# Formal Total Syntheses of the β-Lactam Antibiotics Thienamycin and PS-5

Peter A. Jacobi,* Shaun Murphree, Frederic Rupprecht, and Wanjun Zheng

*Hall-Atwater Laboratories, Wesleyan University, Middletown, Connecticut 06459-0180*

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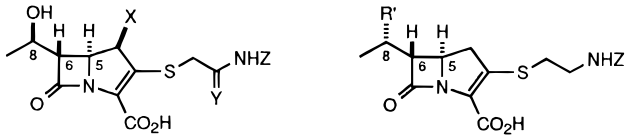
Chiral nonracemic acetylenic acids of general structure **11**, prepared using the Schreiber modification of the Nicholas reaction, have been converted to β-amino acid derivatives of type **12** by a two-step sequence involving Curtius rearrangement followed by oxidative cleavage of the acetylenic bond. Amino acid derivatives **12** are excellent precursors for β-lactams of the carbapenem class, including the important antibiotics thienamycin (**1**) and PS-5 (**4**).

## Introduction

Thienamycin (**1**) is a member of the carbapenem class of antibiotics, which was initially isolated in 1976 from *Streptomyces cattleya*,[1a] and whose structure was determined by an elegant combination of degradative, spectral, and X-ray crystallographic studies (Figure 1).[1b] Interest in **1** derives from its broad spectrum of antibacterial activity, which includes excellent response against both Gram-(+)- and Gram-(−)-bacteria, as well as certain β-lactamase-producing species. This range of activity is exceptional among members of the β-lactam family of antibiotics, whether naturally occurring or semisynthetic. Imipenem (**2**), the *N*-formimidoyl derivative of **1**, is currently marketed in a formulation containing a β-lactamase inhibitor.[1c]

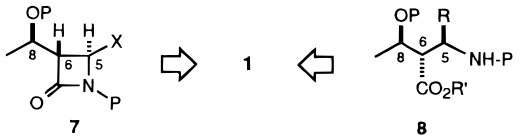
A variety of related carbapenem-type β-lactam antibiotics have been isolated and characterized during the past 10−15 years, some of which have antibacterial activity approaching that of **1**. These include side-chain deoxygenated compounds, such as PS-5 (**4**) and PS-6 (**5**),[2] and members of the olivanic acid class of antibiotics, such as MM-22381 (**6**).[3] MM-22381 (**6**) is isolated from *Streptomyces olivaceus* and differs from thienamycin (**1**) in having the *S*-configuration at $C_8$. In addition, various synthetic analogs, such as 1β-methylcarbapenem (**3**), have attracted considerable attention because of their increased chemical stability and resistance to dehydropeptidase-I (DHP-I).[4] The broad spectrum activity of thienamycin (**1**) and other potent carbapenem antibiotics, taken together with their challenging structural features, has fostered intense and varied synthetic efforts in this area. These studies are important since **1** cannot be efficiently produced in culture, and both **1** and **2** are currently manufactured by total synthesis.[5]




**1** (X,Y,Z = H); **2** (X,Y = H; Z = CH=NH); **3** (X = Me; Y = $NMe_2$; Z = H)

**4** (R' = H; Z = Ac); **5** (R' = Me; Z = Ac); **6** (R' = OH; Z = H)

**Figure 1.**




**7** **8**

**Figure 2.**

Most of the reported syntheses of **1** involve as a key step the preparation of 6-substituted azetidinones of type **7** (X = leaving group), followed by additional elaboration at $N_4$ and $C_5$ (carbapenem numbering) (Figure 2).[6] This approach has the advantage of being highly convergent, and the requisite azetidinones **7** are accessible utilizing [2 + 2] cycloaddition methodology.[6] Alternatively, considerable effort has also been devoted to the synthesis of

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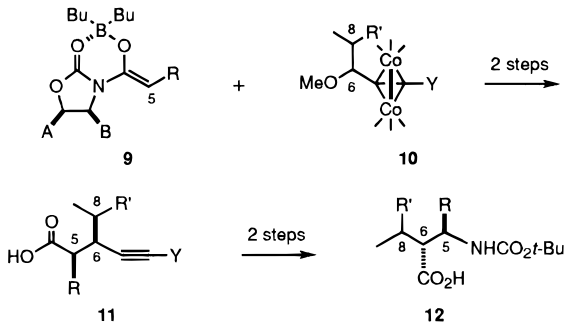
**Scheme 1**




**a**: R' = H; **b**: R' = Me; **c**: R' = *S*-OBn; **d**: R' = *R*-OBn

$\beta$-amino acid precursors such as **8**. Recent approaches include (a) addition of ester enolates or silylketene acetals to imines;[7] (b) Michael addition of amines to unsaturated esters;[8] (c) 1,3-dipolar cycloaddition of nitrones to alkenes;[9] and (d) hydrogenation of acrylic acid derivatives,[10] among others.[11,12] In these examples the 5-substituent is generally introduced prior to cyclization of the $\beta$-lactam ring. In principle, this approach is applicable to the synthesis of a broader range of substrates, and it formed the basis of the first commercial synthesis of **1**.[5] However, in many cases absolute stereochemistry is difficult to control.

In this paper we describe a new approach to $\beta$-amino acids of type **8** which takes advantage of a Nicholas–Schreiber reaction for preparing chiral, enantiomerically pure acetylenic acids of general structure **11** and *ent*-**11** (Scheme 1; *ent* = mirror image of compound shown).[13] Acetylenic acids **11**/*ent*-**11** were then converted to protected $\beta$-amino acids **12**/*ent*-**12** by a two-step sequence involving Curtius rearrangement,[14] followed by oxidative cleavage of the acetylenic bond.[15] The considerable synthetic potential of this methodology derives from its highly convergent nature and the fact that both relative and absolute stereochemistry at all stereogenic centers can be readily controlled.[16] These studies culminated in efficient formal total syntheses of thienamycin (**1**) and PS-5 (**4**).

## Discussion and Results

**I. Model Studies with Simple Nicholas Substrates (R = Me). a. Synthesis of Homochiral Acetylenic Acids.** The Nicholas reaction takes advantage of the fact that cobalt complexes of general structure **14** greatly facilitate the heterolytic cleavage of adjacent alcohols or ethers,[13] which upon $HBF_4$[13b] or Lewis acid[13e] catalysis afford cobalt-stabilized carbocations of type **15** (Figure 3). Capture of these carbocations with nucleophiles such as electron-rich aromatics,[13a] ketone or ester enolates,[13d,e] and enol ethers[13c] then affords the products of nucleophilic displacement **16**, which can be conveniently cleaved to the parent acetylenes **17** under a variety of mild oxidative conditions.[13c] This methodology avoids complications arising from the formation of allenic byproducts, which frequently predominate upon direct displacement of propargyl tosylates and halides.[13f] Since propargyl alcohols are readily derived by addition of acetylides to carbonyl compounds, the overall transfor-

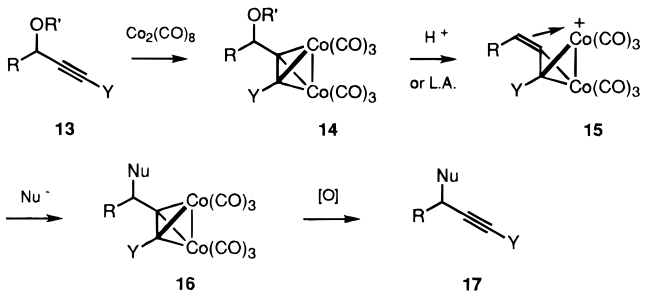



**Figure 3.**

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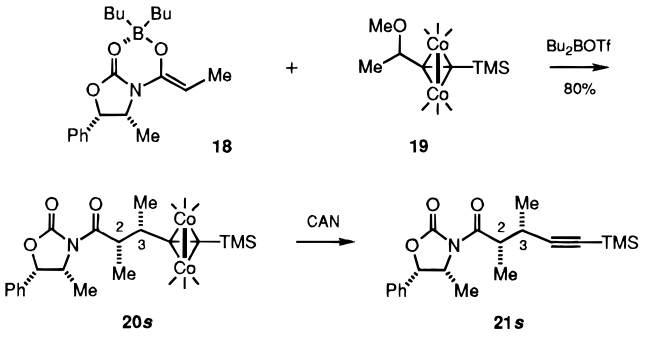
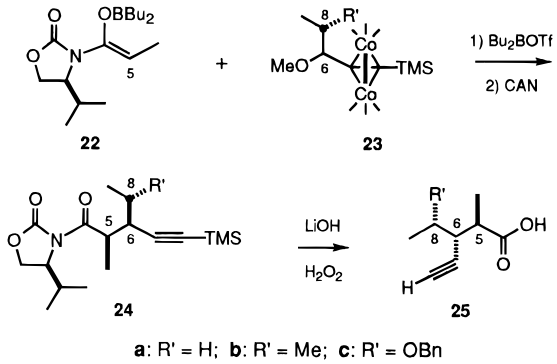



**Figure 4.**

**Scheme 2**




**a**: R' = H; **b**: R' = Me; **c**: R' = OBn

mation constitutes a flexible carbonyl-to-geminal dialkyl transposition.

In 1987, Schreiber *et al.* described the first example of a Nicholas reaction involving a homochiral nucleophile. Thus, alkylation of boron enolate **18** with cobalt complex **19** afforded a 12:1 mixture of *syn*-adduct **20*s*** together with the corresponding 2,3-*anti*-isomer **20*a*** (Figure 4; **20*a*** not shown).[13h] Oxidative cleavage of **20*s*** with cerric ammonium nitrate (CAN) then gave an excellent yield of the parent acetylene **21*s***. This result was rationalized on the basis of a novel double stereodifferentiating process, in which the racemic carbocation derived from **19** interconverts *via* enantiomerization at a rate which is fast relative to alkylation (kinetic resolution).[13h] In principle, this observation provides the basis for a general synthesis of homochiral acetylenic acid derivatives that might find widespread utility in organic synthesis. However, until recently little was known about the effect of chiral substituents on such transformations.[16]

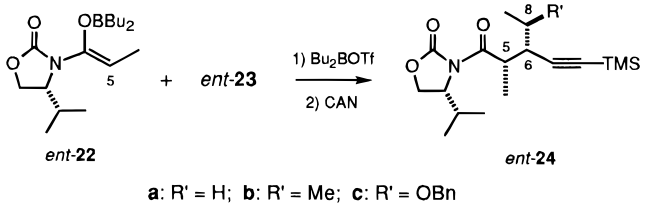
In order to explore the generality of the Nicholas–Schreiber methodology, we initially studied the preparation of acetylenic acids **25a–c** (Scheme 2). Cobalt derivatives **23a–c** were readily obtained by condensation of lithio(trimethylsilyl)acetylene with the appropriate aldehydes R′CHMeCHO (R′ = H, Me, *S*-OBn), followed by *in situ* methylation (DMS),[16] and complexation of the resulting methylpropargyl ethers with $Co_2(CO)_8$.[13] Imide enolate **22** was prepared following the general procedure of Schreiber *et al.*,[13h] employing 1.0 equiv each of $(i\text{-}C_3H_7)_2NEt$ and $Bu_2BOTf$ at 0 °C in $CH_2Cl_2$. The resulting enolate solutions were then cooled to −78 °C, treated with an additional 0.5–1.0 equiv of $Bu_2BOTf$, followed by an equimolar quantity of **23** (based on excess $Bu_2BOTf$), and warmed to 0 °C to afford the desired adducts **24** after oxidative cleavage with CAN (Table 1). In identical fashion, imide enolate *ent*-**22** afforded the enantiomeric adducts *ent*-**24** upon condensation with cobalt complexes *ent*-**23** (Scheme 3).

**Table 1**

| no. | compd | yield,[a] % | $[\alpha]^{25}_D$ (*c*)[d] | compd | yield,[a] % | $[\alpha]^{25}_D$ (*c*)[d] |
|---|---|---|---|---|---|---|
| 1 | 24a | 94[b] | +28.7 (12.4) | 25a | 91 | +11.7 (27.8) |
| 2 | *ent*-**24a** | 80[c] | −26.0 (30.6) | *ent*-**25a** | 91 | −11.5 (60.7) |
| 3 | 24b | 20[b] | +15.9 (4.5) | 25b | 56 | −1.3 (45.8) |
| 4 | 24c | 93[b] | −33.1 (6.4) | 25c | 86 | −31.6 (7.8) |
| 5 | *ent*-**24c** | 78[c] | +37.4 (14.7) | *ent*-**25c** | 79 | +30.2 (19.5) |

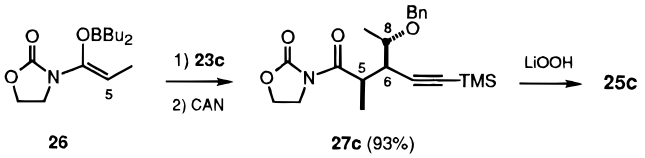
[a] Average yield for several runs. [b] Yield employing 2 equiv of **22**. [c] Yield employing 1 equiv of **22**. [d] Measured in MeOH (*c* = mg/mL).

**Scheme 3**




**a**: R' = H; **b**: R' = Me; **c**: R' = OBn

**Scheme 4**




In general, yields for this reaction were excellent (85–98%), utilizing a ratio of **22:23** = 2:1 (entries 1 and 4, Table 1), and only slightly less satisfactory (75–85%), employing a ratio of **22:23** = 1:1 (entries 2 and 5, Table 1). Not surprisingly, however, **24b** (R′ = Me) was obtained in considerably lower yield (20%, entry 3, Table 1), presumably due to steric hindrance and competing elimination reactions in the stabilized carbocation derived from **23b**.[13] Diastereo- and enantioselectivities were also generally excellent, with *syn:anti* ratios of >98:2 employing chiral enolates **22** and *ent*-**22** with achiral cobalt complexes **23a,b** (entries 1–3, Table 1; slightly lower *syn*-selectivity was observed employing chiral enolates **18** and *ent*-**18**; *cf.* Figure 4). Equally impressive ratios (>98:2) were obtained with the "matched" chiral substrates **22** + **23c** → **25c**, and *ent*-**22** + *ent*-**23c** → *ent*-**24c** (entries 4 and 5, Table 1; the case of "mismatched" substrates will be discussed below). These results are in full accord with the transition state model proposed by Schreiber *et al.* (*vide supra*).[13h]

Once in hand, oxazolidinones **24**/*ent*-**24** were readily converted to the corresponding acetylenic acids **25**/*ent*-**25** by hydrolysis with excess lithium hydroperoxide,[17] which effected concomitant cleavage of the TMS group (Scheme 2). As indicated (Table 1), yields for this step were excellent (80–98%), except for the special case where R′ = Me (entry 3, Table 1). In this example, steric hindrance once again had a deleterious effect on reactivity. Finally, 5*R*,6*R*-diastereoselectivity of >98:2 was also obtained upon condensation of chiral cobalt complex **23c** with the *achiral* enolate **26** (Scheme 4), as judged by conversion of the derived adduct **27c** to the identical homochiral acetylenic acid **25c** obtained employing chiral enolate **22** (*cf.* Scheme 2).[18] This result provides some

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(18) We are grateful to Ms. Gayle Schulte, of Yale University, for carrying out an X-ray analysis of acetylenic acid **25c**.

**Table 2**

| no. | compd | yield,[a] % | $[\alpha]^{25}_D$ (*c*)[b] | compd | yield,[a] % | $[\alpha]^{25}_D$ (*c*)[b] |
|---|---|---|---|---|---|---|
| 1 | 28a | 82 | +61.1 (24.8) | 30a | 97 | +12.7 (2.7) |
| 2 | *ent*-**28a** | 74 | −64.0 (20.1) | *ent*-**30a** | 92 | −13.8 (7.2) |
| 3 | 28b | 64 | +55.2 (20.4) | 30b | 86 | +23.8 (15.1) |
| 4 | 28c | 92 | +34.9 (19.8) | 30c | 68 | +62.4 (16.3) |
| 5 | *ent*-**28c** | 82 | −34.4 (4.7) | *ent*-**30c** | 68 | −64.7(12.8) |

| no. | compd | yield,[a] % | $[\alpha]^{25}_D$ (*c*)[c] |
|---|---|---|---|
| 1 | 32a | 71 | +19.8 (10.3) |
| 2 | *ent*-**32a** | 81 | −18.3 (19.5) |
| 3 | 32b | 82 | +11.3 (23.0) |
| 4 | 32c | 76 | +35.5 (19.8) |
| 5 | *ent*-**32c** | 83 | −36.5 (10.5) |

[a] Average yield for several runs. [b] Measured in MeOH (*c* = mg/mL). [c] Measured in $CH_2Cl_2$ (*c* = mg/mL).

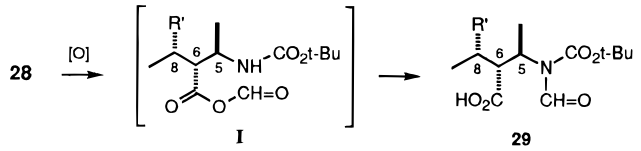
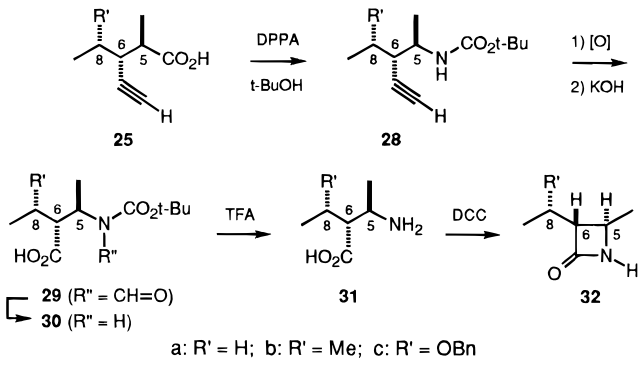



**Figure 5.**

indication of the powerful directing influence which chiral substituents can exert on the Nicholas reaction.

**b. Conversion of Acetylenic Acids 25/*ent*-25 to *β*-Amino Acids 30/*ent*-30 and *β*-Lactams 32/*ent*-32.** We next studied the conversion of acetylenic acids **25** to homochiral amino acid derivatives **30** (Scheme 5). As

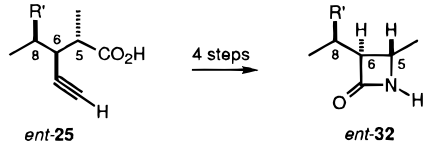
**Scheme 5**




indicated, Curtius rearrangement of **25** to afford carbamates **28** was conveniently carried out with diphenyl phosphorazidate (DPPA),[14a] followed by HCl-catalyzed capture of the intermediate isocyanate (not isolated) with 2-methyl-2-propanol.[14b] Within the limits of detection, this step occurred with complete retention of stereochemistry, as determined by NMR analysis and comparison of the specific rotations for **28a,c** and *ent*-**28a,c** (Table 2). However, we experienced some initial difficulties in effecting the oxidative cleavage of acetylenic carbamates **28** to the desired amino acid derivatives **30**. For **28a,b**, this transformation was best accomplished with $KMnO_4$/$NaIO_4$,[12e] which afforded ~50:50 mixtures of the corresponding acids **30a,b** together with the *N*-formyl derivatives **29a,b**. We believe that formyl derivatives **29** were derived by intramolecular formylation involving oxidation intermediates of type **I** (Figure 5), since **30** itself was unreactive to formic acid.

In any event, these mixtures were usually not separated, but rather were directly hydrolyzed (KOH) to afford pure **30a,b** in >90% overall yield (entries 1 and 3, Table 2). With **28c** (R′ = OBN), however, $KMnO_4$/$NaIO_4$ caused extensive decomposition due to oxidation of the benzyl protecting group to give benzoic acid. This difficulty was eventually circumvented with our finding that $OsO_4$/$NaIO_4$ provided the desired chemoselectivity,[15] leading exclusively to the *N*-formyl derivative **29c**. As with **29a,b** described above, **29c** was then readily cleaved with KOH to afford the desired carbamate **30c** (entry 4, Table 2). The utility of these amino acid derivatives for the synthesis of *β*-lactams was then convincingly demonstrated by their facile conversion to amino acids **31a**−**c** and subsequently to lactams **32a**−**c** upon cyclization with dicyclohexylcarbodiimide (DCC).[12e] Finally, in identical fashion, acetylenic acids *ent*-**25a,c** were converted in four steps to the enantiomeric *β*-lactams *ent*-**32a,c** (Scheme 6), which were also obtained as single isomers (entries 2 and 5, Table 2).

**Scheme 6**




**II. Formal Synthesis of PS-5.** *β*-Lactam **32a** (*cf.* Scheme 5) bears a close structural resemblance to the known alcohol derivative **33** (5*R*,6*R*-stereochemistry), which has previously been employed in the synthesis of the potent antibiotic PS-5 (**4**) (Figure 6).[19] We envisioned

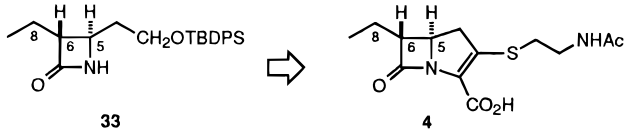
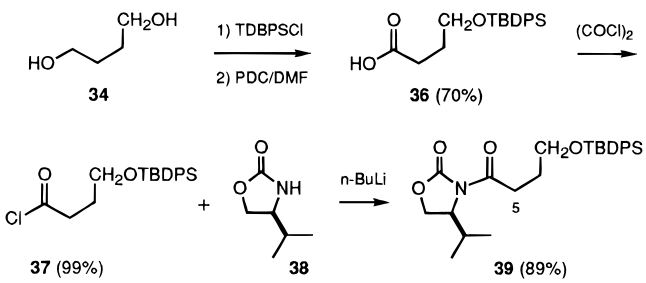



**Figure 6.**

that precursors of type **33** might be conveniently prepared using methodology analogous to that described in Schemes 2 and 5. In order to explore this possibility it was first necessary to prepare the chiral oxazolidinone derivative **39**, which was derived in excellent overall yield beginning with 1,4-butanediol (**34**) (Scheme 7). Thus,

**Scheme 7**




selective monoprotection of **34** with TBDPSCl gave a 90% yield of the corresponding alcohol **35**, which upon oxidation with PDC in DMF afforded carboxylic acid derivative **36** in 75% yield. Treatment of **36** with oxalyl chloride in benzene then provided the acid chloride **37** (99%), which

(19) (a) Tanner, D.; Somfai, P. *Tetrahedron* **1988**, *44*, 619. See also: (b) Shono, T.; Kise, N.; Sanda, F.; Ohi, S.; Yoshioka, K. *Tetrahedron Lett.* **1989**, *30*, 1253.

**Scheme 8**

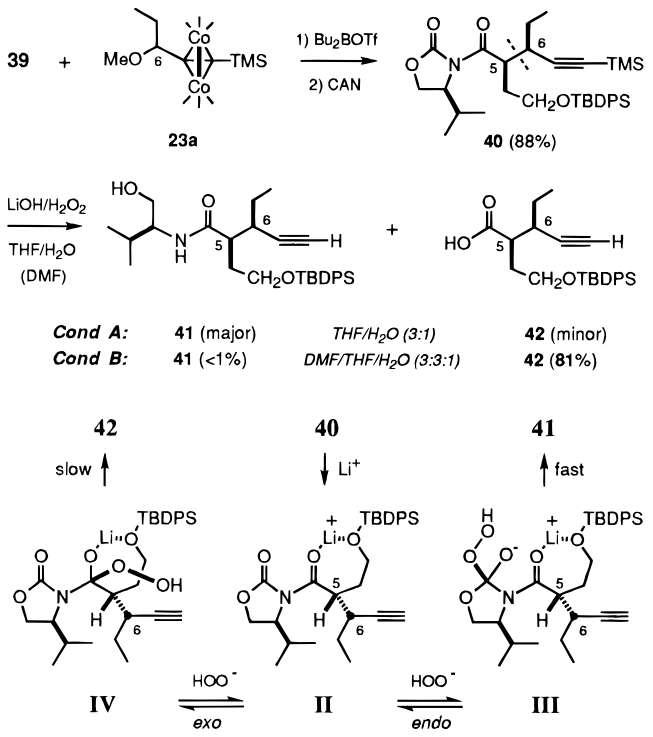
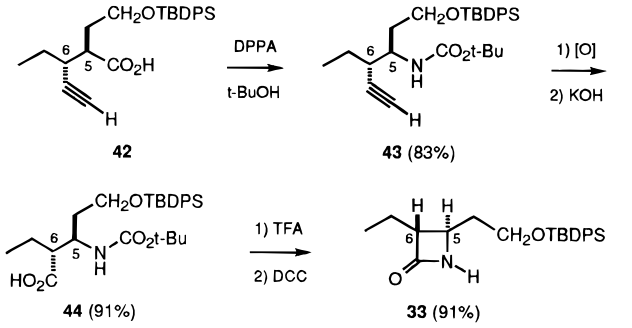



**Figure 7.**

**Scheme 9**




was directly converted to the desired acyl derivative **39** by condensation with the lithium anion derived from oxazolidinone **38** (89% yield from **36**).[20]

Once in hand, oxazolidinone **39** was readily converted to the corresponding boron enolate (*vide supra*),[13h] which underwent smooth Nicholas condensation with cobalt complex **23a** to give *syn*-adduct **40** in 88% overall yield after decomplexation (Scheme 8; >98:2 *syn*-selectivity). Surprisingly, however, hydrolysis of **40** under the standard conditions (LiOOH, 3:1 THF/$H_2O$) afforded complex mixtures of products,[17] consisting in part of *endo*-ring-opened alcohol **41**, together with lesser amounts of the desired carboxylic acid **42** derived by *exo*-hydrolysis (conditions A). This unexpected reaction pathway might be due to complexation of Li cation between the *exo*-carbonyl group and the −OTBDPS functionality (*cf.* **II**, Figure 7), since related alkyl derivatives (OTBDPS = Me) underwent normal hydrolysis (*vide infra*). In any event, addition of DMF to the hydrolysis reaction completely reversed the regioselectivity (3:3:1 DMF/THF/$H_2O$) and afforded an 81% yield of the desired acetylenic acid **42** with no trace of *endo*-ring opened product **41** (conditions B).

We believe that DMF functions by solvating chelated intermediates of type **II**−**IV** (Figure 7), themselves derived by initial coordination of Li cation with adduct **40** (**40** → **II**). This result is in qualitative agreement with the suggestion of Evans *et al.* that the rate-determining step in cleavage by $HOO^-$ is *collapse* of the initially formed tetrahedral intermediate.[17] In the case of *endo*-attack (**II** → **III**), collapse of intermediate **III** to **41** is presumably accelerated by chelation of the type illustrated in **III**, which renders the oxazolidinone C−N bond relatively labile. In contrast, intermediate **IV**, derived by *exo*-attack (**II** → **IV**), is most likely stabilized by chelation. Therefore, collapse of **IV** to the desired carboxylic acid **42** is relatively slow. As expected on the basis of this hypothesis, DMF had no effect on the regioselectivity of hydrolysis by $HO^-$, where the rate-determining step is *formation* of the tetrahedral intermediate (steric control).[17] In both cases (with and without added DMF), hydrolytic cleavage was predominantly endocyclic to afford **41**.

The remaining steps necessary for the conversion of **42** to the PS-5 (**4**) precursor **33** were then accomplished in a straightforward fashion, in exact analogy to our model studies described in Scheme 5. Thus, Curtius rearrangement of **42** with DPPA afforded an 83% yield of the carbamate derivative **43**,[14] which upon oxidative cleavage with $KMnO_4/NaIO_4$ gave the desired protected amino acid **44** in 91% yield (Scheme 9). This last compound, upon TFA-catalyzed deprotection, then gave a quantitative yield of the $\beta$-amino acid **45**, which in turn afforded 91% of the target $\beta$-lactam **33** upon cyclization with DCC. The material thus prepared had chemical and physical properties identical to those reported in the literature[19a] and was obtained as a single enantiomer.

**III. Formal Synthesis of Thienamycin. a. Model Studies with Matched and Mismatched Substrates.** In Schemes 2 and 5 we described an efficient synthesis of $\beta$-amino acid derivative **31c**, making use of a "matched" condensation of oxazolidinone enolate **22** with cobalt complex **23c** (Figure 8). Amino acid **31c** has the 5*R*,6*S*,8*S*-

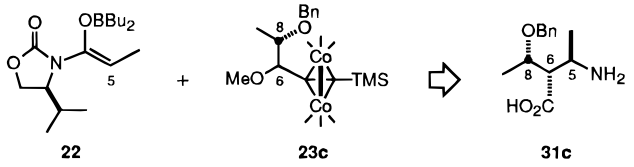



**Figure 8.**

stereochemistry characteristic of MM-22381 (**6**) (*cf.* Figure 1), and it served as a useful probe of stereochemical control in the Nicholas reaction. As employed in this case, the term "matched" refers to those condensations in which the chirality of the oxazolidinone precursor reinforces the directing effect of the C-8 stereogenic center in cobalt complexes **23**. As previously noted (Scheme 4), chiral cobalt complex **23c** combines even with *achiral* oxazolidinone **26** to provide adduct **27c** with excellent diastereo- and enantioselectivity.

On the basis of these results, it was of interest to determine if a similar approach could be applied to the synthesis of amino acids having the 5*R*,6*S*,8*R*-configuration found in thienamycin (**1**) (*cf.* Figure 1).[1] In principle, this substitution pattern was available by "mismatched" condensation of oxazolidinone **39** with cobalt complex *ent*-**23c** (Figure 9). This combination

(20) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem Soc.* **1981**, 103, 2127.

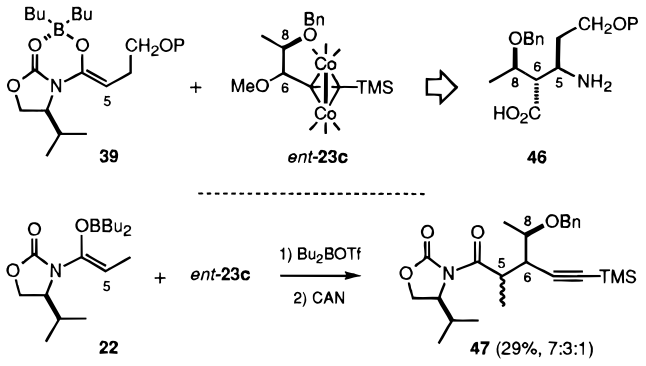
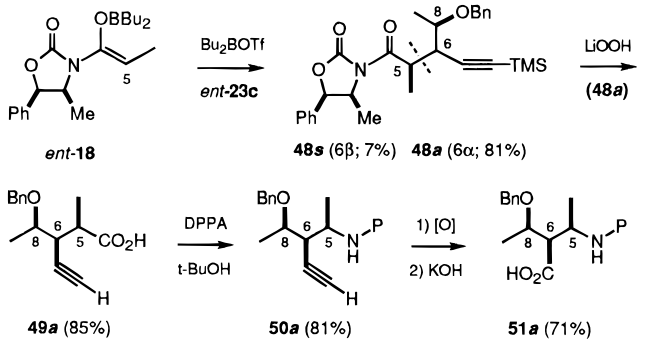
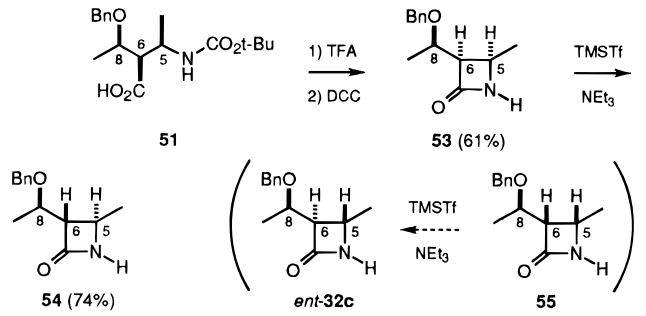



**Figure 9.**

**Scheme 10**




**Scheme 11**




would ultimately lead to the known thienamycin precursor **46** (P = OTBDPS) if transition state interactions were dominated by chiral auxiliary **39**.[12e,13h] However, our initial model studies in this direction were not encouraging. Thus, all attempts at the condensation of boron enolate **22** with *ent*-**23c** provided only complex mixtures of products, which contained at least three isomeric adducts **47** in a ratio of ~7:3:1 (29% combined yield, Figure 9). This result stands in marked contrast to that obtained in the "matched" condensation of oxazolidinone **22** with **23c** (*cf.* Scheme 2), which gave adduct **24c** in 93% yield with >98:2 *syn*-selectivity.

In contrast to the case with **22**, oxazolidinone *ent*-**18** underwent clean "mismatched" condensation with *ent*-**23c** to provide an ~12:1 mixture of two isomeric acetylenic acid derivatives (Scheme 10). These were subsequently identified as *syn*-adduct **48*s*** and *anti*-isomer **48*a***. Interestingly, however, the major isomer proved to be the *anti*-adduct **48*a***, as demonstrated by chemical correlation (it was impossible to distinguish between **48*s*** and **48*a*** on the basis of spectral data alone). Thus, **48*a*** was readily converted to the carboxylic acid **49*a***,[17] which upon Curtius rearrangement (81%)[14] followed by oxidative cleavage (71%)[15] afforded amino acid derivative **51*a*** in exact analogy to our earlier studies with **30c** and *ent*-**30c** (P = $CO_2$t-Bu; *cf.* Schemes 5 and 6).

Upon cyclization of **51** to β-lactam **53** the *cis*-relationship between $H_5$−$H_6$ was immediately apparent from their relatively large coupling constant ($J_{5,6}$ = 6.0 Hz) (Scheme 11). For *trans*-β-lactams this coupling constant is typically <3 Hz.[19b] The remaining question pertaining to the absolute stereochemistry at $C_5$−$C_6$ was then resolved by epimerization studies. As expected, **53** was readily epimerized to the desired *trans*-isomer **54** ($J_{5,6}$ = 1.8 Hz),[21] which proved to be identical to the material obtained directly from the minor *syn*-adduct **48*s*** (*cf.* Experimental Section). If **53** had been of opposite absolute configuration at $C_5$−$C_6$ (*i.e.*, **55**), epimerization would have afforded the previously synthesized β-lactam *ent*-**32c** (*cf.* Scheme 6). These results provide further testimony to powerful directing influence which chiral substituents can exert on the Nicholas reaction (see also Scheme 4). At present we have no detailed rationale for this difference in reaction pathway between "matched" and "mismatched" condensations. However, with further study we hope to develop a transition state model which will permit logical predictions regarding the stereochemical outcome of Nicholas reactions with chiral substrates.

**b. Synthesis of the Key Thienamycin Precursor 63.** Finally, these model studies were readily extended to a formal total synthesis of thienamycin (**1**).[12] As described above for **39** (Scheme 7), the requisite precursor **56** was prepared by acylation of oxazolidinone **38b** with acid chloride **37** (Figure 10). Condensation of the boron enolate of **56** with cobalt complex *ent*-**23c** then provided a 79% yield of the Nicholas adduct **57**, which was obtained with ~17:1 *anti*-selectivity (Scheme 12) (Note

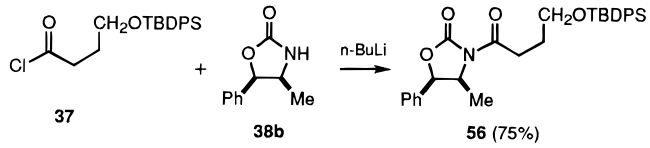
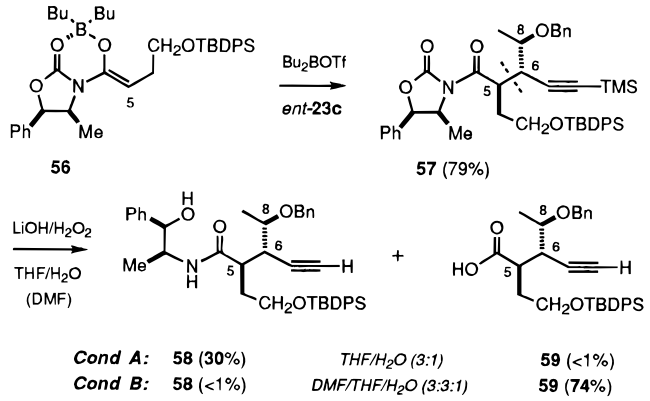



**Figure 10.**

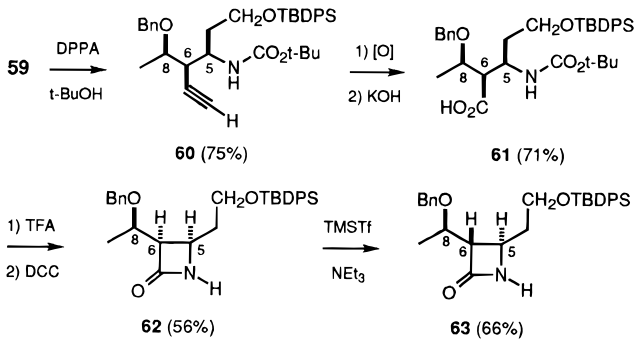
**Scheme 12**




that *ent*-**23c** combines with achiral oxazolidinones to provide *syn*-adducts of 5*S*,6*S*,8*R*-stereochemistry, the incorrect configuration at $C_5$ and $C_6$; *cf.* Scheme 4). As in the case with **40** (*cf.* Scheme 8), hydrolysis of **57** under standard conditions (LiOOH, 3:1 THF/$H_2O$) afforded a complex mixture of products,[17] from which *endo*-ring opened product **58** could be isolated in 30% yield (condi-

(21) Chiba, T.; Nakia, T. *Tetrahedron Lett.* **1985**, *26*, 4647.

**Scheme 13**




tions A). No trace of the desired carboxylic acid **59** derived from *exo*-nucleophilic attack could be detected. Once again, however, addition of DMF to the hydrolysis reaction completely reversed the regioselectivity (3:3:1 DMF/THF/$H_2O$) and afforded a 74% yield of the desired acetylenic acid **59** together with only traces of **58** (conditions B).

As described above for **49** (*cf.* Scheme 10), **59** was then converted in two steps to the homochiral amino acid derivative **61**, which upon deprotection and cyclization with DCC afforded the *cis*-*β*-lactam **62** in 56% yield (Scheme 13). Finally, epimerization of **62** according to the procedure of Nakai *et al.* afforded the known thienamycin precursor **63**,[12e,21] which had spectral data identical to that reported by Grieco *et al.* for the racemic material.[22]

## Summary

The control of relative and absolute stereochemistry at three and more contiguous centers is an important problem in organic synthesis. In some cases we believe that the Nicholas reaction could provide an attractive alternative to more traditional methodology in this area. This will be especially true for molecules containing carboxylate, alkene, amino, and related functionalities which are easily derived from acetylenic acid derivatives of type **11**. To illustrate this potential, we have developed unequivocal syntheses of two of the most important members of the carbapenem class of antibiotics. Extension of this methodology to the synthesis of other biologically important molecules is currently under investigation.

## Experimental Section

Melting points were determined in open capillaries and are uncorrected. $^1$H NMR spectra were recorded at either 200 or 400 MHz and are expressed as ppm downfield from tetramethysilane.

**General Procedure for the Preparation of Methyl Propargylic Ethers.** A solution of (trimethylsilyl)acetylene (1.0 equiv) in THF was cooled to −78 °C under nitrogen and was treated in a dropwise fashion, with vigorous stirring, with 2.5 M *n*-butyllithium/hexanes (1.0 equiv). The resulting mixture was stirred at −78 °C for an additional 10 min and was then treated over 5 min with a solution of the desired aldehyde (1.0 equiv) in THF. After the mixture was stirred for an additional 15 min, dimethyl sulfate (1.0 equiv) was added to the mixture and the cooling bath was removed. The reaction mixture was then stirred at rt for 18−48 h and monitored by TLC. When complete, the reaction was quenched by addition of 140 mL of saturated aqueous $NH_4Cl$, and the separated aqueous layer was extracted with 3 × 100 mL of diethyl ether. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by either chromatography or distillation then afforded the methyl propargylic ether.

**General Procedure for the Preparation of Hexacarbonyldicobalt-Complexed Alkynes 23a−c.** A solution of octacarbonyldicobalt (1.05 or 1.1 equiv) in anhydrous diethyl ether was stirred at rt under nitrogen and was treated in a dropwise fashion with a solution of the desired methyl propargylic ether (1.0 equiv) in anhydrous diethyl ether (see above). The resulting mixture was then stirred at rt for 3−8 h. Following this period, the solvent was concentrated under reduced pressure, and the residue was chromatographed to afford the corresponding cobalt-complexed alkyne.

**3-Methoxy-1-(trimethylsilyl)pentyne, Hexacarbonyldicobalt Complex (23a).** 3-Methoxy-1-(trimethylsilyl)pentyne was prepared following the general procedure described above, using 12.1 mL (86.2 mmol, 1.0 equiv) of (trimethylsilyl)acetylene in 350 mL of THF, 34.3 mL (1.0 equiv) of 2.5 M *n*-butyllithium/hexanes, 6.20 mL (1.0 equiv) of propionaldehyde, and 8.10 mL (1.0 equiv) of dimethyl sulfate. After the mixture was stirred at rt for 23 h, isolation and distillation gave 12.5 g (85%) of 3-methoxy-1-(trimethylsilyl)pentyne as a colorless oil, bp 65−67 °C/18 mm: IR ($CH_2Cl_2$) 2966, 2168, 1675, 1463, 1334, 1252, 1132, 1052 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.16 (s, 9H), 0.97 (t, $J$ = 7.0 Hz, 3H), 1.68 (m, 2H), 3.38 (s, 3H), 3.85 (t, $J$ = 7.0 Hz, 1H). Following the general procedure described above, a solution of 1.90 g (11.1 mmol, 1.0 equiv) of 3-methoxy-1-(trimethylsilyl)pentyne in 10 mL of diethyl ether and 4.00 g (11.7 mmol, 1.05 equiv) of octacarbonyldicobalt in 60 mL of diethyl ether was stirred for 3.5 h at rt. Concentration and chromatography (100:1 hexanes/EtOAc) then afforded 4.90 g (96%) of **23a** as a dark solid: IR ($CH_2Cl_2$) 2962, 2096, 2059, 2026, 1671, 1562 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.32 (bs, 9H), 1.11 (bs, 3H), 1.76 (bs, 2H), 3.56 (bs, 3H), 4.50 (bs, 1H).

**3-Methoxy-4-methyl-1-(trimethylsilyl)pentyne, Hexacarbonyldicobalt Complex (23b).** 3-Methoxy-4-methyl-1-(trimethylsilyl)pentyne was prepared following the general procedure described above, using 12.1 mL (86.2 mmol, 1.0 equiv) of (trimethylsilyl)acetylene in 250 mL of THF, 34.3 mL (1.0 equiv) of 2.5 M *n*-butyllithium/hexanes, 7.80 mL (1.0 equiv) of 2-methylpropionaldehyde, and 8.10 mL (1.0 equiv) of dimethyl sulfate. After the mixture was stirred at rt for 36 h, isolation and distillation gave 13.0 g (82%) of 3-methoxy-4-methyl-1-(trimethylsilyl)pentyne as a colorless oil, bp 77−79 °C/21 mm: MS $m/e$ 169 ($M^+$ − Me), 141, 126, 113, 97, 89, 83, 59; IR ($CH_2Cl_2$) 2963, 2168, 1469, 1349, 1250, 1088, 1028 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.20 (s, 9H), 1.00 (t, $J$ = 7.5 Hz, 6H), 1.92 (m, 1H), 3.42 (s, 3H), 3.72 (d, $J$ = 6.5 Hz, 1H); $^{13}$C NMR ($CDCL_3$) $\delta$ 0.08, 17.65, 18.39, 32.80, 56.52, 77.29, 90.89, 103.40. Anal. Calcd for $C_{10}H_{20}OSi$: C, 65.15; H, 10.93. Found: C, 65.25; H, 10.94. Following the general procedure described above, a solution of 2.05 g (11.1 mmol, 1.0 equiv) of 3-methoxy-4-methyl-1-(trimethylsilyl)pentyne in 10 mL of diethyl ether and 4.00 g (11.7 mmol, 1.05 equiv) of octacarbonyldicobalt in 55 mL of diethyl ether was stirred for 3.5 h at rt. Concentration and chromatography (100:1 hexanes/EtOAc) then afforded 5.05 g (99%) of **23b** as a dark solid: IR ($CH_2Cl_2$) 2962, 2087, 2047, 2021, 1578, 1270, 1088 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.32 (s, 9H), 1.06 (d, $J$ = 7.5 Hz, 3H), 1.10 (d, $J$ = 7.5 Hz, 3H), 1.88 (m, 1H), 3.54 (s, 3H), 3.98 (d, $J$ = 6.0 Hz, 1H).

**4(*S*)-(Benzyloxy)-3-methoxy-1-(trimethylsilyl)pentyne, Hexacarbonyldicobalt Complex (23c).** 4(*S*)-(Benzyloxy)-3-methoxy-1-(trimethylsilyl)pentyne was prepared following the general procedure described above, using 3.50 mL (24.5 mmol, 1.0 equiv) of (trimethylsilyl)acetylene in 100 mL of THF, 9.80 mL (1.0 equiv) of 2.5 M *n*-butyllithium/hexanes, 4.02 g (1.0 equiv) of 2-(*S*)-(benzyloxy)propionaldehyde in 20 mL of THF, and 2.30 mL (1.0 equiv) of dimethyl sulfate. After the mixture was stirred at rt for 22 h, isolation and chromatrography (20:1 hexanes/EtOAc) gave 6.64 g (98%) of 4(*S*)-(benzyloxy)-3-methoxy-1-(trimethylsilyl)pentyne as a colorless oil: MS $m/e$ 232 ($M^+$ − 44), 217, 201, 185, 170, 155, 141, 135, 123, 113; IR ($CH_2Cl_2$) 3033, 2962, 2170, 1453, 1252, 1098, 1028 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.21 (s, 9H), 1.29 (d, $J$ = 6.5 Hz, 3H), 3.45 (s, 3H), 3.67 (m, 1H), 4.02 (m, 1H), 4.67 (m, 2H), 7.27−

(22) We are grateful to Professor Paul Grieco, of Indiana University, for providing an NMR spectra of (±)-**63** (*cf.* ref 12e).

7.41 (m, 5H). Anal. Calcd for $C_{16}H_{24}O_2Si$: C, 69.52; H, 8.75. Found: C, 69.65; H, 8.76. Following the general procedure described above, a solution of 2.00 g (7.23 mmol, 1.0 equiv) of 4(*S*)-(benzyloxy)-3-methoxy-1-(trimethylsilyl)pentyne in 10 mL of diethyl ether and 2.70 g (1.1 equiv) of octacarbonyldicobalt in 38 mL of diethyl ether was stirred for 3.5 h at rt. Concentration and chromatography (100:1 hexanes/EtOAc) then afforded 3.86 g (95%) of **23c** as a dark liquid: IR ($CH_2Cl_2$) 3050, 2957, 2088, 2049, 2022, 1585, 1454, 1376, 1101 $cm^{-1}$; $^1$HNMR ($CDCl_3$) $\delta$ 0.28 (two s, 9H), 1.26 (d, $J$ = 6.5 Hz, 3H), 1.32 (d, $J$ = 6.5 Hz, 3H), 3.60 (s, 3H), 3.45−3.75 (m, 1H), 4.27−4.70 (m, 3H), 7.24−7.40 (m, 5H).

**4(*R*)-(Benzyloxy)-3-methoxy-1-(trimethylsilyl)pentyne, Hexacarbonyldicobalt Complex (*ent*-23c).** This material was prepared in 98% yield from 4.62 g of 4(*R*)-(benzyloxy)-3-methoxy-1-(trimethylsilyl)pentyne following the same procedure as that described above for **23c**. Cobalt complex *ent*-**23c** had spectral data identical to that provided for **23c**.

**General Procedures for the Nicholas Reaction and Oxidative Decomplexation. Method A.** A solution consisting of 11.0 mmol (2.0 equiv) of the appropriate oxazolidone in 37 mL of anhydous methylene chloride was cooled to 0 °C under nitrogen and was treated in dropwise fashion, with vigorous stirring, with 2.0 equiv of freshly distilled *N*,*N*-diisopropylethylamine and 2.0 equiv of a 1.0 M solution of dibutylboron triflate/methylene chloride. After the mixture was stirred for 15 min at 0 °C, an additional 1.0 equiv of dibutylboron triflate was added and the resulting mixture was cooled to −78 °C. A solution consisting of 5.50 mmol (1.0 equiv) of the appropriate cobalt-complexed alkyne in 15 mL of methylene chloride was then added in dropwise fashion and with vigorous stirring. After the addition was complete, the resulting mixture was allowed to warm to 0 °C, and stirring was continued for 20 min each at 0 °C and at rt, respectively. The reaction was then quenched with 90 mL of ice-cold pH 7 buffer, and the separated aqueous layer was extracted with 3 × 40 mL of methylene chloride. The combined organic extracts were dried ($MgSO_4$), filtered, concentrated under reduced pressure, and chromatographed (20:1 or 10:1 hexanes/EtOAc) to afford the desired cobalt complexed Nicholas adduct together with excess oxazolidone. The crude material thus obtained was dissolved in 100 mL of acetone and treated portionwise, at rt and with vigorous stirring, with ammonium cerium(IV) nitrate (CAN) until gas evolution ceased. A slight excess of CAN was then added, and the solvent was removed under reduced pressure at rt. The resultant residue was partitioned between 70 mL of water and 55 mL of diethyl ether, and the separated aqueous layer was extracted with 5 × 55 mL of diethyl ether. The combined organic layers were dried ($MgSO_4$), filtered, concentrated under reduced pressure, and chromatographed (20:1 or 10:1 hexanes/EtOAc) to give the desired product.

**Method B.** Method B was identical to method A but employed equimolar quantities of the appropriate oxazolidones and cobalt-complexed acetylenes.

**Nicholas Adduct 24a.** Following method A, above, a solution of 2.03 g (11.0 mmol, 2.0 equiv) of (*S*)-4-isopropyl-*N*-propionyl-2-oxazolidone (**22**) in 37 mL of $CH_2Cl_2$, 1.89 mL of *i*-$Pr_2NEt$, 11.0 and 5.50 mL (2.0 and 1.0 equiv) of 1.0 M $Bu_2BOTf/CH_2Cl_2$, a solution of 2.50 g (1.0 equiv) of the cobalt-complexed alkyne **23a** in 15 mL of $CH_2Cl_2$, and 100 mL of acetone with excess CAN gave 1.66 g (94%) of adduct **24a** as a light yellow oil: $[\alpha]^{25}_D$ +28.7° (*c* = 12.4, MeOH); MS *m*/*e* 323 ($M^+$), 308, 194, 179, 151, 130, 97, 73; IR ($CH_2Cl_2$) 2967, 2167, 1778, 1701, 1386, 1208 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.12 (s, 9H), 0.92 (t, $J$ = 7.0 Hz, 6H), 1.03 (t, $J$ = 7.5 Hz, 3H), 1.17 (d, $J$ = 7.5 Hz, 3H), 1.40 (m, 1H), 1.56 (m, 1H), 2.38 (m, 1H), 2.73 (m, 1H), 3.98 (quint, $J$ = 7.0 Hz, 1H), 4.20 (dd, $J$ = 3.5, 6.5 Hz, 1H), 4.27 (t, $J$ = 8.5 Hz, 1H), 4.41 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ −0.3, 11.0, 13.8, 14.6, 17.5, 23.1, 28.1, 36.2, 40.9, 57.9, 62.7, 85.7, 107.8, 153.1, 174.6; HRMS(CI) calcd for ($C_{17}H_{29}NO_3Si$ + H) ([M + H]$^+$) 324.1995, found 324.2012.

**Nicholas Adduct *ent*-24a.** Following method B, above, a solution of 1.87 g (10.1 mmol, 1.0 equiv) of (*R*)-4-isopropyl-*N*-propionyl-2-oxazolidone (*ent*-**22**) in 33 mL of $CH_2Cl_2$, 1.74 mL of *i*-$Pr_2NEt$, 10.1 and 10.1 mL (1.0 and 1.0 equiv) of 1.0 M $Bu_2BOTf/CH_2Cl_2$, a solution of 4.60 g (1.0 equiv) of the cobalt complexed alkyne *ent*-**23a** in 27 mL of $CH_2Cl_2$, and 60 mL of acetone with excess CAN gave 2.61 g (80%) of adduct *ent*-**24a** as a light yellow oil: $[\alpha]^{25}_D$ −26.0° (*c* = 30.6, MeOH); IR and $^1$H NMR are identical to those of adduct **24a**.

**Nicholas Adduct 24b.** Following method A, above, a solution of 4.21 g (22.7 mmol, 2.0 equiv) of (*S*)-4-isopropyl-*N*-propionyl-2-oxazolidone (**22**) in 80 mL of $CH_2Cl_2$, 3.93 mL of *i*-$Pr_2NEt$, 22.7 and 11.4 mL (2.0 and 1.0 equiv) of 1.0 M $Bu_2BOTf/CH_2Cl_2$, a solution of 5.35 g (1.0 equiv) of the cobalt-complexed alkyne **23b** in 15 mL of $CH_2Cl_2$, and 50 mL of acetone with excess CAN gave 0.76 g (20%) of adduct **24b** as a white solid, mp 93.0−93.5 °C (hexanes, colorless needles): $[\alpha]^{25}_D$ +15.9° (*c* = 4.5, MeOH); MS *m*/*e* 337 ($M^+$), 322, 294, 208, 193, 165, 130, 123; IR ($CH_2Cl_2$) 2966, 2168, 1778, 1700, 1465, 1386, 1251, 1207 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.10 (s, 9H), 0.93 (m, 9H), 1.04 (d, $J$ = 7.0 Hz, 3H), 1.12 (d, $J$ = 7.5 Hz, 3H), 1.90 (m, 1H), 2.42 (m, 1H), 2.73 (dd, $J$ = 2.9, 10.8 Hz, 1H), 4.04 (m, 1H), 4.23 (m, 2H), 4.48 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 0.1, 14.6, 15.3, 16.1, 21.8, 26.6, 39.4, 42.3, 54.7, 78.4, 87.5, 105.6, 125.5, 128.6, 133.4, 152.4, 176.0. Anal. Calcd for $C_{18}H_{31}NO_3Si$: C, 64.05; H, 9.26; N, 4.15. Found: C, 63.85; H, 9.31; N, 4.09.

**Nicholas Adduct 24c.** Following method A, above, a solution of 8.89 g (48.0 mmol, 2.0 equiv) of (*S*)-4-isopropyl-*N*-propionyl-2-oxazolidone (**22**) in 180 mL of $CH_2Cl_2$, 8.28 mL of *i*-$Pr_2NEt$, 48.0 and 24.0 mL (2.0 and 1.0 equiv) of 1.0 M $Bu_2BOTf/CH_2Cl_2$, a solution of 13.5 g (1.0 equiv) of the cobalt-complexed alkyne **23c** in 45 mL of $CH_2Cl_2$, and 250 mL of acetone with excess CAN gave 9.56 g (93%) of adduct **24c** as a pale yellow oil: $[\alpha]^{25}_D$ −33.1° (*c* = 6.4, MeOH); MS *m*/*e* 370 ($M^+$ − 59), 294, 256, 245, 202, 165, 123, 91; IR ($CH_2Cl_2$) 3062, 2968, 2170, 1780, 1700, 1385, 1256, 1206, 1097 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.12 (s, 9H), 0.92 (d, $J$ = 7.5 Hz, 6H), 1.05 (d, $J$ = 6.8 Hz, 3H), 1.35 (d, $J$ = 6.2 Hz, 3H), 2.39 (m, 1H), 2.89 (dd, $J$ = 3.1, 10.3 Hz, 1H), 3.73 (m, 1H), 4.15−4.48 (m, 4H), 4.47 (d, $J$ = 12.2 Hz, 1H), 4.67 (d, $J$ = 12.2 Hz, 1H), 7.23−7.42 (m, 5H); $^{13}$C NMR ($CDCl_3$) $\delta$ 0.0, 15.0, 15.6, 17.0, 17.9, 28.4, 39.2, 41.0, 58.3, 62.9, 69.8, 72.0, 87.3, 105.5, 127.2, 127.4, 128.1, 138.5, 153.2, 175.5; HRMS(CI) calcd for ($C_{24}H_{35}NO_4Si$ + H) ([M + H]$^+$) 430.2415, found 430.2398.

**Nicholas Adduct *ent*-24c.** Following method B, above, a solution of 1.67 g (9.02 mmol, 1.0 equiv) of (*R*)-4-isopropyl-*N*-propionyl-2-oxazolidone (*ent*-**22**) in 30 mL of $CH_2Cl_2$, 1.55 mL of *i*-$Pr_2NEt$, 9.0 and 9.0 mL (1.0 and 1.0 equiv) of 1.0 M $Bu_2BOTf/CH_2Cl_2$, a solution of 5.07 g (1.0 equiv) of the cobalt complexed alkyne *ent*-**23c** in 25 mL of $CH_2Cl_2$, and 100 mL of acetone with excess CAN gave 3.04 g (78%) of the adduct *ent*-**24c** as a pale yellow oil: $[\alpha]^{25}_D$ +37.4° (*c* = 14.7, MeOH); IR and $^1$H NMR are identical to those of adduct **24c**.

**Nicholas Adduct 27c.** Following method A, above, a solution of 0.91 g (34.9 mmol, 2.0 equiv) of *N*-propionyl-2-oxazolidone (**26**) in 123 mL of $CH_2Cl_2$, 5.53 mL of *i*-$Pr_2NEt$, 34.9 and 17.5 mL (2.0 and 1.0 equiv) of 1.0 M $Bu_2BOTf/CH_2Cl_2$, a solution of 9.82 g (1.0 equiv) of the cobalt-complexed alkyne **23c** in 34 mL of $CH_2Cl_2$, and 250 mL of acetone with excess CAN gave 6.30 g (93%) of the adduct **27c** as a pale yellow oil: $[\alpha]^{25}_D$ −66.9° (*c* = 9.2, $CH_2Cl_2$); MS *m*/*e* 372 ($M^+$ − 15), 328, 256, 252, 192, 165, 160, 143, 123, 97, 91; IR ($CH_2Cl_2$) 3031, 2967, 2171, 1782, 1701, 1480, 1454, 1385, 1250, 1221, 1106, 1044 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.10 (s, 9H), 1.10 (d, $J$ = 6.9 Hz, 3H), 1.31 (d, $J$ = 6.3 Hz, 3H), 2.80 (dd, $J$ = 9.3 , 3.3 Hz, 1H), 3.77 (m, 2H), 3.92 (m, 1H), 4.13 (m, 1H), 4.28 (m, 2H), 4.39 (d, $J$ = 12.0 Hz, 1H), 4.62 (d, $J$ = 12.0 Hz, 1H), 7.31 (m, 5H); $^{13}$C NMR ($CDCl_3$) $\delta$ 0.0, 15.6, 17.0, 38.1, 42.4, 42.6, 61.5, 69.9, 73.0, 88.2, 104.8, 127.3, 127.4, 128.1, 138.6, 153.0, 175.7; HRMS(CI) calcd for ($C_{21}H_{29}NO_4Si$ + H) ([M + H]$^+$) 388.1944, found 388.1936.

**Nicholas Adduct *ent*-27c.** Following method A, above, a solution of 0.91 g (6.33 mmol, 2.0 equiv) of *N*-propionyl-2-oxazolidone (**26**) in 22 mL of $CH_2Cl_2$, 1.10 mL of *i*-$Pr_2NEt$, 6.33 and 3.16 mL (2.0 and 1.0 equiv) of 1.0 M $Bu_2BOTf/CH_2Cl_2$, a solution of 1.78 g (1.0 equiv) of the cobalt-complexed alkyne *ent*-**23c** in 6.3 mL of $CH_2Cl_2$, and 50 mL of acetone with excess CAN gave 1.01 g (83%) of the adduct *ent*-**27c** as a pale yellow

oil: $[\alpha]^{25}_D$ +63.5° ($c$ = 17.1, $CH_2Cl_2$); $^1$HNMR and IR are identical to those of adduct **27c**.

**Nicholas Adducts 48*a* and 48*s*.** Following method A, above, a solution of 3.22 g (13.8 mmol, 2.0 equiv) of (*S*)-4-methyl-(*R*)-5-phenyl-*N*-propionyl-2-oxazolidone (*ent*-**18**) in 60 mL of $CH_2Cl_2$, 2.35 mL of *i*-$Pr_2NEt$, 13.8 and 6.90 mL (2.0 and 1.0 equiv) of 1.0 M $Bu_2BOTf/CH_2Cl_2$, a solution of 3.88 g (1.0 equiv) of the cobalt-complexed alkyne *ent*-**23c** in 15 mL of $CH_2Cl_2$, and 100 mL of acetone with excess CAN gave 2.68 g (81%) of adduct **48*a*** and 0.24 g (7%) of adduct **48*s***.

Analytical data for **48*a***: mp 96.5−97.0 °C (hexanes, colorless cotton-like crystals); $[\alpha]^{25}_D$ −27.6° ($c$ = 3.5, MeOH); IR ($CH_2Cl_2$) 3032, 2963, 2170, 1780, 1698, 1496, 1456, 1346, 1197, 1121 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.17 (s, 9H), 0.65 (d, $J$ = 6.7 Hz, 3H), 1.36 (d, $J$ = 6.5 Hz, 6H), 3.36 (dd, $J$ = 5.0, 9.5 Hz, 1H), 3.67 (quint, $J$ = 5.5 Hz, 1H), 4.20 (quint, $J$ = 8.0 Hz, 1H), 4.42 (d, $J$ = 12.5 Hz, 1H), 4.50 (d, $J$ = 12.5, 1H), 4.72 (quint, $J$ = 7.0 Hz, 1H), 6.62 (d, $J$ = 7.5 Hz, 1H), 7.22−7.42 (m, 10H). Anal. Calcd for $C_{28}H_{35}NO_4Si$: C, 70.41; H, 7.39; N, 2.93. Found: C, 70.48; H, 7.40; N, 2.89.

Analytical data for **48*s***: mp 117.0−117.5 °C (pentane, colorless cotton-like crystals); $[\alpha]^{25}_D$ +1.9° ($c$ = 13.3, $CH_2Cl_2$); IR ($CH_2Cl_2$) 3033, 2974, 2170, 1780, 1703, 1456, 1344, 1250, 1198, 1121 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.18 (s, 9H), 0.77 (d, $J$ = 6.6 Hz, 3H), 1.31 (d, $J$ = 7.0 Hz, 3H), 1.40 (d, $J$ = 6.1 Hz, 3H), 3.13 (t, $J$ = 7.2 Hz, 1H), 3.74 (quint, $J$ = 6.2 Hz, 1H), 4.15 (m, 1H), 4.49 (d, $J$ = 11.9 Hz, 1H), 4.57 (d, $J$ = 11.9, 1H), 4.80 (quint, $J$ = 6.7 Hz, 1H), 5.67 (d, $J$ = 7.6 Hz, 1H), 7.23−7.47 (m, 10H). Anal. Calcd for $C_{28}H_{35}NO_4Si$: C, 70.41; H, 7.39; N, 2.93. Found: C, 70.48; H, 7.42; N, 2.89.

**1-*O*-(*tert*-Butyldiphenylsilyl)-1,4-butanediol (35).** A solution of 6.0 g (66.6 mmol, 3.0 equiv) of 1,4-butanediol in 35 mL of THF was cooled to −78 °C under nitrogen, and the resulting white suspension was treated in dropwise fashion, with vigorous stirring, with 8.9 mL (22.2 mmol, 1.0 equiv) of 2.5 M *n*-butyllithium/hexanes. The reaction mixture became very viscous. After being stirred for additional 5 min, the reaction mixture was treated in dropwise fashion with 5.76 mL (22.2 mmol, 1.0 equiv) of TBDPSCl, and the resulting mixture was allowed to warm to rt to give a white suspension. After being stirred at rt for 40 min, the reaction mixture was treated with 35 mL of water and 35 mL of saturated aqueous $NH_4Cl$ solution, and the separated aqueous layer was extracted with 3 × 50 mL of diethyl ether. The combined organic extracts were dried ($MgSO_4$), filtered, concentrated under reduced pressure, and chromatographed (100:15 hexanes/EtOAc) to yield 6.58 g (90%) of **35** as a colorless oil: IR ($CH_2Cl_2$) 3616, 3436, 3048, 2933, 2859, 1472, 1427, 1390, 1267, 1111, 1056 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.06 (s, 9H), 1.67 (m, 4H), 3.68 (m, 4H), 7.37−7.69 (m, 10H).

**4-[(*tert*-Butyldiphenylsilyl)oxy]butyric Acid (36).** A solution of 5.70 g (17.4 mmol, 1.0 equiv) of **35** in 45 mL of DMF was cooled to 0 °C under nitrogen and was treated portionwise with 22.9 g (60.7 mmol, 3.5 equiv) of PDC. The resulting mixture was allowed to warm to rt and was stirred overnight (15 h). The reaction was then poured into a separatory funnel containing 320 mL of water and extracted with 5 × 180 mL of diethyl ether. The combined organic extracts were dried ($MgSO_4$), filtered, concentrated under reduced pressure, and chromatographed (100:5 hexanes/EtOAc and 75:25:0.3 hexanes/EtOAc/AcOH) to afford 4.43 g (75%) of **36** as a colorless oil: IR ($CH_2Cl_2$) 3288−2500, 1749, 1711, 1472, 1428, 1288, 1111 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.07 (s, 9H), 1.91 (quint, $J$ = 6.6 Hz, 2H), 2.53 (t, $J$ = 7.4 Hz, 2H), 3.73 (t, $J$ = 6.0 Hz, 2H), 7.36−7.69 (m, 10H); $^{13}$CNMR ($CDCl_3$) $\delta$ 19.2, 26.8, 27.5, 30.8, 62.8, 127.6, 129.6, 133.6, 135.5, 180.1.

**4-[(*tert*-Butyldiphenylsilyl)oxy]butyryl Chloride (37).** A solution of 4.77 g (13.9 mmol, 1.0 equiv) of **36** in 48 mL of benzene was treated with 6.9 mL (79.4 mmol, 5.7 equiv) of oxalyl chloride at rt, and the reaction was stirred at rt for 6 h. The solvent and excess oxalyl chloride were then removed under reduced pressure to afford a quantitative yield of acid chloride **37** as a pale yellow, unstable oil: IR ($CH_2Cl_2$) 3072, 2932, 1797, 1472, 1428, 1112 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.07 (s, 9H), 1.95 (quint, $J$ = 6.0 Hz, 2H), 3.07 (t, $J$ = 7.2 Hz, 2H), 3.70 (t, $J$ = 5.7 Hz, 2H), 7.38−7.68 (m, 10H).

**4(*S*)-Isopropyl-*N*-[4′-[(*tert*-butyldiphenylsilyl)oxy]-butyryl-2-oxazolidone (39).** A solution of 0.55 g (4.29 mmol, 1.0 equiv) of (*S*)-4-isopropyl-2-oxazolidone (**38**) in 55 mL of THF was cooled to −78 °C under nitrogen and was treated in dropwise fashion, with vigorous stirring, with 1.72 mL (1.0 equiv) of 2.5 M *n*-butyllithium/hexanes. After being stirred for an additional 10 min at −78 °C, the reaction was treated with a solution of 1.55 g (1.0 equiv) of acid chloride **37** in 10 mL of THF. The reaction mixture was then allowed to warm slowly to rt and was treated with 50 mL of saturated aqueous $NH_4Cl$ solution. The aqueous layer was extracted with 3 × 50 mL of diethyl ether, and the combined organic extracts were dried ($MgSO_4$), filtered, concentrated, and chromatographed (10:1 hexanes/EtOAc) to afford 1.74 g (89%) of **39** as a colorless oil: $[\alpha]^{25}_D$ +40.6° ($c$ = 8.4, $CH_2Cl_2$); MS $m/e$ 396 ($M^+ - CMe_3$), 324, 318, 310, 267, 224, 199, 181, 161, 135, 105; IR ($CH_2Cl_2$) 3072, 2963, 2932, 2859, 1780, 1702, 1472, 1428, 1387, 1302, 1208, 1112, 1022, 971, 909 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.83 (d, $J$ = 6.9 Hz, 3H), 0.87(d, $J$ = 7.2 Hz, 3H), 1.02 (s, 9H), 1.90 (quint, $J$ = 6.8 Hz, 2H), 2.33 (m, 1H), 3.03 (t, $J$ = 7.4 Hz, 2H), 3.70 (t, $J$ = 6.3 Hz, 2H), 4.18 (m, 2H), 4.37 (m, 1H), 7.32−7.65 (m, 10H). Anal. Calcd for $C_{26}H_{35}NO_4Si$: C, 68.84; H, 7.78; N, 3.09. Found: C, 68.67; H, 7.86; N, 2.95.

**4(*S*)-Methyl-5(*R*)-phenyl-*N*-[4′-[(*tert*-butyldiphenylsilyl)oxy]butyryl-2-oxazolidone (56).** A solution of 2.47 g (13.9 mmol, 1.0 equiv) of 4(*S*)-methyl-5(*R*)-phenyl-2-oxazolidone (**38b**) in 180 mL of THF was cooled to −78 °C under nitrogen and was treated in dropwise fashion, with vigorous stirring, with 5.60 mL (1.0 equiv) of 2.5 M *n*-butyllithium/hexanes. After being stirred for an additional 10 min at −78 °C, the reaction mixture was treated with a solution of 5.03 g (1.0 equiv) of acid chloride **37** in 30 mL of THF. The resulting light brown solution was stirred for 20 min at −78 °C, warmed to 0 °C, and stirred for 20 min at 0 °C. The reaction mixture was then treated with 50 mL of saturated aqueous $NH_4Cl$ and 10 mL of water, and the aqueous layer was extracted with 3 × 60 mL of diethyl ether. The combined organic extracts were dried ($MgSO_4$), filtered, concentrated, and chromatographed (silica gel; 100:5 hexanes/EtOAc) to afford 5.22 g (75%) of **56** as a colorless oil: $[\alpha]^{25}_D$ −17.8° ($c$ = 18.1, $CH_2Cl_2$); IR ($CH_2Cl_2$) 3071, 2932, 1781, 1703, 1472, 1428, 1348, 1198, 1111, 1032 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.88 (d, $J$ = 7.0 Hz, 3H), 1.08 (s, 9H), 1.96 (quint, $J$ = 7.0 Hz, 2H), 3.09 (t, $J$ = 7.4 Hz, 2H), 3.74 (t, $J$ = 6.2 Hz, 2H), 4.73 (quint, $J$ = 6.9 Hz, 1H), 5.62 (d, $J$ = 7.3 Hz, 1H), 7.28−7.69 (m, 15H); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.6, 19.2, 26.9, 27.0, 32.3, 54.7, 62.9, 78.8, 125.5, 127.6, 128.6, 129.5, 133.3, 133.7, 135.5, 152.9, 172.7.

**Nicholas Adduct 40.** A solution of 1.50 g (3.31 mmol, 2.0 equiv) of 4(*S*)-isopropyl-*N*-[4-[(*tert*-butyldiphenylsilyl)oxy]-butyryl]-2-oxazolidone (**39**) in 12 mL of anhydrous methylene chloride was cooled to 0 °C under nitrogen and was treated in dropwise fashion, with vigorous stirring, with 0.57 mL (3.31 mmol, 2.0 equiv) of freshly distilled *N*,*N*-diisopropylethylamine and 3.3 mL (3.30 mmol, 2.0 equiv) of a 1.0 M solution of dibutylboron triflate/methylene chloride. After being stirred for 15 min, the reaction mixture was cooled to −78 °C and treated with an additional 1.65 mL (1.65 mmol, 1.0 equiv) of 1.0 M dibutylboron triflate/methylene chloride. A solution of 0.75 g (1.65 mmol, 1.0 equiv) of the cobalt-complexed alkyne **23a** in 3.5 mL of methylene chloride was then added in dropwise fashion and with vigorous stirring. The resulting mixture was stirred for 5 min at −78 °C and was then warmed to 0 °C and stirred for 20 min at 0 °C. The reaction was then quenched with 15 mL of pH 7 buffer, and the aqueous layer was extracted with 3 × 15 mL of methylene chloride. The combined organic extracts were dried ($MgSO_4$), filtered, concentrated, and chromatographed (10:1 hexanes/EtOAc) to afford the desired cobalt-complexed product together with a small amount of excess oxazolidone **39**. The material thus obtained was dissolved in 50 mL of acetone and treated portionwise, at rt and with vigorous stirring, with ammonium cerium(IV) nitrate (CAN) until gas evolution ceased. The solvent was then concentrated under reduced pressure at rt, and the residue was partitioned between 20 mL of water and 20 mL of diethyl ether. The aqueous layer was extracted with 5 × 20 mL of diethyl ether, and the combined organic extracts

were dried ($MgSO_4$), filtered, concentrated, and chromatographed (10:1 hexanes/EtOAc) to give 859 mg (88%) of adduct **40** as a pale yellow oil: $[\alpha]^{25}_D$ +14.3° ($c$ = 2.9, $CH_2Cl_2$); IR ($CH_2Cl_2$) 3072, 2964, 2932, 2859, 2168, 1777, 1701, 1464, 1428, 1387, 1256, 1204, 1112, 845 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.12 (s, 9H), 0.88 (t, $J$ = 6.8 Hz, 3H), 1.03 (m, 15H), 1.19−1.54 (m, 2H), 1.96 (m, 1H), 2.07 (m, 1H), 2.33 (m, 1H), 2.76 (m, 1H), 3.66 (m, 2H), 4.01−4.14 (m, 2H), 4.23 (m, 1H), 4.33 (m, 1H), 7.33−7.68 (m, 10 H). Anal. Calcd for $C_{34}H_{49}NO_4Si_2$: C, 68.99; H, 8.34; N, 2.37. Found: C, 68.91; H, 8.36; N, 2.36.

**Nicholas Adduct 57.** A solution of 5.03 g (10.0 mmol, 2.0 equiv) of 4(*S*)-methyl-5(*R*)-phenyl-*N*-[4-[(*tert*-butyldiphenylsilyl)oxy]butyryl]-2-oxazolidone (**56**) in 35 mL of anhydrous methylene chloride was cooled to 0 °C under nitrogen and was treated in dropwise fashion, with vigorous stirring, with 1.74 mL (10.0 mmol, 2.0 equiv) of freshly distilled *N*,*N*-diisopropylethylamine and 10.0 mL (10.0 mmol, 2.0 equiv) of a 1.0 M solution of dibutylboron triflate/methylene chloride. After being stirred for 15 min, the reaction mixture was cooled to −78 °C and treated with an additional 5.00 mL (5.00 mmol, 1.0 equiv) of 1.0 M dibutylboron triflate/methylene chloride. A solution of 2.82 g (5.00 mmol, 1.0 equiv) of the cobalt-complexed alkyne *ent*-**23c** in 10.0 mL of methylene chloride was then added in dropwise fashion and with vigorous stirring. The resulting mixture was stirred for 5 min at −78 °C and was then warmed to 0 °C and stirred for 20 min at 0 °C. The reaction was then quenched with 65 mL of pH 7 buffer, and the aqueous layer was extracted with 3 × 55 mL of methylene chloride. The combined organic extracts were dried ($MgSO_4$), filtered, concentrated, and chromatographed (10:1 hexanes/EtOAc) to afford the desired cobalt complexed product together with a small amount of excess oxazolidone **56**. The material thus obtained was dissolved in 225 mL of acetone and treated portionwise, at rt and with vigorous stirring, with ammonium cerium(IV) nitrate (CAN) until gas evolution ceased. The solvent was then concentrated under reduced pressure at rt, and the residue was partitioned between 90 mL of water and 80 mL of diethyl ether. The aqueous layer was extracted with 5 × 80 mL of diethyl ether, and the combined organic extracts were dried ($MgSO_4$), filtered, concentrated, and chromatographed (10:1 hexanes/EtOAc) to give 2.97 g (79%) of adduct **57** as a pale yellow oil: $[\alpha]^{25}_D$ 0.00° ($c$ = 68.3, $CH_2Cl_2$); IR ($CH_2Cl_2$) 3055, 2935, 1781, 1704, 1348, 1198, 1112 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.17 (s, 9H), 0.64 (d, $J$ = 6.5 Hz, 3H), 1.09 (s, 9H), 1.42 (d, $J$ = 6.2 Hz, 3H), 2.21 (m, 2H), 3.35 (m, 1H), 3.69−3.88 (m, 3H), 4.37 (m, 1H), 4.46 (d, $J$ = 12.3 Hz, 1H), 4.52 (d, $J$ = 12.3 Hz, 1H), 4.53 (m, 1H), 5.16 (d, $J$ = 6.3 Hz, 1H), 7.13−7.73 (m, 20 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 0.1, 14.2, 16.6, 19.2, 27.0, 33.8, 39.3, 40.6, 54.7, 62.0, 70.5, 75.8, 78.3, 89.4, 104.8, 125.5, 127.2, 127.3, 127.5, 127.6, 128.1, 128.4, 129.6, 133.4, 133.7, 133.9, 135.5, 138.7, 152.4, 173.9. Anal. Calcd for $C_{45}H_{55}NO_5Si_2$: C, 72.44; H, 7.43; N,1.88. Found: C, 72.70; H, 7.47; N,1.84.

**General Procedure for the Preparation of Acetylenic Acids by Hydrolysis of *N*-Acyloxazolidones.** A solution of 10.9 mmol (1.0 equiv) of the *N*-acyloxazolidone in 120 mL of THF and 40 mL of water was cooled to 0 °C with stirring and was treated with 4.0 equiv of 30% aqueous hydrogen peroxide and 2.0 equiv of lithium hydroxide monohydrate. The reaction mixture was then allowed to warm to rt and was stirred overnight (12−17 h) before being cooled back to 0 °C and treated with 32 mL of a 1.5 N sodium sulfite solution. The resulting mixture was warmed to rt, and stirring was continued for 1 h. At the end of this period, the reaction was treated with 140 mL of a saturated aqueous sodium bicarbonate solution, and the THF was evaporated under reduced pressure. The remaining alkaline aqueous solution was then washed with 3 × 50 mL of methylene chloride and acidified to pH = 1−3 first with concd HCl and then with 5 N aqueous HCl. The resulting suspension was then extracted with 6 × 80 mL of ethyl acetate, and the combined extracts were dried ($MgSO_4$), filtered, concentrated under reduced pressure, and chromatographed (silica gel; 75:25:0.3 hexanes/EtOAc/HOAc) to afford the corresponding acetylenic acid.

**Acetylenic Acid 25a.** This material was prepared in 91% yield following the general procedure described above, employing 3.54 g (10.9 mmol, 1.0 equiv) of *N*-acyloxazolidone **24a** in 120 mL of THF and 40 mL of water, 4.96 g (4.0 equiv) of 30% aqueous hydrogen peroxide, 0.92 g (2.0 equiv) of lithium hydroxide monohydrate for 17 h, 32 mL of 1.5 N sodium sulfite, and 140 mL of saturated aqueous sodium bicarbonate. Chromatography (silica gel; 75:25:0.3 hexanes/EtOAc/HOAc) gave 1.40 g (91%) of **25a** as a colorless oil: $[\alpha]^{25}_D$ +11.7° ($c$ = 27.8, MeOH); MS $m/e$ 140 ($M^+$), 125, 111, 97, 83, 74, 67; IR ($CH_2Cl_2$) 3303, 3303−2428, 2115, 1748, 1711, 1463, 1416, 1288, 1233 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.06 (t, $J$ = 7.0 Hz, 3H), 1.27 (d, $J$ = 7.0 Hz, 3H), 1.46−1.63 (m, 2H), 2.14 (d, $J$ = 2.0 Hz, 1H), 2.63−2.74 (m, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 11.8, 13.5, 24.0, 35.9, 43.1, 70.8, 84.6, 181.1; HRMS(CI) calcd for ($C_8H_{12}O_2$ + H) ([M + H]$^+$) 141.0916, found 141.0925.

**Acetylenic Acid *ent*-25a.** This material was prepared in 91% yield following a procedure identical to that described above for acetylenic acid **25a**, employing 2.58 g (7.98 mmol, 1.0 equiv) of *N*-acyloxazolidone *ent*-**24a** in 87 mL of THF and 29 mL of water, 3.62 g (4.0 equiv) of 30% aqueous hydrogen peroxide, 0.67 g (2.0 equiv) of lithium hydroxide monohydrate for 16 h, 23 mL of 1.5 N sodium sulfite, and 102 mL of saturated aqueous sodium bicarbonate. Chromatography (silica gel; 75:25:0.3 hexanes/EtOAc/HOAc) gave 1.02 g (91%) of *ent*-**25a** as a colorless oil: $[\alpha]^{25}_D$ −11.5° ($c$ = 60.7, MeOH); IR and $^1H$ NMR are identical to those of acid **25a**.

**Acetylenic Acid 25b.** This material was prepared in 56% yield following the general procedure described above, employing 0.83 g (2.45 mmol, 1.0 equiv) of *N*-acyloxazolidone **24b** in 36 mL of THF and 12 mL of water, 1.11 g (4.0 equiv) of 30% aqueous hydrogen peroxide, 0.21 g (2.0 equiv) of lithium hydroxide monohydrate for 2.5 days, 7 mL of 1.5 N sodium sulfite, and 31 mL of saturated aqueous sodium bicarbonate. Chromatography (silica gel; 75:25:0.3 hexanes/EtOAc/HOAc) gave 0.21 g (56%) of **25b** as a white solid: mp 68.5−70.0 °C (hexanes, colorless needles); $[\alpha]^{25}_D$ −1.3° ($c$ = 45.8, MeOH); IR ($CH_2Cl_2$) 3303, 3303−2562, 1748, 1711, 1462 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.94 (d, $J$ = 6.6 Hz, 3H), 1.03 (d, $J$ = 6.6 Hz, 3H), 1.22 (d, $J$ = 7.0 Hz, 3H), 1.90 (m, 1H), 2.11 (d, $J$ = 2.4 Hz, 1H), 2.47 (m, 1H), 2.66 (m, 1H). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.11; H, 9.18.

**Acetylenic Acid 25c.** From *N*-acyloxazolidone **24c**: This material was prepared in 86% yield following the general procedure described above, employing 4.00 g (9.31 mmol, 1.0 equiv) of *N*-acyloxazolidone **24c** in 118 mL of THF and 39 mL of water, 4.22 g (4.0 equiv) of 30% aqueous hydrogen peroxide, 0.78 g (2.0 equiv) of lithium hydroxide monohydrate for 18 h, 27 mL of 1.5 N sodium sulfite, and 118 mL of saturated aqueous sodium bicarbonate. Chromatography (silica gel; 75:25:0.3 hexanes/EtOAc/HOAc) gave 1.97 g (86%) of **25c** as a white solid: mp 62.0−62.5 °C (8:1 hexanes/ether, colorless needles); $[\alpha]^{25}_D$ −31.6° ($c$ = 7.8, MeOH); MS $m/e$ 246 ($M^+$), 202, 140, 111, 91, 65; IR ($CH_2Cl_2$) 3303, 3302−2550, 1750, 1712, 1455, 1379, 1140, 1082 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.13 (d, $J$ = 7.0 Hz,3H), 1.37 (d, $J$ = 6.0 Hz, 3H), 2.20 (d, $J$ = 2.5 Hz, 1H), 2.66 (m, 1H), 2.84 (quint, $J$ = 7.5 Hz, 1H), 3.73 (m, 1H), 4.46 (d, $J$ = 12.0 Hz, 1H), 4.70 (d, $J$ = 12.0 Hz, 1H), 7.34 (m, 5H). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.22; H, 7.31.

From *N*-acyloxazolidone **27c**: 6.30 g (16.26 mmol, 1.0 equiv) of *N*-acyloxazolidone **27c** in 180 mL of THF and 60 mL of water, 7.38 g (4.0 equiv) of 30% aqueous hydrogen peroxide, 0.98 g (2.0 equiv) of lithium hydroxide monohydrate for 18 h, 47 mL of 1.5 N sodium sulfite, and 210 mL of saturated aqueous sodium bicarbonate gave 3.64 g (91%) of **25c** as a white solid, having identical physical and spectral properties as those described above: $[\alpha]^{25}_D$ −31.7° ($c$ = 5.5, MeOH).

**Acetylenic Acid *ent*-25c.** From *N*-acyloxazolidone *ent*-**24c**: This material was prepared in 79% yield following the general procedure described above, employing 2.36 g (5.49 mmol, 1.0 equiv) of *N*-acyloxazolidone *ent*-**24c** in 70 mL of THF and 23 mL of water, 2.49 g (4.0 equiv) of 30% aqueous hydrogen peroxide, 0.46 g (2.0 equiv) of lithium hydroxide monohydrate for 16 h, 16 mL of 1.5 N sodium sulfite, and 70 mL of saturated aqueous sodium bicarbonate. Chromatography (silica gel; 75:25:0.3 hexanes/EtOAc/HOAc) gave 1.06 g

(79%) of *ent*-**25c**: $[\alpha]^{25}_D$ +30.2° (*c* = 19.5, MeOH). Melting point, IR, and $^1$H NMR are identical to those of acid **25c**.

From *N*-acyloxazolidone *ent*-**27c**: 0.406 g (1.05 mmol, 1.0 equiv) of *N*-acyloxazolidone *ent*-**27c** in 12 mL of THF and 4 mL of water, 0.476 g (4.0 equiv) of 30% aqueous hydrogen peroxide, 0.088 g (2.0 equiv) of lithium hydroxide monohydrate for 16 h, 3 mL of 1.5 N sodium sulfite, and 13 mL of saturated aqueous sodium bicarbonate gave 0.242 g (94%) of *ent*-**25c**, having physical and spectral properties identical to those described above: $[\alpha]^{25}_D$ +28.2° (*c* = 14.9, MeOH).

**Acetylenic Acid 49*a*.** This material was prepared in 85% yield following the general procedure described above, employing 3.25 g (7.56 mmol, 1.0 equiv) of *N*-acyloxazolidone **48*a*** in 96 mL of THF and 32 mL of water, 3.43 g (4.0 equiv) of 30% aqueous hydrogen peroxide, 0.63 g (2.0 equiv) of lithium hydroxide monohydrate for 16 h, 22 mL of 1.5 N sodium sulfite, and 96 mL of saturated aqueous sodium bicarbonate. Chromatography (silica gel; 75:25:0.3 hexanes/EtOAc/HOAc) gave 1.43 g (85%) of **49*a*** as a pale yellow oil: $[\alpha]^{25}_D$ +4.1° (*c* = 25.8, MeOH); IR ($CH_2Cl_2$) 3303, 3303−2500, 1747, 1706, 1456, 1286, 1065 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.35 (d, *J* = 6.5 Hz, 3H), 1.41 (d, *J* = 7.0 Hz, 3H), 2.21 (d, *J* = 2.5 Hz,1H), 2.86 (m, 1H), 2.95 (m, 1H), 3.69 (m, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.50 (d, *J* = 11.5 Hz, 1H), 7.25−7.39 (m, 5H); $^{13}$CNMR ($CDCl_3$) $\delta$ 16.4, 17.3, 39.4, 40.7, 70.9, 72.9, 74.1, 81.4, 127.5, 127.7, 128.2, 138.1, 181.7; HRMS(CI) calcd for ($C_{15}H_{18}O_3$ + H) ([M + H]$^+$) 247.1335, found 247.1337.

**Acetylenic Acid 49*s*.** This material was prepared in 39% yield following the general procedure described above, employing 0.28 g (0.65 mmol, 1.0 equiv) of *N*-acyloxazolidone **48*s*** in 8.2 mL of THF and 2.7 mL of water, 0.30 g (4.0 equiv) of 30% aqueous hydrogen peroxide, 0.05 g (2.0 equiv) of lithium hydroxide monohydrate for 16 h, 1.9 mL of 1.5 N sodium sulfite, and 8.2 mL of saturated sodium bicarbonate. Chromatography (silica gel; 75:25:0.3 hexanes/EtOAc/HOAc) gave 62 mg (39%) of **49*s*** as a pale yellow oil: $[\alpha]^{25}_D$ −38.6° (*c* = 12.2, $CH_2Cl_2$); IR ($CH_2Cl_2$) 3303, 3303−2400, 1708, 1454, 1376, 1285, 1242, 1111 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.28 (d, *J* = 7.5 Hz, 3H), 1.39 (d, *J* = 6.5 Hz, 3H), 2.18 (d, *J* = 2.5 Hz, 1H), 2.85 (m, 1H), 3.02 (m, 1H), 3.79 (m, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.60 (d, *J* = 11.5 Hz, 1H), 7.25−7.36 (m, 5H); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.9, 18.0, 39.4, 42.1, 71.0, 72.2, 74.2, 82.0, 127.5, 127.9, 128.2, 137.9, 180.2.

**Acetylenic Acid 42.** A solution of 859 mg (1.45 mmol, 1.0 equiv) of *N*-acyloxazolidone **40** in 24 mL of THF, 24 mL of DMF, and 8 mL of water was cooled to 0 °C with stirring and was treated with 1.67 g (10.0 equiv) of 30% aqueous hydrogen peroxide and 304 mg (5.0 equiv) of lithium hydroxide monohydrate. The reaction mixture was then allowed to warm to rt and was stirred overnight (12 h) before being cooled back to 0 °C and treated with 11 mL of 1.5 N sodium sulfite solution. The reaction was then warmed to rt, stirred for an additional 1 h, acidified to pH = 3 with 5 N aqueous HCl, and extracted with 6 × 40 mL of ethyl acetate. The combined extracts were dried ($MgSO_4$), filtered, and concentrated at rt under high vacuum to remove DMF. The remaining residue was then dissolved in 14 mL of THF and 14 mL of water, and the resulting solution was treated with 304 mg (5.0 equiv) of lithium hydroxide monohydrate at rt for 1 day to complete cleavage of the TMS group. The reaction mixture was then diluted with 10 mL of water, acidified with 5 N aqueous HCl to pH = 3.5, and extracted with 6 × 30 mL of ethyl acetate. The combined organic extracts were dried ($Na_2SO_4$), filtered, concentrated under reduced pressure, and chromatographed (silica gel; 100:10:0.2 hexanes/EtOAc/HOAc) to afford 481 mg (81%) of acetylenic acid **42** as a pale yellow oil: $[\alpha]^{25}_D$ +12.4° (*c* = 13.4, $CH_2Cl_2$); MS *m*/*e* 199 (M$^+$ − 209), 181, 139, 135, 123, 105, 91, 77; IR ($CH_2Cl_2$) 3304, 3304−2400, 3056, 2964, 2934, 2860, 1747, 1709, 1473, 1428, 1391, 1112 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.05 (m, 12H), 1.55 (m, 2H), 1.88−2.10 (m, 2H), 2.11 (d, *J* = 2.4 Hz, 1H), 2.67 (m, 1H), 2.86 (m, 1H), 3.74 (t, *J* = 6.0 Hz, 2H), 7.33−7.69 (m, 10H); $^{13}$C NMR ($CDCl_3$) $\delta$ 12.0, 19.2, 24.9, 26.8, 31.7, 35.6, 45.2, 61.9, 71.1, 84.3, 127.7, 129.7, 133.6, 135.6, 179.4. Anal. Calcd for $C_{25}H_{32}O_3Si$: C, 73.49; H, 7.89. Found: C, 73.55; H, 7.94.

**Acetylenic Acid 59.** A solution of 2.16 g (2.89 mmol, 1.0 equiv) of *N*-acyloxazolidone **57** in 39 mL of THF, 39 mL of DMF, and 13 mL of water was cooled 0 °C with stirring and was treated with 2.63 g (8.0 equiv) of 30% aqueous hydrogen peroxide and 0.48 g (4.0 equiv) of lithium hydroxide monohydrate. The reaction mixture was then allowed to warm to rt and was stirred overnight (20 h) before being cooled back to 0 °C and treated with 17.5 mL of 1.5 N sodium sulfite solution. The reaction was then warmed to rt, stirred for an additional 1 h, diluted with 40 mL of water, acidified to pH = 2 with 5 N aqueous HCl, and extracted with 6 × 80 mL of ethyl acetate. The combined extracts were dried ($MgSO_4$), filtered, and concentrated at rt under high vacuum to remove DMF. The remaining residue was then dissolved in 27 mL of THF and 27 mL of water, and the resulting solution was treated with 0.73 g (6.0 equiv) of lithium hydroxide monohydrate at rt for two days to complete cleavage of the TMS group. The reaction mixture was then diluted with 40 mL of water, acidified with 5 N aqueous HCl to pH = 3.5, and extracted with 6 × 60 mL of ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered, concentrated under reduced pressure, and chromatographed (silica gel; 100:10:0.2 hexanes/EtOAc/HOAc) to afford 1.06 (74%) of acetylenic acid **59** as a pale yellow oil: $[\alpha]^{25}_D$ +9.6° (*c* = 25.7, $CH_2Cl_2$); IR ($CH_2Cl_2$) 3302, 3350−2413, 1746, 1706, 1472, 1428, 1144, 1112 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.05 (s, 9H), 1.35 (d, *J* = 6.1 Hz, 3H), 2.01 (m,1H), 2.17 (d, *J* = 2.4 Hz, 1H), 2.26 (m, 1H), 2.88 (m, 1H), 3.06 (m, 1H), 3.66 (m, 1H), 3.75 (m,1H), 4.45 (d, *J* = 11.8 Hz, 1H), 4.56 (d, *J* = 11.8 Hz, 1H), 7.21−7.70 (m, 15H); $^{13}$C NMR ($CDCl_3$) $\delta$ 17.5, 19.2, 26.8, 33.6, 40.4, 42.2, 61.9, 71.0, 73.1, 74.3, 81.5, 127.5, 127.6, 128.3, 129.6, 133.4, 133.5, 135.6, 138.2, 179.8; HRMS-(CI) calcd for ($C_{32}H_{38}O_4Si$ + H) ([M + H]$^+$) 515.2619, found 515.2642.

**General Procedures for the Curtius Rearrangement of Acetylenic Acids**. **Method A.** A solution consisting of 5.56 mmol (1.0 equiv) of the appropriate acetylenic acid in 32 mL of benzene was treated in dropwise fashion, and with vigorous stirring, with 1.0 equiv each of DPPA and triethylamine at rt under a nitrogen atmosphere. After addition was complete, the reaction mixture was heated at reflux for 3.5 h, and the solvent was evaporated under reduced pressure. The residue was taken up in 32 mL of *t*-BuOH containing 0.1 equiv of CuCl, and the resulting mixture was heated at reflux under nitrogen for 1−2 h before *t*-BuOH was removed under reduced pressure. The remaining residue was partitioned between 30 mL of diethyl ether and 25 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 3 × 30 mL of diethyl ether, and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure and chromatographed (silica gel; 20:1−50:1 hexanes/EtOAc) to give the corresponding acetylenic *N*-Boc-amine.

**Method B.** A solution consisting of 3.37 mmol (1.0 equiv) of the appropriate acetylenic acid in 19 mL of benzene or toluene was treated in dropwise fashion, and with vigorous stirring, with 1.0 equiv each of DPPA and triethylamine at rt under a nitrogen atmosphere. After addition was complete, the reaction mixture was heated at reflux for 3.5 h, and the solvent was evaporated under reduced pressure. The residue was taken up in 14 mL of methylene chloride containing 3.0 equiv of *t*-BuOH and 5% (v/v) of TMSCl, and the resulting mixture was stirred at rt under nitrogen for 10−36 h until reaction was complete (TLC). The reaction was then quenched by slow addition of 15 mL of saturated aqueous $NaHCO_3$. The mixture was then diluted with 20 mL of diethyl ether, and the separated aqueous layer was extracted with 3 × 15 mL of diethyl ether. The combined organic extracts were dried ($MgSO_4$), filtered, concentrated under reduced pressure, and chromatographed (silica gel; 20:1−50:1 hexanes/EtOAc) to give the corresponding acetylenic *N*-Boc-amine.

**Acetylenic Amine 28a.** This material was prepared in 82% yield following method A above, employing 779 mg (5.57 mmol, 1.0 equiv) of acetylenic acid **25a**, 1.20 mL (1.0 equiv) of DPPA, and 0.78 mL (1.0 equiv) of triethylamine in 32 mL of benzene for 3.5 h and 55 mg (0.1 equiv) of CuCl in 32 mL of *t*-BuOH for 1.25 h. Chromatography (silica gel; 20:1−50:1 hexanes/EtOAc) gave 963 mg (82%) of acetylenic amine **28a**

as a pale yellow solid: mp 46.0−47.0 °C (hexanes, colorless rectangular crystals); $[\alpha]^{25}_D$ +61.1° (*c* = 24.8, MeOH); MS *m*/*e* 155 ($M^+$ − 56), 144, 138, 126, 109, 96, 88, 67, 57; IR ($CH_2Cl_2$) 3429, 3302, 2974, 2112, 1708, 1503, 1455, 1367, 1232, 1164, 1095 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.99 (t, *J* = 7.0 Hz, 3H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.42 (s, 9H), 1.49 (m, 2H), 2.09 (d, *J* = 2.5 Hz, 1H), 2.28 (m, 1H), 3.79 (m, 1H), 4.64 (d, *J* = 10.0 Hz, 1H). Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.01; N, 6.63. Found: C, 68.12; H, 10.07; N, 6.60.

**Acetylenic Amine *ent*-28a.** This material was prepared in 74% yield following method A above, employing 673 mg (4.80 mmol, 1.0 equiv) of *ent*-**25a**, 1.04 mL (1.0 equiv) of DPPA, and 0.67 mL (1.0 equiv) of triethylamine in 27 mL of benzene for 3.5 h and 48 mg (0.1 equiv) of CuCl in 27 mL of *t*-BuOH for 1.25 h. Chromatography (silica gel; 20:1−50:1 hexanes/EtOAc) gave 748 mg (74%) of acetylenic amine *ent*-**28a** as a pale yellow solid: mp 46.0−47.0 °C (hexanes, colorless rectangular crystals); $[\alpha]^{25}_D$ −64.0° (*c* = 20.1, MeOH); IR and $^1H$ NMR are identical those of acetylenic amine **28a**.

**Acetylenic Amine 28b.** This material was prepared in 64% yield following method B above, employing 380 mg (2.46 mmol, 1.0 equiv) of acetylenic acid **25b**, 0.53 mL (1.0 equiv) of DPPA, and 0.34 mL (1.0 equiv) of triethylamine in 14 mL of benzene for 3.5 h and 0.70 mL (3.0 equiv) of *t*-BuOH in 9.7 mL of methylene chloride containing 5% (v/v) of TMSCl for 14 h. Chromatography (silica gel; 20:1−50:1 hexanes/EtOAc) gave 357 mg (64%) of acetylenic amine **28b** as a pale yellow oil: $[\alpha]^{25}_D$ +55.2° (*c* = 20.4, MeOH); IR ($CH_2Cl_2$) 3429, 3302, 2977, 1708, 1504, 1454, 1367, 1231, 1164, 1096, 1022 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.99 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.7 Hz, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.44 (S, 9H), 1.72 (m, 1H), 2.06 (m, 1H), 2.15 (d, *J* = 2.4 Hz. 1H), 3.97 (m, 1H), 4.69 (bs, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.5, 20.8, 21.1, 26.2, 29.6, 45.6, 45.8, 72.4, 78.8, 82.7, 155.0; HRMS(CI) calcd for ($C_{13}H_{23}NO_2$ + H) ([M + H]$^+$) 226.1807, found 226.1799.

**Acetylenic Amine 28c.** This material was prepared in 92% yield following method B above, employing 587 mg (2.38 mmol, 1.0 equiv) of acetylenic acid **25c**, 0.51 mL (1.0 equiv) of DPPA, and 0.33 mL (1.0 equiv) of triethylamine in 14 mL of benzene for 3.5 h and 0.68 mL (3.0 equiv) of *t*-BuOH in 9.5 mL of methylene chloride containing 5% (v/v) of TMSCl for 18 h. Chromatography (silica gel; 20:1−50:1 hexanes/EtOAc) gave 698 mg (92%) of acetylenic amine **28c** as a pale yellow solid: mp 58.0−58.5 °C (hexanes, colorless fluffy crystals); $[\alpha]^{25}_D$ +34.9° (*c* = 19.8, MeOH); MS *m*/*e* 261 ($M^+$ − 56), 244, 217, 183, 154, 144, 108, 91, 57; IR ($CH_2Cl_2$) 3429, 3302, 3033, 2979, 2174, 1708, 1491, 1188, 1175, 1100 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.22 (d, *J* = 6.5 Hz, 3H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.41 (s, 9H), 2.12 (d, *J* = 2.5 Hz, 1H), 2.51 (m, 1H), 3.60 (quint, *J* = 6.5 Hz, 1H), 3.94 (m, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.83 (d, *J* = 8.0 Hz, 1H), 7.31 (m, 5H). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.81; H, 8.61; N, 4.43.

**Acetylenic Amine *ent*-28c.** This material was prepared in 82% yield following method B above, employing 793 mg (3.22 mmol, 1.0 equiv) of acetylenic acid *ent*-**25c**, 0.69 mL (1.0 equiv) of DPPA, and 0.45 mL (1.0 equiv) of triethylamine in 18.5 mL of benzene for 3.5 h and 0.91 mL (3.0 equiv) of *t*-BuOH in 12.8 mL of methylene chloride containing 5% (v/v) of TMSCl for 18 h. Chromatography (silica gel; 20:1−50:1 hexanes/EtOAc) gave 838 mg (82%) of acetylenic amine *ent*-**28c** as a pale yellow solid: mp 58.0−58.5 °C (hexanes, colorless fluffy crystals); $[\alpha]^{25}_D$ −34.4° (*c* = 4.7, MeOH); IR and $^1H$ NMR are identical to those of acetylenic amine **28c**.

**Acetylenic Amine 50*a*.** This material was prepared in 81% yield following method B above, employing 390 mg (1.59 mmol, 1.0 equiv) of acetylenic acid **49*a***, 0.34 mL (1.0 equiv) of DPPA, and 0.22 mL (1.0 equiv) of triethylamine in 9.6 mL of toluene at 105 °C for 4.5 h and 0.45 mL (3.0 equiv) of *t*-BuOH in 6.4 mL of methylene chloride containing 5% (v/v) of TMSCl for 18 h. Chromatography (silica gel; 20:1−50:1 hexanes/EtOAc) gave 409 mg (81%) of acetylenic amine **50*a*** as a pale yellow solid: mp 54.5−55.0 °C (hexanes, colorless needles); $[\alpha]^{25}_D$ +12.8° (*c* = 15.0, MeOH); IR ($CH_2Cl_2$) 3430, 3302, 3050, 2980, 1708, 1501, 1367, 1266, 1165, 1052 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.22 (d, *J* = 6.7 Hz, 3H), 1.30 (d, *J* = 6.2 Hz, 3H), 1.44 (s, 9H), 2.18 (d, *J* = 2.5 Hz, 1H), 2.69 (m, 1H), 3.68 (quint, *J* = 6.2 Hz, 1H), 3.86 (m, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.99 (bs, 1H), 7.26−7.40 (m, 5H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 17.4, 18.0, 28.3, 44.1, 46.9, 70.9, 72.3, 73.9, 79.0, 81.7, 127.4, 127.7, 128.2, 138.1, 154.9. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.82; H, 8.63; N, 4.40.

**Acetylenic Amine 50*s*.** This material was prepared in 72% yield following method B above, employing 55.6 mg (0.23 mmol, 1.0 equiv) of acetylenic acid **49*s***, 0.049 mL (1.0 equiv) of DPPA, and 0.032 mL (1.0 equiv) of triethylamine in 1.4 mL of toluene at 100 °C for 4.5 h and 0.064 mL (3.0 equiv) of *t*-BuOH in 1 mL of methylene chloride containing 5% (v/v) of TMSCl for 11 h. Chromatography (silica gel; 20:1−50:1 hexanes/EtOAc) gave 51.5 mg (72%) of acetylenic amine **50*s*** as a pale yellow oil: IR ($CH_2Cl_2$) 3427, 3302, 3033, 2980, 2141, 1711, 1501, 1454, 1367, 1231, 1164, 1092, 1021 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.22 (d, *J* = 6.6 Hz, 3H), 1.36 (d, *J* = 6.1 Hz, 3H), 1.46 (s, 9H), 2.18 (d, *J* = 2.4 Hz, 1H), 2.59 (m, 1H), 3.55 (m, 1H), 4.33 (m, 1H), 4.46 (d, *J* = 10.6 Hz, 1H), 4.53 (d, *J* = 10.6 Hz, 1H), 4.86 (bd, J= 9.9 Hz, 1H), 7.24−7.45 (m, 5H); HRMS-(CI) calcd for ($C_{19}H_{27}NO_3$ + H) ([M + H]$^+$) 318.2069, found 318.2090.

**Acetylenic Amine 43.** This material was prepared in 83% yield following method B above, employing 481 mg (1.18 mmol, 1.0 equiv) of acetylenic acid **42**, 0.25 mL (1.0 equiv) of DPPA, and 0.17 mL (1.0 equiv) of triethylamine in 7.5 mL of toluene at 100 °C for 5 h and 1.7 mL (15.0 equiv) of *t*-BuOH in 4.5 mL of methylene chloride containing 5% (v/v) of TMSCl for 4 days. Chromatography (silica gel; 20:1−50:1 hexanes/EtOAc) gave 469 mg (83%) of acetylenic amine **43** as a colorless oil: $[\alpha]^{25}_D$ +28.1° (*c* = 6.3, $CH_2Cl_2$); MS *m*/*e* 225 ($M^+$ − 254), 211, 199, 197, 183, 181, 155, 135, 121, 105; IR ($CH_2Cl_2$) 3429, 3302, 3073, 2963, 2933, 2860, 2139, 1712, 1504, 1428, 1392, 1367, 1236, 1172, 1112 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.03 (t, *J* = 7.5 Hz, 3H), 1.06 (s, 9H), 1.43 (s, 9H), 1.57 (m, 2H), 1.59 (d, *J* = 1.5 Hz, 1H), 1.82 (m, 2H), 2.48 (m, 1H), 3.64−3.81 (m, 2H), 3.91 (m, 1H), 4.70 (d, *J* = 10.0 Hz, 1H), 7.34−7.70 (m, 10H). Anal. Calcd for $C_{29}H_{41}NO_3Si$: C, 72.61; H, 8.61; N, 2.92. Found: C, 72.44; H, 8.68; N, 3.20.

**Acetylenic Amine 60.** This material was prepared in 75% yield following method B above, employing 697 mg (1.35 mmol, 1.0 equiv) of acetylenic acid **59**, 0.29 mL (1.0 equiv) of DPPA, and 0.19 mL (1.0 equiv) of triethylamine in 8.4 mL of toluene at 100 °C for 4.5 h and 1.3 mL (10.0 equiv) of *t*-BuOH in 5.5 mL of methylene chloride containing 5% (v/v) of TMSCl for 16 h. Chromatography (silica gel; 20:1−50:1 hexanes/EtOAc) gave 597 mg (75%) of acetylenic amine **60** as a pale yellow oil: $[\alpha]^{25}_D$ +20.8° (*c* = 6.8, $CH_2Cl_2$); IR ($CH_2Cl_2$) 3427, 3302, 3072, 2931, 1711, 1501, 1366, 1172, 1112, 1067 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.08 (s, 9H), 1.32 (d, *J* = 6.1 Hz, 3H), 1.43 (s, 9H), 2.16 (d, *J* = 2.5 Hz, 1H), 2.82 (m, 1H), 3.71 (m, 2H), 3.80 (m, 1H), 3.98 (m, 1H), 4.51 (d, *J* = 11.7 Hz, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 5.13 (d, *J* = 8.7 Hz, 1H), 7.25−7.69 (m, 15H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 17.8, 19.2, 26.9, 28.4, 34.0, 43.2, 49.4, 61.3, 71.0, 72.3, 73.7, 78.9, 82.0, 127.5, 127.6, 127.9, 128.3, 129.6, 133.4, 133.5, 135.5, 138.4, 155.4; HRMS(CI) calcd for ($C_{36}H_{47}O_4Si$ + H) ([M$^+$ + H]) 586.3354, found 586.3339.

**General Procedures for the Oxidative Cleavage of the Acetylenic Bond**. **Method A.** A solution of 2.47 mmol (1.0 equiv) of the appropriate acetylenic *N*-Boc-amine in 58 mL of *t*-BuOH was treated in dropwise fashion, and with vigorous stirring, with a solution consisting of 0.3 equiv of $KMnO_4$, 6.0 equiv of $NaIO_4$, and 5.0 equiv of $NaHCO_3$ in 58 mL of water. After being stirred at rt for 3 h, the reaction mixture was treated with 8.1 mL of ethanol, and the resulting mixture was filtered through Celite and washed with 145 mL of 50% aqueous *t*-BuOH. The filtrate was concentrated to about 90 mL, acidified with 122 mL of 10% aqueous acetic acid, and extracted with 6 × 80 mL of ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was taken up in 50 mL of benzene. The benzene was concentrated again under reduced pressure to remove any traces of acetic acid. The remaining residue was dissolved in 8 mL of THF and 8 mL of 15% aqueous KOH and stirred at rt for 2.5 h to cleave any *N*-formyl substituent. The reaction

mixture was then acidified to pH = 2 with 5 N aqueous HCl and extracted with 6 × 35 mL of ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered, concentrated under reduced pressure, and chromatographed (silica gel; 75:25:0.3 hexanes/EtOAc/HOAc) to afford the corresponding carboxylic acid.

**Method B.** A solution of 2.10 mmol (1.0 equiv) of the appropriate acetylenic *N*-Boc-amine in 12 mL of THF and 12 mL of water was treated portionwise, with vigorous stirring, with 103 mg (0.2 equiv) of $OsO_4$ at rt to give a dark reaction mixture. After addition was complete (~5 min), the reaction was treated with 6.0 equiv of $NaIO_4$, and the mixture immediately turned light yellow in color. After the mixture was stirred for 3 days, an additional 1.5 equiv of $NaIO_4$ was added and stirring was continued until reaction was complete (TLC; 2−3 days). The reaction mixture was then diluted with 50 mL of water and extracted with 6 × 50 mL of ethyl acetate. The combined extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a dark sticky oil. This material was dissolved in 11 mL of THF and 2.4 mL of water and was treated with 1.0 equiv of $NaIO_4$ for 5 min to give a bright yellow solution. This solution was then treated with 10 mL of 15% aqueous KOH, and the resulting mixture was stirred at rt for 1.5 h to cleave the *N*-formyl substituent. The THF was then removed under reduced pressure, and the remaining aqueous solution was diluted with 24 mL of water, washed with 3 × 40 mL of methylene chloride, acidified to pH = 2 with 5 N aqueous HCl, and extracted with 6 × 40 mL of ethyl acetate. The combined extracts were dried ($MgSO_4$), filtered, concentrated under reduced pressure, and chromatographed (silica gel; 75:25:0.3 hexanes/EtOAc/HOAc) to afford the corresponding carboxylic acid.

***β*-Amino Acid 30a.** This material was prepared in 97% yield following method A above, employing 522 mg (2.47 mmol, 1.0 equiv) of acetylenic amine **28a** in 58 mL of *t*-BuOH, a solution consisting of 0.72 mmol (0.3 equiv) of $KMnO_4$, 14.7 mmol (6.0 equiv) of $NaIO_4$, and 12.2 mmol (5.0 equiv) of $NaHCO_3$ in 58 mL of water at rt for 3 h, and a solution of 8 mL of THF and 8 mL of 15% aqueous KOH at rt for 2.5 h. Chromatography (silica gel; 75:25:0.3 hexanes/EtOAc/HOAc) afforded 554 mg (97%) of *β*-amino acid **30a** as a white solid: mp 72.0−74.0 °C (hexanes, colorless fluffy crystals); $[\alpha]^{25}_D$ +12.7° (*c* = 2.7, MeOH); MS *m*/*e* 158 ($M^+ - 73$), 144, 116, 98, 88, 73, 57; IR ($CH_2Cl_2$) 3433, 3500−2350, 1706, 1504, 1368, 1165 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.98 (t, *J* = 7.4 Hz,3H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.44 (s, 9H), 1.61 (m, 1H), 1.71 (m, 1H), 2.41 (m, 1H), 3.97 (m, 1H), 5.20 (bd, *J* = 10.0 Hz, 1H). Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.16; H, 9.18; N, 6.08.

***β*-Amino Acid *ent*-30a.** This material was prepared in 92% yield following method A above, employing 722 mg (3.42 mmol, 1.0 equiv) of acetylenic amine *ent*-**28a** in 80 mL of *t*-BuOH, a solution consisting of 1.01 mmol (0.3 equiv) of $KMnO_4$, 20.3 mmol (6.0 equiv) of $NaIO_4$, and 16.9 mmol (5.0 equiv) of $NaHCO_3$ in 80 mL of water at rt for 2.5 h, and a solution of 12 mL of THF and 10 mL of 15% aqueous KOH at rt for 2 h. Chromatography (silica gel; 75:25:0.3 hexanes/EtOAc/HOAc) afforded 724 mg (92%) of *β*-amino acid *ent*-**30a** as a white solid: mp 72.0−74.0 °C (hexanes, colorless fluffy crystals); $[\alpha]^{25}_D$ −13.8° (*c* = 7.2, MeOH); IR and $^1$HNMR are identical to those of *β*-amino acid **30a**.

***β*-Amino Acid 30b.** This material was prepared in 86% yield following method A above, employing 348 mg (1.54 mmol, 1.0 equiv) of acetylenic amine **28b** in 37 mL of *t*-BuOH, a solution consisting of 0.46 mmol (0.3 equiv) of $KMnO_4$, 9.25 mmol (6.0 equiv) of $NaIO_4$, and 7.71 mmol (5.0 equiv) of $NaHCO_3$ in 37 mL of water at rt for 3 h, and a solution of 5 mL of THF and 5 mL of 15% aqueous KOH at rt for 2.5 h. Chromatography (silica gel; 75:25:0.3 hexanes/EtOAc/HOAc) afforded 326 mg (86%) of *β*-amino acid **30b** as a colorless oil: $[\alpha]^{25}_D$ +23.8° (*c* = 15.1, MeOH); IR ($CH_2Cl_2$) 3430, 3430−2425, 1703, 1504, 1368, 1234, 1166, 1098 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.90 (d, *J* = 6.4 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 1.36 (s, 9H), 1.90 (m, 1H), 2.05 (dd, *J* = 4.5, 10.0 Hz, 1H), 3.99 (m, 1H), 5.32 (d, *J* = 10.0 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.2, 20.5, 21.0, 28.0, 28.3, 44.4, 57.3, 79.3, 155.6, 179.7; HRMS(CI) calcd for ($C_{12}H_{23}NO_4$ + H) ([M + H]$^+$) 246.1706, found 246.1708.

***β*-Amino Acid 30c.** This material was prepared in 68% yield following method B above, employing 297 mg (0.94 mmol, 1.0 equiv) of acetylenic amine **28c** in 4 mL of THF and 4 mL of water, 52 mg (0.2 equiv) of $OsO_4$, and 2.20 g (11.0 equiv) of $NaIO_4$ for 6 days at rt. After cleavage, chromatography (silica gel; 75:25:0.3 hexanes/EtOAc/HOAc) afforded 215 mg (68%) of *β*-amino acid **30c** as a colorless oil: $[\alpha]^{25}_D$ +62.4° (*c* = 16.3, MeOH); IR ($CH_2Cl_2$) 3429, 3429−2538, 1707, 1502, 1368, 1163, 1088 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.20 (d, *J* = 6.7 Hz, 3H), 1.34 (d, *J* = 7.0 Hz, 3H), 1.44 (m, 9H), 2.60 (dd, *J* = 4.0, 9.0 Hz, 1H), 3.86 (m, 1H), 4.04 (m, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.64 (d, *J* = 11.5 Hz, 1H), 5.33 (d, *J* = 10.0 Hz, 1H), 7.30 (m, 5H); HRMS(CI) calcd for ($C_{18}H_{27}NO_5$ + H) ([M + H]$^+$) 338.1968, found 338.1986.

***β*-Amino Acid *ent*-30c.** This material was prepared in 68% yield following method B above, employing 665 mg (2.10 mmol, 1.0 equiv) of acetylenic amine *ent*-**28c** in 12 mL of THF and 12 mL of water, 103 mg (0.2 equiv) of $OsO_4$, and 4.93 g (11.0 equiv) of $NaIO_4$ for 6 days at rt. After cleavage, chromatography (silica gel; 75:25:0.3 hexanes/EtOAc/HOAc) afforded 482 mg (68%) of *β*-amino acid *ent*-**30c** as a colorless oil: $[\alpha]^{25}_D$ −64.7° (*c* = 12.8, MeOH); IR and $^1H$ NMR are identical to those of compound *β*-amino acid **30c**.

***β*-Amino Acid 51*a*.** This material was prepared in 71% yield following method B above, employing 696 mg (2.19 mmol, 1.0 equiv) of acetylenic amine **50*a*** in 12.5 mL of THF and 12.5 mL of water, 99 mg (0.2 equiv) of $OsO_4$, and 5.16 g (11.0 equiv) of $NaIO_4$ for 6 days at rt. After cleavage, chromatography (silica gel; 75:25:0.3 hexanes/EtOAc/HOAc) afforded 527 mg (71%) of *β*-amino acid **51*a*** as a white solid: mp 81.0−82.0 °C (15:1 hexanes/diethyl ether, colorless cotton-like crystals); $[\alpha]^{25}_D$ +14.7° (*c* = 19.8, MeOH); IR ($CH_2Cl_2$) 3431, 3431−2500, 1750, 1710, 1503, 1455, 1392, 1368, 1237 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.20 (d, *J* = 6.2 Hz, 3H), 1.34 (d, *J* = 5.1 Hz, 3H), 2.73 (m, 1H), 3.88 (m, 1H), 4.06 (m, 1H), 4.51 (d, *J* = 11.2 Hz, 1H), 4.66 (d, *J* = 11.2 Hz, 1H), 5.02 (d, *J* = 8.5 Hz, 1H), 7.23−7.45 (m, 5H). Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 64.10; H, 8.10; N, 4.12.

***β*-Amino Acid 51*s*.** This material was prepared in 57% yield following method B above, employing 49 mg (0.15 mmol, 1.0 equiv) of acetylenic amine **50*s*** in 1 mL of THF and 1 mL of water, 11 mg (0.3 equiv) of $OsO_4$, and 361 mg (11.0 equiv) of $NaIO_4$ for 6 days at rt. After cleavage, chromatography (silica gel; 75:25:0.3 hexanes/EtOAc/HOAc) afforded 29 mg (57%) of *β*-amino acid **51*s*** as a colorless oil: IR ($CH_2Cl_2$) 3430, 3430−2500, 1709, 1501, 1367, 1166, 1095, 1038 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.19 (d, *J* = 6.8 Hz,3H), 1.27 (d, *J* = 6.2 Hz, 3H), 1.44 (s, 9H), 2.64 (bd, *J* = 6.5 Hz, 1H), 3.88 (m, 1H), 4.33 (m, 1H), 4.45 (d, *J* = 10.8 Hz, 1H), 4.55 (d, *J* = 10.8 Hz, 1H), 5.57 (bs, 1H), 7.25−7.43 (m, 5H).

***β*-Amino Acid 44.** This material was prepared in 91% yield following method A above, employing 361 mg (0.75 mmol, 1.0 equiv) of acetylenic amine **43** in 19 mL of *t*-BuOH, a solution consisting of 0.22 mmol (0.3 equiv) of $KMnO_4$, 4.51 mmol (6.0 equiv) of $NaIO_4$, and 3.76 mmol (5.0 equiv) of $NaHCO_3$ in 19 mL of water at rt for 6 h, and a solution of 6 mL of THF and 3 mL of 15% aqueous KOH at rt for 2.5 h. Chromatography (silica gel; 75:25:0.3 hexanes/EtOAc/HOAc) afforded 342 mg (91%) of *β*-amino acid **44** as a colorless oil: $[\alpha]^{25}_D$ +7.5° (*c* = 5.1, $CH_2Cl_2$); IR ($CH_2Cl_2$) 3430, 3400−2500, 3073, 2969, 2932, 2857, 1707, 1504, 1468, 1392, 1367, 1242, 1170, 1111 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.00 (t, *J* = 7.4 Hz, 3H), 1.06 (s, 9H), 1.42 (s, 9H), 1.55−1.83 (m, 4H), 2.58 (m, 1H), 3.73 (m, 2H), 4.05 (m, 1H), 5.19 (d, *J* = 8.6 Hz, 1H), 7.35−7.70 (m, 10H); $^{13}C$NMR ($CDCl_3$) $\delta$ 12.1, 19.1, 22.6, 26.9, 28.4, 36.5, 48.5, 50.7, 61.1, 79.1, 127.7, 129.7, 133.5, 133.6, 135.3, 135.5, 155.7, 179.9. HRMS(FAB) calcd for ($C_{28}H_{41}NO_5Si$ + H) ([M + H]$^+$) 500.2832, found 500.2844.

***β*-Amino Acid 61.** This material was prepared in 71% yield following method B above, employing 410 mg (0.70 mmol, 1.0 equiv) of acetylenic amine **60** in 4.2 mL of THF and 4.2 mL of water, 37 mg (0.2 equiv) of $OsO_4$, and 1.65 g (11.0 equiv) of $NaIO_4$ for 6 days at rt. After cleavage, chromatography (silica gel; 75:25:0.3 hexanes/EtOAc/HOAc) afforded 302 mg (71%)

of β-amino acid **61** as a colorless oil: $[\alpha]^{25}_D$ −1.3° (*c* = 17.4, $CH_2Cl_2$); IR ($CH_2Cl_2$) 3430, 3500−2500, 1753, 1712, 1656, 1501, 1368, 1169, 1111 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.06 (s, 9H), 1.37 (d, *J* = 6.1 Hz, 3H), 1.44 (s, 9H), 1.69 (m, 1H), 1.84 (m, 1H), 2.85 (bt, *J* = 6.0 Hz, 1H), 3.68 (m, 1H), 3.80 (m, 1H), 3.92 (m, 1H), 4.21 (m, 1H), 4.52 (d, *J* = 10.9 Hz, 1H), 4.66 (d, *J* = 10.9 Hz, 1H), 5.23 (d, *J* = 8.8 Hz, 1H), 7.26−7.68 (m, 15); HRMS-(CI) calcd for ($C_{35}H_{47}NO_6Si$ + H) ([M + H]$^+$) 606.3252, found 606.3253.

**General Procedure for the Cyclization of β-Amino Acids.** A solution of 0.85 mmol (1.0 equiv) of the appropriate β-amino acid derivative in 16 mL of trifluoroacetic acid (TFA) was kept at 0 °C for 20 min under nitrogen to cleave the *t*-BOC protecting group. The reaction was then concentrated under reduced pressure, and the residue was concentrated once more from 30 mL of dry benzene to remove any remaining TFA. The resulting oil was dissolved in 60 mL of acetonitrile and was treated sequentially with 3.0 equiv of triethylamine and 2.2 equiv of dicyclohexylcarbodiimide (DCC) at rt. The reaction mixture was then stirred at 65−68 °C for 5 h, cooled to rt, and concentrated under reduced pressure. The residue was dissolved in a small amount of diethyl ether and filtered to remove suspended material (thorough washing with ether). The filtrate was then concentrated under reduced pressure and chromatographed (silica gel; 7:3 hexanes/EtOAc) to give the corresponding β-lactam.

***β*-Lactam 32a.** This material was prepared in 71% yield following the general procedure described above, employing 198 mg (0.85 mmol, 1.0 equiv) of β-amino acid derivative **30a**, 16 mL of trifluoroacetic acid, 60 mL of acetonitrile, 0.36 mL (3.0 equiv) of triethylamine, and 388 mg (2.2 equiv) of dicyclohexylcarbodiimide at 65−68 °C for 5 h. Chromatography (silica gel; 7:3 hexanes/EtOAc) afforded 68 mg (71%) of **32a** as a pale yellow oil: $[\alpha]^{25}_D$ +19.8° (*c* = 10.3, $CH_2Cl_2$); IR ($CH_2Cl_2$) 3408, 2968, 1754, 1462, 1382, 1272, 1181 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.96 (t, *J* = 7.4 Hz, 3H), 1.30 (d, *J* = 6.4 Hz, 3H), 1.61 (m, 1H), 1.74 (m, 1H), 2.61 (bt, *J* = 6.8 Hz, 1H), 3.40 (dq, *J* = 2.0, 6.1 Hz, 1H), 6.58 (bs, 1H); $^{13}C$ NMR ($CDCl_3$) δ 11.3, 20.6, 21.2, 50.2, 59.4, 171.3; HRMS(CI) calcd for ($C_6H_{11}$-NO + H) ([M + H]$^+$) 114.0920, found 114.0923.

***β*-Lactam *ent*-32a.** This material was prepared in 81% yield following the general procedure described above, employing 201 mg (0.87 mmol, 1.0 equiv) of β-amino acid derivative *ent*-**30a**, 16 mL of trifluoroacetic acid, 70 mL of acetonitrile, 0.36 mL (3.0 equiv) of triethylamine, and 361 mg (2.0 equiv) of dicyclohexylcarbodiimide at 65−68 °C for 5 h. Chromatography (silica gel; 7:3 hexanes/EtOAc) afforded 80 mg (81%) of *ent*-**32a** as a pale yellow oil: $[\alpha]^{25}_D$ −18.3° (*c* = 19.5, $CH_2Cl_2$); IR and $^1$HNMR are identical to those of β-lactam **32a**.

***β*-Lactam 32b.** This material was prepared in 82% yield following the general procedure described above, employing 320 mg (1.30 mmol, 1.0 equiv) of β-amino acid derivative **30b**, 25 mL of trifluoroacetic acid, 91 mL of acetonitrile, 0.55 mL (3.0 equiv) of triethylamine, and 592 mg (2.2 equiv) of dicyclohexylcarbodiimide at 65−68 °C for 5 h. Chromatography (silica gel; 7:3 hexanes/EtOAc) afforded 136 mg (82%) of **32b** as a pale yellow solid: mp 37.0−38.0 °C (diethyl ether, colorless cubes); $[\alpha]^{25}_D$ +11.3° (*c* = 23.0, $CH_2Cl_2$); IR ($CH_2Cl_2$) 3407, 2965, 1751, 1468, 1368, 1274, 1173, 1053 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.00 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 6.4 Hz, 3H), 1.36 (d, *J* = 6.3 Hz, 3H), 2.01 (octet, *J* = 7.0 Hz, 1H), 2.53 (bd, *J* = 8.2 Hz, 1H), 3.52 (dt, *J* = 1.4, 7.0 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 19.8, 20.1, 20.6, 27.6, 48.4, 64.7, 170.8. Anal. Calcd for $C_7H_{13}NO$: C, 66.11; H, 10.35; N, 11.01. Found: C, 66.26; H, 10.35; N, 10.93.

***β*-Lactam 32c.** This material was prepared in 76% yield following the general procedure described above, employing 448 mg (1.33 mmol, 1.0 equiv) of β-amino acid derivative **30c**, 25 mL of trifluoroacetic acid, 93 mL of acetonitrile, 0.56 mL (3.0 equiv) of triethylamine, and 603 mg (2.2 equiv) of dicyclohexylcarbodiimide at 65−68 °C for 5.5 h. Chromatography (silica gel; 7:3 hexanes/EtOAc) afforded 220 mg (76%) of **32c** as a pale yellow oil: $[\alpha]^{25}_D$ +35.5° (*c* = 19.8, $CH_2Cl_2$); MS *m*/*e* 176 ($M^+$ − 43), 161, 128, 113, 98, 91, 69; IR ($CH_2Cl_2$) 3408, 3033, 2974, 1759, 1375, 1186, 1099, 1055 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.30 (d, *J* = 6.5 Hz, 3H), 1.32 (d, *J* = 6.1 Hz, 3H), 2.97 (dd, *J* = 2.0, 5.0 Hz, 1H), 3.70 (dq, *J* = 2.0, 6.1 Hz, 1H), 3.85 (quint, *J* = 6.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 6.04 (bs, 1H), 7.24−7.32 (m, 5H); $^{13}C$ NMR ($CDCl_3$) δ 16.7, 20.3, 46.1, 62.6, 70.4, 71.1, 127.4, 128.1, 138.2, 168.6; HRMS(CI) calcd for ($C_{13}H_{17}NO_2$ + H) ([M + H]$^+$) 220.1338, found 220.1346.

***β*-Lactam *ent*-32c.** This material was prepared in 83% yield following the general procedure described above, employing 386 mg (1.14 mmol, 1.0 equiv) of β-amino acid derivative *ent*-**30c**, 21 mL of trifluoroacetic acid, 81 mL of acetonitrile, 0.48 mL (3.0 equiv) of triethylamine, and 520 mg (2.2 equiv) of dicyclohexylcarbodiimide at 65−68 °C for 5 h. Chromatography (silica gel; 7:3 hexanes/EtOAc) afforded 208 mg (83%) of *ent*-**32c** as a pale yellow oil: $[\alpha]^{25}_D$ −36.5° (*c* = 10.5, $CH_2Cl_2$); IR and $^1H$ NMR are identical to those of β-lactam **32c**.

***β*-Lactam 53.** This material was prepared in 61% yield following the general procedure described above, employing 53 mg (0.16 mmol, 1.0 equiv) of β-amino acid derivative **51**, 3 mL of trifluoroacetic acid, 22 mL of acetonitrile, 0.066 mL (3.0 equiv) of triethylamine, and 71 mg (2.2 equiv) of dicyclohexylcarbodiimide at 65−68 °C for 8 h. Chromatography (silica gel; 7:3 hexanes/EtOAc) afforded 21 mg (61%) of **53** as a pale yellow oil: $[\alpha]^{25}_D$ −56.8° (*c* = 11.4, $CH_2Cl_2$); IR ($CH_2Cl_2$) 3407, 3034, 2977, 1759, 1381, 1060 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.32 (d, *J* = 6.4 Hz, 3H), 1.36 (d, *J* = 6.3 Hz, 3H), 3.24 (m, 1H), 3.80 (m, 2H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.67 (d, *J* = 11.8 Hz, 1H), 6.39 (bs, 1H), 7.23−7.39 (m, 5H); $^{13}C$ NMR ($CDCl_3$) δ 16.2, 18.8, 47.2, 58.6, 70.2, 71.0, 127.3, 127.5, 128.2, 138.4, 168.8; HRMS-(CI) calcd for ($C_{13}H_{17}NO_2$ + H) ([M + H]$^+$) 220.1338, found 220.1342.

***β*-Lactam 54. Method A.** This material was prepared in 70% yield following the general procedure described above, employing 29 mg (0.09 mmol, 1.0 equiv) of β-amino acid derivative ***48s***, 1.6 mL of trifluoroacetic acid, 12 mL of acetonitrile, 0.036 mL (3.0 equiv) of triethylamine, and 38 mg (2.2 equiv) of dicyclohexylcarbodiimide at 65−68 °C for 5 h. Chromatography (silica gel; diethyl ether) afforded 13 mg (70%) of **54** having identical chemical and physical properties as described below in method B.

**Method B: Epimerization of *β*-Lactam 53.** A solution of 27 mg (0.12 mmol, 1.0 equiv) of β-lactam **53** in 0.5 mL of dry methylene chloride was stirred at rt under nitrogen and was treated with 0.052 mL (3.0 equiv) of triethylamine and 0.059 mL (2.5 equiv) of trimethylsilyl triflate. After the mixture was stirred for 3 h, the reaction was treated with 1 mL of 1 N aqueous hydrogen chloride and 0.5 mL of THF. The resulting mixture was stirred at rt for 1.5 h, diluted with 1 mL of water and 1 mL of saturated aqueous $NaHCO_3$, and extracted with 3 × 6 mL of methylene chloride and 6 mL of diethyl ether. The combined organic extracts were dried ($MgSO_4$), filtered, concentrated under reduced pressure, and chromatographed (silica gel; diethyl ether) to afford 20 mg (74%) of **54** as a pale yellow oil: $[\alpha]^{25}_D$ −26.4° (*c* = 7.7, $CH_2Cl_2$); IR ($CH_2Cl_2$) 3408, 3033, 2974, 1761, 1496, 1454, 1381, 1348, 1274, 1197, 1160, 1096, 1055 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.31 (d, *J* = 6.2 Hz, 3H), 1.38 (d, *J* = 6.2 Hz, 3H), 2.81 (dd, *J* = 2.0, 6.4 Hz, 1H), 3.73 (dq, *J* = 1.9, 6.1 Hz, 1H), 3.89 (quint, *J* = 6.3 Hz, 1H), 4.51 (d, *J* = 11.7 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 6.21 (bs, 1H), 7.25−7.36 (m, 5H); $^{13}$CNMR ($CDCl_3$) δ 18.1, 20.8, 48.0, 64.0, 70.6, 72.3, 127.5, 128.2, 138.4, 168.4; HRMS-(CI) calcd for ($C_{13}H_{17}NO_2$ + H) ([M + H]$^+$) 220.1338, found 220.1342.

***β*-Lactam 33.** This material was prepared in 91% yield following the general procedure described above, employing 213 mg (0.43 mmol, 1.0 equiv) of β-amino acid derivative **44**, 8.4 mL of trifluoroacetic acid, 30 mL of acetonitrile, 0.018 mL (3.0 equiv) of triethylamine, and 191 mg (2.2 equiv) of dicyclohexylcarbodiimide at 70 °C for 5 h. Chromatography (silica gel; 7:3 hexanes/EtOAc) afforded 147 mg (91%) of **33** as a colorless oil: $[\alpha]^{25}_D$ +11.8° (*c* = 6.6, $CH_2Cl_2$); MS *m*/*e* 281 ($M^+$ − 100), 254, 224, 199, 183, 181, 176, 135, 105, 77; IR ($CH_2Cl_2$) 3406, 3072, 2962, 2933, 2860, 1755, 1472, 1428, 1388, 1362, 1188, 1112 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.02 (m, 3H), 1.07 (s, 9H), 1.66−1.87 (m, 4H), 2.75 (m, 1H), 3.47 (m, 1H), 3.74 (m, 2H), 5.74 (bs, 1H), 7.38−7.68, (m, 10H); $^{13}C$ NMR ($CDCl_3$) δ 11.3, 19.1, 21.4, 26.9, 37.5, 52.7, 58.4, 61.9, 170.8.[19a]

***β*-Lactam 62.** This material was prepared in 56% yield following the general procedure described above, employing 153 mg (0.25 mmol, 1.0 equiv) of *β*-amino acid derivative **61**, 5 mL of trifluoroacetic acid, 35 mL of acetonitrile, 0.11 mL (3.0 equiv) of triethylamine, and 115 mg (2.2 equiv) of dicyclohexylcarbodiimide at 65−68 °C for 10 h. Chromatography (silica gel; 7:3 hexanes/EtOAc) afforded 68 mg (56%) of **62** as a pale yellow oil: $[\alpha]^{25}_D$ −24.6° ($c$ = 12.2, $CH_2Cl_2$); IR ($CH_2Cl_2$) 3406, 3071, 2932, 1758, 1389, 1112 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.04 (s, 9H), 1.37 (d, $J$ = 6.4 Hz, 3H), 1.81 (m, 1H), 2.02 (m, 1H), 3.27 (m, 1H), 3.70 (m, 2H), 3.80 (m, 2H), 4.43 (d, $J$ = 11.9 Hz, 1H), 4.65 (d, $J$ = 11.9 Hz, 1H), 5.87 (bs, 1H), 7.21−7.66 (m, 15H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 18.5, 19.1, 26.9, 32.8, 50.1, 58.7, 62.3, 70.0, 70.6, 127.3, 127.5, 127.7, 128.2, 128.4, 129.8, 133.1, 133.2, 135.4, 138.2, 168.3; HRMS(CI) calcd for ($C_{30}H_{37}NO_3Si$ + H) ($[M + H]^+$) 488.2622, found 488.2639.

***β*-Lactam 63.** A solution of 59 mg (0.12 mmol, 1.0 equiv) of *β*-lactam **62** in 0.5 mL of dry methylene chloride was stirred at rt under nitrogen and was treated with 0.05 mL (3.0 equiv) of triethylamine and 0.06 mL (2.5 equiv) of trimethylsilyl triflate. After the mixture was stirred for 3.5 h, the reaction was treated with 1 mL of 1 N aqueous hydrogen chloride and 0.5 mL of THF. The resulting mixture was stirred at rt for 1.5 h, diluted with 1 mL of water and 1 mL of saturated aqueous $NaHCO_3$, and extracted with 3 × 6 mL of methylene chloride and 6 mL of diethyl ether. The combined organic extracts were dried ($MgSO_4$), filtered, concentrated under reduced pressure, and chromatographed (silica gel; 1:1 hexanes/EtOAc) to afford 39 mg (66%) of **63** as a pale yellow oil: $[\alpha]^{25}_D$ −1.9° ($c$ = 6.3, $CH_2Cl_2$); IR ($CH_2Cl_2$) 3414, 3072, 2932, 1753, 1472, 1428, 1112 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.04 (s, 9H), 1.27 (d, $J$ = 6.2 Hz, 3H), 1.79 (m, 1H), 1.88 (m, 1H), 2.85 (dd, $J$ = 1.5, 5.9 Hz, 1H), 3.74 (m, 3H), 3.87 (quint, $J$ = 6.2 Hz, 1H), 4.48 (d, $J$ = 11.7 Hz, 1H), 4.61 (d, $J$ = 11.7 Hz, 1H), 5.78 (bs, 1H), 7.24−7.65 (m, 15H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 18.2, 19.1, 26.9, 37.5, 50.4, 62.0, 62.8, 70.7, 72.2, 127.5, 127.8, 128.3, 129.78, 129.82, 133.2, 135.4, 138.4, 168.2; HRMS(CI) calcd for ($C_{30}H_{37}NO_3Si$ + H) ($[M + H]^+$) 488.2622, found 488.2628.[12e,22]

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**Supporting Information Available:** Copies of $^1H$ and $^{13}C$ NMR spectra for compounds **24a**−**c**, **25a**−**c**, **27c**, **28a**−**c**, **30a**−**c**, **32a**−**c**, **33**, **39**, **40**, **42**, **43a**, **44**, **49*a***, **49*s***, **50*a***, **50*s***, **51*a***, **51*s***, **53**, **54, 56**, **57**, and **59**−**63** (31 pages). This material is contained in 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.

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