Olefinic Nitrone and Nitrile Oxide [3 + 2] Cycloadditions. A Short Stereospecific Synthesis of Biotin from Cycloheptene[1]

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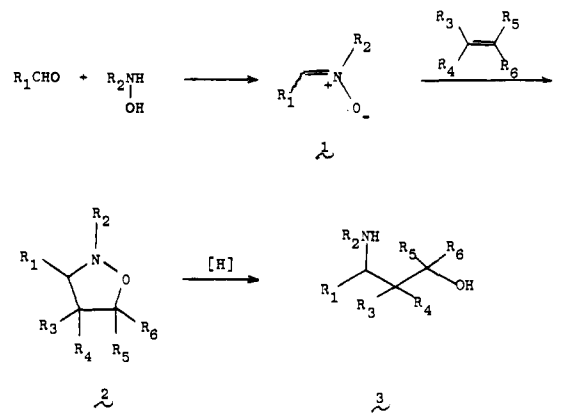
Abstract: A novel synthesis of biotin (**6**) from cycloheptene (**4**) via the key amino alcohol **5** is described. The synthetic scheme is based upon an intramolecular nitrone–olefin [3 + 2] cycloaddition of the reactive intermediate **13**, generated in situ from the aldehyde **12**. The resulting isoxazolidine **14** is produced stereospecifically with the correct relative stereochemistry for elaboration into the target molecule. An even more efficient route involving a [3 + 2] cycloaddition of the nitrile oxide **40**, prepared from the nitro olefin **39** and leading to the tricyclic adduct **41**, was discovered. Structural and mechanistic aspects of a complex series of Beckmann rearrangements and fragmentations of closely related substances are discussed.

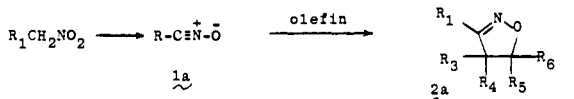
Although the [3 + 2] cycloaddition reaction of nitrones and aryl isocyanates was first reported[3] in 1890, extension of this observation to the nitrone–olefin system has only recently[4] been studied. The thorough and systematic investigations of Huisgen[5] resulted in the preparation of a diverse array of heterocyclic compounds. In 1964 LeBel[6] reported an intramolecular nitrone cycloaddition of the reactive intermediate obtained upon the condensation of melonal with *N*-methylhydroxylamine. The product cyclopentane derivative was generated with complete stereochemical control over its three contiguous asymmetric centers.

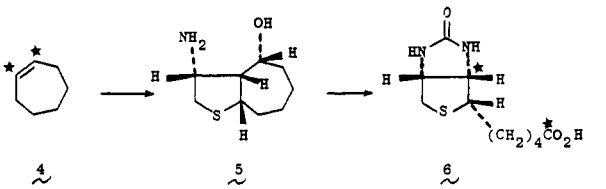
The synthetic utility of these reactions is illustrated in Scheme I. Condensation of an aldehyde with a hydroxylamine derivative affords a nitrone **1** which then undergoes a [3 + 2] cycloaddition with an olefin. This process yields an isoxazolidine **2** which after a mild reduction of the labile N–O bond produces a 1,3-N-substituted amino alcohol **3**, thus appending a host of carbon atoms and functionality onto the starting aldehyde. Alternatively, dehydration of a primary nitro compound yields a nitrile oxide **1a** which also can undergo a [3 + 2] cycloaddition with an olefin[7] to yield an isoxazoline **2a**. Reduction of this system then leads to **3** (R_2 = H). Not surprisingly, therefore, such cycloaddition reactions, which not only form a carbon–carbon bond but also generate carbocyclic systems from an acyclic precursor in intramolecular versions, have been applied to the synthesis of natural products, notably corrins[8] and several alkaloids.[9]

We wish to report a novel synthesis of the naturally occurring vitamin *d*-biotin (**6**), which utilizes the above concepts.[10] This effort further demonstrates the prowess of intramolecular [3 + 2] cycloaddition reactions in the stereospecific preparation of the key intermediate amino alcohol **5** from a most unlikely starting material, cycloheptene (**4**). This simple hydrocarbon not only lacks all the heteroatoms of the target molecule including even simple oxygen functionality but also is totally devoid of stereochemistry. Yet its sole functional group, the C–C double bond, is slated to map unto the starred carbon atoms of the biotin structure **6**.

Scheme I



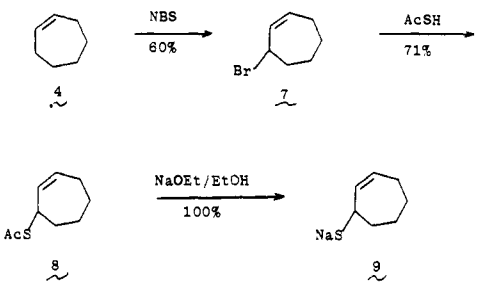




Allylic bromination[11] of cycloheptene with NBS easily led to the 3-bromo derivative **7** (Scheme II). Reaction with thiolacetic acid afforded the desired thiol ester **8**, serving to introduce the requisite sulfur atom at an early stage in the synthesis. The reactive intermediate mercaptide **9** was then generated in situ by the action of sodium ethoxide in refluxing ethanol. This ethanolic solution of **9** proved to be a branch point in our studies of approaches to biotin utilizing [3 + 2] cycloaddition reactions.

Alkylation of **9** with bromoacetaldehyde diethyl acetal (**10**) afforded the olefinic acetal **11** (Scheme III) which underwent mild acid hydrolysis to the desired aldehyde **12**. Treatment of this compound with *N*-methyl- or *N*-benzylhydroxylamine[12] led cleanly and stereospecifically to the tricyclic adducts **14**. This result implicates the intermediacy of the nitrones **13**, which then undergo an intramolecular [3 + 2] cycloaddition reaction. The obtention of the highly convex molecules **14** assures the desired all-cis stereochemistry with respect to the four methine hydrogens imbedded in the outer face of this system. Transition states leading to other possible stereoisomers are more highly strained and presumably precluded on this basis.

Scheme II



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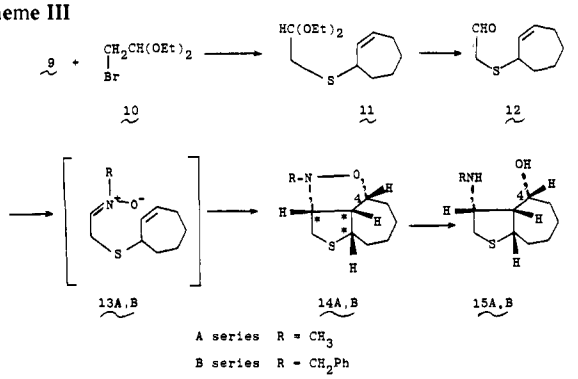
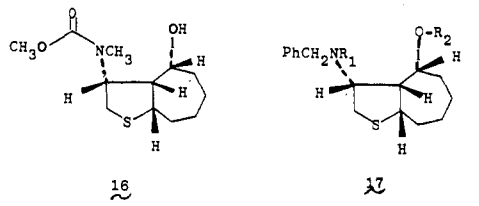
Scheme III



This stereospecific cyclization generated in one step a molecule containing the three contiguous asymmetric centers (starred in **14**) of the target molecule biotin. The additional center at C(4) was of less importance since that carbon was destined to be oxidized to a carbonyl later in the synthesis. Reduction of the N-O bond was readily achieved with zinc in acetic acid/water and the amino alcohols **15**, specific examples of the class represented by **3**, were produced.

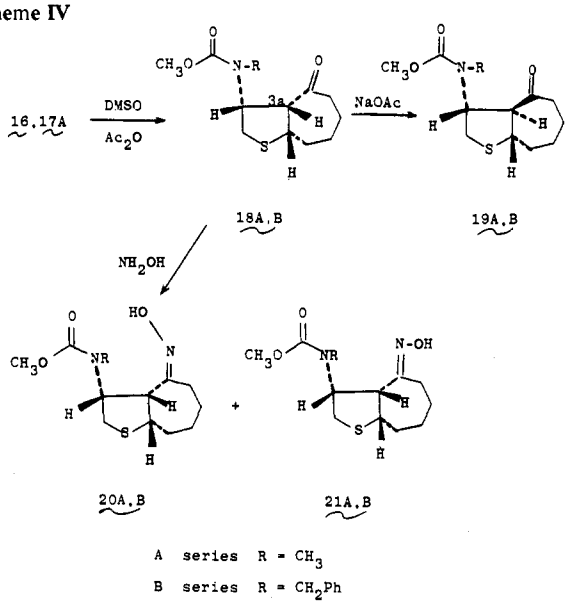
Our synthetic strategy next required a selective oxidation of the C(4) alcohol of **15** to a ketone in the presence of a sulfide and an amino functionality. Protection of the nitrogen atom was required and achieved by acylation with methyl chloroformate, thus affording the *N*-methylurethane **16** from its



precursor **15A**. Presumably owing to steric factors, acylation of **15B** yielded not only the desired urethane **17** (R_1 = CO_2CH_3; R_2 = H) but also the amino carbonate **17** (R_1 = H; R_2 = CO_2CH_3) and the urethane carbonate **17** (R_1 = R_2 = CO_2CH_3). These substances could be separated by chromatography. Furthermore, **17** (R_1 = R_2 = CO_2CH_3) was the sole observed product when 2 equiv of the acylating agent was employed, a fact which was to be of some importance later in the first synthesis of the key intermediate amino alcohol **5**. Most oxidants could not be made to oxidize the alcohol function of either **16** or **17** (R_1 = CO_2CH_3; R_2 = H) without contamination by significant amounts of sulfoxide byproducts. Fortunately, dimethyl sulfoxide/acetic anhydride[13] smoothly effected the desired transformation and the urethane ketones **18** were produced (Scheme IV).

Incorporating these compounds into our synthetic scheme represented some risk since the C(3a) hydrogen was now susceptible to an irreversible epimerization. This was demonstrated by brief treatment of **18** to mild base, which resulted in a quantitative transformation to the more stable trans-fused octahydrocyclohepta[*b*]thiophene system **19**. This result indicated that the stereochemistry of the C(3a) hydrogen of the ketones **18** was still locked in the desired cis configuration. Treatment of **18** with hydroxylamine led to the syn (**20**) and anti (**21**) oximes in a ratio of 1:4. Similar exposure of **19** to hydroxylamine yielded different oximes, implying that *no* C(3a) epimerization had occurred during the oximation step. Furthermore, the major oxime was assumed to possess the desired anti configuration **21** owing to the serious steric crowding present in the syn series between the oxime OH and the bulky urethane function. This result was predicted and deemed crucial to ensure the migration of the C(3a) carbon in the ensuing Beckmann rearrangement.[14] An unequivocal proof of the entirety of our structural assignments was obtained

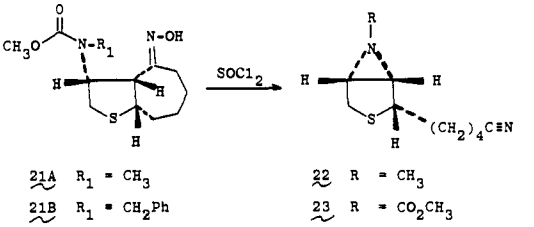
Scheme IV



by a complete X-ray structure determination on the major oxime **21A**. The X-ray proved the all-cis hydrogen stereochemistry about the tetrahydrothiophene nucleus and the desired anti configuration of the adjacent oxime.

So far the chemistry of the A and B series was devoid of major differences, and the easily prepared anti oximes **21** appeared perfectly set up for a Beckmann rearrangement which would effectively insert nitrogen between C(4) and C(3a) and lead readily to the target molecule, biotin (**6**).

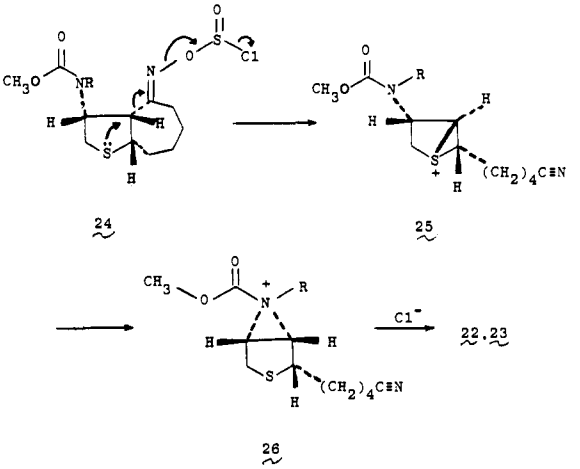
Treatment of the *N*-methyl anti oxime **21A** with thionyl chloride in various solvents at 0 °C unexpectedly yielded the deacylated *N*-methylaziridinonitrile **22**. The same set of



conditions were applied to the *N*-benzyl case **21B** and afforded a debenzylated *N*-acylaziridinonitrile **23**. These reactions were instantaneous and readily occurred even at −78 °C with a host of reagents designed to activate the oximino moiety toward the Beckmann rearrangement.

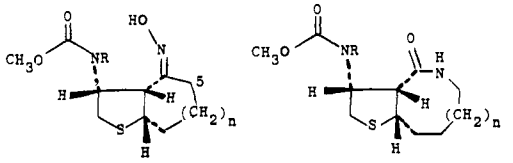
The formation of these undesired aziridines **22** and **23** is the result of a novel Beckmann fragmentation,[15,24] presumably initiated by the lone pair on sulfur (Scheme V). This electron

Scheme V



density is used to quench the developing cationic charge at the activated oxime site in **24** by a transannular reaction. This presumption leads to the transient episulfonium cation **25**[16] with the simultaneous generation of a nitrile function at the side-chain terminus. The lone pair on the urethane nitrogen then presumably attacks the reactive vicinal position from the backside to yield the acylated aziridinium cation **26**.[17] This species finally undergoes reaction with chloride ion to either deacylate as in the A series (with loss of CO_2 and CH_3Cl) or debenzylate as is observed in the B series.

Interestingly, the syn oximes **27** underwent a normal Beckmann rearrangement under identical conditions. In this case, the opposite oxime stereochemistry precluded the fragmentation reaction allowing a smooth migration of the C(5) carbon. The resultant alternate lactams **28** were of no further



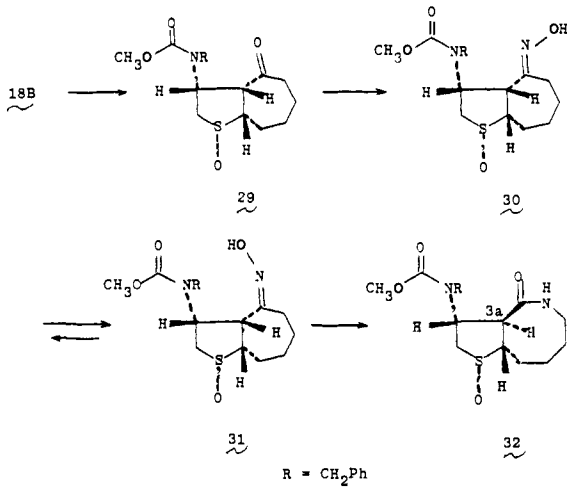
27A,B n = 1,2 **28A,B**

A series R = CH_3
B series R = CH_2Ph

use, however, lacking the correct positioning of the lactam nitrogen. Collectively, these results strongly support our premise that the fragmentation is initiated by the sulfur lone pair and suggest that a deactivation of the sulfide functionality present in the anti oximes **21** is required.

To this end, the oximino sulfoxide **30** was prepared by oxidation of the ketone **18B** with MCPBA to the sulfoxy ketone **29** followed by treatment with hydroxylamine (Scheme VI). The unexpected[18] α stereochemistry of the sulfoxide implicates a directive effect of the urethane moiety, inducing the sulfide oxidation to occur from the more hindered concave face[19] of the molecule.[25] The ketone **29** was subjected to the epimerizing conditions (NaOAc/EtOH) and found to have retained the cis ring fusion. Finally, the oximino sulfoxide **30** was shown to be different from that derived from the trans-fused intermediate **19B**, proving that the all-cis hydrogen stereochemistry had been retained. When the oximino sulfoxide **30** was treated with hot PPA, no Beckmann fragmentation occurred and a 5,8-lactam **32**, a result of a Beckmann rearrangement, was obtained. An X-ray analysis elucidated the structure of this substance to be that derived by migration of the C(5) carbon, which possessed a syn relationship to the oxime OH in the precursor **30**! This unexpected result is explained by the observation that the reaction conditions were isomerizing the initially pure anti oxime **30** to an equilibrium mixture containing its syn isomer **31**. This was proven by an examination of the reaction mixture after 10% consumption of starting material had occurred. The syn isomer **31** is presumably more reactive since a Beckmann rearrangement relieves the severe steric crowding between its oxime OH and the bulky urethane substituent. It could not be determined at which point epimerization of C(3a) is occurring.

Scheme VI

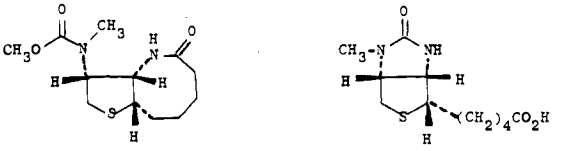


18B → **29** → **30** ⇌ **31** → **32**

R = CH_2Ph

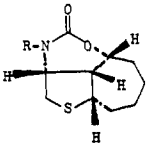
A thorough investigation of a great variety of reaction conditions was carried out utilizing the main-line substrates—the sulfido oximes **21**. Although the *N*-benzyl species **21B** could not be induced to undergo a Beckmann rearrangement under any circumstances, the *N*-methyl analogue **21A** did convert to the desired all-cis 5,8-lactam **33** in PPA at 100 °C.

This result implies that decreasing the steric bulk around the urethane moiety facilitates the rearrangement pathway, presumably by retarding the competing fragmentation. Therefore, the anti oxime **44**, the *N*-demethyl derivative of **33**, became the obvious intermediate for our synthesis. Moreover, demethylation of **33** or the *N*-methylbiotin **34** derived from it would then be unnecessary.



33 **34**

Hence, it was established that the required substrate for our projected synthesis of biotin must be the fully unsubstituted amino alcohol **5**. The synthesis of **5** from an intermediate obtained from the nitrone olefin [3 + 2] cycloaddition route just described was therefore carried out. All attempts to debenzylate the isoxazolidone **14B** led to reductive fissure of the N–O bond, affording the *N*-benzylamino alcohol **15B** (Scheme III). Neither **15B** nor its diacyl derivative **17** ($R_1 = R_2 = CO_2CH_3$) could be debenzylated under a variety of conditions. However, it was found that treatment of the latter compound with aqueous base afforded the *N*-benzyl cyclic urethane **35**, which



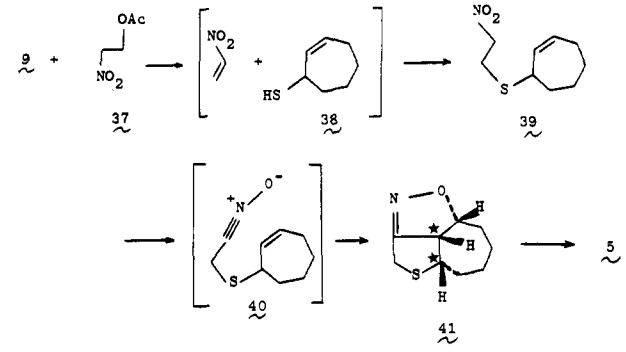
35 R = CH_2Ph
36 R = H

was smoothly debenzylated with sodium in liquid ammonia to the tricyclic urethane **36**. This substance was then hydrolyzed to the desired amino alcohol **5**, best isolated as its crystalline hydrochloride.

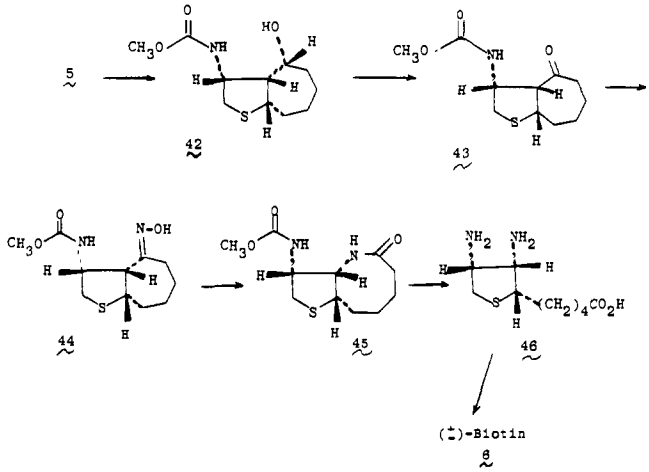
At this point an alternate synthesis of **5** was needed, since the overall yield of 15% from cycloheptene was deemed too low for our purposes. We therefore returned to the sodium mercaptide **9** and treated this early intermediate with 1-nitro-2-acetoxyethane (**37**)[20] (Scheme VII). This combination presumably generated nitroethylene and the mercaptan **38** in situ. These reactive substances then underwent a facile Michael reaction leading to the nitro olefin **39** in quantitative yield.

This readily obtained compound was obtained in a high state of purity and was used directly in the next step. Dehydration of **39**, preferably with phenyl isocyanate, predictably generated the olefinic nitrile oxide **40** as a reactive intermediate. This species underwent spontaneous cyclization to the observed product, the tricyclic isoxazoline **41**. This compound is the result of another intramolecular [3 + 2] cycloaddition reaction and is related to the previous conversion of the aldehyde **12** to the isoxazolidine **14**. The reaction proceeds stereospecifically

Scheme VII



Scheme VIII



and, despite considerable strain in the tricyclic system, **41** proved to be a stable molecule. Unlike the previous nitrone-olefin cyclization, this approach afforded only two of the three asymmetric centers that were to become part of the biotin framework (starred in **41**). Fortunately, this highly convex molecule **41** ensured that hydride delivery would occur from the less hindered face. Indeed, $LiAlH_4$ reduction cleaved the N-O bond and reduced the imine function to lead stereospecifically and in high yield to the target amino alcohol **5**.

The overall yield of the amino alcohol **5** by way of the nitrile oxide **40** was 31% based on cycloheptene and is the method of choice for the preparation of **5**. The completion of the total synthesis of biotin from **5** is presented in Scheme VIII. Selective acylation of the primary amino function proved to be uncomplicated, paralleling our experience with the *N*-methyl series and avoiding the production of O-acylated byproducts related to **17** ($R_1 = R_2 = CO_2CH_3$). Oxidation of the resultant alcohol **42** smoothly afforded the required ketone **43**, whose structure was firmly based on analogy to the previous studies. Treatment of **43** with hydroxylamine produced in 89% yield the desired anti oxime **44**, which was readily separated from its syn isomer by one recrystallization from ethyl acetate. The anti oxime **44** did undergo the Beckmann rearrangement to yield the all-cis 5,8-lactam **45** in accord with the chemistry of the *N*-methyl analogue **21A**. The major pathway still consisted of the fragmentation reaction, however, and the aziridine **23**, previously obtained from **21B**, was also obtained. In this case, the postulated aziridinium cation **26** (R = H) merely deprotonates to afford **23**. The yield of lactam vs. aziridine was found to be influenced by the nature of the protecting group on nitrogen in the anti oxime **44**. A number of analogues of **44** were prepared from the amino alcohol **5** using the general process of Scheme VIII. The highest lactam yield of 35% was recorded for the Beckmann rearrangement of the sulfonamide analogous to **44**. Even the parent free amino oxime derived from **44** was prepared.[21] This compound only underwent fragmentation under a variety of conditions. Hydrolysis of the 5,8-lactam **45** to the diamino acid **46** followed by treatment with phosgene, yielded (±)-biotin (**6**), identical in all respects with an authentic sample. Since the resolution of (±)-biotin to the biologically active *d* enantiomer has been reported,[22] this work constitutes the total synthesis of the naturally occurring vitamin.

In summation, we have developed a short, stereospecific synthesis of biotin that utilizes intramolecular [3 + 2] cycloaddition reactions to prepare the crucial intermediate **5**. Further applications of this powerful reaction mode toward the synthesis of natural products await only the imagination and energy of the synthetic organic chemist.

Experimental Section

Melting points were determined on a Rinco Model M-50 melting point apparatus and are uncorrected. IR spectra were obtained using a Beckman IR-9 spectrophotometer. A Cary 14 recording spectrophotometer was used for UV absorption spectra. NMR spectra were determined with Varian T-60 and HA-100 spectrometers using tetramethylsilane as the internal reference. Mass spectra were recorded on a CEC 21-110B mass spectrometer at 70 eV using a direct insertion probe. Thin layer chromatography was carried out using Merck F-254 silica gel plates.

3-Acetylmercaptocycloheptene (8). To a solution of 81.55 g (0.466 mol) of 3-bromocycloheptene (**7**) (prepared from cycloheptene (**4**) according to the procedure of Hatch[11]) in 300 mL of acetonitrile cooled to 0 °C was added 13.13 mL (0.466 mol) of thiolacetic acid. The system was treated dropwise with 64.55 mL (0.466 mol) of triethylamine, during which time a precipitate of triethylamine hydrobromide separated. The cooling bath was removed and the reaction allowed to proceed at 25 °C for an additional 2.0 h. The reaction mixture was partitioned between 1 N HCl/methylene chloride. The aqueous phase was further extracted with methylene chloride. The organic extracts were pooled, dried over sodium sulfate, and evaporated. The residue was distilled in vacuo to afford 45.18 g (0.330 mol, 71%), bp 64–65 °C (0.25 mm), of 3-acetylmercaptocycloheptene (**8**) as a colorless liquid: IR ($CHCl_3$) 1685 (SAc), 1100 cm^{-1}; NMR ($CDCl_3$) δ 5.80 (m, 2 H, olefin), 4.40 (bm, 1 H, CH), 2.31 (s, 3 H, Ac), 2.5–1.5 (bm, 8 H); mass spectrum *m/e* 170 (M^+), 128, 95 (base), 67, 43.

3-(2,2-Diethoxyethylthio)-1-cycloheptene (11). A solution of fresh sodium ethoxide prepared from 7.6 g (0.330 g-atom) of metallic sodium in 200 mL of absolute ethanol was treated dropwise with 56.18 g (0.33 mol) of the thiol ester **8** in 10 mL of absolute ethanol. The reaction mixture was heated under reflux for 0.25 h and then cooled to 25 °C. To this solution of the sodium mercaptide **9** was added dropwise 49.69 mL (0.33 mol) of bromoacetaldehyde diethyl acetal (**10**) dissolved in 30 mL of absolute ethanol. The reaction mixture was heated under reflux for 2.0 h and cooled. The precipitated sodium bromide was filtered and washed well with absolute ethanol. The filtrate was concentrated and the residue partitioned between ether/brine. The aqueous phase was further extracted with ether. The organic extracts were pooled, dried over magnesium sulfate, and evaporated to afford 80.1 g (0.328 mol, 99%) of pure 3-(2,2-diethoxyethyl)thiol-1-cycloheptene (**11**) as a colorless oil: IR (neat) 1655 (olefin), 1125, 1060 (C-O-C) cm^{-1}; NMR ($CDCl_3$) δ 5.82 (m, 2 H, C=C), 4.65 [t, 1 H, C*H*$(OR)_2$], 4.1–3.5 [m, 5 H, $(OCH_2CH_3)_2$ + CHS], 2.73 (d, 2 H, CH_2), 2.6–1.5 (m, 8 H), 1.22 (t, 6 H, 2 CH_3); mass spectrum *m/e* 198 (M^+ − EtOH), 104 (base), 95. Anal. ($C_{13}H_{24}O_2S$, 244.39) C, H, S.

2-[(1-Cyclohepten-3-yl)thio]acetaldehyde (12). A solution of 108.13 g (0.433 mol) of the acetal **11** in 1000 mL of acetone/water (9:1) was treated with 1.1 g of *p*-toluenesulfonic acid hydrate, heated under reflux for 1.0 h, cooled, and concentrated. The residue was partitioned between ether/10% sodium bicarbonate. The aqueous phase was further extracted with ether. The organic extracts were pooled, dried over magnesium sulfate, and evaporated to afford 75.30 g (0.433 mol, 100%) of the aldehyde **12** as a colorless oil: IR ($CHCl_3$) 1725 (CHO), 1230 (C-O) cm^{-1}; NMR ($CDCl_3$) δ 9.47 (t, 1 H, CHO), 6.0–5.0 (m, 2 H, olefin), 3.9–2.30 (bm, 3 H, CH_2SCH), 3.18 (d, 2 H, CH_2CHO), 2.3–1.5 (m, 8 H); mass spectrum *m/e* 170 (M^+), 95 (base), 67. Anal. ($C_9H_{14}OS$, 170.27) C, H, S.

2aβ,4aβ,5,6,7,8,8aβ,8bβ-Octahydro-2-benzyl-2*H*,3*H*-thieno[3',-

4′,5′:3,3a,4]cyclohept[*d*]isoxazole (14B). A solution of 21.30 g (0.125 mol) of the aldehyde **12** in 150 mL of acetonitrile was treated with 15.3 g (0.125 mol) of benzylhydroxylamine and 1 mL of triethylamine. The reaction mixture was heated under reflux for 2.0 h, cooled, and evaporated to dryness. The residue was triturated with benzene/ethyl acetate (98:2) in which the product is soluble. An insoluble impurity was filtered off and the filtrate was concentrated and chromatographed over silica using the same solvent system for elution. The product was eluted after a less polar byproduct was obtained as 22.80 g (0.083 mol, 66%) of the *N*-benzylisoxazolidone **14B:** mp 56–57 °C (petroleum ether); IR ($CHCl_3$) 3010, 2920 (CH), 1605, 1500 (aryl), 1228 (C–O), 700 cm^{-1}; NMR ($CDCl_3$) δ 7.4–7.2 (m, 5 H, Ph), 4.33 (septet, 1 H, C*H*OR), 4.1–3.3 (m, 5 H), 2.91 (d, 2 H, CH_2S), 2.7–1.1 (m, 8 H); mass spectrum *m/e* 275 (M^+), 228, 91 (base). Anal. ($C_{16}H_{21}NOS$, 275.40) C, H, N, S.

A similar procedure using *N*-methylhydroxylamine afforded the *N*-methyl analogue **14A,** obtained as a colorless oil: IR ($CHCl_3$) 1450 (NCH_3), 1230 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 4.28 (m, 1 H, CHO), 3.9–3.4 (m, 3 H, 3 CH), 3.1 (m, 2 H, CH_2S), 2.70 (s, 3 H, NCH_3), 2.9–1.5 (m, 8 H); mass spectrum *m/e* 199 (M^+, base), 152, 136, 96, 42. Anal. ($C_{10}H_{17}NOS$, 199.32) C, H, N, S.

2,3β,3aβ,5,6,7,8,8aβ-Octahydro-3α-benzylamino-4*H*-cyclopenta[*b*]thiophen-4α-ol (15B). To a suspension of 37.69 g (0.137 mol) of the *N*-benzylisoxazolidone **14B** in 400 mL of acetic acid/water (1:2) was added 37.69 g (0.577 g-atom) of zinc. The reaction mixture was heated at 70 °C for 18 h with efficient stirring and then cooled. The zinc salts were filtered off and the filtrate was concentrated. The residue was partitioned between 10% ammonium hydroxide/methylene chloride. The aqueous phase was further extracted, and the organic extracts were combined, dried over sodium sulfate, and evaporated to yield 36.28 g (0.13 mol, 96%) of the *N*-benzylamino alcohol **15B** as a colorless oil: IR ($CHCl_3$) 3280–3020 (bonded OH, NH), 1450, 700 cm^{-1}; NMR ($CDCl_3$) δ 7.35 (s, 5 H, Ph), 5.8–4.5 (bm, 1 H, NH), 4.54 (m, 2 H, 2 CH), 3.87 (d, 2 H, CH_2S), 3.8–3.5 (m, 2 H, –CH + OH), 2.93 (m, 2 H, CH_2N), 2.6–1.2 (m, 9 H); mass spectrum *m/e* 277 (M^+), 166, 165, 132 (base), 91. Anal. ($C_{16}H_{23}NOS$, 277.43) C, H, N, S.

A similar procedure starting with the *N*-methyl analogue **14A** yielded the *N*-methylamino alcohol **15A:** mp 56–57 °C (ethyl acetate/petroleum ether); IR (KBr) 3262 (NH), 3150 (OH), 1455 (NCH_3) cm^{-1}; NMR ($CDCl_3$) δ 5.0 (bm, 1 H, NH), 4.8–4.6 (m, 2 H, CH + OH), 3.8–3.5 (m, 2 H, 2 CH), 2.90 (m, 2 H, CH_2S), 2.45 (s, 3 H, NCH_3), 2.4–1.2 (m, 9 H); mass spectrum *m/e* 201 (M^+), 154, 150, 96, 89 (base). Anal. ($C_{10}H_{19}NOS$, 201.33) C, H, N, S.

2,3β,3aβ,5,6,7,8,8aβ-Octahydro-3α-methylamino-4*H*-cyclohepta[*b*]thiophen-4α-ol (16). A solution of 2.2 g (0.011 mol) of the *N*-methylamino alcohol **15A** in 40 mL of methanol was treated dropwise with 1.28 mL (0.0165 mol) of methyl chloroformate. The reaction mixture was kept at pH 8 by the addition of 10% sodium bicarbonate. After 0.5 h the pH was made acidic with 1 N HCl and the mixture was extracted with 3 × 100 mL of methylene chloride. The organic extracts were dried (Na_2SO_4) and evaporated to afford 2.68 g (0.0103 mol, 94%) of the *N*-methylurethane alcohol **16:** mp 139–140 °C (ethyl acetate); IR (KBr) 3410 (OH), 1660 (urethane) cm^{-1}; NMR ($CDCl_3$) δ 4.52 (sextet, 1 H, CHN), 4.11 (bt, 1 H, CHO) 3.68 (s, 3 H, OCH_3), 3.8–2.6 (m, 3 H, 3 CH), 3.03 (s, 3 H, NCH_3), 2.9–1.2 (m, 10 H); mass spectrum *m/e* 259 (M^+), 227 ($M^+ - CH_3OH$), 170, 114 (base). Anal. ($C_{12}H_{21}NO_3S$, 259.37) C, H, N, S.

Using an identical procedure, the amino alcohol **5** was converted in 94% yield to the urethane alcohol **42:** mp 109–110 °C (ethyl acetate/petroleum ether); IR (KBr) 3510 (OH), 3330 (NH), 1695 (urethane), 1550 cm^{-1}; NMR ($CDCl_3$) δ 5.58 (bd, 1 H, NH), 4.60 (dd, 1 H, CHN), 4.27 (bt, 1 H, CHO), 3.8–3.6 (m, 1 H, CHS), 3.71 (s, 3 H, OCH_3), 3.01–2.95 (m, 2 H, SCH_2), 2.5 (bd, 1 H, OH), 2.4 (m, 1 H, CH), 2.2–1.2 (m, 8 H); mass spectrum *m/e* 245 (M^+), 227 ($M^+ - H_2O$), 198, 170 (base), 152, 123, 85. Anal. ($C_{11}H_{19}NO_3S$, 245.34) C, H, N, S.

2,3β,3aβ,5,6,7,8,8aβ-Octahydro-3α-benzylcarbomethoxyamino-4*H*-cyclohepta[*b*]thiophen-4α-ol (17, R_1 = CO_2CH_3; R_2 = H). A solution of 11.08 g (0.04 mol) of the *N*-benzylamino alcohol **15B** in 200 mL of methanol was treated in one portion with 80 mL of 10% $NaHCO_3$ and 2 mL of methyl chloroformate. After 0.8 h an additional 2 mL of methyl chloroformate was added and the reaction was allowed to proceed at 25 °C for 1 h. The mixture was partitioned between water and methylene chloride. The organic extracts were dried (Na_2SO_4) and evaporated, and the residue was chromatographed over 1.0 kg of silica. The desired product **17** (R_1 = CO_2CH_3; R_2 = H), mp 137–137.5 °C (ethyl acetate), was isolated (R_f 0.2) in a yield of 6.2 g (0.018 mol, 46%), eluting with benzene/EtOAc (95:5): IR (KBr) 3420 (OH), 1683 (urethane), 702 cm^{-1}; NMR ($CDCl_3$) δ 7.2 (m, 5 H, Ph), 5.1–4.5 (m, 2 H, CH_2Ph), 4.51 (m, 1 H, CHN), 4.17 (bt, 1 H, CHO), 3.75 (s, 3 H, OCH_3), 3.8–2.6 (m, 4 H, 3 CH + OH), 2.5–1.1 (m, 9 H); mass spectrum *m/e* 335 (M^+), 303 ($M^+ - CH_3OH$), 209, 190, 170, 91 (base). Anal. ($C_{18}H_{25}NO_3S$, 335.47) C, H, N, S.

Benzyl[2,3β,3aβ,5,6,7,8,8aβ-octahydro-4α-methoxycarbonyl-4*H*-cyclohepta[*b*]thiophen-3α-yl]carbamic Acid Methyl Ester (17, R_1 = R_2 = CO_2CH_3). A solution of the *N*-benzylamino alcohol **15B** in 200 mL of methanol and 100 mL of 10% sodium bicarbonate was treated with 6.79 mL (0.088 mol) of methyl chloroformate. After 2.0 h of stirring, an additional 3.0 mL of methyl chloroformate was added and the reaction was allowed to proceed for an additional 1 h. The mixture was partitioned between methylene chloride/water. The aqueous phase was further extracted with 3 × 200 mL of methylene chloride. The organic extracts were pooled, dried over sodium sulfate, and evaporated to yield 15.65 g (0.040 mol, 100%) of the urethane carbonate **17** (R_1 = R_2 = CO_2CH_3) as a colorless oil: IR ($CHCl_3$) 1740 (ester), 1693 (urethane) cm^{-1}; NMR ($CDCl_3$) δ 7.4–7.0 (m, 5 H, Ph), 5.2–4.0 (m, 4 H, 2 CH + NCH_2), 3.84 (s, 3 H, OCO_2CH_3), 3.73 (s, 3 H, NCO_2CH_3), 3.9–2.5 (m, 3 H, $CHSCH_2$), 2.8–1.2 (m, 9 H); mass spectrum *m/e* 393 (M^+), 362, 334, 318, 190, 152 (base), 91. Anal. ($C_{20}H_{27}NO_5S$, 393.50) C, H, N, S.

Benzyl[2,3β,3aβ,5,6,7,8,8aβ-octahydro-4-oxo-4*H*-cyclohepta[*b*]-thiophen-3α-yl]carbamic Acid Methyl Ester (18B). A solution of 4.0 g (11.94 mmol) of the alcohol **17** (R_1 = CO_2CH_3; R_2 = H) in 30 mL of dimethyl sulfoxide was treated with 20 mL of acetic anhydride. The reaction was allowed to proceed at room temperature overnight. The volatiles were removed at the pump to yield 3.55 g (10.65 mmol, 89%) of pure ketone **18B:** mp 119–120 °C (ethyl acetate/petroleum ether); IR (KBr) 1707 (ketone), 1695 (urethane) cm^{-1}; NMR ($CDCl_3$) δ 7.4–7.0 (m, 5 H, Ph), 4.71 (d, 2 H, PhCH_2), 4.52 (m, 1 H, CHN), 3.9 (m, 1 H, CHCO), 3.69 (s, 3 H, OCH_3), 3.8–2.6 (m, 3 H, $CHSCH_2$), 2.37 (bt, 2 H, CH_2CO), 2.2–1.4 (bm, 6 H); mass spectrum *m/e* 334 (M^+ + H), 223, 168, 91 (base). Anal. ($C_{18}H_{23}NO_3S$, 333.45) C, H, N, S.

In similar fashion, the *N*-methyl analogue **18A,** mp 97–98 °C (ethyl acetate/petroleum ether), was prepared from the urethane alcohol **16** in 80% yield. Data on **18A:** IR (KBr) 1710–1690 (ketone + urethane), 1500 cm^{-1}; NMR ($CDCl_3$) δ 4.46 (m, 1 H, CHN), 3.9 (m, 1 H, CHCO), 3.66 (s, 3 H, OCH_3), 3.7–2.8 (m, 3 H, $CHSCH_3$), 2.92 (s, 3 H, NCH_3), 2.43 (bt, 2 H, CH_2CO), 2.1–1.4 (m, 6 H); mass spectrum *m/e* 257 (M^+), 168 (M^+ – urethane, base), 147, 140, 114. Anal. ($C_{12}H_{19}NO_3S$, 256.34) C, H, N, S.

Using a similar procedure, the urethane alcohol **42** was converted in 100% yield to the N-unsubstituted ketone **43:** mp 102–103 °C (EtOAc); IR (KBr) 3385 (NH), 1703 (urethane + ketone), 1528 cm^{-1}; NMR ($CDCl_3$) δ 5.5 (bd, 1 H, NH), 4.50 (m, 1 H, CHN), 3.9–2.8 (m, 3 H, $CHSCH_2$), 3.67 (s, 3 H, OCH_3), 2.44 (t, 2 H, CHCO), 2.2–1.5 (bm, 6 H); mass spectrum *m/e* 243 (M^+), 168 ($M^+ - NHCO_2CH_3$, base), 135, 111, 97. Anal. ($C_{11}H_{17}NO_3S$, 243.33) C, H, N, S.

Epimerization of C(3a) of the Urethane Ketone 18B. A sample of 300 mg (0.9 mmol) of the ketone **18B** was dissolved in 15 mL of ethanol and treated with 500 mg of sodium acetate. The mixture was heated under reflux for 1.25 h, cooled, and partitioned between water/methylene chloride. The organic extracts were dried (Na_2SO_4) and evaporated, and the 250-mg residue was chromatographed on three thick layer silica plates, eluting with EtOAc/hexane (1:1). The epimeric ketone **19B** (R_f 0.80) was isolated and afforded 190 mg (0.57 mmol, 63%) of product: mp 150–151 °C (ethyl acetate); IR (CH_2Cl_2) 1705–1690 (ketone + urethane), 1450, 1230 cm^{-1}; NMR ($CDCl_3$) δ 7.4 (s, 5 H, Ph), 4.8 (m, 2 H, PhCH_2), 4.51 (m, 1 H, CHN), 3.8 (m, 1 H, CHCO), 3.7 (s, 3 H, OCH_3), 3.8–2.4 (m, 3 H, $CHSCH_2$), 2.2 (bt, 2 H, CH_2CO), 2.2–1.2 (bm, 6 H); mass spectrum *m/e* 333 (M^+), 274, 242, 168 (base), 91. Anal. ($C_{18}H_{23}NO_3S$, 333.45) C, H, N, S.

Methyl[2,3β,3aβ,5,6,7,8,8aβ-octahydro-4-hydroxyimino-4*H*-cyclohepta[*b*]thiophen-3α-yl]carbamic Acid Methyl Ester: *syn-* (20A) and *anti-* (21A). A solution of 2.57 g (0.01 mol) of the ketone **18A** in 50 mL of ethanol was treated with 1.04 g of hydroxylamine hydrochloride and 10 mL of pyridine. The mixture was heated under reflux for 2 h and concentrated. The residue was partitioned between 1 N

HCl and methylene chloride to afford 2.60 g (95%) of a 4:1 mixture of **21A** and **20A**, respectively. The compounds could be separated by either fractional crystallization from ethyl acetate or chromatography over silica, eluting with EtOAc/hexane (1:1).

20A: mp 161–162 °C (ethyl acetate); IR (KBr) 3325, 1690 (urethane) cm^{-1}; NMR ($CDCl_3$) δ 9.1 (bs, 1 H, OH), 4.8 (b, 1 H, CHN), 4.39 (t, 1 H, CHC=N), 4.00 (bt, 1 H, CHS), 3.66 (s, 3 H, OCH_3), 3.3–2.8 (m, 2 H, CH_2S), 2.77 (bs, 3 H, NCH_3), 2.52 (bt, 2 H, CH_2C=N), 2.2–1.2 (m, 6 H); mass spectrum *m/e* 272 (M^+), 255, 183, 147, 126, 114 (base). Anal. ($C_{12}H_{20}NO_3S$, 272.37) C, H, N, S.

21A: mp 155–156 °C (ethyl acetate); IR (KBr) 3400 (OH), 1705 (urethane) cm^{-1}; NMR ($CDCl_3$) δ 8.48 (bs, 1 H, OH), 4.80 (m, 1 H, CHN), 3.97 (m, 1 H, CHC=N), 3.70 (s, 3 H, OCH_3), 3.6–2.8 (m, 3 H, $CHSCH_2$), 2.79 (s, 3 H, NCH_3), 2.4 (bt, 2 H, CH_2C=N), 2.2–1.4 (m, 6 H); mass spectrum *m/e* 272 (M^+), 240, 223, 183, 166. Anal. ($C_{12}H_{20}N_2O_3S$, 272.37) C, H, N, S.

In similar fashion, the *N*-benzyl ketone **18B** was converted into the oximes **20B** and **21B**, which were obtained in yields of 43 and 12%, respectively. The compounds were chromatographed over silica, eluting with EtOAc/hexane (1:1). By this technique, a pure sample of the desired anti oxime **21B**, mp 147–148 °C (ethyl acetate), was obtained by eluting the band at R_f 0.4: IR (KBr) 3240 (OH), 1700 (urethane), 1655 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 7.98 (bs, 1 H, OH), 7.4–7.0 (m, 5 H, Ph), 4.8 (m, 1 H, CHN), 4.7–4.1 (dd, 2 H, PhCH_2), 3.92 (q, 1 H, CHS), 3.72 (s, 3 H, OCH_3), 3.46 (bt, 1 H, CHC=N), 3.3–2.6 (m, 2 H, CH_2S), 2.9–1.2 (m, 8 H); mass spectrum *m/e* 348 (M^+), 331, 317, 223, 190 (base), 183, 91. Anal. ($C_{18}H_{24}N_2O_3S$, 348.47) C, H, N, S. The syn oxime **21A**, R_f 0.3, was obtained as a colorless oil: IR (CH_2Cl_2) 3500–3200 (OH), 1700 (urethane), 1450, 1220 cm^{-1}; NMR ($CDCl_3$) δ 7.4 (bs, 5 H, Ph), 6.2 (bs, 1 H, OH), 4.8 (m, 1 H, CHN), 5.0–4.4 (m, 2 H, PhCH_2), 4.1 (m, 1 H, CHS), 3.80 (s, 3 H, OCH_3), 3.4–2.5 (m, 3 H, $CHSCH_2$), 2.2–1.4 (m, 8 H).

Using similar conditions, the ketone **43** was converted in 89% yield to the desired anti oxime **44.** In this case, the product was separated from the corresponding syn oxime by one recrystallization from ethyl acetate/pentane. Data on **44:** mp 123–124 °C; IR (KBr) 3330 (OH), 3220 (NH), 1690 (urethane), 1565 cm^{-1}; NMR ($CDCl_3$) δ 7.51 (bs, 1 H, OH), 5.70 (bd, 1 H, NH), 4.55 (m, 1 H, CHN), 3.9–2.8 (m, 3 H, $CHSCH_2$), 3.69 (s, 3 H, OCH_3), 3.30 (t, 1 H, CHC=N), 2.4–1.5 (m, 8 H); mass spectrum *m/e* 258 (M^+), 241 ($M^+ - OH$), 227 ($M^+ - CO_2CH_3$), 183 (base), 166, 126. Anal. ($C_{11}H_{18}N_2O_3S$, 258.34) C, H, N, S.

Beckmann Fragmentations of the Anti Oximes 21A,B and 44. A solution of 129 mg (0.474 mmol) of the anti oxime **21A** in 2 mL of anhydrous methylene chloride was treated with 100 μL of thionyl chloride at 0 °C. The reaction mixture was immediately washed with 10% sodium bicarbonate. The organic layer was dried (Na_2SO_4) and evaporated to yield 70 mg (0.357 mmol, 75%) of the *N*-methylaziridine **22** as a colorless oil (R_f 0.4), after chromatography over silica, eluting with ethyl acetate: IR (CH_2Cl_2) 2950, 1590, 1450 (N-CH_3) cm^{-1}; NMR ($CDCl_3$) δ 4.1–3.8 (m, 2 H, C*H*C*H*N), 3.6 (m, 1 H, CHS), 3.2 (m, 2 H, CH_2S), 2.8 (s, 3 H, NCH_3), 2.5–1.2 (m, 8 H).

Using similar conditions, the anti oximes **21B** and **44** were each converted to the same *N*-carbomethoxyaziridine **23** as a colorless oil: IR (CH_2Cl_2) 1700 (urethane), 1475, 1400, 1350 cm^{-1}; NMR ($CDCl_3$) δ 5.2–4 2 (m, 2 H, CHCHN), 4.0 (s, 3 H, OCH_3), 3.9–2.8 (m, 3 H, $CHSCH_2$), 2.7–1.5 (m, 8 H); mass spectrum *m/e* 240 (M^+), 151, 140 (base), 135.

Benzyl[2,3β,3aβ,5,6,7,8,8aβ-octahydro-4-oxo-4*H*-cyclohepta[*b*]-thiophen-3α-yl]carbamic Acid Methyl Ester 1α-Oxide (29). A solution of 666 mg (2 mmol) of the *N*-benzyl ketone **18B** in 10 mL of dry methylene chloride was treated at 0 °C with 260 mg of sodium bicarbonate and 400 mg (2 mmol) of MCPBA. The reaction mixture was washed with 1 N NaOH, dried (Na_2SO_4), and evaporated to yield 698 mg (2 mmol, 100%) of pure sulfoxide **29:** mp 163–165 °C (ethyl acetate); IR (KBr) 1708 (ketone), 1688 (urethane), 1128 (C-O), 1035 (S-O) cm^{-1}; NMR ($CDCL_3$) δ 7.5–7.2 (m, 5 H, Ph), 5.10 (m, 1 H, CHN), 4.72 (bs, 2 H, PhCH_2), 4.23 (dd, 1 H, CHCO), 3.69 (s 3 H, OCH_3), 3.38–2.7 (m, 3 H, $CHSCH_2$), 2.4–1.3 (m, 8 H); mass spectrum *m/e* 349 (M^+), 332, 318 ($M^+ - OCH_3$), 300, 165, 136, 91 (base). Anal. ($C_{18}H_{23}NO_4S$, 349.45) C, H, N, S.

Benzyl[2,3β,3aβ,5,6,7,8,8aβ-octahydro-4-hydroxyimino-4*H*-cyclohepta[*b*]thiophen-3α-yl]carbamic Acid Methyl Ester 1α-Oxide (30). A solution of 490 mg (1.34 mmol) of the sulfoxide **29** in 15 mL of ethanol and 1.5 mL of pyridine was treated at 25 °C with 138.9 mg (2.01 mmol) of hydroxylamine hydrochloride. The reaction mixture was heated under reflux of 1.5 h, cooled, and partitioned between 1 N HCl/methylene chloride. From the organic phase was isolated 489 mg (1.34 mmol, 100%) of the oximino sulfoxide **30:** mp 223–224 °C (methanol); IR (KBr) 3200 (OH), 1690 (CO), 1028 (S-O) cm^{-1}; NMR ($CDCl_3$) δ 9.91 (bs, 1 H, OH), 7.5–7.2 (m, 5 H, Ph), 5.12 (bm, 1 H, CHN), 4.8–4.2 (q, 2 H, PhCH_2), 3.8 (m, 1 H, CHS), 3.59 (s, 3 H, OCH_3), 3.0–2.6 (m, 2 H, CH_2S), 2.5–2.2 (m, 3 H, C*H*CNCH_2), 2.0–1.1 (bm, 6 H); mass spectrum *m/e* 364 (M^+), 347 ($M^+ - OH$), 331, 315, 299, 239, 91 (base). Anal. ($C_{18}H_{24}N_2O_4S$, 364.46) C, H, N, S.

Benzyl[2,3β,3aα,4,5,6,7,8,9,9aβ-decahydro-4-oxothieno[3,2-*c*]-azocin-3α-yl]carbamic Acid Methyl Ester 1α-Oxide (32). A sample of 1.850 g (5.082 mmol) of the oximino sulfoxide **30** was suspended in 80 mg of PPA and the mixture was stirred mechanically at 25 °C for 24 h. The PPA was hydrolyzed with ice-water, and the mixture was extracted with methylene chloride. The organic phases were dried (Na_2SO_4) and evaporated. The residue was chromatographed over silica, eluting with benzene/ethyl acetate/methanol (60:35:5), to afford 609 mg of recovered **30** (R_f 0.35) and 950 mg (76%, corrected) of the alternate lactam **32:** mp 228–229 °C (ethyl acetate); IR (KBr) 1695 (urethane), 1655 (amide), 1020 (S-O) cm^{-1}; NMR ($CDCl_3$) δ 7.28 (bs, 5 H, Ph), 5.9 (bs, 1 H, NH), 6.62 (m, 1 H, CHN), 5.2–4.3 (bq, 2 H, PhCH_2), 3.9 (m, 1 H, CHS), 3.78 (s, 3 H, OCH_3), 3.5–2.8 (m, 2 H, CH_2S), 2.7–2.4 (m, 3 H, C*H*CONHCH_2), 2.4–1.2 (m, 6 H); mass spectrum *m/e* 364 (M^+), 347 ($M^+ - OH$), 315, 225, 164, 91 (base). Anal. ($C_{18}H_{24}N_2O_4S$, 364.46) C, H, N, S.

Decahydro-3-benzyl-3aβ,5aβ,9aβ,9bβ-2*H*-thieno[3,4,5-*de*]cyclohepta[1,3]oxazin-2-one (35). A solution of 23.0 g (0.058 mol) of the urethane carbonate **17** ($R_1 = R_2 = CO_2CH_3$) in 150 mL of methanol was treated with 75 mL of 1 N sodium hydroxide and heated under reflux for 18.0 h. The reaction mixture was cooled and partitioned between methylene chloride/water. The aqueous phase was further extracted. The organic extracts were pooled, dried over sodium sulfate, and evaporated to give 18.0 g (0.058 mol, 100%) of the *N*-benzyl cyclic urethane **35:** mp 153–154 °C (methanol); IR (KBr) 1690, 1676 (urethane), 1450, 730 cm^{-1}; NMR ($CDCl_3$) δ 7.3 (s, 5 H, Ph), 5.14–4.16 (q, 2 H, PhCH_2), 4.60 (dd, 1 H, CHO), 3.97 (dd, 1 H, CHN), 3.75–2.80 (m, 3 H, $CHSCH_2$), 2.6 (m, 1 H, CH), 2.4–1.3 (m, 8 H); mass spectrum *m/e* 303 (M^+), 258, 209, 152, 91 (base). Anal. ($C_{17}H_{21}NO_2S$, 303.42) C, H, N, S.

Decahydro-3aβ,5aβ,9aβ,9bβ-2*H*-thieno[3,4,5-*de*]cyclohepta-[1,3]oxazin-2-one (36). A solution of 8.0 g (26.4 mmol) of the *N*-benzyl cyclic urethane **35** in 100 mL of dry tetrahydrofuran was added to 400 mL of liquid ammonia cooled to −78 °C. To this solution, 3.0 g (0.130 g-atom) of metallic sodium was added in small portions over 0.5 h. Reaction was allowed to proceed until the blue color disappeared, at which point 5.0 g of ammonium chloride was added. The cooling bath was removed and the ammonia was allowed to evaporate overnight at 25 °C. The residue was partitioned between 1 N HCl/methylene chloride. The aqueous phase was further extracted with methylene chloride. The organic extracts were pooled, dried over sodium sulfate, and evaporated to yield 5.0 g (23.4 mmol, 89%) of the debenzylated tricyclic **36:** mp 197–198 °C (ethyl acetate); IR ($CHCl_3$) 3430 (NH), 1704 (urethane) cm^{-1}; NMR ($CDCl_3$) δ 6.75 (b, 1 H, NH), 4.81 (dd, 1 H, CHO), 4.27 (m, 1 H, CHN), 3.80–2.80 (m, 3 H, $CHSCH_2$), 2.7–1.2 (m, 9 H); mass spectrum *m/e* 213 (M^+, base), 170, 152, 94. Anal. ($C_{10}H_{15}NO_2S$, 213.299) C, H, N, S.

3-(2-Nitroethylthio)cycloheptene (39). To 40 mL of absolute ethanol was added 1.38 g (0.06 g-atom) of metallic sodium. When the reaction was completed, 10.2 g (0.06 mol) of the thiol ester **8** in 20 mL of absolute ethanol was added and the reaction mixture was brought up to reflux for 15 min. The solution was then cooled to 0 °C and 7.98 g (0.060 mol) of 1-nitro-2-acetoxyethane in 20 mL of absolute ethanol was added. The reaction was allowed to proceed for 3.0 h at 0 °C and then the mixture was partitioned between 1 N HCl and methylene chloride. The aqueous phase was further extracted with methylene chloride. The organic layers were pooled, dried over sodium sulfate, and evaporated to afford 12 g (99%) of pure nitro olefin **39** as a colorless oil: IR ($CHCl_3$) 1640 (C=C), 1555, 1378 (NO_2) cm^{-1}; NMR ($CDCl_3$) δ 6.0–5.6 (o, 2 H, olefin), 4.52 (t, 2 H, CH_2NO_2), 3.58 (bm, 1 H, CHS), 3.08 (t, 2 H, CH_2S), 2.3–1.4 (m, 8 H); mass spectrum *m/e* 201 (M^+), 184, 154, 126, 95 (base). Anal. ($C_9H_{15}NO_2S$ 201.29) C, H, N, S.

3,4aβ,5,6,7,8,9β,9aβ-Octahydrocycloheptano[5,5a,6-*f,q*]thieno-[3,4-*c*]isoxazole (41). A solution of 15.2 g (0.075 mol) of the nitro

olefin **39** in 200 mL of dry benzene was treated with 24 mL (0.224 mol) of phenyl isocyanate and 0.5 mL of triethylamine. The mixture was stirred for 24 h at 25 °C. The white solid (carbanilide) which had separated was filtered off and washed well with benzene. The filtrate was evaporated to dryness and the residue was chromatographed over 1 kg of silica eluting with benzene/ethyl acetate (98:2). Fractions containing the product were combined and evaporated to afford 10.8 g (0.060 mol, 79%) of pure tricyclic adduct **41** as a colorless oil: IR ($CHCl_3$) 1717 (C=N), 1630, 1450, 900 cm^{-1}; NMR ($CDCl_3$) δ 4.8 (dd, 1 H, CHO), 4.2–3.5 (m, 3 H, $CHSCH_2$), 3.1 (m, 1 H, CHCN), 2.4–1.0 (m, 8 H); mass spectrum *m/e* 183 (M^+ + base), 166, 157, 141, 101, 83. Anal. ($C_9H_{13}NOS$, 183.27) C, H, N, S.

2,3β,3aβ,5,6,7,8,8aβ-Octahydro-3β-amino-4*H*-cyclohepta[*b*]thiophen-4β-ol (5). Procedure A. From 17 ($R_1 = R_2 = CO_2CH_3$). A suspension of 5.01 g (23.4 mmol) of the urethane carbonate **17** ($R_1 = R_2 = CO_2CH_3$) in 50 mL of 2 N sodium hydroxide was heated under reflux for 16.0 h and cooled. The reaction mixture was partitioned between methylene chloride/1 N HCl. The aqueous phase was further extracted with methylene chloride and the organic extracts were discarded. The pH of the aqueous phase was adjusted to 10 by the addition of concentrated ammonium hydroxide. The aqueous phase was now further extracted with 4 × 100 mL of methylene chloride. The organic extracts were pooled, dried over sodium sulfate, and evaporated to yield 2.78 g (14.9 mmol, 64%) of the amino alcohol **5** as a colorless oil: IR (CH_2Cl_2) 3400, 3200 (OH, NH_2), 1540, 1450, 1050 cm^{-1}; NMR ($CDCl_3$) δ 4.6 (dd, 1 H, C*H*OH), 4.2–3.4 (m, 3 H, $CHSCH_2$), 3.2 (dd, 1 H, C*H*NH_2), 2.8–1.2 (m, 9 H); mass spectrum *m/e* 187 (M^+), 136, 85, 75 (base). The compound was taken up in methanolic HCl and evaporated to yield the crystalline hydrochloride **5A**, mp 192–193 °C (ethanol/ether). Anal. ($C_9H_{17}NOS\cdot HCl$, 223.77) C, H, N, S, Cl.

Procedure B. From 41. A solution of 3.66 g (0.02 mol) of the tricyclic adduct **41** in 150 mL of anhydrous ether was added dropwise at 25 °C (water bath) under argon to 1.64 g (0.043 mol) of lithium aluminum hydride suspended in 50 mL of anhydrous ether. The mixture was refluxed for 4.0 h, cooled, and quenched dropwise with 50 mL of concentrated sodium sulfate. The reaction mixture was extracted four times with ether. The organic extracts were combined, dried over sodium sulfate, and evaporated to yield 3.43 g (0.018 mol, 92%) of the amino alcohol **5**, identical in all respects with the sample prepared by procedure A.

Beckmann Rearrangements of the Anti Oximes 44 and 21A. *all-cis*-3-(Aminocarbomethoxy)-2,3,3a,6,7,8,9,9a-octahydro-5-oxo-4*H*-thieno[3,2-*b*]azocine (*Z*) (45). A sample of 0.35 g (1.35 mmol) of the anti oxime **44** was stirred mechanically at 100 °C in 10 g of PPA for 0.25 h. The reaction mixture was hydrolyzed with ice water and then partitioned between brine (methylene chloride/methanol) (9:1). The aqueous phase was further extracted with methylene chloride/methanol (9:1). The organic extracts were pooled, dried over sodium sulfate, and evaporated to leave a 160-mg residue. This material was chromatographed on two thick layer silica plates using ethyl acetate as the eluent. The Beckmann product was isolated at R_f 0.2 and afforded 0.069 g (0.27 mmol, 20%) of the 5,8-lactam **45**, mp 242–243 °C.

Using similar conditions, the anti oxime **21A** was converted to the *N*-methyl-5,8-lactam **33**, isolated as a colorless oil: IR (CH_2Cl_2) 3400 (N–H), 1710 (urethane), 1660 (lactam), 1450, 1320 cm^{-1}; NMR ($CDCl_3$) δ 6.30 (bd, 1 H, NH), 4.8–4.3 (m, 2 H, 2 CHN), 3.73 (s, 3 H, OCH_3), 3.6–2.9 (m, 3 H, $CHSCH_2$), 3.00 (s, 3 H, NCH_3), 2.38 (t, 2 H, CHCO), 2.1–1.2 (m, 6 H); mass spectrum *m/e* 272 (M^+), 240, 183 (base), 114, 99.

(±)-Biotin (6). A suspension of 90 mg (0.349 mmol) of the 5,8-lactam **45** in 15 mL of water was treated under argon with 3.0 g of barium hydroxide monohydrate. The reaction mixture was heated under reflux for 20 h and cooled, and the barium salts were filtered off and washed with water. The filtrate was concentrated, cooled to 0 °C, and treated with gaseous phosgene until the solution was acidic to congo red. The reaction mixture was allowed to stand for 1.5 h at 25 °C and then was evaporated to dryness. This residue, which is a mixture of biotin and inorganic salts, was taken up in 15 mL of dry methanol and treated with 2 drops of concentrated sulfuric acid. The mixture was heated under reflux for 1.5 h and then cooled to 25 °C. The inorganic salts were filtered off and washed with chloroform/methanol (4:1). The filtrate was partitioned between water/(chloroform/methanol) (4:1). The organic extract was dried over sodium sulfate and evaporated to yield 45 mg (0.174 mmol, 50%) of pure (±)-biotin methyl ester, mp 132–133 °C (ethyl acetate), identical in all respects with an authentic sample. The conversion of (±)-biotin methyl ester to (±)-biotin was accomplished according to the procedure of du Vigneaud.[23]

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References and Notes

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