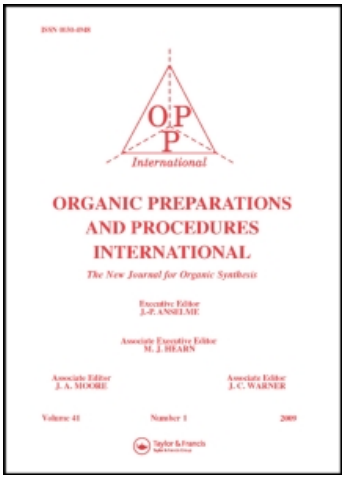

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INTRODUCTION

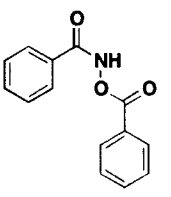
The utility of hydroxylamine as a reagent in organic chemistry for various transformations is well documented.[1-3] Its application in synthesis, however, is more limited primarily due to its amibident nature. In 1982, Marvin Miller stated the need for a hydroxylamine reagent bearing removable protecting groups which would afford the needed control.[4] The efforts of Miller, and others (*vida infra*), have now generated more than twelve distinct species of *bis*-protected hydroxylamine reagents. The impetus for these reagents is predominantly derived from their application to the synthesis of iron sequestering siderophores (macrocyclic polyhydroxamic acids that solubilize ferric ion from the environment) and 5-lipoxygenase inhibitors (N-hydroxyureas that act as antiinflamatory agents). Moreover, the ubiquitous presence of the nitrogen-oxygen bond as found in N-hydroxyamides (peptides and amino acids), N-hydroxyureas, N-hydroxyheterocycles, isoxazoles, oximes, and other functionality which incorporate the nitrogen-oxygen bond as a core structural unit,[5] all contribute to a variety of biological activity observed for these compounds (*e. g.* antibacterial, antitumor, antifungal, antiinflamatory, antistroke).[6-9]

In view of the above discussion and the emergence of recent publications describing *bis*-protected hydroxylamine reagents, it is the purpose herein to detail both the origin and distinction of *bis*-protected hydroxylamines reagents as applied to organic synthesis.

I. ALKYLATION STUDIES

1. N,O-*bis*(Benzoyl)hydroxylamine (1)

In 1964, Bachman and Goldmacher[10] described the conversion of benzoic acid into aniline upon being heated with nitromethane in polyphosphoric acid. O-Benzoylbenzhydroxamate **1**[11] was identified as an intermediate in a sequence shown to proceed through a Lossen rearrangement.[12] Their study showed that **1** could be induced to undergo Lossen rearrangement upon treatment with either acid or base in accordance with earlier observations.[13] Much attention has been devoted to the Lossen rearrangement of **1** including studies on rate,[14,15] solvent effects,[16,17] and the contribution of substituents.[18] Indeed, concern that reagents of this type could be employed without competitive Lossen rearrangement was mentioned as late as 1980.[19]

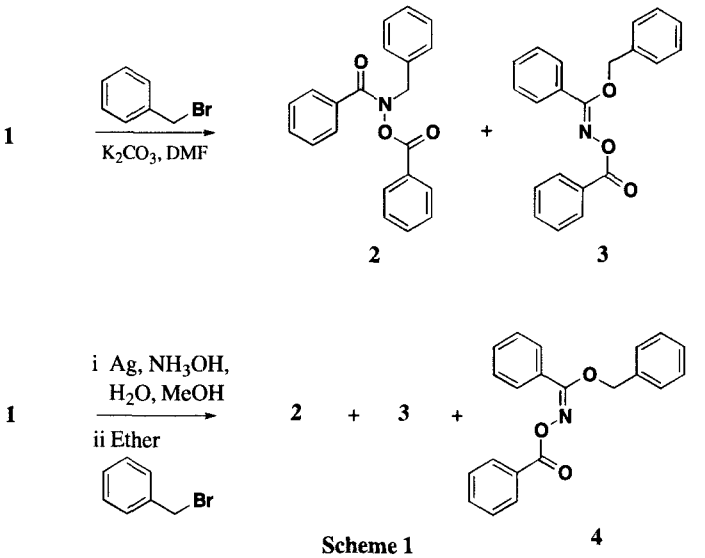


1

In a study on the alkylation of hydroxamates,[20] a mixture of benzoylbenzhydroxamate **1**,

benzyl bromide, and potassium carbonate were stirred together in DMF at 42° for 24 hrs (*Scheme 1*). Under these reaction conditions, an 88% yield of a mixture of N-alkylated product **2** and O-alkylated Z-hydroximate **3** were obtained in a ratio of 4:1, respectively. The tendency for O-alkylation is consistently observed for reagents that bear an acyl group on nitrogen. As will be seen below, O-alkylation is circumvented by use of "carbamate" type protecting groups on nitrogen, which have also been reported to suppress Lossen rearrangement for activated substrates.[21,22] While E-hydroximate **4** was not observed in this reaction, alkylation of the silver salt of **1** in anhydrous ether at room temperature over 3 days resulted in enhanced O-alkylation, and **4** was isolated in 32% yield after recrystallization.

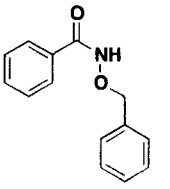
In addition to alkylation with alkyl halides, *bis*-protected hydroxylamine reagents participate readily in the Mitsunobu reaction.[23] Thus, admixture of **1** with triphenylphosphine and benzyl alcohol in THF prior to addition of diethyl azodicarboxylate (DEAD) at room temperature (25 hrs) was reported to give an 82% yield of a mixture favoring the N-alkylation product **2** by almost two to one.[19] The poorer ratio of N- to O-alkylation for the Mitsunobu reaction is a result that is generally observed for *bis*-protected reagents. When the same reaction was performed with methyl alcohol at 50°, a shorter reaction time (6 hrs) gave an 88% yield of N-methyl & O-methyl alkylation product mixture in a 4:1 ratio. A corrigendum, however, was later published which indicated that O-alkylation may have been the favored pathway for this example.[24]



Scheme 1

Benzoylbenzhydroxamate **1** has thus served as a starting point for *bis*-protected reagents from which much improvement has been achieved through the appropriate choice of protecting groups on nitrogen and oxygen.

2. N-Benzoyl-O-benzylhydroxylamine (5)

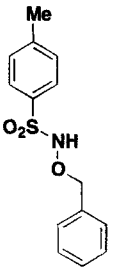


5

Replacement of the benzoyl group with a benzyl group on oxygen gives the hydroxylamine synthon **5**.[25-27] This protecting group, as will be seen below, is the most common oxygen protecting group observed in the literature for these reagents. The reason for this is due to its stability to a variety of reaction conditions and its ease of removal upon mild hydrogenolysis.

A hydrogenolysis study performed on **5** in 1973 revealed that N-acyl derivatives would undergo selective O-benzyl cleavage without competitive N-O cleavage as was observed for N-alkyl derivatives.[28] Although reagent **5** has not been employed in synthesis, the study cited exemplifies the utility of N-acyl derivatives to serve as latent hydroxamic acids in that hydrogenolysis of **5** leads directly to benzohydroxamic acid.

3. N-Tosyl-O-benzylhydroxylamine (6)

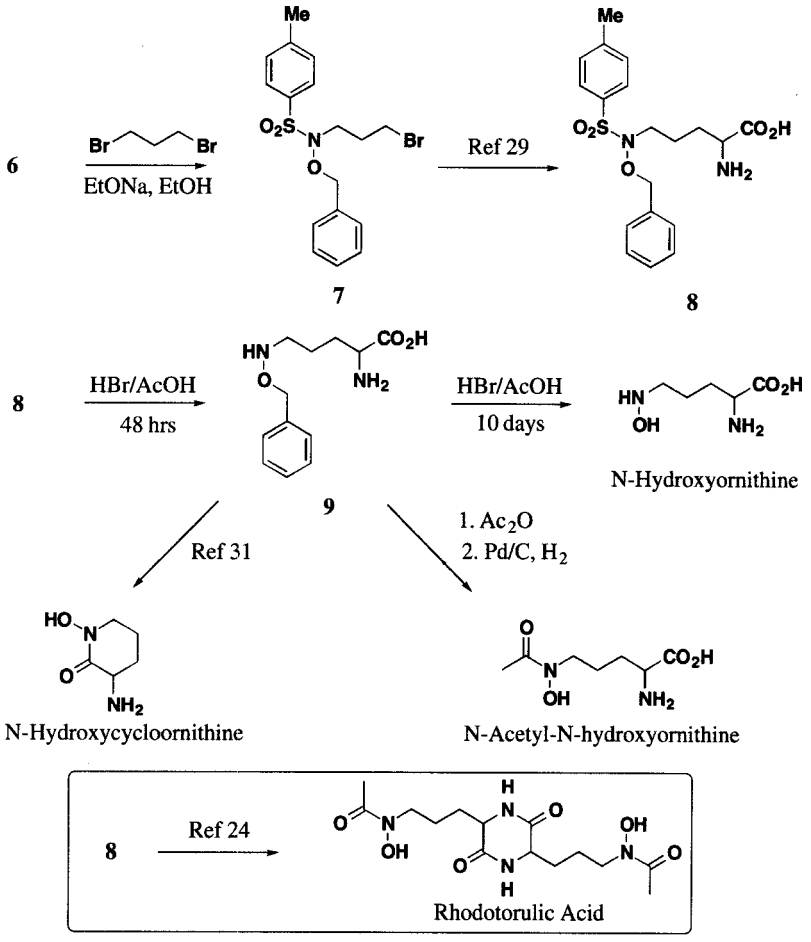


6

Between the years of 1972 to 1974, Isowa *et al.* published a series of papers which employed the N-tosyl reagent **6** which, not being an acyl derivative, does not suffer from O-alkylation. Dissolution of **6** in sodium ethoxide/ethanol at reflux on a one mole scale in the presence of 1,3-dibromopropane reacted to give an 88% yield (350g) of bromide **7** (*Scheme 2*).[29] Subsequent bromide displacement with diethyl sodioacetamidomalonate (70%) and hydrolysis in HCl/acetic acid at gentle reflux over 8 hrs gave the N-tosyl-N-benzyloxy ornithine derivative **8**.[30] Further hydrolysis, 36% HBr/acetic acid at room temperature, selectively cleaved the tosyl group to give **9**. The O-benzyl group was cleaved upon prolonged reaction time (10 days) to generate N-hydroxyornithine. Acylation and hydrogenation of **9** lead to the N-acetyl-N-hydroxyornithine, and further manipulation gave N-hydroxycycloornithine.[31] The utility of **8** was also demonstrated in the total synthesis of rhodotorulic acid, a siderophore first isolated from supernatants which were cultured from the red yeast *Rhodotorula pilimanae*.[32] Moreover, alkylation of **6** under the same conditions with 1,4-dibromobutane gave an 86% yield of bromide **10** (*Scheme 3*). This one carbon homolog gave rise to N-hydroxylysine upon subjection to the same synthetic sequence.[33]

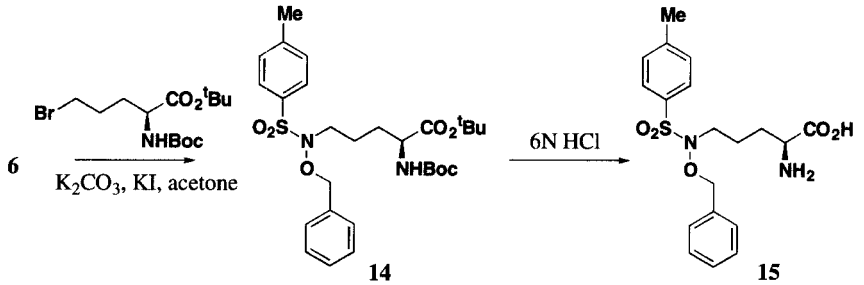
Reagent **6** was also employed in the synthesis of alanosine (*Scheme 3*),[34] where selective alkylation was observed at the terminal carbon of dibromide **11**. Hydrolysis and bromide displacement on **12** in concentrated ammonium hydroxide gave the N-tosyl amino acid in 75% overall yield which upon further manipulation lead to the antimicrobial agent alanosine.

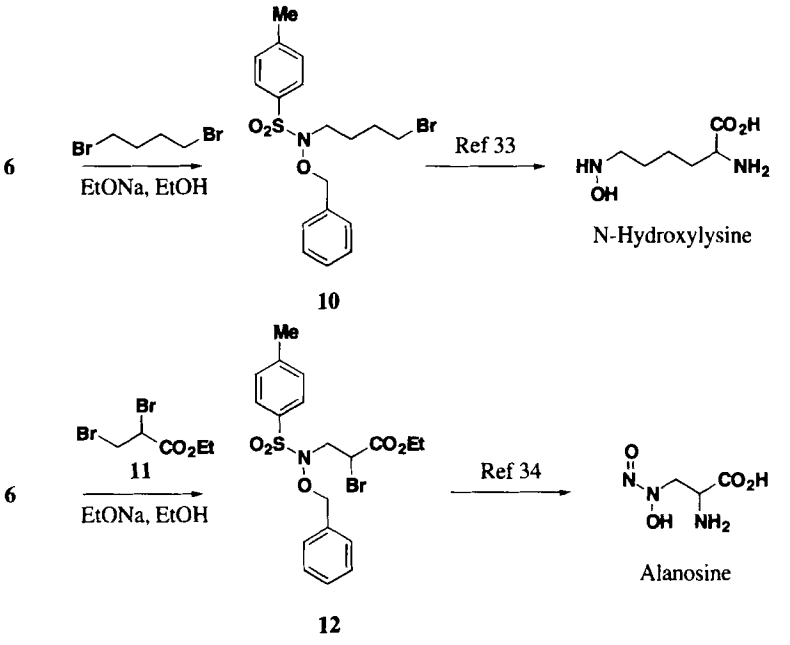
About ten years after the work of Isowa, bromide **7** was used to synthesize the semi-synthetic antibiotic FR-31564 (fosmidomycin) and some of its analogs.[35] Displacement of the bromide on **7** with a phosphinate followed by hydrolysis and formylation gave the antibiotic. Similarly, alkylation of **6** with ethylene dibromide in sodium methoxide/methanol at reflux was reported to give an 82% yield of **13** (100g scale) which was carried forward to the ethano homolog of FR-31564 (*Scheme 4*).



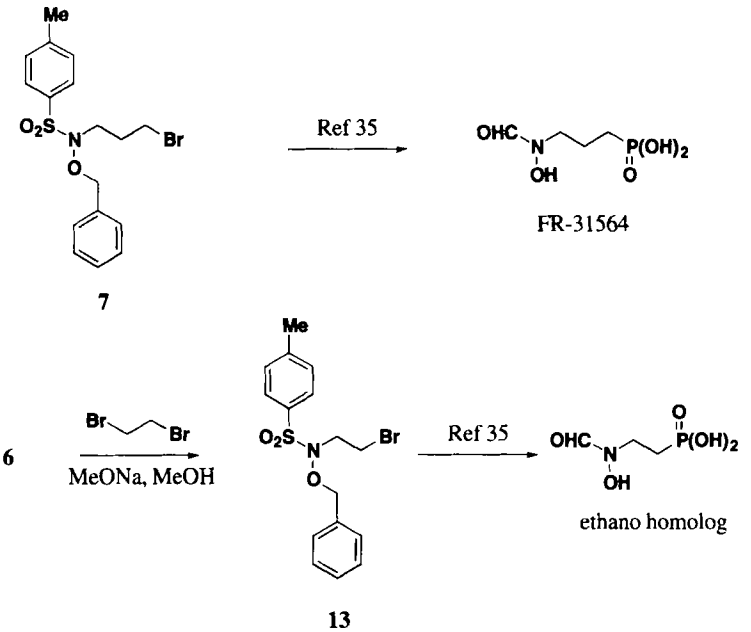
Scheme 2

The O-benzyl-N-tosylhydroxamate **14** was prepared upon alkylation of **6** with t-butyl 2-[(t-butoxy)carbonyl) amino]-5-bromopentanoate[36] when freshly dried potassium iodide was added to a solution of potassium carbonate/acetone at reflux (80%). Treatment with a biphasic solution of 6N HCl and ethyl acetate at room temperature selectively liberated the amino acid to afford ornithine derivative **15** with no loss in optical activity observed over the two step sequence.





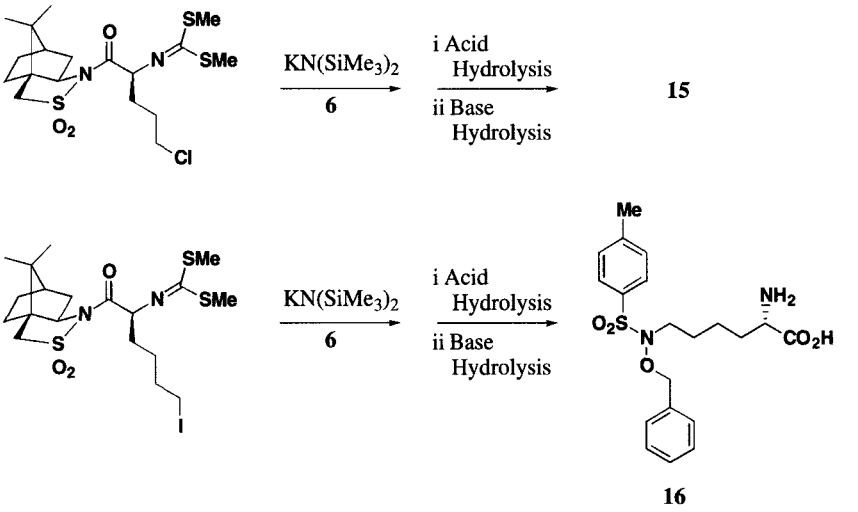
Scheme 3



Scheme 4

More recently, Oppolzer *et al.* has applied reagent **6** to the generation of optically active amino acids (Scheme 5). Reagent **6** was deprotonated with potassium hexamethyldisilazide and treated with the 3-chloro- and 4-iodo- chiral sultams.[37] Subjection of the alkylation products (93% and 83%

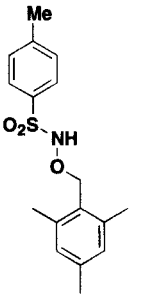
yields, respectively) to consecutive acidic and basic hydrolysis gave N-tosyl-O-benzyl ornithine **15** (93%) and lysine derivative **16** (94%) in good overall yields with high optical purity (97% - 99% ee).



Scheme 5

4. N-Tosyl-O-2,4,6-(trimethylbenzyl)hydroxylamine (17)

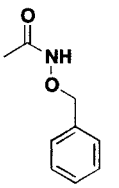
The 2,4,6-trimethylbenzyl analog **17** was reported by Isowa to afford simultaneous deprotection of both tosyl and O-benzyl groups under HBr/AcOH hydrolysis conditions (*Scheme 6*).[38] Thus, treatment of **17** with benzyl chloride in sodium methoxide/methanol at reflux gave a 78% yield of **18**. Hydrolysis in 36% HBr/acetic acid gave N-benzylhydroxylamine **19.** Alternatively, the trimethylbenzyl group could be selectively cleaved to give **20** in trifluoroacetic acid leaving the tosyl group intact. The 4-methoxybenzyl derivative **21** has also been reported to undergo facile acid hydrolysis in the preparation of mono alkylated hydroxylamines.[39]



17

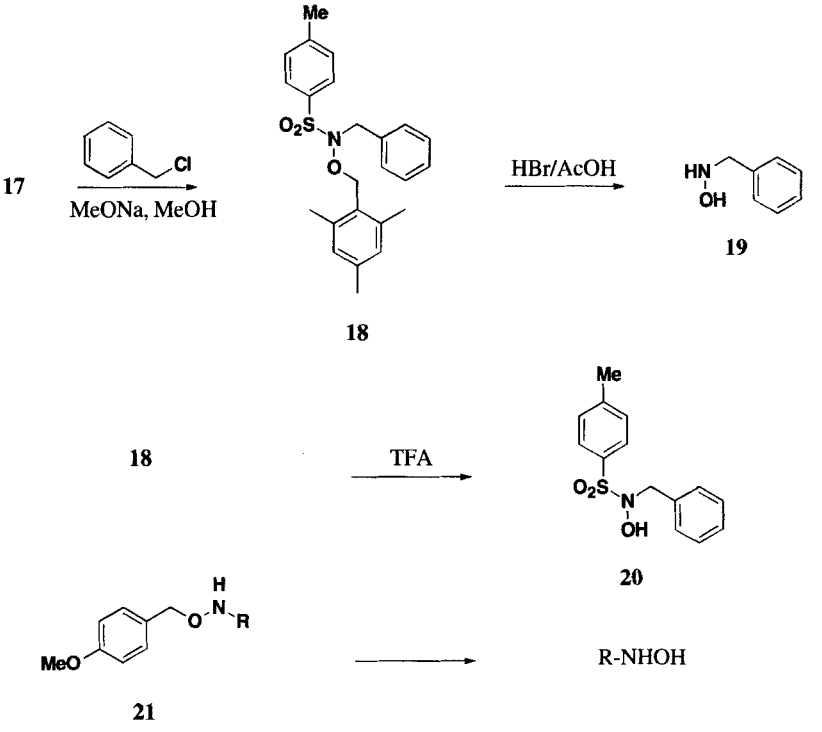
5. N-Acetyl-O-benzylhydroxylamine (22)

O-Benzyl acetohydroxamate **22**, first reported in 1893,[40] is another early example of a *bis*-protected hydroxylamine to be used as a reagent in synthesis.[11,41] As reported by Miller,[4] the advantage to the N-acetyl reagent is that natural products, often being N-acetyl derivatives, are secured directly without need for further manipulation at the end of a synthesis.

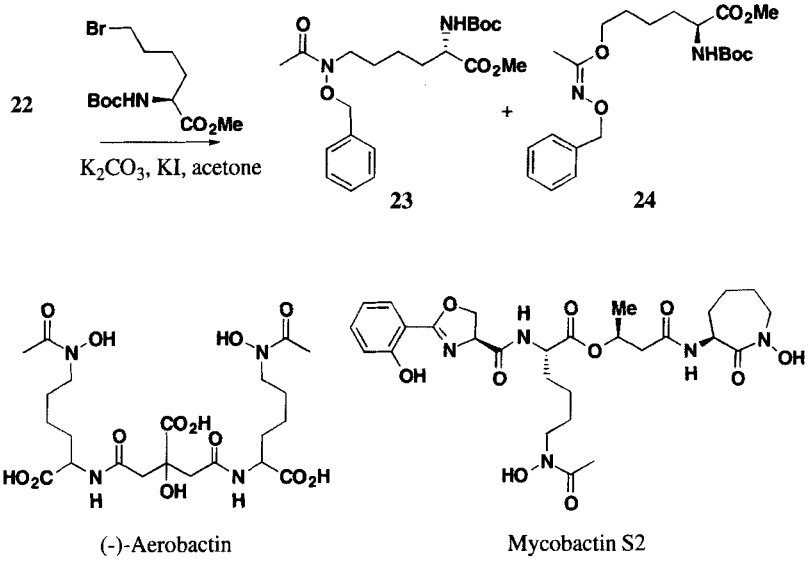


22

In the synthesis of (-)-aerobactin,[4] reagent **22** was stirred with potassium carbonate in anhydrous acetone at reflux for 24 hrs (*Scheme 7*), and exposed to (L)-N-Boc-ε-bromonorleucine methyl ester to give hydroxamate **23** in 66% yield after silica gel separation from E-hydroximate **24**. Addition of catalytic potassium iodide was reported to accelerate the reaction, however, purification proved more difficult due to formation of the Z-hydroximate



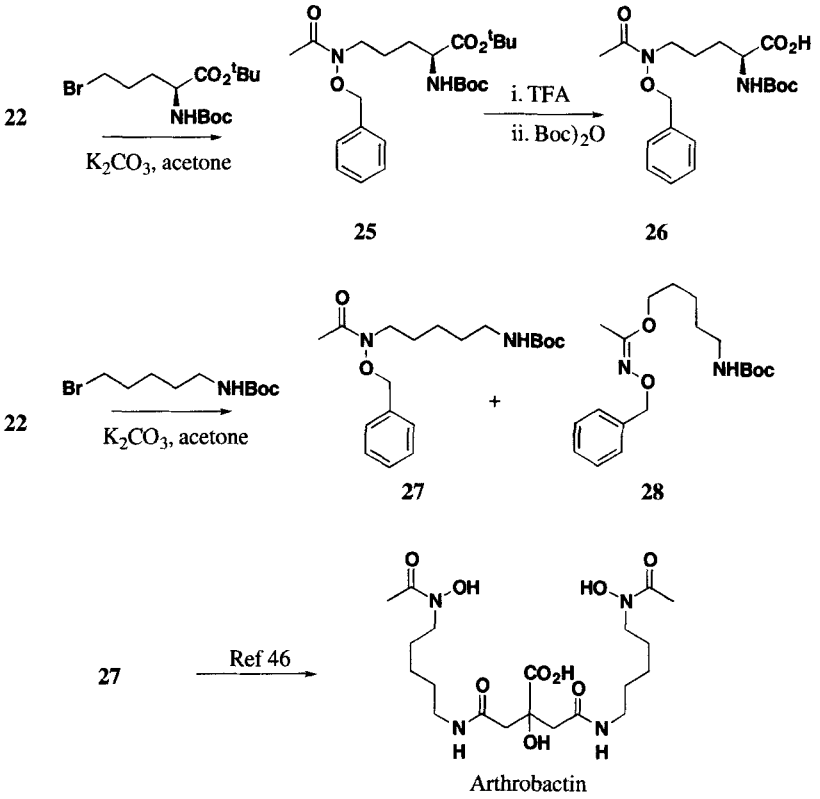
Scheme 6



Scheme 7

isomer. In addition to (-)-aerobactin, aceto derivative **23** was also carried forward in the total synthesis of mycobactin S2.[42]

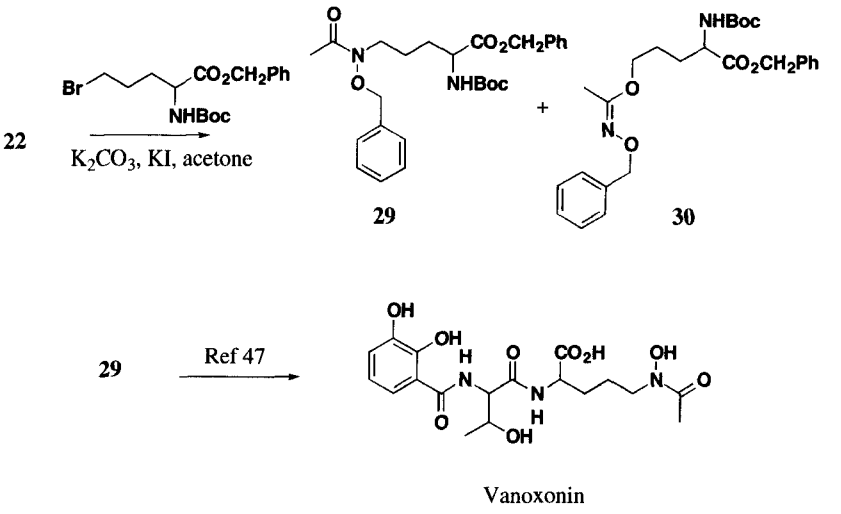
Alkylation of **22** with t-butyl 2-[(*tert*-butoxy)carbonyl)amino]-5-bromopentanoate[36] under the same reaction conditions gave N-alkylated product **25** in 60% isolated yield (*Scheme 8*). Addition of catalytic potassium iodide to the reaction offered no advantage and a lower yield (54%) was obtained even though the reaction time was reduced three fold. Selective deprotection of the carboxylic acid gave the protected N-hydroxyornithine derivative **26**; a precursor to the hydroxamate antibiotic ferrichrome.[43,44]



Scheme 8

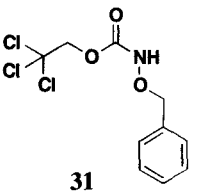
A similar result was obtained in the total synthesis of microbial iron chelator arthrobactin.[45] Alkylation of **22** in potassium carbonate/acetone was performed in the presence of catalytic potassium iodide (*Scheme 8*) with 5-[(*tert*-butoxycarbonyl)amino]-1-pentyl bromide and gave a 4:1 mixture in favor of hydroxamate **27** isolated in 62% yield.[46] Further elaboration over four additional steps yielded arthrobactin.

The thymidylate synthetase inhibitor, vanoxonin, also bears an aceto substituted hydroxylamine (*Scheme 9*).[47] Reagent **22** was admixed with L-(N-*tert*-butoxycarbonyl-δ-bromo)norvaline benzyl ester, potassium carbonate, and potassium iodide, in acetone at 60° for 13 hrs. Silica gel chromatography separated N-alkylation product **29** (44%) from the O-alkylation product **30** (9%). Removal of the Boc group followed by a coupling reaction and hydrogenolysis gave vanoxonin in 3 steps, 54% overall yield from **29**.

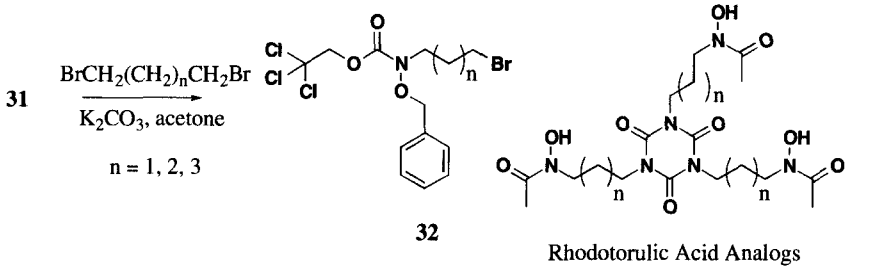


Scheme 9

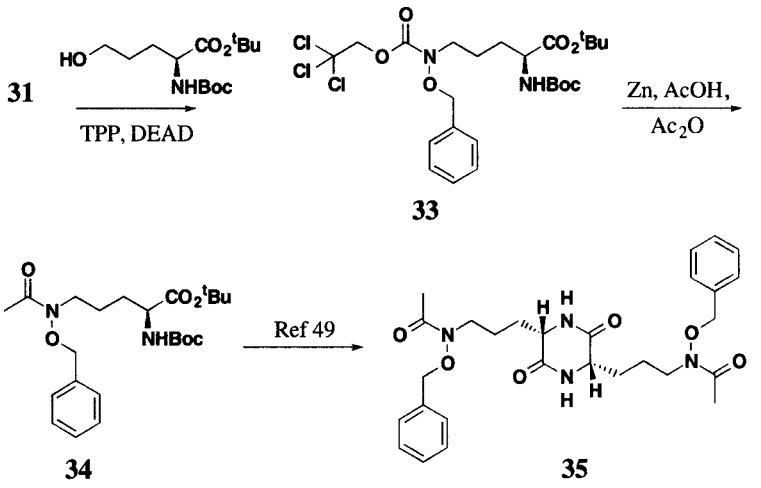
6. N-[(Trichloroethoxy)carbonyl]-O-benzylhydroxylamine (31)



In an effort to by-pass the need for chromatographic removal of O-alkylation products, the N-substituted trichloroethoxycarbonyl "Troc" reagent **31** was introduced as a suitable substrate for alkylation. As mentioned above, "carbamate" derivatives do not suffer from O-alkylation. Exposure of **31** to a series of dibromides ($BrCH_2(CH_2)_nCH_2Br$) where n = 1,2,3 gave the anticipated products with no evidence of hydroximate formation (*Scheme 10*).[48] Although a modest yield of N-alkylated product **32** (40% yield) was obtained with 1,4-dibromobutane under the reaction conditions of sodium hydride in dimethylformamide for 30 min, a better yield was secured in acetonitrile at reflux with one equivalent of DBU. Thus, a 60% yield was obtained for 1,3-dibromopropane (n = 1) and a 62% yield for 1,5-dibromopentane (n=3). Exposure of Troc derivative **32** to acetic acid solutions of zinc dust in the presence of acetic anhydride affected concomitant Troc removal and acetylation. Further elaboration lead to rhodotorulic acid analogs bearing an isocyanuric acid nucleus.

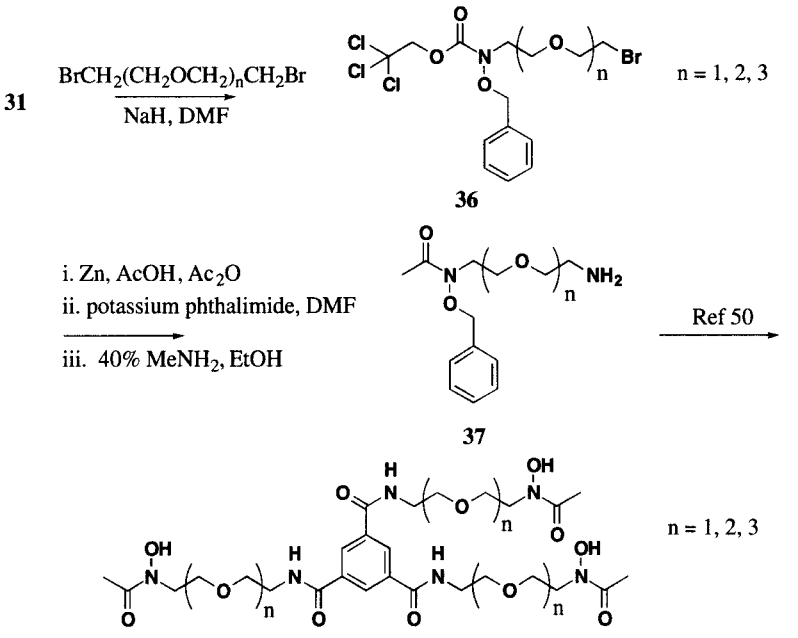


Scheme 10



Scheme 11

Reagent **31** was also applied in the total synthesis of rhodotorulic acid itself (*Scheme 11*).[49] Mitsunobu conditions (triphenylphosphine, DEAD, THF) in presence of L-N-Boc-δ-hydroxynorvaline *tert*-butyl ester converted **31** into N-alkylated hydroxamate **33** in 80% yield. Concomitant Troc removal and acetylation was accomplished without loss of the amino acid protecting groups, and **34** was obtained in 85% yield. Selective hydrolysis prior to coupling produced chiral nucleus **35**, and



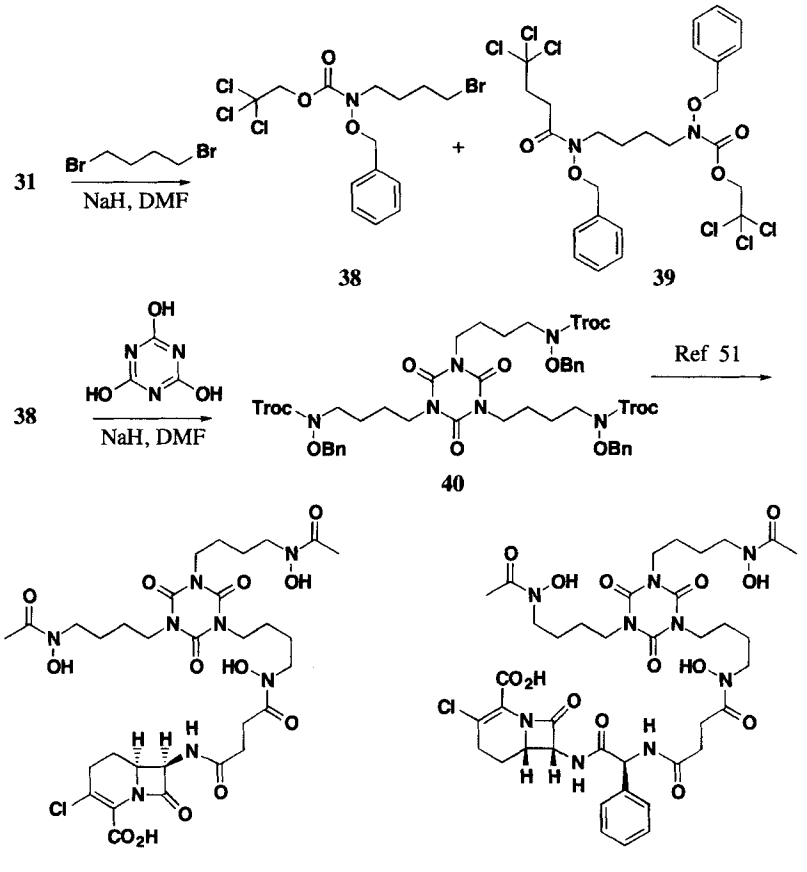
Rhodotorulic Acid Analogs

Scheme 12

hydrogenolysis gave rhodotorulic acid.

Analogs of rhodotorulic acid bearing a more lipophilic benzene nucleus, but with more oxygenated side arms have also been prepared as artificial siderophores (*Scheme 12*).[50] In this example, alkylation of Troc reagent **31** in NaH/DMF solution with oligo(ethyleneoxy)ethyl dibromides occurred in good yield (71%) and substrates **36** were isolated after chromatography. After acetylation as above, the pendant bromides were displaced with potassium phthalimide in DMF, and the primary amines were liberated upon treatment with methylamine in ethanol to produce **37**. These intermediates were coupled with benzenetricarboxylic acid chloride to give analogs of varying side arm length (n = 1,2,3).

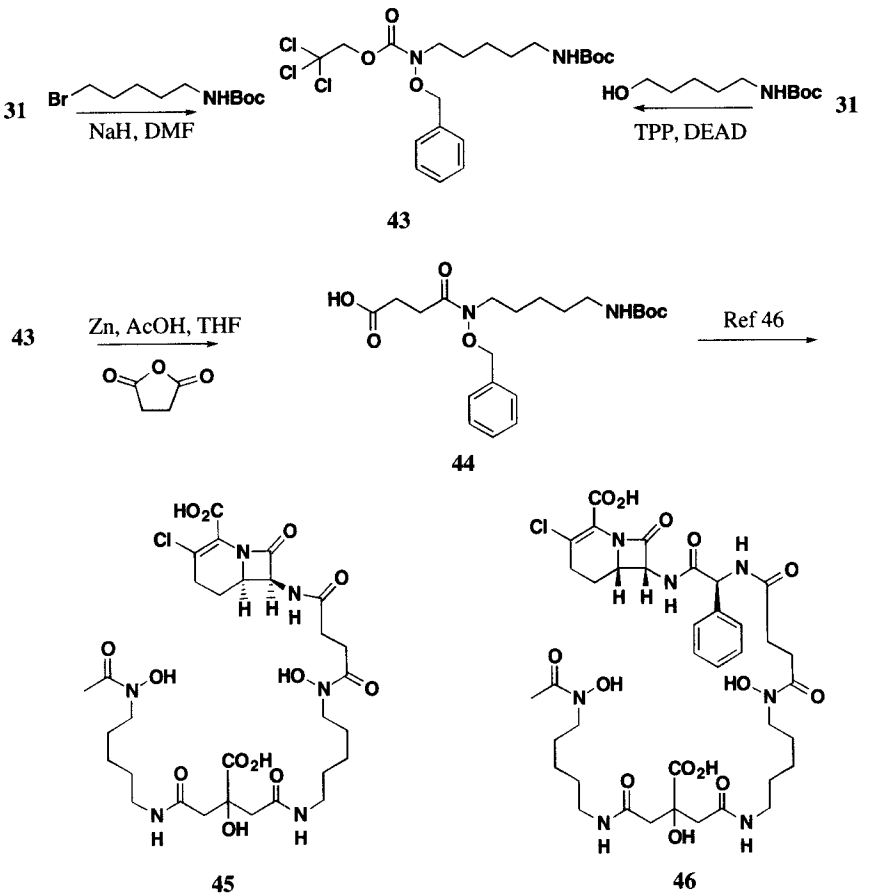
More recently, Troc reagent **31** was applied to the preparation of beta-lactam/siderophore conjugates. These conjugates were designed in view of active transport systems within bacteria which recognize and assimilate extracellular iron/siderophore complexes in the hope of identifying more effective antibiotics.[51] Alkylation of **31** with 1,4-dibromobutane in NaH and DMF gave **38** in 75% yield along with 10% of *bis*-alkylation product **39** (*Scheme 13*). This material was treated with



Scheme 13

isocyanuric acid to affect tris alkylation, and **40** was carried through to beta-lactam conjugates of rhodotorulic acid **41** and **42**.

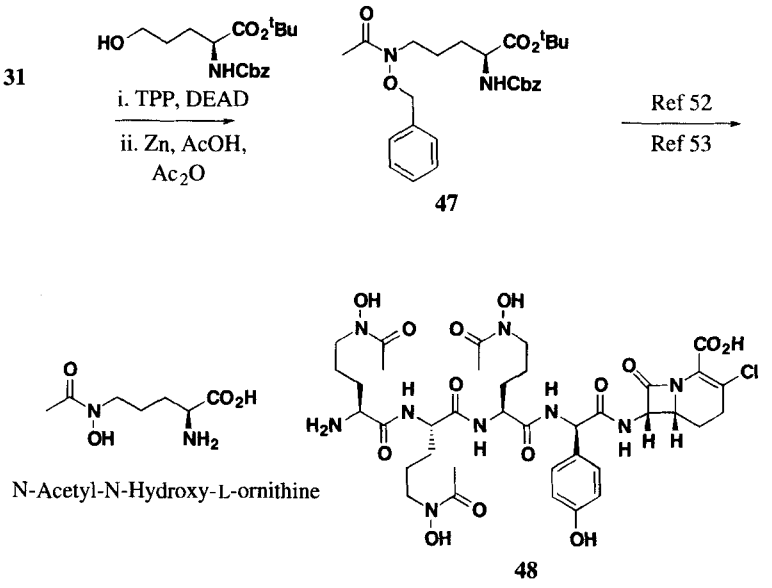
Conjugate formation with other siderophores has lead to products of arthrobactin as well. Alkylation of **31** in NaH/DMF with 5-[(*tert*-butoxy)carbonyl)amino]-1-pentyl bromide provided **43** in 80% yield (*Scheme 14*).[46] A more efficient access to **43** was gained through Mitsunobu mediated



Scheme 14

alkylation on the corresponding alcohol to give a 95% yield. Activated zinc treatment in the presence of succinic anhydride produced a near quantitative yield of carboxylic acid **44**. This acid was carried forward to arthrobactin and coupled to give **45** and **46**.

Albomycin, a polyhydroxamic acid siderophore containing a N-hydroxyornithine peptide backbone, has also been prepared as a conjugate from Troc reagent **31** (*Scheme 15*).[52,53] Mitsunobu alkylation with N-(benzyloxycarbonyl)-5-hydroxy-L-norvaline *tert*-butyl ester and subsequent exposure to zinc in acetic acid/acetic anhydride gave a 50% overall yield of N-acetyl derivative **47** (49g). The amino acid protecting groups remained intact under these conditions, and no racemization was



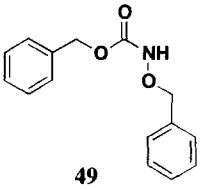
Scheme 15

observed at the chiral center. Conversion of **47** to N-acetyl-N-hydroxyornithine was accomplished in two steps, and conjugate **48** was synthesized as reported.

As seen in scheme 15, the multigram scale preparation of **47** without competitive O-alkylation, and the ability to affect protecting group removal in the presence of chiral centers illustrates improved utility of *bis*-protected hydroxylamine reagents over those described previously.

7. N-(Benzyloxycarbonyl)-O-benzylhydroxylamine (49)

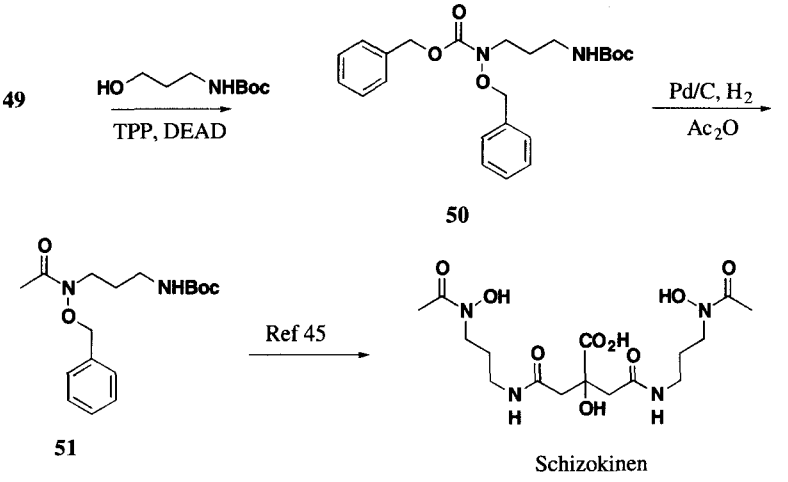
The O-benzyl-N-carbobenzyloxyhydroxamate **49** offers the same improvements seen in Troc reagent **31** of selective N-alkylation and ease of protecting group removal. Furthermore, while either nitrogen or oxygen protecting groups can be removed selectively as is true for **31**, reagent **49** also affords the option of simultaneously deprotecting both nitrogen and oxygen upon mild hydrogenolysis.



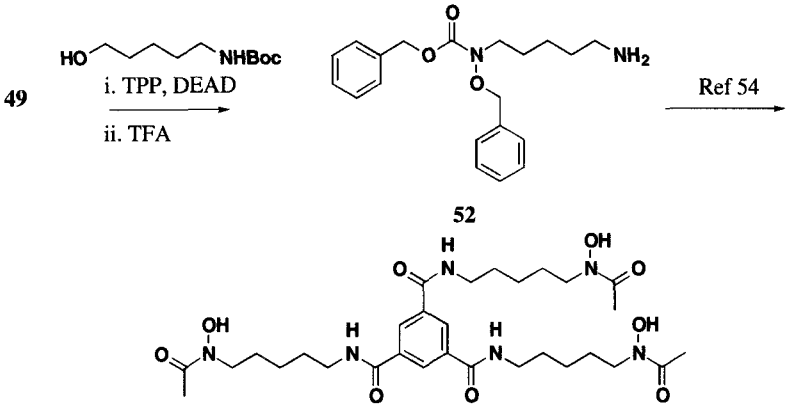
Mitsunobu alkylation of **49** with 3-[(*tert*-butoxycarbonyl)amino]-1-propanol gave N-alkylated hydroxamate **50** in 78% yield (*Scheme 16*).[45] This material was subjected to mild hydrogenolysis in the presence of acetic anhydride to generate the N-acetyl derivative **51** in a single step (65%). Compound **51** was carried forward in the total synthesis of schizokinen.

In the synthesis of an artificial siderophore,[54] reagent **49** was alkylated under Mitsunobu conditions with 5-[(*tert*-butoxy) carbonyl)amino]-1-pentanol (*Scheme 17*). Subsequent exposure to TFA provided primary amine **52** (70% overall) which was coupled with 1,3,5-benzenetricarboxylic acid chloride. Hydrogenolysis lead to a rhodotorulic acid artificial siderophore bearing an internal

benzene nucleus (44% yield over two steps).



Scheme 16

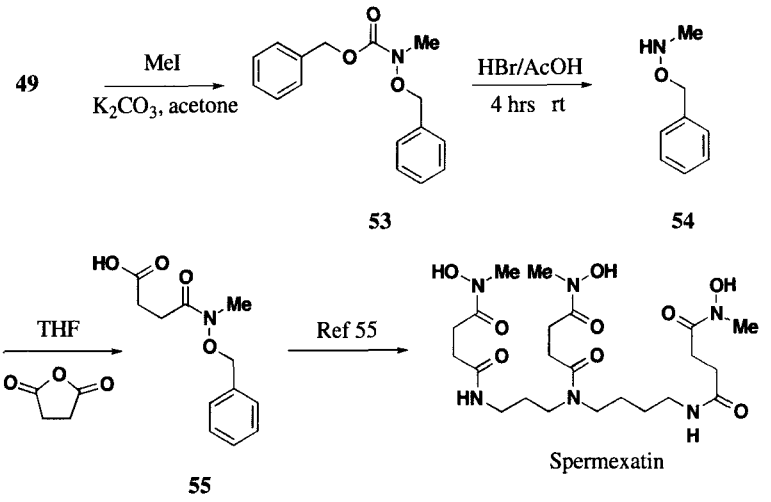


Scheme 17

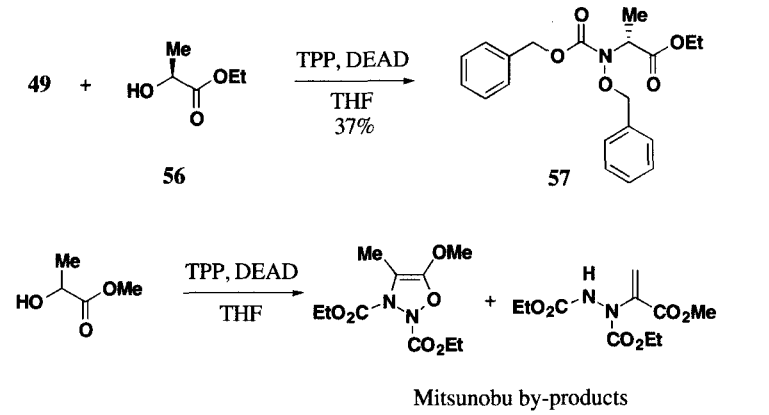
Reagent **49** was methylated (potassium carbonate/MeI/acetone /reflux) to give N-methyl derivative **53** in 98% yield in synthesis of the natural product spermexatin (*Scheme 18*).[55] Hydrolysis at room temperature in HBr/acetic acid removed the Cbz group (93%) selectively, and the resultant N-methyl-O-benzylhydroxylamine **54** was treated with succinic anhydride in THF at reflux to generate carboxylic acid **55** (87%). Multiple equivalents of **55** were coupled with polyamine substrate spermidine to arrive at spermexatin as shown.

In a study toward the synthesis of mycelianamide, Mitsunobu alkylation of **49** with optically active α-hydroxy ester **56** met with limited success and desired product **57** was isolated in only 37% yield after flash column chromatography (*Scheme 19*).[56] This result was consistent with an earlier report which showed that α-hydroxy esters react with Mitsunobu reagents.[57] In the absence of a nucle-

ophile, good yields of Mitsunobu reagent by-products were obtained.

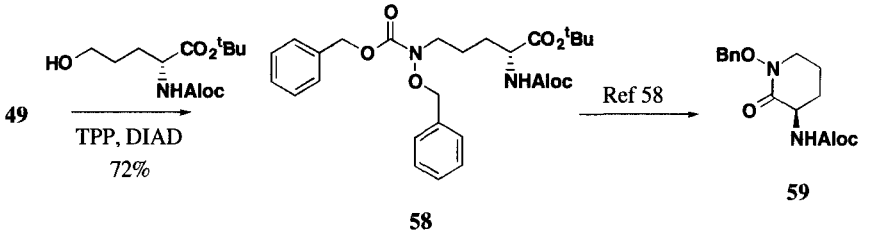


Scheme 18



Scheme 19

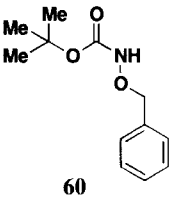
Reagent **49** has also been applied to the acquisition of chiral N-hydroxycycloornithine derivatives (*Scheme 20*).[58] Mitsunobu alkylation mediated by diisopropyl azodicarboxylate (DIAD) on **49** with D-N-(allyloxycarbonyl)-δ-hydroxynorvaline *tert*-butyl ester (prepared from pyroglutamate) gave



Scheme 20

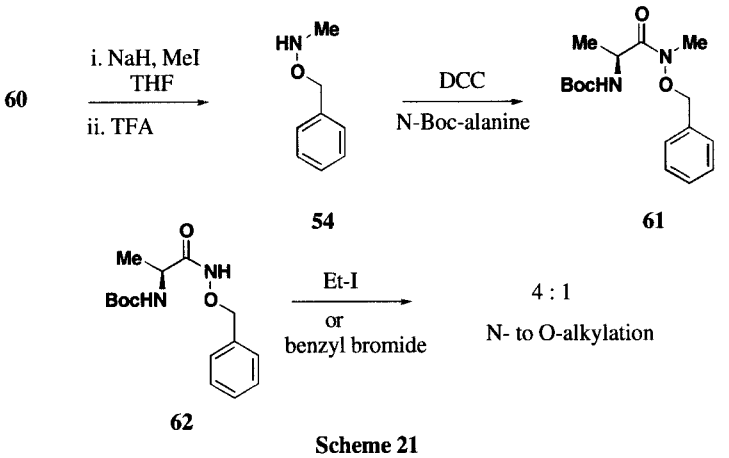
N-alkylation product **58** in 72% yield. Sequential hydrolysis in trifluoroacetic acid to cleave the *t*-butyl ester and then HBr/acetic acid to remove the Cbz group allowed for cyclization to N-allyloxycarbonyl protected ornithine derivative **59** obtained in 53% overall yield from **58**.

8. N-(*tert*-Butoxycarbonyl)-O-benzylhydroxylamine 60



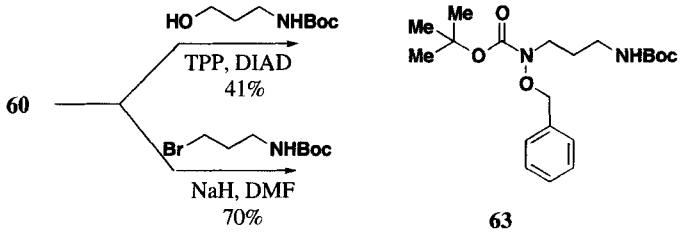
60

The N-Boc reagent **60** has proven qualitatively equivalent to N-Cbz reagent **49** in terms of utility. Although it does not offer the option of simultaneous deprotection at both nitrogen and oxygen, it has been the most extensively employed reagent in synthesis to date. Reagent **60** was first introduced in 1981,[59] where it was subjected to methylation (NaH, MeI, THF, 94%) and deprotection (TFA, 82%) to provide N-methyl-O-benzylhydroxylamine **54** (*Scheme 21*). Compound **54** was coupled with amino acid alanine upon activation with DCC. Deprotection of **61** gives rise to an α-amino hydroxamic acid; isosteric to α-amino acids wherein the carboxylic acid has been exchanged for a hydroxamic acid. Alternatively, **61** was prepared from the protected amino hydroxamic acid derivative **62** (Mitsunobu with methyl alcohol), but in poor yield (39%). This result is consistent with the tendency for O-alkylation observed for N-acyl hydroxylamines, and alkylation on **62** with either ethyl iodide or benzyl bromide gave a mixture (4:1, N- to O-).

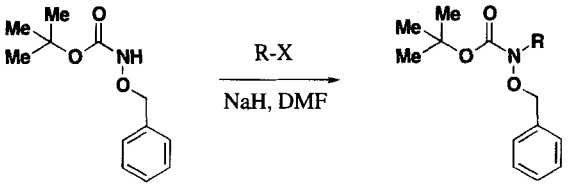


Scheme 21

Alkylation of **60** has also been reported. A direct comparison showed that Mitsunobu alkylation (triphenylphosphine/DIAD) with 3-[(*tert*-butoxycarbonyl)amino]-1-propanol to give **63** was less effective (41%) than alkylation with 3-[(*tert*-butoxycarbonyl) amino]-1-propyl bromide upon deprotonation with sodium hydride at 100° for 3 hrs in DMF which gave **63** in 70% yield (*Scheme 22*).[45] An even more formal study conducted under the conditions of NaH/ DMF revealed that alkylation with a variety of electrophiles could be achieved at lower temperatures (25° to 70°) and in good yields to give N-alkylation products **64 - 68** (*Table 1*).[60]

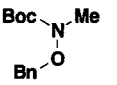
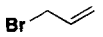
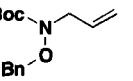
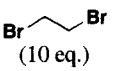
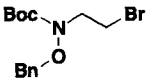
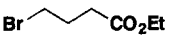
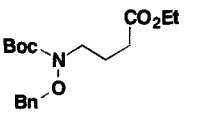
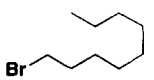
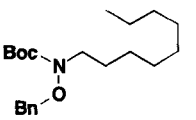


Scheme 22

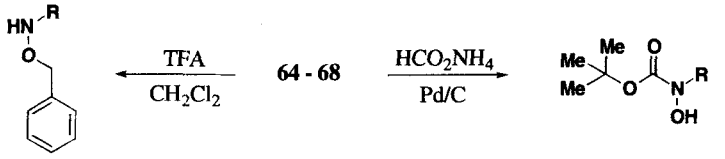


60 **64 - 68**

Table 1. Alkylation of N-(*tert*-Butoxycarbonyl)-O-benzylhydroxylamine **60**

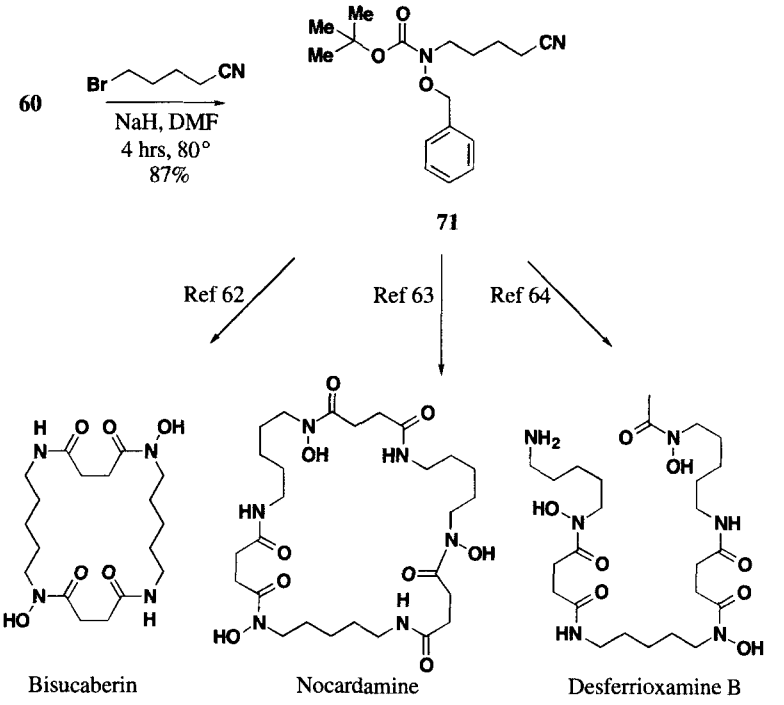
Substrate	Conditions	Product		Yield
Me-I	1 hr, 25°		**64**	95%
	1 hr, 50°		**65**	99%
 (10 eq.)	1 hr, 25°		**66**	61%
	1 hr, 70°		**67**	94%
	16 hrs, 60°		**68**	88%

The products, **64 - 68**, were readily hydrolyzed to their corresponding benzyloxyamines **69** upon treatment with trifluoroacetic acid in dichloromethane, or alternatively, mild hydrogenolysis produced N-hydroxy-N-*tert*-butylcarbamates **70**.



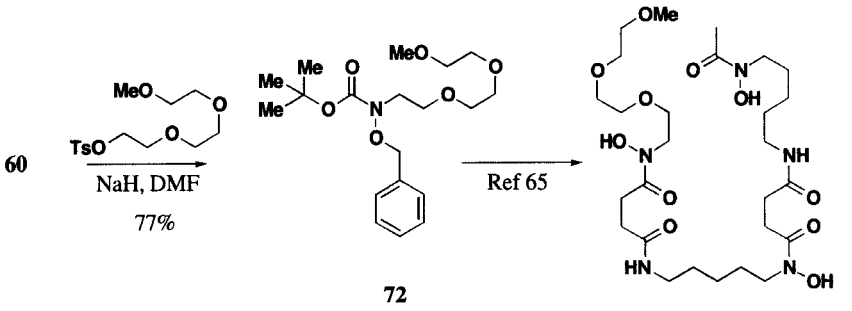
69 **70**

Reagent **60** has been most extensively employed in the synthesis of iron chelating siderophores. Bisucaberin is a macrocyclic lactam reported to sensitize tumor cells to macrophage promoted cytolysis.[61] Bergeron reported in 1989 that **60** reacted well with 5-chlorovaleronitrile to give nitrile **71** in 87% yield upon deprotonation with sodium hydride in DMF and heating at 80° for 4 hrs (*Scheme 23*).[62] Nitrile **71** was reduced, and a series of couplings reactions prior to cyclization gave rise to the macrocyclic lactam. In a similar manner, substrate **71** has been carried forward in the total synthesis of the larger macrocycle nocardamine,[63] and the linear compound desferrioxamine B.[64]



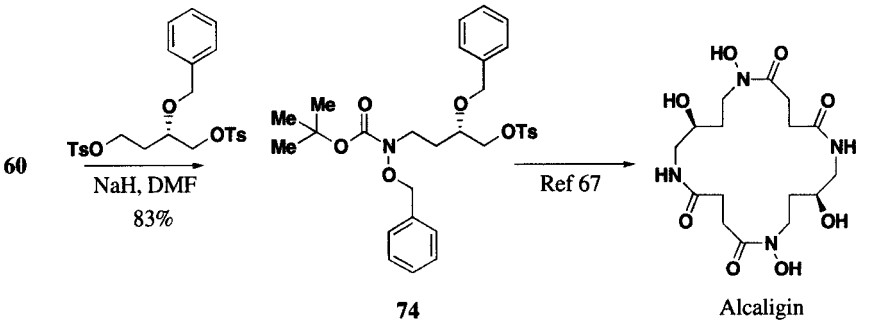
Scheme 23

Desferrioxamine B is the parent of a family of linear trihydroxamate ligands and shows therapeutic utility in the treatment of iron overload, and several analogs of this family have been reported.[65,66] In one example, reagent **60** reacted smoothly with a tosylate under the conditions above (NaH, DMF) and gave **72** in 77% yield (*Scheme 24*). The polyether derivative **72** was carried forward to the desferrioxamine analog **73**.



Scheme 24

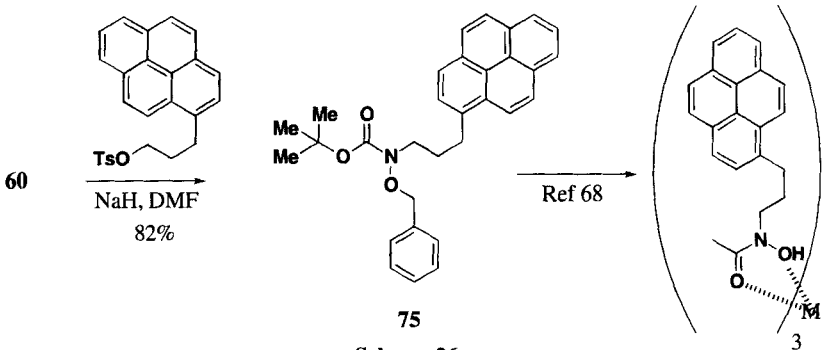
The siderophores shown above are derived from a cadaverine backbone. The macrocyclic lactam alcaligin, however, is derived from a 2-hydroxy putrescine backbone. Upon exposure to sodium hydride/DMF at room temperature for several hours, reagent **60** underwent selective alkylation (ascribed to steric congestion) and gave **74** in 83% yield (*Scheme 25*).[67] Further elaboration over eight synthetic steps provided the macrocylic lactam alcaligin.



Scheme 25

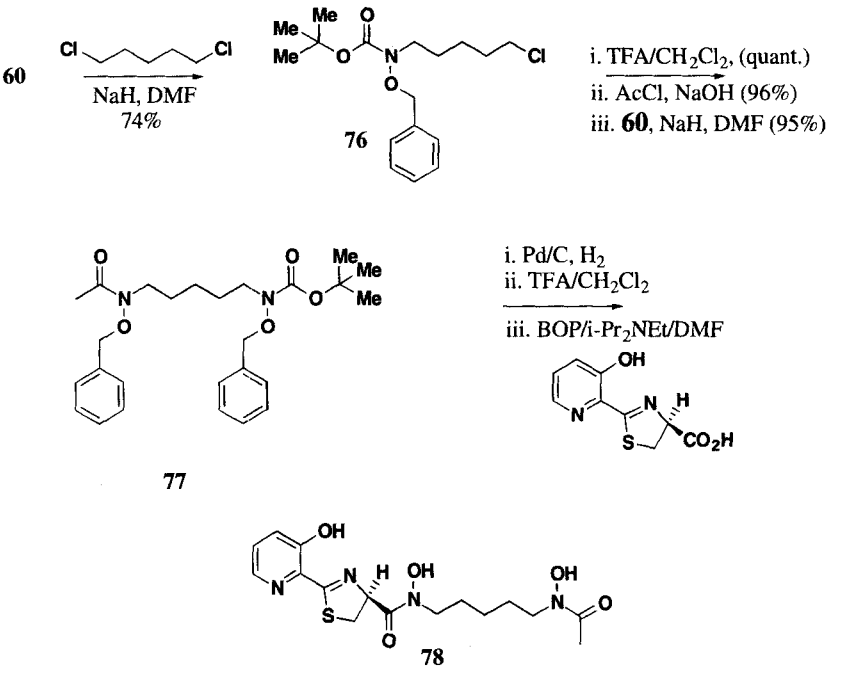
The ability of **60** to alkylate tosylates was taken advantage of in the preparation of photoactive pyrene tethered hydroxamic acid based ligands for the purpose of a fluorescence study (*Scheme 26*).[68] Pyrene **75** was secured in 82% yield upon alkylation in NaH/DMF. Further elaboration over three additional steps produced the desired metal trimer.

In addition to tosylates, alkyl chlorides are also good electrophiles for reagent **60** as depicted in synthesis of the *bis*-hydroxamate derivative of (S)-desmethyldesferrithiocin (*Scheme 27*). Treatment of **60** with 1,5-dichloropentane (NaH/DMF at 70°) gave a 74% yield of **76**.[69] The aceto derivative was generated, now over a two step sequence, but in excellent yield (96%) upon TFA hydrolysis of the N-Boc group followed by acylation under Shotten-Baumann conditions. Displacement of the pendant chloride with reagent **60** gave *bis*-hydroxamate derivative **77** (95%) followed by deprotection and coupling yielded **78**. Although longer, this route proved more efficient than either direct alkylation of 1,5-dichloropentane with two equivalents N-acetyl-O-benzylhydroxylamine **22**, or



Scheme 26

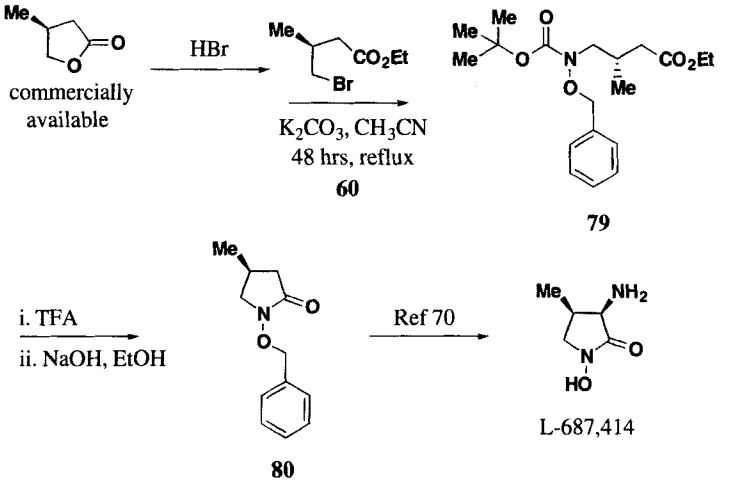
displacement of the pendant chloride on **76** with N-acetyl reagent **22**. While the latter reaction was reported to provide **77** (50%), the choice to proceed through the longer route again emphasizes the attractiveness of avoiding formation of O-alkylation by-products.



Scheme 27

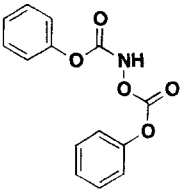
In a more recent report, reagent **60** was applied to the synthesis of a glycine site antagonist at the NMDA receptor. L-687,414 (3-amino-1-hydroxy-4-methylpyrrolidin-2-one) is considered one of the most potent agents to have shown efficacy in animal models for stroke,[70] and has been prepared as outlined below (*Scheme 28*). Alkylation of **60** (K_2CO_3/acetonitrile at reflux for 48 hrs) with an optically active bromide prepared in a single step from a commercially available lactone gave N-alkylation product **79**. Hydrolysis of the N-Boc group in trifluoroacetic acid and subsequent treatment with

base caused cyclization and pyrrolidinone **80** was isolated in 51% overall yield for three steps. Amination and debenzylation provided a very efficient synthesis of L-687-414.



Scheme 28

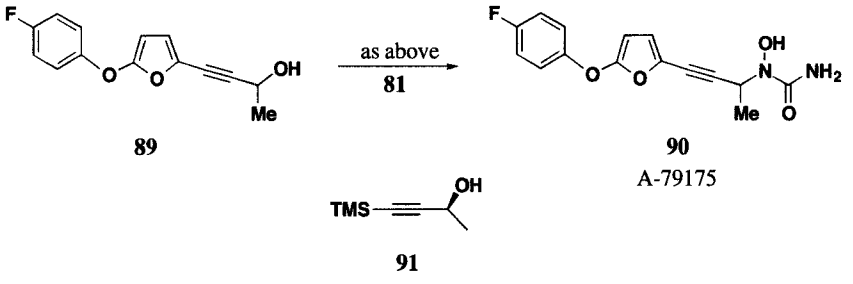
9. N,O-*bis*(Phenoxycarbonyl)hydroxylamine (81)



81

As mentioned in the introduction, N-hydroxyureas are useful as inhibitors of the enzyme 5-lipoxygenase which is the first key enzyme in leukotriene biosynthesis, and therefore a strategy for intervention in inflammatory disease and allergic disorder is promised. *bis*-Protected hydroxylamine reagents such as N,O-*bis*(phenoxycarbonyl) **81**, bearing the same protecting group on nitrogen and oxygen, afford simultaneous deprotection in single step. Reagent **81**, however, possesses an added utility in that phenol displacement with ammonia gives rise to an urea, and thus **81** serves as a latent form of N-hydroxy urea. Participation of **81** in the Mitsunobu reaction with a variety of alcohols was reported to proceed in good yields to give products **82** as depicted in Table 2.[71] Subsequent exposure to high pressure ammonia (sealed tube) generated the N-hydroxy ureas **83 -88** directly, and without need for further protecting group manipulation. As applied here, this methodology provides a short synthesis of zileuton **87**, a 5-lipoxygenase inhibitor in phase III clinical trials[72] which has demonstrated efficacy in ulcerative colitis and asthma.[73,74]

As a second generation 5-lipoxygenase inhibitor, Abbott compound A-79175 **90**, has proven more potent at inhibiting leukotriene formation than zileuton (*Scheme 29*).[75] Propargyl alcohol **89** was subjected to Mitsunobu conditions as above in the presence of **81** (59%), and after ammonia treatment **90** was isolated in 57% yield. Moreover, a synthetic precursor to **89**, propargyl alcohol **91**, was recently reported in optically pure form.[76]



Scheme 29

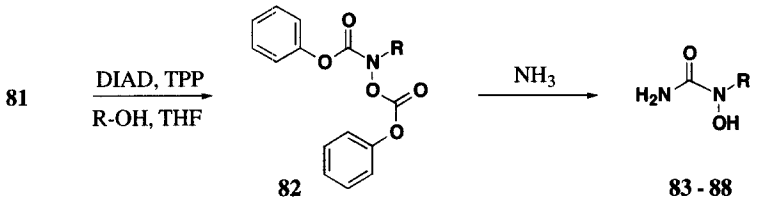
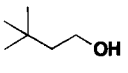
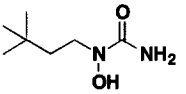
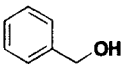
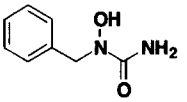
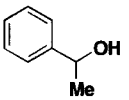
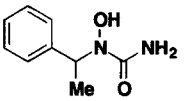
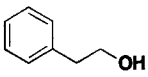
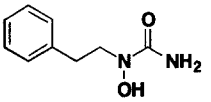
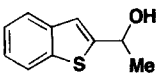
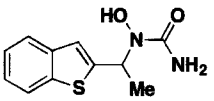
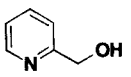
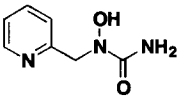


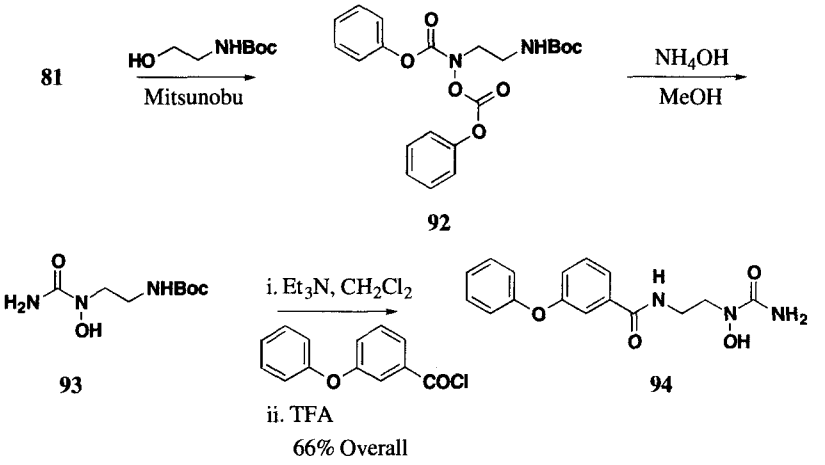
Table 2. Synthesis of N-Hydroxyureas from N,O-Bis(phenoxycarbonyl)hydroxylamine **81**

Substrate	Alkylation Yield	Product	Yield
	92%	 **83**	68%
	92%	 **84**	71%
	79%	 **85**	61%
	95%	 **86**	73%
	48% [a]	 **87** Zileuton	56%
	93%	 **88**	54%

a) Obtained as the major product from N- to O-alkylation (3 : 1).

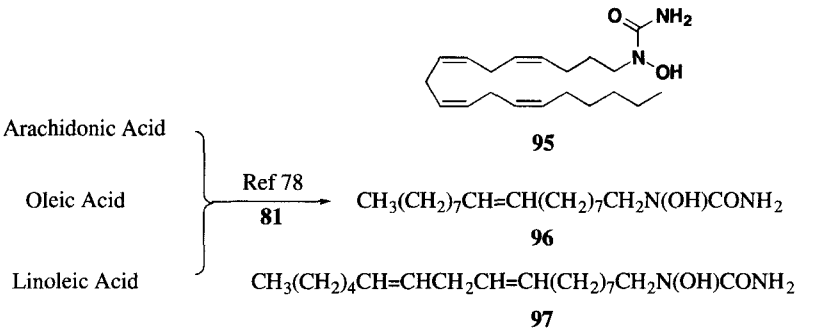
A third example of this method was reported in the synthesis of "amide-linked" 5-lipoxygenase inhibitors.[77] Mitsunobu reaction on N-Boc-ethanolamine with reagent **81** gave the N-alkylation product **92** in 90% yield (*Scheme 30*). Exposure to ammonium hydroxide in methanol at room temper-

ature, what has now become the common method for phenolic hydrolysis, gave N-hydroxyurea **93**. Acylation with 4-phenyoxybenzoyl chloride occurred on oxygen, and N-Boc hydrolysis was accompanied by intramolecular acyl migration to arrive at **94**.



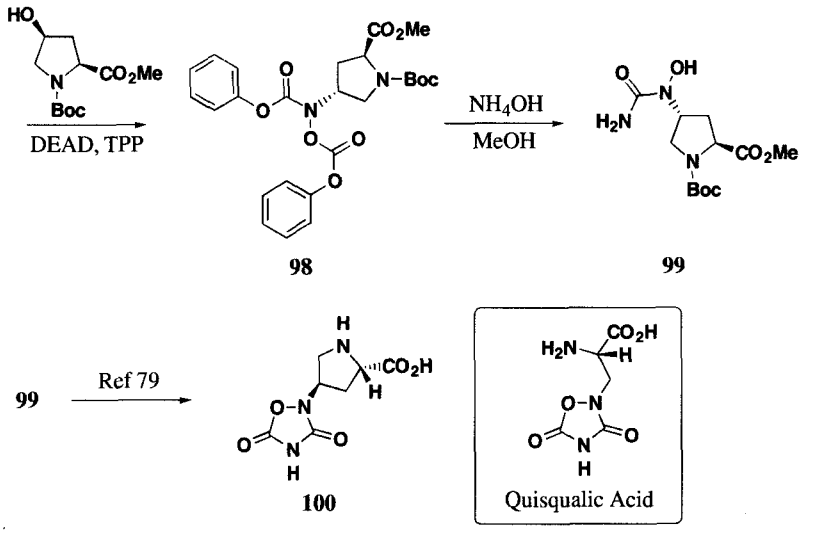
Scheme 30

Polyunsaturated N-hydroxyurea **95** was prepared as a natural substrate for the 5-lipoxygenase enzyme (*Scheme 31*).[78] Oleic and linoleic acids were first reduced to their corresponding alcohols, and Mitsunobu alkylation on **81** followed by methanolic ammonium hydroxide treatment gave N-hydroxyureas **96** and **97**.



Scheme 31

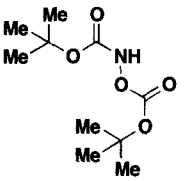
The quisqualic acid receptor is another of the excitatory amino acid subtypes associated with neurotransmission, the inhibition of which is therefore postulated to be effective in stroke therapy. *bis*-Phenoxy reagent **81** was reported to undergo Mitsunobu alkylation on protected pyrrolidine derivative **98** and gave N-hydroxyurea **99** in 50% overall yield after ammonia hydrolysis (*Scheme 32*).[79] Subsequent manipulation gave the conformationally restricted analog **100** found to be equipotent with quisqualic acid.



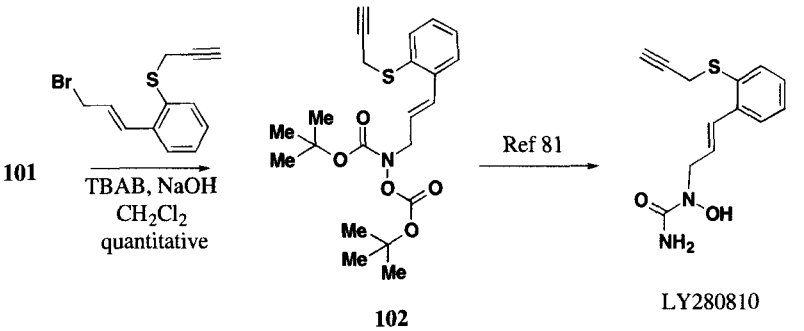
Scheme 32

10. N,O-*bis*(*tert*-Butoxycarbonyl)hydroxylamine (101)

In 1994, *bis*-Boc reagent **101**[80] was reported in an improved method for the synthesis of LY280810, a potent 5-lipoxygenase inhibitor in clinical trials for treatment of asthma.[81] A variety of conditions for the alkylation of **101** were reportedly successful, however phase transfer conditions (methylene chloride/1N sodium hydroxide solution/tetrabutylammonium bromide) proved optimal, and hydroxamate **102** was isolated in quantitative yield (*Scheme 33*).



101



Scheme 33

Table 3 depicts a series of reaction products **103 - 107** which were obtained upon alkylation of **101**. The corresponding alkyloxyamines were secured upon treatment with trifluoroacetic acid in cold (0°) methylene chloride which simultaneously deprotected both nitrogen and oxygen.

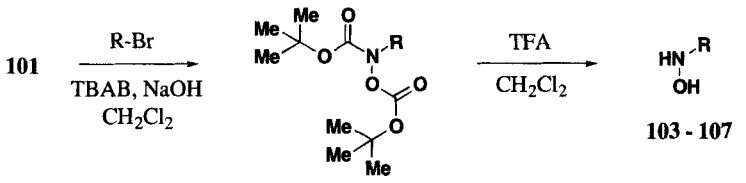
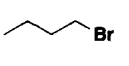
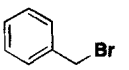
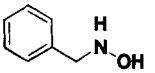
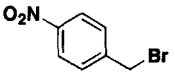
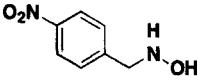
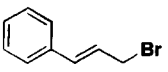
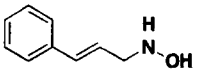
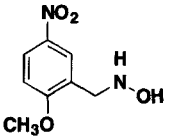
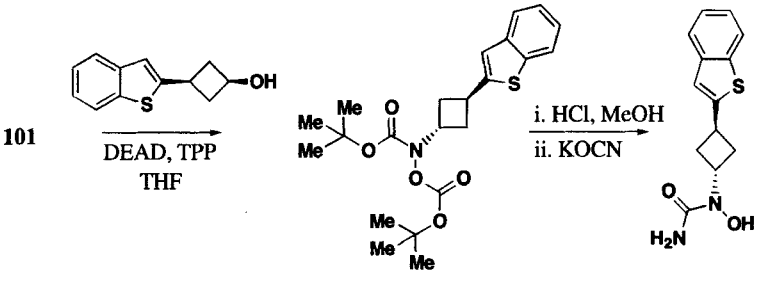


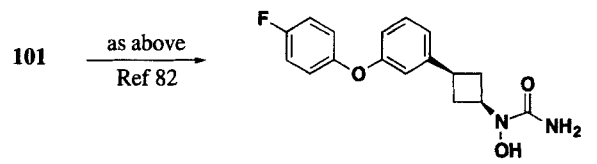
Table 3. Synthesis of Hydroxylamines from N,O-Bis(*tert*-butoxycarbonyl)hydroxylamine **101**

Substrate	Alkylation Yield	Product[a]	Yield
	85%		**103** 79%
	96%		**104** 80%
	97%		**105** 89%
	96%		**106** 81%
	98%		**107** 83%

a) Products isolated as their TFA salt.

In an effort to remove complications associated with chirality, the zileuton analog 858C, a meso compound, was prepared and found to have improved *in-vivo* potency over zileuton (*Scheme 34*).[82] Mitsunobu alkylation of **101** with a *cis*-cyclobutylthiophene derivative proceeded with

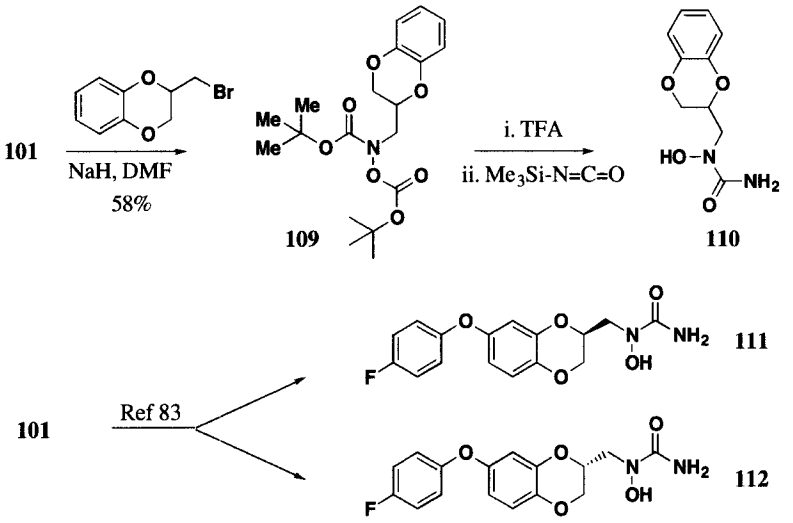




Scheme 34

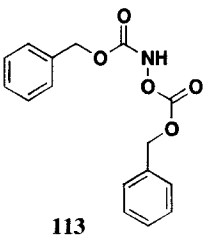
inversion of configuration to give **108** in 65% yield. Carboxamide formation from reagent **101** must be performed over two steps (as opposed to a single operation from reagent **81**), and was achieved by methanolic HCl hydrolysis which cleaved both Boc groups prior to addition of potassium isocyanate to the intermediate hydroxylamine (32% overall yield). Compound 862C was prepared in a similar manner from Mitsunobu alkylation on the corresponding *trans*-cyclobutyl alcohol and was reported to offer high potency and good oral availability as a 5-lipoxygenase inhibitor.

5-Lipoxygenase inhibitors bearing a benzodioxane ring system were described very recently. Deprotonation of **101** with sodium hydride in DMF and alkylation with 2-(bromomethyl)-1,4-benzodioxan gave N-alkylation product **109** in 58% yield.[83] Trifluoroacetic acid hydrolysis removed the Boc groups and addition of the resultant hydroxylamine to trimethylsilyl isocyanate gave urea **110**. A similar sequence lead to optically active ureas **111** and **112** (*Scheme 35*).



Scheme 35

11. N,O-*bis*(Benzyloxycarbonyl)hydroxylamine (113)



113

The *bis*-Cbz reagent **113**, first reported 1969 in a study aimed at the synthesis of cyclocanaline,[84] was more recently employed by Hanessian *et al.*[85] in an asymmetric synthesis of N-hydroxy amino acids. Mitsunobu inversion of enantiomerically pure α-hydroxy esters at 0° in THF was reported to give good yields of N-alkylation products. Noteworthily, the competitive reactivity of α-hydroxy esters with Mitsunobu reagents (mentioned above for reagent **49**, *Scheme 19*) was not observed for this reagent.[57] The difference in reactivity is attributed primarily to reaction conditions (0° for 5 hrs as compared to room temperature/overnight) rather than substrate. Hydrolysis in concentrated HCl/dioxane at reflux over four hours liberated N-hydroxy amino acids **114 - 118** (*Table 4*). Verifica-

tion of optical purity was ascertained by reduction to the corresponding N-hydroxy esters **119** (5% Pd-C/H_2/30psi/12 hrs) which allowed comparison to authentic samples (*Scheme 36*).

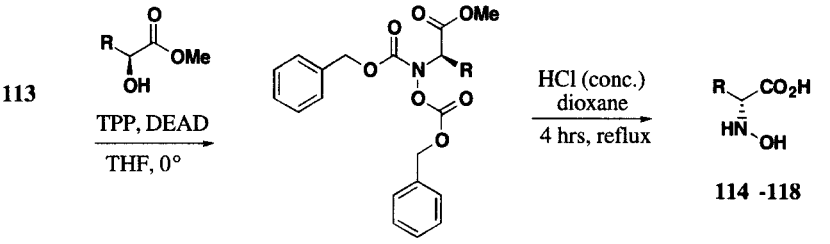
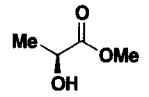
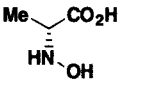
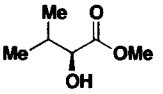
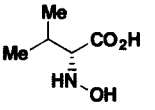
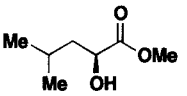
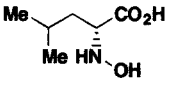
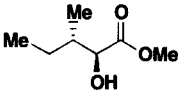
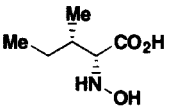
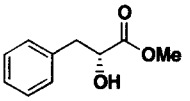
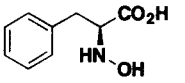
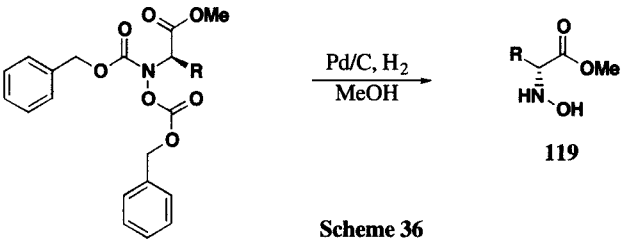


Table 4. N-Hydroxyamino Acids from *bis*(Benzyloxycarbonyl)hydroxylamine**113**

Substrate	Alkylation Yield	e.e.	Final Product	
	90%	96%		**114**
	62%	93%		**115**
	85%	96%		**116**
	66%	82% [a]		**117**
	81%	95%		**118**

a) The d.e. of the starting hydroxy ester was 92%



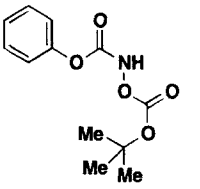
Scheme 36

In the choice between a reagent bearing different protecting groups or the same groups (as in reagents **81**, **101**, or **113**) one need only consider whether selective deprotection or simultaneous deprotection is preferable. In selecting between reagents which afford simultaneous deprotection

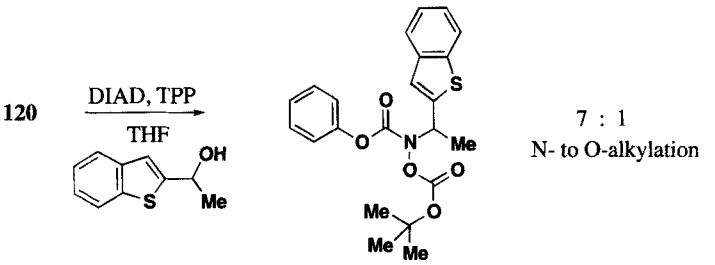
(including reagent **49**), the choice should predominately be based on the type of deprotection conditions are most suitable for one's substrates (*i. e.* hydrolytic or hydrogenolytic conditions) as their utility appears quite comparable.

12. N-Phenoxycarbonyl-O-*tert*-(butoxycarbonyl)hydroxylamine (120)

Reagent **120** is a differentially protected reagent with a *tert*-butoxycarbonyl group on oxygen. The significance of this reagent was seen in synthesis of zileuton (*Table 2*, **87**). Although carbamate protected reagents don't suffer from O-alkylation, a poor ratio of N- to O-alkylation (3:1) was observed for this entry and a suggestion was put forward that the thiophene sulfur may play a role.[71] In this regard, reagent **120** was found to yield an improved ratio of products (7:1) under the same reaction conditions and **121** was secured in good yield (*Scheme 37*).



120



121

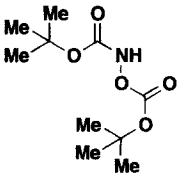
Scheme 37

Reagent **120** was also reported to participate in the generation of N-hydroxy amino acids comparable to reagent **113** (*see Table 4*).[85] Mitsunobu mediated alkylation to **122** followed by dissolution in 20% trifluoroacetic acid/dichloromethane selectively cleaved the Boc group to N-hydroxy-N-(phenoxycarbonyl) amino acid derivatives **123 - 126** which were obtained without racemization (*Table 5*).

II. ACYLATION STUDIES

1. N,O-*bis*(*tert*-Butoxycarbonyl)hydroxylamine (101)

Acylation of *bis*-protected hydroxylamines gives rise to hydroxamic acids. Reagent **101** was treated with a series of acid chlorides (*Table 6*) and excellent yields of N-acyl derivatives **127** we obtained.[81] Trifluoroacetic acid hydrolysis produced hydroxamic acids **128 - 131** in good yields (80 - 94%).



101

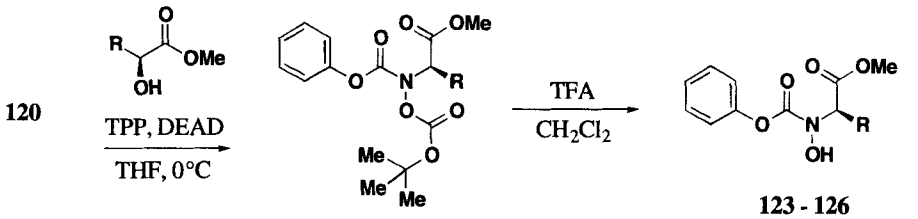
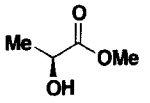
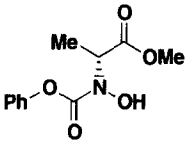
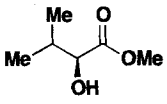
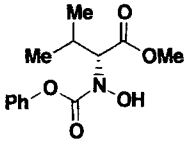
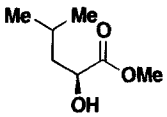
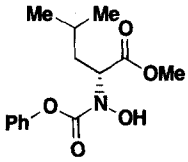
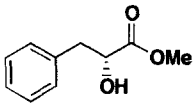
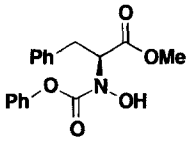


Table 5. N-Hydroxy Amino Esters from N-Phenoxycarbonyl-O-(*tert*-butoxycarbonyl) hydroxylamine **120**

Substrate	Alkylation Yield	e.e.	Product	Hydrolysis Yield
	88%	96%	 **123**	91%
	68%	96%	 **124**	95%
	81%	96%	 **125**	96%
	91%	96%	 **126**	93%

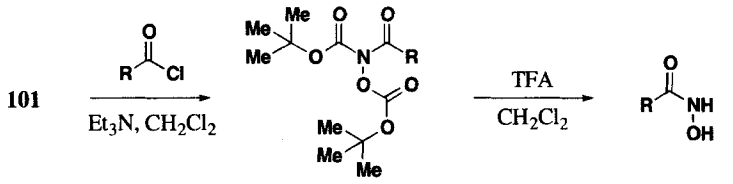
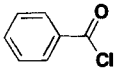
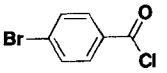
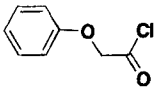
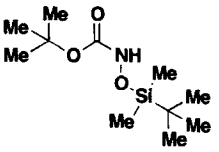


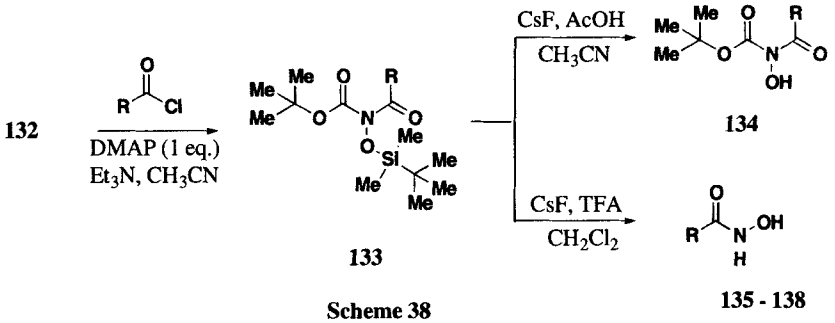
Table 6. Acylation of N,O-*bis*(*tert*-butoxycarbonyl)hydroxylamine **101**

Substrate	Acylation Yield	Product	Yield Hydrolysis
	93%	**128**	80%
	94%	**129**	81%
	95%	**130**	94%
	94%	**131**	81%

2. N-(*tert*-Butoxycarbonyl)-O-(*tert*-butyldimethylsilyl)hydroxylamine (132)

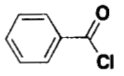
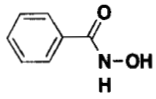
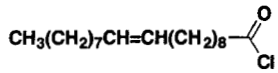
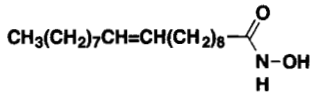
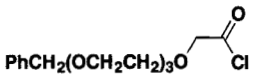
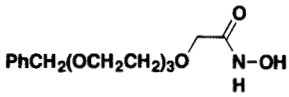
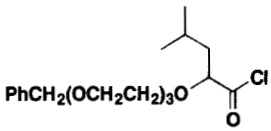
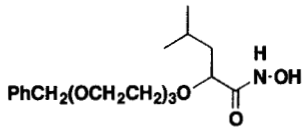

132

Upon exposure to acid chlorides, O-tBDMS reagent **132** was readily acylated in the presence of triethylamine and DMAP in acetonitrile (*Scheme 38*).[86] The resultant N-acyl derivatives **133** were reported to undergo selective hydrolysis of the O-tBDMS group when treated with CsF and acetic acid to afford products **134**. Simultaneous hydrolysis of both protecting groups occurred with TFA in the presence of CsF and gave hydroxamic acids **135 - 138** (*Table 7*). The authors noted that hydrolysis proved more complete when cesium fluoride was added to the reaction mixture.



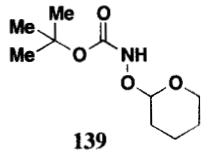
Scheme 38

Table 7. Acylation of N-*tert*-Butoxycarbonyl-O-*tert*-butyldimethylsilylhydroxylamine **132**

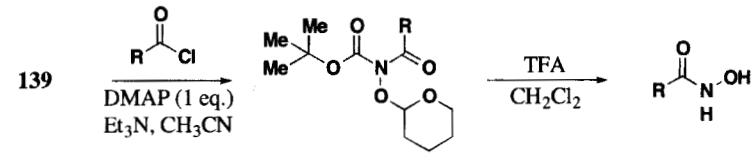
Substrate	Yield Acylation	Product		Yield Hydrolysis
	90%		**135**	85%
	90%		**136**	75%
	85%		**137**	75%
	80%		**138**	75%

3. N-(*tert*-Butoxycarbonyl)-O-(tetrahydropyranyl)hydroxylamine (139)

Similarly, reagent **139** was also reported to undergo acylation in good yield (*Scheme 39*).[86] Table 8 depicts hydroxamic acid products **141** and **142** prepared after hydrolysis with trifluoroacetic acid in dichloromethane with concomitant removal of the protecting groups.

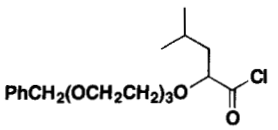
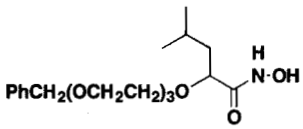
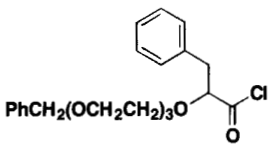
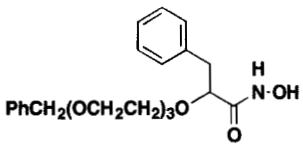


139



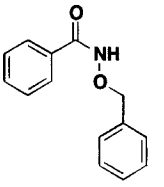
Scheme 39

Table 8. Acylation of N-*tert*-Butoxycarbonyl-O-tetrahydopyranylhydroxylamine **139**

Substrate	Yield Acylation	Product		Yield Hydrolysis
	85%		**141**	72%
	80%		**142**	70%

4. N-(Benzoyl)-O-benzylhydroxylamine (5)

In selecting a reagent for acylation, one can not employ harsh conditions hydrolytic for fear of cleaving the newly formed N-acyl bond. The three reagents listed above (**101, 132, 139**) all have relatively labile protecting groups. Although reagent **5** would not meet this requirement, acylation studies with acid chlorides and isocyanates have been reported and are referenced here for the interested reader.[87-90]

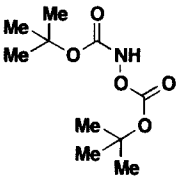


5

III. OXYAMINATION STUDIES

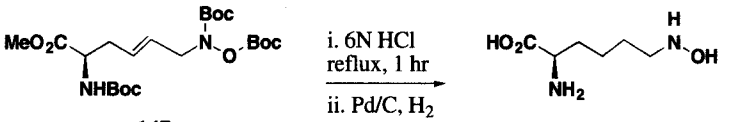
N,O-*bis*(*tert*-Butoxycarbonyl)hydroxylamine (101)

Palladium catalyzed oxyamination of allylic esters with *bis*-protected hydroxylamine reagents has been demonstrated to give N-hydroxyallylamines. Earlier work showed that coupling was possible with N-alkylhydroxylamines in good conversion,[91] but unsubstituted hydroxylamines yielded *bis*-allyl derivatives. Palladium catalyzed coupling of *bis*-protected reagents provides a means of securing mono substituted N-allylamines.



101

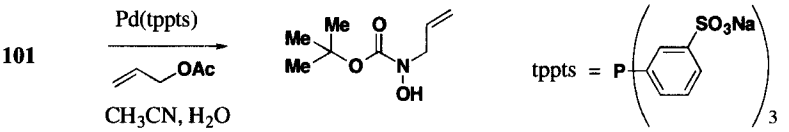
Reagent **101** was stirred together with catalyst $Pd(dppe)_2$ (generated upon addition of dppe to 3% $Pd(dpa)_2$ in THF/DMF) and either allylic esters or allylic carbonates and products **143 - 147** were obtained in good yields (*Table 9*).[92] Hydrolysis of **147** in 6N HCl at reflux for 1 hr cleaved the four protecting groups and subsequent reduction of the double bond gave N-hydroxylysine (*Scheme 40*).[93]



147 N-Hydroxylysine

Scheme 40

In a second example, coupling **101** with allylic acetate was performed in the presence of Pd(0)-tpps (*Scheme 41*).[94] Upon being stirred in acetonitrile/water (15:1) at 70°, N-hydroxy product **148** was formed in 81% yield where hydrolysis of the O-Boc group had also occurred.



148

Scheme 41

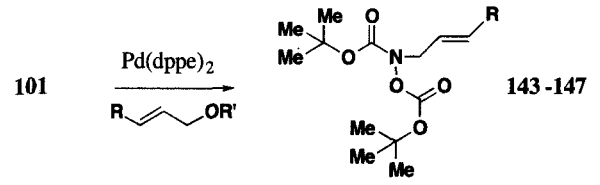
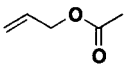
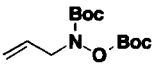
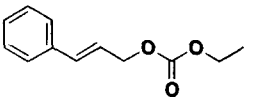
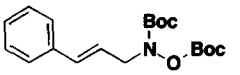
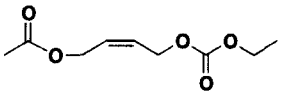
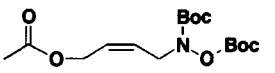
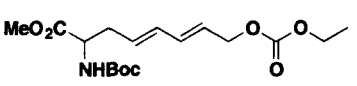
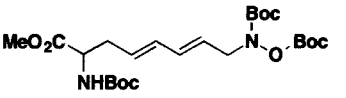
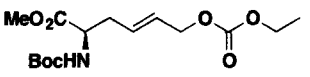
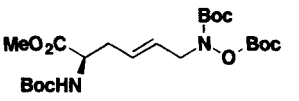
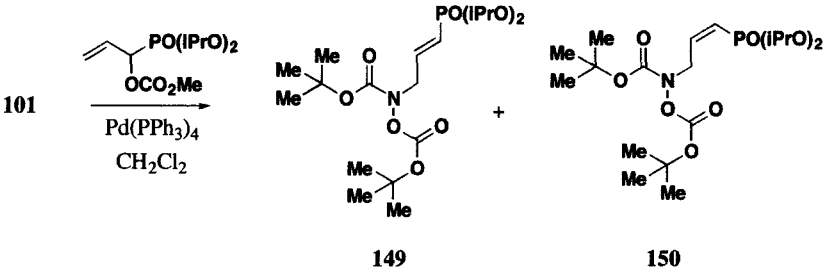
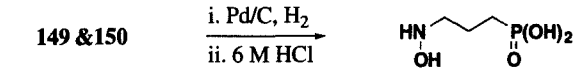


Table 9. Oxyamination of N,O-*bis*(*tert*-butoxycarbonyl)hydroxylamine **101**

Substrate	Yield	Product
	77%	 **143**
	80%	 **144**
	86%	 **145**
	63%	 **146**
	87%	 **147**

Palladium-catalyzed amination of allylic phosphonates provided an improved synthetic route to antibiotic FR-31564 mentioned above (see Scheme 4). A solution of **101** was stirred with diisopropyl (1-methoxycarbonyloxy-2-propenyl)phosphonate and $Pd[P(Ph_3)_3]_4$ in dichloromethane and gave the E/Z mixture **149** (87%) and **150** (7%) with complete regiocontrol (*Scheme 42*).[95] Hydrolysis and reduction generated the hydroxylamine precursor to FR-31654 in three steps from **101** (78% overall).





FR-31564 Precursor

Scheme 42

IV. CONCLUSION

The chemistry described herein demonstrates the utility of *bis*-protected hydroxylamines as applied in organic synthesis. The driving force behind their development can predominately be attributed to the areas of siderophore natural product synthesis, and the preparation of N-hydroxyureas as 5-lipoxygenase inhibitors. The many recent publications indicate that theses reagents are of current interest.

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