A Thio-Diels−Alder Route to the Azocine Ring System. Total Synthesis of (±)-Otonecine

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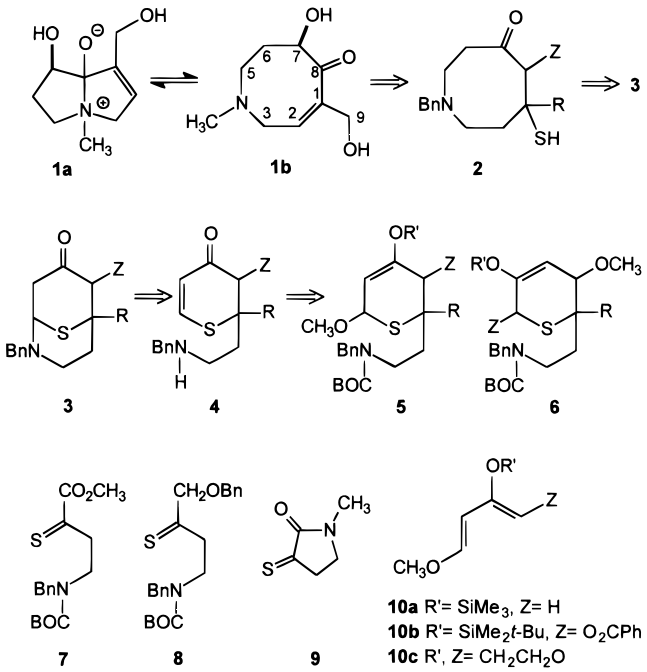
Received October 3, 1997

Abstract: A sulfur-based strategy for synthesis of otonecine is described. Key steps include the thio-Diels−Alder trapping of thioketone **8** by the Danishefsky diene, followed by conversion into the enone **27** and internal Michael addition to afford bicyclic thioaminal **28**. Selective C−S bond cleavage was achieved after conversion to alcohol **36** or its derivatives **38**, resulting in the azocine ring system. The successful route proceeded from **40b** via **49a** and sulfoxide elimination to the alkene **50a**. The final conversions to otonecine were accomplished via low-temperature osmylation of **56**, a crucial OsO_4-mediated oxidation of diol **58** to ketol **60**/**61**, and Burgess elimination to **68**/**69**. Several of the intermediates in late stages of the synthesis exist largely in the bicyclic valence bond tautomer form that is characteristic of the otonecine ring system.

We describe synthetic studies targeted at the eight-membered ring system of the pyrrolizidine alkaloid otonecine (**1**).[2] There has been some interest in the biological activity of this family of cytotoxic agents,[3] and a total synthesis of otonecine has been described by Yamada et al.[4] Our own investigation was initiated with the primary goal of exploring the thioketone cycloaddition approach to dihydrothiopyrans that could serve as precursors of functionalized azocine derivatives (Scheme 1). The plan depends on internal 1,4 addition of a tethered amine to an enone acceptor, as in the conversion of **4** into the thioaminal **3**, followed by controlled C−S cleavage and elimination. A similar approach was described in a preliminary report from our laboratory, but the desulfurization sequence was not sufficiently versatile for applications in the otonecine series.[5] Another goal of the current study was to explore functional group compatibility in the highly substituted azocine ring. Otonecine experiences strong interactions between basic nitrogen and ketone carbonyl,[2b] described by the equilibrium between the valence bond tautomers **1a** and **1b**. Other unusual transannular effects involving nitrogen were encountered, and some of these resulted in unexpected synthetic challenges in this deceptively simple ring system. Satisfactory solutions are reported for several problems encountered in the conversion of

Scheme 1



organosulfur precursors into the azocine ring system, as well as in the eventual elaboration into racemic otonecine.

Our plans for the synthesis of the dihydrothiopyranone **4** assumed that one of the thioketone dienophiles **7**−**9** might undergo [2 + 4] cycloaddition with the Danishefsky diene derivatives **10** to give adducts having the regiochemistry of **5**. At the outset of our work, there was little precedent for the regiochemistry of thioketone Diels−Alder reactions containing donor alkyl as well as π-acceptor substituents as in **7** or **9**,[6] and no confident prediction could be made whether these dienophiles would react with useful selectivity for the desired regioisomer **5** rather than **6**. On the other hand, a number of analogous reactions of thioaldehydes had been studied, and the general trends were shown to correlate with the FMO approximation.[7,8] Much of the data could be explained by assuming that regiochemistry is controlled by polarization in the thiocarbonyl

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(2) (a) Zhdanovich, E. S.; Men'shikov, G. P. *Zh. Obsch. Khim.* **1941**, *11*, 835. Leonard, N. J. *Rec. Chem. Prog.* **1956**, *17*, 243. Bürgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153. (b) Wunderlich, J. A. *Acta Crystallogr.* **1967**, *23*, 846. Culvenor, C. C. J.; O'Donovan, G. M.; Smith, L. W. *Aust. J. Chem.* **1967**, *20*, 801. Bernbaum, G. I. *J. Am. Chem. Soc.* **1974**, *96*, 6165. Peřez-Salazar, A.; Cano, F. H.; Fayos, J.; Martinez-Carrera, S.; Garcia-Blanco, S. *Acta Crystallogr.* **1977**, *B33*, 3525.

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S0002-7863(97)03464-1 CCC: $15.00
Published on Web 04/02/1998

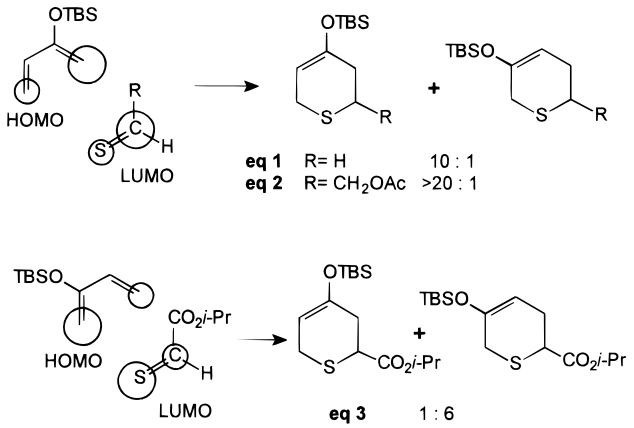
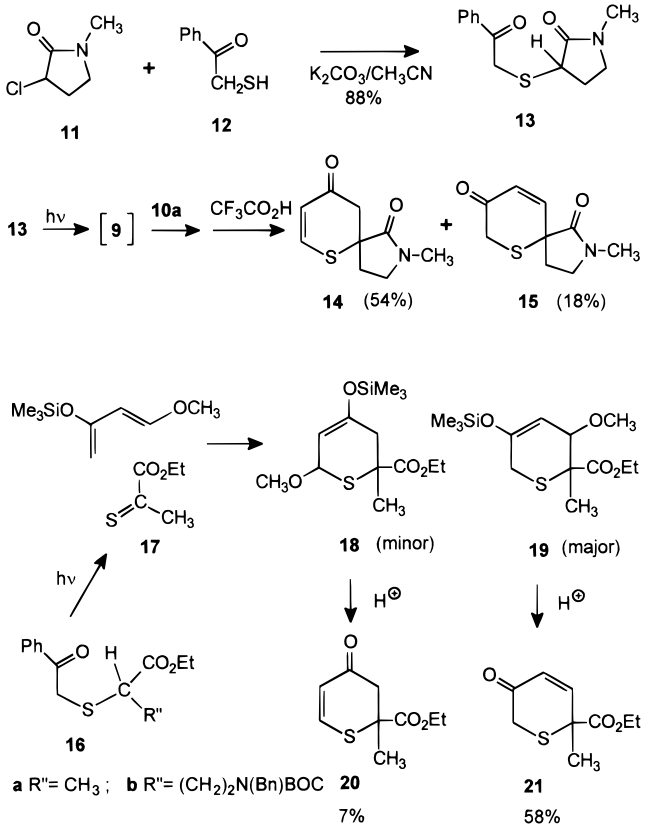


Figure 1. Thioaldehyde cycloaddition regiochemistry.

LUMO and diene HOMO.[8b] Carbon has the larger LUMO coefficient in the C═S bond of thioformaldehyde, and LUMO polarization is somewhat enhanced by replacing a thioformyl hydrogen with a saturated alkyl group. The Diels−Alder reaction of this class of thioaldehyde dienophiles with unsymmetrical dienes follows the regiochemistry shown in eqs 1 and 2 (Figure 1) and corresponds to preferred interaction of thioaldehyde carbon with the enol ether terminus of the unsymmetrical diene, the site that has the larger HOMO coefficient. On the other hand, the selectivity pattern is inverted for thioaldehydes containing an unsaturated acceptor group at the α-carbon (eq 3). In this case, LUMO polarization places the larger coefficient on thioaldehyde sulfur.

On the basis of the above considerations, thioketones such as **7** might be expected to react with low selectivity because the ester and alkyl substituents have opposing directive effects in the thioaldehyde examples. On the other hand, steric factors should work against the undesired regiochemistry **6**, depending on the nature of the substituent Z, and might promote the desired selectivity for **5**. The alternative of using an unactivated thioketone **8** would provide a more predictable solution to the problem of controlling regiochemistry according to the pattern of eq 1. However, lower dienophilic reactivity was expected in the absence of an unsaturated electron acceptor group and there was the added risk of competing thioenolization. A third thioketone (**9**) was therefore included in the preliminary survey of options. The relatively electron-rich lactam carbonyl group should be less likely to dominate the regiochemistry of cycloaddition but might still provide a reasonable level of activation for the cycloaddition by lowering the thioketone LUMO energy level compared to that of the saturated analogue **8**. Our study began with a comparison of the regiochemical preferences for these dienophiles.

Scheme 2



Results and Discussion

Lactam thioketone **9** was the most accessible thioketone in the series **7**−**9** and was generated following the thioaldehyde precedents by the photochemical cleavage of the corresponding phenacyl sulfide **13** (Scheme 2). The latter was easily made from phenacylmercaptan **12** and α-chloro-*N*-methylbutyrolactam **11** using potassium carbonate as the base. Sun lamp irradiation of **13** in the presence of the Danishefsky diene **10a**[9] followed by workup with trifluoroacetic acid gave two enones **14** and **15** in 72% yield. The major isomer **14** was determined to have the desired regiochemistry, based on characteristic chemical shift data for the enone protons (**14**, δ 7.34, 6.23 ppm; **15**, δ 6.63, 6.13 ppm). However, the isomer ratio (3:1 **14**:**15**) was deemed too low for an early step in the intended synthetic application. Another concern was that regiochemical control might be lost if it became necessary to use more highly oxygenated Danishefsky diene analogues such as **10b** or **10c** to introduce the C-8 oxygen of otonecine. These dienes contain terminal substituents with opposing directive effects.

The modest regiochemical preference in the reaction of **9** with **10a** suggested that a scheme based on the ester thioketone **7** would not be viable. The corresponding phenacyl sulfide (**16b**) was relatively difficult to make, so the regiochemistry issue was probed in a model study using **16a** for generation of methyl thionopyruvate **17**. Larsen et al. have reported several examples of the reaction of **17** with unsymmetrical dienes using a different method to generate the thionopyruvate,[10] and a relevant [2 + 4] cycloaddition of the arylthionoglyoxylate *m*-$CF_3C_6H_4C(S)CO_2$-Me with 2-(trimethylsiloxy)butadiene is also known.[6c] Our regiochemical results are consistent with these earlier reports.

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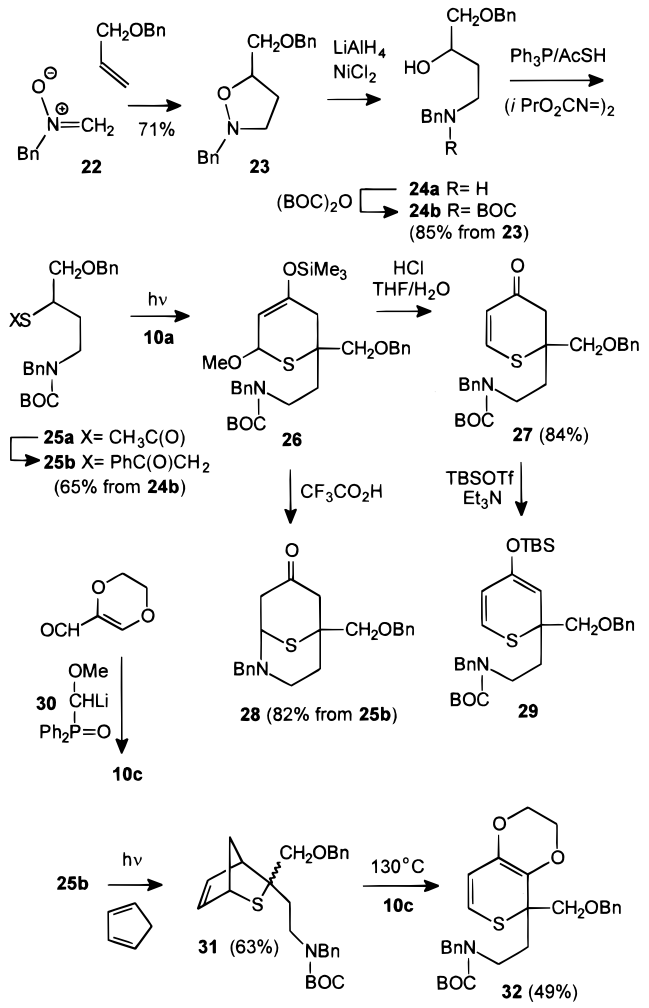
(9) Danishefsky, S.; Kitahara, T.; Schuda, P. F. *Org. Synth.* **1983**, *61*, 147.

(10) Larsen, S. D.; Fisher, P. V.; Libby, B. E.; Jensen, R. M.; Mizsak, S. A.; Watt, W.; Ronk, W. R.; Hill, S. T. *J. Org. Chem.* **1996**, *61*, 4725.

Scheme 3



Thus, sun lamp irradiation of **16a** in the presence of the Danishefsky diene (**10a**) afforded a mixture of labile adducts **18** + **19** (multiple CH_3O signals detected by ^1H NMR assay of the crude product). Acidic workup gave two enones **20** and **21** in 65% combined yield based on **16a**. The minor product (7% isolated; **20**) has the characteristic downfield ^1H NMR chemical shifts for the vinylic hydrogens of the desired isomer (δ 7.29, 6.17 ppm in **20**; δ 6.74, 6.05 in **21**). In FMO terminology, the preference for **21** indicates that the LUMO of **17** has the larger coefficient at sulfur, similar to the thioaldehyde example of eq 3, while the polarization in **9** is inverted and resembles that of thioformaldehyde. On the basis of the above findings and the literature analogies,[10,6c] there was little reason to expect useful results with the more complex ester thione **7**.

The unactivated thione **8** was the logical alternative for control of cycloaddition regiochemistry, and studies were initiated to determine whether **8** can be intercepted in practical yield. A synthesis of the phenacyl sulfide precursor of **8** is outlined in Scheme 3. Thus, reaction of allyl benzyl ether with nitrone **22** (from *N*-benzylhydroxylamine and formaldehyde)[11] gave the [2 + 3] cycloadduct **23** (71%) and reductive N−O cleavage using $LiAlH_4/NiCl_2$[12] afforded the alcohol **24a**. After conventional protection and Mitsunobu conversion to the thioacetate **25a**,[13] the corresponding mercaptan was generated using methanolic potassium carbonate and was trapped in situ with phenacyl chloride to afford the key phenacyl sulfide **25b** (65% overall yield from **24a**). Initial experiments to generate thione **8** by photolytic fragmentation of **25b** succeeded, but thione trapping with the Danishefsky diene was difficult to control and complications were encountered upon attempted scale-up. However, thioenolization of **8** was not the problem, despite our initial concerns. Instead, the reaction was found to be critically dependent on the quality of solvents and reagents in the photolysis step. Careful deoxygenation of the benzene solvent was the key to obtaining good yields on gram scale, and it was also important to use a large excess of the Danishefsky diene (ca. 20:1 weight ratio, **10a**:**25b**). When these precautions were taken, the desired adduct **26** was formed, and distillation of volatiles followed by brief treatment with aqueous HCl gave the dihydropyranone **27** in 84% overall yield. Excess Danishefsky diene **10a** was recovered by distillation and was recycled multiple times in the photochemical step without affecting the yield of thioketone trapping products. None of the regioisomeric cycloadduct was detected in the trapping experiments of **8** with **10a**, and an acceptable solution to the regiochemistry problem was in hand. It was also found that crude **26** could be converted directly into the bicyclic thioaminal **28** by treatment with CF_3CO_2H, 82% based on **25b** (77% after recrystallization). This procedure is suitable for multigram scale experiments and involves deprotection of the initially formed **27** followed by spontaneous cyclization of the resulting N-benzylamine intermediate during workup.

The next problem was to determine the best stage for introduction of the C-8 oxygen functionality of otonecine. Experiments designed to introduce oxygen via enolate oxidation from **27** failed due to competing β-elimination of sulfur, but conversion to the enol silane **29** was possible using TBSOTf/Et_3N (TBSOTf = *tert*-butyldimethylsilyl triflate). However, attempts to oxidize this substrate were foiled by the presence of the relatively unhindered and easily oxidized vinyl sulfide subunit. We therefore explored the possibility of thioketone trapping using the more highly oxygenated dienes **10b** and **10c**. Either of these structures might afford analogues of **4** with Z = oxygen if the regiochemistry of cycloaddition could be controlled. Attempts to use **10b**[14] in place of **10a** in the photolytic generation of thioketone **8** were frustrated because this diene proved to be unstable to sun lamp irradiation. The cyclic analogue **10c** was easily made by reaction of 2-formyl-1,4-dioxane[15] with the Horner−Emmons reagent **30**[16] as a mixture of *E*/*Z* isomers (63% isolated), but it too decomposed upon photolysis. This prompted an investigation of thermal generation[7] of the thioketone **8** from the cyclopentadiene adduct **31** (available in 63% yield from the photolysis of **25b** in the presence of excess cyclopentadiene). When **31** was heated with excess **10c** at 130 °C, the reaction produced one major cycloadduct that was tentatively assigned the pyran structure **32** (49% isolated) on the basis of ^1H and ^{13}C NMR chemical shift data and the structural analogy to **29**. However, attempts to hydrolyze **32** produced complex mixtures, and oxidation chemistry was not promising in view of the experience with **29**. These problems were not unexpected, and several alternatives had been considered where the C-8 oxidation would be performed after removal of sulfur. Efficient routes could be

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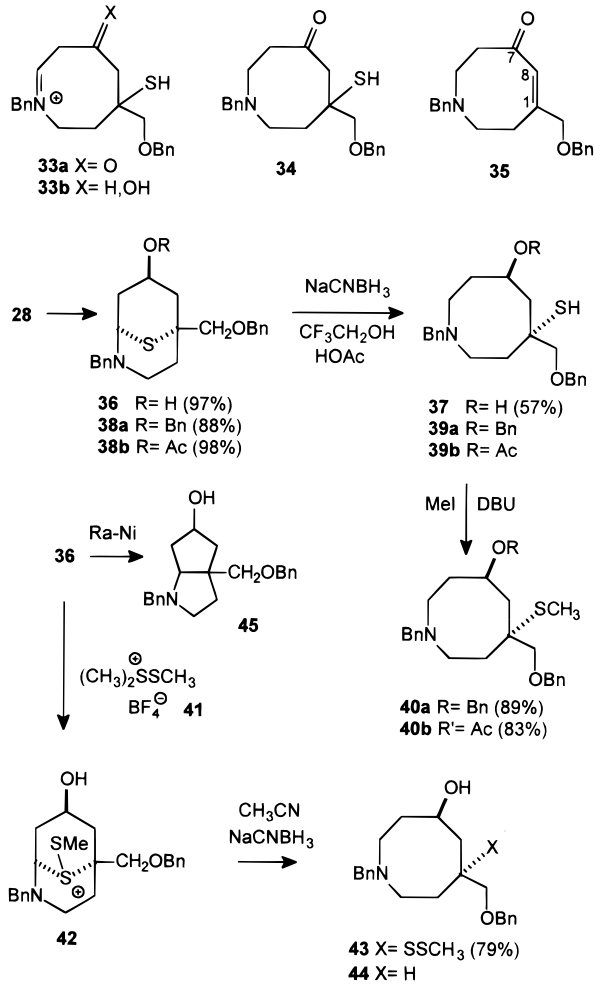
(12) Tufariello, J. J.; Meckler, H.; Pushpananda, K.; Senaratne, A. *Tetrahedron* **1985**, *41*, 3447.
(13) Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119.
(14) Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 1269.
(15) Shostakovskii, M. F.; Kuznetsov, N. V.; Che-min, Y. *Dokl. Akad. Nauk SSSR* **1961**, *9*, 1570.
(16) Warren, S.; Earnshaw, C.; Wallis, C. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3099.

Scheme 4



envisioned from **28** if thioaminal C−S cleavage to **34** (Scheme 4) and subsequent sulfur elimination could be controlled to selectively form the unsaturated ketone **35**.

Reductive C−S bond cleavage from **28** to **34** proved to be a difficult problem. A number of literature desulfurization procedures including nickel boride, Raney Ni, and triphenyltin hydride/2,2′-azobisisobutyronitrile (AIBN) failed to give the desired azocine product. Sodium cyanoborohydride treatment did produce small amounts of a mercaptan alcohol (**37**), but **34** was never detected as an intermediate. Control experiments established that the reductive C−S cleavage is considerably faster after the ketone has been reduced to the alcohol **36**. This rate difference is probably due to the unfavorable dipole interaction in the keto iminium salt **33a** derived from **28** compared to the alcohol iminium salt **33b**. Efficient reductive trapping of **33b** by cyanoborohydride is essential for the conversion to the azocine mercaptan **37**. Thus, treatment of **28** with lithium tri(*sec*-butyl)borohydride produced **36** as a single diastereomer (relative stereochemistry is shown; racemic product), with stereochemistry tentatively assigned assuming least hindered attack syn to the compact sulfur bridge. Subsequent reduction of **36** with $NaBH_3CN$ gave **37** in 57% yield. For preparative purposes, the best results were obtained from **36** after O-benzylation ($NaH,PhCH_2Br$) or O-acetylation [Ac_2O/Et_3N/DMAP(4-(dimethylamino)pyridine)]. The resulting benzyl ether **38a** or acetate **38b** was reduced cleanly using $NaBH_3CN$ in trifluoroethanol−acetic acid, and S-methylation with CH_3I/DBU (DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene) produced the azocine methyl sulfides **40a** and **40b**, respectively, in 78−80% overall yield from **36**.

Several additional techniques for thioaminal desulfurization were explored, and two of these gave interesting results. Caserio et al. have reported a method for hydrolysis of thioaminals using the dimethyl disulfide derived sulfonium salt **41** as an electrophilic sulfenylating agent that selectively activates sulfur in the presence of basic nitrogen.[17] Attempts to use this method to activate **28** for cyanoborohydride reduction resulted in undesired C−S elimination to an enamine and further sulfenylation,[5] but the corresponding experiment with alcohol **36** produced an intermediate salt **42** that was converted into the azocine disulfide **43** (79%) by $NaBH_3CN$ reduction in acetonitrile. This potentially useful conversion was not exploited because elimination of sulfur from derivatives of **40** using conventional methods proved to be more efficient than from **43**. However, the desired selectivity for sulfur activation was demonstrated and efficient reductive thioaminal C−S cleavage was observed. Another result worth mentioning was encountered during efforts to control Raney nickel desulfurizations. These experiments afforded complex mixtures from **28**, but an attempt to desulfurize the alcohol **36** resulted in a sulfur-free product with promising changes in the ^1H NMR spectrum. However, exact mass determination established that the product has a molecular weight 2 amu below that expected for the azocine **44**. This observation was not pursued, but the tentative structure **45** (two diastereomers according to ^1H NMR) is in accord with the absence of vinylic hydrogen signals in the NMR spectrum.[18]

Elimination of sulfur was the next obstacle. Selective conversion of **40a** or **40b** to the sulfoxides **46a** or **46b** (Scheme 5) was readily achieved using the tetrabutylammonium Oxone (TBA Oxone) reagent[19] without interference by basic amine nitrogen. Subsequent sulfoxide elimination in refluxing xylene produced mixtures of alkene regioisomers, ca. 2.5−3:1 **47**:**48**. On the other hand, a single dominant (>20:1) isomer **50a** (89%) was obtained starting from the *N*-benzyloxycarbonyl (*N*-Cbz) derivative **49a** (from **40a** by treatment with $ClCO_2CH_2C_6H_5$)[21] in a similar oxidation−thermolysis sequence. The reasons for this dramatic improvement in selectivity may be related to electrostatic effects in the transition state for sulfoxide elimination,[20] but a detailed rationale is not warranted because the sulfoxide stereochemistry is not known.

Initial experiments for introduction of the C-8 oxygen of otonecine focused on the *m*-chloroperoxybenzoic acid (MCPBA) or OsO_4 oxidations of the acetoxy alkene **50b**, prepared from **47b** and $ClCO_2CH_2C_6H_5$. It was anticipated that the tertiary C−O bond in the epoxide **51** or the diol **52** might undergo elimination to the desired trisubstituted alkene **53** corresponding to the substitution pattern of otonecine. However, exposure of **51** to conditions for epoxide elimination afforded complex product mixtures. In one of the more promising experiments, treatment of **51** with the TMSOTf/2,6-lutidine/DBU reagent[22] gave 29% of an enal (**55**) as the major product, presumably formed via the exocyclic enol ether **54**. Similarly, **55** was obtained along with unidentified products from the diol **52** (1:1

(17) Caserio, M. C.; Kim, J. K.; Souma, Y.; Beutow, N.; Ibbeson, C. *J. Org. Chem.* **1989**, *54*, 1714.

(18) Analogies: Pettit, G. R.; van Tamelen, E. E. *Org. React. (N.Y.)* **1962**, *12*, 356. Guziec, F.; Sanfilippo, L. J. *Tetrahedron* **1988**, *44*, 6241. de Mayo, P.; Nicholson, A. A. *Isr. J. Chem.* **1972**, *10*, 341. Omote, Y.; Yoshioka, M.; Yamada, K.; Sugiyama, N. *J. Org. Chem.* **1967**, *32*, 3676.

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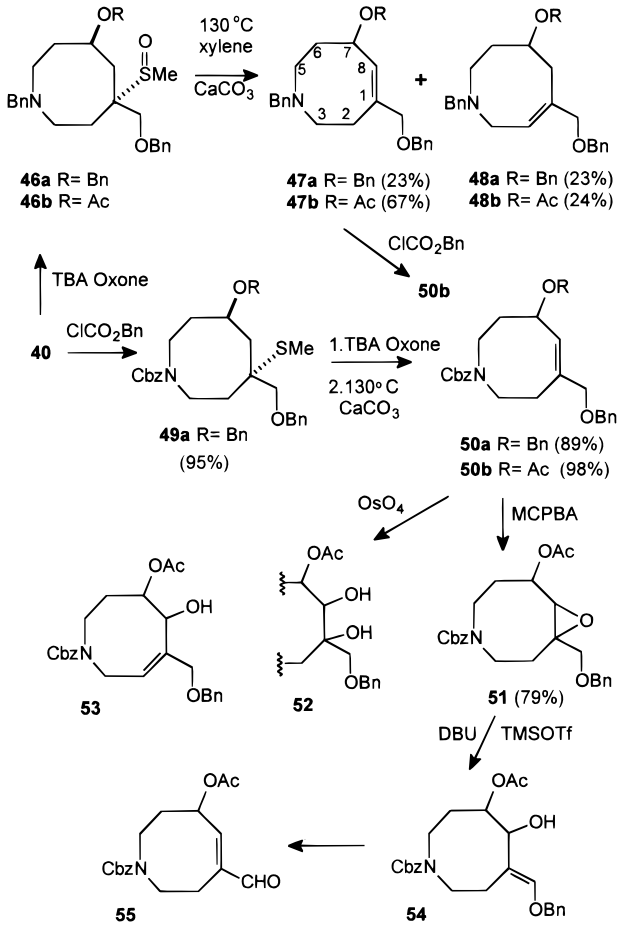
(21) Cooley, J. H.; Evain, E. J. *Synthesis* **1989**, 1.

(22) Noyori, R.; Murata, S.; Suzuki, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 247.

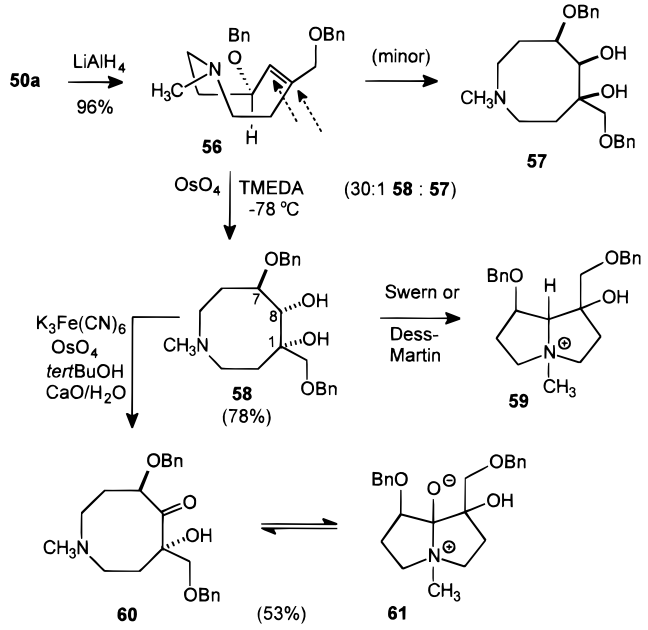
Scheme 5



diastereomer mixture from catalytic osmylation of **50b**) upon attempted dehydration of the tertiary alcohol with the Burgess reagent.[23] Good results were eventually obtained after conversion of the *N*-Cbz group to the otonecine *N*-methyl substitution pattern by $LiAlH_4$ reduction and introduction of the C-8 carbonyl group of otonecine. This sequence was conveniently performed in the *O*-benzyl series starting from **50a** (Scheme 6). The corresponding *N*-methyl derivative **56** was obtained in 96% yield upon treatment of **50a** with $LiAlH_4$, and the necessary oxidation pattern was introduced using an osmylation−elimination sequence as described below.

Osmylation of **56** using stoichiometric OsO_4 at room temperature gave an 18:1 mixture of **58**:**57**, but the reaction also produced a side product having an unusual downfield signal in the ^1H NMR spectrum at δ 5.07 ppm and lacking the C-3 NCH_2 signals of **56**.[24a] Fortunately, the complication could be avoided under TMEDA-accelerated osmylation conditions at −78 °C.[24b]

Scheme 6



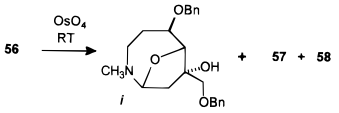
This procedure gave an improved 30:1 ratio of **58**:**57** (81%), a result that acquired special significance later, when it was found that only the major diastereomer **58** is useful for the eventual oxidation at C-8 as well as regiospecific elimination of the tertiary C-1 OH group. The stereochemistry of **58** is assigned by comparison of the H−C-7−C-8−H coupling constants in the corresponding acetonides (acetonide from **58**, $J_{7,8} = 7.5$ Hz; acetonide from **57**, $J_{7,8} < 2$ Hz) and by evaluation of the relevant conformational options. The stereochemistry also corresponds to that expected from the precedented transition state where OsO_4 interacts with the more available alkene face of a local conformer having the allylic ether substituent in a pseudoequatorial orientation as shown.[25] The alternative of internal delivery of OsO_4 via coordination to the ring nitrogen is conceivable, but this would be unlikely under the TMEDA-accelerated conditions because the combination of alkene and bidentate amine ligands occupies the available coordination sites at osmium in the transition state.[26] The stereochemical assignment is not critical because neither C-1 nor C-8 is stereogenic at the otonecine stage, but a knowledge of the geometry of **58** was helpful in understanding subsequent transformations.

It was now necessary to oxidize the secondary C-8 hydroxyl of **58**. The oxidant must tolerate basic nitrogen and must oxidize the diol to a ketol without C-1−C-8 bond cleavage, a situation where Dess−Martin or Swern oxidations are generally used. However, attempts to oxidize either diol diastereomer **58** or **57** using these methods did not result in loss of the C-8 hydrogen. Instead, rapid conversion was observed to polar products having the *N*-methyl signal at δ ca. 3.2 ppm, compared to a shift of δ 2.33 ppm in the starting diol. The formation of an ammonium salt **59** by transannular nitrogen participation appears likely and is supported by molecular weight determination using FAB mass spectroscopy.

In view of the limitations imposed by substrate functionality, an OsO_4-mediated oxidation of the diol **58** to the ketol **60** was investigated. Osmium tetroxide had already been used successfully to introduce the diol functionality, and Mehrotra et

(23) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26. Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A.; Williams, W. M. *Org. Synth.* **1977**, *56*, 40.

(24) (a) Structure **i** is tentatively assigned to the major sideproduct, based on ^1H NMR data indicating a hemiaminal $CHCH_2$ ABX pattern [δ 5.06 (1H, dd, J = 8.7, 4.5 Hz), 2.08 (1H, dd, 15.3, 8.7 Hz), 1.98 (1H, 15.3, 4.5 Hz)].

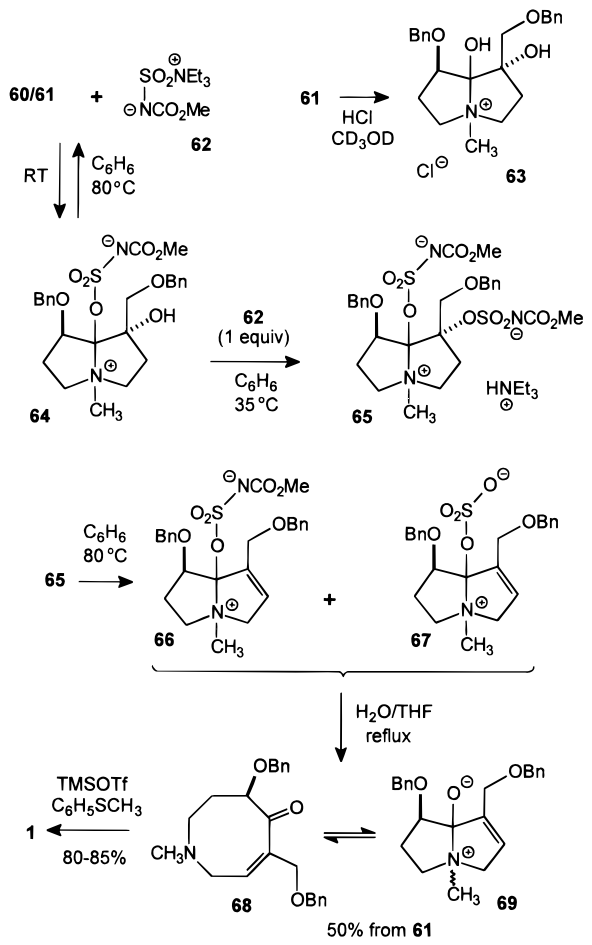


(b) The low-temperature osmylation procedure was based on the following precedent where a chiral diamine is the accelerating ligand: Tomioka, K.; Nakajuma, M.; Koga, K. *J. Am. Chem. Soc.* **1987**, *109*, 6213.

(25) Vedejs, E.; Dent, W. H., III.; Gapinski, D. M.; McClure, C. K. *J. Am. Chem. Soc.* **1987**, *109*, 5437.

(26) Corey, E. J.; Sarshar, S.; Azimioara, Newbold, R. C.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 7851.

Scheme 7



al. have reported diol oxidations using $K_3Fe(CN)_6$ and catalytic OsO_4 under strongly basic conditions.[27] Related osmium reagents have also been used to convert alkenes directly into ketols.[28] Attempts to follow the latter precedent for the conversion of the alkene **56** into **60** gave low yields of ketol at room temperature, but this approach was not explored in detail because of concerns about oxidation α to amine nitrogen[24a] as well as the possibility of diastereomer formation at the higher temperature. On the other hand, a reagent made by the substitution of CaO for K_2CO_3 in the Yamamoto conditions for catalytic olefin hydroxylation with $K_3Fe(CN)_6$ as the stoichiometric oxidant[29] converted the diol **58** to the ketol **60** in modest, yet functional 53% yield at room temperature. Among the oxidation conditions investigated, the osmium-based methods were the only ones to produce detectable quantities of **60**.

Ketol **60** is the first intermediate in the synthetic route that contains basic azocine nitrogen as well as the otonecine carbonyl oxidation state at C-8. A similar environment is responsible for strong transannular interactions in otonecine (represented by the equilibrium of **1a** with **1b** in Scheme 1),[2b] resulting in unusual spectroscopic properties. Analogous behavior was seen in **60**, including broad carbonyl absorptions in the infrared spectrum. A carbonyl carbon was also apparent at δ 200 ppm in the ^{13}C NMR spectrum in CD_3CN, suggesting that both **60** and **61** are present (Scheme 7). The ^1H NMR spectrum was temperature dependent, and several signals including the ring protons between δ 1.6−2.8 ppm were extensively broadened at room temperature. The signals sharpened upon warming or upon addition of HCl to the NMR sample. In the latter case, some of the ^1H NMR and ^{13}C chemical shifts were also displaced substantially to lower field due to conversion into the bicyclic **63**, and a typical ammonium *N*-methyl signal was observed at δ 2.89 ppm in CD_3OH/HCl. Under these conditions, the carbonyl carbon in the ^{13}C spectrum was replaced by a new singlet at δ 117.5 ppm, corresponding to the bridgehead carbon in **63**. Related transannular bonding interactions proved to be important in subsequent chemistry.

The dehydration of the ketol **60/61** to dibenzylotonecine (**68/69**) was especially interesting. Treatment of **60/61** with the Burgess reagent ($Et_3NSO_2NCO_2Me$, **62**)[23] in C_6D_6 at room temperature produced changes in the chemical shift of the CO_2-CH_3 subunit derived from **62** as well as a downfield shift of the *N*-methyl group consistent with the conversion of **60/61** into a bicyclic structure having a formal positive charge at nitrogen. The 1:1 adduct structure **64** is consistent with this evidence and with the presence of a quaternary carbon signal at 116.5 ppm in the ^{13}C spectrum. Upon heating to 80 °C, **64** reverted to the starting ketol **60/61** without detectable elimination to alkene products. In a separate experiment, the solution containing the initial 1:1 adduct **64** and excess Burgess reagent was heated to 35−40 °C, resulting in the slow formation of a 2:1 adduct believed to have the structure **65**. Heating **65** to 80 °C followed by hydrolysis in refluxing aqueous THF gave dibenzyl otonecine **68/69** in 50% yield. Further investigation revealed that the crude product prior to hydrolysis contains four distinct precursors of the desired **68/69**. Chromatographic separation afforded samples that could be partially characterized by ^1H NMR, IR, and low-resolution FAB mass spectroscopy. Two of these products are assigned the diastereomeric sulfate structures **67** (two cis-fused diastereomers) because the same NMR signals were produced by treating dibenzylotonecine **68/69** with the pyridine−SO_3 complex. The other two products contain methoxy signals in the ^1H NMR spectrum as well as other signals that are consistent with the bicyclic valence bond tautomer form of the otonecine nucleus, as in the sulfamate structure **66** (pair of diastereomers). The molecular weights corresponding to **66** and **67** were detected in the corresponding diastereomer mixtures using FAB mass spectroscopy.

Adduct **64** cannot easily undergo Burgess elimination via ion pair formation due to the presence of positively charged nitrogen, but elimination is possible from the bis-adduct **67**. The elimination precursors as well as the products are in the bicyclic form, and the same is true of dibenzylotonecine **68/69** when the ^{13}C NMR spectrum is recorded in acidic methanol (δ 118.6 ppm for C-8). Under neutral conditions, the ^1H NMR spectrum of **68/69** shows sharper signals at room temperature compared to **60/61** and warming to 55 °C results only in a relatively small improvement in resolution. Presumably, two diastereomers of the bicyclic form interconvert under the higher temperature conditions in **68/69** as well as **60/61**. The ^{13}C spectrum ($CDCl_3$) contains no clear carbonyl signal in the region between δ 195 and 205 ppm, suggesting that the bicyclic valence bond tautomer **69** is dominant in this case.

Deprotection of dibenzyl otonecine **68/69** was best achieved under Lewis acid catalyzed conditions for nucleophilic debenzylation. Treatment of **68/69** with TMSOTf in the presence of thioanisole in acetonitrile at 0 °C gave crude otonecine as the triflic acid salt and neutralization using ion exchange chromatography resulted in otonecine free base. The product (ca. 80%

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(28) VanRheenen, V.; Kelly, R. C.; Chan, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973. Lohray, B. B.; Bhushan, V.; Kumar, R. K. *J. Org. Chem.* **1994**, *59*, 1375.

(29) Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766.

isolated) was identified by comparison of NMR chemical shifts with those of authentic material.

Conclusion. Access to the otonecine ring system has been demonstrated by a combination of thioketone Diels−Alder addition and desulfurization technology. The sulfur-free azocine **50a** was produced in 15 steps, 20% overall yield from benzylhydroxylamine and allyl benzyl ether, the starting materials for Scheme 3. The final steps to otonecine followed a more conventional strategy, but they proved to be more difficult because of the challenging oxidation−elimination sequence (ca. 30% yield from **50a** to racemic otonecine **1**, 5 steps). Regiochemical problems in the thioketone Diels−Alder step were solved by using the nonactivated thione **8**, and the cycloaddition was surprisingly efficient. Methods for selective C−S bond cleavage at the thioaminal stage were developed, and regiochemical complications in the sulfur elimination step were solved by modifying the electronic environment at azocine nitrogen. All of the chemistry involving intermediates with C-8 at the carbonyl oxidation state (Scheme 6) was dominated by the transannular interactions between C-8 and the basic ring nitrogen that is characteristic of the otonecine ring sytem.[2b] These interactions complicate the use of electrophilic reagents because the substrate is likely to exist in the cationic, bicyclic valence bond tautomer form. Nevertheless, it was possible to manipulate the molecule under electrophilic conditions at several stages, including the key oxidation to **60/61**, the Burgess elimination to **68/69**, and the final deprotection to otonecine **1**.

Experimental Section

General Procedures. Flash chromatography on ammonia-impregnated silica gel (designated in the Experimental Section by silica gel-NH_3) was performed by packing a dry column with silica gel (EM Silica Gel 60 230−400 mesh) and eluting with 4% NH_4OH in THF until ammonia vapors could be detected in the eluent (wet pH paper). The column was then equilibrated with NH_4OH-saturated $CHCl_3$, followed by the chromatography solvent. High- and low-resolution FAB mass spectra were obtained on a VG Analytical AutoSpec using nitrobenzyl alcohol as matrix (high resolution, PEG standard, 30−35 KV Cs ions (SIMS), 10K resolution).

2-Benzyl-4-(benzyloxymethyl)oxazolidine (23). Nitrone **22**[11] (11.38 g, 84.2 mmol) and allyl benzyl ether[31] (11.16 g, 75.3 mmol) were dissolved in 100 mL of benzene and heated to reflux for 25 h. Concentration followed by distillation to remove excess allyl benzyl ether gave crude isoxazolidine **23**. The residue was purified by column chromatography on silica gel (4.5 cm × 45 cm), 1:1 EtOAc/hexane eluent, to give 15.9 g (74%) of pure **23**: analytical TLC on silica gel, 1:1 EtOAc/hexane, $R_f = 0.33$; molecular ion (M^+) calcd for $C_{18}H_{21}NO_2$ 283.15723, found $m/e = 283.1549$, error = 8 ppm, base peak = 91 amu; IR ($CDCl_3$, cm^{-1}) 2875 C−H, 1100 C−O, 1660 C═O; 200 MHz NMR ($CDCl_3$, ppm) δ 7.58−7.12 (10H, m), 4.59 (2H, s), 4.50−4.26 (1H, m), 3.71−2.22 (2H, m), 3.68−3.41 (2H, m), 3.29−2.55 (2H, m), 2.50−2.23 (1H, m), 2.16−1.93 (1H, m).

Amino Alcohol 24a. The procedure of Tufariello was used.[12] Isoxazolidine **23** (16 mg, 56 mmol) and nickel(II) chloride (20.1 g, 155 mmol) were stirred in THF at 0 °C. Lithium aluminum hydride (Aldrich; 6 g, 155 mmol) was added in portions, and the mixture was warmed slowly to room temperature. After 10 h of stirring, anhydrous potassium carbonate was added, and the solution was stirred for 0.5 h. The mixture was filtered through a pad of Celite and washed extensively with ether. Drying ($MgSO_4$) and concentration gave the amino alcohol **24a** (16 g, 72%) which was used without further purification: M^+ calcd for $C_{18}H_{23}NO_2$ 285.17288, found $m/e = 285.1673$, base peak = 91 amu; IR ($CDCl_3$, cm^{-1}) 3585 O−H, 3220 N−H; 200 MHz NMR ($CDCl_3$, ppm) δ 7.36−7.24 (10H, m), 4.56 (2H, s), 4.08−3.96 (1H, m), 3.78 (2H, AB q, $J_{AB} = 13.1$ Hz), 3.44 (2H, dd, $J = 3.7$, 1.8 Hz), 3.05−2.74 (2H, m), 1.80−1.60 (2H, m).

N-Protected Alcohol 24b. Di-*tert*-butyl dicarbonate (Aldrich; 3.34 g, 15.3 mmol) was added to a solution of amino alcohol **24a** (3.53 g, 12.4 mmol) and anhydrous potassium carbonate (2.6 g, 18.5 mmol) in 75 mL of 2:1 dioxane/water. This was allowed to stir overnight. The mixture was concentrated to remove dioxane, and the solution was saturated with sodium chloride. Extraction with ethyl acetate followed by drying ($MgSO_4$) gave crude **24b**. The residue was purified by flash chromatography on silica gel (3 cm × 45 cm), 1:1 EtOAc/hexane eluent, to give 4.73 g (99%) of **24b**: analytical TLC on silica gel, 1:1 EtOAc/hexane, $R_f = 0.52$; M^+ calcd for $C_{19}H_{23}NO_4$ 329.16266, found m/e = 329.1617 (M − 56), error = 3 ppm, base peak = 91 amu; IR ($CDCl_3$, cm^{-1}) 3600 O−H, 3440 O−H; 200 MHz NMR ($CDCl_3$, ppm) δ 7.48−7.13 (10H, br m), 4.70−4.15 (4H, br m), 3.93−3.01 (6H, br m), 1.85−1.47 (2H, br m), 1.47 (9H, br s).

Thiol Acetate 25a. The procedure of Volante was used.[13] Diisopropylazodicarboxylate (Aldrich; 1.5 mL, 7.4 mmol) was added to triphenylphosphine (Aldrich; 1.95 g, 7.46 mmol) in 35 mL of THF. A white precipitate formed after several minutes. After 1 h, a mixture of alcohol **24b** (1.42 g, 3.70 mmol) and thiolacetic acid (Aldrich; 0.5 mL, 7.40 mmol) in 15 mL of THF was added dropwise, and the resulting solution was allowed to stir overnight. The resulting clear yellow solution was concentrated, the residue was diluted in ether to precipitate triphenylphosphine oxide and filtered, and the solution was then concentrated to an oil. Flash chromatography on silica gel (3 cm × 20 cm), 1:4 EtOAc/hexane eluent, gave thiolacetate **25a** (1.7 g) contaminated with diisopropylazodicarboxylate byproducts. Pure individual fractions were collected for characterization. The crude thiolacetate **25a** was routinely used as is in the next step. For **25**: analytical TLC on silica gel, 1:4 EtOAc/hexane, $R_f = 0.43$; M^+ calcd for $C_{25}H_{33}NO_4S$ 443.21307, found $m/e = 387.1531$ (M − 56); calcd for $C_{21}H_{25}NO_4S$ 387.15045, error = 7 ppm, base peak = 91 amu; IR ($CDCl_3$, cm^{-1}) 1685 C═O; 200 MHz NMR ($CDCl_3$, ppm) δ 7.35−7.22 (10H, m), 4.55 (2H, s), 4.50−4.43 (2H, m), 3.80−2.90 (5H, m), 2.34 (3H, s), 2.26−1.98 (1H, m), 1.95−1.70 (1H, m), 1.50 (9H, s).

Phenacyl Sulfide 25b. The crude thiolacetate **25a** (1.7 g) was dissolved in 20 mL of methanol and cooled to 0 °C. Anhydrous potassium carbonate (1.31 g, 9.50 mmol) followed by α-chloroacetophenone (Aldrich; 715 mg, 4.63 mmol) in 25 mL of methanol was added. After stirring overnight, the mixture was concentrated and diluted in methylene chloride, washed once with saturated $NaHCO_3$, and dried ($MgSO_4$). After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (3 cm × 45 cm), gradient elution using 50 mL of 3:17, 50 mL of 1:5, and 200 mL of 3:7 EtOAc/hexane as the eluents, to give 1.25 g (65% from **24b**) of **25b** as an oil: analytical TLC on silica gel, 1:4 EtOAc/hexane, R_f = 0.35; M^+ calcd for $C_{31}H_{37}NO_4S$ 519.24432, found $m/e = 446.1803$ (M − 73); calcd for $C_{27}H_{28}NO_3S$ 446.17902, error = 3 ppm, base peak = 91 amu; IR (CH_2Cl_2, cm^{-1}) 1684 C═O, 3595 N−H, 3475 O−H; 200 MHz NMR ($CDCl_3$, ppm) δ 7.99−7.15 (15H, m), 4.49 (2H, s), 4.48−4.25 (2H, m), 3.98−3.75 (2H, br m), 3.66−3.05 (4H, br m), 3.00−2.60 (1H, br m), 2.15−1.85 (1H, br m), 1.80−1.50 (1H, br m), 1.47 (9H, s), 2.30−2.17 (1H, br m), 2.00−1.80 (1H, br m), 1.47 (9H, br s).

Photolysis of 25b with Danishefsky's Diene: Preparation of 27 and 28 (5-(Benzyloxymethyl)-2-aza-9-thiabicyclo[3.3.1]octan-7-one). Photograde benzene was prepared by washing 3 L of benzene with a mixture of $KMnO_4$ (100 mL, saturated aqueous) and H_2SO_4 (10 mL, concentrated) four times. Caution! Saturated $KMnO_4$ and concentrated sulfuric acid should not be premixed, as solid $KMnO_4$ may detonate in the presence of H_2SO_4. The benzene was then washed with water (100 mL), H_2SO_4 (8 × 50 mL, concentrated), water (100 mL), $NaHCO_3$ (2 × 100 mL), and brine (2 × 100 mL), dried over $MgSO_4$, and distilled from CaH_2.

Phenacyl sulfide **25b** (395 mg, 0.76 mmol) was divided into four parts in 50 mL round-bottom flasks with 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene[9] (2 mL, 10.3 mmol), and photograde benzene (7.5 mL; degassed by repeated freeze−thaw cycles under vacuum and argon) was photolyzed (Sun Lamp through a water-cooled solution of $CuSO_4$; saturated, ca. 4 cm layer, 22−24 °C) with magnetic stirring and a gentle

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argon sparge. After 8 h of photolysis, the mixtures were combined and concentrated. The excess diene was removed under vacuum with gentle warming. The residue was diluted in THF and treated with 1 N HCl for 5 min. The solution was neutralized with saturated $NaHCO_3$ and concentrated to remove the THF. The solution was extracted with ether and dried ($MgSO_4$). After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (2.2 cm × 30 cm), gradient elution using first 25 mL of 1:5 then 3:7 EtOAc/hexane as the eluents, to give 300 mg (84%) of enone **27**: analytical TLC on silica gel, 1:4 EtOAc/hexane, $R_f = 0.22$; M^+ calcd for $C_{27}H_{33}NO_4S$ 467.21307, found $m/e = 467.2138$, error = 2 ppm, base peak = 91 amu; IR (CH_2Cl_2, cm^{-1}) 1685 C═O, 1665 C═O, 1125 C−O; 200 MHz NMR ($CDCl_3$, ppm) δ 7.36−7.22 (11H, m), 6.10 (1H, d, J = 10.2 Hz), 4.48 (2H, br s), 4.37 (2H, br s), 3.57−3.09 (4H, br m), 2.83 (1H, br d, J = 15.7 Hz), 2.63 (1H, br d, J = 15.7 Hz), 2.08−1.78 (2H, br m), 1.46 (9H, br s). **Bicyclic thioaminal 28:** A solution of the phenacyl sulfide (2.57 g, 4.94 mmol) and Danishefsky's diene (50 mL) in photograde benzene (115 mL) was photolyzed as described above for 12 h. The solvent was removed (aspirator), and the excess diene was distilled off under vacuum (95 °C, ca. 1 Torr) and recycled. The reaction mixture was heated under vacuum (1 Torr, 110 °C, 3 h), and the resulting oil was taken up in CH_2Cl_2 (100 mL), cooled to 0 °C, and treated with trifluoroacetic acid (6.5 mL, dropwise). The mixture was then stirred at room temperature for 5 h and concentrated (aspirator). The resulting black oil was redissolved in CH_2Cl_2, extracted once with 2 N NaOH and once with brine, and dried (Na_2SO_4), and the solvent was evaporated (aspirator). Filtration through a plug of silica gel with ether gave an eluant that was concentrated and purified by flash chromatography on silica gel, 15% EtOAc/hexane eluent, to yield the bicyclic ketone **28** as a pale yellow solid (1.48 g, 4.03 mmol, 82% yield). Crystallization from EtOAc/hexane gave 1.40 g of slightly yellow crystals (mp 88.5−89.5 °C, 3.81 mmol, 77% yield). An analytical sample was obtained by recrystallization from EtOAc/hexane (mp 90.0−90.5 °C): M^+ calcd for $C_{22}H_{25}NO_2S$ 367.16064, found m/e = 367.1605, error = 0 ppm; IR ($CDCl_3$, cm^{-1}) 1700 C═O, 1090 C−O; 200 MHz NMR ($CDCl_3$, ppm) δ 7.37−7.24 (10H, m), 4.60 (2H, s), 4.37−4.34 (1H, m), 4.07 (1H, d, J = 13.5 Hz), 3.86 (1H, d, J = 13.5 Hz), 3.43 (1H, d, J = 9.3 Hz), 3.35 (1H, d, J = 9.3 Hz), 3.18−2.68 (6H, m), 2.09 (1H, dddd, J = 1.0, 4.9, 13.5, 13.5 Hz), 1.28 (1H, ddd, J = 2.5, 2.5, 13.5 Hz). Anal. Calcd: C, 71.89; H, 6.87. Found: C, 71.78; H, 6.90.

Bicyclic Thioaminal Alcohol 36 (5-(Benzyloxymethyl)-2-aza-9-thiabicyclo[3.3.1]octan-7-ol). Ketone **28** (226 mg, 0.61 mmol) and L-Selectride (Aldrich; 1.2 mL, 1.2 mmol, 1M) were stirred in THF at room temperature for 3 h. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (2 cm × 30 cm), 1:1 EtOAc/hexane eluent, to give 221 mg (97%) of **36**: analytical TLC on silica gel, 1:1 EtOAc/hexane, $R_f = 0.16$; M^+ calcd for $C_{22}H_{27}NO_2S$ 369.17630, found m/e = 369.1776, error = 4 ppm, base peak = 91 amu; IR ($CDCl_3$, cm^{-1}) 3580 O−H; 200 MHz NMR ($CDCl_3$, ppm) δ 7.36−7.26 (10H, m), 4.58 (2H, s), 4.21−4.04 (2H, m), 3.85 (2H, AB q, J_{AB} = 16.6 Hz), 3.30 (2H, s), 3.33−3.12 (1H, m), 2.85 (1H, dt, J = 14.6, 5.2 Hz), 2.36−2.17 (2H, m), 2.05−1.62 (4H, m).

Azocine Mercaptan Alcohol 37. Bicyclic thioaminal alcohol **36** (40 mg, 0.11 mmol), sodium cyanoborohydride (Aldrich; 31 mg, 0.50 mmol), and acetic acid (17 μL, 0.30 mmol) in 2,2,2-trifluoroethanol (Aldrich) were stirred at room temperature for 2 days. The mixture was quenched with 5% NaOH, extracted with CH_2Cl_2, and dried ($MgSO_4$). After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (1.2 cm × 10 cm), 3:2 EtOAc/hexane eluent, to give 21 mg (57%) of azocine **37**: analytical TLC on silica gel, 3:2 EtOAc/hexane, $R_f = 0.37$; M^+ calcd for $C_{22}H_{29}NO_2S$ 371.19196, found m/e = 371.1936, error = 4 ppm, base peak = 338 (M − SH) amu; IR (CH_2Cl_2, cm^{-1}) 3690 O−H; 200 MHz NMR ($CDCl_3$, ppm) δ 7.36−7.24 (10H, m), 4.50 (1H, d, J = 12.1 Hz), 4.43 (1H, d, J = 12.1 Hz), 4.12−4.02 (1H, m), 3.55 (1H, d, J = 12.8 Hz), 3.46 (1H, d, J = 12.8 Hz), 3.40 (1H, d, J = 9.2 Hz), 3.35 (1H, d, J = 9.2 Hz), 2.74−2.33 (5H, m), 2.19 (1H, br s), 2.10−1.47 (6H, m).

5-(Benzyloxymethyl)-7-(benzyloxy)-2-aza-9-thiabicyclo[3.3.1]-octane (38a). A solution of the alcohol **36** (286 mg, 0.774 mmol) in 5:1 THF/DMF (25 mL) at 0 °C under nitrogen was treated with an excess of hexane-washed NaH (175 mg) and a catalytic amount of imidazole. Benzyl bromide (500 μL, 4.20 mmol) was added, followed by tetrabutylammonium iodide (45 mg). The mixture was stirred for 1 h at 0 °C and 10 h at room temperature. The reaction was quenched with methanol and stirred overnight. Aqueous workup (CH_2Cl_2, NH_4Cl) and flash chromatography on silica gel, 10% to 20% EtOAc/hexane eluent, gave the benzyl ether **38a** as a clear colorless oil (314 mg, 0.684 mmol, 88% yield): analytical TLC on silica gel, 20% EtOAc/hexane, $R_f = 0.36$; M^+ calcd for $C_{29}H_{33}NO_2S$ 459.22327, found m/e = 459.2209, error = 5 ppm: (M − S) 427.2524, error = 3 ppm; IR (neat, cm^{-1}) 3028 ═C−H, 1095 C−O, 1073 C−O; 200 MHz NMR ($CDCl_3$, ppm) δ 7.40−7.15 (15H, m), 4.56 (2H, s), 4.53 (2H, s), 4.23 (1H, d, J = 2.8, 9.2 Hz), 4.03 (1H, d, J = 13.7 Hz), 3.96−3.73 (1H, m), 3.85 (1H, d, J = 13.7 Hz), 3.58 (1H, ddd, J = 3.5, 13.8, 14.3 Hz), 3.28 (2H, s), 2.81−2.57 (2H, m), 2.36 (1H, dd, J = 6.5, 13.5 Hz), 2.05 (1H, ddd, J = 4.6, 13.1, 13.8 Hz), 1.79 (1H, ddd, J = 2.8, 10.0, 14.0 Hz), 1.59 (1H, dd, J = 9.9, 13.5 Hz), 1.15 (1H, ddd, J = 13.1, 3.5, 3.5 Hz).

Methylthioazocine (40a). A solution of **38a** (263 mg, 0.573 mmol) in trifluoroethanol (10 mL) at room temperature under nitrogen was treated with $NaBH_3CN$ (280 mg, 4.45 mmol) and acetic acid (275 μL, 4.80 mmol). The resulting suspension was stirred at room temperature for 48 h. The reaction mixture was concentrated, quenched with NH_4Cl, and extracted with degassed methylene chloride. The combined organic layers were dried over Na_2SO_4 and concentrated to yield a cloudy colorless oil of the crude mercaptan **39a**. A solution of **39a** and DBU (500 μL) in benzene (20 mL) was treated with methyl iodide (200 μL), and the mixture was stirred at room temperature for 14 h. After aqueous workup (ether, NH_4Cl, $NaHCO_3$, brine), the residue was purified by flash chromatography on silica gel, 10% to 20% EtOAc/hexane eluent, to yield **40a** as a clear colorless oil (232 mg 0.488 mmol). In addition, a mixture of starting material **38a** and product were recovered which were resubmitted to the same reaction conditions to yield an additional 11 mg of the desired product (combined yield 243 mg, 0.511 mmol, 89% yield): M^+ calcd for $C_{30}H_{38}NO_2S$ 476.2623, found [HRFAB] m/e = 276.2615, error = 2 ppm; (M − SCH_3) 428.2590, error = 0 ppm; 500 MHz NMR ($CDCl_3$, ppm) δ 7.40−7.17 (15H, m), 4.54 (1H, d, J = 11.8 Hz), 4.48 (1H, d, J = 11.8 Hz), 4.34 (2H, AB q, J = 7.4 Hz, J = 8.3 Hz), 3.72 (1H, ddd, J = 3.6, 7.9, 10.6 Hz), 3.48 (1H, d, J = 12.7 Hz), 3.42 (1H, d, J = 12.7 Hz), 3.33 (1H, d, J = 9.7 Hz), 3.27 (1H, d, J = 9.7 Hz), 2.66 (1H, ddd, J = 4.1, 4.1, 14.9 Hz), 2.62−2.53 (2H, m), 2.49 (1H, ddd, J = 1.8, 12.7, 14.4 Hz), 2.28 (1H, ddd, J = 3.4, 3.5, 12.2 Hz), 2.02 (3H, s), 1.87−1.78 (3H, m), 1.67 (1H, ddd, J = 4.2, 12.9, 14.9 Hz), 1.53 (1H, dddd, J = 4.2, 12.0, 12.5, 12.7 Hz); ^{13}C NMR (128 MHz, DEPT, $CDCl_3$, ppm), δ 139.6 s, 139.0 s, 138.2 s, 129.1 d, 128.1 d, 128.0 d, 127.9 d, 127.5 d, 127.4 d, 127.3 d, 127.1 d, 126.8 d, 75.6 d, 74.8 t, 73.0 t, 69.8 t, 63.7 t, 52.0 t, 49.5 t, 49.4 s, 39.9 t, 36.8 t, 30.6 t, 11.2 q.

Sulfenylation of 36. Disulfide 43. Bicyclic sulfide alcohol **36** (57 mg, 0.15 mmol) in 7 mL of acetonitrile was treated with dimethyl(thiomethyl)sulfonium tetrafluoroborate[17] (110 mg, 0.56 mmol) and stirred at room temperature for 1 h. Sodium cyanoborohydride (Aldrich; 189 mg, 3.00 mmol) was added, and the mixture was allowed to stir for 2 days. The mixture was quenched with saturated NH_4Cl, extracted with CH_2Cl_2, and dried ($MgSO_4$). After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (1.2 cm × 13 cm), 1:5 EtOAc/hexane eluent, to give 50 mg (79%) of disulfide **43**: analytical TLC on silica gel, 1:1 EtOAc/hexane, $R_f = 0.38$; M^+ calcd for $C_{22}H_{29}NO_2S$ (M − CH_2S) 371.1920, found m/e = 371.1903, error = 4 ppm, base peak = 91 amu; IR (CH_2Cl_2, cm^{-1}) 3600 O−H; 200 MHz NMR ($CDCl_3$, ppm) δ 7.35−7.15 (10H, m), 4.33 (2H, s), 3.96−3.85 (1H, br m), 3.49 (1H, d, J = 12.8 Hz), 3.40 (1H, d, J = 12.8 Hz), 3.25 (1H, d, J = 9.8 Hz), 3.21 (1H, d, J = 9.8 Hz), 2.70−2.34 (5H, m), 2.30 (3H, s), 2.09−1.80 (3H, m), 1.78−1.44 (3H, m).

***N*-Carbobenzylmethylthioazocine (49a).** A solution of the *N*-benzyl azocine **40a** (837 mg, 1.76 mmol) in dry THF (50 mL) at −78 °C under nitrogen was treated with benzyl chloroformate (2.5 mL, dropwise). The mixture was warmed to room temperature and stirred for 16 h. After aqueous workup (CH_2Cl_2, $NaHCO_3$), excess reagent was removed under vacuum (1 Torr). The residue was purified by flash chromatography on silica gel, 10% to 30% EtOAc/hexane eluent,

to give **49a** as a colorless oil (872 mg, 95%): M^+ calcd for $C_{31}H_{37}NO_4S$ 519.24432, found *m*/*e* = 519.2443, error = 0 ppm, base peak = 320 amu; IR (neat, cm^{-1}) 1697 C═O, 1235 C(O)−N, 1097 C−O; 500 MHz NMR ($CDCl_3$, ppm) δ 7.38−7.21 (15H, m), 5.19 (0.6H, d, J = 12.4 Hz), 5.15 (0.4H, d, J = 12.2 Hz), 5.08 (0.6H, d, J = 12.4 Hz), 5.02 (0.4H, d, J = 12.2 Hz), 4.63 (0.6H, d, J = 12.1 Hz), 4.55 (0.6H, d, J = 11.6 Hz), 4.55 (0.6H, d, J = 12.1 Hz), 4.50 (0.6H, d, J = 11.6 Hz), 4.53 (0.8H, s), 4.39 (0.8H, AB q, J = 8.4 Hz), 4.05 (4.6H, ddd, J = 2.7, 12.2, 14.8 Hz), 3.88−3.74 (2H, m), 3.89 (0.4H, ddd, J = 2.7, 12.1, 14.8 Hz), 3.59 (0.6H, d, J = 9.8 Hz), 3.46 (0.6H, d, J = 9.8 Hz), 3.32 (0.4H, d, J = 9.8 Hz), 3.39 (0.4H, d, J = 9.8 Hz), 3.05−2.93 (2H, m), 2.01 (1.2H, s), 2.04 (1.8H, s), 2.05−1.70 (6H, m); ^{13}C NMR (128 MHz, DEPT, $CDCl_3$, ppm) δ 155.8 s, 155.0 s, 138.8 s, 138.7 s, 138.2 s, 138.1 s, 136.8 s, 136.6 s, 128.4−127.3 (13×) d, 75.2 t, 74.8 d, 74.7 d, 70.1 t, 70.1 t, 67.1 t, 66.9 t, 49.1 s, 44.0 t, 43.8 t, 43.7 t, 42.9 t, 40.2 t, 34.6 t, 33.3 t, 31.5 t, 30.8 t, 11.2 q, 11.1 q.

Sulfoxide Pyrolysis: 50a. A solution of **49a** (240 mg, 0.462 mmol) in CH_2Cl_2 at 0 °C under nitrogen was treated with a solution of tetrabutylammonium oxone[19] (3.2 mL, 150 mg/mL in CH_2Cl_2, 0.15 M activity) while monitoring for complete conversion by TLC ($CHCl_3$ eluant). The reaction mixture was stirred at 0 °C for 1.5 h, diluted with EtOAc (30 mL), and concentrated (aspirator). The product was taken up in EtOAc and filtered through Celite (1 in.). The solids were rinsed thoroughly with EtOAc (35 mL), and the organic filtrates were concentrated (aspirator). The crude mixture of sulfoxides **50** was dissolved in xylene (20 mL) and was added dropwise to a refluxing suspension of $CaCO_3$ (750 mg) in xylene (20 mL) at such a rate as to maintain a gentle reflux. The mixture was refluxed under nitrogen for 15 min. Flash chromatography on silica gel, 20% EtOAc/hexane eluent, gave the *N*-Cbz azocine allyl ether as a clear colorless oil (194 mg, 0.411 mmol, 89% yield): M^+ calcd for $C_{30}H_{34}NO_4$ 472.2489, found [HRFAB] *m*/*e* = 472.2487, error = 1 ppm, base peak = 472 amu; IR (neat, cm^{-1}) 2942 C−H, 1698 C═O, 1082 C−O; 500 MHz NMR ($CDCl_3$, ppm) δ 7.45−7.20 (15H, m), 5.71 (0.4H, d, J = 7.9 Hz), 5.69 (0.6H, d, J = 7.9 Hz), 5.14 (0.6H, d, J = 12.5 Hz), 5.11 (0.4H, d, J = 12.5 Hz), 5.09 (0.6H, d, J = 12.5 Hz), 5.06 (0.4H, d, J = 12.5 Hz), 4.53 (0.6H, d, J = 11.8 Hz), 4.55 (0.4H, d, J = 11.7 Hz), 4.50 (1.2H, s), 4.43 (0.4H, d, J = 11.7 Hz), 4.46 (0.8H, s), 4.32 (0.6H, d, J = 11.8 Hz), 4.17−4.09 (1H, m), 4.07−3.83 (3H, m), 3.65−3.53 (1H, m), 3.02−2.84 (2H, m), 2.63−2.53 (0.4H, m), 2.46−2.14 (2.6H, m), 1.70−1.56 (1H, m); ^{13}C NMR (128 MHz, DEPT, $CDCl_3$, ppm) δ 156.2 s, 155.3 s, 138.3 s, 138.2 s, 138.0 s, 137.9 s, 137.2 s, 136.8 s, 136.6 s, 131.7 d, 130.9 d, 128.4−127.4 (11×) d, 74.4 d, 74.2 t, 74 d, 1t, 72.3 t, 72.1 t, 71.0 t, 70.9 t, 67.1 t, 66.8 t, 49.3 t, 49.2 t, 46.5 t, 45.7 t, 34.5 t, 33.1 t, 29.6 t, 29.4 t.

***N*-Methylazocine 56.** A solution of **50a** (331 mg, 0.702 mmol) in THF (35 mL) was added dropwise to a suspension of $LiAlH_4$ (120 mg, 3.16 mmol) in dry THF (25 mL) at 0 °C under nitrogen. The mixture was warmed to room temperature and stirred for 8 h. The reaction was quenched with EtOAc (50 mL), followed by Glauber's salt ($Na_2SO_4 \cdot 10H_2O$), and the mixture was stirred vigorously overnight. The mixture was filtered through Celite, and the pad was rinsed thoroughly with EtOAc. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel-NH_3 (see General Experimental), 2:3 hexane/$CHCl_3$ eluent, to yield the *N*-methylazocine **56** as a clear colorless oil (238 mg, 0.676 mmol, 96% yield): analytical TLC on silica gel, 1:9 methanol/$CHCl_3$, R_f = 0.50; M^+ calcd for $C_{23}H_{30}NO_2$ 352.2277, found [HRFAB] *m*/*e* = 352.2287, error = 3 ppm, base peak = 352 amu; IR (neat, cm^{-1}) 3004 ═C−H, 2791 NCH_3, 1090 C−O; 500 MHz NMR ($CDCl_3$, ppm) δ 7.40−7.27 (10H, m), 5.68 (1H, d, J = 7.2 Hz), 4.61 (1H, d, J = 11.7 Hz), 4.50 (2H, AB q, J = 11.9 Hz), 4.45 (1H, d, J = 11.7 Hz), 4.03 (1H, d, J = 12.2 Hz), 3.94 (1H, d, J = 12.2 Hz), 2.67 (1H, ddd, J = 3.9, 3.9, 12.4 Hz), 2.50−2.42 (2H, m), 2.57 (1H, ddd, J = 4.4, 4.4, 14.6 Hz), 2.48−2.41 (1H, m), 2.41−2.32 (1H, m), 2.37 (3H, s), 2.28−2.07 (2H, m), 1.47 (1H, dddd, J = 3.8, 3.9, 11.4, 12.1 Hz); ^{13}C NMR (125 MHz, DEPT, $CDCl_3$, ppm) δ 138.7 s, 138.3 s, 137.5 s, 130.7 d, 128.3 d, 128.3 d, 127.7 d, 127.6 d, 127.5 d, 127.4 d, 75.8 d, 74.0 t, 71.9 t, 71.0 t, 58.1 t, 56.9 q, 53.6 t, 36.3 t, 29.7 t.

***N*-Methylazocine Diol 58.** A solution of OsO_4 (95.0 mg, 0.374 mmol) in THF (5 mL) at −78 °C under nitrogen was treated with TMEDA (60 μL, 0.40 mmol) and stirred at −78 °C for 10 min. A solution of the *N*-methylazocine **56** (113 mg, 0.321 mmol) in THF (20 mL) was added dropwise, and the mixture was stirred at −70 °C for 42 h. The reaction was warmed to room temperature, quenched with saturated aqueous $NaHSO_3$, stirred at room temperature for 2 h, and then refluxed under nitrogen for 4 h. The mixture was extracted with EtOAc, and the organic layer was washed with Na_2CO_3 and brine. The combined aqueous layers were taken to pH > 9 and extracted with $CHCl_3$. The organic layers were dried over Na_2SO_4/K_2CO_3. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (NH_3, $CHCl_3$ eluent), to give the diol as a clear colorless oil, 30:1 mixture of diastereomers (99 mg, 0.26 mmol, 81%): M^+ calcd for $C_{23}H_{32}NO_4$ 386.2331, found [HRFAB] *m*/*e* = 386.2336, error = 1 ppm, base peak = 386 amu; IR (neat, cm^{-1}) 3493 O−H, 2857 C−H, 1069 C−O; 500 MHz NMR ($CDCl_3$, ppm) δ 7.40−7.20 (10H, m), 4.57 (2H, s), 4.52 (2H, AB q, $\Delta\upsilon$ = 0.0266 ppm, J = 11.7 Hz), 4.01 (1H, d, J = 6.5 Hz), 3.95 (1H, ddd, J = 3.9, 6.5, 7.3 Hz), 3.61 (1H, d, J = 9.7 Hz), 3.56 (1H, d, J = 9.7 Hz), 2.83 (1H, ddd, J = 5.2, 12.4, 12.5 Hz), 2.51 (1H, ddd, J = 5.7, 8.7, 13.5 Hz), 2.58 (1H, ddd, J = 5.1, 6.0, 13.5 Hz), 2.33 (3H, s), 2.34 (1H, ddd, J = 2.8, 5.4, 12.5 Hz), 2.14 (1H, ddd, J = 5.4, 12.4, 15.4 Hz), 2.04 (1H, dddd, J = 3.9, 5.7, 6.0, 15.3 Hz), 1.98 (1H, dddd, J = 5.1, 7.3, 8.7, 15.3 Hz), 1.81 (1H, ddd, J = 2.8, 5.2, 15.4 Hz); ^{13}C NMR (125 MHz, DEPT, $CDCl_3$, ppm) δ 138.6 s, 138.2 s, 128.3 d, 128.2 d, 127.6 d, 127.5 d, 127.5 d, 127.3 d, 79.9 d, 76.4 t, 74.5 s, 73.5 t, 71.8 t, 52.2 t, 51.7 t, 46.5 q, 33.2 t, 30.7 t.

Ketol 60/61. A vigorously stirred solution of diol **58** (53 mg, 0.14 mmol) in *tert*-butyl alcohol (1 mL) and water (1.5 mL) was treated with CaO (155 mg), OsO_4 (0.5 mL, 2.8 mg/mL in *tert*-butyl alcohol) and $K_3Fe(CN)_6$ (350 mg, 1.06 mmol, all at once). The resulting bright yellow suspension was stirred in the dark for 55 min. The mixture was extracted with THF [Caution! OsO_4 present]. The combined THF extracts were quenched with a mixture of $NaHSO_3$ and Na_2SO_3 (1.5 g ea) in water (5 mL) and stirred at room temperature overnight. The reaction was worked up by the same procedure as used for the previous step (diol **58**). The residue was purified by flash chromatography on silica gel-NH_3, 1:1 Hex/$CHCl_3$ (saturated), $CHCl_3$ (saturated), gradient 10% (0.4%) to 33% (1.3%) THF/$CHCl_3$ (%NH_4OH) eluent, to give the ketol **60/61** as a colorless oil (27 mg, 0.071 mmol, 53% yield): M^+ calcd for $C_{23}H_{30}NO_4$ 384.2175, found [HRFAB] *m*/*e* = 384.2178, error = 1 ppm, base peak = 384 amu; IR (neat, cm^{-1}) 3403 O−H, 1676 C═O, 1095 C−O. The NMR spectrum shows both acid- and temperature-dependent phenomena. The NMR spectrum of the free base is fluxional at room temperature and sharpens at elevated temperature (70 °C, CD_3CN). Free base: 500 MHz NMR (CD_3CN, 70 °C, ppm) δ 7.40−7.23 (10H, m), 4.54 (1H, d, J = 11.6 Hz), 4.44 (1H, d, J = 11.9 Hz), 4.46 (1H, d, J = 11.6 Hz), 4.48 (1H, d, J = 11.9 Hz), 4.12 (1H, dd, J = 3.5, 3.5 Hz), 3.89 (1H, d, J = 9.6 Hz), 3.56 (1H, d, J = 9.6 Hz), 2.74 (1H, ddd, J = 3.5, 12.9, 13.2 Hz), 2.63−2.50 (3H, m), 2.48 (1H, ddd, J = 2.6, 4.8, 13.2 Hz), 2.25 (1H, dddd, J = 3.5, 4.8, 12.9, 14.1 Hz), 2.03 (3H, s), 2.06 (1H, dddd, J = 2.6, 3.5, 3.5, 14.1 Hz), 1.73−1.67 (1H, m); ^{13}C NMR (125 MHz, DEPT, CD_3CN, 70 °C, ppm) δ 200.4 s, 140.3 s, 139.3 s, 129.5 d, 129.4 d, 129.0 d, 128.9 d, 128.8 d, 128.7 d, 128.6 d, 84.1 br d, 80.3 s, 77.6 t, 74.5 t, 72.7 t, 51.3 t, 50.6 t, 42.2 q, 37.4 br t, 36.6 t. Protonated (**63**): 500 MHz NMR (CD_3OD/HCl, ppm) δ 7.40−7.20 (10H, m), 4.64 (1H, d, J = 12.4 Hz), 4.57 (1H, d, J = 12.4 Hz), 4.50 (1H, d, J = 11.9 Hz), 4.56 (1H, d, J = 11.9 Hz), 4.38 (1H, dd, J = 2.6, 5.4 Hz), 3.75−3.65 (2H, m), 3.69 (1H, d, J = 9.7 Hz), 3.52 (1H, d, J = 9.7 Hz), 3.55 (1H, ddd, J = 2.0, 7.7, 11.8 Hz), 3.45 (1H, ddd, J = 7.3, 9.0, 11.8 Hz), 2.89 (3H, s), 2.55−2.48 (1H, m), 2.30 (1H, ddd, J = 7.8, 12.0, 13.8 Hz), 2.18−2.10 (1H, m), 2.06 (1H, ddd, J = 1.0, 6.0, 14.1 Hz); ^{13}C NMR (125 MHz, DEPT, CD_3OD/HCl, ppm) δ 139.3 s, 138.4 s, 129.5 d, 129.4 d, 129.4 d, 129.2 d, 129.0 d, 128.8 d, 117.5 s, 81.7 s, 74.8 d, 73.9 t, 73.8 t, 63.3 t, 62.6 t, 47.0 q, 36.1 t, 31.2 t.

Dibenzylotonecine 68/69. Ketol **60/61** (13 mg, 0.033 mmol) was treated with excess Burgess reagent **2**[23] (29 mg, recrystallized from toluene, 0.12 mmol) and C_6D_6 (0.25 mL). After 15 min, the mixture was concentrated to dryness (1 Torr), redissolved in C_6D_6 (0.25 mL), and heated at 36 °C (water bath temperature) for 38 h. The reaction mixture was diluted with C_6D_6 (1 mL) and added dropwise to refluxing

benzene (15 mL). The tube was rinsed with C_6H_6 (2 × 1 mL) and $CHCl_3$ (1 mL). The mixture was refluxed for 10 min and quenched at reflux with Na_2CO_3 (saturated aqueous). After aqueous workup ($CHCl_3$, Na_2CO_3), drying (Na_2SO_4), and evaporation, the crude product was dissolved in wet THF (15 mL, 6.5 μL H_2O + 5 μL additional H_2O after 20 min reflux), refluxed under nitrogen for 30 min, and quenched at reflux with Na_2CO_3 (satd aq). Aqueous workup ($CHCl_3$, Na_2CO_3) and purification by flash chromatography on silica gel-NH_3 (1 × 4 cm), 20%(0.6) to 100%(4) THF/$CHCl_3$(% NH_4OH) eluent, gave dibenzylotonecine **68/69** as a clear colorless oil (6.0 mg, 0.0170 mmol, 50% yield): M^+ calcd for $C_{23}H_{28}NO_3$ 366.2069, found [HRFAB] *m*/*e* = 366.2067, error = 1 ppm, base peak = 366 amu; IR (neat, cm^{-1}), 2806 NCH_3, 1665 C═O, 1099 C−O; 500 MHz NMR ($CDCl_3$, ppm) δ 7.38−7.23 (10H, m), 5.74 (1H, s), 4.87 (1H, br d, J = 12.5 Hz), 4.56 (1H, d, J = 12.5 Hz), 4.47 (2H, s), 4.19 (1H, dddd, J = 1.8, 1.8, 1.8, 11.8 Hz), 4.05 (1H, d, J = 11.8 Hz), 3.87 (1H, dd, J = 3.9, 3.9 Hz), 3.20 (1H, d, J = 18.0 Hz), 3.11 (1H, d, J = 18.0 Hz), 2.83 (1H, ddd, J = 4.2, 11.7, 12.2 Hz), 2.62 (1H, ddd, J = 3.9, 4.7, 12.2 Hz), 2.29 (3H, s), 2.15 (1H, dddd, J = 3.9, 4.7, 11.4, 14.2 Hz), 1.96 (1H, dddd, J = 3.9, 3.9, 4.2, 14.2 Hz); ^{13}C NMR (125 MHz, DEPT, CD_3OD/HCl, ppm) δ 138.5 s, 138.1 s, 136.9 s, 129.6 d, 129.5 d, 129.4 d, 129.3 d, 129.3 d, 129.2 d, 129.1 d, 129.0 d, 128.9 d, 128.6 d, 126.1 d, 126.1 d, 124.7 d, 118.6 s, 84.1 s, 77.8 d, 74.0 t, 74.0 t, 73.6 t, 73.2 t, 71.2 t, 70.4 t, 66.0 t, 65.9 t, 64.0 t, 63.5 t, 47.6 q, 47.3 q, 29.1 t, 29.0 t.

Otonecine (1). A solution of dibenzylotonecine **68/69** (9.7 mg) and thioanisole (150 μL) in dry CD_3CN (0.5 mL) at 0 °C was treated with TMSOTf (30 μL). The mixture was shaken and allowed to stand at 0 °C for 30 min. The reaction was quenched with H_2O (50 μL) and concentrated under vacuum (aspirator, then <1 Torr). The mixture was triturated with $CHCl_3$, and the $CHCl_3$ layers were filtered. The product was recovered from the filter with CH_3CN. Ion exchange chromatography through a Bio-Rex 5 column (0.4 cm^3, basic form), onto a weakly acid column (Bio-Rex 70, 0.5 mL, H^+ form) in 1:1 methanol/water (35 mL), followed by elution of the acid column with a gradient of AcOH (0.6 mL) in methanol/water (5 mL), gave otonecine·HOAc salt as a pale yellow oil (4.6 mg). The product was filtered through a basic ion-exchange resin (Bio-Rex 5, 0.5 cm^3, basic form) in 1:1 methanol/water, to yield otonecine as a pale yellow oil (3.5 mg, ca. 73−77%). Minor signals of a contaminant were detected (δ 5.9−5.8, 4.4−4.2, 3.70−3.55, 2.5−2.3; estd 5−10% by comparison of the downfield signals). The other NMR signals in CD_3OD (room temperature) matched a spectrum of natural otonecine at 270 MHz provided by Prof. K. Yamada according to chemical shift, but with improved resolution due to the higher field. For **1**: LRFAB 186.1; 500 MHz NMR (CD_3OD, 60 °C, ppm) δ 5.71 (1H, br s), 4.11 (1H, dddd, J = 1.6, 1.6, 1.6, 14.1 Hz), 4.09 (1H, dddd, J = 1.8, 1.8, 1.8, 14.1 Hz), 3.92 (1H, dd, J = 3.2, 3.8 Hz), 3.50−3.0 (2H, m), 2.97 (1H, ddd, J = 1.6, 5.8, 12.2 Hz), 2.86 (1H, ddd, J = 4.8, 12.2, 12.5 Hz), 2.29 (3H, s), 2.13 (1H, dddd, J = 3.8, 5.8, 12.5, 14.4 Hz), 1.98 (1H, dddd, J = 1.6, 3.2, 4.8, 14.4 Hz).

Acknowledgment. We are indebted to Professor K. Yamada of Nagoya University for kindly providing us with ^{1}H NMR, IR, and mass spectra of natural otonecine. This work was supported by NIH (CA17918; postdoctoral fellowship GM 15045 to P.G.G.).

Supporting Information Available: Experimental details and characterization for **10c**, **11**, **13**−**16a**, **20**, **21**, **31**, **32**, **38b, 40b**, **45**, **47a**, **48a**, **47b**, **48b**, **50b**, **51**, **55**, and **52** (13 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA973464E