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TOTAL SYNTHESIS OF (−)-SAFRACIN B
TOTAL SYNTHESIS OF (−)-THIANGAZOLE
DEVELOPMENT OF SULFONAMIDE CHEMISTRY

by

MUI CHEUNG

A THESIS SUBMITTED
IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE
DOCTOR OF PHILOSOPHY

APPROVED, THESIS COMMITTEE

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Chemistry, Chairman

Marco A. Ciufolini, Associate Professor
Chemistry

Frederick B. Rudolph, Professor
Biochemistry and Cell Biology

Houston, Texas

April, 1997
ABSTRACT

Total Synthesis of (−)-Safracin B
Total Synthesis of (−)-Thiangazole
Development of Sulfonamide Chemistry

by

Mui Cheung

Chapter I describes the stereocontrolled total synthesis of (−)-safracin B with antibacterial and antitumor activities. The convergent approach for the synthesis of safracin B can be readily applied to the synthesis of the related isoquinolinequinone family such as saframycins and ecteinascidins.

Chapter II discusses the total synthesis of (−)-thiangazole, a substance with potent anti-HIV-1 activity in vitro. An efficient synthetic pathway is developed to enable diverse modification of both ends of thiangazole and thus provide a rapid access to a variety of analogs.

Chapter III outlines the development of new chemistry of nitrobenzenesulfonamides, N-Boc and N-Alloc nitrobenzenesulfonamides, and alkylsulfonamides for the efficient preparation of secondary amines and protected primary amines.
ACKNOWLEDGMENTS

I wish to express my sincere gratitude to Professor Tohru Fukuyama for his guidance during my graduate studies. His dedication, perseverance, and love for the art of organic chemistry have provided a constant inspiration and motivation to me.

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<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Alloc</td>
<td>allyloxyacarbonyl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxyacarbonyl</td>
</tr>
<tr>
<td>BOP-Cl</td>
<td>bis(2-oxo-3-oxazolidinyl)-phosphinic chloride</td>
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<td>ceric ammonium nitrate</td>
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<td>DEAD</td>
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<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
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<tr>
<td>MS</td>
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<td>NMO</td>
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<tr>
<td>NMR</td>
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</tr>
<tr>
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<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PLE</td>
<td>pig liver esterase</td>
</tr>
<tr>
<td>psi</td>
<td>pounds per square inch</td>
</tr>
<tr>
<td>p-Ts</td>
<td>4-toluenesulfonyl</td>
</tr>
<tr>
<td>PyBroP</td>
<td>bromotris(pyrrolidino)-phosphonium hexafluorophosphate</td>
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<tr>
<td>PyBOP</td>
<td>benzotriazol-1-yloxytripyrrolidino-phosphonium PF$_6$</td>
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<td>structure activity relationship</td>
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<td>TBAF</td>
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</tr>
<tr>
<td>$t$-Bu</td>
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</tr>
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<td>tetrahydrofuran</td>
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<tr>
<td>Thr</td>
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<td>TMSCN</td>
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<tr>
<td>TROC</td>
<td>2,2,2-trichloroethoxycarbonyl</td>
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To my parents and sister
Chapter I
Total Synthesis of (−)-Safracin B

Introduction

Safracins A (1a) and B (1b), new members of isoquinolinequinone family,\(^1\) were first isolated by a group at Yoshitomi Pharmaceutical Ind. Ltd. from *Pseudomonas fluorescens* A2-2 in 1983.\(^2\) A group at Squibb Institute for Medical Research independently isolated safracin B (1b) from *Pseudomonas fluorescens* SC 12695 in the same year.\(^3\) Both safracins have been shown to exhibit in vitro activity against a variety of Gram-positive and Gram-negative bacteria, and to exhibit antitumor activity against the L1210 and P388 leukemia, B16 melanoma and IMC carcinoma in mouse.\(^2,4\) However, the toxic and effective doses of safracin B (1b) were much lower than those of safracin A (1a).\(^4\) The absolute and relative configuration of the safracins was elucidated by X-ray crystallographic studies of the 4-brominated derivative of safracin A (1c).\(^5\)

![Safracin Diagram]

**Safracin**

\( A: \quad (1a) \quad R=\text{X=H} \)
\( B: \quad (1b) \quad R=\text{OH}, \text{X=H} \)
\( 1c) \quad R=\text{H}, \text{X=Br} \)
In 1990, ecteinascidins (2), substances with potent in vivo antitumor activity, were isolated from the colonial tunicate *Ecteinascidia turbinata* by Rinehart *et al.*\(^6\) and Wright *et al.*\(^7\) independently. The structures of ecteinascidins were found similar to those of safracins. The safracins also share structural similarities with saframycins A (3a), B (3b), C (3c), D (3d), F (3f), G (3g), Mx1 (3y), Mx2 (3z), S (3s), and renieramycins (4).\(^8,9,10,11\) These highly functionalized, unique pentacyclic isoquinolinequinone antibiotics have been popular synthetic targets and have imposed a serious challenge to synthetic chemists. To date, total syntheses of (±)-saframycins A-D (3a-d)\(^12,13,14\), (±)-renieramycin A (4a)\(^15\) and ecteinascidin 743 (2b)\(^16\) have been achieved.

\[ \text{Ecteinascidin} \]

<table>
<thead>
<tr>
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<td>729:</td>
<td>(2a)</td>
<td>R=H, X=OH</td>
</tr>
<tr>
<td>743:</td>
<td>(2b)</td>
<td>R=CH(_3), X=OH</td>
</tr>
<tr>
<td>731:</td>
<td>(2c)</td>
<td>R=CH(_3), X=H</td>
</tr>
<tr>
<td>815:</td>
<td>(2d)</td>
<td>R=CH(_3), X=OH(CHO)(_2)</td>
</tr>
<tr>
<td>743 N-12 oxide:</td>
<td>(2e)</td>
<td>R=CH(_3), oxide, X=OH</td>
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<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Formula</th>
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<tbody>
<tr>
<td>722:</td>
<td>(2f)</td>
<td>R=H, X=OH</td>
</tr>
<tr>
<td>736:</td>
<td>(2g)</td>
<td>R=CH(_3), X=OH</td>
</tr>
<tr>
<td>808:</td>
<td>(2h)</td>
<td>R=CH(_3), X=CH(CHO)(_2)</td>
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Among isoquinolinequinone antibiotics, saframycin A (3a)$^9$ and S (3s)$^{10}$ and ecteinaclidin 743 (2b)$^6,7$ have the most pronounced antitumor activities. Studies on saframycins and safracins suggest that the mode of action of isoquinolinequinone is similar to that of the antitumor agents
containing the pyrrolo[1,4]benzodiazepine skeleton. Moreover, the antitumor activity of saframycins is greatly enhanced by reduction of one or both of the quinone rings to a hydroquinone, which increases the lability of the C-21 substituents involved in iminium ion formation (Scheme 1).

![Scheme 1](image)

The iminium ion is envisioned to bind in the minor groove of double helical DNA and result in the alkylation of the 2-amino group of a guanine moiety as shown in Figure 1.
To date, there has been no report on the total synthesis of the safracins. However, Kubo and coworkers reported their model studies on the synthesis of the ABC ring of the safracins in 1992 as summarized in Scheme 2.19
Perkin-type condensation\textsuperscript{20} of commercially available 1,4-diacetyl-2,5-piperazinedione 5 and 4-methoxy-3-methylbenzaldehyde 6 followed by several chemical transformations gave tricyclic amine 7. In order to introduce the phenol functionality in the ring A, amine 7 was nitrated and hydrogenated to form aniline 8. Diazotization of aniline 8 followed by acid treatment afforded the desired phenol 9 in very low yield.

\[ 5 \quad + \quad 6 \rightarrow 11 \text{ 36\% (8 steps)} \]

Despite the difficulties in forming the phenol in the tricyclic ABC system, Kubo and coworkers reported the construction of the pentacyclic skeleton in 1995 as shown in Scheme 3.\textsuperscript{21} Unfortunately, numerous
attempts to introduce a phenolic hydroxyl group at the C-1 position of ring A were totally unsuccessful. Bromination of intermediate 13 under various conditions failed, as did the reduction of the nitro group of intermediate 14.

We are interested in safracin B (1b) as a synthetic target not only because it exhibits antibacterial and antitumor activities but also because it may serve as a plausible and important biogenetic intermediate for antibiotic isoquinolinequinone family such as ecteinascidins (2) and saframycins (3).

The stereocontrolled total synthesis of (−)-safracin B has been completed in our laboratory in 1994. Our synthesis features (i) the construction of the optically active diazabicyclo[3.3.1]nonane nucleus 21 from L-tyrosine derivative 33 and amino alcohol 36, and (ii) the formation of the desired β-epimer of tetrahydroisoquinoline 50 from amino nitrile 46 and cinnamaldehyde via a stereocontrolled Pictet-Spengler cyclization. Details of the total synthesis of (−)-safracin B (1b) are described fully in this thesis.
Retrosynthetic Analysis

Our retrosynthetic analysis of (−)-Safracín B (1b) is outlined in Scheme 4. The unstable hemiaminal functional group of 1b has to be introduced at the last stage of synthesis. Oxidation of ring E of 15 would introduce the quinone. Condensation of alanine derivative 16 with amine 15 would provide the amide side chain. Stereocontrolled Pictet-Spengler cyclization of amino nitrile 17 with aldehyde 18 would furnish the desired β-epimer of the tetrahydroisoquinoline. The phenol in ring E of 17 could be introduced from 19 by Friedel-Crafts type formylation followed by Baeyer-Villiger oxidation and methanolysis of the resultant formate. Amino nitrile 17 could easily be obtained by reduction of lactam 19. Debromination of intermediate 20 using palladium-mediated hydrogenation conditions would deliver 19. A stereocontrolled reduction of olefin 21 could be applied to control the stereochemistry at the C-D ring junction of the lactam 20.

The preparation of compounds similar to the key intermediate 21 has been extensively studied in our laboratories in connection with synthetic work on the saframycins (3) and ecteinascidins (2). In general, the construction of 25, structure of the type 21, can be achieved via two different pathways as shown in Scheme 5. Path A involves two Perkin type condensations between \( N,N' \)-diacetylpyrazinedione 5 and a highly substituted aldehyde 22. An acylinium ion-mediated cyclization of intermediate 24 furnished the main framework 25 which is similar to the key intermediate 21. Path B involves the condensation of amino alcohol 26 with acid 27 to form amide 28. Acetylation of alcohol 28 followed by ozonolysis and acetate elimination gave the same intermediate 24.
We favored Path B for the preparation of intermediate 21 because we realized that optically pure (-)-safracin B (1b) could be obtained starting with an optically pure acid of the type 27. The stereocontrolled synthesis of
intermediate 21 utilizing the optically pure L-tyrosine derivative 27 has been reported from our laboratories.22

![Chemical structures](image)

Scheme 5

As shown in Scheme 6, the readily available L-tyrosine derivative 29,29 which was obtained by esterification, N-acetylation, O-methylation, and formylation of commercially available L-tyrosine, was hydrogenated and formylated to yield aldehyde 30. Baeyer-Villiger oxidation of 30 followed by methanolysis of the resultant formate gave phenol 31. Selective bromination of 31 and subsequent deacetylation afforded amine 32.
Protection of amine 32 followed by alkaline hydrolysis of ester provided the optically pure acid 33 with enantiomeric excess (ee) greater than 98%.\textsuperscript{22}

![Chemical structures and reactions](image)

Scheme 6

Addition of anion 34, generated by treatment of cinnamyl isocyanide\textsuperscript{30,31} with n-butyl lithium, to aldehyde 35 at low temperature, followed by acidic hydrolysis of the resultant formamide at 80 °C, gave a diastereomeric mixture of the amino alcohols 36 (Scheme 7).\textsuperscript{13a}

![Chemical structures and reactions](image)

Scheme 7
Condensation of acid 33 with amino alcohol 36 gave an amide, which was then acetylated to give acetate 37. Oxidative cleavage of olefin 37 followed by elimination of acetate and alkaline hydrolysis of the phenolic acetate provided aldehyde 38. Upon treatment with trifluoroacetic acid in refluxing benzene, 38 underwent Pictet-Spengler cyclization, with concomitant deprotection of the t-Boc group, to furnish the key intermediate 21 in 65% overall yield from the acid 33.
Total Synthesis of (-)-Safracin B

Having succeeded in the synthesis of optically pure intermediate 21, we turned our attention to the total syntheses of (-)-safracin B (1b) and ecteinascidin 743 (2b). The stereocontrolled total synthesis of (-)-safracin B (1b) is described herein. A convergent synthetic approach to ecteinascidin 743 (2b) is described elsewhere.22

As shown in Scheme 9, protection of the amino group of the advanced intermediate 21 with 2,2,2-trichloroethyl chloroformate (Troc-Cl) gave the corresponding carbamate 39. In our previous syntheses of the saframycins, the reduction of the corresponding olefin was performed by catalytic hydrogenation over W-2 Raney nickel in ethanol under high pressure (1500 psi) of hydrogen at 120 °C for 20 hours. As part of our ongoing synthetic endeavor in the area of ecteinascidins, a facile reduction of the olefin using sodium cyanoborohydride and trifluoroacetic acid in acetic acid was realized.22 The hydride was delivered to the olefin 39 from the less hindered exo side, giving exclusively the desired endo product 40 in nearly quantitative yield.

Protection of phenol 40 with methanesulfonyl chloride (MsCl) under standard conditions yielded the robust mesylate 41. Subsequent Friedel-Crafts-type formylation25 with α,α-dichloromethyl methyl ether and titanium tetrachloride at low temperature furnished aldehyde 42. Baeyer-Villiger oxidation26 of 42 with 3-chloroperoxybenzoic acid (m-CPBA) in chloroform, followed by methanolysis of the resultant formate gave the phenol 43 (Scheme 9).
In order to effect the most critical Pictet-Spengler cyclization\textsuperscript{24} to complete the required pentacyclic skeleton, phenol 43 was converted to amino nitrile 46 in a five-step sequence as outlined in Scheme 10. Thus deprotection of the Troc group\textsuperscript{32} of 43 with active zinc dust in acetic acid
followed by reductive methylation\textsuperscript{33} of the resultant amine afforded tertiary amine \textbf{44}. Debromination by hydrogenolysis over Pearlman's catalyst, Pd(OH)\textsubscript{2}, produced \textbf{45}. Reduction of the lactam \textbf{45} with diisobutylaluminum hydride (DIBAL-H) at -78 °C furnished a hemiaminal, which was too unstable to handle. Therefore, this material was immediately converted to amino nitrile \textbf{46} by treatment with sodium cyanide in methanol at room temperature.

![Scheme 10](image)

Pictet-Spengler cyclization to form Ring D of the saframycins and eceinascidins has been studied extensively in our laboratories. As outlined in Scheme 11, we carried out the Pictet-Spengler cyclization of amino nitrile \textbf{47}, an intermediate that strongly resembles \textbf{46}, with various aldehydes in the
presence of (+)-camphorsulfonic acid (CSA) under a variety of conditions. To our disappointment, the tetrahydroisoquinolines 48a-e thus formed proved to be the wrong isomers (α-epimers) on the basis of the NOE studies.

![Scheme 11]

\[
\begin{align*}
48a & \quad R = -\text{CO}_2\text{Bu} \\
48b & \quad R = -\text{CH}_2\text{NHCOOCH}_3 \\
48c & \quad R = -\text{CH}_2\text{NHBz} \\
48d & \quad R = -\text{CH} = \text{CHCH}_3 \\
48e & \quad R = -\text{CH}_2\text{CH}_2\text{CH}_3
\end{align*}
\]

At this juncture, we observed an interesting and encouraging result when cinnamaldehyde was used as a substrate for the Pictet-Spengler cyclization. As shown in Scheme 12, when 47 was treated with cinnamaldehyde in the presence of CSA and trimethylsilyl cyanide (TMSCN) in acetonitrile at 60 °C, a mixture of the α-epimer 48f and β-epimer 48g of tetrahydroisoquinolines was obtained. To our delight, upon prolonged heating of the reaction mixture at 100 °C, the α-epimer 48f was converted to the thermodynamically favorable β-epimer 48g presumably via the highly conjugated quinomethide intermediate 49. The β-epimer 48g was isolated as the predominant product in 65% yield.
Based on the above studies, a stereocontrolled Pictet-Spengler cyclization of the amino nitrile 46 with cinnamaldehyde was achieved to
give the desired thermodynamically stable β-epimer 50 in 62% yield as the sole product (Scheme 13).
Benzylation of phenol 50 with potassium tert-butoxide and benzyl bromide gave 51. Direct conversion of olefin 51 to alcohol 53 by means of ozonolysis followed by sodium borohydride reduction was unsuccessful. As a result, a stepwise conversion was developed. Treatment of the olefin 51 with a catalytic amount of osmium tetroxide and N-methylmorpholine N-oxide (NMO) gave diol 52, which was cleaved with periodic acid to yield the expected aldehyde. In our earlier studies, all attempts to convert similar aldehydes into the corresponding amines were unsuccessful. Thus, the aldehyde was reduced with sodium borohydride to afford alcohol 53, which was mesylated and subsequently treated with sodium azide to give azide 54 (Scheme 13).

\[
\text{Scheme 14}
\]
At this stage, the mesylate group of 54 was converted to a more readily deprotectable t-Boc group. Alkaline hydrolysis of mesylate 54 in the presence of sodium cyanide provided phenol 55, which was subsequently protected as t-butyl carbonate 56 by treatment with di-tert-butyl dicarbonate. Upon reaction with active zinc dust and acetic acid in diethyl ether, azide 56 was reduced to primary amine 57 (Scheme 14).

Condensation of the amine 57 with N-t-Boc-L-alanine 58 by means of 1,3-dicyclohexylcarbodiimide (DCC) afforded the amide 59.
Hydrogenolysis of the benzyl group of 59 under careful conditions furnished phenol 60. Oxidation of the para-methoxy phenol 60 with ceric ammonium nitrate (CAN) gave the para-quinone 61 in excellent yield (Scheme 15).35

![Chemical Structures]

Scheme 16

Amino nitrile 61 was then carefully converted to aminal 62 upon treatment with silver nitrate in aqueous acetonitrile (Scheme 16).36 Finally, deprotection of the t-Boc groups with trifluoroacetic acid (TFA) followed by sodium bicarbonate treatment gave (−)-safracin B (1b). To
our knowledge, no authentic sample of (−)-safracin B is currently available. However, the spectroscopic (1H NMR, 13C NMR, IR, MS, HRMS) and physical properties of synthetic (−)-safracin B (1b) and its hydrochloride salt (63) (\([\alpha]_b^{23} -106^\circ (c=0.665, \text{MeOH}), \text{lit.}^{2b} [\alpha]_b^{20} -106^\circ (c=0.5, \text{MeOH})\)) were identical to those reported in the literature.
Experimental

Technical Notes

Melting points (mp), determined on a Mel-Temp melting point apparatus, are uncorrected.

Infrared (IR) spectra were recorded on a Nicolet 205 Infrared Spectrophotometer and are reported in wave numbers (cm\(^{-1}\)).

Nuclear magnetic resonance (NMR) spectra were determined on a Bruker AC250 Nuclear Magnetic Resonance spectrometer, unless otherwise noted. Chemical shifts are reported in parts per million downfield from tetramethylsilane (\(\delta = 0\)) as the internal standard. The following abbreviations are used for spin multiplicity:

s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet and b = broad.

Mass spectra (MS) were obtained on a Finnigan MAT95 mass spectrometer with electron impact ion source at 70 eV, unless otherwise noted, using probe insertion at temperatures between 50 to 300 °C. High resolution mass spectra were obtained under similar conditions.

Optical rotations were measured on a JASCO DP-370 polarimeter at ambient temperature.

Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F\(_{254}\). All reactions were monitored by thin layer chromatography, unless otherwise indicated. Preparative TLC separations were made on 10 x 20 cm or 20 x 20 cm plates prepared with a 2 mm layer of Merck silica gel 60 PF\(_{254}\). Compounds were eluted from the adsorbent with 10 % methanol in dichloromethane.
All evaporations were performed under reduced pressure on a rotary evaporator.

Column chromatography was performed on Merck silica gel, 32-63 mesh.

Hydrogenations were carried out in a stainless Parr general purpose bomb, unless otherwise noted.

Commercial grades reagents and solvents were used as supplied with the following exceptions:

Dichloromethane and ether: distilled through a 24 inch Snyder column.

Tetrahydrofuran (dry): distilled from sodium benzophenone ketyl.

$t$-Butanol: distilled from calcium hydride.

$N, N$-dimethylformamide, methanol, toluene, acetonitrile, and benzene: dried over 4Å molecular sieves.

All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.
2,2,2-Trichloroethyl urethane (39)

To a stirred solution of 2.95 g (6.03 mmol) of amine 21 and 1.52 g (18.09 mmol) of powdered sodium bicarbonate in 60 ml of dichloromethane was added 0.83 ml (6.63 mmol) of 2,2,2-trichloroethyl chloroformate at room temperature under an argon atmosphere. After 30 minutes, the reaction mixture was poured into a solution of 1N hydrochloric acid, and the aqueous layer was extracted thoroughly with ether (3X). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of ether in hexanes (40% to 80%), afforded carbamate 39 (3.85 g, 96.0%) as a yellow solid.
Characterization of 39:

Note: This material was obtained as an approximately 2:1 mixture of two TROC rotamers.

mp (Et₂O): 122-125 °C

IR (CHCl₃): 3280, 3020, 2970, 2880, 1720, 1690, 1610, 1480, 1420, 1400, 1300, 1280, 1230, 1110, 750

¹H NMR (CDCl₃): 2.11 (3H, s), 2.34 (3H, s), 3.15 (1H, dd, J = 17.6, 6.7 Hz), 3.33 (1H, AB, J = 17.6 Hz), 3.43 (3H, s), 3.71 & 3.72 (3H, s), 3.82 (3H, s), 4.66-4.98 (2H, m), 5.20-5.22 (1H, m), 6.10-6.19 (3H, m), 6.63 (1H, d, J = 8.5 Hz), 7.03 (1H, d, J = 8.5 Hz), 8.39 & 8.48 (1H, s)

¹³C NMR (CDCl₃): 8.8, 16.8, 33.5, 33.9, 49.6, 50.4, 52.7, 53.2, 55.7, 60.2, 61.2, 75.3, 77.2, 105.0, 105.4, 106.7, 117.9, 118.0, 119.5, 119.9, 120.0, 120.5, 128.0, 128.2, 128.4, 130.2, 130.5, 131.3, 144.3, 144.8, 145.1, 151.7, 152.0, 155.5, 158.4, 167.8, 168.0

MS: 668 (19, M+6), 667 (13, M+5), 666 (59, M+4), 665 (34, M+3), 664 (100, M+2), 663 (16, M+1), 662 (54, M+), 447 (11), 446 (19), 445 (17), 444 (29), 442 (12), 270 (18), 268 (19), 176 (15), 165 (17), 36 (25)

[α]D²⁰: +73.3° (c = 2.275, CHCl₃)

Exact Mass: Calculated for C₂₆H₂₆BrCl₃N₂O₇ 661.9989
Found 661.9988
Compound 39 continued:
Tetracyclic phenol (40)

A mixture of 3.64 g (5.48 mmol) of olefin 39 and 688 mg (10.96 mmol) of sodium cyanoborohydride in 4 ml of acetic acid and 10 ml of trifluoroacetic acid was heated at 65 °C for 45 minutes. Additional 344 mg (5.48 mmol) of sodium cyanoborohydride was added in several portions, and heating was continued until all of the 39 had been consumed as evidenced by thin layer chromatography. The reaction mixture was carefully poured into an ice cold saturated sodium bicarbonate solution, and the aqueous layer was extracted thoroughly with ether (3X). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of ether in hexanes (40% to 80%), yielded phenol 40 (3.60 g, 98.6%) as a yellow solid.
Characterization of 40:

Note: This material was obtained as an approximately 2 : 1 mixture of two TROC rotamers.

mp (Et₂O): 118-120 °C

IR (CHCl₃): 3380, 3300, 3020, 2960, 2850, 1720, 1670, 1590, 1490, 1460, 1420, 1300, 1260, 1230, 1110, 750

¹H NMR (CDCl₃): 2.06-2.22 (1H, m), 2.12 (3H, s), 2.39 (3H, s), 3.08 (1H, dd, J = 17.7, 7.1 Hz), 3.29 (1H, AB, J = 17.7 Hz), 3.45-3.51 (1H, m), 3.66 (3H, s), 3.79-3.80 (6H, s), 4.22-4.33 (1H, m), 4.67-4.92 (2H, m), 4.98-5.05 (1H, m), 5.74-5.85 (2H, m), 6.06 (1H, bs), 6.55 (1H, d, J = 8.3 Hz), 6.84&6.87 (1H, d, J = 8.3 Hz)

¹³C NMR (CDCl₃): 9.3, 16.9, 32.4, 32.6, 34.2, 34.8, 48.1, 48.7, 52.0, 52.6, 55.7, 57.9, 58.1, 60.5, 60.6, 61.2, 75.1, 75.2, 95.0, 95.4, 106.5, 117.6, 117.7, 118.2, 120.5, 120.9, 121.0, 128.0, 128.1, 129.7, 130.0, 131.6, 144.1, 144.2, 145.2, 145.5, 151.8, 151.9, 157.7, 158.4, 168.9, 169.2

MS: 668 (10, M+4), 667 (6, M+3), 666 (18, M+2), 665 (3, M+1), 664 (10, M⁺), 475 (13), 473 (20), 446 (12), 445 (14), 444 (17), 270 (13), 268 (12), 166 (73), 165 (100), 131 (20)

[α]D²⁰: -36.1° (c = 3.035, CHCl₃)

Exact Mass: Calculated for C₂₆H₂₈BrCl₃N₂O₇ 664.0146
            Found 664.0139
Compound 40 continued:
Tetracyclic mesylate (41)

To a stirred solution of 3.61 g (5.41 mmol) of phenol 40 and 1.51 ml (10.82 mmol) of triethylamine in 30 ml of dichloromethane was added 0.50 ml (4.32 mmol) of methanesulfonyl chloride at room temperature under an argon atmosphere. After 30 minutes, the reaction mixture was poured into a solution of 1N hydrochloric acid, and the aqueous layer was extracted thoroughly with ether (3X). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of ether in hexanes (40% to 80%), provided mesylate 41 (3.97 g, 98.4%) as a yellow solid.
Characterization of 41:

Note: This material was obtained as an approximately 2 : 1 mixture of two TROC rotamers.

mp (Et₂O): 123-125 °C

IR (CHCl₃): 3360, 3010, 2920, 2820, 1720, 1690, 1620, 1460, 1440, 1380, 1280, 1180, 1110, 800, 750

¹H NMR (CDCl₃): 1.97-2.08 (1H, m), 2.13 (3H, s), 2.44 (3H, s), 3.13 (1H, dd, J = 17.8, 7.0 Hz), 3.33 (1H, dd, J = 17.8, 4.7 Hz), 3.42 (3H, s), 3.51-3.56 (1H, m), 3.67 & 3.68 (3H, s), 3.80 (3H, s), 3.84 (3H, s), 4.29-4.41 (1H, m), 4.53-5.11 (3H, m), 5.64 & 5.73 (1H, s), 6.03-6.11 (1H, m), 6.55 & 6.58 (1H, d, J = 8.3 Hz), 6.84 & 6.88 (1H, d, J = 8.3 Hz)

¹³C NMR (CDCl₃): 9.2, 17.1, 32.3, 32.8, 34.8, 34.9, 35.0, 40.0, 48.8, 49.7, 51.5, 51.6, 52.3, 55.7, 57.5, 58.0, 60.4, 60.5, 61.3, 75.3, 95.1, 106.4, 106.5, 120.3, 120.7, 120.8, 125.6, 127.7, 127.8, 130.9, 131.5, 134.6, 140.1, 149.4, 149.7, 151.5, 157.7, 158.6, 168.4, 168.6

MS: 748 (3, M+6), 746 (7, M+4), 744 (13, M+2), 742 (10, M+), 665 (14), 446 (8), 444 (10), 270 (14), 268 (19), 166 (100), 165 (100), 133 (12), 105 (17)

[α]D²⁰: -35.6° (c = 3.385, CHCl₃)
Compound 41 continued:
Tetracyclic aldehyde (42)

To a stirred solution of 3.97 g (5.34 mmol) of 41 and 1.58 ml (16.02 mmol) of titanium tetrachloride in 50 ml of dichloromethane was slowly added 0.63 ml (8.01 mmol) of α,α-dichloromethyl methyl ether at 0 °C under an argon atmosphere. After one hour, the reaction mixture was slowly poured into a stirring solution of ice chips. After the solution turned clear, it was extracted thoroughly with dichloromethane (4X). The combined organic extracts were washed with 3N hydrochloric acid solution, 1N hydrochloric acid solution, saturated sodium bicarbonate solution, and brine. The extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to yield aldehyde 42 (3.71 g, 90%) as a yellow solid which was used in the next step without purification.
Characterization of 42:

Note: This material was obtained as an approximately 2 : 1 mixture of two TROC rotamers.

mp (Et₂O): 146-148 °C

IR (CHCl₃): 3200, 3030, 2950, 2850, 1720, 1690, 1580, 1450, 1380, 1300, 1180, 1100, 1020, 800, 750

¹H NMR (CDCl₃): 2.02-2.18 (1H, m), 2.26 (3H, s), 2.46 (3H, s), 3.13 (1H, dd, J = 17.9, 6.8 Hz), 3.32 (1H, AB, J = 17.9 Hz), 3.42 (3H, s), 3.53-3.64 (1H, m), 3.80 (3H, s), 3.85 (3H, s), 3.88 (3H, s), 4.37-4.48 (1H, m), 4.53-5.13 (3H, m), 5.41&5.49 (1H, s), 6.09 (1H, d, J = 16.0 Hz), 7.41&7.44 (1H, s), 10.24 (1H, s)

¹³C NMR (CDCl₃): 9.6, 17.1, 32.8, 33.3, 34.7, 34.9, 40.0, 40.1, 48.8, 49.6, 51.6, 52.4, 56.6, 57.1, 60.5, 60.6, 61.4, 63.5, 75.3, 77.3, 95.1, 125.3, 125.4, 125.7, 126.7, 127.9, 128.1, 130.9, 131.5, 134.9, 140.0, 140.1, 149.4, 151.4, 163.2, 163.7, 168.5, 168.7, 188.8

MS: 774 (11, M+4), 772 (10, M+2), 770 (10, M+), 695 (20), 694 (26), 693 (32), 692 (29), 691 (13), 579 (39), 473 (30), 444 (44), 410 (41), 366 (37), 364 (43), 270 (82), 268 (100), 222 (60), 194 (52), 193 (69), 80 (52)

[α]D²⁰: -29.0° (c = 1.925, CHCl₃)

Exact Mass: Calculated for C₂₈H₃₀BrCl₃N₂O₁₀S 769.9871

Found 769.9872
Compound 42 continued:
**o,p-Dimethoxy phenol (43)**

To a stirred solution of 3.71 g (4.80 mmol) of aldehyde 42 in 40 ml of chloroform was slowly added 1.55 g (7.20 mmol) of 80% 3-chloroperoxybenzoic acid (m-CPBA) at room temperature. After heating at 85 °C for 2 hours, the reaction mixture was cooled to room temperature. The mixture was poured into a saturated sodium sulfite solution, and the aqueous layer was extracted thoroughly with ether (3X). The combined organic extracts were washed with sodium bicarbonate solution and brine. The extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give crude formate which was used in the subsequent step without purification.

The crude formate was dissolved in 20 ml of methanol and 0.67 ml (4.80 mmol) of triethylamine was added at room temperature. After stirring for one hour, the reaction mixture was evaporated to small volume under reduced pressure. The mixture was poured into a solution of 3N hydrochloric acid, and the aqueous layer was extracted thoroughly with ether (3X). The combined organic extracts were washed brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*.
Purification of the crude product by column chromatography on silica gel, eluted with a gradient of ether in hexanes (40% to 80%), gave phenol 43 (3.37 g, 92.3%) as a yellow solid.

Characterization of 43:

Note: This material was obtained as an approximately 2 : 1 mixture of two TROC rotamers.

mp (Et₂O): 136-138 °C

IR (CHCl₃): 3360, 3020, 2940, 2850, 1720, 1680, 1500, 1480, 1440, 1380, 1300, 1180, 1120, 1020, 800, 750

¹H NMR (CDCl₃): 1.95-2.10 (1H, m), 2.20 (3H, s), 2.44 (3H, s), 3.13 (1H, dd, J = 17.8, 7.1 Hz), 3.33 (1H, dd, J = 17.8, 4.1 Hz), 3.41 (3H, s), 3.47-3.50 (1H, m), 3.62&3.65 (3H, s), 3.74 (3H, s), 3.83 (3H, s), 4.28-4.58 (1H, m), 4.53-5.07 (3H, m), 5.79&5.86 (1H, s), 6.02-6.10 (2H, m), 6.52&6.55 (1H, s)

¹³C NMR (CDCl₃): 9.7, 16.9, 32.1, 32.6, 34.6, 34.8, 39.9, 48.6, 49.5, 51.3, 52.1, 57.2, 57.7, 60.3, 60.4, 60.5, 61.1, 75.1, 77.1, 94.7, 94.8, 113.9, 114.0, 124.3, 125.3, 125.4, 127.5, 127.6, 130.7, 131.3, 134.5, 139.9, 145.3, 145.6, 145.7, 149.2, 149.5, 150.3, 151.3, 151.4, 168.5, 168.8

MS: 762 (15, M⁺4), 761 (6, M⁺3), 760 (17, M⁺2), 758 (10, M⁺), 683 (12), 682 (19), 681 (16), 680 (16), 679 (7), 446 (11), 444 (14), 270 (33), 268 (38), 182 (100), 181 (94), 80 (28), 64 (21)

[α]D²⁰: -35.3° (c = 2.320, CHCl₃)

Exact Mass: Calculated for C₂₇H₃₀BrCl₃N₂O₁₀S 757.9871

Found 757.9873
Compound 43 continued:
Tetracyclic $N$-methylamine (44)

To a stirred solution of 3.66 g (4.81 mmol) of urethane 43 and 1.57 g (24.05 mmol) of active zinc dust in 20 ml of $N,N$-dimethyl-formamide was slowly added 0.41 ml (7.22 mmol) of acetic acid at 80 °C. After 30 minutes, 273 µl (4.81 mmol) of acetic acid was added in several portions, and the reaction was monitored carefully by thin layer chromatography until all of the 43 had been consumed. After cooling, the reaction mixture was filtered through celite, washed with methanol, and concentrated in vacuo to give secondary amine which was used in the subsequent step without purification.

The secondary amine was dissolved in 40 ml of methanol and 1.95 ml (24.05 mmol) of 37 % aqueous formaldehyde, 302 mg (4.81 mmol) of sodium cyanoborohydride, and 185 µl (2.41 mmol) of trifluoroacetic acid were added consecutively. After stirring for 20 minutes, the reaction mixture was poured into a saturated sodium bicarbonate solution, and the aqueous layer was extracted thoroughly with ether (3X). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of methanol
in dichloromethane (2% to 5%), afforded N-methyl amine 44 (2.74 g, 95.0%) as a yellow oil.

Characterization of 44:

IR (CHCl₃): 3380, 3020, 2920, 1680, 1500, 1470, 1380, 1350, 1180, 1120, 1060, 1020, 820, 750

¹H NMR (CDCl₃): 1.94 (1H, dd, J = 13.3, 12.2 Hz), 2.20 (3H, s), 2.42 (3H, s), 2.44 (3H, s), 2.93 (1H, dd, J = 18.4, 1.1 Hz), 3.04 (1H, dd, J = 18.4, 6.6 Hz), 3.30-3.37 (1H, m), 3.37 (3H, s), 3.60 (3H, s), 3.76 (1H, d, J = 6.1 Hz), 3.75 (3H, s), 3.81 (3H, s), 4.28-4.35 (1H, m), 4.56 (1H, d, J = 4.2), 5.57 (1H, s), 5.87 (1H, bs), 6.52 (1H, s)

¹³C NMR (CDCl₃): 9.8, 16.9, 29.0, 32.0, 39.5, 39.7, 55.6, 56.6, 58.6, 60.5, 60.7, 61.3, 114.1, 125.3, 126.6, 127.6, 131.1, 133.5, 141.3, 145.2, 145.8, 149.2, 150.5, 171.8

MS: 600 (18, M⁺2), 598 (20, M⁺), 521 (13), 519 (13), 363 (41), 362 (100), 361 (37), 360 (93), 285 (17), 284 (94), 283 (42), 282 (95), 281 (30), 204 (41), 160 (28), 69 (19)

[α]D²⁰: -102.4° (c = 2.120, CHCl₃)

Exact Mass: Calculated for C₂₅H₃₁BrN₂O₈S 598.0985
             Found 598.0986
Compound 44 continued:
Tetracyclic debrominated benzene (45)

To a mixture of 3.37 g (5.62 mmol) of 44 and 337 mg (0.56 mmol) of Pearlman's catalyst in the Parr bomb was added 35 ml of ethanol. High pressure hydrogen gas (1000 psi) was applied to the Parr bomb. The reaction mixture was stirred and heated at 65 °C for 2 hours. After all of the 44 had been consumed as evidenced by thin layer chromatography, the reaction mixture was filtered through celite, washed with ethyl acetate, and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of methanol in dichloromethane (2% to 5%), furnished debrominated benzene 45 (2.34 g, 80.0%) as a yellow solid.
Characterization of 45:

mp (Et₂O): 118-120 °C

IR (CHCl₃): 3350, 3030, 2950, 1680, 1500, 1450, 1380, 1360, 1250, 1180, 1120, 1020, 810, 760

¹H NMR (CDCl₃): 1.98 (1H, dd, J = 13.1, 13.1 Hz), 2.19 (3H, s), 2.31 (3H, s), 2.46 (3H, s), 2.82 (1H, AB, J = 17.6 Hz), 3.20 (1H, dd, J = 17.6, 7.0 Hz), 3.29 (1H, dd, J = 13.1, 2.5 Hz), 3.35 (3H, s), 3.56 (3H, s), 3.56-3.60 (1H, m), 3.75 (3H, s), 3.81 (3H, s), 4.27-4.34 (1H, m), 4.52 (1H, d, J = 4.2 Hz), 5.56 (1H, s), 5.79 (1H, bs), 6.53 (1H, s), 6.97 (1H, s)

¹³C NMR (CDCl₃): 9.8, 15.7, 26.4, 31.9, 39.4, 39.5, 55.3, 56.7, 58.3, 60.5, 60.6, 60.8, 77.3, 114.1, 124.8, 125.3, 125.4, 130.5, 132.2, 141.9, 145.2, 145.9, 148.8, 150.5, 172.3

MS: 521 (8, M+1), 520 (26, M+), 441 (16), 284 (15), 283 (41), 282 (100), 205 (19), 204 (93), 203 (31), 189 (16), 188 (24), 174 (12), 160 (11)

[α]D²⁰: -162.5° (c = 3.205, CHCl₃)

Exact Mass: Calculated for C₂₅H₃₂N₂O₈S 520.1879
Found 520.1875
Compound 45 continued:
Amino nitrile (46)

To a stirred solution of 1.94 g (3.73 mmol) of lactam 45 in 40 ml of dichloromethane was slowly added 9.94 ml (14.92 mmol) of 1.5 M diisobutylaluminum hydride in toluene at -78 °C under an argon atmosphere. After 30 min, the reaction mixture was slowly quenched with 40 ml of methanol, and 0.91 g (18.65 mmol) of sodium cyanide was then added. The solution was allowed to warm to room temperature over a period of 30 minutes. After stirring the reaction mixture for 1 hour at room temperature, all of the hemiaminal had been consumed as evidenced by thin layer chromatography. The reaction mixture was filtered through celite and washed with 10% methanol in dichloromethane. The filtrate was concentrated in vacuo to a small volume and was poured into a saturated sodium bicarbonate solution. The aqueous layer was extracted thoroughly with dichloromethane (4X), and the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give amino nitrile 46 (1.90 g, 96.0%) as a yellow solid which was used in the next step without purification.
Characterization of 46:

mp (Et₂O): 120-122 °C

IR (CHCl₃): 3480, 3360, 3030, 2970, 2860, 2230, 1480, 1450, 1420, 1370, 1240, 1180, 1000, 800, 750

¹H NMR (CDCl₃): 1.98 (1H, dd, J = 13.8, 11.2 Hz), 2.19 (3H, s), 2.30 (3H, s), 2.37 (3H, s), 2.51 (1H, AB, J = 17.9 Hz), 3.08 (1H, dd, J = 13.8, 7.9 Hz), 3.09-3.16 (1H, m), 3.23-3.27 (1H, m), 3.32 (3H, s), 3.57 (3H, s), 3.73-3.77 (1H, m), 3.76 (3H, s), 3.80 (3H, s), 3.91 (1H, d, J = 2.2 Hz), 4.34 (1H, d, J = 2.6 Hz), 5.41 (1H, bs), 6.55 (1H, s), 6.91 (1H, s)

¹³C NMR (CDCl₃): 9.9, 15.7, 25.4, 31.8, 39.4, 41.7, 53.7, 54.6, 56.2, 57.7, 60.6, 77.3, 113.3, 119.8, 124.8, 125.8, 126.7, 128.9, 131.1, 132.1, 141.8, 144.6, 145.2, 148.2, 150.8

MS: 531 (<1, M⁺), 504 (100), 473 (34), 426 (33), 425 (92), 283 (34), 282 (66), 243 (29), 216 (58), 204 (79), 203 (28), 181 (61), 160 (17)

[α]D²⁰: -42.9° (c = 2.495, CHCl₃)

Exact Mass: Calculated for C₂₆H₃₃N₃O₇S 531.2039
           Found 531.2036
Compound 46 continued:
Pentacyclic phenol (50)

To a stirred solution of 1.90 g (3.57 mmol) of amino nitrile 46 in 30 ml of acetonitrile in a sealed tube was added 1.89 ml (14.28 mmol) of cinnamaldehyde, 2.49 g (10.71 mmol) of (+)-camphorsulfonic acid (CSA), and 476 µl (3.57 mmol) of trimethylsilyl cyanide (TMSCN) consecutively. After heating at 100 °C for 6 hours, the reaction mixture was cooled to room temperature. The mixture was poured into a saturated sodium bicarbonate solution, and the aqueous layer was extracted thoroughly with dichloromethane (3X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of ether in hexanes (40% to 80%), provided pentacyclic phenol 50 (1.42 g, 61.5%) as a yellow solid.
Characterization of 50:

mp (Et₂O): 140-142 °C

IR (CHCl₃): 3450, 3020, 2940, 2820, 2220, 1650, 1500, 1470, 1420, 1370, 1180, 1070, 1110, 970, 800, 750

¹H NMR (CDCl₃): 1.88 (1H, dd, J = 15.1, 11.7 Hz), 2.18 (3H, s), 2.41 (3H, s), 2.52 (3H, s), 2.55 (1H, AB, J = 18.0 Hz), 3.13 (1H, dd, J = 18.0, 7.9 Hz), 3.26 (1H, dd, J = 15.1, 2.4 Hz), 3.34-3.38 (2H, m), 3.38 (3H, s), 3.65 (3H, s), 3.74 (3H, s), 3.77 (3H, s), 3.99 (1H, d, J = 2.3 Hz), 4.42 (1H, d, J = 2.7 Hz), 4.63 (1H, d, J = 5.4 Hz), 5.56 (1H, s), 6.14 (1H, dd, J = 15.7, 5.4 Hz), 6.36 (1H, d, J = 15.7 Hz), 6.98 (1H, s), 7.13-7.28 (5H, m)

¹³C NMR (CDCl₃): 9.6, 15.8, 25.6, 25.8, 39.5, 41.5, 55.3, 56.4, 57.6, 59.1, 60.0, 60.6, 60.7, 60.9, 77.3, 118.1, 119.4, 122.1, 123.4, 126.4, 126.6, 127.3, 128.5, 128.9, 129.2, 129.9, 131.4, 132.1, 137.2, 141.7, 142.2, 143.8, 148.4, 148.5

MS: 646 (4, M+1), 645 (12, M+), 618 (23), 566 (10), 540 (14), 539 (27), 322 (20), 283 (18), 282 (55), 220 (34), 218 (17), 205 (29), 204 (100), 203 (29), 189 (15), 188 (18)

[α]D²⁰: -27.6° (c = 1.560, CHCl₃)

Exact Mass: Calculated for C₃₅H₃₉N₃O₇S 645.2509
Found 645.2510
Compound 50 continued:
Pentacyclic benzyl ether (51)

To a stirred solution of 1.42 g (2.20 mmol) of phenol 50 in 20 ml of N,N-dimethylformamide was added 2.20 ml (2.20 mmol) of 1M t-BuOK in t-BuOH solution followed by 0.26 ml (2.20 mmol) of benzyl bromide at room temperature under an argon atmosphere. After 30 min, 2.20 ml (2.20 mmol) of 1N silver nitrate solution was added to the reaction mixture. The reaction mixture was filtered through celite and washed with ether. The filtrate was poured into a dilute sodium chloride solution, and the aqueous layer was extracted thoroughly with ether (3X). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of ether in hexanes (40% to 80%), afforded benzyl ether 51 (1.37 g, 84.6%) as a yellow solid.
Characterization of 51:

mp (Et₂O): 116-118 °C

IR (CHCl₃): 3030, 2950, 2820, 2220, 1580, 1500, 1450, 1420, 1380, 1350, 1180, 1080, 1010, 980, 800, 750

¹H NMR (CDCl₃): 1.87 (1H, dd, J = 14.9, 11.8 Hz), 2.19 (3H, s), 2.35 (3H, s), 2.41 (3H, s), 2.50 (1H, AB, J = 18.0 Hz), 3.12 (1H, dd, J = 18.0, 7.9 Hz), 3.25-3.38 (3H, m), 3.38 (3H, s), 3.69 (3H, s), 3.76 (3H, s), 3.79 (3H, s), 3.94 (1H, d, J = 2.2 Hz), 4.42 (1H, d, J = 2.4 Hz), 4.64 (1H, d, J = 5.2 Hz), 5.04 (2H, AB, J = 11.1 Hz), 5.97 (1H, dd, J = 15.8, 5.2 Hz), 6.13 (1H, d, J = 15.8 Hz), 6.95-6.98 (3H, m), 7.13-7.23 (3H, m), 7.34-7.51 (5H, m)

¹³C NMR (CDCl₃): 9.4, 15.8, 25.6, 25.8, 39.5, 41.5, 55.3, 56.8, 57.7, 59.7, 60.2, 60.5, 60.8, 74.6, 77.3, 118.2, 123.7, 124.1, 126.4, 126.7, 127.3, 127.8, 127.9, 128.4, 128.5, 128.9, 130.7, 131.4, 132.2, 137.1, 138.1, 142.1, 145.0, 148.4, 150.3, 151.6

MS: 736 (4, M+1), 735 (9, M⁺), 657 (12), 656 (22), 322 (30), 283 (23), 282 (65), 244 (14), 243 (15), 205 (31), 204 (100), 203 (29), 189 (11), 188 (22), 91 (22)

[α]D²⁰: -78.9° (c = 1.980, CHCl₃)

Exact Mass: Calculated for C₄₂H₄₅N₃O₇S 735.2978
             Found 735.2976
Compound 51 continued:
**Pentacyclic diol (52)**

To a stirred solution of 1.30 g (1.77 mmol) of olefin 51 in 15 ml of acetone and 3 ml of water was added one small crystal of osmium tetroxide and 310 mg (2.66 mmol) of N-methylmorpholine N-oxide at room temperature. After 2 hours, the reaction mixture was poured into a saturated sodium sulfite solution, and the aqueous layer was extracted thoroughly with dichloromethane (4X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of ether in hexanes (40% to 80%), gave diol 52 (1.09 g, 80.1%) as a white solid.
Characterization of 52:

mp (Et₂O): 144–146 °C

IR (CHCl₃): 3520, 3040, 2950, 2850, 2260, 1600, 1480, 1450, 1360, 1060, 1000, 960, 800, 750

¹H NMR (CDCl₃): 1.89 (1H, dd, J = 14.7, 11.7 Hz), 2.21 (3H, s), 2.28 (3H, s), 2.42 (3H, s), 2.72 (1H, AB, J = 18.0 Hz), 2.80-2.84 (2H, m), 3.17-3.38 (5H, m), 3.38 (3H, s), 3.72 (3H, s), 3.79 (3H, s), 3.80 (3H, s), 4.35-4.48 (3H, m), 4.63 (1H, d, J = 2.2 Hz), 4.91 (1H, AB, J = 10.6 Hz), 5.21 (1H, AB, J = 10.6 Hz), 6.76-6.80 (2H, m), 6.95 (1H, s), 7.12-7.19 (3H, m), 7.35-7.56 (5H, m)

¹³C NMR (CDCl₃): 9.5, 15.6, 25.6, 26.2, 39.5, 41.0, 55.4, 57.9, 59.0, 60.4, 60.5, 60.7, 60.8, 62.3, 70.9, 75.8, 77.3, 79.9, 118.2, 124.8, 125.2, 125.3, 125.6, 126.1, 126.3, 127.0, 128.0, 128.2, 128.3, 128.6, 128.8, 129.3, 131.7, 137.2, 141.8, 142.0, 144.7, 148.7, 150.5, 152.1

MS: 742 (<1, M⁺ - HCN), 663 (3), 606 (18), 605 (21), 530 (23), 529 (54), 282 (21), 221 (17), 220 (100), 206 (23), 204 (43), 107 (25), 105 (52), 91 (34), 77 (40)

[α]D₂₀: +4.8° (c = 2.360, CHCl₃)

Exact Mass: Calculated for (M⁺ - HCN)
C₄₁H₄₆N₂O₉S 742.2938
Found 742.2921
Compound 52 continued:
Pentacyclic alcohol (53)

To a stirred solution of 950.6 mg (1.23 mmol) of diol 52 in 5 ml of ethanol and 1 ml of water was slowly added 562.9 mg (2.46 mmol) of periodic acid at room temperature. After 30 min, the reaction mixture was poured into a solution of sodium bicarbonate, and the aqueous layer was extracted thoroughly with dichloromethane (3X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give crude aldehyde which was used in the subsequent step without purification.

The crude aldehyde was dissolved in 10 ml of methanol and 70.1 mg (1.85 mmol) of sodium borohydride was added. After one hour, the reaction mixture was poured into a saturated sodium chloride solution, and the aqueous layer was extracted thoroughly with dichloromethane (4X). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of ether in
hexanes (40% to 80%), afforded alcohol 53 (725.4 mg, 88.5%) as a white solid.

Characterization of 53:

mp (Et$_2$O): 128-130 °C

IR (CHCl$_3$): 3500, 3030, 2950, 2830, 2220, 1490, 1460, 1410, 1360, 1180, 1080, 1010, 970, 800, 750

$^1$H NMR (CDCl$_3$): 1.70-1.81 (2H, m), 2.20 (3H, s), 2.27 (3H, s), 2.41 (3H, s), 2.53 (1H, AB, $J = 18.1$ Hz), 3.10-3.37 (5H, m), 3.37 (3H, s), 3.45-3.53 (1H, m), 3.70 (3H, s), 3.74 (3H, s), 3.79 (3H, s), 4.03 (1H, d, $J = 2.3$ Hz), 4.09 (1H, t, $J = 4.5$ Hz), 4.40 (1H, d, $J = 2.3$ Hz), 4.87 (1H, AB, $J = 11.0$ Hz), 5.16 (1H, AB, $J = 11.0$ Hz), 6.92 (1H, s), 7.33-7.50 (5H, m)

$^{13}$C NMR (CDCl$_3$): 9.4, 15.7, 25.6, 25.7, 39.4, 41.3, 55.2, 56.9, 57.6, 58.9, 60.4, 60.5, 60.7, 61.0, 66.2, 75.0, 77.2, 117.6, 124.4, 125.5, 126.1, 127.9, 128.5, 128.6, 131.3, 131.7, 137.7, 141.8, 144.8, 148.5, 150.1, 151.4

MS: 663 (<1, M$^+$), 636 (7), 632 (19), 584 (4), 559 (29), 558 (36), 557 (93), 282 (24), 262 (23), 261 (24), 204 (100), 203 (23), 91 (50)

$[\alpha]_D^{20}$: +18.1° (c = 2.485, CHCl$_3$)

Exact Mass: Calculated for C$_{35}$H$_{41}$N$_3$O$_8$S 663.2614
Found 663.2609
Compound 53 continued:
Pentacyclic azide (54)

To a stirred solution of 675.4 mg (1.02 mmol) of alcohol 53 in 10 ml of dichloromethane was added 0.22 ml (1.53 mmol) of triethylamine and 94.5 μl (1.23 mmol) of methanesulfonyl chloride at room temperature under an argon atmosphere. After 1 hour, the reaction mixture was poured into a saturated sodium chloride solution, and the aqueous layer was extracted thoroughly with dichloromethane (3X). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give the crude mesylate product which was used in the subsequent step without purification.

The mesylate product was dissolved in 10 ml of N,N-dimethylformamide, and 307 mg (5.10 mmol) of sodium azide was added at room temperature. After heating the reaction mixture at 85 °C for one hour, the reaction mixture was poured into a solution of sodium chloride, and the aqueous layer was extracted thoroughly with ether (3X). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Purification of the crude product by column
chromatography on silica gel, eluted with a gradient of ether in hexanes (40% to 80%), provided azide 54 (600.6 mg, 85.7%) as a white solid.

Characterization of 54:

mp (Et₂O): 105-107 °C

IR (CHCl₃): 3050, 2960, 2870, 2120, 1500, 1460, 1420, 1360, 1180, 1070, 1000, 960, 800, 750

⁵¹H NMR (CDCl₃): 1.83 (1H, dd, J = 15.4, 12.1 Hz), 2.21 (3H, s), 2.26 & 2.28 (3H, s), 2.38 (3H, s), 2.66 (1H, AB, J = 17.9 Hz), 2.75-2.91 (1H, m), 3.12 (1H, dd, J = 17.9, 7.8 Hz), 3.24-3.44 (4H, m), 3.37 (3H, s), 3.72 (3H, s), 3.76 (3H, s), 3.79 (3H, s), 4.07-4.11 (1H, m), 4.17 (1H, d, J = 2.3 Hz), 4.35 (1H, s), 4.87 (1H, AB, J = 10.8 Hz), 5.16 (1H, AB, J = 10.8 Hz), 6.92 (1H, s), 7.34-7.53 (5H, m)

¹³C NMR (CDCl₃): 9.3, 15.6, 25.4, 25.6, 39.3, 41.2, 55.2, 57.5, 57.7, 58.5, 60.3, 60.5, 61.8, 75.0, 77.1, 117.9, 124.6, 124.8, 124.9, 125.6, 127.9, 128.5, 128.9, 131.1, 131.8, 137.5, 141.5, 144.6, 147.9, 150.1, 151.4

MS: 688 (<1, M⁺), 633 (27), 632 (68), 554 (11), 323 (10), 322 (50), 283 (33), 282 (93), 244 (21), 205 (34), 204 (100), 203 (38), 189 (14), 188 (14), 91 (44)
Compound 54 continued:
Azide phenol (55)

To a stirred solution of 769.0 mg (1.12 mmol) of mesylate 54 in 5 ml of methanol was added 1.11 ml (3.36 mmol) of 3N sodium hydroxide solution and 547 mg (11.2 mmol) of sodium cyanide at room temperature under an argon atmosphere. After refluxing at 85 °C for 3 hours, the reaction mixture was cooled to room temperature and was then poured into a solution of 3N hydrochloric acid. The aqueous layer was extracted thoroughly with dichloromethane (3X), and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of ether in hexanes (40% to 80%), gave phenol 55 (622.2 mg, 91.0%) as a yellow solid.
Characterization of 55:

mp (Et₂O): 89-91 °C

IR (CHCl₃): 3450, 2950, 2860, 2110, 1600, 1500, 1460, 1420, 1300, 1240, 1070, 1020, 760, 700

¹H NMR (CDCl₃): 1.93 (1H, dd, J = 15.8, 12.3 Hz), 2.20 (3H, s), 2.25 (3H, s), 2.33 (3H, s), 2.65 (1H, AB, J = 17.8 Hz), 2.80 (1H, dd, J = 11.6, 8.4 Hz), 3.06 (1H, dd, J = 17.8, 7.9 Hz), 3.21-3.33 (4H, m), 3.67 (3H, s), 3.76 (3H, s), 3.80 (3H, s), 4.08-4.14 (2H, m), 4.20 (1H, d, J = 2.3 Hz), 4.88 (1H, AB, J = 10.9 Hz), 5.15 (1H, AB, J = 10.9 Hz), 5.78 (1H, bs), 6.49 (1H, s), 7.33-7.51 (5H, m)

¹³C NMR (CDCl₃): 9.4, 15.7, 25.7, 25.8, 41.7, 55.5, 56.8, 57.5, 58.1, 58.8, 60.4, 60.6, 60.7, 62.1, 75.1, 77.2, 116.7, 118.4, 121.1, 124.5, 125.0, 125.5, 128.0, 128.4, 128.5, 131.1, 137.6, 142.6, 144.7, 146.4, 150.0, 151.5

MS: 610 (<1, M⁺), 555 (27), 554 (67), 245 (9), 244 (47), 205 (37), 204 (100), 190 (6), 189 (15), 91 (17)

[α]D²₀: -32.1° (c = 2.485, CHCl₃)
Compound 55 continued:
Pentacyclic t-butyl carbonate (56)

To a stirred solution of 622.2 mg (1.02 mmol) of phenol 55 in 10 ml of dichloromethane was added 284.2 µl (2.04 mmol) of triethylamine, 267.1 mg (1.22 mmol) of di-tert-butyl dicarbonate and 12.5 mg (0.1 mmol) of 4-dimethylaminopyridine (DMAP) at room temperature under an argon atmosphere. After 30 minutes, the reaction mixture was poured into a solution of 1N hydrochloric acid, and the aqueous layer was extracted thoroughly with dichloromethane (3X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of ether in hexanes (40% to 80%), furnished 56 (695.5 mg, 95.9%) as a white solid.
Characterization of 56:

mp (Et₂O): 96-98 °C

IR (CHCl₃): 3020, 2970, 2800, 2350, 2100, 1760, 1460, 1420, 1280, 1250, 1150, 1080, 1010

¹H NMR (CDCl₃): 1.58 (9H, s), 1.94 (1H, dd, J = 15.0, 11.9 Hz), 2.20 (3H, s), 2.26 (3H, s), 2.30 (3H, s), 2.69 (1H, AB, J = 17.8 Hz), 2.79 (1H, dd, J = 11.6, 8.6 Hz), 3.04-3.33 (6H, m), 3.70 (3H, s), 3.75 (3H, s), 3.80 (3H, s), 4.07-4.11 (1H, m), 4.19 (1H, d, J = 2.3 Hz), 4.88 (1H, AB, J = 10.9 Hz), 5.15 (1H, AB, J = 10.9 Hz), 6.84 (1H, s), 7.34-7.51 (5H, m)

¹³C NMR (CDCl₃): 9.4, 15.8, 25.6, 25.9, 27.7, 41.5, 55.4, 57.5, 57.7, 57.8, 58.8, 60.4, 60.5, 60.6, 62.1, 75.1, 77.2, 83.2, 118.2, 123.1, 124.7, 124.8, 125.0, 127.5, 128.0, 128.5, 130.5, 130.6, 137.6, 142.5, 144.6, 147.8, 150.1, 151.4, 151.5

MS: 710 (<1, M⁺), 655 (25), 654 (55), 554 (26), 304 (13), 244 (36), 205 (29), 204 (100), 189 (12), 91 (12)

[α]D²⁰: -35.0° (c = 2.445, CHCl₃)

Exact Mass: Calculated for C₃₉H₄₆N₆O₇ 710.3428
Found 710.3430
Compound 56 continued:
Pentacyclic amine (57)

To a stirred solution of 491.1 mg (0.69 mmol) of t-butyl carbonate 56 in 7 ml of ether was added 226 mg (3.45 mmol) of active zinc dust and 59.3 µl (1.04 mmol) of acetic acid at room temperature. The reaction mixture was stirred vigorously for one hour, and additional 59.3 µl (1.04 mmol) of acetic acid was added. After another hour, the reaction mixture was filtered through celite and washed with ether thoroughly. The filtrate was poured into a solution of sodium bicarbonate, and the aqueous layer was extracted thoroughly with dichloromethane (4X). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel, with a gradient of methanol in dichloromethane (5% to 50%), afforded amine 57 (422.0 mg, 89.2%) as a white solid.
Characterization of 57:

mp (Et₂O): 99-102 °C

IR (CHCl₃): 3400, 3020, 2970, 2860, 1760, 1460, 1420, 1280, 1250, 1150, 1100, 1030, 750

¹H NMR (CDCl₃): 1.58 (9H, s), 1.89 (1H, dd, J = 15.3, 12.1 Hz), 2.20 (3H, s), 2.25 (3H, s), 2.32 (3H, s), 2.50-2.61 (3H, m), 3.06-3.36 (4H, m), 3.70 (3H, s), 3.74 (3H, s), 3.80 (3H, s), 3.84 (1H, d, J = 1.8 Hz), 3.99-4.03 (2H, m), 4.88 (1H, AB, J = 11.1 Hz), 5.13 (1H, AB, J = 11.1 Hz), 6.82 (1H, s), 7.32-7.50 (5H, m)

¹³C NMR (CDCl₃): 9.2, 15.7, 25.6, 26.1, 27.5, 41.4, 47.1, 55.2, 56.5, 57.5, 59.7, 60.2, 60.3, 60.4, 60.9, 74.6, 77.1, 83.1, 117.9, 123.4, 123.7, 124.8, 126.1, 127.0, 127.7, 128.3, 130.2, 130.7, 137.7, 142.6, 144.5, 147.9, 150.0, 151.2

MS: 684 (<1, M⁺), 555 (11), 529 (14), 465 (11), 464 (20), 463 (36), 462 (15), 206 (11), 205 (39), 204 (100), 203 (14), 189 (15)

[α]D²⁰: -11.6° (c = 2.045, CHCl₃)
Compound 57 continued:
Pentacyclic amide (59)

To a stirred solution of 328.4 mg (480 µmol) of amine 57 in 5 ml of dichloromethane was added 90.7 mg (480 µmol) of N-Boc alanine 58 and 108.8 mg (528 µmol) of 1,3-dicyclohexylcarbodiimide (DCC) at room temperature under an argon atmosphere. After 30 minutes, the reaction mixture was evaporated to a small volume and 20 ml of ether was added. The reaction mixture was filtered through celite and washed with ether. The filtrate was concentrated in vacuo. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of ether in hexanes (40% to 80%), furnished amide 59 (394.2 mg, 96.0%) as a white solid.
Characterization of 59:

mp (Et$_2$O): 113-115 °C

IR (CHCl$_3$): 3360, 3030, 2940, 2400, 1760, 1730, 1700, 1500, 1460, 1380, 1260, 1160, 1100, 1080, 1030

$^1$H NMR (CDCl$_3$): 0.86 (3H, d, J = 6.9 Hz), 1.33 (9H, s), 1.57 (9H, s), 1.90 (1H, dd, J = 15.6, 12.2 Hz), 2.20 (3H, s), 2.27 (3H, s), 2.28 (3H, s), 2.62 (1H, AB, J = 18.0 Hz), 3.01-3.22 (4H, m), 3.35-3.54 (3H, m), 3.71 (3H, s), 3.76 (3H, s), 3.79-3.84 (1H, m), 3.84 (3H, s), 4.04 (1H, d, J = 2.2 Hz), 4.07-4.10 (1H, m), 4.72 (1H, bs), 4.85 (1H, AB, J = 10.6 Hz), 5.18 (1H, AB, J = 10.6 Hz), 5.73 (1H, bs), 6.84 (1H, s), 7.35-7.53 (5H, m)

$^{13}$C NMR (CDCl$_3$): 9.2, 15.7, 18.1, 25.2, 26.2, 27.5, 28.1, 28.2, 33.7, 41.5, 44.1, 55.0, 56.3, 57.2, 57.5, 60.3, 60.4, 75.1, 77.1, 79.4, 83.2, 117.8, 123.2, 124.3, 124.6, 125.5, 127.2, 128.1, 128.2, 128.5, 130.4, 130.7, 137.2, 142.7, 144.5, 147.9, 150.0, 151.1, 151.7, 154.8, 171.9

MS: 728 (2, M$^+$ - CN, - Boc), 555 (19), 554 (60), 530 (14), 529 (49), 464 (15), 439 (11), 244 (12), 219 (12), 205 (22), 204 (100), 189 (10), 91 (16)

$[\alpha]_D^{20}$: -18.9° (c = 2.385, CHCl$_3$)
Compound 59 continued:

[Graph of infrared spectrum with wavenumber in cm⁻¹ and intensity in % transmission.]

[Detailed spectrum with peaks at specific wavenumbers: 181, 204, 351, 439, 554, 556, 568, 654, 728, 244, 259, 310, 466, 522, and 91.]
Pentacyclic amide (60)

To a mixture of 149.7 mg (174.9 μmol) of benzyl ether 59 and 15 mg of 10% palladium on carbon was added 2 ml of ethanol under one atmosphere of hydrogen balloon. After stirring the reaction mixture for 3 hours, all of the 59 had been consumed as evidenced by thin layer chromatography. The reaction mixture was filtered through celite and washed with ethanol. The filtrate was concentrated in vacuo. Purification of the crude product by preparative thin layer chromatography (60% ether in hexanes) afforded pentacyclic amide 60 (97.0 mg, 76.0%) as a peach solid.
Characterization of 60:

mp (Et₂O): 128-130°C

IR (CHCl₃): 3400, 3000, 2950, 2850, 2380, 1760, 1720, 1680, 1490, 1450, 1420, 1360, 1280, 1260, 1160, 1050

¹H NMR (CDCl₃): 0.92 (3H, d, J = 7.0 Hz), 1.32 (9H, s), 1.54 (9H, s), 1.90 (1H, dd, J = 15.8, 12.5 Hz), 2.17 (3H, s), 2.26 (6H, s), 2.65 (1H, AB, J = 18.0 Hz), 2.98-3.20 (3H, m), 3.35-3.54 (4H, m), 3.64 (3H, s), 3.72 (3H, s), 3.73 (3H, s), 3.80 (1H, m), 4.07 (1H, m), 4.13 (1H, m), 4.94 (1H, bs), 5.60 (1H, bs), 5.95 (1H, bs), 6.83 (1H, s)

¹³C NMR (CDCl₃): 9.5, 15.7, 18.3, 25.1, 26.1, 27.6, 28.1, 41.5, 41.7, 55.1, 56.0, 56.9, 57.3, 59.8, 60.3, 60.4, 60.7, 77.1, 79.5, 83.2, 117.9, 118.0, 122.5, 123.4, 124.6, 127.3, 130.5, 130.8, 141.4, 142.8, 143.6, 147.9, 148.4, 151.1, 155.0, 172.1

MS: 638 (<1, M⁺ - CN, -Boc), 464 (6), 463 (20), 440 (29), 439 (100), 438 (15), 437 (47), 205 (6), 204 (34), 189 (6)

[α]D²⁰: -19.6° (c = 2.120, CHCl₃)
Compound 60 continued:
Pentacyclic quinone (61)

To a stirred solution of 67 mg (87.5 μmol) of phenol 60 in 800 μl of acetonitrile and 200 μl of water was added 96 mg (175 μmol) of ceric ammonium nitrate (CAN) at room temperature under an argon atmosphere. After 30 minutes, the reaction mixture was poured into a dilute sodium chloride solution, and the aqueous layer was extracted thoroughly with dichloromethane (3X). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Purification of the crude product by preparative thin layer chromatography (60% ether in hexanes) afforded quinone 61 (59.9 mg, 90.7%) as a yellow solid.
Characterization of 61:

mp (Et₂O): 116-118 °C

IR (CHCl₃): 3400, 3020, 2950, 2850, 1760, 1720, 1670, 1650, 1480, 1450, 1380, 1280, 1250, 1160, 1080

¹H NMR (CDCl₃): 0.92 (3H, d, J = 7.1 Hz), 1.35 (9H, s), 1.59 (9H, s), 1.65-1.77 (1H, m), 1.89 (3H, s), 2.29 (3H, s), 2.31 (3H, s), 2.53 (1H, AB, J = 18.1 Hz), 2.95-3.21 (4H, m), 3.39-3.42 (2H, m), 3.72-3.77 (1H, m), 3.77 (3H, s), 3.87-3.90 (2H, m), 4.01 (3H, s), 4.05 (1H, d, J = 1.8 Hz), 4.49 (1H, bs), 5.54 (1H, bs), 6.87 (1H, s)

¹³C NMR (CDCl₃): 8.5, 8.8, 15.8, 18.0, 24.0, 25.4, 27.6, 28.1, 40.6, 41.6, 50.5, 54.3, 54.8, 56.4, 56.6, 58.9, 60.6, 60.8, 77.5, 79.8, 83.8, 117.1, 123.0, 126.9, 127.6, 130.0, 131.3, 135.6, 140.9, 143.1, 148.3, 151.1, 154.6, 156.0, 172.8, 180.8, 185.3, 185.6

MS: 749 (<1, M⁺), 594 (2), 426 (26), 425 (100), 424 (24), 423 (81), 422 (14), 421 (31), 218 (7), 206 (8), 204 (37), 189 (9), 59 (8), 57 (15)

[α]D²⁰: -39.1° (c = 2.375, CHCl₃)
Compound 61 continued:
Hemiaminal (62)

To a stirred solution of 17.8 mg (23.7 μmol) of amino nitrile 61 in 800 μl of acetonitrile and 200 μl of water was added 40 mg (237 μmol) of silver nitrate over a period of 3 hours at room temperature under an argon atmosphere. After all of the 61 had been consumed as evidenced by thin layer chromatography, the reaction mixture was concentrated in vacuo. Purification of the crude product by preparative thin layer chromatography (60% ether in hexanes) furnished hemiaminal 62 (13.5 mg, 76.8%) as a yellow oil.
(−)-Safracin B (1b)

13.5 mg (18.0 μmol) of hemiaminal 62 was treated with 1 ml (excess) of trifluoroacetic acid. After 5 minutes, the reaction mixture was evaporated to dryness under reduced pressure. The crude mixture was then dissolved in 800 μl of dichloromethane and 200 μl of acetonitrile, and 50 mg (excess) of powdered sodium bicarbonate was added. The reaction mixture was stirred for 5 minutes, filtered through celite, and washed with acetonitrile and dichloromethane. Filtrate was concentrated in vacuo to give (−)-safracin B (1b) (9.8 mg, 99%) as an oil.

Characterization of 1b:

IR(CHCl₃): 3400, 3100, 3020, 2950, 2800, 1680, 1660, 1620, 1540, 1480, 1320, 1250, 1210, 1160, 1010

MS: 540 (<1, M⁺), 439 (8), 426 (27), 425 (100), 424 (21), 423 (61), 421 (10), 218 (9), 206 (11), 205 (11), 204 (45), 203 (9), 189 (13), 91 (20)

Exact Mass: Calculated for C₂₈H₃₆N₄O₇ 540.2584
Found 540.2566
Compound 1b continued:
(-)-Safracin B hydrochloride salt (63)

To a solution of 9.8 mg (18.1 μmol) of (-)-safracin B (1b) in 50 μl of deuterium water was added 5 drops of 0.5 M hydrochloric acid in deuterium water. After 5 minutes, the reaction mixture was concentrated in vacuo to give 10.5 mg (100%) of 63. The spectroscopic and physical properties of 63 were identical to those reported in the literature.

Characterization of 63:

$^1$H NMR (D$_2$O): 0.93 (3H, d, $J = 7.1$ Hz), 1.51-1.63 (1H, m), 1.94 (3H, s), 2.30 (3H, s), 2.77 (3H, s), 3.07 (1H, dd, $J = 18.2$, 2.8 Hz), 3.20-3.49 (4H, m), 3.59-3.69 (2H, m), 3.76 (3H, s), 3.89 (3H, s), 3.89-3.92 (1H, m), 4.29 (1H, m), 4.86-4.89 (2H, m), 5.04 (1H, d, $J = 2.5$ Hz), 6.81 (1H, s)

$^{13}$C NMR (D$_2$O): 10.8, 17.4, 18.3, 26.5, 26.6, 42.0, 43.4, 51.1, 52.1, 55.2, 59.2, 61.9, 63.0, 63.7, 83.3, 113.6, 123.9, 130.9, 133.0, 135.7, 139.5, 144.4, 146.1, 149.6, 158.1, 172.5, 184.3, 189.9

[$\alpha$]$_D^{20}$: -106.0° (c = 0.665, MeOH)
Chapter II
Total Synthesis of (−)-Thiangazole

Introduction

Thiangazole (64), a new member of the tantazole-mirabazole class of natural products, was isolated from the myxobacterium, *Polyangium sp.* strain Pl 3007, by Jansens and co-workers in 1992. Reports of its antihelmintic and antifungal effects, and, especially, its extremely high inhibitory activities against HIV-1 have triggered several synthetic, structural, and biological investigations.

Thiangazole was originally reported to be quite effective against HIV-1 infection in MT-4 cell assays (*IC*$_{100}$ = 4.7 pM) but totally ineffective against HIV-2 in vitro. Thiangazole was also reported to exhibit no cell toxicity at 4.7 mM. This result appeared to be interesting because the structurally related mirabazoles and tantazoles had moderate to high levels of cytotoxicity. Recently, Wipf's group reported structure-activity relationship
(SAR) studies for thiangazole and a series of closely related compounds.\textsuperscript{42d,e} Contrary to the earlier claims, \((-\)-thiangazole did exhibit a high level of cytotoxicity, which is consistent with the other thiazoline-containing natural products. Moreover, \((-\)-thiagazole did not show significant anti-HIV-1 activity in CEM-T4 and H9 assays.

![Chemical structures](image)

Tantazole I 65i  Didehydrotantazole A 66  Didehydromirabazole A 68

Thiagazole (64), along with the tantazoles (65) and the mirabazoles (67), represents a new and exciting class of natural products, and they show novel structures which have in common a unique chain of thiazoline as well as oxazole and/or thiazole rings. The biosynthesis of this family of natural products appears to be dependent upon the iterative use of 2-methylcysteine. The only other natural product which accommodates a 2-methylcysteine unit is the siderophore desferritiochin, isolated from cultures of \textit{Streptomyces antibioticus}.\textsuperscript{45}

The tantazoles and the mirabazoles were all isolated from the terrestrial blue-green algae \textit{Scytanema mirabile},\textsuperscript{38} and several of this class of alkaloids, including tantazole B (65b) and didehydromirabazole A (68), possess selective cytotoxicity against murine solid tumors.
Didehydrotantazole A (66) was an oxidation product of tantazoles A (65a) and I (65i), and didehydromirabazole A (68) was suggested to be an artifact, formed by oxidation of mirabazole A (67a) during isolation.

The structures of the tantazoles and the mirabazoles were originally assigned to have a S-configuration at the ring A stereocenter. Later synthetic work by Fukuyama and Xu\textsuperscript{46} showed that tantazole B has the alternative R-configuration at the quaternary center in ring A. Moore et al.\textsuperscript{38c} then re-examined the structures of the several other tantazoles and mirabazoles and revised the stereochemistry at the ring A of those to R-configuration. Synthetic work by Parsons and Heathcock\textsuperscript{47a} confirmed the revised assignment for mirabazole C by total synthesis.

Synthesis of these novel natural products has received considerable attention since they were isolated. To date, total syntheses of didehydromirabazole A (68)\textsuperscript{48}, mirabazole B (67b),\textsuperscript{49} mirabazole C (67c),\textsuperscript{47} tantazole B (65b),\textsuperscript{46} and thiangazole (64)\textsuperscript{42} have been reported.

Similar to the tantazoles and the mirabazoles, thiangazole has a linear assembly of three thiazoline rings (rings A, B and C) followed by an oxazole ring (ring D). However, it possesses a styryl group at the C-2 position of the first thiazoline ring (ring A) instead of an isopropyl group. In addition, all three asymmetric centers of thiangazole have the same S-configuration.

We are interested in the total synthesis of thiangazole not only because of its reported potent antiviral activity, but also because of the anticipated difficulties in modifying this class of compounds. Herein we report an efficient synthetic pathway that enables diverse modification of both ends of thiangazole and thus allows a rapid access to a variety of its analogs. Our enantioselective total synthesis of (−)-thiargazole features (a)
a facile construction of the thiazolines through acid-catalyzed cyclization of ammonium thiol ester, and (b) the formation of thiazolidinone that can be converted to various side chain at the C-2 position of the first thiazoline ring (ring A). Details on the total synthesis of (−)-thiangles (64) are discussed fully in this thesis.
Synthetic Background

To date, the total synthesis of (−)-thiangazole (64) has been accomplished by four different groups: Pattenden,42a Ehrler,42b Heathcock,42c and Wipf42d Before discussing in full detail our total synthesis of (−)-thiangazole (64), works reported by the aforementioned groups are described to show some markedly different, yet highly interesting ideas.

Pattenden's Total Synthesis of (−)-Thiangazole

The first total synthesis of (−)-thiangazole (64) was achieved by Pattenden, Boyce and Mulqueen in 1994.42a Their strategy was based on the cyclocondensation between (R)-2-methylcysteine-derived bis-thiazoline nitrile 69 and the oxazole 70 as a key step, as illustrated in Scheme 17.

Starting from (R)-2-methylcysteine methyl ester hydrochloride 7148b and cinnaminitrile, cyclocondensation reaction led to the corresponding thiazoline 72.50 The ester 72 was converted to nitrile 74 via amide 73.51 The second cyclocondensation followed by ammonolysis and nitrile formation gave bis-thiazoline nitrile 69 (Scheme 17). The oxazole 70 was prepared from bis-Boc-protected (R)-2-methylcysteine 76.52 Condensation of 76 with (±)-threonine methyl ester hydrochloride in the presence of benzotriazol-1-yl oxytripyrrolidino-phosphonium hexafluorophosphate (PyBOP)53 gave amide 77 which was converted to oxazoline 78 with Burgess reagent,54 methoxycarbonylsulfamoyl-triethylammonium inner salt. Oxidation of oxazoline55 78 followed by deprotection of the Boc groups gave oxazole 70 (Scheme 18). Cyclocondensation reaction between nitrile 69 and oxazole 70 followed by reaction with methylamine provided (−)-thiangazole (64).
Ehrler's Total Synthesis of (−)-Thiangazole

Ehrler's total synthesis of (−)-thiangazole relied upon the stepwise construction of the three thiazoline rings. A 2-(diphenylphosphinyl)methyl unit occupied the C-2 position of the first thiazoline ring (ring A). The styryl group was introduced by a Wittig-type reaction on the phosphine oxide with benzaldehyde, and the oxazole ring (ring D) was assembled at the end of the synthesis.

As illustrated in Scheme 19, starting from (R)-2-methylcysteine hydrochloride 80,42b condensation with cyanomethylidiphenylphosphine oxide 81 gave the corresponding thiazoline 82. Hydrolysis of ester to acid followed by the condensation with (R)-2-methylcysteine and subsequent cyclization with titanium tetrachloride according to Heathcock's procedure,47a yielded bis-thiazoline 83. Iteration of the same procedure gave rise to the third thiazoline ring.

The styryl group was then introduced by a Wittig-type reaction of the phosphine oxide 84 with benzaldehyde. The ester of the bis-thiazoline 85 was converted to amide 86 by a three-step sequence. Saponification of ester 85 followed by treatment with Ghosez reagent,56 (1-dimethylamino)-1-chloro-2-methylprop-1-ene, yielded an acid chloride, and ammonolysis of which resulted in the formation of amide 86.

The terminal oxazole ring was formed by a slight modification of Masamune's procedure57 starting from the amide 86. Coupling of 86 and ethyl 3-bromo-2-oxo-butyrate in the presence of cyclohexene oxide gave the corresponding 4-hydroxyoxazoline which was dehydrated in the presence of trifluoroacetic acid and pyridine to form oxazole 87. Hydrolysis of 87
followed by treatment with Ghosez reagent gave an acid chloride, which was reacted with methylamine to furnish (−)-thiangazole (64).
Heathcock's Total Synthesis of (−)-Thiangazole

An interesting strategy for the assembly of the thiazoline/thiazole rings has recently been reported by Heathcock and coworkers.\textsuperscript{47b} As illustrated in Scheme 20, construction of an oligopeptide containing all the necessary functional groups followed by cyclization with titanium tetrachloride afforded a \textit{tris}-thiazoline. The oxazole ring was subsequently assembled at the end of the synthesis.

Condensation of (\textit{R})-\textit{N}-(carbobenzyloxy)-\textit{S}-benzyl-2-methylcysteine \textbf{88} and the hydrochloride salt \textbf{89} with bromotris(pyrrolidino)-phosphonium hexafluorophosphate (PyBroP) as the condensing reagent afforded dipeptide, which was deprotected by treatment with hydrogen bromide in glacial acetic acid containing thioanisole\textsuperscript{58} to give amine \textbf{90}. Condensation of \textbf{90} with \textbf{88} followed by deprotection afforded tripeptide \textbf{91}. Coupling of \textbf{91} with dihydrocinnamoyl chloride gave an amide, which upon hydrolysis of the methyl ester, yielded acid \textbf{92}.

\textit{O}-benzylthreonine \textit{N}-methylamide \textbf{93} was prepared from the commercially available \textit{t}-Boc derivative of \textit{O}-benzylthreonine via a four-step procedure reported by Coste and coworkers.\textsuperscript{59} This procedure involved esterification of the acid with diazomethane, aminolysis of the methyl ester with methylamine, and deprotection of the Boc group with trifluoroacetic acid to give \textbf{93} in 89\% overall yield.

Condensation of \textbf{92} and \textbf{93} gave tetrapeptide \textbf{94} which was then reductively debenzylated. The crude product was cyclized by treatment with titanium tetrachloride to give \textit{tris}-thiazoline \textbf{95}. Oxidation of \textbf{95} with Dess-Martin reagent\textsuperscript{60} followed by cyclization under acidic condition installed the
oxazole.\textsuperscript{61} Dehydrogenation of the phenethyl side chain with dichlorodicyanoquinone (DDQ)\textsuperscript{62} provided (−)-thiangazole (64).

Scheme 20
Wipf's Total Synthesis of (−)-Thiangazole

The most recent synthesis of (−)-thiangazole was completed by Wipf and coworkers in 1995. Wipf's strategy was based on the selective oxazoline-thiazoline conversion via cysteines or thioamide intermediates.

As shown in Scheme 21, acylation of D-threonic methyl ester with \( N-[(\text{trimethylsilyl})\text{ethyl}]\)-sulfonyl (Ses)-protected (S)-α-methylserine \( 96^{63} \) in the presence of PyBroP\( ^{59b} \) gave dipeptide \( 97 \). Oxazole synthesis\( ^{64} \) via Dess-Martin oxidation and cyclodehydration of dipeptide with triphenylphosphine/iodine provided the highly functionalized oxazole \( 98 \). Aminolysis of the C-terminal methyl ester \( 98 \) gave an amide whose Ses group was deprotected with tetra-\( n \)-butylammonium fluoride (TBAF) to form an amine. Condensation of the amine with acid \( 96 \) gave peptide \( 99 \). Iterative sequence of deprotection with TBAF and coupling with \( 96 \) provided \( 100 \). Deprotection of \( 100 \) with TBAF followed by condensation of the resultant amine with dihydrocinnamic acid afforded the \( N \)-dihydrocinnamoyl tetrapeptide \( 101 \).

Debenzylation of \( 101 \) was carried out under catalytic hydrogenation conditions in the presence of Pearlman's catalyst. Triple cyclization reaction was effected upon treatment with Burgess reagent\( ^{54} \) to give \( \text{tris-oxazoline} \) \( 102 \). A facile oxazoline-thiazoline conversion was achieved by conversion of the \( \text{tris-oxazoline} \) to the \( \alpha \)-methylcysteine derivative \( 103 \) using thioacetic acid.\( ^{65} \) Ammonolysis of thiol ester \( 103 \), followed by Lewis acid-catalyzed cyclodehydration with titanium tetrachloride according to Heathcock's procedure,\( ^{47a} \) and oxidation of phenethyl side chain with benzeneseleninic acid, completed the total synthesis of (−)-thiangazole (64).
Total Synthesis of (−)-Thiangazole

The tantazoles, mirabazoles, and thiangazole have in common a unique array of four or five consecutive 2,4-disubstituted thiazoline, and oxazole or thiazole rings. An efficient synthesis of these polythiazoline-type natural products requires a concise construction of the thiazoline unit in combination with an effective means of concatenating the rings. As part of our synthetic efforts on the total synthesis of (−)-tantazole B (65b), a facile transformation of ammonium thiol ester 104 into thiazoline 105 in hot benzene was developed in our laboratories (Scheme 22).

We anticipated no major problems with the application of this protocol to the synthesis of thiangazole (64) and its analogs. However, modification of these polythiazoline-type natural products is difficult and it seemed worthwhile to develop a versatile pathway that allows extensive modification of these interesting natural products for structure-activity relationship (SAR) studies. Our strategy features a late construction of the ring A thiazoline. The precursor to this ring is an aminothiol, which is carried through the synthesis as a thiazolidinone. Reaction of the aminothiol with various acyl chlorides will result in diverse ring A analogs of thiangazole.

The biosynthesis of the thiangazole-tantazole-mirabazole class of natural products appears to depend on the iterative incorporation of 2-
methylcysteine. As a result, the most logical way to start the total synthesis of this class is to obtain optically pure 2-methylserine or 2-methylcysteine. There are several synthetic methods available in the literature; however, none of them appeared to be amenable to a large-scale operation. In the course of synthesizing (−)-tantazole B, an interesting approach using an enzyme was developed in our laboratories. As illustrated in Scheme 23, enzymatic hydrolysis of malonate derivative 106 by pig liver esterase (PLE) in 0.1 M phosphate buffer with pH adjusted to 7.5 gave the acid 107 with enantiomeric excess of 93%. Selective reduction of the ester 107 with sodium borohydride provided (S)-N-(t-Boc)-2-methylserine (−)-108. Alternatively, selective reduction of the acid group 107 via a mixed anhydride formation followed by acid hydrolysis of the ester and reprotention of the amine gave (R)-N-(t-Boc)-2-methylserine (+)-108.

In order to efficiently extend the thiazole array for the synthesis of the thiangazole-tantazole-type natural products, we envisioned that β-lactone 109 would be a good building block for thiol acid 110 as shown in Scheme 24. Cyclization of (S)-N-(t-Boc)-2-methylserine (−)-108 to β-lactone 109 was effected by the Mitsunobu reaction as reported by Vederas. Since the
most reactive site of a β-lactone towards soft nucleophiles is the C-4 position, the more nucleophilic sulfur atom of a thiocarboxylate 108 would cleave the β-lactone to give the acid 111. Removal of the t-butoxycarbonyl group followed by cyclization would result in thiazoline acid 112.

![Chemical reaction diagram]

Scheme 2.4

As illustrated in Scheme 25, treatment of the readily available (-)-β-lactone 109 with hydrogen sulfide cleaved the β-lactone to give thiol carboxylic acid 113. The Boc group was removed using trifluoroacetic acid. Upon reaction with phosgene under Schotten-Baumann conditions, thiol amine 113 provided thiazolidinone 114.70 Condensation of acid 114 with methyl 3-mercaptopropionate was effected by means of bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (BOP-Cl)71 and triethylamine, giving thiol ester 115 in 46% yield from β-lactone 109. Upon treatment with two equivalent of potassium t-butoxide, thiol ester 115 underwent facile retro-Michael reaction to provide the thiol acid after work-up. The thiol acid was then reacted with β-lactone 109 in the presence of potassium carbonate to give acid 116 in 85% yield. The t-butoxycarbonyl group was removed and
the resulting amine salt was heated in benzene to furnish thiazoline 117 in 84% yield.

With this advanced intermediate 117 in hand, our next target was to construct the oxazole ring. Due to the instability of the thiazoline ring, it would be wise to construct the oxazole with the requisite functionalities before the formation of the final thiazoline ring. As shown in Scheme 26, treatment of β-lactone 109 with thiolacetic acid gave acid 118. Condensation of acid 118 with threonine t-butyl ester 119 followed by oxidation of the resultant alcohol with Jones reagent provided ketone 120. The acid was protected as its t-butyl ester because t-butyl ester group and t-butyl carbamate group could be deprotected at the same time near the end of the synthesis. Cyclization and dehydration of 120 was achieved by
treatment with thionyl chloride and pyridine.\textsuperscript{72} Alkaline hydrolysis\textsuperscript{73a} of the thiol ester afforded thiol oxazole 121.

![Scheme 26]

As illustrated in Scheme 27, condensation of thiazolidinone acid 117 with thiol oxazole 121 by means of BOP-Cl afforded thiol ester 122 in 83% yield. Selective deprotection of \( t \)-butyl carbamate was achieved by treatment with 2% trifluoroacetic acid in dichloromethane at 30 °C for 4 hours. Subsequent cyclization by heating in benzene provided the tetracyclic intermediate 123 in 70% yield. The thiazolidinone ring was activated by introduction of a Boc group on the nitrogen.\textsuperscript{73b} Alkaline methanolysis of the resultant \( N \)-Boc-thiazolidinone 124 gave thiol 125 which was acylated with cinnamoyl chloride to give thiol ester 126 in 70% yield. Deprotection of both \( t \)-butyl carbamate and \( t \)-butyl ester followed by cyclization by heating in benzene gave acid 127. Finally, treatment of acid 127 with ethyl chloroformate followed by ammonolysis of the resultant mixed anhydride with methylamine provided (−)-thianguazole (64).
The physical properties (optical rotation) and spectroscopic data (\(^1\)H NMR, \(^{13}\)C NMR, IR, MS, HRMS) of the synthetic (−)-thiangazole were identical to those reported in the literature. An obvious advantage of our
synthesis of (−)-thiangledole is that a variety of modification can easily be made by manipulating the late synthetic intermediates such as 126 and 127; therefore, a variety of analogs can be obtained that can be evaluated for biological activity. In conclusion, we have devised an efficient and versatile pathway that allows extensive modification of these interesting natural products.
Experimental

![Chemical structure]

(-)-109

H₂S, Et₃N
CH₂Cl₂
0 °C

113

Thiol acid (113)

To a stirred solution of 976 mg (4.85 mmol) of β-lactone 109 and 1.35 ml (9.70 mmol) of triethylamine in 24 ml of dichloromethane was bubbled hydrogen sulfide gas at 0 °C. After 5 minutes, all of the 109 had been consumed as evidenced by thin layer chromatography. The reaction mixture was purged with argon for 5 minutes to remove excess hydrogen sulfide. The reaction mixture was then poured into a solution of 1N hydrochloric acid, and the aqueous layer was extracted thoroughly with ether (5X). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give 1.18 g of thiol acid 113 as a clear oil which was used in the next step without purification.
Characterization of 113:

IR (CHCl₃): 3400, 2990, 2940, 1700, 1600, 1500, 1450, 1400, 1370, 1300, 1260, 1170, 1060, 780

¹H NMR (CDCl₃): 1.43 (9H, s), 1.51 (3H, s), 3.10 (2H, m), 5.67 (1H, bs), 8.57 (1H, bs)

¹³C NMR (CDCl₃): 23.0, 28.4, 31.1, 60.8, 80.0, 154.9, 178.5

MS: 188 (4, M⁺-CH₂SH), 179 (27, M⁺-C₄H₈), 162 (8), 132 (10), 118 (17), 101 (9), 100 (15), 90 (10), 88 (27), 57 (100)

[α]D²⁰: +28.0° (c = 3.70, CHCl₃)

Exact Mass: Calculated for (M⁺-C₄H₈) C₅H₉NO₄S 179.0252

Found 179.0251
Compound 113 continued:
Thiazolidinone thiol ester (115)

Crude 1.18 g thiol acid 113 was treated with 5 ml of trifluoroacetic acid at room temperature. After 5 minutes, the reaction mixture was concentrated in vacuo and 8.5 ml of water followed by 6.8 ml (48.5 mmol) of 40% KOH solution were added. The reaction mixture was cooled at 0 °C and 3.9 ml (4.95N, 19.4 mmol) of phosgene in dichloromethane was added under an argon atmosphere. After one and a half hours, the reaction mixture was diluted with 20 ml of dichloromethane and quenched with 3N hydrochloric acid solution. The acidified aqueous layer was extracted thoroughly with ethyl acetate (5X), and the combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give crude product which was used in the subsequent step without purification.

The crude product was dissolved in 20 ml of dichloromethane and 2.71 ml (19.4 mmol) of triethylamine, 3.09 g (12.1 mmol) of BOP-Cl and 1.07 ml (9.7 mmol) of methyl 3-mercaptopropionate were added consecutively under an argon atmosphere. After 2 hours, the reaction mixture was poured into a solution of 1N hydrochloric acid, and the aqueous layer was extracted thoroughly with ether (4X). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate,
filtered, and concentrated \textit{in vacuo}. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of ether in hexanes (40\% to 90\%), gave thiazolidinone thiol ester \textbf{115} (548 mg, 45.8\%) from \(\beta\)-lactone \textbf{109} as a clear oil.

**Characterization of 115:**

<table>
<thead>
<tr>
<th><strong>IR (CHCl(_3))</strong></th>
<th>3300, 3000, 2950, 1750, 1700, 1680, 1440, 1370, 1250, 1230, 1200, 980, 720, 530</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^1)H NMR (CDCl(_3))</td>
<td>1.59 (3H, s), 2.66 (2H, t), 3.17 (2H, t), 3.38 (1H, d, (J = 11.4) Hz), 3.67 (1H, d, (J = 11.4) Hz), 3.71 (3H, s), 7.51 (1H, bs)</td>
</tr>
<tr>
<td>(^{13})C NMR (CDCl(_3))</td>
<td>23.9, 24.5, 33.6, 39.1, 51.9, 69.0, 171.8, 174.7, 203.4</td>
</tr>
<tr>
<td><strong>MS (Cl):</strong></td>
<td>266 (6, M+2), 265 (7, M+1), 264 (56, M+), 144 (5), 118 (10), 117 (6), 116 (100), 89 (6)</td>
</tr>
<tr>
<td>([\alpha])(_D)(^{20}):</td>
<td>-106.6° (c = 2.68, CHCl(_3))</td>
</tr>
<tr>
<td><strong>Exact Mass (Cl):</strong></td>
<td><strong>Calculated for C(<em>9)H(</em>{14})NO(_4)S(_2)</strong> 264.0364 &lt;br&gt;<strong>Found</strong> 264.0353</td>
</tr>
</tbody>
</table>
Compound 115 continued:
Thiazolidinone carboxylic acid (116)

To a stirred solution of 137.1 mg (0.52 mmol) of thiol ester 115 in 20 ml of tetrahydrofuran was added 747 µl (1.39N, 1.04 mmol) of potassium t-butoxide in tetrahydrofuran over a period of 10 min at 0 °C under an argon atmosphere. After one hour, the reaction mixture was quenched with aqueous sodium chloride solution. The mixture was poured into a solution of 1N hydrochloric acid, and the aqueous layer was extracted thoroughly with dichloromethane (4X). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give the crude thiol acid which was used in the subsequent step without purification.

The crude thiol acid was dissolved in 10 ml of tetrahydrofuran at room temperature under an argon atmosphere. 180 mg (1.3 mmol) of potassium bicarbonate and 126 mg (0.6 mmol) of β-lactone 109 were added to the reaction mixture. After 1 hour, the reaction mixture was quenched with aqueous sodium chloride solution, and was poured into a solution of 1N hydrochloric acid. The aqueous layer was extracted thoroughly with dichloromethane (4X). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel, eluted with a
gradient of methanol in dichloromethane (5% to 50%), provided thiazolidinone carboxylic acid 116 (167.2 mg, 85%) as a white solid.

Characterization of 116:

mp (Et₂O): 168-170 °C

IR (CHCl₃): 3390, 2980, 2940, 1680, 1600, 1480, 1440, 1390, 1370, 1280, 1240, 1170, 1060, 800

¹H NMR (CDCl₃): 1.41 (9H, s), 1.54 (6H, s), 3.30 (1H, d, J = 11.2 Hz), 3.38 (1H, d, J = 12.4 Hz), 3.63 (1H, d, J = 11.2 Hz), 3.78 (1H, d, J = 12.4 Hz), 5.18 (1H, bs), 5.85 (1H, bs), 8.52 (1H, bs)

¹³C NMR (CDCl₃): 24.0, 28.4, 36.0, 39.4, 50.5, 59.7, 69.6, 79.6, 154.9, 175.7, 178.4, 203.7

MS: 234 (1, M⁺-C₄H₈-2CO₂), 232 (2), 215 (2), 178 (18), 161 (7), 123 (8), 121 (11), 117 (19), 115 (18), 99 (16), 89 (10), 87 (30), 58 (38), 57 (33), 56 (86), 55 (99), 54 (35), 44 (42), 43 (92), 41 (98), 40 (97), 39 (59), 38 (90), 21 (56)

[α]D²⁰: -31.8° (c = 2.535, CHCl₃)
Compound 116 continued:
Oxazole thiol ester (122)

167.2 mg (0.44 mmol) of carbamate 116 was treated with 5 ml of trifluoroacetic acid at room temperature. After 10 minutes, the reaction mixture was concentrated in vacuo. The residue was dissolved in 10 ml of benzene and heated at 85 °C. After 4 hours, the reaction mixture was concentrated in vacuo to give crude product which was purified by preparative thin layer chromatography (10% methanol in dichloromethane) to afford oxazoline (96.5 mg, 84%) as a white foam. The crude oxazoline could also be used in the subsequent step without purification.

96.5 mg (0.37 mmol) of oxazoline was dissolved in 2 ml of dichloromethane and 206 μl (1.48 mmol) of triethylamine, 188.4 mg (0.74 mmol) of BOP-Cl, and 138 mg (0.37 mmol) of thiol oxazole 121 were added consecutively under an argon atmosphere. After 2 hours, the reaction mixture was poured into a solution of 1N hydrochloric acid, and the aqueous layer was extracted thoroughly with dichloromethane (3X). The combined organic extracts were washed with brine, dried over anhydrous sodium
sulfate, filtered, and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of methanol in dichloromethane (2% to 10%), furnished oxazole thiol ester 122 (189.1 mg, 83%) as a clear oil.

Characterization of 122:

IR (CHCl₃): 3280, 2990, 2940, 1700, 1690, 1600, 1500, 1450, 1400, 1380, 1260, 1170, 1080, 980

¹H NMR (CDCl₃): 1.41 (9H, s), 1.57 (3H, s), 1.59 (9H, s), 1.80 (3H, s), 1.85 (3H, s), 2.56 (3H, s) 3.05 (1H, d, J = 11.5 Hz), 3.45 (1H, d, J = 11.1 Hz), 3.63 (1H, d, J = 11.5 Hz), 3.66 (1H, d, J = 13.8 Hz), 3.72 (1H, d, J = 11.1 Hz), 3.83 (1H, d, J = 13.8 Hz), 5.89 (1H, bs), 6.66 (1H, bs)

¹³C NMR (CDCl₃): 12.3, 23.9, 25.1, 25.4, 28.3, 28.3, 35.8, 40.8, 41.8, 56.0, 63.0, 79.9, 82.5, 90.9, 128.4, 154.0, 155.7, 161.8, 162.1, 173.3, 180.2, 201.8

MS: 615 (6, M+1), 614 (17, M+), 502 (30), 485 (19), 325 (33), 269 (37), 259 (22), 225 (22), 215 (56), 214 (15), 213 (19), 169 (100), 159 (51), 158 (37), 116 (18), 109 (15), 102 (15), 58 (15), 57 (83)

[α]D²⁰: -5.4° (c = 1.11, CHCl₃)

Exact Mass: Calculated for C₂₆H₃₈N₄O₇S₃ 614.1902
Found 614.1904
Compound 122 continued:
**Bis-thiazoline oxazole (123)**

48.2 mg (78.3 μmol) of carbamate 122 was treated with 2 ml of 2% trifluoroacetic acid in dichloromethane at room temperature. After refluxing at 30 °C for 4 hours, the reaction mixture was treated with 3 ml of benzene, and the resultant mixture was concentrated *in vacuo*. The residue was dissolved in 2 ml of benzene and heated at 85 °C. After 4 hours, the reaction mixture was concentrated *in vacuo* to give crude product which was purified by preparative thin layer chromatography (5% methanol in dichloromethane) to give *bis*-thiazoline oxazole 123 (27.4 mg, 70.2%) as a clear oil.
Characterization of **123**:  

**IR (CHCl₃):**  
3320, 3000, 2940, 1700, 1690, 1620, 1440, 1400, 1380, 1260, 1180, 1100, 1020, 850

**¹H NMR (CDCl₃):**  
1.58 (9H, s), 1.59 (3H, s), 1.67 (3H, s), 1.70 (3H, s), 2.59 (3H, s), 3.25 (1H, d, J = 11.4 Hz), 3.38 (1H, d, J = 11.1 Hz), 3.40 (1H, d, J = 11.4 Hz), 3.78 (1H, d, J = 11.1 Hz), 3.87 (1H, d, J = 11.4 Hz), 4.00 (1H, d, J = 11.4 Hz), 5.96 (1H, bs)

**¹³C NMR (CDCl₃):**  
12.4, 24.3, 25.8, 28.2, 40.3, 42.0, 44.0, 62.8, 79.4, 81.9, 84.3, 128.7, 155.8, 161.4, 163.0, 173.4, 175.8, 176.9

**MS:**  
497 (2, M+1), 496 (6, M⁺), 440 (26), 425 (34), 423 (27), 394 (11), 380 (18), 326 (10), 325 (19), 324 (100), 323 (12), 267 (45), 225 (14), 224 (15), 215 (13), 200 (18), 199 (17), 182 (20), 140 (16), 116 (10), 88 (12), 73 (13), 57 (20)

**[α]D²⁰:**  
-145.6° (c = 0.285, CHCl₃)

**Exact Mass:**  
Calculated for C₂₁H₂₈N₄O₄S₃ 496.1273  
Found 496.1276
Compound 123 continued:
N-Boc thiazolidinone (124)

To a stirred solution of 23 mg (46.3 µmol) of thiazolidinone 123 in 2 ml of dichloromethane was added 16 mg (69.5 µmol) of di-tert-butyl dicarbonate, 14 µl (92.6 µmol) of triethylamine and a small crystal of 4-dimethylaminopyridine (DMAP) at room temperature under an argon atmosphere. After 30 minutes, the reaction mixture was poured into a solution of 1N hydrochloric acid, and the aqueous layer was extracted thoroughly with ether (3X). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Purification of the crude product by preparative thin layer chromatography (70% ether in hexanes) gave N-Boc thiazolidinone oxazole 124 (24.2 mg, 87.6%) as a clear oil.
Characterization of 124:

IR (CHCl₃): 2990, 2940, 1780, 1740, 1710, 1610, 1460, 1440, 1400, 1380, 1280, 1260, 1160, 1120, 1090, 1010, 1000, 850, 760

¹H NMR (CDCl₃): 1.51 (9H, s), 1.53 (3H, s), 1.58 (9H, s), 1.65 (3H, s), 1.94 (3H, s), 2.59 (3H, s) 3.07 (1H, d, J = 11.5 Hz), 3.24 (1H, d, J = 11.5 Hz), 3.43 (1H, d, J = 11.5 Hz), 3.52 (1H, d, J = 11.4 Hz), 3.79 (1H, d, J = 11.4 Hz), 4.01 (1H, d, J = 11.5 Hz)

¹³C NMR (CDCl₃): 12.4, 23.3, 24.0, 25.4, 28.0, 28.2, 37.1, 42.1, 43.6, 67.4, 81.9, 84.0, 84.3, 128.7, 148.6, 155.8, 161.4, 163.1, 169.6, 173.4, 177.2

MS: 597 (<1, M+1), 596 (<1, M+), 523 (3), 425 (17), 423 (9), 390 (4), 381 (10), 380 (23), 326 (10), 325 (16), 324 (100), 267 (7), 215 (7), 200 (6), 199 (6), 198 (5), 182 (9), 172 (5), 168 (13), 140 (6), 57 (23)

[α]D²⁰: -166.2° (c = 0.250, CHCl₃)

Exact Mass: Calculated for (M⁺-C₄H₉O)
C₂₂H₂₇N₄O₅S₃ 523.1143
Found 523.1141
Compound 124 continued:
Cinnamoyl thiol ester (126)

To a stirred solution of 23 mg (38.5 µmol) of N-Boc thiazolindinone 124 in 4 ml of methanol was added 130 µl (385 µmol) of 3N sodium hydroxide solution at room temperature under an argon atmosphere. After 20 minutes, the reaction mixture was poured into a solution of 1N hydrochloric acid, and the aqueous layer was extracted thoroughly with dichloromethane (4X). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give crude thiol which was used in the subsequent step without purification.

The crude thiol was dissolved in 2 ml of dichloromethane, and 11 µl (77 µmol) of triethylamine, 9.6 mg (57.8 µmol) of cinnamoyl chloride, and a small crystal of 4-dimethylaminopyridine were added consecutively under an argon atmosphere. After 20 minutes, the reaction mixture was poured into a solution of 1N hydrochloric acid, and the aqueous layer was extracted thoroughly with dichloromethane (3X). The combined organic extracts were
washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Purification of the crude product by preparative thin layer chromatography (70% ether in hexanes) yielded cinnamoyl thiol ester **126** (19 mg, 70.3%) as a clear oil.

**Characterization of 126:**

**IR (CHCl₃):**
3350, 2990, 2920, 1720, 1670, 1660, 1620, 1500, 1450, 1400, 1360, 1250, 1170, 1090, 1040, 1020, 780

**¹H NMR (CDCl₃):**
1.46 (9H, s), 1.58 (12H, s), 1.61 (3H, s), 1.64 (3H, s), 2.58 (3H, s), 3.17 (1H, d, J = 11.4 Hz), 3.36 (1H, d, J = 11.4 Hz), 3.74-3.83 (3H, m), 3.95 (1H, d, J = 11.4 Hz), 5.55 (1H, bs), 6.74 (1H, d, J = 15.8 Hz), 7.35-7.42 (3H, m), 7.52-7.56 (2H, m), 7.63 (1H, d, J = 15.8 Hz)

**¹³C NMR (CDCl₃):**
12.4, 24.3, 25.5, 28.2, 28.4, 36.8, 42.0, 43.3, 54.3, 58.3, 79.4, 81.8, 83.8, 124.7, 127.6, 128.4, 128.6, 129.0, 130.1, 134.0, 140.8, 154.0, 155.8, 161.4, 163.2, 177.6, 188.9

**MS:**
571 (18, M⁺-C₉H₇O), 570 (31, M⁺+1-C₉H₇O), 569 (98, M⁺-C₉H₇O), 513 (28), 452 (21), 367 (35), 324 (17), 231 (18), 182 (19), 181 (37), 169 (28), 131 (100), 119 (43), 103 (25), 69 (94), 57 (53)

**[α]D²⁰:**
-76.7° (c = 0.850, CHCl₃)

**Exact Mass:**
Calculated for (M⁺-C₉H₇O)
C₂₅H₃₇N₄O₅S₃ 569.1926
Found 569.1926
Compound 126 continued:
(-)-Thiangazole (64)

15 mg (21.4 µmol) of carbamate 126 was treated with 2 ml of trifluoroacetic acid at room temperature. After 5 minutes, the reaction mixture was concentrated in vacuo. The residue was dissolved in 3 ml of benzene and heated at 85 °C. After 4 hours, the reaction mixture was concentrated in vacuo, and the residue was purified by preparative thin layer chromatography (10% methanol in dichloromethane) to give acid (9.4 mg, 83.7%) as a clear oil.

9.4 mg (17.8 µmol) of acid was dissolved in 1 ml of dichloromethane, and the mixture was cooled at 0 °C. 2.6 µl (26.6 µmol) of ethyl chloroformate and 3.7 µl (26.6 µmol) of triethylamine were added to the reaction mixture under an argon atmosphere. After stirring the reaction mixture at 0 °C for 10 minutes, 3.8 µl (35.6 µmol) of methylamine (40% in water) was added. After 10 min at room temperature, the reaction mixture was poured into a saturated sodium chloride solution, and the aqueous layer
was extracted thoroughly with dichloromethane (4X). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by preparative thin layer chromatography to give (−)-thiangazole (64) (9.4 mg, 97.6%) as a clear oil.

Characterization of 64:

IR (CHCl₃): 3450, 2990, 2950, 2850, 1670, 1630, 1580, 1560, 1540, 1450, 1210, 1160, 1100, 1010, 960, 750, 700

¹H NMR (CDCl₃): 1.62 (3H, s), 1.68 (3H, s), 1.71 (3H, s), 2.66 (3H, s), 2.95 (3H, d, J = 5.1 Hz), 3.23 (1H, d, J = 11.5 Hz), 3.30 (1H, d, J = 11.3 Hz), 3.39 (1H, d, J = 11.2 Hz), 3.77 (1H, d, J = 11.5 Hz), 3.85 (1H, d, J = 11.3 Hz), 3.87 (1H, d, J = 11.2 Hz), 6.94 (1H, bs), 7.08 (1H, d, J = 16.2 Hz), 7.18 (1H, d, J = 16.2 Hz), 7.36-7.43 (3H, m), 7.49-7.53 (2H, m)

¹³C NMR (CDCl₃): 11.7, 24.3, 25.5, 25.6, 26.1, 41.9, 42.4, 43.2, 79.4, 83.2, 83.6, 122.2, 127.7, 128.9, 129.1, 129.8, 135.0, 142.4, 153.4, 162.3, 162.5, 168.3, 177.9, 178.1

MS: 540 (11, M+1), 539 (52, M⁺), 493 (36), 337 (41), 301 (97), 260 (83), 231 (34), 219 (33), 213 (35), 202 (100), 181 (38), 172 (35), 169 (47), 131 (63), 119 (44), 73 (45)

[α]D²⁰: -285.0° (c = 0.1, MeOH)

Exact Mass: Calculated for C₂₆H₂₉N₅O₂S₃ 539.1483
Found 539.1481
Compound 64 continued:
Chapter III
Development of Sulfonamide Chemistry

Introduction

Nitrogen, along with oxygen and sulfur, has been one of the most important elements present in heterocyclic natural products. In order to accomplish a total synthesis of a multifunctional natural product, protective groups that can temporarily block reactive sites have to be in place so that a reaction can be selectively carried out at one particular reactive site. Many protective groups have been, and are being, developed for amines, such as carbamates, amides and sulfonamides. Sulfonamides are some of the most stable nitrogen protecting groups and have two distinct advantages over carbamates and amides. First, sulfonamides are highly crystalline, and second, the NMR spectra of sulfonamides are sharp, while spectra of carbamates often show signal broadening due to rotational restriction.\textsuperscript{74}

Not all the existing protecting groups can survive a series of synthetic transformations for a particular system, and oftentimes, a new protecting group has to be developed to satisfy a particular need. We came across a synthetic problem in our efforts to synthesize (±)-vincadifformine (130).\textsuperscript{75} As shown in Scheme 28, we have developed a concise synthetic pathway to the advanced intermediate \textbf{128}. The success of the synthesis relies on the efficient removal of the amino protecting group to give a free secondary amine, which must intramolecularly condense with the aldehyde to form an enamine named secodine, \textbf{129}. Secodine, which has never been isolated from natural sources, is believed to be the biogenic precursor to vincadifformine.
Various amino protecting groups were investigated in the course of this synthesis, such as \( t \)-butyl carbamate and 2-carbomethoxyethyl sulfonamide. None of these could be cleaved without destroying the rest of the molecules. Toluenesulfonamides\(^{76}\) and trifluoroacetamides\(^{77}\) proved to be useless because of the harsh conditions required for the deprotection. After numerous attempts, we realized that a 2,4-dinitrobenzenesulfonyl group would be the protecting group of choice because of its facile cleavage under mild conditions. As shown in Scheme 29, 2,4-dinitrobenzenesulfonamides were easily cleaved upon treatment with appropriate nucleophiles. Deprotection is believed to involve a nucleophilic aromatic substitution (\( S_NAr \)) process.\(^{78}\) Thus, decomposition of a Meisenheimer complex gives the desired secondary amine after spontaneous extrusion of \( SO_2 \).
The application of 2,4-dinitrobenzenesulfonamide chemistry to the total synthesis of (±)-vincadifformine (130) is shown in Scheme 30. Mitsunobu reaction\(^7\) of the indole alcohol 131 with 2,4-dinitrobenzenesulfonamide 132, which was derived from the corresponding primary amine and 2,4-dinitrobenzenesulfonyl chloride, gave the alkylated sulfonamide 133 in excellent yield. Exposure of this material to trifluoroacetic acid released both the Boc group and the dimethyl acetal, giving aldehyde 134. At this stage, the 2,4-dinitrobenzenesulfonamide had to be removed via the addition-elimination process. Use of such nucleophiles\(^8\) as PhSH and HSCH\(_2\)CO\(_2\)H\(^8\) was unsuccessful because of facile Michael addition to the acrylate moiety. Luckily, treatment with potassium phenoxide, which is a harder nucleophile and thus less prone to Michael addition, promoted clean deblocking of the 2,4-dinitrobenzenesulfonamide. While the formation of the secodine 129 could not be detected, (±)-vincadifformine (130) was isolated in good yield (Scheme 31).\(^8\)
Scheme 30

Scheme 31
Development of Sulfonamide Chemistry

Having succeeded in developing a new protecting group during the total synthesis of (±)-vincadifformine (130), we turned our attention to further development of 2,4-dinitrobenzenesulfonamides.

2,4-Dinitrobenzenesulfonamides

$N$-monosubstituted 2,4-dinitrobenzenesulfonamide 135, readily prepared from 2,4-dinitrobenzenesulfonyl chloride and the corresponding primary amine in the presence of a base such as pyridine, can be alkylated efficiently under Mitsunobu conditions (R'OH, DEAD, PPh$_3$, benzene, 23 °C) or under conventional conditions (R'X, K$_2$CO$_3$, DMF, 23 °C) to give $N,N$-disubstituted 2,4-dinitrobenzenesulfonamide 136 in excellent yield.

Facile deprotection of 136 was achieved upon treatment with excess $n$-propylamine (20 eq) in dichloromethane at room temperature for 10 min via the formation of the Meisenheimer complex 137, giving, after the spontaneous extrusion of SO$_2$, the desired secondary amine 138 in nearly quantitative yield. Alternatively, 136 can be deprotected by treatment with mercaptoacetic acid (1.3 eq) and triethylamine (2 eq) in dichloro-methane at room temperature for 5 min (Scheme 32 and Table 1). The latter procedure is more convenient in that the by-product 139 (2,4-dinitro-phenylthioacetic acid) can be removed easily by partitioning between ether and an aqueous
sodium bicarbonate solution. A practically pure amine can thus be obtained without chromatographic separation.

However, a shortcoming of the 2,4-dinitrobenzenesulfonamide is that it is not very stable under basic conditions. As shown in Table 1, alkylation of N-(4-methoxybenzyl)-2,4-dinitrobenzenesulfonamide 135a with n-propyl bromide \([R'X \text{ (2 eq), } K_2CO_3 \text{ (8 eq), DMF, 23 °C, 24 hr, 48% yield}]\) gave the alkylated sulfonamide 136a in poor yield. Alkylation of 2,4-dinitrobenzenesulfonamides 135a with poor alkylating agents such as n-propyl bromide gave low yields because of the concomitant decomposition of the starting materials 135a when exposed to the basic conditions for a prolonged period of time through the intramolecular Meisenheimer complex formation shown in Scheme 33.

![Scheme 33](image)

However, this problem was easily overcome by reducing the electron deficiency of the aromatic ring. By having one nitro group instead of two in the aromatic ring, the undesired intramolecular Meisenheimer complex formation was completely inhibited. As shown in the case of alkylation of 2-nitrobenzenesulfonamide with n-propyl bromide, the alkylated sulfonamide was isolated in 98% yield (Table 2).
<table>
<thead>
<tr>
<th>R'X or R'OH</th>
<th>Alkylation&lt;sup&gt;a&lt;/sup&gt; 136&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt; (% yield)</th>
<th>Deprotection 138&lt;sup&gt;b,c,d&lt;/sup&gt;&lt;br&gt; (% yield)</th>
<th>Alkylation&lt;sup&gt;a&lt;/sup&gt; 136&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt; (% yield)</th>
<th>Deprotection 138&lt;sup&gt;b,c,d&lt;/sup&gt;&lt;br&gt; (% yield)</th>
<th>Alkylation&lt;sup&gt;a&lt;/sup&gt; 136&lt;sup&gt;c&lt;/sup&gt;&lt;br&gt; (% yield)</th>
<th>Deprotection 138&lt;sup&gt;b,c,d&lt;/sup&gt;&lt;br&gt; (% yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph—Br</td>
<td>20 min (87)</td>
<td>91</td>
<td>1 hr (97)</td>
<td>90</td>
<td>4 hr (95)</td>
<td>90</td>
</tr>
<tr>
<td>C—Br</td>
<td>20 min (97)</td>
<td>91</td>
<td>1 hr (97)</td>
<td>92</td>
<td>7 hr (99)</td>
<td>88</td>
</tr>
<tr>
<td>C—I</td>
<td>2 hr (89)</td>
<td>91</td>
<td>7 hr (96)</td>
<td>89</td>
<td>12 hr (87)</td>
<td>94</td>
</tr>
<tr>
<td>C—Br</td>
<td>24 hr (48)&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph—OH</td>
<td>20 min (99)</td>
<td>91</td>
<td>20 min (99)</td>
<td>90</td>
<td>20 min (94)</td>
<td>89</td>
</tr>
<tr>
<td>CO₂Et—OH</td>
<td>20 min (96)</td>
<td>92</td>
<td>20 min (97)</td>
<td>93</td>
<td>20 min (97)</td>
<td>93</td>
</tr>
</tbody>
</table>

<sup>a</sup>For alkyl halides: R'X (1.5 eq), K₂CO₃ (5 eq), DMF, 23 °C. For n-propyl bromide: R'X (2 eq), K₂CO₃ (8 eq), DMF, 23 °C. For alcohols: R'OH (2 eq), DEAD (2 eq), PPh₃ (2 eq), benzene, 23 °C, 20 min. <sup>b</sup>Satisfactory spectroscopic data were obtained on all new compounds. <sup>c</sup>PA: n-propylamine (20 eq), CH₂Cl₂, 23 °C, 10 min. MA: HSCH₂COOH (1.3 eq), Et₃N (2 eq), CH₂Cl₂, 23 °C, 5 min. <sup>d</sup>Separated by silica gel chromatography after partitioning between Et₂O and an aqueous NaHCO₃ solution. <sup>e</sup>Poor alkylating agents such as n-propyl bromide gave low yields due to the deterioration of starting materials 136 when exposed to the basic conditions for a prolonged period of time.
2- and 4-Nitrobenzenesulfonamides\textsuperscript{80}

\(N\)-(4-Methoxybenzyl)-2-nitrobenzenesulfonamide 140a, prepared from 4-methoxybenzylamine (PMB-NH\(_2\)) and 2-nitrobenzenesulfonyl chloride in 97\% yield (Et\(_3\)N, CH\(_2\)Cl\(_2\), 23 °C), can be alkylated efficiently under the Mitsunobu conditions\textsuperscript{79} (ROH, DEAD, Ph\(_3\)P, CH\(_2\)Cl\(_2\), 23 °C) or under the more conventional conditions (RX, K\(_2\)CO\(_3\), DMF, 23 °C) to give the \(N,N\)-disubstituted 2-nitrobenzenesulfonamide 141a. Upon treatment with thiophenol (1.3 eq) and potassium carbonate (2 eq) in DMF at room temperature, facile deprotection of 141a was achieved presumably via the Meisenheimer complex 142a, giving the desired secondary amine 143 in excellent yields. Alternatively, 141a can be deprotected by treatment with mercaptoaetic acid (2 eq) and lithium hydroxide (4 eq) in DMF at room temperature (Scheme 34 and Table 2).\textsuperscript{81} Because a 2-nitrobenzenesulfonamide and 4-nitrobenzenesulfonamide have comparable electronic properties, similar results were obtained using the corresponding 4-nitrobenzenesulfonamide 141b (Scheme 34).

In addition to the mild reaction conditions involved, 2- and 4-nitrobenzenesulfonamides are stable under acidic [HCl (10 eq), MeOH, 60 °C, 4 hr] as well as basic [NaOH (10 eq), MeOH, 60 °C, 4 hr] conditions, and they
can be used for protection of primary and secondary amines. Because of the extreme ease of the entire procedure for the alkylation and deprotection of nitrobenzenesulfonamides, we believe that the use of 2,4-dinitrobenzenesulfonamides in conjunction with 2- and 4-nitrobenzenesulfonamides serves as a method of choice for the preparation of a wide variety of secondary amines. Moreover, these nitrobenzenesulfonamides proved to be quite amenable to the solid-state synthesis of secondary amines for combinatorial chemistry.

**N-Boc-2-nitro- and N-Boc-2,4-dinitro-benzenesulfonamides**

In 1989 Weinreb and co-workers reported the use of *N*-Boc *p*-toluenesulfonamides in conjunction with the Mitsunobu reaction for the synthesis of protected primary amines. However, deprotection of the *p*-toluenesulfonyl group requires relatively harsh conditions where sensitive functional groups would not survive. To circumvent these deprotection problems, we turned our attention to *N*-acyl nitrobenzenesulfonamides and developed *N*-Boc-2-nitrobenzenesulfonamide 145 and *N*-Boc-2,4-dinitrobenzenesulfonamide 146 that provide an efficient method for the preparation of a wide range of protected primary amines.
Table 2. Alkylation and Deprotection of 2- & 4-Nitrobenzenesulfonamides

<table>
<thead>
<tr>
<th>140</th>
<th>RX or ROH</th>
<th>Alkylation condition&lt;sup&gt;a&lt;/sup&gt;</th>
<th>141&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Deprotection conditions&lt;sup&gt;c&lt;/sup&gt;</th>
<th>143&lt;sup&gt;b,d&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% isolated yield</td>
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<td>% isolated yield</td>
</tr>
<tr>
<td>140a</td>
<td>Ph&lt;sub&gt;H&lt;/sub&gt;Br</td>
<td>A</td>
<td>Ph&lt;sub&gt;Ph&lt;/sub&gt;N&lt;sub&gt;SO&lt;sub&gt;2&lt;/sub&gt;Ar&lt;sup&gt;PMB&lt;/sup&gt;&lt;/sub&gt; (98)</td>
<td>TP</td>
<td>Ph&lt;sub&gt;Ph&lt;/sub&gt;N&lt;sub&gt;SO&lt;sub&gt;2&lt;/sub&gt;Ar&lt;sup&gt;PMB&lt;/sup&gt;&lt;/sub&gt; (94)</td>
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<td></td>
<td>MA</td>
<td></td>
</tr>
<tr>
<td>140a</td>
<td>n-Bu&lt;sub&gt;H&lt;/sub&gt;Br</td>
<td>B</td>
<td>n-Bu&lt;sub&gt;n&lt;/sub&gt;N&lt;sub&gt;SO&lt;sub&gt;2&lt;/sub&gt;Ar&lt;sup&gt;PMB&lt;/sup&gt;&lt;/sub&gt; (98)</td>
<td>TP</td>
<td>n-Bu&lt;sub&gt;n&lt;/sub&gt;N&lt;sub&gt;SO&lt;sub&gt;2&lt;/sub&gt;Ar&lt;sup&gt;PMB&lt;/sup&gt;&lt;/sub&gt; (94)</td>
</tr>
<tr>
<td>140a</td>
<td>Ph&lt;sub&gt;H&lt;/sub&gt;OH</td>
<td>C</td>
<td>Ph&lt;sub&gt;Ph&lt;/sub&gt;N&lt;sub&gt;SO&lt;sub&gt;2&lt;/sub&gt;Ar&lt;sup&gt;PMB&lt;/sup&gt;&lt;/sub&gt; (91)</td>
<td>TP</td>
<td>Ph&lt;sub&gt;Ph&lt;/sub&gt;N&lt;sub&gt;SO&lt;sub&gt;2&lt;/sub&gt;Ar&lt;sup&gt;PMB&lt;/sup&gt;&lt;/sub&gt; (88)</td>
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<td>140a</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Et&lt;sub&gt;H&lt;/sub&gt;</td>
<td>C</td>
<td>EtO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;n&lt;/sub&gt;N&lt;sub&gt;SO&lt;sub&gt;2&lt;/sub&gt;Ar&lt;sup&gt;PMB&lt;/sup&gt;&lt;/sub&gt; (87)</td>
<td>TP</td>
<td>EtO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;n&lt;/sub&gt;N&lt;sub&gt;SO&lt;sub&gt;2&lt;/sub&gt;Ar&lt;sup&gt;PMB&lt;/sup&gt;&lt;/sub&gt; (93)</td>
</tr>
<tr>
<td>140b</td>
<td>Ph&lt;sub&gt;H&lt;/sub&gt;Br</td>
<td>A</td>
<td>Ph&lt;sub&gt;Ph&lt;/sub&gt;N&lt;sub&gt;SO&lt;sub&gt;2&lt;/sub&gt;Ar&lt;sup&gt;PMB&lt;/sup&gt;&lt;/sub&gt; (99)</td>
<td>TP</td>
<td>Ph&lt;sub&gt;Ph&lt;/sub&gt;N&lt;sub&gt;SO&lt;sub&gt;2&lt;/sub&gt;Ar&lt;sup&gt;PMB&lt;/sup&gt;&lt;/sub&gt; (96)</td>
</tr>
<tr>
<td>140b</td>
<td>Ph&lt;sub&gt;H&lt;/sub&gt;OH</td>
<td>C</td>
<td>Ph&lt;sub&gt;Ph&lt;/sub&gt;N&lt;sub&gt;SO&lt;sub&gt;2&lt;/sub&gt;Ar&lt;sup&gt;PMB&lt;/sup&gt;&lt;/sub&gt; (97)</td>
<td>TP</td>
<td>Ph&lt;sub&gt;Ph&lt;/sub&gt;N&lt;sub&gt;SO&lt;sub&gt;2&lt;/sub&gt;Ar&lt;sup&gt;PMB&lt;/sup&gt;&lt;/sub&gt; (90)</td>
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</tbody>
</table>

<sup>a</sup>A: RX (1.1 eq), K<sub>2</sub>CO<sub>3</sub> (2 eq), DMF, 23 °C, 1 hr. B: RX (1.1 eq), K<sub>2</sub>CO<sub>3</sub> (2 eq), DMF, 60 °C, 30 min. C: ROH (1.3 eq), DEAD (1.3 eq), PPh<sub>3</sub> (1.3 eq), CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 1 hr. 
<sup>b</sup>Satisfactory spectroscopic data were obtained on all new compounds. 
<sup>c</sup>TP: PhSH (1.2 eq), K<sub>2</sub>CO<sub>3</sub> (3 eq), DMF, 23 °C, 40 min. MA: HSCH<sub>2</sub>CO<sub>2</sub>H (2 eq), LiOH (4 eq), DMF, 23 °C, 1 hr. 
<sup>d</sup>Separated by silica gel chromatography after partitioning between Et<sub>2</sub>O and a dilute NaHCO<sub>3</sub> solution.
N-Boc-2-nitrobenzenesulfonamide 145 was prepared in 95% yield from commercially available 2-nitrobenzenesulfonamide [Boc₂O (1.2 eq), Et₃N (1.3 eq), DMAP (0.1 eq), CH₂Cl₂, 23 °C, 25 min]. N-Boc-2,4-dinitrobenzenesulfonamide 146 was obtained in 97% yield from the similar procedure using readily available 2,4-dinitrobenzenesulfonamide. The Mitsunobu reaction (ROH, DEAD, Ph₃P, CH₂Cl₂, 23 °C) of 145 and 146 gave N-alkylated sulfonamides 147 in excellent yields. Mononitrobenzenesulfonamide 145 can be alkylated smoothly even with poor alkylating agents such as n-heptyl bromide in the presence of K₂CO₃ in DMF at 23 °C. On the other hand, alkylation of the less stable 2,4-dinitrobenzenesulfonamide 146 was effective only with reactive alkyl halides (Scheme 35 and Table 3).

![Scheme 35](image)

Either the nitrobenzenesulfonyl group or the Boc group of N-Boc-nitrobenzenesulfonamides 147 can be selectively deprotected to give protected primary amines in excellent yields. As shown in Table 3, deprotection of 147 under the established thiolate conditions such as [HSCH₂CO₂H (2 eq), LiOH (4 eq), DMF, 23 °C, 1 hr] and [HSCH₂CO₂H (1.3 eq), Et₃N (2 eq), CH₂Cl₂, 23 °C, 10 min] gave N-Boc amines 148 in high yields. Alternatively, treatment of 147 with excess trifluoroacetic acid resulted in quantitative formation of the deacylated sulfonamides 149, which in turn could serve as the precursors for the synthesis of secondary amines.
Table 3. Alkylation and Deprotection of N-Boc-nitrobenzenesulfonamides

<table>
<thead>
<tr>
<th>ArSO₂NH₂</th>
<th>RX or ROH</th>
<th>Alkylation condition&lt;sup&gt;a&lt;/sup&gt;</th>
<th>147&lt;sup&gt;b&lt;/sup&gt; (% isolated yield)</th>
<th>Deprotection&lt;sup&gt;c&lt;/sup&gt; (% isolated yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>145</td>
<td>PhBr</td>
<td>A 23 °C, 1 hr</td>
<td>Ph-N&lt;sub&gt;Boc&lt;/sub&gt;SO₂Ar (95)</td>
<td>MA 148&lt;sup&gt;b&lt;/sup&gt; (92)</td>
</tr>
<tr>
<td>145</td>
<td>nC&lt;sub&gt;7&lt;/sub&gt;H&lt;sub&gt;15&lt;/sub&gt;Br</td>
<td>A 80 °C, 4 hr</td>
<td>nC&lt;sub&gt;7&lt;/sub&gt;H&lt;sub&gt;15&lt;/sub&gt;-N&lt;sub&gt;Boc&lt;/sub&gt;SO₂Ar (97)</td>
<td>(100)</td>
</tr>
<tr>
<td>145</td>
<td>PhOH</td>
<td>C 1 hr</td>
<td>Ph-N&lt;sub&gt;Boc&lt;/sub&gt;SO₂Ar (97)</td>
<td>(100)</td>
</tr>
<tr>
<td>145</td>
<td>CO₂EtOH</td>
<td>C 1 hr</td>
<td>Et₂O-C-N&lt;sub&gt;Boc&lt;/sub&gt;SO₂Ar (91)</td>
<td>(100)</td>
</tr>
<tr>
<td>146</td>
<td>PhBr</td>
<td>A 65 °C, 30 min</td>
<td>Ph-N&lt;sub&gt;Boc&lt;/sub&gt;SO₂Ar' (100)</td>
<td>(100)</td>
</tr>
<tr>
<td>146</td>
<td>Br</td>
<td>B</td>
<td>N&lt;sub&gt;Boc&lt;/sub&gt;SO₂Ar' (89)</td>
<td>(100)</td>
</tr>
<tr>
<td>146</td>
<td>PhOH</td>
<td>C 30 min</td>
<td>Ph-N&lt;sub&gt;Boc&lt;/sub&gt;SO₂Ar' (100)</td>
<td>(100)</td>
</tr>
<tr>
<td>146</td>
<td>CO₂EtOH</td>
<td>C 30 min</td>
<td>Et₂O-C-N&lt;sub&gt;Boc&lt;/sub&gt;SO₂Ar' (99)</td>
<td>(100)</td>
</tr>
</tbody>
</table>

<sup>a</sup>A: RX (1.5 eq), K₂CO₃ (5 eq), DMF. B: RX (3 eq), NaHCO₃ (10 eq), DMPU, 23 °C, 3 hr, then 65 °C, 1 hr. C: ROH (2 eq), DEAD (2 eq), PPh₃ (2 eq), benzene, 23 °C. 

<sup>b</sup>Satisfactory spectroscopic data were obtained on all new compounds. 

<sup>c</sup>For N-Boc-2-nitrobenzenesulfonamides: MA: HSCH₂CO₂H (2 eq), LiOH (4 eq), DMF, 23 °C, 1 hr. For N-Boc-2,4-dinitrobenzenesulfonamides: MA: HSCH₂CO₂H (1.3 eq), Et₃N (2 eq), CH₂Cl₂, 23 °C, 10 min. TFA: neat TFA (20 eq), 23 °C, 5 min.
N-Alloc-2-nitro- and N-Alloc-2,4-dinitro-benzenesulfonamides

In order to expand the scope of this approach, we prepared N-Alloc-2-nitrobenzenesulfonamide 150, and N-Alloc-2,4-dinitrobenzenesulfonamide 151 from the corresponding nitrobenzenesulfonamides [Allyl chloroformate (1.5 eq), Et₃N (2 eq), DMAP (0.1 eq), CH₂Cl₂, 23 °C, 25 min]. Under the standard Mitsunobu conditions (ROH, DEAD, Ph₃P, CH₂Cl₂, 23 °C), both 150 and 151 gave excellent yields of N-alkyl sulfonamides 152. Likewise, alkylation of 150 with alkyl halides (RX, K₂CO₃, DMF, 23 °C) proceeded smoothly. On the other hand, alkylation of the less stable N-Alloc-2,4-dinitrobenzenesulfonamide 151 under the similar conditions gave moderate yields of 152 (Scheme 36 and Table 4).

As in the case of N-Boc-nitrobenzenesulfonamides, the nitrobenzenesulfonyl group and the Alloc group of N-alkyl, N-Alloc-nitrobenzenesulfonamides 152 can be selectively deprotected in excellent yields. As shown in Scheme 2, treatment of 152 with thiolates,⁹¹ [PhSH (1.3 eq), K₂CO₃ (2 eq), DMF, 23 °C, 10 min, or HSCH₂CO₂H (1.3 eq), Et₃N (2 eq), CH₂Cl₂, 23 °C, 10 min], provided N-Alloc amines 153 in high yields. Alternatively, subjection of 152 to palladium-mediated deprotection conditions⁹² [Pd(PPh₃)₄ (0.05 eq), PPh₃ (0.2 eq), pyrrolidine (5 eq), CH₂Cl₂, 23 °C, 10 min, or Pd(PPh₃)₄ (0.05 eq), PPh₃ (0.2 eq), dimedone (5
eq), THF, 23 °C, 15 min] afforded deacylated sulfonamides 154 in good yields (Scheme 36 and Table 4).

**Table 4. Alkylation and Deprotection of N-Alloc-nitrobenzenesulfonamides**

<table>
<thead>
<tr>
<th>ArSO₂NH₂</th>
<th>RX or ROH</th>
<th>Alkylation conditions&lt;sup&gt;a&lt;/sup&gt;</th>
<th>152&lt;sup&gt;b&lt;/sup&gt; (% isolated yield)</th>
<th>Deprotection&lt;sup&gt;c&lt;/sup&gt; (% isolated yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>C₅H₁₂SO₂Ar&lt;sup&gt;d&lt;/sup&gt; (94)</td>
<td>R'S'&lt;sup&gt;−&lt;/sup&gt; 153&lt;sup&gt;b,d&lt;/sup&gt; (94) Pd(0) 154&lt;sup&gt;b&lt;/sup&gt; (91)</td>
</tr>
<tr>
<td>150</td>
<td>nC₇H₁₅Br</td>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>CO₂Et</td>
<td>C</td>
<td>EtO₂SO₂Ar&lt;sup&gt;d&lt;/sup&gt; (93)</td>
<td></td>
</tr>
<tr>
<td>151</td>
<td>PhBr</td>
<td>B</td>
<td>PhSO₂Ar&lt;sup&gt;r&lt;/sup&gt; (90)</td>
<td></td>
</tr>
<tr>
<td>151</td>
<td>PhOH</td>
<td>C</td>
<td>PhSO₂Ar&lt;sup&gt;r&lt;/sup&gt; (90)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>A: RX (1.5 eq), K₂CO₃ (5 eq), DMF, 80 °C, 2 hr. B: RX (2 eq), NaHCO₃ (10 eq), DMF, 40 °C, 8 hr. C: ROH (2 eq), DEAD (2 eq), PPh₃ (2 eq), benzene, 23 °C, 30 min.  
<sup>b</sup>Satisfactory spectroscopic data were obtained on all new compounds.  
<sup>c</sup>For N-Alloc-2-nitrobenzenesulfonamides: R'S': PhSH (1.3 eq), K₂CO₃ (2 eq), DMF, 23 °C, 10 min. Pd(0): Pd(PPh₃)₄ (0.05 eq), PPh₃ (0.2 eq), pyrrolidine (5 eq), CH₂Cl₂, 23 °C, 10 min.  
<sup>d</sup>For N-Alloc-2,4-dinitrobenzenesulfonamides: R'S': HSCH₂CO₂H (1.3 eq), Et₃N (2 eq), CH₂Cl₂, 23 °C, 10 min. Pd(0): Pd(PPh₃)₄ (0.05 eq), PPh₃ (0.2 eq), dimedone (5 eq), THF, 23 °C, 15 min.  
<sup>d</sup>Separated by silica gel chromatography after partitioning between Et₂O and an aqueous NaHCO₃ solution.

In conclusion, we have demonstrated that both N-Boc- and N-Alloc-nitrobenzenesulfonamides can be readily alkylated under conventional methods to give a variety of N-alkylated N-Boc- and N-Alloc-nitrobenzenesulfonamides.
sulfonamides, respectively. Because of the efficient conversion of these protected sulfonamides into the corresponding $N$-Boc and $N$-Alloc amines under mild conditions, we believe that the present methodology might be comparable or superior to the Gabriel synthesis$^{93}$ of primary amines.

**Alkylsulfonamides**

Nitrobenzenesulfonamides can be readily applied to the synthesis of a variety of secondary amines and protected primary amines. However, because of the presence of the nitro group in the benzene ring, nitrobenzenesulfonamides cannot survive the reductive conditions such as $\text{H}_2$-$\text{Pd/C}$ and $\text{Zn/AcOH}$. As a result, we decided to further explore sulfonamides of general applicability. There are two different ways to deprotect sulfonamides: cleavage of a S-N bond and cleavage of a C-S bond. Cleavage of S-N bond of sulfonamides often requires such harsh conditions as $\text{LiAlH}_4$, $\text{Li/NH}_3$, and sodium naphthalenide. On the other hand, cleavage of C-S bond of sulfonamides such as phenacylsulfonamides (Eq. 1)$^{94}$, β-trimethylsilylethylsulfonamides (Eq. 2)$^{95}$, and 2- and 4-nitrobenzenesulfonamides$^{80}$ and 2,4-dinitrobenzenesulfonamides$^{84}$ (Eq. 3) is carried out in a relatively mild fashion.

Allylsulfonyl groups$^{96}$ and 2-cyanoethylsulfonyl groups$^{97}$ have been reported to protect hydroxy functional groups; however, no result has been reported on the protection of amino functional groups. As a consequence, we developed allylsulfonamides, 2-cyanoethylsulfonamides, and 2-carbo-methoxyethylsulfonamides that can be utilized as convenient and general protecting groups for amines.
**Eq. 1**
\[
\text{R'RN-S_O2} \xrightarrow{\text{Zn/AcOH/HCl}} \text{R'R*NH} + \text{SO}_2 + \text{Ph}
\]

**Eq. 2**
\[
\text{R'RN-S} \xrightarrow{\text{TBAF}} \text{R'R*NH} + \text{SO}_2 + \text{H}_2\text{C}=\text{CH}_2 + \text{FSiMe}_3
\]

**Eq. 3**
\[
\text{Y-SO}_2\text{NR'R*} \xrightarrow{\text{RS}^-} \text{R'R*NH} + \text{SO}_2 + \text{Y-SR} \quad \text{a: X=NO}_2, \text{Y=H} \\
\text{b: X=H, Y=NO}_2
\]

\[
\text{O}_2\text{N-SO}_2\text{NR'R*} \xrightarrow{\text{Nu}} \text{R'R*NH} + \text{SO}_2 + \text{O}_2\text{N-S}-\text{Nu}
\]

*N-(4-Methoxyphenyl)allylsulfonamide 155*, readily prepared from 4-methoxyaniline [allylsulfonyl chloride\textsuperscript{98} (2 eq), 2,6-lutidine (3 eq), CH\textsubscript{2}Cl\textsubscript{2}, 23 °C, 30 min] in 92% yield, can be easily deprotected in the presence of excess sodium cyanide\textsuperscript{99} [NaCN (10 eq), K\textsubscript{2}CO\textsubscript{3} (3 eq), DMF, 85 °C, 5 hr] in 86% yield. The deprotection is envisioned to involve isomerization of the allylsulfonamide olefin followed by Michael-type addition of cyanide ion into the olefin and irreversible retro-Michael reaction (Scheme 37).
In addition to allylsulfonamides, 2-cyanoethylsulfonamides and 2-carbomethoxyethylsulfonamides have been demonstrated to be convenient amino protecting groups. 2-Cyanoethylsulfonamides were prepared from amines [2-cyanoethylsulfonyl chloride\textsuperscript{100} (2 eq), 2,6-lutidine (3 eq), $\text{CH}_2\text{Cl}_2$, 23 °C, 30 min] in excellent yields. Similarly, 2-carbomethoxyethylsulfonamides were prepared from amines and 2-carbomethoxyethylsulfonyl chloride\textsuperscript{101} in good yields. Both 2-cyanoethylsulfonamides and 2-carbomethoxyethyl-sulfonamides can be effectively deprotected under relatively mild deprotection conditions [DBU (5 eq), $\text{CH}_3\text{CN}$, 65 °C, 2 hr] to give the deprotected amines in good yields (Table 5).

Allylsulfonamides such as 4-(methoxyphenyl)allylsulfonamide \textbf{155} are stable under acidic conditions [3N HCl (10 eq), MeOH, 100 °C, 4 hr] and mild basic conditions [3N NaOH (10 eq), MeOH, 50 °C, 4 hr]. In addition, the ease of alkylation and deprotection of sulfonamides in conjunction with the relatively distinctive NMR spectra of sulfonamides compared to the corresponding carbamates have proved that the allylsulfonamides, 2-cyanoethylsulfonamides and 2-carbomethoxyethyl-sulfonamides to be the convenient and general protecting groups for amines.
Table 5. Protection (P) and Deprotection (D) of Alkylsulfonamides

<table>
<thead>
<tr>
<th>Amines RNH₂</th>
<th>Pᵃᵇ % yields</th>
<th>Dᵇ,c,d % yields</th>
<th>Pᵃᵇ % yields</th>
<th>Dᵈ,e % yields</th>
<th>Pᵃᵇ % yields</th>
<th>Dᵈ,e % yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO</td>
<td>(92)</td>
<td>5 hr (86)</td>
<td>(94)</td>
<td>(91)</td>
<td>(82)</td>
<td>(90)</td>
</tr>
<tr>
<td>Ph-</td>
<td>(82)</td>
<td>12 hr (71)</td>
<td>&gt;98% ee</td>
<td>(91)</td>
<td>(90)</td>
<td>&gt;98% ee</td>
</tr>
<tr>
<td>MeO</td>
<td>(72)</td>
<td>3 hr (65)</td>
<td></td>
<td>(95)</td>
<td>(97)</td>
<td>(86)</td>
</tr>
<tr>
<td>Ph-CO₂Me</td>
<td></td>
<td></td>
<td>(95)</td>
<td></td>
<td>(86)</td>
<td>(83)</td>
</tr>
<tr>
<td>NH₂⋅HCl</td>
<td>(92)</td>
<td></td>
<td>(91)</td>
<td>&gt;98% ee</td>
<td>(83)</td>
<td>&gt;98% ee</td>
</tr>
</tbody>
</table>

ᵃProtection conditions: sulfonyl chloride (2 eq), 2,6-lutidine (3 eq), CH₂Cl₂, 23 °C, 30 min. ᵇSeparated by silica gel chromatography. ᶜDeprotection conditions: NaCN (10 eq), K₂CO₃ (3 eq), DMF, 85 °C, 3-12 hr. ᵈYields on the deprotection of aliphatic amines are lower than that of the aromatic amines because of the loss of desired amines during work-up procedure. ᵉDeprotection conditions: DBU (5 eq), CH₃CN, 65 °C, 2 hr. ᶠee was determined by condensation of deprotected amine with (R)-(+-)-methoxytrifluorophenyl acetic acid.

In conclusion, we have demonstrated that 2,4-dinitrobenzenesulfonamides in conjunction with 2- and 4-nitrobenzenesulfonamides can be efficiently used for the synthesis of a wide range of secondary amines. In addition, N-Boc and N-Alloc nitrobenzenesulfonamides can be effectively applied for the synthesis of a variety of protected primary amines, and the methodology for the use of N-Boc and N-Alloc sulfonamides is comparable to the Gabriel synthesis for the preparation of primary amines. Moreover,
we have developed alkylsulfonamides such as allylsulfonamides, 2-cyanoethylsulfonamides, and 2-carbomethoxyethylsulfonamides that can be utilized as convenient and general protecting groups for amines.
Experimental

\[ \text{SO}_2\text{Cl}_2 \quad \text{NO}_2 \quad \text{H}_2\text{N} \quad \text{OMe} \quad \text{pyridine} \quad \text{CH}_2\text{Cl}_2 \quad \text{23 °C, 30 min} \quad 90\% \quad \text{135a} \]

*p*-Methoxybenzyl-2,4-dinitrobenzenesulfonamide (135a)

A typical procedure for the formation of nitrobenzenesulfonamides from primary amines is as follows: To a stirred solution of 119.5 mg (0.448 mmol) of 2,4-dinitrobenzenesulfonyl chloride in 4 ml of dichloromethane was added 58.5 μl (0.448 mmol) of p-methoxybenzylamine and 72.5 μl (0.896 mmol) of pyridine\textsuperscript{85} at room temperature under an argon atmosphere. After 30 minutes, the reaction mixture was poured into a solution of 3N hydrochloric acid, and the aqueous layer was extracted thoroughly with ether (3X). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated \textit{in vacuo}. Purification of the crude product by trituration with ether gave *p*-methoxybenzyl-2,4-dinitrobenzenesulfonamide 135a (148.1 mg, 90%) as a yellow solid.
Characterization of 135a:

mp (Et₂O): 155-157 °C

IR (CHCl₃): 3350, 3120, 2970, 2870, 1540, 1520, 1420, 1350, 1250, 1170, 1040, 840, 760

¹H NMR (CDCl₃): 3.72 (3H, s), 4.32 (2H, s), 5.82 (1H, bs), 6.70 (2H, d, J=8.6 Hz), 7.10 (2H, b, J=8.6 Hz), 8.08 (1H, d, J=8.6 Hz), 8.36 (1H, dd, J=8.6, 2.1 Hz), 8.59 (1H, d, J=2.1 Hz)

¹³C NMR (CDCl₃/ DMSO): 46.7, 55.2, 113.6, 119.6, 126.3, 128.5, 129.4, 132.2, 139.9, 147.6, 149.0, 159.1

MS: 368 (1, M+1), 367 (7, M+), 136 (22), 135 (99), 134 (76), 122 (10), 121 (84), 109 (16), 108 (19), 78 (13), 77 (25)
Compound 135a continued:
**N- Allyl-**-p-methoxybenzyl-2,4-dinitrobenzenesulfonamide (136a)**

A typical procedure for the alkylation of nitrobenzenesulfonamides with alkyl halides is as follows: To a stirred solution of 205.5 mg (0.560 mmol) of p-methoxybenzyl-2,4-dinitrobenzenesulfonamide 135a and 387 mg (2.798 mmol) of potassium carbonate in 3 ml of DMF was added 72.6 µl (0.839 mmol) of allyl bromide at room temperature under an argon atmosphere. After 20 minutes, the reaction mixture was poured into a solution of 3N hydrochloric acid, and the aqueous layer was extracted thoroughly with ether (3X). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of ether in hexanes (40% to 80%), furnished N-allyl-p-methoxybenzyl-2,4-dinitrobenzenesulfonamide 136a (221.1 mg, 97%) as a yellow solid.
Characterization of 136a:

mp (Et₂O): 86-87 °C

IR (CHCl₃): 3110, 2950, 2850, 1610, 1560, 1540, 1510, 1440, 1350, 1310, 1260, 1170, 1110, 1040, 910, 750

¹H NMR (CDCl₃): 3.78 (3H, s), 3.89 (2H, d, J=6.2 Hz), 4.46 (2H, s), 5.09-5.21 (2H, m), 5.53-5.68 (1H, m), 6.78-6.83 (2H, m), 7.14 (2H, dd, J=11.4, 2.8 Hz), 8.13 (1H, d, J=8.7 Hz), 8.39 (1H, dd, J=8.7, 2.1 Hz), 8.46 (1H, d, J=2.1 Hz)

¹³C NMR (CDCl₃): 49.7, 50.4, 55.3, 114.1, 119.7, 120.1, 126.0, 126.6, 130.1, 131.5, 132.7, 139.7, 147.8, 149.5, 159.6

MS: 408 (1, M+1), 407 (13, M+), 390 (35), 260 (11), 175 (23), 174 (79), 148 (30), 135 (11), 134 (7), 122 (58), 121 (99), 120 (26), 92 (32), 78 (32), 77 (52), 68 (35), 41 (57)
Compound 136a continued:
Alkylated 2,4-dinitrobenzenesulfonamide (136c)

A typical procedure for the alkylation of nitrobenzenesulfonamides with alkyl alcohol under Mitsunobu reaction is as follows: To a stirred solution of 122.5 mg (0.299 mmol) of 2,4-dinitrobenzenesulfonamide 135c, 68.8 µl (0.598 mmol) of L-ethyl lactate and 157 mg (0.598 mmol) of triphenylphosphine in 3 ml of benzene was slowly added 94.2 ml (0.598 mmol) of diethylazodicarboxylate at room temperature under an argon atmosphere. After 30 minutes, the reaction mixture was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel, eluted with a gradient of dichloromethane in hexanes to give alkylated 2,4-dinitrobenzenesulfonamide 136c (147.9 mg, 97%) as a yellow solid.
Characterization of 136c:

mp: 86-88 °C

IR (CHCl₃): 3110, 3040, 2990, 2960, 2900, 1750, 1600, 1560, 1540, 1460, 1450, 1350, 1300, 1240, 1180, 1020, 750

¹H NMR (CDCl₃): 1.29 (3H, t, J=7.2 Hz), 1.73 (2H, d, J=7.2 Hz), 3.24-3.42 (2H, m), 3.57 (3H, s), 4.21 (2H, q, J=7.2 Hz), 4.61 (1H, dd, J=9.6, 4.6 Hz), 4.75 (1H, q, J=7.2 Hz), 7.19-7.26 (5H, m), 8.31-8.43 (3H, m)

¹³C NMR (CDCl₃): 14.1, 17.5, 38.2, 52.5, 56.6, 61.7, 62.1, 119.5, 126.0, 127.0, 128.6, 129.4, 132.6, 136.6, 138.8, 148.7, 149.7, 170.1, 170.9

MS: 451 (<1, M+1-CO₂Me), 450 (1, M+-CO₂Me), 436 (1), 418 (3), 376 (7), 231 (62), 219 (20), 163 (18), 162 (99), 146 (24), 131 (16), 121 (21), 117 (58), 114 (33), 91 (65), 59 (34), 47 (36), 35 (20), 29 (31)

[α]D²³: -27.0° (c = 4.135, CHCl₃)
Compound 136c continued:

[Graphs showing various data points and trends related to the compound 136c.]
**N- Allyl- \( p \)-methoxybenzylamine (138a)**

A typical procedure for the deprotection of alkylated 2,4-dinitrobenzenesulfonamides by treatment with \( n \)-propylamine: To a stirred solution of 101 mg (0.248 mmol) of \( N \)-allyl-\( p \)-methoxybenzyl-2,4-dinitrobenzenesulfonamide 136a in 2 ml of dichloromethane was added a large excess of \( n \)-propylamine (408 \( \mu \)l, 4.96 mmol) at room temperature. After 10 min, the reaction mixture was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel, eluted with a gradient of ether in hexanes to remove the side product 139a followed by a gradient of methanol in dichloromethane, to give the desired \( N \)-allyl-\( p \)-methoxybenzylamine 138a (40 mg, 91\%) as an oil.
Characterization of 138a:

IR (CHCl₃): 3300, 3080, 2900, 2830, 1610, 1510, 1450, 1300, 1240, 1170, 1040, 920, 810

¹H NMR (CDCl₃): 1.83 (1H, bs), 3.27 (2H, d, J = 5.7 Hz), 3.73 (2H, s), 3.80 (3H, s), 5.09-5.24 (2H, m), 5.85-6.01 (1H, m), 6.84-6.89 (2H, m), 7.22-7.27 (2H, m)

¹³C NMR (CDCl₃): 51.5, 52.5, 55.2, 113.8, 116.2, 129.4, 132.1, 136.5, 158.7

MS: 177 (4, M⁺), 176 (21), 148 (3), 136 (1), 135 (6), 134 (4), 122 (11), 121 (99), 91 (6), 78 (4), 77 (5), 56 (4), 41 (6), 36 (3), 28 (9)
Compound 138a continued:
Amine (138c)

A typical procedure for the deprotection of alkylated 2,4-dinitrobenzenesulfonamides by treatment with mercaptoacetic acid: To a stirred solution of 101.6 mg (0.199 mmol) of sulfonamide 136c in 2 ml of dichloromethane was added 84 μl (0.594 mmol) of triethylamine followed by 19.8 μl (0.285 mmol) of mercaptoacetic acid at room temperature. After 5 minutes, the reaction mixture was poured into a solution of sodium bicarbonate, and the aqueous layer was extracted thoroughly with ether (3X). The by-product 139c remained in the aqueous layer and thus was removed from the organic extracts. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. While practically pure amine 138c was obtained after work-up, further purification by column chromatography on silica gel, eluted with a gradient of methanol in dichloromethane, furnished pure amine 138c (50.4 mg, 91%) as an oil.
Characterization of 138c:

IR (CHCl₃): 3320, 3020, 2980, 2950, 1740, 1460, 1400, 1200, 1170, 1040, 770, 720

¹H NMR (CDCl₃): 1.21-1.26 (6H, m), 2.29 (1H, bs), 2.92-2.96 (2H, m), 3.25 (1H, q, J = 7.0 Hz), 3.53 (1H, t, J = 6.8 Hz), 3.62 (3H, s), 4.12 (2H, qd, J = 7.0, 1.8 Hz), 7.17-7.31 (5H, m)

¹³C NMR (CDCl₃): 15.8, 20.3, 41.6, 53.4, 56.9, 62.5, 62.8, 128.3, 130.0, 130.9, 139.1, 176.0, 176.4

MS: 280 (<1, M+1), 279 (1, M⁺), 221 (3), 220 (21), 207 (4), 206 (43), 189 (9), 188 (99), 160 (3), 147 (4), 146 (34), 114 (37), 91 (7)

[α]D²³: +30.7° (c = 5.08, CHCl₃)
Compound 138c continued:
**N-Boc-2-nitrobenzenesulfonamide (145)**

To a stirred solution of 2.08 g (10.3 mmol) of 2-nitrobenzenesulfonamide in 20 ml of dichloromethane was added 2.15 ml (15.4 mmol) of triethylamine, 2.69 g (12.4 mmol) of di-tert-butyl dicarbonate, and a catalytic amount of DMAP (126 mg, 1.03 mmol) at room temperature under an argon atmosphere. After 25 minutes, the reaction mixture was poured into a solution of 1N hydrochloric acid, and the aqueous layer was extracted thoroughly extracted with ether (4X). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product by trituration with 40% ether in hexanes gave *N*-Boc-2-nitrobenzenesulfonamide 145 (2.96 g, 95%) as a yellow powder.
Characterization of 145:

mp (Et$_2$O): 138-140 °C

IR (CHCl$_3$): 3320, 3150, 3000, 2950, 1750, 1740, 1550, 1460, 1440, 1360, 1250, 1180, 1150, 1130, 1060, 760

$^1$H NMR (CDCl$_3$): 1.43 (9H, s), 7.69-7.90 (3H, m), 8.34-8.37 (1H, m)

$^{13}$C NMR (CDCl$_3$): 27.9, 84.6, 125.0, 132.1, 132.4, 133.1, 134.6, 148.1, 148.9

MS: 250 (5), 249 (16), 248 (44), 245 (26), 244 (56), 189 (46), 188 (10), 151 (84), 138 (80), 124 (84), 123 (92), 108 (54), 91 (76), 90 (75), 86 (75), 84 (90), 78(75), 74 (74), 66 (62), 52 (76), 54 (87), 49 (93), 37 (69)
Compound 145 continued:
**N-Boc-2,4-dinitrobenzenesulfonamide (146)**

To a stirred solution of 1.00 g (4.05 mmol) of 2,4-dinitrobenzenesulfonamide in 20 ml of dichloromethane was added 0.74 ml (5.26 mmol) of triethylamine, 1.06 g (4.85 mmol) of di-tert-butyl dicarbonate, and a catalytic amount of DMAP (49 mg, 0.41 mmol) at room temperature under an argon atmosphere. After 20 min, the reaction mixture was poured into a solution of 1N hydrochloric acid, and the aqueous layer was extracted thoroughly with ether (3X). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Purification of the crude product by trituation with 40% ether in hexanes to afford N-Boc-2,4-dinitrobenzenesulfonamide 146 (1.36 g, 97%) as a yellow powder.
Characterization of 146:

mp (Et₂O): 138-140 °C

IR (CHCl₃): 3300, 3140, 3000, 1750, 1740, 1540, 1430, 1350, 1180, 1150, 1120, 910, 830, 750, 740

¹H NMR (CDCl₃): 1.45 (9H, s), 8.59 (2H, s), 8.66 (1H, s)

¹³C NMR (CDCl₃): 27.9, 85.7, 120.4, 126.7, 135.3, 136.9, 148.3, 150.5, 178.3

MS: 294 (2), 293 (1), 290 (4), 289 (1), 233 (71), 232 (100), 184 (19), 76 (79), 74 (83), 63 (80), 55 (82), 45 (78), 38 (85)
Compound 146 continued:
A typical procedure for the deprotection of alkylated mononitrobenzenesulfonamides by treatment with mercaptoacetic acid: To a stirred solution of 101.6 mg (0.259 mmol) of N-Boc, N-benzyl-2-nitrobenzenesulfonamide 147 in 2 ml of DMF was added 43.5 mg (1.036 mmol) of LiOH.H₂O followed by 36.0 µl (0.518 mmol) of mercaptoacetic acid at room temperature. After 25 minutes, the reaction mixture was poured into a solution of sodium bicarbonate, and the aqueous layer was extracted thoroughly with ether (4X). The by-product 139 remained in the aqueous layer and thus was removed from the organic extracts. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. While practically pure N-Boc-benzylamine 148 was obtained after work-up, further purification by column chromatography on silica gel, eluted with a gradient of methanol in dichloromethane, furnished amine 148 (69.6 mg, 92%) as an oil.
Characterization of **148**:

**IR (CHCl₃):** 3330, 2990, 2940, 1680, 1560, 1460, 1370, 1260, 1190, 740, 700

**¹H NMR (CDCl₃):** 1.44 (9H, s), 4.26 (2H, d, J = 5.9 Hz), 5.11 (1H, bs), 7.19-7.32 (5H, m)

**¹³C NMR (CDCl₃):** 28.2, 44.4, 79.1, 127.0, 127.2, 128.3, 138.9, 155.8

**MS:** 154 (8), 153 (97), 150 (92), 149 (41), 134 (33), 108 (41), 106 (66), 105 (100), 91 (50), 90 (51), 80 (50), 79 (66), 78 (84), 77 (57), 69 (84), 66 (81), 39 (68)
Compound 148 continued:
\textbf{N-Benzyl-2-nitrobenzenesulfonamide (149)}

A typical procedure for the deprotection of alkylated \textit{N}-\textit{Boc}-nitrobenzenesulfonamides by treatment with trifluoroacetic acid: 150.8 mg (0.384 mmol) of \textit{N}-\textit{Boc}, \textit{N}-benzyl-2-nitrobenzenesulfonamide 147 was treated with excess trifluoroacetic acid (1 ml), and the reaction mixture was allowed to stand at room temperature for 5 min before it was concentrated \textit{in vacuo}. While practically pure \textit{N}-benzyl-2-nitrobenzenesulfonamide 149 was obtained after evaporation, further purification by column chromatography on silica gel, eluted with a gradient of methanol in dichloromethane, provided amine 149 (69.6 mg, 92\%) as a yellow solid.
Characterization of 149:

IR (CHCl₃): 3350, 3100, 3050, 2900, 1540, 1410, 1370, 1340, 1170, 1130, 1060, 740, 710

¹H NMR (CDCl₃): 4.29 (2H, d, J = 6.3 Hz), 5.85 (1H, t, J = 6.3 Hz), 7.18-7.24 (5H, m), 7.55-7.67 (2H, m), 7.73-7.77 (1H, m), 7.91-7.95 (1H, m)

¹³C NMR (CDCl₃): 47.6, 125.0, 127.6, 127.7, 128.4, 130.7, 132.7, 133.4, 135.6, 147.4

MS: 247 (2), 246 (3), 245 (1), 211 (28), 210 (39), 187 (48), 182 (52), 181 (79), 171 (100), 166 (80), 153 (50), 108 (76), 93 (98), 90 (65), 66 (70), 64 (82), 30 (70)
Compound 149 continued:
N-Alloc-2-nitrobenzenesulfonamide (150)

To a stirred solution 2.08 g (8.4 mmol) of 2-nitrobenzenesulfonamide in 20 ml of dichloromethane was added 1.64 ml (15.4 mmol) of allyl chloroformate, 2.87 ml (20.6 mmol) of triethylamine, and a catalytic amount of DMAP (126 mg, 0.84 mmol) at room temperature under an argon atmosphere. After 25 min, the reaction mixture was poured into a solution of 1N hydrochloric acid, and the aqueous layer was extracted thoroughly with ether (4X). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Purification of the crude product by trituation with 40% ether in hexanes afforded N-Alloc-2-nitrobenzenesulfonamide 150 (2.96 g, 95%) as a yellow solid.
Characterization of 150:

mp (Et₂O): 96-98 °C

IR (CHCl₃): 3250, 3130, 2920, 1750, 1540, 1450, 1370, 1220, 1170, 1140, 850

¹H NMR (CDCl₃): 4.61 (2H, d, J = 5.9 Hz), 5.28 (1H, dd, J = 10.3, 1.0 Hz), 5.32 (1H, dd, J = 15.9, 1.0 Hz), 5.78-5.94 (1H, m), 7.77-7.90 (3H, m), 7.96 (1H, bs), 8.36-8.40 (1H, m)

¹³C NMR (CDCl₃): 67.7, 119.8, 125.1, 130.5, 131.4, 132.6, 133.4, 135.0, 149.9, 161.0

MS: 230 (20), 229 (15), 214 (40), 213 (46), 188 (45), 186 (68), 140 (76), 124 (90), 123 (48), 106 (47), 105 (46), 94 (56), 93 (100), 91 (59), 78 (56), 76 (84), 75 (72), 74 (83), 51 (71), 38 (88)
Compounds 150 continued:
\[ \text{SO}_3\text{NH}_2 \quad \text{Alloc-Cl} \quad \text{Et}_3\text{N}, \text{DMAP} \quad \text{CH}_2\text{Cl}_2 \quad 23^\circ\text{C}, 25\text{ min} \quad \text{96\%} \quad \text{SO}_3\text{NHAlloc} \]

\text{N-Alloc-2,4-dinitrobenzenesulfonamide (151)}

To a stirred solution of 1.00 g (4.05 mmol) of 2,4-dinitrobenzenesulfonamide in 20 ml of dichloromethane was added 0.74 ml (5.26 mmol) of triethylamine, 0.52 ml (4.85 mmol) of allyl chloroformate, and a catalytic amount of DMAP (49 mg, 0.41 mmol) at room temperature under an argon atmosphere. After 25 minutes, the reaction mixture was poured into a solution of 1N hydrochloric acid, and the aqueous layer was extracted thoroughly extracted with ether (4X). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated \textit{in vacuo}. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of ethyl acetate in hexanes, yielded \textit{N-Alloc-2,4-dinitrobenzenesulfonamide 151} (1.36 g, 97%).
Characterization of 151:

IR (CHCl₃): 3250, 3060, 2920, 1760, 1540, 1440, 1350, 1280, 1240, 1170, 870, 760

¹H NMR (CDCl₃): 4.62 (2H, d, J = 5.9 Hz), 5.29 (1H, d, J = 9.7 Hz), 5.34 (1H, d, J = 15.4 Hz), 5.78-5.94 (1H, m), 6.57 (1H, bs), 8.56 (2H, s), 8.65 (1H, s)

¹³C NMR (CDCl₃): 68.1, 120.1, 120.3, 126.8, 130.4, 135.3, 136.6, 148.4, 150.5

MS: 260 (4), 259 (26), 258 (35), 233 (98), 232 (97), 185 (11), 169 (22), 150 (16), 123 (20), 94 (52), 80 (54), 76 (88), 75 (83), 74 (89), 64 (85), 63 (89), 62 (81), 59 (85), 56 (76), 42 (76), 38 (89)
Compound 151 continued:
$N$-Alloc-$n$-heptylamine (153)

A typical procedure for the deprotection of alkylated mononitrobenzenesulfonamides by treatment with thiophenol: To a stirred solution of 154.4 mg (0.402 mmol) of $N$-Alloc, $N$-$n$-heptyl-2-nitrobenzenesulfonamide 152 in 1 ml of DMF was added 110 mg (0.803 mmol) of potassium carbonate followed by 54 μl (0.522 mmol) of thiophenol at room temperature. After 10 minutes, the reaction mixture was poured into a solution of sodium bicarbonate, and the aqueous layer was extracted thoroughly with ether (4X). The by-product 139 remained in the aqueous layer and thus was removed from the organic extracts. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. While practically pure $N$-Alloc-$n$-heptylamine 153 was obtained after work-up, further purification by silica gel column chromatography, eluted with a gradient of methanol in dichloromethane, furnished amine 153 (75.5 mg, 94.3%) as an oil.
Characterization of 153:

IR (CHCl₃): 3340, 2960, 2930, 2850, 1700, 1540, 1460, 1250, 1200, 1000, 930

¹H NMR (CDCl₃): 0.88 (3H, t, J = 6.4 Hz), 1.21-1.39 (8H, m), 1.49 (2H, sep, J = 6.7 Hz), 3.17 (2H, q, J = 6.6 Hz), 4.56 (2H, d, J = 5.5 Hz), 4.80 (1H, bs), 5.18 (1H, dd, J = 10.4, 1.0 Hz), 5.30 (1H, dd, J = 17.2, 1.0 Hz), 5.85-6.00 (1H, m)

¹³C NMR (CDCl₃): 14.0, 22.5, 26.6, 28.9, 29.9, 31.7, 41.0, 65.3, 117.4, 133.0, 156.2

MS: 187 (1), 186 (1), 169 (2), 165 (2), 164 (2), 163 (2), 154 (3), 153 (3), 152 (5), 151 (3), 150 (3), 112 (12), 99 (20), 85 (46), 84 (22), 56 (22), 45 (34), 44 (100), 43 (49), 42 (48), 41 (40), 31 (28), 29 (60), 26 (52)
Compound 153 continued:
**N-n-Heptyl-2-nitrobenzenesulfonamide (154)**

A typical procedure for the deprotection of alkylated N-Alloc-nitrobenzenesulfonamides by treatment with palladium(0) conditions: To a stirred solution of 140.8 mg (0.366 mmol) of N-Boc, N-n-heptyl-2-nitrobenzenesulfonamide 152 in 2 ml of dichloromethane was added 19.2 mg (0.073 mmol) of triphenylphosphine, 153 µl (1.83 mmol) of pyrrolidine and 21 mg (0.018 mmol) of Pd(PPh3)4 consecutively at room temperature under an argon atmosphere. After 10 min, the reaction mixture was concentrated in vacuo to give crude amine which was purified by column chromatography on silica gel, eluted with a gradient of ether in hexanes, to give amine 154 (100.5 mg, 91.4%) as a yellow solid.
Characterization of 154:

IR (CHCl₃): 3340, 3100, 2950, 2940, 2870, 1540, 1420, 1360, 1340, 1170, 1140, 740

¹H NMR (CDCl₃): 0.85 (3H, t, J = 6.3 Hz), 1.22 (8H, bs), 1.52 (2H, sep, J = 7.1 Hz), 3.09 (2H, q, J = 6.8 Hz), 5.26 (1H, t, J = 5.8 Hz), 7.73-7.79 (2H, m), 7.83-7.88 (1H, m), 8.12-8.16 (1H, m)

¹³C NMR (CDCl₃): 13.8, 22.3, 26.2, 28.4, 29.3, 31.3, 43.7, 125.1, 130.8, 132.7, 133.2, 133.6, 147.8

MS: 218 (2), 217 (35), 216 (22), 189 (36), 188 (98), 185 (42), 170 (28), 114 (67), 113 (75), 93 (57), 79 (47), 78 (67), 77 (77), 76 (48), 56 (63), 55 (68), 44 (58), 40 (64)
Compound 154 continued:
References


37. Dihydrochloride monohydrate of 1b.


This procedure has an advantage over the one with PhSH in that the byproduct 5, O₂NC₆H₄SCH₂CO₂H, can be removed easily by partition between Et₂O and a dilute NaHCO₃ solution.


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(a) Somewhat lower yields of sulfonamides 1 were obtained using triethylamine as a base because of the concomitant decomposition of 1 through the intramolecular Meisenheimer complex formation as shown below.

(b) For formation of 2-nitrobenzenesulfonamides from primary amines and 2-nitrobenzenesulfonyl chloride, triethylamine as a base was used because there is no observed intramolecular Meisenheimer formation.

*n*-Propylamine was chosen because it is easy to remove (b.p. 48 °C) and inexpensive.


Private communications from Drs. John Nuss (Chiron) and Lihu Yang (Merck).

Fukuyama, T.; Cheung, M. Manuscript in preparation.

90. (a)Willgerodt, C.; Mohr, P. J. Prakt. Chem. 1886, 34, 124. (b) 2,4-Dinitrobenzenesulfonamide was prepared by bubbling ammonia into the solution of 2,4-dinitrobenzenesulfonyl chloride in Et₂O at 23 °C. After the reaction was complete, the reaction mixture was filtered through celite and washed with ethyl acetate to remove ammonium chloride salt. The filtrate was evaporated and trituated with 40% ether in hexanes to give pure 2,4-dinitrobenzenesulfonamide as yellow solid (97% yield).

91. Deprotection of 2-nitrobenzenesulfonyl group on N-Alloc-2-nitrobenzenesulfonamides 8 was achieved cleanly using PhSH and K₂CO₃ conditions.

92. For the deprotection of Alloc group on 2,4-dinitrobenzenesulfonamides 8, dimedone was used as a nucleophile to avoid the formation of Meisenheimer complex caused by pyrrolidine.


99. Other deprotection conditions include: (a) NaCN (10 eq), DBU (5 eq), DMF or CH₃CN, 85 °C, 3-12 hr. (b) Bu₄NCN (10 eq), DBU (5
eq), CH$_3$CN, 85 °C. (c) This step-wise procedure is only good for aromatic amines: Pd(PPh$_3$)$_4$ (0.05 eq), PPh$_3$ (0.2 eq), pyrrolidine (10 eq), 37% formaldehyde (30 eq), CH$_2$Cl$_2$, 23 °C, 4 hr, Ar; 3N HCl, reflux, 2 hr. (d) This procedure requires continuous addition of reagents and is only good for aromatic amines: Bu$_3$SnH (4 eq), AIBN (0.4 eq), benzene, 85 °C, Ar.
