Ruthenium-Catalyzed Chlorine Atom Transfer Cyclizations of N-Allylic α-Chloro-α-thioacetamides. Synthesis of (−)-Trachelanthamidine and Formal Total Synthesis of (±)-Haemanthidine and (±)-Pretazettine

Hiroyuki Ishibashi,* Nahoko Uemura, Hiroshi Nakatani, Mika Okazaki, Tatsunori Sato, Nobuyuki Nakamura, and Masazumi Ikeda*

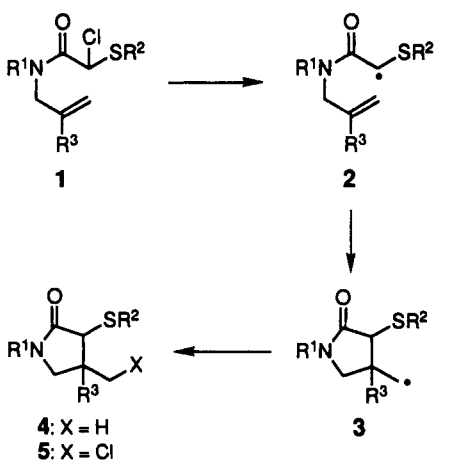
Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607, Japan

Received October 27, 1992

A new method for the synthesis of five-membered lactams by ruthenium-catalyzed chlorine atom transfer cyclizations of N-allylic α-chloro-α-thioacetamides and the application of the method to the synthesis of the title alkaloids are described. A benzene solution of *N*-allyl-*N*-methyl-α-chloro-α-(phenylthio)acetamide (**6**) was heated at 140 °C in the presence of $RuCl_2(PPh_3)_3$ to give α-thio-β-(chloromethyl)-substituted γ-lactam **8** as a mixture of cis and trans isomers in a ratio of ca. 3:7. NH congener **11**, however, gave no cyclization product. Heating chloro sulfides **18** and **19**, prepared from L-prolinol, with $RuCl_2(PPh_3)_3$ afforded bicyclic lactams **20** and **21**, respectively. Treatment of **20** with cesium propanoate gave predominantly cyclopropane derivative **25**, whereas *S*-methyl congener **21** provided esters **24** in good yield. Desulfurization of **24** with Raney nickel followed by reduction with $LiAlH_4$ furnished (−)-trachelanthamidine (**28**). On the other hand, *N*-(cyclohex-2-en-1-yl) derivative **30**, when heated with $RuCl_2(PPh_3)_3$, afforded octahydroindol-2-ones **31a,b**. The formation of **31a,b** indicated that the intramolecular addition of the chloro sulfide of **30** to the olefinic bond proceeded in an anti-mode. By contrast, 2-phenyl-substituted derivative **38** gave syn-addition product **39**. The difference between the modes of cyclization of **30** and **38** can be explained by assuming the intermediacy of radical **34**. When R = H, the chlorine atom attacks the convex face of the fused bicyclic system of **34** to lead to **31a,b**, whereas the steric bulk of the angular phenyl group (R = Ph) is apparently sufficient to direct the chlorine atom to the concave face. Heating chloro sulfide **48**, prepared in a highly stereocontrolled manner from cyclohexene **42**, with $RuCl_2(PPh_3)_3$ afforded bicyclic lactam **49**. Oxidation of **49** with *m*-CPBA followed by Pummerer rearrangement/hydrolysis gave keto lactam **51**, which was dehydrochlorinated with DBU to give olefin **52**. $LiAlH_4$ reduction of **52** and acylation with pivaloyl chloride provided ester **54**, a key intermediate in Martin's total synthesis of (±)-haemanthidine (**41**) and (±)-pretazettine (**40**).

Introduction

The atom transfer cyclizations of ω-halo olefins are currently emerging as valuable tools for the construction of carbo- and heterocyclic molecules.[1,2] In contrast to the commonly employed Bu_3SnH-mediated radical cyclizations, in which the last step is a simple reduction by Bu_3SnH, the atom transfer method can introduce a versatile halogen atom to the cyclization products. In previous papers,[3] we reported that N-allylic α-chloro-α-thioacetamides **1**, upon treatment with Bu_3SnH in the presence of azobis(isobutyronitrile) (AIBN), underwent cyclization via α-thio-substituted carbamoylmethyl radicals **2** to give five-membered lactams **4**. One of the characteristic features of the method is that α-chloro sulfides **1** give higher



(1) For reviews of radical cyclizations including atom transfer methods, see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986. (b) Curran, D. P. *Synthesis* **1988**, 489. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

(2) For recent references to atom transfer cyclizations, see: (a) Jolly, R. S.; Livinghouse, T. *J. Am. Chem. Soc.* **1988**, *110*, 7536. (b) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1989**, *111*, 6265. (c) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140. (d) Nagashima, H.; Ozaki, N.; Seki, K.; Ishii, M.; Itoh, K. *J. Org. Chem.* **1989**, *54*, 4497. (e) Mori, M.; Kubo, Y.; Ban, Y. *Heterocycles* **1990**, *31*, 433. (f) Nagashima, H.; Seki, K.; Ozaki, N.; Wakamatsu, H.; Itoh, K.; Tomo, Y.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 985. (g) Lee, G. M.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 1281. (h) Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1990**, *31*, 933. (i) Curran, D. P.; Seong, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 9410. (j) Udding, J. H.; Hiemsta, H.; van Zanden, M. N. A.; Speckamp, W. N. *Tetrahedron Lett.* **1991**, *32*, 3123. (k) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746. (l) Belvisi, L.; Gennari, C.; Poli, G.; Scolastico, C.; Salom, B.; Vassallo, M. *Tetrahedron* **1992**, *48*, 3945. (m) Nagashima, H.; Wakamatsu, H.; Ozaki, N.; Ishii, T.; Watanabe, M.; Tajima, T.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 1682. (n) Seijas, J. A.; Vázquez-Tato, M. P.; Castedo, L.; Estévez, R.; Ónega, M. G. Ruíz, M. *Tetrahedron* **1992**, *48*, 1637.

(3) (a) Sato, T.; Wada, Y.; Nishimoto, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc. Perkin Trans. 1* **1989**, 879. (b) Sato, T.; Tsujimoto, K.; Matsubayashi, K.; Ishibashi, H.; Ikeda, M. *Chem. Pharm. Bull.* **1992**, *40*, 2308.

0022-3263/93/1958-2360$04.00/0

yields of the cyclization products than do the corresponding desulfurized precursors, i.e., monochloroacetamides. The high efficiency of the cyclization of radicals **2** may be ascribed to a radical stabilizing effect of a pair of the captodative substituents.[4] The high regioselectivity of the cyclizations is remarkable; even the cyclization of a compound having an internal substituent (e.g., R^3 = Me) on the olefinic bond, the 5-exo-trig cyclization of radicals **2** to form **3**, took place smoothly, giving the corresponding five-membered lactam **4** (R^3 = Me) in good yield. These findings have now prompted us to investigate the atom transfer cyclizations of α-chloro sulfides **1** in the hope that β-(chloromethyl) substituted γ-lactams **5** might result. The high regioselectivity of the reaction coupled with the versatility of the sulfur substituent retained in the products make the method useful for the synthesis of complex alkaloids containing a pyrrolidine ring. The present paper describes an application of this methodology to the synthesis of pyrrolizidine alkaloid (−)-trachelanthamidine (**28**) and the formal total synthesis of *Amaryllidaceae* alkaloids (±)-haemanthidine (**41**) and (±)-pretazettine (**40**).[5]

Results and Discussion

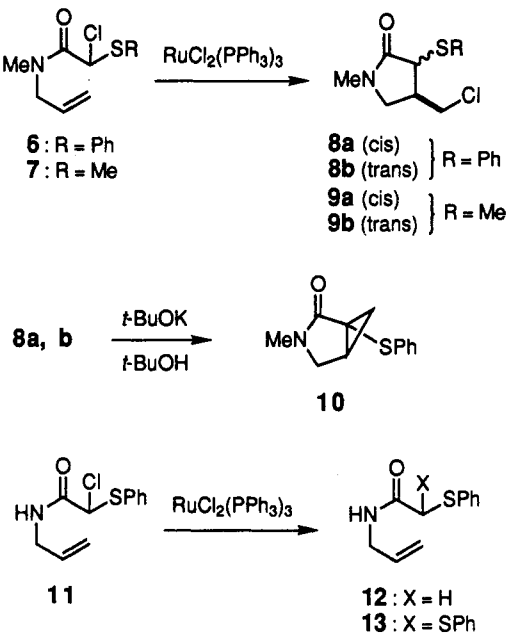
Synthesis of (−)-Trachelanthamidine. Prior to our studies on the alkaloid synthesis, we briefly examined the cyclizations of simple N-allylic α-chloro-α-thioacetamides under reported atom transfer conditions. Thus, a benzene solution of **6** was heated in the presence of 10 mol% of $RuCl_2(PPh_3)_3$[6] at 140 °C in a sealed tube for 1 h to give the expected five-membered lactam **8** in 62% yield as an approximately 3:7 mixture of cis and trans isomers **8a** and **8b** (ratio determined by ^1H NMR spectroscopy). The use of CuCl[6] as a catalyst in acetonitrile at 140 °C, however, gave no cyclization product. The cyclization of *S*-methyl congener **7** with $RuCl_2(PPh_3)_3$ gave a mixture of cis and trans lactams **9a** and **9b** (ca. 4:6 ratio) in 57% yield.[7]

The stereochemical assignments of cyclization products **8a,b** and **9a,b** were made by comparing the ^1H NMR spectra of *trans*-lactams **8b** and **9b** with those of authentic samples prepared by Lewis acid-promoted reactions of chlorides **6**[9] and **7**,[10] respectively.

Treatment of the mixture of **8a,b** thus obtained with potassium *tert*-butoxide in *tert*-butyl alcohol gave cyclopropane **10** (91% yield) by means of a base-initiated 1,3-elimination.[11]

When NH congener **11** was heated with $RuCl_2(PPh_3)_3$, only dechlorinated product **12** and dithioacetal **13** were

Scheme I



obtained in 35 and 8% yields, respectively; no cyclization product was isolated.[12]

Encouraged by the success of the ruthenium-catalyzed atom transfer cyclization of α-chloro sulfides **6** and **7**, we then examined an application of the method to the synthesis of pyrrolizidine alkaloid (−)-trachelanthamidine (**28**).[13,14]

The requisite chlorides **18** and **19** were prepared from L-prolinol (**14**) according to the following reaction sequence reported previously by us:[3b] (1) N-protection of **14** with ClCOOEt, (2) oxidation of the alcohol with sulfur trioxide–pyridine complex and DMSO, (3) Wittig reaction of aldehyde **15** with $CH_2{=}PPh_3$, (4) deprotection of *N*-ethoxycarbonyl group with hydrazine and KOH, (5) acylation of amine **16** with (phenyl- or methylthio)acetyl chloride, and (6) treatment of sulfides **17** with *N*-chlorosuccinimide (NCS).

Heating a benzene solution of **18** in the presence of $RuCl_2(PPh_3)_3$ at 140 °C gave bicyclic lactam **20** in 59% yield as crystalline material.[15] The GLC analysis of **20**, however, showed it to be a mixture of the four possible diastereoisomers in a ratio of 84:11:3:2. Treatment of **20** with Raney nickel in refluxing ethanol brought about the reduction of both the sulfur and the chlorine substituents to give a mixture of 1α-methyl lactam **22a**[16] and the corresponding 1β-methyl isomer **22b**[16] in a ratio of 95:5. The results of the reduction indicated that the two major

(4) Viehe, H. G.; Merényi, R.; Stella, L.; Janousek, Z. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 917.

(5) For a preliminary account of a portion of this work, see: Ishibashi, H.; Nakatani, H.; Iwami, S.; Sato, T.; Nakamura, N.; Ikeda, M. *J. Chem. Soc. Chem. Commun.* **1989**, 1767.

(6) Nagashima, H.; Wakamatsu, H.; Itoh, K. *J. Chem. Soc. Chem. Commun.* **1984**, 652.

(7) All cyclizations herein described must proceed via the disfavored *Z* rotamer[8] of the amides in which the large allylic group is cis to the reactive radical center. The high temperature employed would make it possible to convert the *E* rotamer (which cannot cyclize) to the required *Z* rotamer. Curran and Tamine[2k] reported that the ditin-mediated atom transfer cyclizations of *N*-allyl-*N*-methyliodoacetamides were much more efficient at 80 °C than at 25 °C.

(8) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296.

(9) Ishibashi, H.; Okada, M.; Sato, K.; Ikeda, M.; Ishiyama, K.; Tamura, Y. *Chem. Pharm. Bull.* **1985**, *33*, 90.

(10) Ishibashi, H.; Ikeda, M.; Maeda, H.; Ishiyama, K.; Yoshida, M.; Akai, S.; Tamura, Y. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1099.

(11) For analogous cyclopropane formations, see: Mori, M.; Kanda, N.; Ban, Y.; Aoe, K. *J. Chem. Soc., Chem. Commun.* **1988**, 12.

(12) This result is consistent with the previous observation that the Bu_3SnH-mediated reaction of the SMe congener of **11** gave no cyclization product.[3a] However, when treated with $RuCl_2(PPh_3)_3$, the corresponding trichloroacetamides were reported to give the expected cyclization products in good yields.[2d,m] The reason why compound **11** does not cyclize is unclear at the moment.

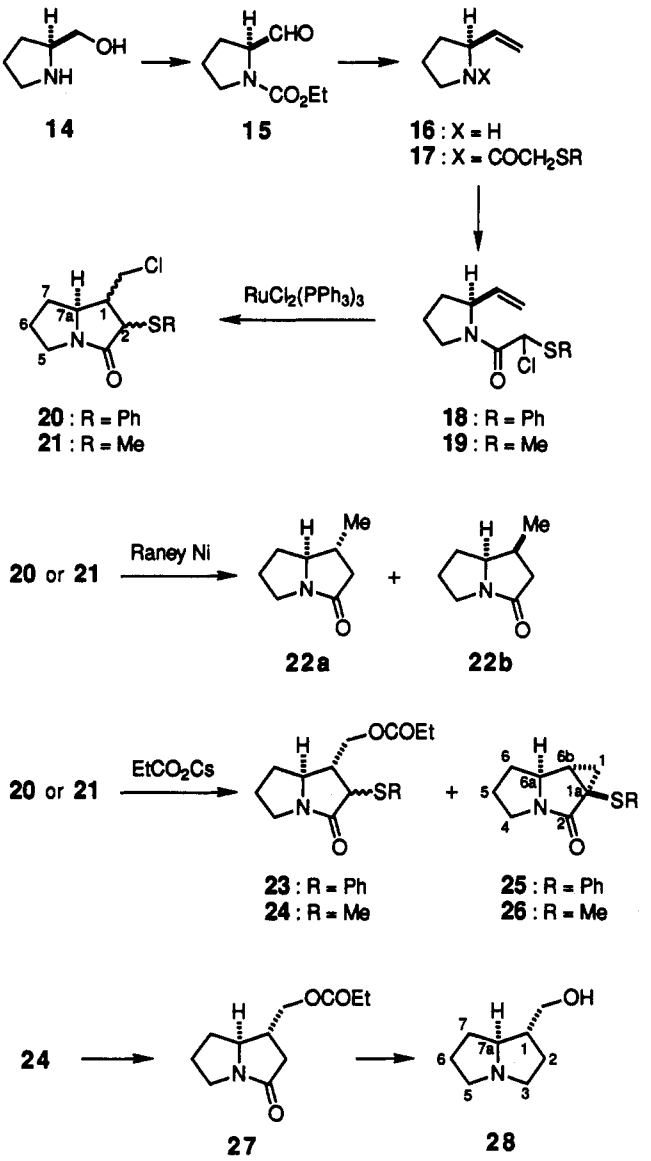
(13) For reviews of pyrrolizidine alkaloids, see: (a) Warren, F. L. *Fortschr. Chem. Org. Naturst.* **1966**, *24*, 329. (b) Bull, L. B.; Culvenor, C. C. J.; Dick, A. T. *The Pyrrolizidine Alkaloids*; North-Holland Publishing Co.: Amsterdam, 1968. (c) Robins, D. J. *Adv. Heterocyclic Chem.* **1979**, *24*, 247.

(14) For reviews on the synthesis of pyrrolizidine alkaloids, see: (a) Ikeda, M.; Sato, T.; Ishibashi, H. *Heterocycles* **1988**, *27*, 1465. (b) Dai, W.-M.; Nagao, Y.; Fujita, E. *Heterocycles* **1990**, *30*, 1231. (c) Robins, D. J. *Nat. Prod. Rep.* **1984**, *1*, 235; **1985**, *2*, 213; **1986**, *3*, 297; **1987**, *4*, 577; **1989**, *6*, 221; **1989**, *6*, 577; **1990**, *7*, 377; **1991**, *8*, 213; **1992**, *9*, 313.

(15) Lewis acid-mediated reactions of **18** and **19** gave no cyclization product.

(16) Mori, M.; Kanda, N.; Oda, I.; Ban, Y. *Tetrahedron* **1985**, *41*, 5465.

Scheme II



components (84 and 11%) of **20** had α-chloromethyl groups, and the minor components (3 and 2%) had β-chloromethyl groups. Recrystallization of **20** gave one of the major stereoisomers, and NOE difference spectroscopy showed its phenylthio group to be trans to the neighboring chloromethyl group; irradiation of the signal due to H-2 (C*H*SPh) at δ 3.98 caused a 5% enhancement in intensity of the signal at δ 3.66 due to one of the CH_2Cl hydrogens.

Similarly, when chloride **19** was heated with $RuCl_2(PPh_3)_3$, **21** was obtained in 67% yield.[15] The ^1H NMR spectrum of **21** exhibited two large singlets at δ 2.19 and 2.28, ascribable to the *S*-methyl protons, in a ratio of ca. 7:3. Reduction of **21** with Raney nickel afforded a mixture of **22a** and **22b** in essentially the same ratio (94:6) as that obtained from **20** (95:5). The similarity of the ratios implied that the chloromethyl group of two major components of **21** also occupied the α-configuration as did that of **20**.

With **20** and **21** in hand, we then studied the transformation of the chlorine atom to the oxygen functionality. When compound **20** was heated in the presence of cesium propanoate[17] in DMF at 150 °C, only an 11% yield of desired ester **23** was obtained along with a considerable amount of cyclopropane derivative **25** (83%). We assumed that the bulkiness of the phenylthio group prevented an attack of the propanoate anion on the carbon α to the chlorine atom of **20**. Therefore, we were forced to examine the reaction of **21**, which bears a sterically less demanding methylthio group. Heating **21** with cesium propanoate in DMF at 80 °C gave desired ester **24** as a major product in 50% yield together with cyclopropane **26** (39%). A more satisfactory result was obtained when the reaction was conducted in boiling chlorobenzene in the presence of 18-crown-6;[18] these conditions gave **24** in 73% yield with a decrease in the amount of **26** (8%).

Examination of the ^1H NMR spectra of **23–26** showed that compounds **23** and **24** were approximately 1:2 and 1:4 mixtures, respectively, of cis and trans isomers having 1α-acyloxymethyl groups.[19] Compounds **25** and **26** were single stereoisomers. The products derived from the minor 1β-chloromethyl isomers of **20** and **21** were probably lost during chromatographic separation of the reaction mixture because they were present only in small quantities.

Compound **24** was desulfurized with Raney nickel to afford **27** as a single stereoisomer in 86% yield. Subsequent reduction of **27** with $LiAlH_4$ in refluxing THF furnished (−)-trachelanthamidine (**28**)[20] in 88% yield: $[\alpha]^{24}_D$ −10.3° (*c* 0.65, EtOH)[21], lit.[20a] $[\alpha]_D$ −13.5° (*c* 2.0, EtOH).

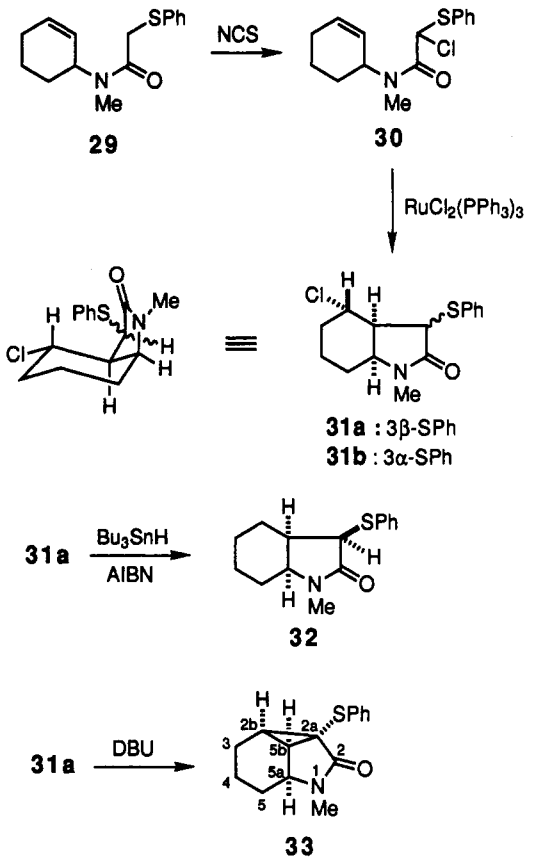
Formal Total Synthesis of (±)-Haemanthidine and (±)-Pretazettine. The *cis*-3a-arylhydroindole skeleton is a basic structural element of *Sceletium* alkaloids[22] and a key subunit of many crinine-type *Amaryllidaceae* alkaloids.[23] We next turned our attention to the construction of this class of molecules.

We first examined the cyclization of α-chloro sulfide **30**, which was prepared by acylation of *N*-(cyclohex-2-en-1-yl)-*N*-methylamine[24] with (phenylthio)acetyl chloride and treatment of the resulting sulfide **29** with NCS.

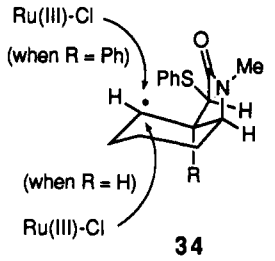
When a benzene solution of **30** was heated with $RuCl_2(PPh_3)_3$, bicyclic lactams **31a** and **31b** were obtained in 68 and 4% yields, respectively. The stereochemistry of **31a** and **31b** depicted in Scheme III was determined by a combination of spectral and chemical evidence. The ^1H NMR spectrum of the major lactam **31a** exhibited a signal at δ 2.38 due to H-3a with coupling constants J = 7.8, 5.3, and 4.9 Hz, which were clearly indicative of the axial disposition. The proton at C(4) appeared at δ 4.00 with coupling constants J = 8.5, 7.8, and 4.0 Hz, indicating the equatorial nature of the chlorine atom. Similar spectral

(17) Kruizinga, W. H.; Strijtveen, B.; Kellogg, R. M. *J. Org. Chem.* **1981**, *46*, 4321.
(18) Torisawa, Y.; Okabe, H.; Ikegami, S. *Chem. Lett.* **1984**, 1555.
(19) The disagreement in the cis/trans ratios for **20** (11:84) vs **23** (1:2) and **21** (3:7) vs **24** (1:4) may be ascribed to the partial isomerization of **23** and **24** under the basic conditions employed.
(20) For other syntheses of (−)-trachelanthamidine, see: (a) Robins, D. J.; Sakdarat, S. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 909. (b) Rüeger, H.; Benn, M. *Heterocycles* **1982**, *19*, 1677. (c) Ishibashi, H.; Ozeki, H.; Ikeda, M. *J. Chem. Soc., Chem. Commun.* **1986**, 654. (d) Moriwake, T.; Hamano, S.; Saito, S. *Heterocycles* **1988**, *27*, 1135. (e) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Am. Chem. Soc.* **1988**, *110*, 289. See also refs 2a and 2n.
(21) The low optical purity of **28** may be attributable to a partial epimerization of aldehyde **15**, an intermediate for the synthesis of **19**.
(22) For a review of the *Sceletium* alkaloids, see: Jeffs, P. W. In *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic Press: New York, 1981; Vol. 19, pp 1–80.
(23) For an excellent review covering structure, synthesis, and biological activity of the *Amaryllidaceae* alkaloids, see: Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, pp 251–376.
(24) Ishibashi, H.; So, T. S.; Okochi, K.; Sato, T.; Nakamura, N.; Nakatani, H.; Ikeda, M. *J. Org. Chem.* **1991**, *56*, 95.

Scheme III

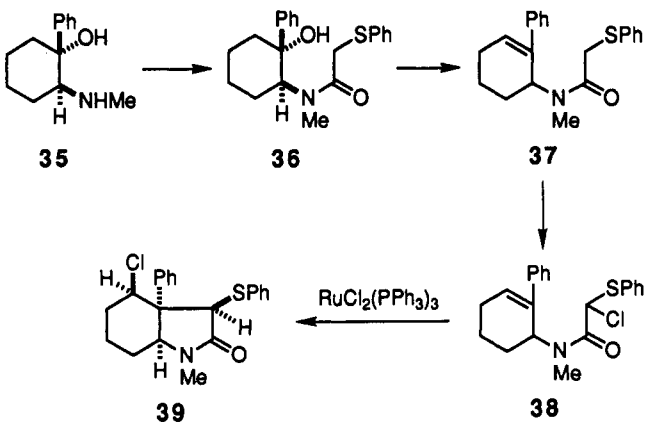


features were observed for minor isomer **31b**; δ 2.68 (dt, J = 7.8, 5.9 Hz, H-3a), 4.32 (dt, J = 7.8, 5.1 Hz, H-4). Treatment of **31a** with Bu_3SnH and AIBN in boiling toluene afforded 3β-phenylthio lactam **32**. The spectral data of **32** were identical with those of an authentic sample,[25] thereby confirming the β-configuration of the phenylthio group of **31a**. Accordingly, the corresponding phenylthio group of minor isomer **31b** was assigned as the α-disposition. The stereochemical outcome of the anti-addition of the α-chloro sulfide of **30** to the olefinic bond can easily be explained by assuming the intermediacy of radical **34** (R = H).[26] The chlorine atom attacks the convex face of the cis-fused bicyclic system of **34** to lead to **31a,b**.



(25) The Bu_3SnH-mediated 5-endo-trig radical cyclization of *N*-(cyclohex-1-en-1-yl)-*N*-methyl-α,α-bis(phenylthio)acetamide gave approximately equal amounts of lactam **32** (29%) and the corresponding 3α-phenylthio isomer (30%). Heating the sulfoxide derived from the latter afforded 2,4,5,6,7,7a-hexahydro-1-methylindol-2-one as a result of a thermal syn-elimination of sulfenic acid. However, heating the sulfoxide derived from **32** afforded recovered starting material. The recovery of starting material indicated the β-configuration of the phenylthio group of **32**. See: (a) Ishibashi, H.; Nakamura, N.; Sato, T.; Takeuchi, M.; Ikeda, M. *Tetrahedron Lett.* **1991**, *32*, 1725. (b) Sato, T.; Nakamura, N.; Ikeda, K.; Okada, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2399.

Scheme IV



However, the reason why the phenylthio group prefers the sterically disfavored β-configuration is not clear at the moment.

Treatment of compound **31a** with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) gave tricyclic compound **33** in 61% yield. This result supported the assignment of the α-configuration of the chlorine substituent of **31a**, since, if the chlorine atom had occupied the β-configuration, the resulting carbanion and the chlorine substituent could not have adopted the required W-shaped transition state for 1,3-elimination.[11]

2-Phenylcyclohex-2-enyl congener **38** was readily prepared by means of N-acylation of amino alcohol **35**[24] with (phenylthio)acetyl chloride followed by dehydration of **36** and treatment of **37** with NCS. Heating chloro sulfide **38** in the presence of 20 mol% of $RuCl_2(PPh_3)_3$ in boiling benzene at 140 °C gave the expected *cis*-3a-phenyloctahydroindol-2-one **39** in 48% yield accompanied by a trace amount of an unidentified product [probably the 3α-phenylthio isomer of **39**: δ 3.78 (s, 1 H, H-4), 4.24 (br s, $W_{1/2}$ = 8 Hz, H-4), 4.98 (br s, $W_{1/2}$ = 9 Hz, H-7a)].

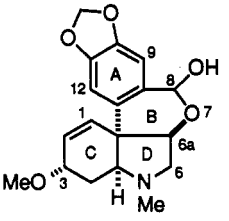
In contrast to that of **31**, the chlorine atom of **39** was found to be axial by examination of the ^1H NMR spectrum, which exhibited a triplet at δ 4.69 due to H-7a with a small coupling constant (J = 3.4 Hz) and a broad singlet ($W_{1/2}$ = 8 Hz) at δ 3.84 due to H-4. These coupling constants clearly indicated that both hydrogens were equatorial. The result suggested the intramolecular addition of **38** occurred in a syn-mode. The steric bulk of the angular phenyl group was apparently sufficient to direct the chlorine atom to the concave face of radical intermediate **34** (R = Ph). The stereochemistry of the 3β-phenylthio group of **39** was deduced from NOE experiments; irradiation of the signal due to H-7a caused a 5.5% enhancement in the intensity of the signal due to H-3 (δ 4.17, s).

Pretazettine (**40**) is one of the most complex molecules of the crinine class of *Amaryllidaceae* alkaloids,[23] which contain a *cis*-3a-arylhydroindole ring system as the basic structural element. Its potent antiviral and anticancer properties[23] render this molecule a worthwhile synthetic target.[27,28] Since haemanthidine (**41**), another member of

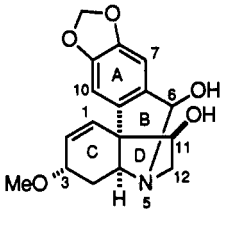
(26) The termination of the ruthenium-catalyzed atom transfer reaction has been suggested to proceed via a radicaloid intermediate in which the carbon radical is complexed with a ruthenium(III) species. Only for simplicity, we use here free radical intermediate **34**. For a discussion of the mechanism of ruthenium-catalyzed atom transfer reactions, see: (a) Kameyama, M.; Kamigata, N. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3687. (b) Kameyama, M.; Kamigata, N.; Kobayashi, M. *J. Org. Chem.* **1987**, *52*, 3312.

(27) For a total synthesis of (±)-pretazettine, see: Martin, S. F.; Davidsen, S. K.; Puckette, T. A. *J. Org. Chem.* **1987**, *52*, 1962.

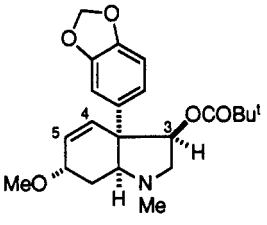
the same family, can be converted into pretazettine in a single step,[29] much effort has gone into the synthesis of **41** as the pivotal relay to pretazettine.[27,30] Our interest was then focussed on the application of the present method to the synthesis of pivalate ester **54**, a key intermediate in Martin's total synthesis of haemanthidine and pretazettine.[27] We envisioned that the sulfur substituent of cyclization product **49**, attainable from chloro sulfide **48**,



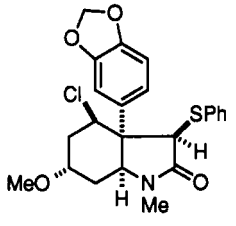
40



41



54



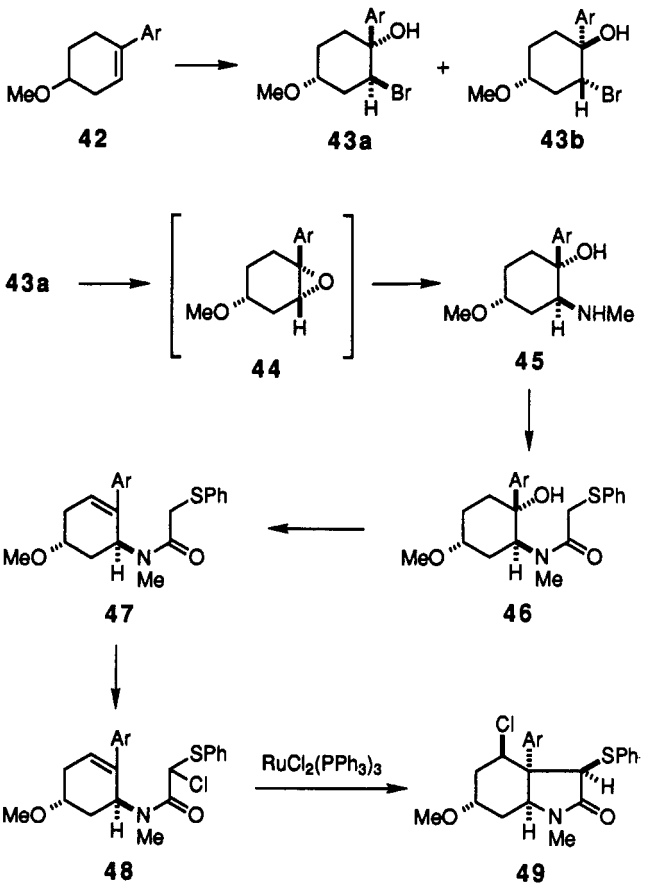
49

would play a role in providing the oxygen functionality at the C(3) position of **54** and that the chlorine atom might serve to install the olefinic bond between C(4) and C(5).

The requisite cyclization substrate **48**, having a methoxy group and relative stereochemistry characteristic of the cyclohexene ring in **54**, was prepared from amino alcohol **45**, which in turn was synthesized in a highly stereoselective manner from cyclohexene **42** by the method previously described by us.[24] Thus, treatment of **42** with *N*-bromosuccinimide (NBS) in aqueous acetonitrile gave two bromohydrins **43a** and **43b** in 73 and 18% yields, respectively, after chromatographic separation. The major bromohydrin **43a** was then heated with 40% methylamine in methanol at 100 °C to afford amino alcohol **45** in 98% yield. The retention of configuration in the displacement of the bromine of **43a** with methylamine can be explained by consideration of epoxide intermediate **44**, in which methylamine attacks the epoxide ring in an S_N2 manner to lead to **45**. The ^1H NMR spectral properties of **45**, which showed the equatorial nature (br s, $W_{1/2}$ = 7 Hz) of H-2 (C*H*NHMe) and the axial disposition (double t, J = 10.7, 4.4 Hz) of H-4 (C*H*OMe), established the desired trans relationship between the methoxy and the methylamino groups.

N-Acylation of **45** with (phenylthio)acetyl chloride, dehydration of the resulting alcohol **46** with *p*-toluenesulfonic acid (TsOH), and successive treatment of sulfide **47** with NCS gave chloro sulfide **48**, which was heated with $RuCl_2(PPh_3)_3$ to afford cyclization product **49** in 57% yield.

Scheme V



Ar = 3,4-Methylenedioxyphenyl

With the requisite bicyclic lactam **49** so conveniently assembled, we then examined a transformation of the sulfur substituent into the oxygen functionality by way of the Pummerer rearrangement. Thus, oxidation of **49** with *m*-CPBA afforded quantitatively sulfoxide **50**, which was heated in boiling toluene in the presence of TsOH to give the expected dioxo compound **51** in low yield (30%). We found, however, that compound **51** could be obtained in high yield (87%) by sequential treatment of a solution of **50** in CH_2Cl_2 with 2 equiv of trifluoroacetic anhydride (TFAA) in the presence of 2,6-lutidine and then with a saturated $NaHCO_3$ solution. The structure of **51** was confirmed by its IR spectrum, which showed absorptions at 1770 and 1720 cm^{-1}. The subsequent dehydrochlorination of **51** was effected by heating with DBU in CH_3CN at 160 °C to give olefin **52** in 48% yield. The ^1H NMR spectrum of **52** exhibited signals due to two olefinic protons at δ 5.56 (br d, J = 10 Hz, 1 H, H-4) and 6.26 (dd, J = 10, 2 Hz, 1 H, H-5).

Reduction of **52** with $LiAlH_4$ proceeded in a highly stereoselective manner to give 3β-alcohol **53**[31] in 63% yield as a single stereoisomer. The 3α-alcohol (**56**) was not detected (^1H NMR spectroscopy and TLC) in the crude reaction mixture. Danishefsky and co-workers[28a] reported that the reduction of compound **55** with $NaBH_4$ gave a mixture of the 3β- and 3α-alcohols **53** and **56** in a ratio of 3:1. The difference in the selectivities of the reductions of **52** and **55** may be explained in terms of the conformational differences in the starting materials. Inspection

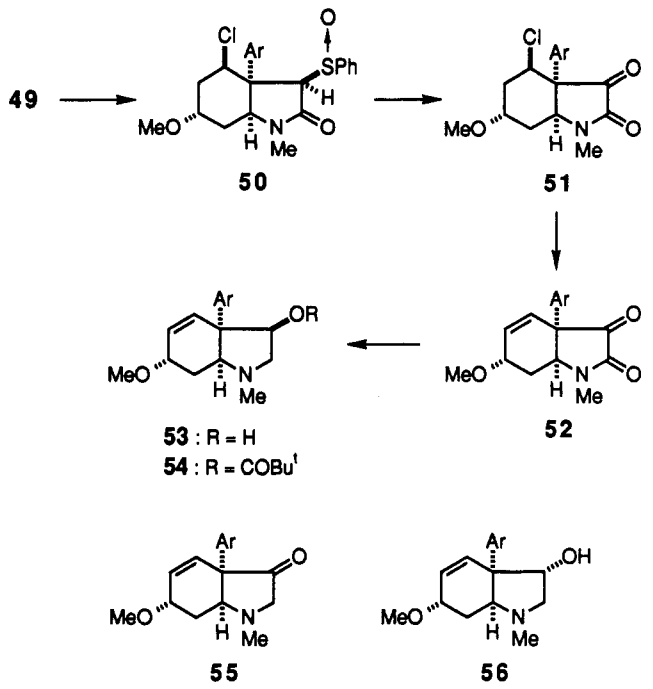
(28) For syntheses of 6a-epipretazettine, see (a) Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1982**, *104*, 7591. (b) White, J. D.; Chong, W. K. M.; Thirring, K. *J. Org. Chem.* **1983**, *48*, 2302. (c) Overman, L. E.; Wild, H. *Tetrahedron Lett.* **1989**, *30*, 647. (d) Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959.

(29) Wildman, W. C.; Bailey, D. T. *J. Am. Chem. Soc.* **1969**, *91*, 150.

(30) For syntheses of (±)-haemanthidine, see: (a) Tsuda, Y.; Isobe, K. *J. Chem. Soc., Chem. Commun.* **1971**, 1555. (b) Tsuda, Y.; Ukai, A.; Isobe, K. *Tetrahedron Lett.* **1972**, 3153. (c) Hendrickson, J. B.; Bogard, T. L.; Fisch, M. E.; Grossert, S.; Yoshimura, N. *J. Am. Chem. Soc.* **1974**, *96*, 7781.

(31) We thank Professor S. J. Danishefsky (Yale University) for providing spectra of compound **53**.

Scheme VI



of molecular models indicates that compound **55** exists with the cyclohexene ring in the half-chair conformation in which the C(3)–C(3a) bond is quasiequatorial, whereas the corresponding cyclohexene ring of keto lactam **52** exists predominantly in the half-boat conformation in which the C(3)–C(3a) bond is quasiaxial. Accordingly, the concave face of **52** is considered sterically more crowded than that of **55**, so that the reducing agent attacks exclusively the convex face of **52** to lead to only the observed 3β-alcohol **53**.[32]

Finally, alcohol **53** was acylated with pivaloyl chloride in pyridine to give, in 83% yield, ester **54**, which had spectral characteristics identical with those of an authentic sample.[33] Since compound **54** has previously been converted into (±)-pretazettine (**40**) via (±)-haemanthidine (**41**) in five steps,[27] the present preparation of **54** constitutes, in a formal sense, a total synthesis of pretazettine.

In conclusion, we have shown that, when heated with $RuCl_2(PPh_3)_3$, the N-allylic α-chloro-α-thioacetamides undergo chlorine atom transfer cyclization to give α-thio-β-(chloromethyl) substituted γ-lactams. The chlorine and the sulfur substituents incorporated into the cyclization products serve as handles for the elaboration of functionalities required for the synthesis of natural alkaloids. Further applications of this methodology are under intense investigation.

Experimental Section[34]

General Procedure for the Preparation of α-Chloro Sulfides. α-Chlorosulfides **6**,[3a] **7**,[3a] **18**,[3b] and **19**[3b] were prepared according to the reported procedure. Chloro sulfide **11** was prepared as follows. To a solution of allylamine (314 mg, 5.5 mmol) and triethylamine (557 mg, 5.5 mmol) in dry diethyl ether (20 mL) at 0 °C was added a solution of chloro(phenylthio)acetyl chloride (1.22 g, 5.5 mmol) in diethyl ether (5 mL), and the mixture was stirred at room temperature for 1 h. The precipitated salts were filtered off, and the filtrate was concentrated in vacuo to give **11**, quantitatively. Chloro sulfides **30**, **38**, and **48** were prepared as follows. To a solution of sulfide **39**, **37**, or **47** (2 mmol) in CCl_4 (30 mL) at 0 °C was added NCS (267 mg, 2 mmol) by portions, and the mixture was stirred at room temperature for 15 h. The precipitated succinimide was filtered off, and the filtrate was concentrated in vacuo to give **30**, **38**, or **48** in almost quantitative yield, respectively. α-Chloro sulfides **11**, **30**, **38**, and **48** thus obtained were used immediately in the next stage.

***cis*- and *trans*-4-(Chloromethyl)-1-methyl-3-(phenylthio)-pyrrolidin-2-ones (8a and 8b).** A mixture of chloride **6** (924 mg, 3.62 mmol) and $RuCl_2(PPh_3)_3$ (347 mg, 0.362 mmol) in dry benzene (30 mL) was heated in a sealed tube at 140 °C for 1 h. After the reaction mixture cooled, pentane (40 mL) was added, and the precipitate was filtered off. The filtrate was concentrated in vacuo, and the residue was chromatographed on silica gel (hexane/AcOEt, 1:1) to give a mixture of **8a** and **8b**[9] (575 mg, 62%) as an oil: IR (CCl_4) ν 1710 cm^{-1}; ^{1}H NMR for **8a** (300 MHz) δ 2.82 (d, J = 0.5 Hz, 3 H, NMe), 2.92–3.02 (m, 1 H, H-4), 3.03 (dd, J = 9.8, 7.0 Hz, 1 H, one of H-5), 3.43 (dd, J = 9.8, 7.0 Hz, 1 H, one of H-5), 3.71 (dd, J = 11.1, 9.1 Hz, 1 H, one of CH_2Cl), 3.90 (dd, J = 11.1, 5.4 Hz, 1 H, one of CH_2Cl), 3.94 (d, J = 7.5 Hz, 1 H, H-3), 7.27–7.35 (m, 3 H), 7.54–7.60 (m, 2 H). ^{1}H NMR for **8b** (300 MHz) δ 2.59–2.71 (m, 1 H, H-4), 2.83 (d, J = 0.7 Hz, 3 H, NMe), 3.18 (dd, J = 11.0, 10.0 Hz, 1 H, one of H-5), 3.21 (dd, J = 12.0, 10.0 Hz, 1 H, one of H-5), 3.60 (dd, J = 11.3, 6.8 Hz, 1 H, one of CH_2Cl), 3.62 (d, J = 7.5 Hz, 1 H, H-3), 3.67 (dd, J = 11.3, 4.6 Hz, 1 H, one of CH_2Cl), 7.27–7.34 (m, 3 H), 7.54–7.60 (m, 2 H).

***cis*- and *trans*-4-(Chloromethyl)-1-methyl-3-(methylthio)-pyrrolidin-2-ones (9a and 9b).** A mixture of **7** (1.52 g, 7.86 mmol) and $RuCl_2(PPh_3)_3$ (754 mg, 0.786 mmol) in benzene (40 mL) was heated in a sealed tube at 140 °C for 1 h. After workup as described above for **6**, the crude material was purified by chromatography on silica gel (hexane–AcOEt, 1:4) to give a mixture of **9a** and **9b**[10] (872 mg, 57%) as an oil: ^{1}H NMR (300 MHz) δ 2.24 (s, 3 H × 3/5, SMe for **9b**), 2.28 (s, 3 H × 2/5, SMe for **9a**), 2.50–2.67 (m, 3/5 H, H-4 for **9b**), 2.90 (s, 3 H, NMe for **9a**,**b**), 2.90–3.02 (m, 2/5 H, H-4 for **9a**), 3.20–3.31 (m, 7/5 H, H-3 for **9a**, one of H-5 for **9a**,**b**), 3.46 (d, J = 7.8 Hz, 3/5 H, H-3 for **9b**), 3.49 (dd, J = 10.0, 7.5 Hz, 2/5 H, one of H-5 for **9a**), 3.54 (dd, J = 10.1, 8.1 Hz, 3/5 H, one of H-5 for **9b**), 3.59 (dd, J = 11.1, 9.4 Hz, 2/5 H, one of CH_2Cl for **9a**), 3.67 (dd, J = 11.1, 7.0 Hz, 3/5 H, one of CH_2Cl for **9b**), 3.75 (dd, J = 11.1, 4.7 Hz, 3/5 H, one of CH_2Cl for **9b**), 3.82 (dd, J = 11.1, 6.0 Hz, 2/5 H, one of CH_2Cl for **9a**).

3-Methyl-1-(phenylthio)-3-azabicyclo[3.1.0]hexan-2-one (10). To a solution of **8a**,**b** (321 mg, 1.26 mmol) in *tert*-BuOH (7 mL) was added *tert*-BuOK (141 mg, 1.26 mmol), and the mixture was heated under reflux for 1.5 h. Water (20 mL) was added to the reaction mixture, and the whole was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/AcOEt, 1:1) to give **10** (251 mg, 91%): mp 69 °C (hexane/AcOEt); IR (CCl_4) ν 1705 cm^{-1}; ^{1}H NMR (60 MHz) δ 1.16 (t, J = 5 Hz, 1 H, one of H-6), 1.46 (dd, J = 8, 5 Hz, 1 H, one of H-6), 1.9–2.4 (m, 1 H, H-5), 2.79 (s, 3 H, NMe), 3.24 (d, J = 10 Hz, 1 H, one of H-4), 3.57 (dd, J = 10, 5 Hz, 1 H, one of H-4), 7.1–7.6 (m, 5 H). Anal. Calcd for $C_{12}H_{13}NOS$: C, 65.42; H, 6.41; N, 6.36. Found: C, 65.52; H, 6.22; N, 6.52.

2-(Phenylthio)-*N*-(2-propenyl)acetamide (12) and 2,2-Bis(phenylthio)-*N*-(2-propenyl)acetamide (13). A mixture of chloride **11** (1.25 g, 5.17 mmol) and $RuCl_2(PPh_3)_3$ (500 mg, 0.52 mmol) in benzene (50 mL) was heated in a sealed tube at 140 °C for 5 h. After workup as described above for **6**, the crude material was purified by chromatography on silica gel (hexane/AcOEt, 2:1). The first eluate gave **13** (124 mg, 8%): mp 94.5–95.5 °C (from hexane/AcOEt); IR (CCl_4) ν 1690 cm^{-1}; ^{1}H NMR (60 MHz) δ 3.79 (br t, J = 6 Hz, 2 H), 4.8–5.3 (m, 2 H), 4.89 (s, 1 H), 5.4–6.1 (m, 1 H), 6.3–6.8 (br, 1 H), 7.05–7.8 (m, 10 H). Anal. Calcd for $C_{17}H_{17}NOS_2$: C, 64.73; H, 5.43; N, 4.44. Found: C, 64.86; H,

(32) A similar result was reported for the reduction of *cis*-2,3,3a,4,7,7a-hexahydro-1-methyl-3a-phenylindole-2,3-dione, see: Tsuda, Y.; Isobe, K.; Ukai, A. *J. Chem. Soc., Chem. Commun.* 1971, 1554.

(33) We thank Professor S. F. Martin (The University of Texas at Austin) for providing spectra of compound **54**.

(34) ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ solutions with tetramethylsilane as an internal standard. For other general experimental details, see ref 24.

5.58; N, 4.58. The second eluate gave **12** (377 mg, 35%): mp 32–33 °C (from hexane/AcOEt); IR (CCl_4) ν 1680 cm^{-1}; ^1H NMR (60 MHz) δ 3.63 (s, 2 H), 3.85 (br t, J = 6 Hz, 2 H), 4.8–5.3 (m, 2 H), 5.4–6.1 (m, 1 H), 6.6–7.4 (br, 1 H), 7.26 (s, 5 H). Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.74; H, 6.32; N, 6.76. Found: C, 63.72; H, 6.30; N, 6.74.

Hexahydro-1-(chloromethyl)-2-(phenylthio)-3*H*-pyrrolizin-3-one (20). A mixture of chloride **18** (215 mg, 0.76 mmol) and $RuCl_2(PPh_3)_3$ (73 mg, 0.076 mmol) in benzene (20 mL) was heated in a sealed tube at 140 °C for 2 h. After workup as described above for **6**, the crude material was purified by chromatography on silica gel (hexane/AcOEt, 1:1) to give **20** (127 mg, 59%) as an oily mixture of four diastereoisomers in a ratio of 2:3:84:11 (by GLC analysis). Recrystallization of the mixture from hexane/AcOEt gave a pure sample of the (1*S*,2*R*,7a*S*)-isomer of **20**: mp 80–81 °C; IR (CCl_4) ν 1710 cm^{-1}; ^1H NMR (300 MHz) δ 1.11–1.27 (m, 1 H, H-7$_\beta$), 1.91–2.16 (m, 3 H, H_2-6 and H-7$_\alpha$), 2.29 (dtd, J = 10.8, 7.4, 3.5 Hz, 1 H, H-1), 3.07–3.17 (m, 1 H, H-5$_\alpha$), 3.55 (dt, J = 11.5, 7.9 Hz, 1 H, H-5$_\beta$), 3.66 (dd, J = 11.3, 7.4 Hz, 1 H, one of CH_2Cl), 3.71 (ddd, J = 9.0, 7.4, 5.6 Hz, 1 H, H-7a), 3.79 (dd, J = 11.3, 3.5 Hz, 1 H, one of CH_2Cl), 3.98 (d, J = 10.8 Hz, 1 H, H-2), 7.26–7.33 (m, 3 H), 7.53–7.60 (m, 2 H); ^{13}C NMR (75.4 MHz) δ 26.4, 31.6, 41.8, 44.3, 50.4, 56.0, 62.4, 128.2, 129.1, 132.7, 133.5, 169.6. Anal. Calcd for $C_{14}H_{16}ClNOS$: C, 59.70; H, 5.72; N, 4.97. Found: C, 59.46; H, 5.58; N, 5.39.

1-(Chloromethyl)-hexahydro-2-(methylthio)-3*H*-pyrrolizin-3-one (21). A mixture of **19** (1.45 g, 6.58 mmol) and $RuCl_2(PPh_3)_3$ (631 mg, 0.66 mmol) in benzene (60 mL) was heated in a sealed tube at 140 °C for 2 h. After workup as described above for **6**, the crude material was purified by chromatography on silica gel (hexane/AcOEt, 1:1) to give a diastereoisomeric mixture of **21** (969 mg, 67%) as an oil: IR (CCl_4) ν 1705 cm^{-1}; ^1H NMR (300 MHz) δ 1.38–1.58 (m, 1 H, one of H-7), 1.80–2.38 (m, 4 H, H-1, H_2-6, one of H-7), 2.19, 2.28 (both s, total 3 H, SMe), 3.08–3.19 (m, 1 H, one of H-5), 3.48–3.84 (m, 3 H, H-2, one of H-5, H-7a), 3.73 (dd, J = 11.4, 7.7 Hz, 1 H, one of CH_2Cl), 3.87 (dd, J = 11.4, 3.5 Hz, 1 H, one of CH_2Cl). Anal. Calcd for $C_9H_{14}ClNOS$: C, 49.20; H, 6.42; N, 6.37. Found: C, 49.55; H, 6.53; N, 6.53.

(1*R*,7a*S*)- and (1*S*,7a*S*)-Hexahydro-1-methyl-3*H*-pyrrolizin-3-ones (22a and 22b). From 20. To a solution of a diastereoisomeric mixture of **20** (91 mg, 0.32 mmol) in ethanol (5 mL) was added Raney nickel (ca. 200 mg), and the mixture was heated under reflux for 2 h. The Raney nickel was filtered off, and the filtrate was concentrated in vacuo to give a mixture of **22a**[16] and **22b**[16] (35 mg, 79%) as an oil: ^1H NMR for **22a** (300 MHz) δ 1.16 (d, J = 6.6 Hz, 3 H, CH_3), 1.33–1.46 (m, 1 H, one of H-7), 1.92–2.22 (m, 4 H, H-1, H_2-6, one of H-7), 2.41 (dd, J = 15.9, 11.0 Hz, 1 H, one of H-2), 2.53 (dd, J = 15.9, 8.3 Hz, 1 H, one of H-2), 3.04 (dddd, J = 11.8, 8.7, 4.3, 1.3 Hz, 1 H, one of H-5), 3.49 (td, J = 7.8, 6.0 Hz, H-7a), 3.55 (dt, J = 11.8, 7.2 Hz, 1 H, one of H-5). A small peak due to the methyl protons of **22b** appeared at δ 0.98 (d, J = 7.2 Hz). The ratio of **22a** and **22b** was estimated to be 95:5 by a integrated intensity of the peak heights of the signals due to their methyl protons.

From 21. According to a procedure similar to that described above for **20**, a diastereoisomeric mixture of compound **21** (114 mg, 0.52 mmol) was treated with Raney nickel (ca. 200 mg) to give a mixture of **22a** and **22b** (61 mg, 84%). The ratio **22a**/**22b** was estimated to be 94:6 by ^1H NMR spectroscopy.

(1*R*,2*R*,7a*S*)- and (1*R*,2*S*,7a*S*)-Hexahydro-2-(phenylthio)-1-[(propanoyloxy)methyl]-3*H*-pyrrolizin-3-one (23) and (1a*R*,6a*S*,6b*S*)-Hexahydro-1a-(phenylthio)-1*H*,2*H*-cyclopropa[*a*]pyrrolizin-2-one (25). To a solution of a diastereoisomeric mixture of **20** (50 mg, 0.177 mmol) in DMF (3 mL) was added cesium propanoate[17] (730 mg, 3.54 mmol), and the mixture was heated at 150 °C for 3 h. After the reaction mixture was cooled, water (90 mL) was added, and the whole was extracted with CH_2Cl_2. The extract was washed with a saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated in vacuo, and the residue was chromatographed on silica gel (hexane/AcOEt, 1:1). The first eluate gave **25** (36 mg, 83%): mp 92.5–93.5 °C (from hexane); IR (CCl_4) ν 1705 cm^{-1}; ^1H NMR (300 MHz) δ 0.9–1.08 (m, 1 H), 1.56 (t, J = 4.8 Hz, 1 H, H-1$_\alpha$), 1.63 (dd, J = 8.5, 4.8 Hz, 1 H, H-1$_\beta$), 1.70–1.92 (m, 2 H), 1.93–2.06 (m, 1 H), 2.32 (dd, J = 8.5, 4.8 Hz, 1 H, H-6b), 2.94 (ddd, J = 11.6, 9.5, 3.8 Hz, 1 H, one of H-4), 3.47 (dd, J = 10.8, 4.9 Hz, 1 H, H-6a), 3.61–3.71 (m, 1 H, one of H-4), 7.20–7.32 (m, 3 H), 7.45–7.50 (m, 2 H). Anal. Calcd for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71. Found: C, 68.26; H, 6.49; N, 5.89. The second eluate gave a 2:1 mixture of the (1*R*,2*R*,7a*S*)- and (1*R*,2*S*,7a*S*)-isomers of **23** (36 mg, 11%) as an oil: IR (CCl_4) ν 1735, 1700 cm^{-1}; ^1H NMR (300 MHz) δ 1.14 (t, J = 7.6 Hz, 3 H × 2/3), 1.23 (t, J = 7.6 Hz, 3 H × 1/3), 1.25–1.45 (m, 1 H), 1.84–2.15 (m, 3 H), 2.15–2.29 (m, 1 H), 2.33 (q, J = 7.6 Hz, 2 H), 3.0–3.16 (m, 1 H), 3.39–3.68 (m, 2 H), 3.67 (d, J = 11.3 Hz, 1/3 H), 3.93 (d, J = 11.0 Hz, 2/3 H), 4.18 (dd, J = 11.4, 6.8 Hz, 2/3 H), 4.34 (dd, J = 11.4, 3.9 Hz, 2/3 H), 4.36 (dd, J = 11.1, 7.6 Hz, 1/3 H), 4.46 (dd, J = 11.1, 7.1 Hz, 1/3 H), 7.23–7.35 (m, 3 H), 7.52–7.61 (m, 2 H). Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39. Found: C, 64.22; H, 6.81; N, 4.54.

(1*R*,2*R*,7a*S*)- and (1*R*,2*S*,7a*S*)-Hexahydro-2-(methylthio)-1-[(propanoyloxy)methyl]-3*H*-pyrrolizin-3-one (24) and (1a*R*,6a*S*,6b*S*)-Hexahydro-1a-(methylthio)-1*H*,2*H*-cyclopropa[*a*]pyrrolizin-2-one (26). Method A. To a solution of **21** (105 mg, 0.478 mmol) in DMF (4.5 mL) was added cesium propanoate (1.97 g, 9.56 mmol), and the mixture was heated at 80 °C for 1 h. After workup as described above for **20**, the crude material was purified by chromatography on silica gel (hexane/AcOEt, 1:1). The first eluate gave **26** (34 mg, 39%) as an oil: IR (CCl_4) ν 1705 cm^{-1}; ^1H NMR (300 MHz) δ 1.07–1.27 (m, 1 H), 1.41 (t, J = 4.6 Hz, 1 H, H-1$_\alpha$), 1.56 (dd, J = 8.3, 4.6 Hz, 1 H, H-1$_\beta$), 1.80–2.15 (m, 3 H), 2.18 (s, 3 H, SMe), 2.21 (dd, J = 8.3, 4.6 Hz, 1 H, H-6b), 2.95 (ddd, J = 11.9, 9.7, 3.2 Hz, 1 H, one of H-4), 3.46 (dd, J = 10.9, 5.1 Hz, 1 H, H-6a), 3.67 (dt, J = 11.9, 8.1 Hz, 1 H, one of H-4); ^{13}C NMR (75.4 MHz) δ 15.8, 24.4, 24.9, 30.5, 31.0, 34.7, 42.4, 61.4, 175.7; exact mass calcd for $C_9H_{13}NOS$, 183.0716, found 183.0694. The second eluate gave a 4:1 mixture of the (1*R*,2*R*,7a*S*)- and (1*R*,2*S*,7a*S*)-isomers of **24** (61 mg, 50%) as an oil: IR (CCl_4) 1740, 1700 cm^{-1}; ^1H NMR for (1*R*,2*R*,7a*S*)-isomer of **24** (300 MHz) δ 1.17 (t, J = 7.6 Hz, 3 H), 1.38–1.50 (m, 1 H, one of H-7), 1.97–2.33 (m, 4 H, H-1, H_2-6, one of H-7), 2.19 (s, 3 H, SMe), 2.38 (q, J = 7.6 Hz, 2 H), 3.07–3.19 (m, 1 H, one of H-5), 3.49–3.68 (m, 2 H, one of H-5, H-7a), 3.58 (d, J = 10.7 Hz, 1 H, H-2), 4.24 (dd, J = 11.4, 7.2 Hz, 1 H, one of OCH_2), 4.41 (dd, J = 11.4, 4.1 Hz, 1 H, one of OCH_2): a small singlet due to the *S*-methyl protons of (1*R*,2*S*,7a*S*)-isomer of **24** appeared at δ 2.27; exact mass calcd for $C_{12}H_{19}NO_3S$ 257.1084, found 257.1090.

Method B. A mixture of **21** (1.23 g, 5.61 mmol), cesium propanoate (3.47 g, 16.8 mmol), and 18-crown-6 (741 mg, 2.8 mmol) in chlorobenzene (90 mL) was heated under reflux for 10 h. After the reaction mixture cooled, water (20 mL) was added, and the organic layer was separated. The aqueous layer was further extracted with CH_2Cl_2, and the combined organic phases were washed with a saturated $NaHCO_3$ solution, dried over $MgSO_4$, and then concentrated in vacuo. The residue was chromatographed on silica gel (hexane/AcOEt, 1:1). The first eluate gave **26** (86 mg, 8%). The second eluate gave **24** (1.05 g, 73%).

(1*R*,7a*S*)-Hexahydro-1-[(propanoyloxy)methyl]-3*H*-pyrrolizin-3-one (27). A mixture of **24** (257 mg, 1 mmol) and Raney nickel (ca. 1 g) in ethanol (10 mL) was heated under reflux for 2.5 h. The Raney nickel was filtered off, the filtrate was concentrated in vacuo, and the residue was chromatographed on silica gel (AcOEt) to give **27** (182 mg, 86%) as an oil: $[\alpha]^{24}_D$ −15.2° (*c* 0.42, EtOH); IR (CCl_4) 1740, 1700 cm^{-1}; ^1H NMR (300 MHz) δ 1.16 (t, J = 7.6 Hz, 3 H), 1.34–1.51 (m, 1 H, one of H-7), 1.95–2.20 (m, 3 H, H_2-6, one of H-7), 2.36 (q, J = 7.6 Hz, 2 H), 2.40–2.60 (m, 3 H, H-1, H_2-2), 3.06 (ddd, J = 11.7, 8.1, 3.9 Hz, 1 H, one of H-5), 3.56 (dt, J = 11.7, 7.6 Hz, 1 H, one of H-5), 3.65–3.73 (m, 1 H, H-7a), 4.12 (dd, J = 11.0, 7.1 Hz, 1 H, one of OCH_2), 4.22 (dd, J = 11.0, 5.4 Hz, 1 H, one of OCH_2); ^{13}C NMR (75.4 Hz) δ 9.0, 26.8, 27.4, 31.4, 38.3, 41.1, 41.2, 65.0, 65.1, 173.0, 174.1; exact mass calcd for $C_{11}H_{17}NO_3$ 211.1207, found 211.1221.

(−)-Trachelanthamidine (28). A solution of **27** (63 mg, 0.3 mmol) in dry THF (1 mL) was added to a suspension of $LiAlH_4$ (45 mg, 1.2 mmol) in dry THF (10 mL), and the mixture was heated under reflux for 5 h. To the reaction mixture were added successively water (122 μL), 15% NaOH (122 μL), and water (122 μL) at 0 °C, and the mixture was dried over $MgSO_4$. The solvent was evaporated off, and the residue was chromatographed on silica gel ($CHCl_3$/MeOH/NEt_3, 5:4:1) to give **28** (37 mg, 88%) as an oil: $[\alpha]^{24}_D$ −10.3° (*c* 0.65, EtOH) [lit.[20a] $[\alpha]_D$ −13.5° (*c* 2.0,

EtOH)]; ^{1}H NMR (300 MHz) δ 1.52–2.10 (m, 7 H, H-1, H_2-2, H_2-6, H_2-7), 2.53–2.70 (m, 2 H, one of H-3, one of H-5); 3.08 (dt, J = 10.8, 6.4 Hz, 1 H, one of H-3), 3.26 (ddd, J = 9.6, 7.3, 3.9 Hz, 1 H, one of H-5), 3.41 (q, J = 7.3 Hz, 1 H, H-7a), 3.62 (br d, J = 6 Hz, 2 H, OCH_2), 4.45 (br s, 1 H, OH); ^{13}C NMR (75.4 MHz) δ 25.5, 29.6, 31.7, 48.0, 54.4, 54.6, 64.5, 67.8.

***N*-(Cyclohex-2-en-1-yl)-*N*-methyl-α-(phenylthio)acetamide (29).** To an ice-cooled solution of *N*-(cyclohex-2-en-1-yl)-*N*-methylamine[24] (1.9 g, 17.1 mmol) and pyridine (1.35 g, 17.1 mmol) in diethyl ether (50 mL) was added (phenylthio)acetyl chloride (3.43 g, 17.1 mmol), and the mixture was stirred at room temperature for 1 h. The reaction mixture was washed with water (5 mL) and dried over $MgSO_4$. The solvent was evaporated off, and the residue was chromatographed on silica gel (hexane/AcOEt, 2:1) to give **29** (3.25 g, 73%) as an oil: IR (CCl_4) ν 1640 cm^{-1}; ^{1}H NMR (60 MHz) δ 1.1–2.3 (m, 6 H), 2.75, 2.83 (both s, total 3 H), 3.73, 3.80 (both s, total 2 H), 4.2–4.5 (br, 1 H), 4.9–5.55 (m, 1 H), 5.7–6.1 (m, 1 H), 7.1–7.55 (m, 5 H); exact mass calcd for $C_{15}H_{19}NOS$ 261.1185, found 261.1181.

(3*R,3a*R**,4*S**,7a*S**)- and (3*S**,3a*R**,4*S**,7a*S**)-4-Chlorooctahydro-1-methyl-3-(phenylthio)indol-2-ones (31a and 31b).** A mixture of **30** (550 mg, 1.9 mmol) and $RuCl_2(PPh_3)_3$ (178 mg, 0.19 mmol) in benzene (40 mL) was heated in a sealed tube at 150 °C for 2 h. After workup as described above for **6**, the crude material was purified by chromatography on silica gel (hexane/AcOEt, 2:1). The first eluate gave **31a** (371 mg, 68%) as an oil: IR (CCl_4) ν 1705 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.29–1.43 (m, 1 H), 1.61–1.84 (m, 4 H), 1.92–2.05 (m, 1 H), 2.38 (ddd, J = 7.8, 5.3, 4.9 Hz, 1 H, H-3a), 2.76 (s, 3 H, NMe), 3.66 (q, J = 5.3 Hz, 1 H, H-7a), 3.78 (d, J = 4.9 Hz, 1 H, H-3), 4.00 (ddd, J = 8.5, 7.8, 4.0 Hz, 1 H, H-4), 7.26–7.35 (m, 3 H), 7.54–7.60 (m, 2 H); exact mass calcd for $C_{15}H_{18}ClNOS$ 295.0796, found 295.0772. The second eluate gave **31b** (21 mg, 4%) as an oil: IR (CCl_4) ν 1705 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.40–1.65 (m, 2 H), 1.70–1.82 (m, 2 H), 1.87–1.95 (m, 2 H), 2.68 (dt, J = 7.8, 5.9 Hz, 1 H, H-3a), 2.76 (d, J = 0.5 Hz, 3 H, NMe), 3.39 (td, J = 5.9, 4.3 Hz, 1 H, H-7a), 3.90 (d, J = 5.9 Hz, 1 H, H-3), 4.32 (dt, J = 7.8, 5.1 Hz, 1 H, H-4), 7.16–7.35 (m, 3 H), 7.57–7.63 (m, 2 H); exact mass calcd for $C_{15}H_{18}ClNOS$ 295.0796, found 295.0774.

(3*R,3a*R**,7a*S**)-Octahydro-1-methyl-3-(phenylthio)indol-2-one (32).** To a solution of **31a** (324 mg, 1.1 mmol) in toluene (10 mL) were added Bu_3SnH (320 mg, 1.1 mmol) and AIBN (18 mg, 0.11 mmol), and the mixture was heated under reflux for 10 h. After completion of the reaction, the solvent was evaporated off, and the residue was chromatographed on silica gel (hexane/AcOEt, 1:1) to give **32** (73 mg, 26%) as an oil. The spectral data of **32** were identical with those of an authentic sample.[25]

Octahydro-1-methyl-2a-(phenylthio)-1*H*-cycloprop[*cd*]indol-2-one (33). A mixture of **31a** (100 mg, 0.34 mmol) and DBU (259 mg, 1.7 mmol) in acetonitrile was heated in a sealed tube at 160 °C for 3 h. The solvent was evaporated off, and the residue was chromatographed on silica gel (hexane/AcOEt, 1:1) to give **33** (54 mg, 61%): mp 77 °C (hexane/AcOEt); IR (CCl_4) ν 1695 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.77–0.93 (m, 1 H), 1.12–1.30 (m, 2 H), 1.45–1.80 (m, 4 H), 2.13 (dd, J = 8.4, 7.2 Hz, 1 H, H-5b), 2.42 (s, 3 H, NMe), 3.59–3.64 (m, 1 H, H-5a), 6.88–6.95 (m, 1 H), 6.98–7.05 (m, 2 H), 7.14–7.19 (m, 2 H); ^{13}C NMR (75.4 MHz) δ 13.6, 17.8, 21.5, 27.7, 28.5, 29.8, 37.1, 51.3, 125.7, 128.4, 128.5, 136.1, 171.4. Anal. Calcd for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40. Found: C, 69.46; H, 6.68; N, 5.21.

(1*S,2*R**)-*N*-(2-Hydroxy-2-phenylcyclohex-1-yl)-*N*-methyl-α-(phenylthio)acetamide (36).** To an ice-cooled solution of amino alcohol **35**[24] (1 g, 4.87 mmol) and triethylamine (542 mg, 5.36 mmol) in CH_2Cl_2 (50 mL) was added (phenylthio)acetyl chloride (1 g, 5.36 mmol), and the mixture was stirred at 0 °C for 30 min and then at room temperature for 1 h. The reaction mixture was washed with water (10 mL) and dried over $MgSO_4$. The solvent was evaporated off, and the residue was chromatographed on silica gel (benzene/AcOEt, 5:1) to give **36** (1.43 g, 83%): mp 94–95 °C (hexane/AcOEt); IR ($CHCl_3$) ν 3375, 1620 cm^{-1}; ^{1}H NMR (60 MHz) δ 1.35–2.60 (m, 8 H), 2.12 (s, 3 H), 3.69 (s, 2 H), 4.4–4.8 (m, 1 H), 5.28 (s, 1 H), 7.1–7.8 (m, 10 H). Anal. Calcd for $C_{21}H_{25}NO_2S$: C, 70.95; H, 7.09; N, 3.94. Found: C, 70.60; H, 7.28; N, 4.24.

***N*-(2-Phenylcyclohex-2-en-1-yl)-*N*-methyl-α-(phenylthio)acetamide (37).** A solution of **36** (1.41 g, 4 mmol) in benzene (30 mL) containing a catalytic amount of *p*-toluenesulfonic acid monohydrate was heated under reflux for 2 h. The reaction mixture was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (benzene/AcOEt, 10:1) to give **37** (885 mg, 66%) as an oil: IR ($CHCl_3$) ν 1640 cm^{-1}; ^{1}H NMR (60 MHz) δ 1.5–2.5 (m, 6 H), 2.54 (s, 3 H), 3.53 (s, 2 H), 5.6–6.0 (m, 1 H), 6.1–6.4 (m, 1 H), 7.05–7.5 (m, 10 H); exace mass calcd for $C_{21}H_{23}NOS$ 337.1499, found 337.1521.

(3*R,3a*R**,4*R**,7a*S**)-4-Chlorooctahydro-1-methyl-3a-phenyl-3-(phenylthio)indol-2-one (39).** A mixture of **38** (147 mg, 0.4 mmol) and $RuCl_2(PPh_3)_3$ (76 mg, 0.08 mmol) in benzene (5 mL) was heated in a sealed tube at 140 °C for 2 h. After workup as described above for **6**, the crude material was purified by chromatography on silica gel to give **39** (70 mg, 48%): mp 143–145 °C (hexane/AcOEt); IR (CCl_4) ν 1705 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.43–1.55 (m, 1 H, one of H-6), 1.62 (ddt, J = 15.5, 12.7, 3.5 Hz, 1 H, H-7$_a$), 1.76–2.04 (m, 3 H, one of H-5, one of H-6, H-7$_β$), 2.09-2.18 (m, 1 H, one of H-5), 2.78 (s, 3 H, NMe), 3.84 (br s, $W_{1/2}$ = 8 Hz, 1 H, H-4), 4.17 (s , 1 H, H-3), 4.69 (t, J = 3.4 Hz, 1 H, H-7a), 7.15–7.28 (m, 7 H), 7.30–7.43 (m, 3 H); ^{13}C NMR (75.4 MHz) δ 14.2, 23.5, 27.0, 30.2, 51.9, 57.3, 59.0, 67.0, 127.1, 127.5, 128.0, 128.2, 128.3, 128.5, 128.8, 134.0, 140.0, 172.9. Anal. Calcd for $C_{21}H_{22}ClNOS$: C, 67.82; H, 5.96, N, 3.77. Found: C, 67.89; H, 6.01; N, 3.88.

1-(1,3-Benzodioxol-5-yl)-4-methoxycyclohexene (42). 5-Bromo-1,3-benzodioxole (13.15 g, 65.4 mmol) was added to a stirred suspension of magnesium turnings (1.59 g, 65.4 mmol) in dry THF (100 mL) at room temperature, and the mixture was heated under reflux for 5 h. After the reaction subsided, a solution of 4-methoxycyclohexanone (8.38 g, 65.4 mmol) in dry THF (20 mL) was added dropwise to the solution, and the mixture was heated under reflux for additional 3 h. After the reaction was quenched with 5% HCl (300 mL), the mixture was stirred at room temperature for 2 h. The mixture was extracted with diethyl ether, and the extract was dried over $MgSO_4$. The solvent was evaporated off, and the residue was chromatographed on silica gel (benzene) to give **42** (11.8 g, 78%) as an oil: ^{1}H NMR (60 MHz) δ 1.5–3.0 (m, 6 H), 3.36 (s, 3 H), 3.4–3.8 (m, 1 H), 5.86 (s, 3 H), 6.7–6.95 (m, 3 H). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.04; H, 6.81.

(1*R,2*S**,4*R**)- and (1*S**,2*R**,4*R**)-1-(1,3-Benzodioxol-5-yl)-2-bromo-4-methoxycyclohexan-1-ols (43a and 43b).** *N*-Bromosuccinimide (515 mg, 2.9 mmol) was added by portions to a stirred solution of **42** (673 mg, 2.9 mmol) in acetonitrile (10 mL) and water (2 mL) at 0 °C, and the mixture was stirred at room temperature for 3 h. Water (20 mL) was added to the reaction mixture, and the whole was extracted with diethyl ether. The extract was dried over $MgSO_4$, the solvent was evaporated off, and the residue was chromatographed on silica gel (benzene/AcOEt, 10:1). The first eluate gave the (1*S**,2*R**,4*R**)-isomer **43b** (171 mg, 18%) as an oil: ^{1}H NMR (300 MHz) δ 1.41–1.54 (m, 1 H), 1.73 (ddd, J = 13.6, 10.5, 3.4 Hz, 1 H), 1.95–2.06 (m, 1 H), 2.43–2.54 (m, 2 H), 2.51 (s, 1 H), 2.69 (dtd, J = 13.6, 4.6, 1.5 Hz, 1 H), 3.35 (s, 3 H), 3.40–3.49 (m, 1 H), 4.31 (dd, J = 9.8, 4.6 Hz, 1 H), 5.95, 5.96 (AB q, J = 1.4 Hz, 1 H each), 6.75–6.79 (m, 1 H), 7.10–7.14 (m, 2 H). The second eluate gave the (1*R**,2*S**,4*R**)-isomer **43a** (700 mg, 73%) as an oil: ^{1}H NMR (300 MHz) δ 1.69–1.80 (m, 1 H), 1.82–1.91 (m, 1 H), 1.93–2.03 (m, 1 H), 2.30–2.35 (m, 2 H), 2.57 (td, J = 13.2, 3.6 Hz, 1 H), 2.65 (s, 1 H), 3.30 (s, 3 H), 3.60–3.71 (m, 1 H), 4.36 (dd, J = 5.6, 3.4 Hz, 1 H), 5.915, 5.920 (AB q, J = 1.4 Hz, 1 H each), 6.75 (d, J = 8.1 Hz, 1 H), 6.91 (dd, J = 8.1, 1.8 Hz, 1 H), 6.96 (d, J = 1.8 Hz, 1 H). The compound **43a** thus obtained was used immediately in the next stage.

(1*R,2*S**,4*R**)-1-(1,3-Benzodioxol-5-yl)-4-methoxy-2-(methylamino)cyclohexan-1-ol (45).** Bromohydrin **43a** (1.54 g, 4.7 mmol) was dissolved in 40% methylamine in methanol (40 mL) and the mixture was heated in a sealed tube at 100 °C for 7 h. After the solvent and excess methylamine were evaporated off, 10% NaOH (10 mL) was added to the mixture, and the whole was extracted with $CHCl_3$. The extract was dried over $MgSO_4$, and the solvent was evaporated off to give **45** (1.3 g, 98%): mp 153–154 °C (diethyl ether); IR ($CHCl_3$) ν 3600, 3320 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.65–1.80 (m, 2 H), 1.86 (ddd, J = 13.4, 11.1, 3.2 Hz, 1 H), 1.97–2.07 (m, 1 H), 2.07–2.16 (m, 1 H), 2.20 (s, 3 H),

2.37–2.50 (m, 1 H), 2.79 (br s, $W_{1/2}$ = 7 Hz, 1 H, H-2), 3.37 (s, 3 H), 3.58 (double t, J = 10.7, 4.4 Hz, 1 H, H-4), 5.96 (s, 2 H), 6.78 (d, J = 8.1 Hz, 1 H), 6.94 (dd, J = 8.1, 1.9 Hz, 1 H), 7.06 (d, J = 1.9 Hz, 1 H): the signals due to NH and OH protons were not detected. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.25; H, 7.69; N, 5.16.

(1*S,2*R**,5*R**)-*N*-[2-(1,3-Benzodioxol-5-yl)-2-hydroxy-5-methoxycyclohex-1-yl]-*N*-methyl-α-(phenylthio)acetamide (46).** (Phenylthio)acetyl chloride (410 mg, 2.17 mmol) was added dropwise to a solution of **45** (551 mg, 1.97 mmol) and triethylamine (220 mg, 2.17 mmol) in CH_2Cl_2 (30 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction mixture was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (benzene/AcOEt, 2:1) to give **46** (678 mg, 80%) as an oil: IR ($CHCl_3$) ν 3375, 1620 cm^{-1}; ^1H NMR (60 MHz) δ 1.5–2.3 (m, 6 H), 2.28 (s, 3 H), 3.30 (s, 3 H), 3.6–4.0 (m, 1 H), 3.64 (s, 2 H), 4.95 (dd, J = 10, 6 Hz, 1 H), 5.27 (s, 1 H), 5.89 (s, 2 H), 6.70 (d, J = 8 Hz, 1 H), 6.9–7.6 (m, 7 H). Anal. Calcd for $C_{23}H_{27}NO_5 \cdot H_2O$: C, 61.73; H, 6.53; N, 3.12. Found: C, 61.28; H, 6.44; N, 3.02.

(1*S,5*R**)-*N*-[2-(1,3-Benzodioxol-5-yl)-5-methoxycyclohex-2-en-1-yl]-*N*-methyl-α-(phenylthio)acetamide (47).** To a solution of **46** (1.19 g, 3.24 mmol) in benzene (50 mL) was added *p*-toluenesulfonic acid monohydrate (62 mg, 0.32 mmol), and the mixture was heated under reflux for 1 h. The reaction mixture was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (benzene/AcOEt, 2:1) to give **47** (1.1 g, 97%): mp 92–93 °C (hexane/AcOEt); IR ($CHCl_3$) ν 1630 cm^{-1}; ^1H NMR (60 MHz) δ 1.7–2.6 (m, 4 H), 2.63 (s, 3 H), 3.37 (s, 3 H), 3.55–3.9 (m, 1 H), 3.61 (s, 2 H), 5.6–6.1 (m, 4 H), 6.5–6.9 (m, 3 H), 7.0–7.6 (m, 5 H). Anal. Calcd for $C_{23}H_{25}NO_4S$: C, 67.13; H, 6.12; N, 3.40. Found: C, 67.30; H, 6.63; N, 2.94.

(3*R,3a*R**,4*S**,6*S**,7a*R**)-3a-(1,3-Benzodioxol-5-yl)-4-chlorooctahydro-6-methoxy-1-methyl-3-(phenylthio)indol-2-one (49).** A mixture of **48** (277 mg, 0.62 mmol) and $RuCl(PPh_3)_3$ (119 mg, 0.124 mmol) in benzene (10 mL) was heated in a sealed tube at 150 °C for 2.5 h. After workup as described above for **6**, the crude material was purified by chromatography on silica gel (benzene/AcOEt, 2:1) to give **49** (129 mg, 57%) as an oil: IR ($CHCl_3$) 1690 cm^{-1}; ^1H NMR (300 MHz) δ 1.58–1.67 (m, 1 H), 1.86 (ddd, J = 15.2, 10.9, 4.5 Hz, 1 H), 2.17–2.27 (m, 1 H), 2.40–2.51 (m, 1 H), 2.81 (s, 3 H, NMe), 3.35 (s, 3 H, OMe), 3.70 (double t, J = 11.0, 4.0 Hz, 1 H, H-6), 3.98 (t, J = 3.4 Hz, 1 H, H-4), 4.13 (s, 1 H, H-3), 4.74 (t, J = 3.5 Hz, 1 H, H-7a), 6.02 (s, 2 H), 6.69 (dd, J = 8.2, 2.0 Hz, 1 H), 6.73 (d, J = 2.0 Hz, 1 H), 6.81 (d, J = 8.2 Hz, 1 H), 7.20–7.35 (m, 5 H); ^{13}C NMR (75.4 MHz) δ 27.2, 29.8, 35.4, 51.7, 56.1, 58.5, 59.2, 66.4, 70.2, 101.5, 107.8, 109.2, 121.8, 128.3, 128.6, 132.3, 133.0, 134.0, 147.0, 148.0, 172.2; exact mass calcd for $C_{23}H_{24}ClNO_4S$ 445.1113, found 445.1130.

(3a*R,4*R**,6*S**,7a*S**)-3a-(1,3-Benzodioxol-5-yl)-4-chlorooctahydro-6-methoxy-1-methylindole-2,3-dione (51).** To an ice-cooled solution of **49** (151 mg, 0.34 mmol) in CH_2Cl_2 (3 mL) containing a saturated $NaHCO_3$ solution (3 mL) was added *m*-CPBA (80%) (73 mg, 0.34 mmol) by portions, and the whole was stirred at 0 °C for 15 min and then at room temperature for 30 min. The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give quantitatively sulfoxide **50**, which was used without further purification in the next stage. To a 0 °C CH_2Cl_2 solution of **50** thus obtained were added successively 2,6-lutidine (73 mg, 0.68 mmol) and TFAA (137 mg, 0.68 mmol). The mixture was stirred at room temperature for 30 min and then heated under reflux for 1 h. After the reaction mixture cooled, a saturated $NaHCO_3$ solution (10 mL) was added, and the whole was stirred at room temperature for additional 2 h. The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt) to give **51** (105 mg, 87% based on **49**) as an oil: IR ($CHCl_3$) ν 1770, 1720 cm^{-1}; ^1H NMR (60 MHz) δ 1.5–2.9 (m, 4 H), 2.93 (s, 3 H), 3.37 (s, 3 H), 3.5–4.0 (m, 1 H), 4.1–4.6 (m, 2 H), 5.94 (s, 2 H), 6.73 (s, 2 H), 6.82 (s, 1 H); exact mass calcd for $C_{17}H_{18}ClNO_5$ 351.0871, found 351.0867.

(3a*S,6*S**,7a*S**)-3a-(1,3-Benzodioxol-5-yl)-2,3,3a,6,7,7a-hexahydro-6-methoxy-1-methylindole-2,3-dione (52).** A mixture of **51** (105 mg, 0.3 mmol) and DBU (228 mg, 1.5 mmol) in acetonitrile (20 mL) was heated in a sealed tube at 160 °C for 3 h. After the solvent had been evaporated off, CH_2Cl_2 was added to the residue, and the whole was washed with 1% HCl. The organic layer was dried over $MgSO_4$, the solvent was evaporated off, and the residue was chromatographed on silica gel (benzene/AcOEt, 1:1) to give **52** (45 mg, 48%): mp 200–201 °C (hexane/AcOEt); IR ($CHCl_3$) ν 1760, 1710 cm^{-1}; ^1H NMR (60 MHz) δ 1.5–2.7 (m, 2 H), 3.13 (s, 3 H), 3.41 (s, 3 H), 3.55–3.95 (m, 1 H), 4.03 (t, J = 4 Hz, 1 H), 5.56 (br d, J = 10 Hz, 1 H, H-4), 5.92 (s, 2 H), 6.26 (dd, J = 10, 3 Hz, 1 H, H-5), 6.63 (s, 2 H), 6.70 (s, 1 H). Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.78; H, 5.32; N, 4.52.

(3*R,3a*S**,6*S**,7a*S**)-3a-(1,3-Benzodioxol-5-yl)-2,3,3a,6,7,7a-hexahydro-6-methoxy-1-methylindol-3-ol (53).** To a stirred suspension of $LiAlH_4$ (16 mg, 0.42 mmol) in dry THF (5 mL) was added a solution of **52** (45 mg, 0.14 mmol) in dry THF (1 mL), and the mixture was heated under reflux for 1 h. After the usual workup, the crude material was purified by chromatography on silica gel ($CHCl_3$/MeOH, 97:3) to give **53**[28a] (27 mg, 63%) as an oil: IR ($CHCl_3$) ν 3550 cm^{-1}; ^1H NMR (300 MHz) δ 1.44 (ddd, J = 13.5, 11.0, 2.9 Hz, 1 H), 2.12–2.21 (m, 2 H), 2.34 (s, 3 H, NMe), 2.38 (br s, 1 H), 2.62 (dd, J = 10.5, 5.5 Hz, 1 H), 3.12 (d, J = 10.5 Hz, 1 H), 3.42 (s, 3 H), 3.96 (ddt, J = 11.0, 5.4, 1.5 Hz, 1 H), 4.43 (br s, 1 H), 5.79 (dt, J = 10.5, 1.5 Hz, 1 H), 5.93 (s, 2 H), 6.17 (dt, J = 10.5, 1.5 Hz, 1 H), 6.74 (br s, 2 H), 6.80 (br s, 1 H).

(3*R,3a*S**,6*S**,7a*S**)-3a-(1,3-Benzodioxol-5-yl)-2,3,3a,6,7,7a-hexahydro-6-methoxy-1-methyl-3-(pivaloyloxy)indole (54).** Pivaloyl chloride (7 mg, 0.06 mmol) was added to a solution of **53** (14 mg, 0.04 mmol) in dry pyridine (1 mL), and the mixture was stirred at 30–40 °C for 1 h. The solvent was evaporated off, and the residue was chromatographed on silica gel ($CHCl_3$) to give **54**[27] (15 mg, 83%) as an oil: IR ($CHCl_3$) ν 1720, 1485, 1240, 1160, 1040 cm^{-1}; ^1H NMR (200 MHz) δ 1.18 (s, 9 H), 1.43 (ddd, J = 12.5, 10.5, 2.0 Hz, 1 H), 2.14 (dt, J = 12.5, 4.7 Hz, 1 H), 2.35 (s, 3 H), 2.52 (br s, 1 H), 2.77 (dd, J = 11.5, 7.0 Hz, 1 H), 3.09 (dd, J = 11.5, 2.0 Hz, 1 H), 3.42 (s, 3 H), 3.95–4.08 (m, 1 H), 5.46 (dd, J = 7.0, 2.0 Hz, 1 H), 5.66 (dt, J = 10.5, 1.5 Hz, 1 H), 5.94 (s, 2 H), 6.08 (br d, J = 10.5 Hz, 1 H), 6.74 (d, J = 8.0 Hz, 1 H), 6.82 (dd, J = 8.0, 2.0 Hz, 1 H), 6.86 (d, J = 2.0 Hz, 1 H); ^{13}C NMR (50.3 MHz) δ 26.1, 27.1, 38.7, 40.5, 53.6, 55.9, 62.3, 73.0, 73.3, 80.2, 101.0, 107.6, 107.9, 120.2, 128.7, 128.9, 138.2, 146.1, 147.7, 178.2.

Acknowledgment. This work was supported by the Takeda Science Foundation and a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

Supplementary Material Available: ^1H NMR spectra of **24**, **26**, **27**, **29**, **31a**, **31b**, **37**, **43a**, **43b**, **49**, and **51** and ^{13}C NMR spectra of **26**, **39**, and **49** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.