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Synthesis of 5-Substituted Indolizidines and Approaches to 3- and 8-Substituted Indolizidines from a Common Intermediate Accessed via the Remote Dianion of 4-PSBA

James J. Kiddle,[§] Diana L. C. Green[‡] and Charles M. Thompson*†

Department of Chemistry, Loyola University of Chicago, Chicago, IL 60626

Abstract: The dianion of 4-(phenylsulfonyl)butanoic acid (**1**: 4-PSBA) was used to prepare a pivotal intermediate **5** that was used in novel syntheses of indolizidines containing alkyl substituents in a variety of patterns at the 3-, 5- and, 8-positions.

The 1-azabicyclo[4.3.0]nonane skeleton (indolizidine) represents the nucleus of a diverse group of compounds isolated from both plant and animal sources (Figure 1). A recent review of the literature showed that 25 to 30% of the known alkaloids incorporate the indolizidine skeleton in various forms.[1] Among the most interesting are the simple indolizidine alkaloids (formerly the gephyrotoxins)[2] that have been isolated from the skin secretions of the neotropical poison-dart frogs belonging to the genus *Dendrobates*.[3] These alkaloids vary in substitution patterns containing a single substituent at C-5, substituents at C-3 and C-5, or substituents at C-5 and C-8. Many of these alkaloids are potent moderators of neuromuscular transmission. For example, Daly and co-workers[4] showed that indolizidines inhibit the acetylcholine receptor, and are weak antagonists of muscarinic receptors. Daly and co-workers[5] also showed that the indolizidines are inhibitors of the nicotinic acetylcholine receptor ion channel in electric eels. The 3,5-disubstituted indolizidines produce long lasting locomotor difficulties following subcutaneous injections in mice.[3a] In addition, inhibition of the nicotinic acetylcholine receptor ion channels appears universal for most indolizidine substitution patterns.[3a]

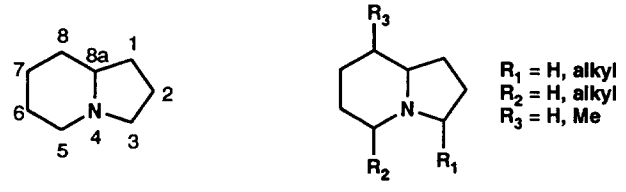


Figure 1

current addresses: ‡ Abbott Laboratories, PPD Analytical Res. Div., North Chicago, IL 60064; § Trophix Pharmaceuticals, 40 Cragwood Road, South Plainfield, NJ 07080; † Department of Chemistry, University of Montana, Missoula, Montana 59812.

A number of syntheses of the indolizidines have been reported,[6] yet most of these processes provide routes to one indolizidine substitution pattern. We felt that a general synthetic strategy to all known substitution patterns of the indolizidines from a common intermediate would be highly desirable.

The chemistry of dianions has recently been reviewed[7] showing a broad application to the synthesis of natural products. The remote dianion of 4-(phenylsulfonyl)butanoic acid (4-PSBA)[8] (**1**) has been extensively studied in our laboratory, and has found utility in four carbon chain extensions,[9] synthesis of substituted 6-[8] and 7-membered[10] lactones, and lactams.[11] Condensation of the 4-PSBA dianion with an aldehyde, ketone or imine **2** followed by anhydride-assisted cyclization provides an efficient one-pot procedure for the synthesis of lactones **3** or lactams **4** (Figure 2). Imines require prior activation with BF_3-OEt_2 before addition of the 4-PSBA dianion. The lactams **4** were of expanded interest because they could possibly serve as intermediates towards the synthesis of the large number of piperidine-based natural products.[12] The preparation of δ-coniceine[13] and the 1-azaspiran skeleton of perhydrohistrionicotoxin[14] are prior examples of this methodology.

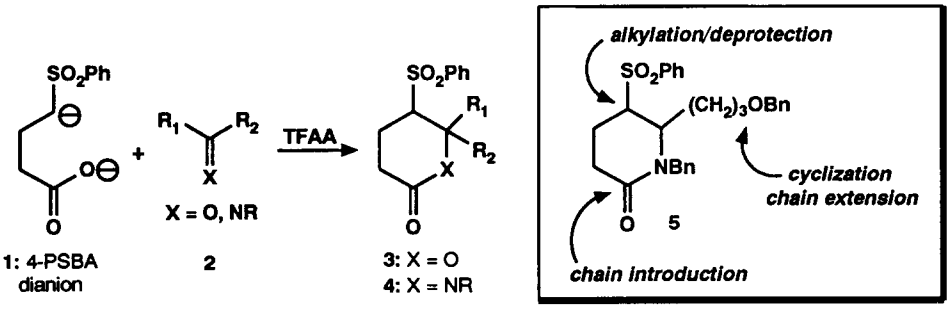


Figure 2. Utility of 4-PSBA$^{=}$ to prepare lactones and lactams and target intermediate.

Our primary goal was to prepare an intermediate that was amenable to installation of substituents at the 3-, 5- or 8-position of the indolizidine nucleus. In principle, the lactam **5** (Figure 2) could be modified to provide the desired substitution patterns present in indolizidine natural products. For example, the 3-(benzyloxy)propyl side chain can be modified to longer alkyl chains which become the needed 3-positional substituents following cyclization. Alkyl groups can be installed at the corresponding 5- and 8-positions through modification of the lactam carbonyl and alkylation of the α-phenylsulfonyl position, respectively. The work reported herein presents successful approaches to 3-, 5-, and 8-substituted intermediates derived from **5**. Last, the effect of substitution at the 5-position on cyclization to the indolizidine nucleus was explored.

RESULTS AND DISCUSSION

The first objective of the synthesis was to prepare the target lactam **5** (Scheme 1).[7] 1,4-Butanediol (**6**) was converted to the monobenzyl ether **7** using excess diol (KOH, benzyl bromide)[15] in 91% yield. The yield of this reaction was increased to 99% by incremental addition of both the KOH and benzyl

bromide to the diol. Compound **7** was oxidized to the aldehyde **8** using PCC[16] in 67% yield. The use of PDC[17] improved the yield to 80-90% when the reaction mixture also was filtered through a Florisil packed funnel,[18] followed by removal of solvent and column chromatography. Swern oxidation[19] using DMSO and trifluoroacetic anhydride (TFAA) gave the aldehyde in 71% yield.

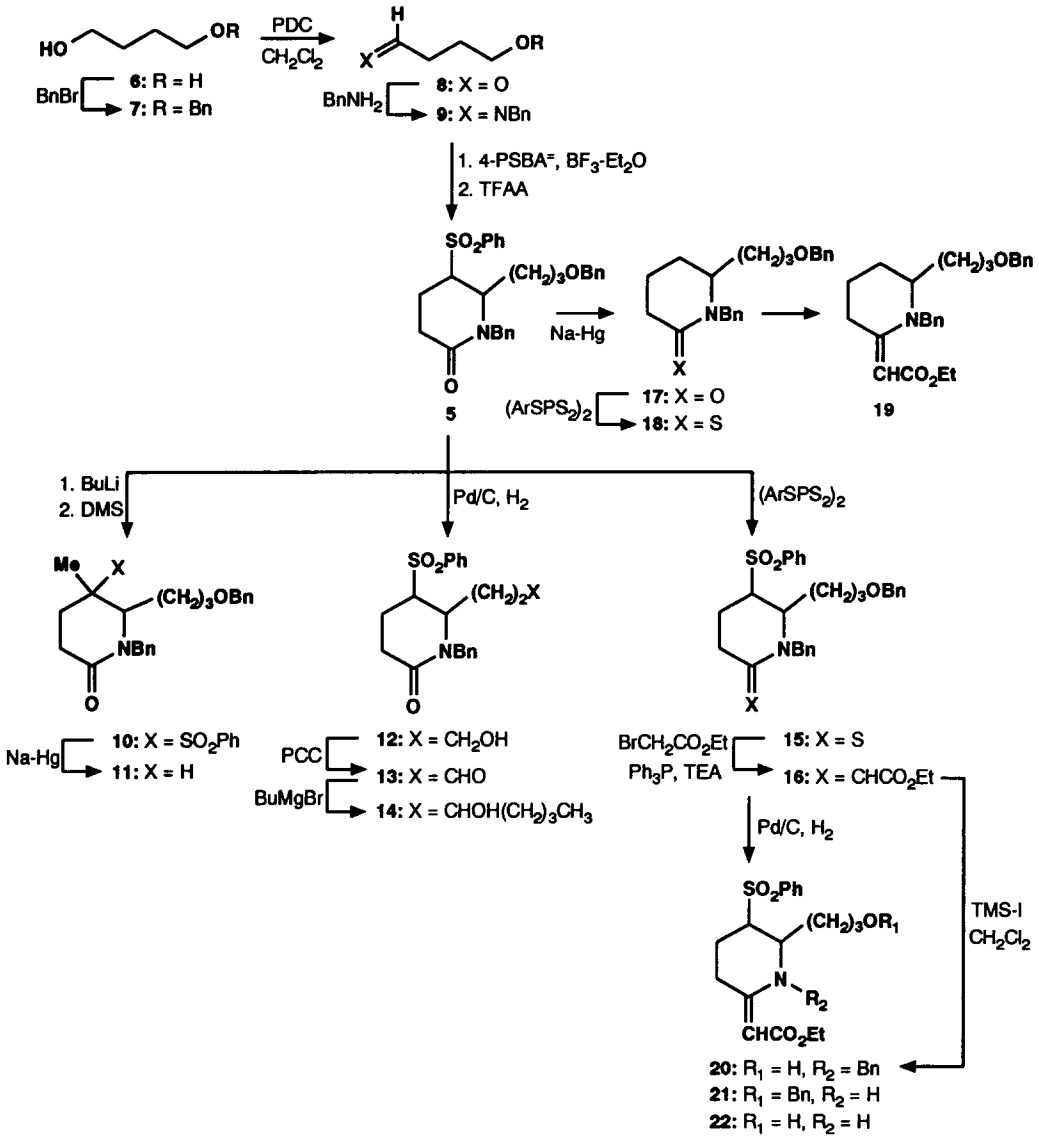
Aldehyde **8** was converted to the imine **9** by adding **8** to benzylamine in toluene followed by decanting the organic layer from the water produced, and drying over barium oxide at -4 °C for 12 hours. The imine **9**, used without further purification, was dissolved in THF and activated with boron trifluoride etherate (BF_3-OEt_2) at -78 °C for 30 minutes and reacted with **1**. The activation probably results in the formation of a Lewis acid-iminium ion that undergoes attack by **1** more readily. The intermediate syn and anti addition products are directly cyclized to the lactam by addition of TFAA. The success of the cyclization is dependent upon the time between dianion reaction and addition of TFAA. If the reaction is allowed to continue for longer than five minutes before addition of TFAA, the reaction yields were much lower. The lower cyclization yields may be due to rearrangement of the kinetic amine anion to the anionic site at the phenylsulfonyl α-carbon. Lactam **5** may be isolated as a mixture of non-polar and polar diastereomers (based on their normal phase chromatographic elution order) in 82% yield after purification. Stereochemical assignments are provided in the following paper. Where possible, diastereomer mixtures produced in the sequence were separated and individually characterized as polar and non-polar fractions.

Because many naturally occurring indolizidines have a methyl group at the 8-position, we sought to find a reliable method for installation of this substituent. Attempts to introduce the 8-methyl moiety in **5** using NaH followed by alkylation with methyl iodide or reaction with sodium amide followed by methyl iodide or dimethyl sulfate (DMS) failed. Deprotonation with n-BuLi followed by reaction with DMS successfully produced the 8-methyl lactam **10** in 91% yield. No alkylation occurred alpha to the amide carbonyl. Desulfonylation of **10** with sodium amalgam in methanol led to the corresponding 8-methyl compound **11** as a diastereomer mixture. The desulfonylation was not accompanied by elimination and ring opening to give an alkene a process that had occurred with an analogous substrate used in a synthesis of azaspirans.[14] Compound **11** showed a doublet at δ 1.74 ppm (CH_3-, 3H) and a multiplet at δ 3.30 ppm (ring CH, 1H) in the ^{1}H NMR confirming the presence of the 8-methyl group. Two α-carbonyl protons [-CH_2C(O)] remained in the ^{1}H NMR indicating that alkylation did not occur at the amide enolate position.

To place substituents at the 3-position of an indolizidine ring system would require conversion of the propyl benzyl ether side chain of lactam **5** to a branched moiety bearing a leaving group at the 3-position. We sought to introduce a butyl chain at the pre-cyclized 3-position because both monomerine and indolizidine 223AB[3e] bear this 3-substituent. Lactam **5** was chemoselectively de-O-benzylated using H_2 (10% Pd/C; < 20 psi) to furnish the alcohol **12** in 82% yield as a separable mixture of diastereomers. Alcohol **12** , as a single diastereomer, was oxidized to aldehyde **13** using PCC in 67% yield which was reacted with n-BuMgBr (4 equiv.) in ether to give the secondary alcohol **14** in modest yield (42%) following chromatography. Significant amounts of starting material (>25%) were recovered suggesting that deprotonation at the α-$CHSO_2Ph$ site may be a competing reaction with the Grignard reagent.

Functionalization of the 5-position was next undertaken because all natural indolizidines contain an alkyl substituent at this position. Attempts to alkylate the carbonyl of lactam **5** followed by reaction with organometallics and reduction of the resulting iminium ion with hydride reagents failed to produce the desired α-monosubstituted piperidines.[21] Conversion of **5** to the imino tetrafluoroborates followed by

nucleophilic addition also failed to provide the desired monosubstituted piperidines. We also thought that the phenylsulfonyl group may be interfering with this transformation. As such, **5** was first desulfonylated to give **17**, which unfortunately did not undergo successful conversion of the lactam carbonyl. These disappointing results suggested that an alternate pathway to functionalize the 5-position was warranted.



Scheme 1. Synthetic scheme leading to substituted piperidines.

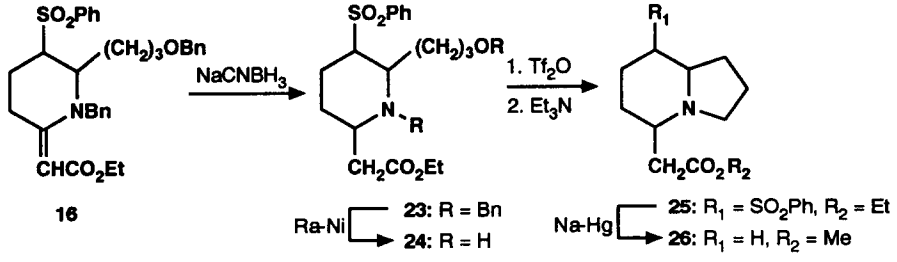
The Eschenmoser sulfur-extrusion sequence,[23] used for the preparation of vinylogous carbamates from amides and lactams, was chosen to install the 5-functional group. The lactam **5** is converted to a separable diastereomeric mixture of thiolactams **15** in 96% yield using Lawessons reagent.[24] Reaction of **15** with ethyl bromoacetate (48 hours) followed by addition of triphenylphosphine and triethylamine gave predominantly the *E*-vinylogous carbamate **16** in 94% yield. Unfortunately, attempts to introduce a three-carbon chain (to give a precursor to the known indolizidine 167B[3a]) via the Eschenmoser reaction, and decarboxylation sequence using a secondary bromide (ethyl 2-bromobutyrate), did not produce the corresponding vinylogous carbamate. It has been noted that secondary halides do not react well in the Eschenmoser reaction because of steric crowding in the formation of the tetrasubstituted olefin.[23] To expand the utility of this process, the identical Eschenmoser sequence was conducted following desulfonylation. Lactam **5** reacted with 6% Na-Hg to give **17**, which was converted to the thiolactam **18** (98%). Eschenmoser coupling to the vinylogous carbamate **19** proceeded in 91% yield. Conversion of intermediates **16** and **19** to the corresponding C-5 methyl appendage were envisioned to proceed via decarboxylation and reduction. However, we were unable to find suitable hydrolysis-decarboxylation conditions.[25]

Because the 5-position now contained a flexible functional group, cyclization to the indolizidine was explored. De-O-benzylation of **16** (polar) using Pd/C (<20 psi) in methanol gave unreacted starting material. Reaction of **16** (polar) using Pd/C, H_2 (45 psi) in methanol gave products of de-O-benzylation **20**, de-N-benzylation **21** and bis-debenzylation **22**, in approximately equal quantities, and a more chemoselective method of de-O-benzylation was sought. Trimethylsilyl iodide (TMS-I) is known to effect cleavage of a variety of carbon-oxygen bonds through dealkylation.[26,27] We were pleased to find that TMS-I cleanly converted **16** to the alcohol **20** as the sole product in 81% yield. The ^{13}C NMR of **20** was compared to that of the de-O-benzylated lactam **12**, which is structurally related. The like upfield shifts of the -CH_2OH and absence of the downfield peak for the methylene of the benzyl group (approximately δ 70 ppm in **5** and the vinylogous carbamate) indicated removal of the O-benzyl group. As additional evidence, a strong absorption at 3485 cm^{-1} corresponding to a C-O-H stretch was observed in the IR spectrum.

In prior studies, we had cyclized the indolizidine by initial conversion of the 3-hydroxypropyl side chain to the mesylate, immediate cyclization to the quaternary amine and, deprotection of the resulting N-benzyl group. Reaction of vinylogous carbamate **22** with mesyl chloride (CH_3SO_2Cl) showed formation of the mesylate product but no cyclization to the quaternary ammonium compound was evidenced (baseline in TLC). It was thought that two factors were hindering cyclization. First, the nucleophilic character of the nitrogen in the vinylogous carbamate is lower than the piperidines used in prior studies. Second, for cyclization to occur the benzyl group attached to nitrogen must adopt a conformation away from the mesyl leaving group, which is not possible in the sp^2 vinylogous carbamate. Because of this it was decided to reduce the double bond prior to cyclization.

Reaction of vinylogous carbamate **16** with $NaBH_4$ did not show reduction of the double bond until the medium was adjusted to pH 4. Therefore, the reduction was conducted with $NaCNBH_3$ in methanol at pH 4, which gives predominantly the trans diastereomeric piperidine **23** in 97% yield (Scheme 2). Isolation of only two diastereomers suggested that the reduction had occurred stereoselectively.

In contrast to the reaction of **16** with TMS-I, de-O-benzylation of **23** using TMS-I now failed to produce the desired alcohol. Upon addition of TMS-I to **20** a baseline spot was immediately detected by TLC, which would be consistent with ammonium salt formation. Reaction of **23** with 2 equivalents of TMS-I also failed to de-O-benzylate the material. Hydrogenolyses of **23** led to a complex mixture of products. Ra-Ni in ethanol to our surprise was found to effect both de-O-benzylation and de-N-benzylation reactions to give **24** with no mono-de-benzylated products isolated after 24 h.



Scheme 2. Preparation of 5-substituted indolizidine

The surprising success with Raney-Nickel prompted an exploration into methods that would provide a one-pot procedure for the conversion of the vinylogous carbamate **16** directly into the deprotected saturated ester **24**. The reaction required a large excess of Raney-Nickel to accomplish the three reductions and showed two side products, which were not seen when the reactions were done sequentially.

Cyclization of **24** was effected with trifluoromethanesulfonic anhydride (Tf_2O), which following free-base with triethylamine provides the 8-phenylsulfonyl indolizidine **25** in 70% yield as a mixture of stereoisomers showing the typical Bohlmann Bands[28] at 2795 cm^{-1} corresponding to indolizidine formation. The ester was reacted with a variety of reducing agents ($LiAlH_4$[29], DIBAL-H[30], $LiBH_4$[31]) but no conditions were found to prepare the corresponding aldehyde or primary alcohol. Reaction of **25** with Na-Hg did provide the 5-substituted indolizidines **26** as a mixture of diastereomers in 38% yield. Compound **26** was fully characterized which supports the structural identity of **25**. However, indolizidine **26** was isolated as its methyl and not ethyl ester owing to transesterification during the sodium amalgam reaction. Due to the volatility of the indolizidine **26** the reaction was filtered into acidic methanol to trap the indolizidine as its hydrochloride salt.

This investigation showed that the remote dianion-cyclization procedure can provide a versatile intermediate for the synthesis of indolizidine alkaloids. Moreover, this synthetic route has allowed entry into substitutions at the 3-, 5- and 8-positions of the indolizidines from a common intermediate. Eschenmoser reaction to furnish the vinylogous carbamate has further extended the potential of this intermediate by providing several possible methods of chain extension for the 5-position.

EXPERIMENTAL

^1H and ^{13}C NMR were recorded at 300 MHz and 75 MHz, respectively, in deuterated chloroform ($CDCl_3$). All chemical shifts are referenced to TMS (tetramethylsilane). Infra-red spectra were recorded neat or as solutions in $CDCl_3$ with only the salient bands reported. Analytical thin layer chromatography (TLC) was conducted with aluminum backed silica plates (E. Merck). Flash chromatography was performed on Kieselgel 60, 230-400 mesh (E. Merck) using nitrogen positive pressure. Florisil (Fisher) 100-200 mesh was used where indicated. All solvents were purified by standard literature procedures.[32] Air and moisture sensitive reactions were conducted under a positive argon atmosphere utilizing standard techniques.[33] Hydrogenolyses were conducted either with double balloon pressure (<2 psi) or in a Parr shaker (45 psi). Ethyl bromoacetate (Aldrich) was distilled prior to use. Trifluoroacetic anhydride, benzylamine and triethylamine were distilled from CaH_2.[32] Triphenylphosphine was recrystallized from hexane[32] and 4-PSBA was recrystallized from chloroform/diethyl ether.[9] All other reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI.), and used without further purification.

1-Benzyl-5-(phenylsulfonyl)-6-(3-benzyloxypropyl)-2-piperidinone **(5).** Imine **9** (3.09 g; 11.55 mmol) was dissolved in 11 mL THF. The mixture was cooled to -78 °C under argon and freshly distilled boron trifluoride etherate (1.76 mL; 14.44 mmol) was added. Concurrently, the dianion of 4-PSBA was generated as follows: 4-PSBA (2.64 g; 11.55 mmol) was dissolved in 180 mL of THF, cooled to -78 °C under argon, and 18.5 mL butyllithium (1.2 M in hexane, 23.10 mmol) was added slowly. After 0.5 h, the activated imine solution was transferred to the dianion solution via cannula. The gold color of the dianion solution quenched immediately, and within 2 minutes trifluoroacetic anhydride (TFAA) (3.26 mL; 23.10 mmol) was added. The solution was allowed to warm to room temperature and 50 mL of ethyl acetate was added. The reaction mixture was extracted twice with Na_2CO_3 (50 mL) and a subsequent brine wash (50 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*. Flash chromatography (6:4, diethyl ether/ethyl acetate) yielded two products 4.52 g as non-polar and polar diastereomers (82%). HRMS m/z calcd for $C_{28}H_{31}NO_4S$ 477.1974, found 477.1938. **5** (non-polar): R_f = 0.33 (ethyl acetate). IR 1625 cm^{-1}. ^1H NMR δ 7.68-7.08 (m, 15H), 5.49 (d, J = 14.4 Hz, 1H), 4.52 (s, 2H), 3.71 (m, 2H), 3.50 (t, J = 6.1 Hz, 2H), 3.06 (m, 2H), 2.75 (m, 1H), 2.54 (m, 2H), 2.21 (m, 1H), 2.03 (m, 1H), 1.82 (m, 2H). ^{13}C NMR δ 169.15, 138.18, 136.34, 133.89, 129.33, 128.70, 128.36, 128.23, 128.03, 127.70, 127.67, 127.58, 73.13, 69.94, 63.15, 54.64, 50.82, 28.54, 27.90, 27.47, 16.86. **5** (polar): R_f = 0.26 (ethyl acetate). IR 1635 cm^{-1}. ^1H NMR δ 7.62-7.24 (m, 15H), 5.29 (d, J = 14.7 Hz, 1H), 4.40 (s, 2H), 3.97 (d, J = 14.8 Hz, 1H), 3.68 (dt, J = 2.6, 9.7 Hz, 1H), 3.19 (m, 3H), 2.77 (m, 1H), 2.26 (m, 3H), 1.79 (m, 1H), 1.59 (m, 1H), 1.32 (m, 1H), 1.21 (m, 1H). ^{13}C NMR δ 169.3, 138.0, 136.8, 136.45, 133.8, 129.2, 129.2, 129.05, 128.6, 128.5, 128.3, 127.6, 127.6, 127.5, 73.0, 68.8, 60.5, 53.45, 48.0, 30.4, 28.9, 25.3, 18.7.

4-Benzyloxy-1-butanol **(7).** 1,4-Butanediol (66 mL) was stirred at room temperature to which powdered KOH (40 g) and benzyl bromide (20 mL, 168.0 mmol) were added in four equal portions over 1 h. After 3 h stirring at room temperature, 100 mL of H_2O was added and reaction extracted thrice with diethyl ether (50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*.

Column chromatography (4:1, diethyl ether/petroleum ether) yielded 29.9 g of a clear oil (99%). Anal. calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.97; H, 9.08. R_f = 0.33 (diethyl ether). IR 3430 cm^{-1} (broad). ^1H NMR δ 7.35-7.26 (m, 5H), 4.52 (s, 2H), 3.64 (t, J = 5.9 Hz, 2H), 3.51 (t, J = 5.8 Hz, 2H), 2.39 (s, 1H), 1.69 (m, 4H). ^{13}C NMR δ 138.0, 128.3, 127.6, 127.5, 73.0, 70.3, 62.6, 30.1, 26.7.

***4-Benzyloxy-1-butanal* (8).** 4-Benzyloxy-1-butanol (**7**) (5.0 g; 27.74 mmol) was dissolved in 5.0 mL of CH_2Cl_2 and added to a stirred mixture of PDC (13.64 g; 36.06 mmol) in 350 mL of CH_2Cl_2. After 5 h, the mixture was filtered through a funnel containing Florisil and the solvent removed *in vacuo*. Column chromatography (4:1, hexane/ethyl acetate) yielded 4.45 g (90%) of a colorless oil. R_f = 0.54 (diethyl ether). IR 1710 cm^{-1}. ^1H NMR δ 9.78 (t, J = 1.5 Hz, 1H), 7.35-7.25 (m, 5H), 4.49 (s, 2H), 3.51 (t, J = 6.1 Hz, 2H), 2.55 (dt, 2H, J = 1.5, 7.0 Hz), 1.95 (m, 2H). ^{13}C NMR δ 202.0, 128.35, 128.3, 127.8, 127.5, 72.9, 69.1, 41.0, 22.6.

***N-Benzylidene-4-(O-benzyl)-butanal* (9).** Aldehyde **8** (2.0 g; 11.22 mmol) was dissolved in approximately 3 mL toluene and was added to a stirring solution of benzylamine (1.32 g; 12.34 mmol) in 2 mL toluene. The mixture turned warm and became cloudy. After stirring for 2 h at room temperature, anhydrous diethyl ether (approx. 5 mL) was added and the organic phase decanted and dried over BaO. The mixture was kept at 0 °C overnight and used without further purification in the dianion reaction. R_f = 0.45 (diethyl ether). IR 1670 cm^{-1}. ^1H NMR δ 7.78 (m, 1H), 7.32-7.19 (m, 10H), 4.53 (s, 2H), 4.47 (s, 2H), 3.50 (t, J = 6.3 Hz, 2H), 2.38 (m, 2H), 1.88 (m, 2H). ^{13}C NMR δ 165.25, 139.1, 136.25, 128.2, 128.1, 127.6, 127.3, 127.3, 126.6, 72.7, 69.5, 64.9, 32.7, 26.1.

***1-Benzyl-5-(phenylsulfonyl)-5'-methyl-6-(3-benzyloxypropyl)-2-piperidinone* (10).** Lactam **5** (polar) (0.313 g; 0.66 mmol) was dissolved in 4 mL of THF and cooled to -78 °C. n-BuLi (0.52 mL; 1.2 M in hexane; 0.66 mmol) was added and the reaction was stirred for 0.5 h. The -78 °C bath was removed and, dimethylsulfate (DMS) (0.07 mL; 0.66 mmol) was added and the mixture allowed to warm to room temperature. The reaction was extracted twice with $NaHCO_3$ followed by brine. The organic phase was dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*. Flash chromatography (ethyl acetate) yielded 0.296 g of a light yellow oil (91%). R_f = 0.58 (ethyl acetate). ^1H NMR δ 7.61-7.21 (m, 15H), 5.28 (d, J = 14.8 Hz, 2H), 4.39 (s, 2H), 3.97 (d, J = 14.8 Hz, 2H), 3.68 (d, J = 9.5 Hz, 1H), 3.22 (m, 2H), 2.28 (m, 2H), 2.04 (s, 3H), 1.77 (m, 1H), 1.57 (m, 1H), 1.25 (m, 2H). ^{13}C NMR δ 169.2, 138.0, 136.8, 136.1, 133.8, 129.1, 129.0, 128.6, 128.4, 128.3, 127.6 127.5, 127.45, 73.0, 68.75, 60.5, 53.5, 53.3, 48.0, 30.3, 28.9, 25.3, 18.7. Converted to **11** for elemental analysis.

***1-Benzyl-5-methyl-6-(3-benzyloxypropyl)-2-piperidinone* (11).** Lactam **10** (0.149 g; 0.30 mmol) was dissolved in 3 mL of methanol and 6% Na/Hg was added until TLC showed consumption of starting material. After 4 h the reaction was filtered and the solvent removed. The residue was taken up in ether and extracted twice with $NaHCO_3$, washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to provide **12** as a yellow oil (0.054 g, 51% yield) Anal. Calcd for $C_{23}H_{29}NO_2 \cdot H_2O$: C, 74.76; H, 7.91; N, 3.79. Found: C, 74.97; H, 8.12; N, 3.94. R_f = 0.51 (diethyl ether). ^1H NMR δ 7.42-7.14 (m, 10H), 5.40 (d, J = 14.9 Hz, 2H), 4.49 (s, 2H), 3.92 (d, J = 14.7 Hz, 2H), 3.54 (t, 2H, J = 6.9 Hz), 3.30 (m,

1H), 2.48 (m, 2H), 1.97-1.38 (m, 8H). ^{13}C NMR δ 170.1, 138.2, 137.6, 128.4, 128.3, 127.6, 127.6, 127.45, 127.0, 73.0, 69.8, 55.1, 47.4, 32.0, 28.8, 26.3, 26.2, 18.1, 17.3.

***1-Benzyl-5-(phenylsulfonyl)-6-(3-hydroxypropyl)-2-piperidinone* (12).** Lactam **5** (1.23 g; 2.57 mmol) was dissolved in 2 mL THF and methanol was added until the solution became cloudy (approx. 3 mL). The reaction vessel was flushed with argon, approx. 50 mg Pd/C was added followed by 0.10 mL trifluoroacetic acid. The mixture was stirred at room temperature under H_2 (<20 psi) overnight. Filtration and solvent removal *in vacuo* yielded 0.811 g (82%) of **12** as a clear oil of (non-polar) and (polar) diastereomers. **12** (non-polar): R_f = 0.12 (ethyl acetate). IR 3400, 1645 cm^{-1}. ^1H NMR δ 7.70 (m, 3H), 7.55 (m, 2H), 7.35 (m, 3H), 7.21 (m, 2H), 5.44 (d, J = 14.5 Hz, 1H), 3.80 (m, 2H), 3.73 (t, J = 5.5 Hz, 2H), 3.15 (m, 1H), 2.70 (m, 1H), 2.55 (m, 2H), 2.23 (m, 1H), 2.20 (m, 1H), 1.77 (m, 4H). ^{13}C NMR δ 169.4, 129.4, 128.7, 128.7, 128.25, 128.2, 63.3, 62.4, 54.5, 50.75, 30.1, 28.6, 27.55, 17.1. **12** (polar): m.p. 135-137 °C. R_f = 0.09 (ethyl acetate). IR 3400, 1635 cm^{-1}. ^1H NMR δ 7.68-7.22 (m, 10H), 5.22 (d, J = 14.6 Hz, 1H), 4.01 (d, J = 14.5 Hz, 1H), 3.67 (dt, J = 2.6, 9.7 Hz, 1H), 3.33 (m, 2H), 3.20 (dt, J = 2.4, 6.3 Hz, 1H), 2.77 (m, 1H), 2.24 (m, 3H), 1.93 (s, 3H), 1.75 (m, 1H), 1.55 (m, 1H), 1.24 (m, 1H), 1.12 (m, 1H). ^{13}C NMR δ 169.5, 136.55, 134.0, 129.3, 129.1, 128.7, 127.7, 61.3, 60.8, 53.3, 48.1, 30.2, 28.8, 27.8, 19.7.

***1-Benzyl-5-(phenylsulfonyl)-6-(propan-3-al)-2-piperidinone* (13).** Lactam **12** (0.081 g; 0.21 mmol) was dissolved in 7 mL of CH_2Cl_2 and added to pyridinium chlorochromate (PCC) (0.085 g; 0.39 mmol) in 15 mL of CH_2Cl_2. After 4 h the reaction was filtered and the solvent removed *in vacuo*. The residue was taken up in ether and extracted with Na_2CO_3 solution. The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (ethyl acetate) yielded 60 mg (67%) as a light yellow oil. Anal. Calcd for $C_{21}H_{23}NO_4S$: C, 65.43; H, 6.01; N, 3.63. Found C, 65.29; H, 5.93; N, 3.57. R_f = 0.35 (ethyl acetate). IR 1730 cm^{-1} (strong). ^1H NMR δ 9.55 (s, 1H), 7.60 (t, J = 5.1 Hz, 2H), 7.48 (m, 3H), 7.35 (s, 5H), 5.20 (d, J = 14.8 Hz, 2H), 4.10 (d, J = 14.7 Hz, 2H), 3.73 (m, 2H), 3.17 (m, 1H), 2.74 (m, 1H), 2.25 (m, 2H), 1.71 (m, 2H). ^{13}C NMR δ 199.6, 170.0, 136.4, 134.1, 129.4, 129.1, 128.75, 128.7, 128.6, 127.8, 61.2, 53.1, 48.4, 39.1, 29.0, 26.3, 20.7, 19.4.

***1-Benzyl-5-(phenylsulfonyl)-6-(3-hydroxyheptane)-2-piperidinone* (14).** Magnesium turnings (0.015 g; 0.60 mmol) were suspended in 7 mL of dry ether and 1-bromobutane (0.09 g; 0.65 mmol) in 4 mL of dry ether were combined. To the resulting solution, aldehyde **13** (0.051 g; 0.13 mmol) was added in 1mL of dry ether. After 1 h the reaction was quenched with 1 mL H_2O, extracted twice with CH_2Cl_2 and the organic layer was dried over Na_2SO_4. The solvent was removed *in vacuo* to give 90% recovery. Significant amounts of starting material (>25%) were routinely recovered after column chromatography (9:1, ethyl acetate/ether) which yielded 24 mg (42%) of product as a clear oil. Anal. Calcd for $C_{25}H_{33}NO_4S$: C, 67.69; H, 7.50; N, 3.16. Found: C, 67.91; H, 7.59; N, 3.28. R_f = 0.58 (ethyl acetate). IR 3340 cm^{-1} (weak), 1730 cm^{-1} (strong). ^1H NMR δ 7.60 (t, J = 6.1 Hz, 2H), 7.43 (m, 3H), 7.33 (bs, 5H), 4.12 (m, 4H), 3.21 (m, 1H), 2.75 (m, 1H), 2.21 (m, 10H), 1.32 (m, 4H), 0.87 (t, J = 7.2 Hz, 3H). ^{13}C NMR δ 170.3, 136.3, 134.0, 129.4, 129.1, 128.7, 128.6, 128.6, 127.8, 71.4, 60.4, 53.7, 48.4, 39.0, 37.3, 28.55, 22.55, 20.8, 19.3, 16.5, 14.1.

***1-Benzyl-5-(phenylsulfonyl)-6-(3-benzyloxypropyl)piperidin-2-thione* (15).** Lawesson's reagent (1.30 g; 3.22 mmol) was added to lactam **5** (3.08 g; 6.45 mmol) in 12 mL of toluene and refluxed for 4 h. The solvent was removed *in vacuo*, and the mixture flash chromatographed (95:5, methylene chloride/ethyl acetate) to yield 3.05 g (96%) of the thiolactam **15** as a diastereomeric mixture. Anal. Calcd for $C_{28}H_{31}NO_3S_2 \cdot 1/2\ H_2O$: C, 66.89; H, 6.41; N, 2.78. Found: C, 66.80; H, 6.34; N, 2.78. **15** (non-polar): R_f = 0.32 (ethyl acetate). ^{1}H NMR δ 7.64 (m, 3H), 7.46 (t, J = 5.7 Hz, 2H), 7.28 (m, 10H), 6.53 (d, J = 14.3 Hz, 1H), 4.52 (s, 2H), 4.10 (d, J = 14.3 Hz, 1H), 4.01 (m, 1H), 3.50 (t, J = 6.1 Hz, 2H), 3.39 (m, 1H), 3.19 (m, 1H), 3.00 (m, 1H), 2.34 (m 1H), 2.22 (m 1H), 1.93 (m, 2H), 1.78 (m, 2H). ^{13}C NMR δ 199.6, 138.05, 137.8, 134.6, 133.9, 129.3, 128.8, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 73.15, 69.7, 62.85, 58.0, 57.4, 38.5, 27.4, 26.7, 17.3. **15** (polar): R_f = 0.29 (ethyl acetate). ^{1}H NMR δ 7.60 (m, 3H), 7.47 (t, J = 4.2 Hz, 2H), 7.32 (m, 10H), 5.86 (d, J = 14.4 Hz, 1H), 4.77 (d, J = 14.7 Hz, 1H), 4.41 (s, 2H), 4.04 (m, 1H), 3.31 (m, 4H), 2.81 (m, 1H), 2.03 (m, 2H), 1.72 (m, 1H), 1.67 (m, 1H), 1.41 (m, 1H), 1.26 (m, 1H). ^{13}C NMR δ 201.1, 137.95, 136.6, 134.9, 134.05, 129.3, 129.0, 128.7, 128.7, 128.4, 127.7, 127.5, 73.1, 68.7, 61.9, 56.1, 55.95, 39.2, 31.6, 25.3, 20.1.

***1-Benzyl-5-(phenylsulfonyl)-6-(3-benzyloxypropyl)-2-[(ethoxycarbonyl)methylidene] piperidine* (16).** Thiolactam **15** (2.77 g; 5.61 mmol) in 7 mL dry acetonitrile was stirred at room temperature with ethyl bromoacetate (1.17 g; 7.01 mmol) for 48 h. The reaction was then diluted with 24 mL of CH_2Cl_2 and after 10 minutes, triphenylphosphine (3.31 g; 12.62 mmol) was added and stirred an additional 0.5 h. Triethylamine (1.70 g; 16.83 mmol) was then added and the reaction stirred for an additional 24 h. The mixture was diluted with ethyl acetate (30 mL), washed with saturated Na_2CO_3, brine, and dried over $MgSO_4$. Flash chromatography (9:1, methylene chloride/ethyl acetate) yielded 2.89 g (94%) of **6** as a gold oil. Anal. Calcd for $C_{32}H_{37}NO_5S \cdot 1/2\ H_2O$: C, 69.04; H, 6.88; N, 2.52. Found: C, 69.09; H, 6.75; N, 2.49. **16** (non-polar): R_f = 0.45 (diethyl ether). IR 1755 cm^{-1}. ^{1}H NMR δ 7.77 (d, J = 5.4 Hz, 2H), 7.63 (t, J = 5.4 Hz, 1H), 7.50 (t, J = 2.3 Hz, 2H), 7.28 (m, 10H), 4.72 (s, 2H), 4.43 (m, 3H), 4.22 (m, 2H), 4.01 (m, 2H), 3.87 (m, 1H), 3.71 (m, 1H), 3.33 (m, 4H), 2.23 (m, 1H), 1.92 (m, 1H), 1.68 (m, 2H), 1.45 (m, 1H), 1.22 (m, 3H). ^{13}C NMR δ 168.5, 161.0, 135.8, 133.9, 129.2, 128.85, 128.6, 128.3, 127.5, 127.35, 88.1, 73.0, 69.3, 63.8, 58.6, 55.9, 55.1, 33.3, 25.5, 23.4, 20.3, 14.6. **16** (polar): R_f = 0.42 (diethyl ether). IR 1750 cm^{-1}. ^{1}H NMR δ 7.75 (d, J = 5.1 Hz, 2H), 7.64 (t, J = 5.4 Hz, 1H), 7.52 (t, J = 2.1 Hz, 2H), 7.26 (m, 10H), 4.69 (s, 1H), 4.43 (m, 3H), 4.20 (m, 2H), 4.01 (m, 2H), 3.86 (m, 1H), 3.34 (m, 4H), 2.23 (m, 1H), 1.95 (m, 1H), 1.56 (m, 4H), 1.19 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 168.3, 160.8, 138.0, 136.7, 135.7, 133.8, 129.1, 128.7, 128.2, 127.4, 127.35, 127.2, 87.9, 72.8, 69.15, 63.55, 58.4, 55.9, 55.1, 33.1, 25.3, 23.2, 20.2, 14.5.

***1-Benzyl-6-(3-benzyloxypropyl)-2-piperidinone* (17).** A mixture of both diastereomers of **5** (2.17 g; 4.55 mmol) were dissolved in 16 mL of methanol and an excess 6% Na/Hg was added. After 3 h the reaction was filtered and the solvent removed *in vacuo*. Flash chromatography (9:1 ethyl acetate/diethyl ether) yields 1.53 g (89%) of a colorless oil. Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.07; N, 4.15. Found: C, 78.28; H, 8.13; N, 4.19. R_f = 0.32 (ethyl acetate). ^{1}H NMR δ 7.28 (m, 10H), 5.38 (d, J = 14.9 Hz, 2H), 4.48 (s, 2H), 3.92 (d, J = 15.1 Hz, 2H), 3.42 (t, J = 6.2 Hz, 2H), 3.28 (m, 1H), 2.48 (m, 2H), 1.98-1.23

(m, 6H). ^{13}C NMR δ 170.1, 138.2, 137.6, 128.4, 128.3, 127.6, 127.5, 127.5, 127.0, 73.0, 69.8, 55.2, 47.4, 32.0, 28.85, 26.3, 26.2, 17.4.

***1-Benzyl-6-(3-benzyloxypropyl)piperidin-2-thione* (18).** Lawesson's reagent (0.998 g; 2.47 mmol) was added to lactam **17** (1.66 g; 4.93 mmol) in 8 mL of toluene and refluxed for 4 h. The solvent was removed *in vacuo*, and the mixture flash chromatographed (48:2:50, methylene chloride/acetonitrile/hexane) to yield 1.70 g (98%) of the thiolactam **18** as a gold oil. Anal. Calcd for $C_{22}H_{27}NOS$: C, 74.74; H, 7.70; N, 3.96. Found: C, 74.78; H, 7.90; N, 3.94. R_f = 0.38 (ethyl acetate). ^1H NMR δ 7.31 (m 10H), 6.47 (d, J = 14.9 Hz, 1H), 4.48 (s 2H), 4.32 (d, J = 14.9 Hz, 1H), 3.47 (m 4H), 3.15 (t, J = 5.8 Hz, 2H), 1.85 (m 2H), 1.72 (m, 4H), 1.66 (m, 1H). ^{13}C NMR δ 201.0, 138.1, 135.6, 128.6, 128.3, 127.6, 127.5, 127.5, 73.1, 69.5, 58.1, 55.4, 41.1, 28.7, 26.5, 25.8, 17.05.

***1-Benzyl-6-(3-benzyloxypropyl)-2-[(ethoxycarbonyl)methylidene]piperidine* (19).** Thiolactam **18** (1.45 g; 4.11 mmol) in 7 mL dry acetonitrile was stirred at room temperature with ethyl bromoacetate (0.859 g; 5.14 mmol) for 48 h. The reaction was then diluted with 22 mL of CH_2Cl_2 and after 10 minutes, triphenylphosphine (1.62 g; 6.17 mmol) was added and stirred an additional 0.5 h. Triethylamine (1.25 g; 12.33 mmol) was then added and the reaction stirred for an additional 24 h. The mixture was diluted with ethyl acetate (30 mL), washed with saturated Na_2CO_3, brine and dried over $MgSO_4$. Flash chromatography (95:5, methylene chloride/ethyl acetate) yielded 1.52 g (91%) of **19** as a gold oil. Anal. Calcd for $C_{26}H_{33}NO_3$: C, 76.62; H, 8.16; N, 3.44. Found: C, 76.81; H, 7.94; N, 3.31. R_f = 0.55 (diethyl ether). IR 1750 cm^{-1}. ^1H NMR δ 7.29 (m, 8H), 7.13 (d, J = 6.8 Hz, 2H), 4.51 (m, 4H), 4.27 (d, J = 16.9 Hz, 1H), 4.40 (m, 2H), 3.41 (t, J = 6.1 Hz, 2H), 3.26 (m, 2H), 3.13 (m, 2H), 1.70 (m, 6H), 1.47 (m, 1H), 1.17 (t, 3H, J = 7.1 Hz). ^{13}C NMR δ 168.8, 162.1, 138.2, 136.5, 128.5, 128.3, 127.5, 126.9, 126.4, 84.2, 73.0, 68.8, 58.2, 58.1, 53.75, 29.7, 26.6, 26.5, 26.4, 16.2, 14.7.

***1-Benzyl-5-(phenylsulfonyl)-6-(3-hydroxypropyl)-2-[(ethoxycarbonyl)methylidene] piperidine* (20).** TMS-I (0.464 g; 2.23 mmol) was added to (polar) vinylogous carbamate **16** (0.554; 1.10 mmol) in 3 mL of CH_2Cl_2 at 0 °C and the reaction was stirred for 6 h. The mixture was diluted with 15 mL of CH_2Cl_2 and 5 mL of sodium bisulfite was added to hydrolyze the excess TMS-I. The organic layer was washed with brine and dried over $MgSO_4$. Flash chromatography (9:1, diethyl ether/petroleum ether) gave 0.374 g (81%) of **20** as a yellow oil. Anal. Calcd for $C_{25}H_{31}NO_5S$: C, 65.62; H, 6.83; N, 3.06. Found: C, 65.39; H, 6.76; N, 2.98. R_f = 0.17 (diethyl ether). IR 3485 cm^{-1}. ^1H NMR δ 7.76 (d, J = 6.2 Hz, 2H), 7.64 (t, J = 6.0 Hz, 1H), 7.51 (t, J = 5.5 Hz, 2H), 7.33 (m, 5H), 4.71 (s, 1H), 4.28 (m, 3H), 3.99 (m, 2H), 3.93 (m, 1H), 3.51 (t, J = 6.0 Hz, 2H), 3.32 (m, 1H), 2.18 (m, 1H), 1.94 (m, 3H), 1.67 (m, 2H), 1.40 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 168.4, 160.9, 136.6, 135.7, 133.95, 129.2, 128.8, 128.5, 127.5, 127.3, 88.1, 63.8, 61.8, 58.6, 55.8, 55.0, 32.9, 28.0, 23.35, 20.4, 14.55.

***1-Benzyl-5-(phenylsulfonyl)-6-(3-benzyloxypropyl)-2-[(ethoxycarbonyl)methyl]-piperidine* (23).** Vinylogous carbamate **16** (1.08 g; 1.97 mmol) was dissolved in 7 mL of methanol and the pH was adjusted to 4 with acetic acid. $NaCNBH_3$ (0.124 g; 1.97 mmol) was added and the reaction bubbled and became warm. After 3 h the reaction mixture was diluted with ethyl acetate and washed with 20% NaOH,

saturated $NaHCO_3$ and brine. The solvent was removed *in vacuo* to provide 1.05 g pure **23** in 97% yield. Anal. Calcd for $C_{32}H_{39}NO_5S$: C, 69.91; H, 7.15; N, 2.55. Found: C, 69.87; H, 7.11; N, 2.50. **23** (non-polar): R_f = 0.60 (diethyl ether). IR 1730 cm^{-1}. ^1H NMR δ 7.88 (m, 2H), 7.53 (m, 5H),7.29 (m, 8H), 4.55 (m, 3H), 4.10 (m, 2H), 3.80 (m, 1H), 3.63 (m, 1H), 3.50 (m, 4H), 3.29 (m, 1H), 2.77 (m, 1H), 2.46 (m, 1H), 1.96 (m, 4H), 1.65 (m, 2H), 1.34 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 170.0, 139.05, 133.3, 129.3, 129.0, 129.0, 128.7, 128.4, 128.35, 128.3, 128.2, 128.2, 128.2, 128.1, 128.05, 127.8, 127.6, 127.5, 127.5, 127.3, 127.3, 126.9, 72.8, 70.3, 61.3, 57.8, 56.8, 52.4, 42.5, 29.2, 27.2, 22.0, 20.8, 20.3, 18.5. **23** (polar): R_f = 0.55 (diethyl ether). IR 1725 cm^{-1}. ^1H NMR δ 7.80 (d, J = 7.3 Hz, 2H), 7.61 (t, J = 7.3 Hz, 1H), 7.50 (t, J = 7.9 Hz, 2H), 7.30 (m, 10H), 4.42 (s, 2H), 4.08 (m, 2H), 3.77 (q, J = 14.1 Hz, 2H), 3.42 (m, 2H), 3.31 (m, 3H), 3.01 (m, 1H), 2.57 (m, 1H), 2.34 (m, 1H), 2.03 (m, 1H), 1.84 (m, 2H), 1.70 (m, 2H), 1.59 (m, 1H), 1.45 (m, 1H), 1.23 (t, J = 7.5 Hz, 3H). ^{13}C NMR δ 171.7, 139.5, 138.5, 138.5, 133.3, 129.0, 128.6, 128.5, 128.2, 128.1, 127.5, 127.3, 126.8, 72.8, 69.8, 61.5, 60.45, 54.4, 51.5, 50.7, 38.5, 27.1, 26.4, 23.2, 21.1, 14.2.

***5-(Phenylsulfonyl)-6-(3-hydroxypropyl)-2-[(ethoxycarbonyl)methyl]piperidine* (24).** Piperidine **23** (1.18 g; 2.14 mmol) was dissolved in 4 mL of ethanol and excess Raney-Nickel W-2 was added. The reaction was stirred for 6 h and an additional portion of Raney-Nickel was added followed by stirring for 18 h. The reaction was filtered through Celite and the solvent removed *in vacuo*. The organic residue was dissolved in 40 mL of ethyl acetate and washed with H_2O, saturated Na_2CO_3, and brine, then dried over $MgSO_4$ and the solvent removed *in vacuo* to yield 0.657 g (83%) of **24** as a colorless oil. Anal. Calcd for $C_{18}H_{27}NO_5S$: C, 59.51; H, 7.37; N, 3.79. Found: C, 59.19; H, 7.65; N, 3.54. **24** (non-polar): R_f = 0.15 (diethyl ether). ^1H NMR δ 7.88 (d, J = 5.2 Hz, 2H), 7.68 (t, J = 5.1 Hz, 1H), 7.59 (t, J = 5.9 Hz, 2H), 4.12 (m, 1H), 3.68 (m, 1H), 3.53 (m, 1H), 3.31 (m, 1H), 3.24 (m, 1H), 2.94 (m, 1H), 2.73 (m, 2H), 2.61 (m, 2H), 2.32 (m, 1H), 1.94 (m, 4H), 1.18 (m, 1H), 1.61 (m, 2H), 1.52 (m, 1H), 1.07 (t, J = 7.2 Hz, 3H). ^{13}C NMR δ 133.6, 129.2, 129.0, 128.3, 63.0, 60.3, 57.8, 46.7, 42.0, 31.8, 25.2, 20.4, 19.8, 13.2. **24** (polar): R_f = 0.12 (diethyl ether). IR 3505 cm^{-1}. ^1H NMR δ 7.88 (d, J = 4.9 Hz, 2H), 7.66 (t, J = 4.1 Hz, 1H), 7.58 (t, J = 4.9 Hz, 2H), 4.14 (m, 3H), 3.55 (m 4H), 3.27 (m, 2H), 2.84 (m, 1H), 2.43 (m, 1H), 2.24 (m, 1H), 2.01 (m, 2H), 1.70 (m 3H), 1.43 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C NMR δ 171.4, 137.7, 133.7, 129.3, 128.3, 62.4, 61.1, 60.7, 50.6, 45.9, 41.0, 30.8, 30.8, 26.8, 19.8, 14.3.

***8-(Phenylsulfonyl)-5-[(ethoxycarbonyl)methyl]indolizidine* (25).** Piperidine **24** (0.025 g; 0.07 mmol) was dissolved in 7 mL of THF and cooled to -78° C. Trifluoromethanesulfonic anhydride (0.022 g; 0.08 mmol) was added and stirred for 10 minutes. The -78 °C bath was removed and triethylamine (0.018 g; 0.18 mmol) added and the reaction allowed to equilibrate to room temperature. The mixture was diluted with 10 mL of ethyl acetate and washed with saturated $NaHCO_3$, and brine, then dried over $MgSO_4$ and the solvent removed *in vacuo*. Flash chromatography (ethyl acetate) yielded 0.023 g (96%) of **25** as a colorless oil. Anal. Calcd for $C_{18}H_{25}NO_4S$: C, 61.51; H, 7.17; N, 3.99. Found: C, 61.29; H, 7.27; N, 3.81. **24** (non-polar): R_f = 0.46 (diethyl ether). IR 2800 cm^{-1}. ^1H NMR δ 7.89 (d, J = 5.3 Hz, 2H), 7.65 (t, J = 5.0 Hz, 1H), 7.56 (t, J = 5.9 Hz, 2H), 3.28 (m, 2H), 2.57 (m, 4H), 1.82 (m, 4H), 1.48 (m, 2H), 1.02 (m, 3H). ^{13}C NMR δ 133.3, 129.0, 129.0, 128.3, 62.1, 57.9, 47.6, 43.6, 21.8, 20.6, 17.8, 14.0, 12.4. **24** (polar): R_f = 0.36 (diethyl ether). IR 2795 cm^{-1}. ^1H NMR δ 7.89 (d, J = 4.0 Hz, 2H), 7.66 (t, J = 4.1 Hz,

1H), 7.57 (t, J = 4.3 Hz, 2H), 4.10 (m 2H), 3.56 (m, 1H), 3.45 (m, 1H), 2.85 (m, 2H), 2.65 (m, 1H), 2.51 (m, 2H), 2.28 (m, 1H), 2.16 (m, 1H), 1.70 (m, 6H), 1.25 (m, 3H). ^{13}C NMR δ 172.5, 138.0, 133.6, 129.0, 128.6, 66.8, 60.5, 53.5, 51.35, 48.6, 30.4, 28.75, 27.9, 21.0, 20.7, 14.25.

***5-[(Methoxycarbonyl)methyl]indolizidine* (26).** Indolizidine **24** (0.358 g; 1.02 mmol) was dissolved in 5 mL of methanol and excess 6% Na/Hg added. The reaction was monitored by TLC for consumption of starting material. After 5 h, the mixture was filtered into 3 mL of methanolic HCl to capture the volatile indolizidine as the hydrochloride salt. The solvent was removed *in vacuo* followed by partitioning between diethyl ether and 20% KOH to liberate the free base. Removal of solvent yielded 0.080 g of indolizidine **26** (38%). HRMS m/z Calcd for $C_{11}H_{19}NO_2$: 197.1416, found: 197.1416. R_f = 0.38 (diethyl ether). IR 2765 cm^{-1}. ^{1}H NMR δ 3.68 (s, 3H), 3.61 (m, 1H), 2.88 (m, 1H), 2.62 (m, 1H), 2.42 (m, 4H), 1.88-1.12 (m, 7H). ^{13}C NMR δ 173.8, 55.0, 52.5, 51.5, 49.0, 31.3, 30.6, 29.15, 28.8, 20.7, 19.3.

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REFERENCES

1. Howard, A.S.; Michael, J.P. in *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 28, p. 185.
2. Daly, J.W.; Myers, C.W. *Science* **1967**, *156*, 970.
3. a) Daly, J.W.; Garraffo, H.M.; Spande, T.F. *The Alkaloids*; Cordell, G.A., Ed.; Academic Press: New York, 1993; Vol 43, pp. 185-288. b) Daly, J.W. *Progress in the Chemistry of Natural Products*; Herz, W.; Grisebach, H.; Kirby, G.W., Eds.; Springer-Verlag: New York, 1982; pp. 283-340. c) Daly, J.W.; Spande, T.F. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S.W., Ed.; Wiley: New York, 1986; Vol 4, p. 1. d) Daly, J.W.; Brown, G.B.; Mensah-Dwumah, M.; Myers, C.W. *Toxicon* **1978**, *16*, 163. e) Daly, J.W.; Myers, C.W.; Whittaker, N. *Toxicon* **1987**, *25*, 1023. f) Daly, J.W.; Highet, R.J.; Myers, C.W. *Toxicon* **1984**, *22*, 905. g) Tokuyama, T.; Tsujita, T.; Shimada, A.; Garraffo, H.M.; Spande, T.F.; Daly, J.W. *Tetrahedron* **1991**, *47*, 5401.
4. Mensah-Dwumah, M.; Daly, J.W. *Toxicon* **1968**, *16*, 189.
5. Aronstam, R.S.; Daly, J.W.; Spande, T.F.; Narayanan, T.K.; Albuquerque, E.X. *Neurochemical Res.* **1986**, *11*, 1227.
6. For reviews see: Rajeswari, S.; Chandrasekharan, S.; Govindachari, T.R. *Heterocycles* **1987**, *25*, 659. Michael, J.P. *Nat. Prod. Rep.* **1993**, *10*, 51. Lamberton, J.A. in *The Alkaloids, Specialists Periodical Reports*; Grundon, M.F., Ed., The Royal Society of Chemistry, London, **1979**, *9*, 67; **1980**, *10*, 63; **1981**, *11*, 59; **1982**, *12*, 69. Kibayashi, C. *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsevier: New York, 1992; Vol 2, pp. 229-275.
7. Thompson, C.M.; Green D.L.C. *Tetrahedron* **1991**, *47*, 4223.

8. Thompson, C.M. *Tetrahedron Lett.* **1987**, *28*, 4243.
9. Thompson, C.M.; Frick, J.A. *J. Org. Chem.* **1989**, *54*, 890.
10. Williams, K.; Thompson, C.M. *Synth. Commun.* **1992**, *22*, 239.
11. Thompson, C.M.; Green D.L.C.; Kubas, R. *J. Org. Chem.* **1988**, *53*, 5389.
12. Stevens, R.V. in *The Total Synthesis of Natural Products*; Ap-Simon, J., Ed.; Wiley: New York, 1977; Vol 3.
13. Green, D.L.C.; Thompson, C.M. *Tetrahedron Lett.* **1991**, *32*, 5051.
14. Thompson, C.M. *Heterocycles* **1992**, *34*, 979.
15. Fletcher, H.G. *Methods Carbohydr. Chem.* **1963**, *2*, 166.
16. Harding, K.E.; Jones, M.W. *Heterocycles* **1987**, *28*, 663.
17. Corey, E.J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
18. Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* **1982**, 245.
19. Mancuso, A.J.; Swern, D. *Synthesis* **1981**, 165.
20. Gunther, H. *NMR Spectroscopy*; Wiley: New York, 1980; p. 112.
21. Hwang, Y.C.; Chu, M.; Fowler, F.W. *J. Org. Chem.* **1985**, *50*, 3885.
22. Borch, R.F. *Tetrahedron Lett.* **1968**, 61.
23. Shiosaki, K. in *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I.; Eds.; Pergamon Press: New York, 1991; p 865.
24. Cava, M.P.; Levinson, M.I. *Tetrahedron* **1985**, *41*, 5061.
25. Clark, J. in *The Chemistry of the Carboxylic Acid and Esters*; Patai, S., Ed.; Wiley: New York, 1969; p 589, and references therein.
26. Olah, G.A.; Surya Prakash, G.K. in *Advances in Silicon Chemistry*; Larson, G.L., Ed.; JAI Press: Greenwich, 1991; p 1.
27. Jung, M.E.; Lyster, M.A. *J. Org. Chem.* **1977**, *42*, 3761.
28. Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157.
29. Moffet, R.B. *Org. Syn. Coll. Vol. 4*, **1963**, 834.
30. Winterfeldt, E. *Synthesis* **1975**, 617.
31. Brown, H.C.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 1604.
32. Perrin, D.D.; Armarego, W.L.F. *Purification of Laboratory Chemicals*; Pergamon Press: Oxford, 1988.
33. Shriver, D.F.; Drezdzon, M.A. *The Manipulation of Air Sensitive Compounds*; Wiley: New York, 1986.

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