-Bu*)), 17.7 (C_{quat}), −4.5 (Si(*Me*)$_2$), −5.0 (Si(*Me*)$_2$). IR (neat): 3600–3000 (CO_2H), 2102 (N_3), 1744 (CO) cm^{-1}.

Preparation of Acid Hydrazide 15. A solution of **14** (106 mg, 0.202 mmol) in 10 mL of CH_2Cl_2 at 0 °C was treated with

Et_3N (63 μL, 0.45 mmol), followed by ethyl chloroformate (23 μL, 0.24 mmol). After 0.5 h, a solution of benzyl 2-(*N*-methylhydrazino)acetate (0.12 M in CH_2Cl_2, 3.3 mL, 0.40 mmol) was added dropwise over 0.2 h. The resulting mixture was stirred at 0 °C for 1 h, warmed to room temperature, and stirred for 20 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2, 4:1 CH_2Cl_2/EtOAc, R_f = 0.41), affording 123 mg (88%; $[\alpha]_D$ = 8.7° (*c* = 1.5, CH_2Cl_2)) of **15** (clear oil) as a mixture of rotamers. The presence of amide-type rotamers was confirmed by variable-temperature ^1H NMR experiments.

^1H NMR (300 MHz, mixture of rotamers): δ 7.79 (s, 1H, N*H*), 7.32 (m, 6H, N*H*, CO_2CH_2*Ph*), 7.05 (m, 6H, 2*Ph*), 6.96 (m, 4H, 2*Ph*), 5.79 (d, 1H, *J* = 8.6 Hz, OC*H*Ph), 5.24 (ap t, 1H, *J* = 8.7 Hz, NC*H*Ph), 5.17 and 5.15 (s, 2H, CO_2CH_2Ph), 3.74 (s) and 3.70 (m) (2H, NCH_2CO_2Bn), 3.75–3.45 (m, 2H, CHN_{oxa}, *CH*OTBS), 2.91 (m, 2H, CH_2CONH, CH_2N_3), 2.80 and 2.75 (s, 3H, NCH_3), 2.70 (m, 1H, CH_2N_3), 2.39 (m) and 2.30 (dd) (1H, *J* = 3.9, 15.3 Hz, CH_2CONH), 2.15 (m, 1H, $CHCH_2CH$), 1.92 (m, 1H, $CHCH_2$-CH), 0.73 and 0.72 (s, 9H, Si(*t-Bu*)), −0.01 and −0.03 (s, 3H, Si-(*Me*)$_2$), −0.02 and −0.05 (s, 3H, Si(*Me*)$_2$). ^{13}C NMR (75.5 MHz): δ 174.2 and 174.1 (CO_2Bn), 170.2 and 168.6 (CONH), 157.0 and 156.9 (CO_{oxa}), 135.4, 135.0, 128.7, 128.6, 128.54, 128.47, 128.4, 128.1, 128.0, 127.8, 127.7, 127.5, 127.4, 125.7 (*Ar*), 79.6 (CH), 68.9 and 68.7 (CH), 67.6 and 67.4 (CH), 66.8 (NCH_2), 57.7 (CH_2Ph), 55.8 and 55.6 (CH_2), 49.1 and 48.5 (CH), 45.0 and 44.1 (NCH_3), 37.6 (CH_2), 36.6 (CH_2), 34.0 (CH_2), 25.6 (Si(*t-Bu*)), 17.7 (C_{quat}), −4.6 (Si(*Me*)$_2$), −4.9 (Si(*Me*)$_2$). Low intensity signals from the minor rotamer about the hydrazine peptide bond were also observed: δ 169.8 and 169.7 (CONH), 66.5 (CH_2), 58.4 (CH_2), 48.3 (CH_3), 45.0 (CH_3). IR (neat): 3246 (NH), 2102 (N_3), 1751 (CO), 1676 (CONH) cm^{-1}. Anal. Calcd for $C_{37}H_{48}N_6O_6Si$: C, 63.40; H, 6.90; N, 11.99. Found: C, 63.16; H, 6.78; N, 12.20.

Desilylation of 15 To Give 16. A solution of **15** (123 mg, 0.175 mmol) in 5 mL of 24:1 CH_3CN/48% HF(aq) was stirred at room temperature for 6 h. The mixture was poured into H_2O (25 mL) and EtOAc (25 mL). The aqueous phase was washed with EtOAc (3 × 20 mL), and organic extracts were combined, washed with H_2O (2 × 25 mL) and brine (1 × 25 mL), and dried (Na_2SO_4). Removal of solvent *in vacuo* and purification of the residue by flash chromatography (SiO_2, 95:5 EtOAc/MeOH, R_f = 0.68) afforded 91 mg (88%; $[\alpha]_D$ = −0.9° (*c* = 1.1, CH_2Cl_2)) of alcohol **16** (clear oil) as a mixture of rotamers. The presence of amide-type rotamers was confirmed by variable-temperature ^1H NMR experiments.

^1H NMR (300 MHz, mixture of rotamers): δ 7.84 (s, 1H, N*H*), 7.32 (m, 5H, CO_2CH_2*Ph*), 7.06 (m, 6H, 2*Ph*), 6.95 (m, 4H, 2*Ph*), 5.84 (d, 1H, *J* = 8.5 Hz, OC*H*Ph), 5.21 (d, 1H, *J* = 8.5 Hz, NC*H*Ph), 5.15 and 5.13 (s, 2H, CO_2CH_2Ph), 3.98 (m, 1H, CHN_{oxa}), 3.72 (s, 2H, NCH_2), 3.47 (m, 1H, *CH*OH), 3.10 (m, 2H, CH_2N_3), 2.81 (dd, 1H, *J* = 9.2, 15.1 Hz, CH_2CONH), 2.77 and 2.62 (s, 3H, NCH_3), 2.32 (dd, 1H, *J* = 5.6, 15.1 Hz, CH_2CONH), 1.96 (m, 2H, $CHCH_2CH$, O*H*), 1.65 (m, 1H, $CHCH_2CH$). ^{13}C NMR (75.5 MHz): δ 174.3 and 174.2 (CO_2Bn), 169.9 and 168.9 (CONH), 157.7 (CO_{oxa}), 135.6, 135.1, 134.9, 134.6, 134.5, 128.7, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.64, 127.60, 127.44, 127.39, 125.7, 125.6 (*Ar*), 79.8 (CH), 68.1 and 67.7 (CH), 66.5 (NCH_2), 66.3 (CH), 57.6 (CH_2), 56.6 and 56.5 (CH_2), 49.9 (CH), 49.0 (CH), 44.0 (NCH_3), 37.2 (CH_2), 36.9 (CH_2), 36.6 (CH_2). Low intensity signals from the minor rotamer about the hydrazine peptide bond were also observed: δ 169.5 and 169.4 (CONH), 65.5 (CH), 65.3 (CH), 58.6 (CH_2), 58.2 (CH_2), 45.0 (CH_3), 44.9 (CH_3). IR (neat): 3600–3150 (NH,OH), 2101 (N_3), 1736 (CO), 1670 (CONH) cm^{-1}.

Preparation of 5-*epi*-Negamycin (2). A solution of **16** (50 mg, 0.085 mmol) in 4 mL of 2:1 MeOH/5% AcOH(aq) was added to 10% Pd/C (83 mg, 0.078 mmol) in a Pyrex pressure tube (Ace Glass) under an argon atmosphere. The mixture was placed under a H_2(g) atmosphere (40 psi) and stirred at room temperature for 8 h. The mixture was filtered through Celite using H_2O as eluent. The solvent was removed by lyophylization, and the residue was purified by ion-exchange chromatography [Amberlite CG-50 (NH_4^+ form)], eluting with H_2O followed by 0.5% NH_4OH(aq). Ninhydrin-active fractions were collected and the solvent was removed by lyophylization, affording 20 mg (95%; $[\alpha]_D$ = −9.4° (*c* = 0.5, H_2O)) of (−)-5-*epi*-negamycin (**2**) (white powder, mp = 149–163° dec).

^1H NMR (300 MHz, D_2O): δ 3.80 (m, 1H, C*H*NH_2), 3.31 (m, 1H, C*H*OH), 3.23 (s, 2H, NCH_2), 2.87 (dd, 1H, *J* = 3.3, 12.8 Hz, CH_2NH_2), 2.68 (dd, 1H, *J* = 8.2, 13.1 Hz, CH_2NH_2), 2.46 (s, 3H, NCH_3), 2.30 (dd, 1H, *J* = 5.5, 15.1 Hz, CH_2CONH), 2.17 (dd, 1H, *J* = 7.3, 14.9 Hz, CH_2CONH), 1.65–1.45 (m, 2H, $CHCH_2CH$). ^{13}C NMR (75.5 MHz; D_2O): δ 179.8 (CO_2H), 173.3 (CONH), 69.6 (CH), 63.7 (CH_2), 48.9 (CH), 47.7 (CH_2), 46.6 (NCH_3), 42.3 (CH_2), 41.5 (CH_2). IR (KBr): 3650–2100 (NH, OH, CO_2H), 1654 (CONH), 1584, 1400, 1317, 1129 cm^{-1}.

Preparation of the *Bis* Cbz Methyl Ester of 2. A solution of **2** (11 mg, 0.044 mmol) in 2 mL of H_2O was treated with Et_3N (19 μL, 0.13 mmol) and *S*-(4,6-dimethylpyrimidin-2-yl) thiocarbonate (27 mg, 0.10 mmol) in 1 mL of DMF and was stirred for 20 h. The mixture was poured into H_2O (30 mL) and EtOAc (30 mL), and the aqueous phase was washed with EtOAc (2 × 25 mL). The aqueous phase was brought to pH = 2 by addition of 0.2 N HCl and washed with EtOAc (3 × 15 mL). The organic extracts were combined and washed with 0.2 N HCl (2 × 10 mL) at 0 °C and brine (1 × 25 mL) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was taken up in 20 mL of diethyl ether. The resulting slurry was treated with an excess of diazomethane (generated from Diazald and 1.0 M KOH) at room temperature over a period of 0.5 h. The solvent was removed *in vacuo* and the residue purified by flash chromatography (SiO_2; EtOAc to 9:1 EtOAc/MeOH; R_f = 0.60), affording 8 mg (34%) of the bis Cbz methyl ester of **2** (white solid; mp = 124–126 °C, lit.[7] mp = 125–127 °C).

^1H NMR (300 MHz, mixture of rotamers): δ 7.80 (s, 1H, N*H*), 7.31 (m, 10H, 2*Ph*), 5.79 (br s, 1H, N*H*CO_2Bn), 5.31 (br s, 1H, N*H*CO_2Bn), 5.10, 5.07, and 5.05 (s, 4H, 2 NHCO_2CH_2Ph), 4.09 (m, 1H, C*H*NHZ), 3.77 (m, 1H, C*H*OH), 3.70 (s, 2H, CO_2Me), 3.64 (s, 2H, NCH_2CO_2Me), 3.54, 3.34, and 3.12 (m, 4H, CH_2NHZ, CH_2CONH), 2.71 and 2.68 (s, 3H, NCH_3), 2.37 (d, 1H, *J* = 5.1 Hz, CHO*H*), 1.71 (m, 2H, $CHCH_2CH$), IR (neat): 3475, 3366, 3307, 3237 (NH, OH), 1743 (CO_2Me), 1695, 1666 (CONH), 1542, 1438, 1264, 1212 cm^{-1}.

Saponification of 9 To Give Hydroxy Acid 17. A solution of **9** (643 mg, 1.47 mmol) in 20 mL of 9:1 THF/H_2O was treated with LiOH·H_2O (84 mg, 2.0 mmol) and was stirred at room temperature for 17 h. The mixture was brought to pH = 2 by the addition of 0.2 N HCl and was then added to EtOAc (50 mL) and H_2O (50 mL). The aqueous phase was washed with EtOAc (3 × 50 mL), and the organic extracts were combined, washed with H_2O (1 × 75 mL) and brine (1 × 75 mL), and dried (Na_2SO_4). The solvent was removed *in vacuo*, affording 605 mg (100%) of **17** (yellow oil), which was used without further purification.

^1H NMR (300 MHz, major diastereoisomer-(3*R*,5*S*)): δ 7.06 (m, 6H, 2*Ph*), 6.96 (m, 4H, 2*Ph*), 5.85 (d, 1H, *J* = 8.3 Hz, OC*H*Ph), 5.18 (d, 1H, *J* = 8.4 Hz, NC*H*Ph), 5.09 (d, 1H, *J* = 8.5 Hz, C*H*═), 4.41 (dt, 1H, *J* = 4.5, 8.3 Hz, C*H*OH), 4.16 (m, 1H, CHN_{oxa}), 2.79 (dd, 1H, *J* = 7.9, 16.8 Hz, CH_2CO_2H), 2.30 (dd, 1H, *J* = 6.3, 16.8 Hz, CH_2CO_2H), 1.96 (m, 1H, $CHCH_2CH$), 1.80 (m, 1H, $CHCH_2$-CH), 1.66 (s, 3H, CH═C(CH_3)$_2$), 1.61 (s, 3H, CH═C(CH_3)$_2$). ^{13}C NMR (75.5 MHz): δ 175.8 (CO_2H), 158.4 (CO_{oxa}), 136.3, 135.9, 134.9, 128.8, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.3, 126.5, 126.2 (*Ar*), 80.4 (CH), 66.9 (CH), 65.3 (CH), 49.9 (CH), 39.8 (CH_2), 37.6 (CH_2), 26.0 (CH_3), 18.5 (CH_3). IR (neat): 3600–3000 (CO_2H, OH), 1739 (CO) cm^{-1}.

Intramolecular Mitsunobu Reaction: Preparation of 18. A solution of **17** (643 mg, 1.47 mmol) and triphenylphosphine (433 mg, 1.65 mmol) in 30 mL of benzene at room temperature was treated dropwise with a solution of DBAD (1.00 M in benzene, 1.65 mL, 1.65 mmol) over a period of 0.2 h, and was stirred at room temperature for 13 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2, 3:1:5 Et_2O/hexane/CH_2Cl_2, R_f = 0.52), affording 366 mg (64%; $[\alpha]_D$ = 5.2° (*c* = 1.0, CH_2Cl_2)) of **18** (white solid, mp = 194–195 °C) as a single diastereoisomer.

^1H NMR (300 MHz diastereoisomer-(3*R*,5*R*)): δ 7.06 (m, 6H, 2*Ph*), 6.90 (m, 4H, 2 *Ph*), 5.83 (d, 1H, *J* = 8.1 Hz, OC*H*Ph), 5.17 (d, 1H, *J* = 8.6 Hz, C*H*═), 5.03 (d, 1H, *J* = 8.1 Hz, NC*H*Ph), 4.86 (m, 1H, C*H*OCO), 4.02 (m, 1H, CHN_{oxa}), 2.70 (dd, 1H, *J* = 5.9, 17.4 Hz, CH_2CO), 2.48 (dd, 1H, *J* = 11.0, 17.4 Hz, CH_2CO), 2.16 (m, 2H, $CHCH_2CH$), 1.71 (s, 3H, CH═C(CH_3)$_2$), 1.63 (s, 3H, CH═C(CH_3)$_2$). ^{13}C NMR (75.5 MHz): δ 169.2 (CO_2), 158.1 (CO_{oxa}), 139.4, 134.7, 133.8, 128.8, 128.5, 127.94, 127.86, 127.5,

125.8, 122.2 (*Ar*), 80.1 (CH), 75.1 (CH), 64.2 (CH), 48.0 (CH), 34.4 (CH_2), 33.5 (CH_2), 25.6 (CH_2), 18.3 (CH_3). IR (neat): 1743 (CO), 1683 (C=C), 1233, 1031 cm^{-1}. Anal. Calcd for $C_{24}H_{25}NO_4$: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.53; H, 6.19; N, 3.36.

Transesterification of 18 to Open-Chain Ester 19. A solution of **18** (310 mg, 0.793 mmol) in 25 mL of absolute EtOH was treated with KCN (1 mg), and the mixture was heated at 50 °C for 4 h. The mixture was filtered through SiO_2 using EtOAc as eluent, and the solvent was removed *in vacuo*, affording 327 mg (95%) of **19** (clear oil), which was used without further purification.

^1H NMR (300 MHz, major diastereoisomer-(3*R*,5*R*)): δ 7.06 (m, 6H, 2*Ph*), 6.98 (m, 4H, 2*Ph*), 5.82 (d, 1H, *J* = 8.3 Hz, OC*H*Ph), 5.13 (d, 1H, *J* = 8.3 Hz, NC*H*Ph), 4.96 (ap dt, 1H, *J* = 1.4, 8.6 Hz, C*H*=), 4.13 (dt, 1H, *J* = 4.6, 8.5 Hz, C*H*OH), 4.07 (q, 2H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 3.96 (m, 1H, C*H*N_{oxa}), 2.88 (dd, 1H, *J* = 9.2, 16.8 Hz, CH_2CO_2Et), 2.34 (dd, 1H, *J* = 5.0, 16.8 Hz, CH_2CO_2Et), 1.94 (ddd, 1H, *J* = 4.6, 8.0, 14.3 Hz, CH_2CHOH), 1.81 (ddd, 1H, *J* = 5.7, 8.5, 14.3 Hz, CH_2CHOH), 1.60 (d, 3H, *J* = 1.2 Hz, CH=C(CH_3)$_2$), 1.56 (d, 3H, *J* = 1.1 Hz, CH=C(CH_3)$_2$), 1.21 (t, 3H, *J* = 7.1 Hz, $CO_2CH_2CH_3$). ^{13}C NMR (75.5 MHz): δ 171.5 (CO_2Et), 157.3 (CO_{oxa}), 135.6, 135.1, 134.7, 128.5, 128.1, 127.8, 127.6, 127.0, 125.7 (*Ar*), 79.8 (CH), 65.7 (CH), 60.6 (CH_2), 49.2 (CH), 40.1 (CH_2), 37.7 (CH_2), 25.6 (CH), 18.1 (CH_3), 14.1 (CH_3). IR (neat): 3448 (OH), 1742 (CO), 1218, 1025 (COH) cm^{-1}.

Protection of 19 To Produce 20. A solution of **19** (327 mg, 0.748 mmol) in 8 mL of DMF was treated with TBDMSCl (301 mg, 2.00 mmol) and imidazole (109 mg, 1.60 mmol), and the mixture was stirred at room temperature for 4 d. The mixture was poured into H_2O (75 mL) and EtOAc (50 mL). The aqueous phase was washed with EtOAc (2 × 50 mL), and the organic extracts were combined, washed with H_2O (1 × 50 mL) and brine (1 × 50 mL), and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2; 9:1 hexane/EtOAc; R_f = 0.17), affording 354 mg (81%) of **20** (clear oil).

^1H NMR (300 MHz, major diastereoisomer-(3*R*,5*R*)): δ 7.07 (m, 6H, 2*Ph*), 6.95 (m, 4H, 2*Ph*), 5.79 (d, 1H, *J* = 8.4 Hz, OC*H*Ph), 5.16 (d, *J* = 8.4 Hz, NC*H*Ph), 4.85 (dt, 1H, *J* = 1.3, 8.8 Hz, C*H*=), 4.11 (dq, 2H, *J* = 2.8, 7.2 Hz, $CO_2CH_2CH_3$), 4.01 (dt, 1H, *J* = 5.5, 8.4 Hz, C*H*N_{oxa}), 3.72 (m, 1H, C*H*OTBS), 3.00 (dd, 1H, *J* = 9.6, 16.8 Hz, CH_2CO_2Et), 2.39 (dd, 1H, *J* = 4.6, 16.8 Hz, CH_2CO_2Et), 2.00 (m, 1H, $CHCH_2CH$), 1.69 (m, 1H, $CHCH_2CH$), 1.55 (d, 3H, *J* = 1.1 Hz, CH=C(CH_3)$_2$), 1.44 (d, 3H, *J* = 1.2 Hz, CH=C-(CH_3)$_2$), 1.24 (t, 3H, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 0.78 (s, 9H, Si(*t-Bu*)), −0.13 (s, 3H, Si(*Me*)$_2$), −0.16 (s, 3H, Si(*Me*)$_2$). ^{13}C NMR (75.5 MHz): δ 172.0 (CO_2Et), 156.9 (CO_{oxa}), 135.7, 134.9, 132.0, 128.5, 128.4, 128.2, 127.8, 127.5, 125.7 (*Ar*), 79.6 (CH), 68.3 (CH), 66.5 (CH), 60.5 (CH_2), 49.7 (CH), 41.4 (CH_2), 38.4 (CH_2), 25.8 and 25.6 (Si(t*Bu*)), 18.1 (CH_3), 18.0 (C_{quat}), 14.2 (CH_3), −4.3 (Si(*Me*)$_2$), −5.1 (Si(*Me*)$_2$). IR (neat): 1754 (CO), 1356, 1072 cm^{-1}. Anal. Calcd for $C_{34}H_{45}NO_5Si$: C, 69.65; H, 8.22; N, 2.53. Found: C, 69.87; H, 8.35; N, 2.49.

Ozonolysis/Reduction of 20 To Give Alcohol 21. The procedure described for **11** was followed using **20** (235 mg, 0.425 mmol), 2:8 MeOH/CH_2Cl_2 (50 mL), Me_2S (100 μL), and $NaBH_4$ (16 mg, 0.42 mmol). Removal of solvent *in vacuo* afforded 225 mg (99%) of **21** (clear oil), which was used without further purification.

^1H NMR (300 MHz, major diastereoisomer-(3*R*,5*R*)): δ 7.00 (m, 10H, 2*Ph*), 5.83 (d, 1H, *J* = 8.2 Hz, OC*H*Ph), 5.16 (d, 1H, *J* = 8.2 Hz, NC*H*Ph), 4.08, 4.07 (q, 2H, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 3.96 (quintet, 1H, C*H*N_{oxa}), 3.54 (m, 1H, C*H*OTBS), 3.36 (m, 2H, CH_2OH), 2.83 (dd, 1H, *J* = 7.9, 16.4 Hz, CH_2CO_2Et), 2.14 (dd, 1H, *J* = 6.5, 16.4 Hz, CH_2CO_2Et), 2.04 (br s, 1H, CH_2OH), 1.91 (m, 2H, $CHCH_2CH$), 1.20 (dt, 3H, *J* = 0.6, 7.2 Hz, $CO_2CH_2CH_3$), 0.83 (s, 9H, Si(*t-Bu*)), −0.01 (s, 3H, Si(*Me*)$_2$), −0.02 (s, 3H, Si-(*Me*)$_2$). ^{13}C NMR (75.5 MHz): δ 171.3 (CO_2Et), 157.2 (CO_{oxa}), 135.6, 134.6, 128.5, 128.4, 128.2, 128.0, 127.6, 125.7 (*Ar*), 79.8 (CH), 70.8 (CH), 66.0 (CH_2), 65.2 (CH), 60.6 (CH_2), 49.0 (CH), 38.6 (CH_2), 36.8 (CH_2), 25.7 (Si(*t-Bu*)), 17.9 (C_{quat}), 14.1 (CH_3), −4.6 (Si(*Me*)$_2$), −4.9 (Si(*Me*)$_2$). IR (neat): 3456 (OH), 1738 (CO), 1039 (COH) cm^{-1}.

Preparation of Mesylate 22. A solution of **21** (225 mg, 0.425 mmol) in 15 mL of CH_2Cl_2 was treated with methanesulfonyl chloride (40 μL, 0.52 mmol) and Et_3N (70 μL, 0.52 mmol) and was stirred for 20 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2, 7:3 hexane/EtOAc, R_f = 0.26), affording 224 mg (87%; $[\alpha]_D$ = −4.3° (*c* = 1.0, CH_2Cl_2)) of **22** (clear oil) as a single diastereoisomer, and 13 mg (5%) as a mixture of diastereoisomers.

^1H NMR (300 MHz): δ 7.03 (m, 10H, 2*Ph*), 5.84 (d, 1H, *J* = 8.1 Hz, OC*H*Ph), 5.12 (d, 1H, *J* = 8.1 Hz, NC*H*Ph), 4.08 (q, 2H, *J* = 7.0 Hz, $CO_2CH_2CH_3$), 4.04 (m, 1H, C*H*N_{oxa}), 4.01 (dd, 1H, *J* = 5.1, 10.3 Hz, CH_2OMs), 3.85 (dd, 1H, *J* = 6.3, 10.3 Hz, CH_2-OMs), 3.74 (m, 1H, C*H*OTBS), 3.00 (s, 3H, OSO_2CH_3), 2.83 (dd, 1H, *J* = 7.5, 16.3 Hz, CH_2CO_2Et), 2.08 (dd, 1H, *J* = 7.0, 16.3 Hz, CH_2CO_2Et), 2.01 (ddd, 1H, *J* = 3.7, 7.8, 14.6 Hz, $CHCH_2CH$), 1.83 (ddd, 1H, *J* = 5.2, 8.2, 14.7 Hz, $CHCH_2CH$), 1.21 (t, 3H, *J* = 7.0 Hz, $CO_2CH_2CH_3$), 0.84 (s, 9H, Si(*t-Bu*)), 0.02 (s, 3H, Si-(*Me*)$_2$), 0.00 (s, 3H, Si(*Me*)$_2$). ^{13}C NMR (75.5 MHz): δ 171.0 (CO_2Et), 157.2 (CO_{oxa}), 135.6, 134.4, 128.6, 128.3, 127.8, 127.6, 125.7 (*Ar*), 80.0 (CH), 72.1 (CH_2), 68.1 (CH), 64.7 (CH), 60.7 (CH_2), 48.7 (CH), 38.7 (CH_2), 37.5 (SO_2CH_3), 37.1 (CH_2), 25.7 (Si(*t-Bu*)), 17.9 (C_{quat}), 14.1 (CH_3), −4.6 (Si(*Me*)$_2$), −5.1 (Si(*Me*)$_2$. IR (neat): 1751 (CO), 1356, 1175 (OSO_2CH_3) cm^{-1}.

Preparation of Azide 23. A solution of **22** (246 mg, 0.405 mmol) in 10 mL of DMF was treated with sodium azide (49 mg, 0.82 mmol), and was heated at 70 °C for 14 h. the mixture was poured into H_2O (50 mL) and EtOAc (50 mL). The aqueous phase was washed with EtOAc (3 × 30 mL), and the organic extracts were combined, washed with H_2O (1 × 30 mL) and brine (1 × 30 mL), and dried (Na_2SO_4). Removal of solvent *in vacuo* and purification of the residue by flash chromatography (SiO_2; 4:1 hexane/EtOAc, R_f = 0.31) afforded 192 mg (86%, $[\alpha]_D$ = −18.2° (*c* = 1.0, CH_2Cl_2)) of **23** (clear oil).

^1H NMR (300 MHz): δ 7.04 (m, 10H, 2*Ph*), 5.82 (d, 1H, *J* = 8.3 Hz, OC*H*Ph), 5.13 (d, 1H, *J* = 8.3 Hz, NC*H*Ph), 4.10, 4.09 (q, 2H, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 3.85 (m, 1H, C*H*N_{oxa}), 3.49 (m, 1H, C*H*OTBS), 3.10 (dd, 1H, *J* = 5.2; 12.5 Hz, CH_2N_3), 3.01 (dd, 1H, *J* = 4.9, 12.5 Hz, CH_2N_3), 2.91 (dd, 1H, *J* = 8.4, 16.6 Hz, CH_2-CO_2Et), 2.17 (dd, 1H, *J* = 6.0, 16.6 Hz, CH_2CO_2Et), 1.92 (m, 2H, $CHCH_2CH$), 1.22 (t, 3H, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 0.83 (m, 9H, Si(*t-Bu*)), −0.01 (s, 3H, Si(*Me*)$_2$), −0.05 (s, 3H, Si(*Me*)$_2$). ^{13}C NMR (75.5 MHz): δ 171.3 (CO_2Et), 157.0 (CO_{oxa}), 135.5, 134.5, 128.6, 128.4, 128.3, 127.8, 127.6, 125.7 (*Ar*), 79.8 (CH), 69.8 (CH), 65.6 (CH), 60.7 (CH_2), 56.2 (CH_2), 49.2 (CH), 38.5 (CH_2), 38.0 (CH_2), 25.7 (Si(t*Bu*)), 17.8 (C_{quat}), 14.1 (CH_3), −4.6 (Si(*Me*)$_2$), −5.0 (Si-(*Me*)$_2$). IR (neat): 2103 (N_3), 1748 (CO) cm^{-1}. Anal. Calcd for $C_{29}H_{40}O_5N_4Si$: C, 63.02; H, 7.29; N, 10.14. Found: C, 63.20; H, 7.41; N, 10.25.

Saponification of Ester 23 To Give Free Acid 24. The procedure described for **14** was followed using **23** (166 mg, 0.300 mmol), 9:1 THF/H_2O (15 mL), and LiOH·H_2O (13 mg, 0.31 mmol). Removal of solvent *in vacuo* afforded 156 mg (99%; $[\alpha]_D$ = −14.9° (*c* = 1.2, CH_2Cl_2)) of **24** (yellow oil), which was used without further purification.

^1H NMR (300 MHz): δ 7.04 (m, 10H, 2*Ph*), 5.86 (d, 1H, *J* = 8.2 Hz, OC*H*Ph), 5.12 (d, 1H, *J* = 8.2 Hz, NC*H*Ph), 3.90 (quintet, 1H, *J* = 6.7 Hz, C*H*N_{oxa}), 3.52 (quintet, 1H, *J* = 5.1 Hz, C*H*OTBS), 3.13 (dd, 1H, *J* = 5.2, 12.5 Hz, CH_2N_3), 3.04 (dd, 1H, *J* = 4.6, 12.5 Hz, CH_2N_3), 2.95 (dd, 1H, *J* = 7.9, 16.9 Hz, CH_2CO_2Et), 2.22 (dd, 1H, *J* = 6.3, 16.9 Hz, CH_2CO_2Et), 1.94 (m, 2H, $CHCH_2CH$), 0.84 (s, 9H, Si(*t-Bu*)), 0.00 (s, 3H, Si(*Me*)$_2$), −0.03 (s, 3H, Si(*Me*)$_2$). ^{13}C NMR (75.5 MHz): δ 176.2 (CO_2H), 157.3 (CO_{oxa}), 135.3, 134.4, 128.8, 128.5, 128.4, 127.9, 127.7, 125.7 (*Ar*), 79.9 (CH), 69.7 (CH), 65.5 (CH), 56.2 (CH_2), 49.0 (CH), 38.3 (CH_2), 38.0 (CH_2), 25.7 (Si(*t-Bu*)), 17.8 (C_{quat}), −4.6 (Si(*Me*)$_2$), −5.0 (Si(*Me*)$_2$). IR (neat): 3600–3000 (CO_2H), 2103 (N_3), 1744 (CO) cm^{-1}.

Preparation of Acid Hydrazide 25. The procedure described for **15** was followed using **24** (156 mg, 0.297 mmol), CH_2Cl_2 (15 mL), Et_3N (84 μL, 0.60 mmol), ethyl chloroformate (30 μL, 0.31 mmol), and benzyl 2-(*N*-methylhydrazino)acetate (0.060 M in CH_2Cl_2, 10 mL, 0.60 mmol). The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2; 7.3 CH_2Cl_2/EtOAc, R_f = 0.62), affording 176 mg (84%; $[\alpha]_D$ = −22.2° (*c* = 1.8, CH_2Cl_2)) of **25** (clear oil) as a mixture of rotamers. The presence of amide-type rotamers was confirmed by variable-temperature ^1H NMR experiments.

^1H NMR (300 MHz, mixture of rotamers): δ 7.78 (s, 1H, N*H*), 7.31 (m, 6H, N*H*, CO_2CH_2Ph), 7.06 (m, 6H, 2*Ph*), 6.96 (m, 4H, 2*Ph*), 5.80 (d, 1H, *J* = 8.5 Hz, OC*H*Ph), 5.22 (ap t, 1H, *J* = 8.5

Hz, NC*H*Ph), 5.15 and 5.13 (s, 2H, CO_2CH_2Ph), 3.72 (s) and 3.47 (m) (2H, NCH_2CO_2Bn), 3.61 and 3.34 (m, 2H, CHN_{oxa}, C*H*OTBS), 2.95 and 2.85 (m, 2H, CH_2CONH, CH_2N_3), 2.77, 2.67 and 2.64 (s, 3H, NCH_3), 2.76 (m, 1H, CH_2N_3), 2.31 (m) and 2.17 (dd) (1H, J = 4.8, 15.1 Hz, CH_2CONH), 2.01 (m, 1H, $CHCH_2CH$), 1.91 (m, 1H, $CHCH_2CH$), 0.80 (m, 9H, Si(*t-Bu*)), −0.06 (s, 3H, $Si(Me)_2$), −0.10 and −0.11 (s, 3H, $Si(Me)_2$). ^{13}C NMR (75.5 MHz): δ 173.9 (CO_2Bn), 170.1 and 168.4 (CONH), 156.9 and 156.8 (CO_{oxa}), 135.7, 135.2, 134.9, 134.8, 134.7, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.5, 127.4, 125.6 (*Ar*), 79.6 and 79.5 (*C*H), 70.0 and 69.7 (*C*H), 67.0, and 66.7 (*C*H), 66.6 and 66.5 (CH_2), 57.6 (CH_2), 56.2 and 56.0 (CH_2), 49.6 and 49.1 (*C*H), 44.0 (NCH_3), 38.6 and 38.5 (CH_2), 38.0 (CH_2), 25.6 (Si(*t-Bu*)), 17.7 (C_{quat}), −4.8 −4.95 and −5.00 ($Si(Me)_2$). Low intensity signals from the minor rotamer about the hydrazine peptide bond were also observed: δ 169.8 and 169.6 (*C*ONH), 58.5 (CH_2), 58.3 (CH_2), 45.1 (CH_3) 44.8 (CH_3). IR (neat): 3319, 3246 (NH), 2102 (N_3), 1748 (CO), 1674 (CONH) cm^{-1}. Anal. Calcd for $C_{37}H_{43}N_6O_6Si$: C, 63.40; H, 6.90; N, 11.99. Found: C, 63.15; H, 6.79; N, 11.86.

Desilylation of 25 To Give 26. The procedure described for **16** was followed using **25** (138 mg, 0.197 mmol) and 12:1 CH_3CN/48% HF(aq) (4 mL). Removal of solvent *in vacuo* and purification of the residue by flash chromatography (SiO_2; 95:5 EtOAc/MeOH; R_f = 0.57) afforded 91 mg (79%; $[\alpha]_D$ = 6.4° (c = 0.9, CH_2Cl_2)) of **26** (clear oil) as a mixture of rotamers. The presence of amide-type rotamers was confirmed by variable-temperature ^1H NMR experiments.

^1H NMR (300 MHz, mixture of rotamers): δ 7.92 (s, 1H, N*H*), 7.31 (m, 6H, N*H*, CO_2CH_2*Ph*), 7.09 (m, 6H, 2*Ph*), 7.00 (m, 4H, 2*Ph*), 5.86 (ap t, 1H, J = 8.6 Hz, OC*H*Ph), 5.22 (d, 1H, J = 8.6 Hz, NC*H*Ph), 5.14 and 5.12 (s, 2H, CO_2CH_2Ph), 4.04 and 3.90 (m, 1H, CHN_{oxa}), 3.72 and 3.43 (s 2H, NCH_2CO_2Bn), 3.45 and 3.24 (m, 1H, C*H*OH), 3.07 (ap dd, 2H, J = 5.0, 18.4 Hz, CH_2N_3), 2.84 (dd, 1H, J = 9.7, 14.8 Hz, CH_2CONH), 2.77 and 2.60 (s, 3H, NCH_3), 2.46 (m 1H, C*H*OH), 2.31 (dd, 1H, J = 4.6, 14.9 Hz, CH_2CONH), 2.06 (m, 1H, $CHCH_2CH$), 1.66 (m, 1H, $CHCH_2CH$). ^{13}C NMR (75.5 MHz) δ 174.0 (CO_2Bn), 170.1 and 168.7 (CONH), 157.5 and 157.2 (CO_{oxa}), 135.8, 135.5, 135.0, 134.7, 134.6, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.5, 125.65, 125.57 (*Ar*), 79.9 and 79.7 (*C*H), 67.8 (*C*H), 66.7 (NCH_2), 57.7 (CH_2), 56.5 (CH_2), 49.8 (*C*H), 44.2 (NCH_3), 37.6, 37.2, 36.9 and 35.3 (CH_2). Low intensity signals from the minor rotamer about the hydrazine peptide bond were also observed: δ 169.6 and 169.5 (CONH), 65.8 (*C*H), 58.7 (CH_2), 58.3 (CH_2), 45.1 (CH_3). IR (neat): 3600–3100 (NH, OH), 2101 (N_3), 1741 (CO), 1670 (CONH) cm^{-1}.

Preparation of (+)-Negamycin (1). The procedure described for **2** was followed using **26** (49 mg, 0.083 mmol), 2:1 MeOH/5% $AcOH_{(aq)}$ (4 mL), and 10% Pd/C (83 mg, 0.078 mmol), which after purification by ion-exchange chromatography afforded 19 mg (91%; $[\alpha]_D$ = 1.7° (c = 0.6, H_2O)) of (+)-negamycin (**1**) (white powder, mp = 103–118 °C dec).

^1H NMR (300 MHz, D_2O): δ 3.84 (m, 1H, C*H*NH_2), 3.29 (m, 1H, C*H*OH), 3.23 (s, 2H, NCH_2), 2.88 (dd, 1H, J = 3.1, 13.2 Hz, CH_2NH_2), 2.71 (dd, 1H, J = 9.1, 13.1 Hz, CH_2NH_2), 2.46 (s, 3H, NCH_3), 2.22 (ap dd, 2H, J = 1.9, 7.7 Hz, CH_2CONH), 1.44 (m, 2H, $CHCH_2CH$). ^{13}C NMR (75.5 MHz, D_2O): δ 179.8 (CO_2H), 173.5 (CONH), 68.2 (*C*H), 63.7 (CH_2), 47.8 (CH_2), 47.7 (*C*H), 46.6 (NCH_3), 43.6 (CH_2), 42.1 (CH_3). IR (KBr): 3650–2100 (NH, OH, CO_2H), 1651 (CONH), 1584, 1402, 1316, 1132 cm^{-1}.

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