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DIASTEREOSELECTIVE ALKYLATION OF CHIRAL TIN(II) ENOLATES ONTO CYCLIC ACYL IMINIUM IONS. ASYMMETRIC TOTAL SYNTHESIS OF (-)-SUPINIDINE

Yoshimitsu Nagao,*[a] Wei-Min Dai,[a] Masahito Ochiai,[a] and Motoo Shiro[b]

[a] Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan
[b] Shionogi Research Laboratories, Shionogi & Co. Ltd., Fukushima-ku, Osaka 553, Japan

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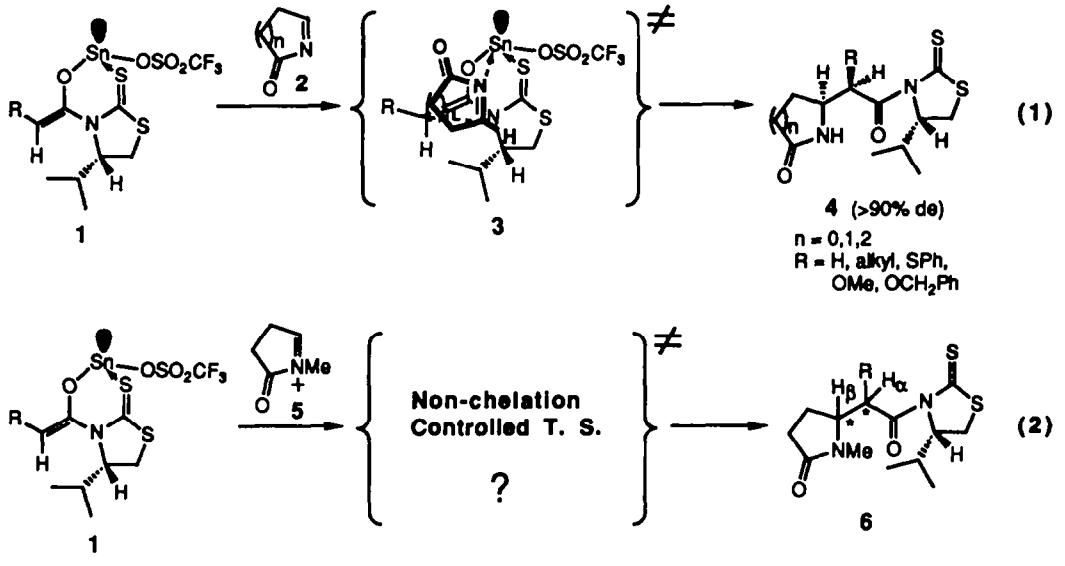
Abstract: The scope and mechanism of the asymmetric alkylation of chiral tin (II) enolate 10 with cyclic acyl iminium ion 5 were investigated. An application of the reaction to the asymmetric synthesis of (-)-supinidine was also achieved.

Recent progress in acyl iminium ion chemistry, especially the development in the formation of carbon-carbon bonds (amidoalkylation) via acyl iminium ions, has led to the wide use of acyl iminium ions in alkaloid synthesis.[1] Of particular interest are cyclic acyl iminium ions with which carbon-carbon bond formation reactions could be performed under very mild conditions because of their high electrophilic reactivity toward nucleophiles. Cyclic acyl iminium ions possessing chiral center(s) in the molecules have been extensively used in asymmetric synthesis of alkaloids via the asymmetric intramolecular cyclization promoted by acyl iminium ion.[2] Intermolecular asymmetric amidoalkylation utilizing chiral acyl iminium ion with achiral nucleophiles has also been reported.[3,4] Previously, we succeeded in a highly diastereoselective alkylation of chiral tin (II) enolates onto cyclic acyl imines, derived *in situ* from 4-acetoxy-2-azetidinone, 5-acetoxy-2-pyrrolidinone, and 6-acetoxy-2-piperidinone, to afford the corresponding alkylation products in >90% diastereomeric excess (de). This asymmetric alkylation methodology was successfully applied to syntheses of 1β-substituted carbapenems[5] and bicyclic alkaloids having a nitrogen atom ring juncture.[6,7] In a preliminary communication,[8] we reported another new type of diastereofacial recognition of chiral tin(II) enolates by cyclic acyl iminium ions and its application to an asymmetric total synthesis of (-)-supinidine (38). We now report a detailed account of this novel amidoalkylation reaction including *X*-ray crystallographic analyses of some major products which support a non-chelation-controlled reaction pathway.

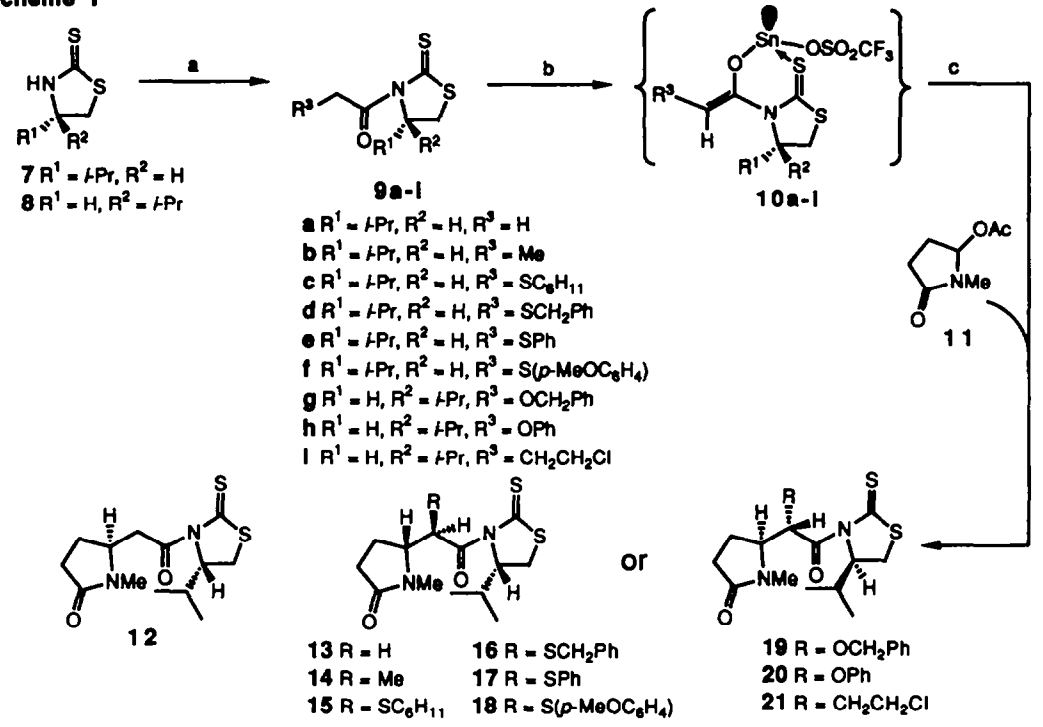
Asymmetric Alkylation of Chiral Tin(II) Enolates onto Cyclic Acyl Iminium Ions. As depicted in Equation 1, reaction of chiral tin(II) enolate 1 with cyclic acyl imine 2 furnished the corresponding alkylation product 4 in a highly diastereo-

selective manner. The stereochemical results of this asymmetric alkylation reaction were rationalized in terms of a six-membered chelated transition state 3.[5-7] If this alkylation could be extended to cyclic acyl iminium ion 5, its reaction with chiral tin(II) enolate 1 would also afford chiral lactam 6 (Equation 2). But, in this case, the nitrogen atom of the electron-deficient cyclic acyl iminium ion 5 does not have the ability to form a chelate with a metal atom. Thus, the reaction of 5 with 1 might take place via a non-chelation-controlled transition state. The stereochemistry of the alkylation product 6 is a very interesting point of the reaction in view of its potential use in organic synthesis.



3-Acyl-4(*S*)- or 3-acyl-4(*R*)-isopropyl-1,3-thiazolidine-2-thiones (9a-i) were prepared from 4(*S*)- or 4(*R*)-isopropyl-1,3-thiazolidine-2-thione (4(*S*)- or 4(*R*)-IPTT) (7 or 8) by our reported methods.[5a,b,7,9] Reaction of tin(II) enolate 10a derived from 9a by the known method[5a,9] with 1-methyl-5-acetoxy-2-pyrrolidinone (11) in THF (-5 - 0 ℃) afforded a diastereomeric mixture of lactam 12 and its C(5) epimer 13 in a 50:50 ratio and in 64% yield (Scheme I and entry 1 in Table I). Methanolysis of the mixture in the presence of K_2CO_3 in absolute MeOH gave the racemic methyl ester 22 in 85% yield (Scheme II). This stereochemical result is quite different from that found in the reaction of the same tin(II) enolate with 5-acetoxy-2-pyrrolidinone under the same reaction conditions.[7] However, similar reaction of tin(II) enolates 10b-i having an α-substituent at the amide moiety with compound 11 furnished the major alkylation products 14-21 with diastereoselectivity. Chromatographic separation of the crude products on a silica gel column afforded an inseparable mixture of 14-21 and one or two of the three minor congenors in all cases (except for 20), and the other minor components in the cases of entries 3-8 were also isolated (Scheme I and entries 2-9 in Table I). A diastereomerically pure sample of compound 14 was obtained by fractional

Scheme I[a]



[a] (a) Method A: NaH, R^3CH_2COCl, THF, rt; Method B: $R^3CH_2CO_2H$, DCC-DMAP, CH_2Cl_2, rt; (b) $Sn(OSO_2CF_3)_2$, *N*-ethylpiperidine, THF; (c) 11 (1.5 mol eq), THF, -5 to 0 °C, 2 h.

Scheme II

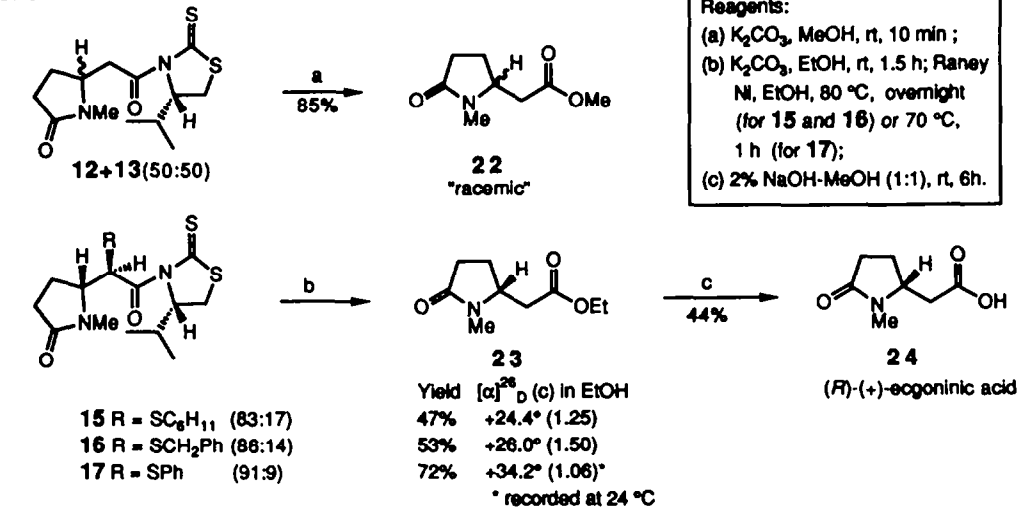


Table I. Diastereoselective Alkylation of Chiral Tin(II) Enolate **10** onto Compound **11**[a] in THF

entry	enolate	major product	diastereomeric ratio[c]	isolated yields[d] major;	minors[e]
1	**10a**, R^3 = H	**12+13**	50 : 50	64% (50:50);[f]	
2	**10b**, R^3 = Me	**14**	75 : 25	53% (76:24);[f]	
3	**10c**, R^3 = SC_6H_{11}	**15**	61 : 22 : 10 : 7	46% (83:17);[f]	15% (70:30)[h]
4	**10d**, R^3 = SCH_2Ph	**16**	61 : 21 : 10 : 8	57% (86:14);[f]	21% (75:25)[h]
5	**10e**, R^3 = SPh	**17**	78 : 11 : 6 : 5	57% (91:9);[f]	5%, 2%
6	**10f**, R^3 = S(*p*-$MeOC_6H_4$)	**18**	81 : 9 : 6 : 4	41% (86:9:5);[g]	4%
7	**10g**, R^3 = OCH_2Ph	**19**	54 : 33 : 7 : 6	56% (66:34);[f]	5%, 4%
8	**10h**, R^3 = OPh	**20**	76 : 16 : 6 : 2	41%;	9%, 5% (72:28)[h]
9	**10i**, R^3 = CH_2CH_2Cl[b]	**21**	78 : 22	65% (78:22)[f]	

[a]Ca. 85% pure **11** was used. [b]Carried out in CH_2Cl_2. [c]Checked by HPLC analysis (see Experimental Section). [d]Calculated based on **10**. [e]The stereochemistry of the minor products was not assigned. [f]Ratio of an inseparable mixture of the major product and a minor component. [g]Ratio of an inseparable mixture of the major product and two minor components. [h]Ratio of an inseparable mixture of two minor components.

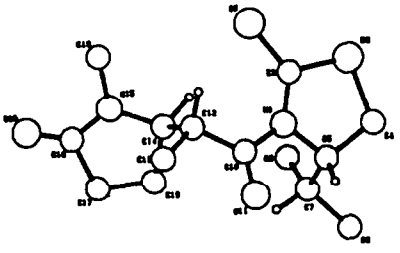


Figure 1. Perspective view of the crystallographic structure of compound **14**.

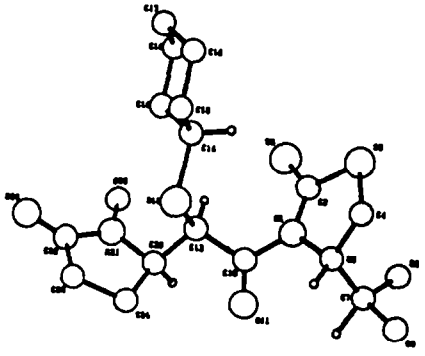


Figure 2. Perspective view of the crystallographic structure of compound **15**.

(Crystallographic details have been submitted to the Cambridge Crystallographic Data Centre)

crystallization and its absolute configuration was established by *X*-ray crystallographic analysis as depicted in Figure 1. The absolute configuration at the C(5) atom of **14** was proved to be *R*. In order to determine the absolute configuration at the C(5) atom, the diastereomeric mixture of the major alkylation products **15**-**17** was converted to the same ethyl ester (+)-**23** via ethanolysis followed by reductive desulfurization (Scheme II). The ethyl ester (+)-**23** ([α]$_D^{24}$ +34.2° (c 1.06, EtOH)) obtained from **17** was further transformed to (*R*)-(+)-ecgoninic acid (**24**) (mp 119-120 °C (CH_2Cl_2-Et_2O), [α]$_D^{27}$ +30.5° (c 0.87, EtOH)), which is the antipode of the known (*S*)-(-)-ecgoninic acid[10] (mp 121-122 °C,

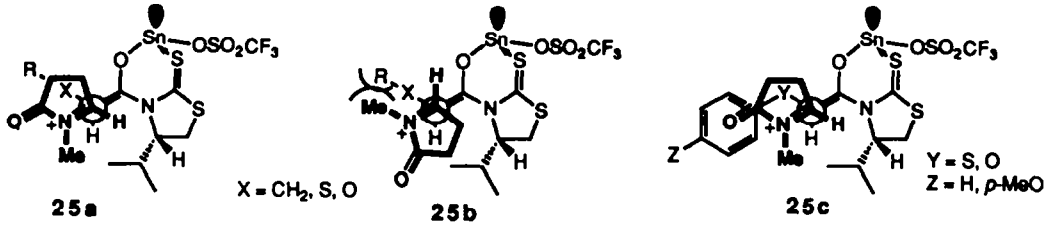
$(\alpha)^{23}_{D}$ -41.6° (EtOH)). Thus, the absolute configuration at C(5) of the major alkylation products 15-17 was also shown to be *R*. This result was also supported by the *X*-ray analysis of the diastereomerically pure compound 15 obtained by fractional crystallization (see Figure 2). The absolute configuration at C(5) of 19-21 was tentatively assigned to be *S*. Assuming consistency of the reaction mechanism, the cis relationship between the C(5) proton and the R group in 16-21 was proposed based on the results found for compounds 14 and 15. The stereochemistry of the minor components could not be assigned based on the chemical shifts of H_α and $J_{\alpha,\beta}$ values (see Table II).

Table II. Chemical Shifts of H_α and $J_{\alpha,\beta}$ Values for Diastereomeric Compounds 6

compound 6	chemical shifts[a] of H_α ($J_{\alpha,\beta}$)[b] major product;	minor products[c]		
R = Me	**14**, 5.11 (3.67);[e]	5.06 (3.67)[e]		
R = SC_6H_{11}	**15**, 5.99 (3.9);	6.14 (6.5),	6.44 (3.91),[e]	6.46 (5.37),[e]
R = SCH_2Ph	**16**, 5.87 (3.9);	6.10 (5.4),	6.12 (6.4),	6.19 (5.4),
R = SPh	**17**, 6.46 (3.9);	6.58 (6.8),	6.69 (4.4),	6.74 (3.9),
R = S(*p*-$MeOC_6H_4$)	**18**, 6.34 (4.4);[f]	6.44 (4.2),[f]	6.51 (4.3),[f]	6.53 (6.9),[f]
R = OCH_2Ph[d]	**19**, 6.17 (1.95);[e]	6.14 (6.35),[e]	6.36 (4.4),	6.42 (2.0),
R = OPh[d]	**20**, 7.08 (2.0);[f]	6.79 (5.7),[f]	6.97 (5.1),[f]	7.10 (3.8),[f]
R = CH_2CH_2Cl[d]	**21**, 5.29 (2.94);[e]	5.11 (3.67)[e]		

[a]Chemical shifts were recorded in $CDCl_3$ at 100 MHz and are given in ppm using $SiMe_4$ as internal standard. [b]$J_{\alpha,\beta}$ values were obtained in Hz. [c]The stereochemistry of the minor products was not assigned. [d]4(*R*)-IPTT was used. [e]Recorded at 400 MHz. [f]Recorded at 200 MHz.

Thus, it was demonstrated that the asymmetric recognition mode of the cyclic acyl iminium ion 5 by chiral tin(II) enolates should be quite different from that of the cyclic acyl imine 2 which has been revealed to undergo via the six-membered chelated transition state 3.[5-7] The stereochemical results shown in Table I can be rationalized in terms of a non-chelation-controlled transition state 25a and/or 25b as illustrated in the Newman projection. The major products 14-21 might be expected to predominate via 25a rather than 25b which would be destablized by the steric repulsion between the *N*-methyl and the R groups. Although the steric bulk of SC_6H_{11}, SPh, and S(*p*-$MeOC_6H_4$) groups is almost

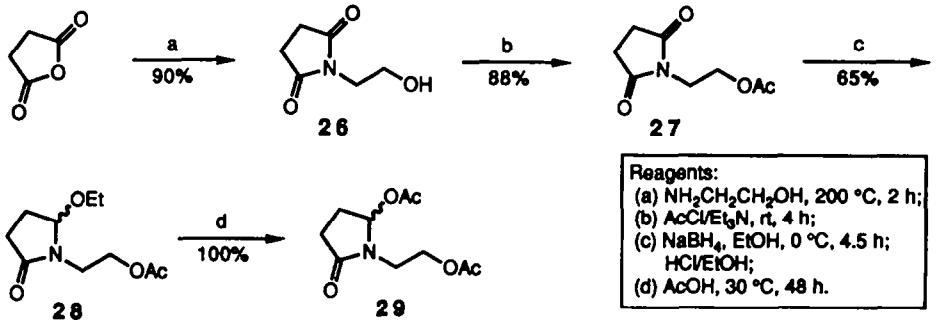


25a 25b 25c

similar, the efficiency of the asymmetric inductions with enolates 10c, e, f was different as shown in Table I. It is reasonable to suggest an electronic effect such as a π-π attraction[11] between the electron-deficient carbonyl group of the acyl iminium moiety and the electron-rich phenyl group of the chiral tin(II) enolate in the transition state as shown in 25c. This rationalization was also applicable to the alkylation of enolates 10e and 10h with higher major/minors ratios compared to enolates 10d and 10g. In the cases of enolates 10d and 10g having one methylene group between the phenyl group and the hetero-atom, such a π-π attraction in the transition state is not available due to the separated distance for each other.

Asymmetric Total Synthesis of (-)-Supinidine (38). Based on the above results, we designed a synthetic route to (-)-supinidine (38) as depicted in Schemes III and IV. The choice of the chiral tin(II) enolate 31 has the following merits: a) use of 4(*R*)-IPTT moiety can produce the desired absolute configuration at C(5) in the major alkylation product 32; b) use of a phenylthio group as the substituent in enolate 31 will provide higher diastereoselectivity for production of the desired compound 32, perhaps due to the π-π attraction mentioned above; c) presence of the phenylthio group in the alkylation product 32 facilitates the introduction of a double bond at the C(1)-C(2)[12] position of 38.

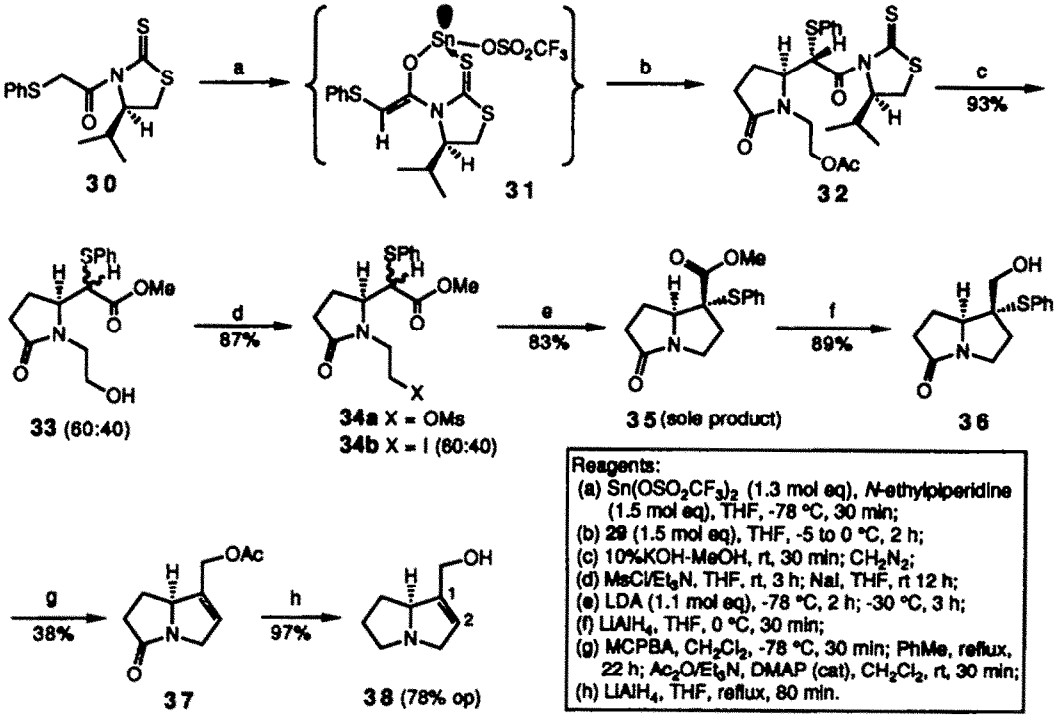
Scheme III



The required cyclic acyl iminium ion precursor 29 was prepared from succinic anhydride as shown in Scheme III. Heating succinic anhydride with 2-aminoethanol at 200 ℃ for 2 h gave *N*-hydroxyethyl succinimide 26 in 90% yield. Acetylation of 26 with AcCl/Et_3N at room temperature for 4 h afforded the acetate 27 in 88% yield. Conversion of 27 to 5-ethoxy-2-pyrrolidinone derivative 28 was achieved by reduction of 27 with $NaBH_4$ in EtOH under the Speckamp conditions[13] in 65% yield. Treatment of 28 with acetic acid[14] at 30 ℃ for 48 h furnished the unstable diacetoxy compound 29 in quantitative yield.

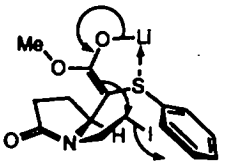
Reaction of chiral tin(II) enolate 31 derived from 30 by the usual method[7] with compound 29 (1.5 mol equiv) in THF at -5 - 0 ℃ for 2 h gave a mixture of the four diastereomeric products in a ratio of 82 : 8 : 7 : 3 (by the HPLC analysis) (Scheme IV). Chromatographic separation of the mixture on a silica gel column afforded an inseparable mixture of the major product 32 and a minor com-

Scheme IV

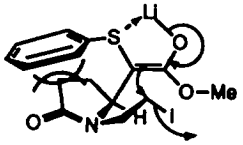


ponent in a 91:9 ratio and in 58% yield. The other two minor components were also isolated in 3% and 2% yields, respectively. The mixture of compound 32 was subjected to saponification with 10% aqueous KOH followed by methylation with CH_2N_2 to give methyl ester 33 in 93% yield. The asymmetric carbon atom substituted with a phenylthio group in 33 was found to epimerize under the saponification conditions and the diastereomeric ratio was determined to be 60:40 by the integration of the two methoxy signals on the ^1H NMR chart. To construct the C(1)-C(2) bond, compound 33 was transformed to the corresponding iodide 34b via mesylation with MsCl/Et_3N followed by replacement of the mesylate group in 34a by iodide anion in 87% yield from 33. Intramolecular annulation of 34b was performed by its treatment with 1.1 mol equiv of LDA in THF at -78 °C (2 h) and then at -30 °C (3 h) to afford the product 35[15] with the desired pyrrolizidine skeleton. The bicyclic compound 35 was shown to be diastereomerically pure by 400 MHz ^1H NMR analysis. The intramolecular annulation could be predicted to undergo via the preferable transition state 39a rather than 39b destablized by the steric repulsion between the phenylthio group and the methylene proton(s) of the lactam moiety. Compound 35 was reduced to alcohol 36 with $LiAlH_4$ in THF at 0 °C for 30 min in 89% yield. Transformation of 36 to compound 37 was accomplished according to the reported method.[15] Thus, oxidation of the sulfide gave the corresponding sulfoxide. Pyrolysis of the sulfoxide formed an allylic alcohol which was acetylated to produce acetate 37 in 38% overall yield from 36. Finally, reducton of

37 with $LiAlH_4$ in THF under reflux[16] furnished (-)-supinidine (38) in 97% yield. The synthesized compound 38 ($[\alpha]_D^{21}$ -8.0° (c 0.55, EtOH)) was proved to be 78% optical purity[17] based on the reported data[18] ($[\alpha]_D^{18}$ -10.3° (c 1.65, EtOH)) and its physical data was consistent with the reported ones.[16,19]



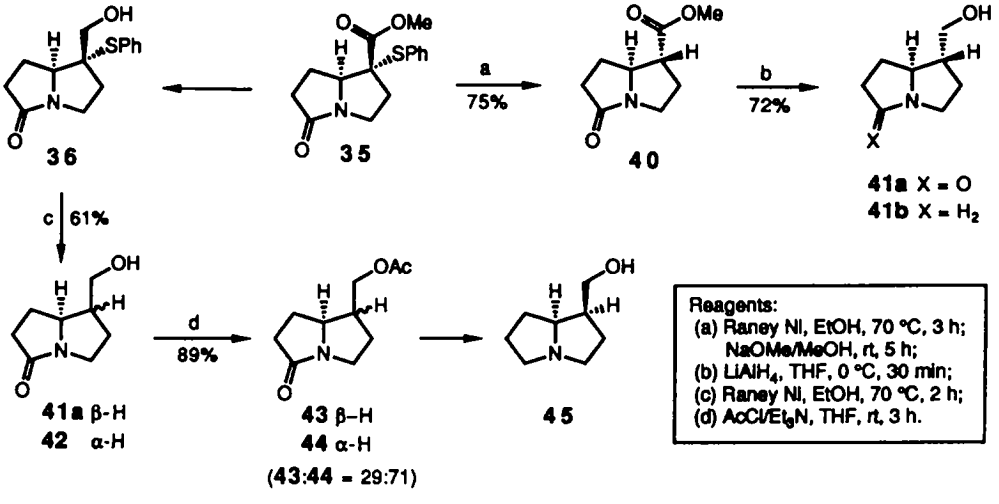
39a



39b

Compound 35 is also a suitable intermediate for syntheses of saturated pyrrolizidine alkaloids, (-)-trachelanthamidine (41b) and (-)-isoretronecanol (45) (Scheme V). Heating 35 with excess Raney Ni in EtOH at 70 ℃ for 3 h[15] followed by treatment with sodium methoxide[20] in MeOH gave the thermodynamically stable exo-ester 40 in 75% overall yield. The stereochemistry of 40 was deduced by comparing its ^{13}C NMR spectrum with reported data.[21] On the other hand, compound 36 was treated with excess Raney Ni in EtOH at 70 ℃ for 2 h to give a mixture of the major product 42 with its minor epimer 41a in 61% yield. The ^{13}C NMR spectrum of compound 42 was distinguishably different from that of compound 41a derived from 40. Acetylation of the mixture gave the corresponding mixture of 43 and 44 in 89% yield. The ratio (29:71) of compounds 43 and 44 was confirmed by the 400 MHz ^1H NMR analysis. Compounds 40 and 44 have been converted to (-)-trachelanthamidine (41b)[22] and (-)-isoretronecanol (45),[23] respectively. Thus, our present work also constitutes formal syntheses of these pyrrolizidine alkaloids.

Scheme V



In summary, we established an asymmetric amidoalkylation utilizing chiral tin(II) enolate onto achiral cyclic acyl iminium ions. This alkylation reaction proceeded via a different asymmetric recognition mode from the case of the same chiral tin(II) enolate toward cyclic acyl imines and the diastereoselectivity of the reaction could be interpreted in terms of a non-chelation-controlled transition state. A non-bonding π-π attraction of the reactants in the transition state may influence diastereoselectivity. This finding seems to be useful for the design of new asymmetric reaction. Based on the results of this asymmetric alkylation, an asymmetric total synthesis of (-)-supinidine (38) was successfully performed.

Experimental Section

General Methods. Melting points were measured on a Yanagimoto apparatus and are uncorrected. Infrared spectra (IR) were recorded on a JASCO A-202 spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained in the indicated solvents with a JEOL JNM-FX 100 spectrometer (100 MHz), a VARIAN Gemini 200 spectrometer (200 MHz), or a JEOL JNM-GX 400 spectrometer (400 MHz); signals are given in ppm using $SiMe_4$ as internal standard. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded in the indicated solvents with a JEOL JNM-FX 100 spectrometer (25 MHz); signals are given in ppm using $CHCl_3$ as internal standard. Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained on a JEOL JMS-DX 300 mass spectrometer. Combustion analyses were performed by Yanaco CHN corder MT-3. Optical rotations were recorded on a JASCO DIP-181 polarimeter in the indicated solvents. High-performance liquid chromatography (HPLC) was performed on a Shimadzu LC-4A instrument equipped with a SPD-2AS UV detector using the indicated column.

All reactions were monitored by thin-layer chromatography employing 0.25 mm E. Merck silica gel plates (60F-254) with UV light irradiation and 10% ethanolic phosphomolybdic acid-heating as detecting methods. Preparative thin-layer chromatography (preparative TLC) was performed on E. Merck silica gel plates (60F-254, 0.5 mm x 20 cm x 20 cm). Flash column chromatography was carried out on E. Merck silica gel (60, particle size 230-400 mesh). Workup means drying over anhydrous Na_2SO_4, filtration, and concentration in vacuo. THF and toluene were distilled from sodium benzophenone ketyl under N_2. Diisopropylamine, *N*-ethylpiperidine, Et_3N, and CH_2Cl_2 were distilled from CaH_2. Absolute MeOH and EtOH were obtained by treating with sodium metal and then distillation under N_2. All other reagents were used as purchased. 4(*S*)- and 4(*R*)-Isopropyl-1,3-thiazolidine-2-thione (4(*S*)- and 4(*R*)-IPTT) was prepared according to our reported method.[9] Tin trifluoromethanesulfonate was prepared according to literature procedures.[24]

Preparation of Compounds 9. Compounds **9a**, **9b**, **9d**, **9e**, and **9g** were obtained by reported procedures.[5a,b,7,9] Compounds **9c**, **9f**, and **9h** were synthesized by Method B[7] (1 mol equiv of 4(*S* or *R*)-IPTT (**7** or **8**), 1.2 mol equiv of $R^3CH_2CO_2H$, 1.2 mol equiv of DCC, and 0.12 mol equiv of DMAP in CH_2Cl_2, room temperature, 5-13 h). Compound **9i** was prepared by Method A[7] (1.1 mol equiv of NaH, 1 mol equiv

of 4(*R*)-IPTT (8), and 1.1 mol equiv of R^3CH_2COCl in THF, room temperature, 1.5 h). Physical data for compounds 9c, 9f, 9h, and 9i are given as follows.

3-((Cyclohexylthio)acetyl)-4(*S*)-isopropyl-1,3-thiazolidine-2-thione (9c): The crude product was purified by column chromatography (elution with 14% EtOAc in hexane) to afford 9c (95%) as a yellow oil; $(\alpha)^{18}_D$ +291.3° (c 0.59, $CHCl_3$); IR ($CHCl_3$) 1680, 1285, and 1135 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.99 and 1.07 (6 H, d, J = 7.0 Hz), 1.14-2.18 (10 H, m), 2.18-2.58 (1 H, m), 2.58-2.94 (1 H, br s), 3.03 (1 H, dd, J = 1.5, 11.5 Hz), 3.54 (1 H, dd, J = 8.0, 11.5 Hz), 4.22 and 4.35 (2 H, AB q, J = 15.0 Hz), 5.17 (1 H, ddd, J = 1.5, 6.5, 8.0 Hz); MS *m/z* 317 (M^+), 234, 202, 162, 156, 118, 83, 55, 41 (100); HRMS calcd for $C_{14}H_{23}NOS_3$ MW 317.0948, found *m/z* 317.0951 (M^+). Anal. Calcd for $C_{14}H_{23}NOS_3$: C, 52.96; H, 7.30; N, 4.41. Found: C, 52.97; H, 7.27; N, 4.51.

3-(((4-Methoxyphenyl)thio)acetyl)-4(*S*)-isopropyl-1,3-thiazolidine-2-thione (9f): The crude product was purified by column chromatography (elution with 20% EtOAc in hexane) to afford 9f (57%) as a yellow oil; $(\alpha)^{18}_D$ +294.7° (c 0.29, $CHCl_3$); IR ($CHCl_3$) 1730 (shoulder), 1688 (br), 1590, 1570, 1488, 1285, 1240, 1210 (shoulder), 1155, 1140, 1120, 1030, 905, and 828 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.98 and 1.06 (6 H, d, J = 6.9 Hz), 2.34 (1 H, m), 3.03 (1 H, dd, J = 1.2, 11.5 Hz), 3.49 (1 H, dd, J = 8.1, 11.5 Hz), 3.80 (3 H, s), 4.58 (2 H, s), 5.10 (1 H, ddd, J = 1.2, 6.1, 8.1 Hz), 6.85 and 7.42 (4 H, A_2B_2 m); MS *m/z* 341 (M^+), 202, 180 (100), 160, 150, 135, 118; Anal. Calcd for $C_{15}H_{19}NO_2S_3$: C, 52.76; H, 5.61; N, 4.10. Found: C, 52.99; H, 5.50; N, 3.96.

3-(Phenoxyacetyl)-4(*R*)-isopropyl-1,3-thiazolidine-2-thione (9h): The crude product was purified by column chromatography (elution with 14% EtOAc in hexane) to afford 9h (73%) as yellow prisms; mp 97-98 °C (recrystallized from EtOAc-hexane); $(\alpha)^{18}_D$ -269.6° (c 0.80, $CHCl_3$); IR ($CHCl_3$) 1708 (br), 1598, 1588, 1498, 1365, 1265, 1232, 1170 (br), 1082, 1070, 1038, and 830 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.00 and 1.09 (6 H, d, J = 7.0 Hz), 2.41 (1 H, m), 3.12 (1 H, d, J = 11.6 Hz), 3.64 (1 H, dd, J = 8.3, 11.7 Hz), 5.21 (1 H, br t, J = 7.0 Hz), 5.50 and 5.64 (2 H, AB q, J = 17.2 Hz), 6.93 (2 H, d, J = 7.7 Hz), 7.01 (1 H, d, J = 7.1 Hz), 7.31 (2 H, t, J = 7.7 Hz); MS *m/z* 295 (M^+), 202 (100), 162, 134, 118, 105, 77, 69; Anal. Calcd for $C_{14}H_{17}NO_2S_2$: C, 56.92; H, 5.80; N, 4.74. Found: C, 56.90; H, 5.71; N, 4.81.

3-(4-Chlorobutyryl)-4(*R*)-isopropyl-1,3-thiazolidine-2-thione (9i): 95% yield; yellow oil; $(\alpha)^{18}_D$ -348.4° (c 0.63, $CHCl_3$). Anal. Calcd for $C_{10}H_{16}NOS_2Cl$: C, 45.18; H, 6.07; N, 5.27. Found: C, 45.50; H, 6.17; N, 5.51. Other spectral data were indentical with its enantiomer.[7]

1-Methyl-5-acetoxy-2-pyrrolidinone (11). A solution of 1-methyl-5-ethoxy-2-pyrrolidinone[13] (5.80 g) in acetic acid (200 mL) was stirred at 30 °C for 24 h and then under slightly reduced pressure for another 24 h. Acetic acid was carefully removed in vacuo below 40 °C (water bath temperature) to give an unstable

red oil (6.0 g, ca. 85% pure by ^{1}H NMR) which was used for further reaction without purification. IR ($CHCl_3$) 1735, 1700, 1220 (br), 1105, and 990 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 2.10 (3 H, s), 1.92-2.52 (4 H, m), 2.85 (3 H, s), 6.10-6.24 (1 H, m).

General Procedure for Alkylation of Chiral Tin(II) Enolate 10 onto Compound 11. To the tin(II) enolate 10 (3.0 mmol), prepared from 9 by the usual method,[7] was added an ca. 1.0 M solution of 1-methyl-5-acetoxy-2-pyrrolidinone (11, 4.5 mmol) in dry THF (in the case of compound 9i, dry CH_2Cl_2 was used instead of THF) at -5 ℃. The whole mixture was then stirred between -5 to 0 ℃ for 2 h. The reaction mixture was poured into a mixture of phosphate buffer solution (pH 7.0, 75 mL) and EtOAc (75 mL) with vigorous stirring. The precipitate was filtered off through Celite and the residue was washed with EtOAc (3 x 50 mL). The combined filtrate was washed with brine and worked up to provide a crude product. A sample of the crude product was submitted to HPLC analysis using UV 305 nm as detection (Conditions for compound 14: column, Finepak sil ϕ 4.6 mm x 25 cm; eluent, EtOAc-CH_2Cl_2 (25:75); flow rate, 2.0 mL/min. For compound 15: column, Nucleo sil 5C 18 ϕ 4.6 mm x 15 cm; eluent, CH_3CN-H_2O (50:50); flow rate, 0.5 mL/min. For compound 16: column, Finepak sil ϕ 4.6 mm x 25 cm; eluent, EtOAc-hexane (65:35); flow rate, 1.0 mL/min. For compound 17: column, Diasil 5C 18 ϕ 4.6 mm x 25 cm; eluent, CH_3CN-H_2O (60:40); flow rate, 0.5 mL/min. For compound 18: column, Finepak sil ϕ 4.6 mm x 25 cm; eluent, EtOAc-hexane (50:50); flow rate, 2.0 mL/min. For compound 19: column, Finepak sil ϕ 4.6 mm x 25 cm; eluent, EtOAc-hexane (65:35 for 25 min, and then 80:20); flow rate, 1.0 mL/min. For compound 20: column, Finepak sil ϕ 4.6 mm x 25 cm; eluent, EtOAc-hexane (20:80); flow rate, 1.0 mL/min. For compound 21: column, Finepak sil ϕ 4.6 mm x 25 cm; eluent, EtOAc-CH_2Cl_2 (20:80); flow rate, 1.0 mL/min. The diastereomeric components 12 and 13 could not be separated by the HPLC analysis and the ratio was obtained by ^{1}H NMR analysis). The diastereomeric ratios were given in Table I. Flash column chromatography of the crude product (elution with EtOAc-hexane-$CHCl_3$ (2:1:4) for 12 and 13, EtOAc-CH_2Cl_2 (1:3) for 14, EtOAc-hexane-$CHCl_3$ (1:1:2) for 15-20, or EtOAc-CH_2Cl_2 (1:6) for 21) afforded the products 12-21, respectively, together with the corresponding minor components (see Table I). Physical data for compounds 12-21 are reported as follows.

3-((1-Methyl-5-oxo-2(*SR*)-pyrrolidinyl)acetyl)-4(*S*)-isopropyl-1,3-thiazolidine-2-thione (12 and 13): yellow oil as a 50:50 mixture of 12 with its C(5) epimer 13; IR ($CHCl_3$) 1680, 1675, and 1165 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 0.99 and 1.08 (6 H, d, J = 7.0 Hz), 1.50-2.60 (5 H, m), 2.80 and 2.83 (3 H, s, ca. 1:1 ratio), 2.92-4.24 (5 H, m), 5.20 (1 H, m); MS *m/z* 300 (M^+), 267, 202, 111, 98 (100); HRMS calcd for $C_{13}H_{20}N_2O_2S_2$ MW 300.0984, found *m/z* 300.0992 (M^+). Anal. Calcd for $C_{13}H_{20}N_2O_2S_2$: C, 51.97; H, 6.71; N, 9.32. Found: C, 51.90; H, 6.73; N, 9.33.

3-(2(*R*)-(1-Methyl-5-oxo-2(*R*)-pyrrolidinyl)propionyl)-4(*S*)-isopropyl-1,3-thiazolidine-2-thione (14): yellow prisms obtained by franctional crystalliza-

tion of a 76:24 mixture of 14 with a minor diastereomer from EtOAc-hexane; mp 107-109.5 ℃; $[\alpha]_D^{25}$ +359.1° (c 0.33, $CHCl_3$); IR ($CHCl_3$) 1685 (shoulder), 1672, 1355, 1248, 1168, 1150, 1113, and 905 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (3 H, d, J = 6.61 Hz), 1.04 (3 H, d, J = 7.34 Hz), 1.06 (3 H, d, J = 7.40 Hz), 1.88-1.98 (1 H, m), 2.02-2.11 (1 H, m), 2.24-2.45 (3 H, m), 2.83 (3 H, s), 3.04 (1 H, dd, J = 1.47, 11.00 Hz), 3.53 (1 H, dd, J = 8.07, 11.00 Hz), 4.28 (1 H, m), 5.11 (1 H, dq, J = 3.67, 6.60 Hz), 5.24 (1 H, ddd, J = 1.47, 6.61, 8.07 Hz); MS *m/z* 314 (M^+), 281, 216, 162, 125, 98 (100), 69; HRMS calcd for $C_{14}H_{22}N_2O_2S_2$ MW 314.1119, found *m/z* 314.1118 (M^+). Anal. Calcd for $C_{14}H_{22}N_2O_2S_2$: C, 53.47; H, 7.05; N, 8.91. Found: C, 53.35; H, 6.87; N, 8.94.

3-(2(*R*)-(1-Methyl-5-oxo-2(*R*)-pyrrolidinyl)(cyclohexylthio)acetyl)-4(*S*)-isopropyl-1,3-thiazolidine-2-thione (15): yellow prisms obtained by fractional crystallization of a 83:17 mixture of 15 with a minor diastereomer from EtOAc-hexane; mp 126-128 ℃; $[\alpha]_D^{25}$ +285.9° (c 0.36, $CHCl_3$); IR ($CHCl_3$) 1673 (br), 1310, 1245, and 1150 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.99 and 1.08 (6 H, d, J = 6.8 Hz), 1.12-2.80 (16 H, m), 2.85 (3 H, s), 3.12 (1 H, dd, J = 1.0, 11.7 Hz), 3.61 (1 H, dd, J = 7.8, 11.7 Hz), 4.04-4.27 (1 H, m), 4.92 (1 H, ddd, J = 1.0, 6.5, 7.8 Hz), 5.99 (1 H, d, J = 3.9 Hz); MS *m/z* 414 (M^+), 316, 299, 234, 202, 162, 138, 118, 98 (100), 55; HRMS calcd for $C_{19}H_{30}N_2O_2S_3$ MW 414.1454, found *m/z* 414.1446 (M^+). Anal. Calcd for $C_{19}H_{30}N_2O_2S_3$: C, 55.04; H, 7.29; N, 6.76. Found: C, 55.02; H, 7.31; N, 6.92.

3-(2(*R*)-(1-Methyl-5-oxo-2(*R*)-pyrrolidinyl)(benzylthio)acetyl)-4(*S*)-isopropyl-1,3-thiazolidine-2-thione (16): yellow oil as a 86:14 mixture of 16 with a minor diastereomer; IR ($CHCl_3$) 1675 (br), 1305, 1240, 1205, and 1150 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.94 (3 H, d, J = 7.3 Hz), 1.02 (3 H, d, J = 8.3 Hz), 1.80-2.60 (5 H, m), 2.71 (2.6 H, s), 2.90 (0.4 H, s), 2.98 (1 H, br d, J = 11.7 Hz), 3.38 (1 H, dd, J = 7.8, 11.7 Hz), 3.75 (1.7 H, s), 3.86 (0.3 H, s), 4.02-4.26 (1 H, m), 4.81 (1 H, br t, J = 6.8 Hz), 5.87 (0.86 H, d, J = 3.9 Hz), 6.12 (0.14 H, d, J = 6.4 Hz), 7.29 (5 H, s); MS *m/z* 422 (M^+), 331, 324, 299, 261, 234, 202, 162, 138, 118, 98 (100), 91; HRMS calcd for $C_{20}H_{26}N_2O_2S_3$ MW 422.1136, found *m/z* 422.1123 (M^+). Anal. Calcd for $C_{20}H_{26}N_2O_2S_3$: C, 56.84; H, 6.20; N, 6.63. Found: C, 56.76; H, 6.22; N, 6.64.

3-(2(*R*)-(1-Methyl-5-oxo-2(*R*)-pyrrolidinyl)(phenylthio)acetyl)-4(*S*)-isopropyl-1,3-thiazolidine-2-thione (17): yellow oil as a 91:9 mixture of 17 with a minor diastereomer; IR ($CHCl_3$) 1685 (shoulder), 1675, 1330, 1305, 1242, 1152, and 905 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.84-1.10 (6 H, m), 1.98-2.80 (5 H, m), 2.60 (3 H, s), 2.98 (1 H, dd, J = 1.0, 11.2 Hz), 3.29 (1 H, dd, J = 7.2, 11.2 Hz), 4.16-4.38 (1 H, m), 4.85 (1 H, ddd, J = 1.0, 6.0, 8.0 Hz), 6.46 (0.91 H, d, J = 3.9 Hz), 6.58 (0.09 H, d, J = 6.8 Hz), 7.24-7.60 (5 H, m); MS *m/z* 408 (M^+), 310, 299, 247, 202, 161, 118 (100), 98 (100), 59; HRMS calcd for $C_{19}H_{24}N_2O_2S_3$ MW 408.0980, found *m/z* 408.0967 (M^+). Anal. Calcd for $C_{19}H_{24}N_2O_2S_3$: C, 55.85; H, 5.92; N, 6.86. Found: C, 55.60; H, 5.91; N, 6.92.

3-(2(*R*)-(1-Methyl-5-oxo-2(*R*)-pyrrolidinyl)((4-methoxyphenyl)thio)acetyl)-4-(*S*)-isopropyl-1,3-thiazolidine-2-thione (18): yellow oil as a 86:9:5 mixture of 18 with two minor diastereomers; IR ($CHCl_3$) 1685 (shoulder), 1675, 1590, 1495, 1245, 1150, 1030, 905, and 825 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90-1.10 (6 H, m), 2.10-1.75 (5 H, m), 2.60 (3 H, s), 2.85-3.20 (1 H, m), 3.31-3.56 (1 H, m), 3.80 (3 H, s), 4.15-4.32 (1 H, m), 4.70-4.92 (1 H, m), 6.34 (0.86 H, d, J = 4.4 Hz), 6.44 (0.09 H, d, J = 4.2 Hz), 6.53 (0.05 H, J = 6.9 Hz), 6.80-6.95 and 7.33-7.50 (4 H, A_2B_2 m); MS *m/z* 439 (M^++1), 340, 277, 202, 180, 161, 118, 98 (100); Anal. Calcd for $C_{20}H_{26}N_2O_3S_3$: C, 54.77; H, 5.97; N, 6.39. Found: C, 54.64; H, 5.97; N, 6.13.

3-(2(*S*)-(1-Methyl-5-oxo-2(*S*)-pyrrolidinyl)(benzyloxy)acetyl)-4(*R*)-isopropyl-1,3-thiazolidine-2-thione (19): yellow oil as a 66:34 mixture of 19 with a minor diastereomer; IR ($CHCl_3$) 1685 (shoulder), 1672, 1247, 1168, 1152, and 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 and 1.02 (4 H, d, J = 6.84 Hz), 0.94 and 1.01 (2 H, d, J = 6.84 Hz), 1.76-1.90 (1 H, m), 2.07-2.38 (3 H, m), 2.53-2.63 (1 H, m), 2.71 (2 H, s), 2.91 (0.34 H, dd, J = 0.98, 11.23 Hz), 2.96 (1 H, s), 3.04 (0.66 H, dd, J = 1.46, 11.23 Hz), 3.13 (0.34 H, dd, J = 8.30, 11.72 Hz), 3.49 (0.66 H, dd, J = 8.30, 11.23 Hz), 4.02-4.08 (0.34 H, m), 4.16-4.22 (0.66 H, m), 4.39 and 4.57 (1.3 H, AB q, J = 12.21 Hz), 4.47 and 4.66 (0.7 H, AB q, J = 12.21 Hz), 4.87 (0.34 H, ddd, J = 0.98, 5.90, 8.30 Hz), 5.21 (0.66 H, ddd, J = 1.46, 6.35, 8.31 Hz), 6.14 (0.34 H, d, J = 6.35 Hz), 6.17 (0.66 H, d, J = 1.95 Hz), 7.24-7.40 (5 H, m); MS *m/z* 406 (M^+), 325, 315, 308, 298, 218, 161, 138, 126, 118, 98 (100), 91, 77; HRMS calcd for $C_{20}H_{26}N_2O_3S_2$ MW 406.1403, found *m/z* 406.1416 (M^+). Anal. Calcd for $C_{20}H_{26}N_2O_3S_2$: C, 59.09; H, 6.45; N, 6.89. Found: C, 59.08; H, 6.53; N, 6.89.

3-(2(*S*)-(1-Methyl-5-oxo-2(*S*)-pyrrolidinyl)phenoxyacetyl)-4(*R*)-isopropyl-1,3-thiazolidine-2-thione (20): yellow powder; mp 121-123 °C; $(\alpha)^{18}_D$ -224.4° (c 0.72, $CHCl_3$); IR ($CHCl_3$) 1680 (br), 1595 (br), 1498, 1255, 1235 (br), 1170, 1158, and 1090 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.96 and 1.05 (6 H, d, J = 6.8 Hz), 1.85-2.80 (5 H, m), 2.88 (3 H, s), 3.10 (1 H, dd, J = 1.6, 11.7 Hz), 3.60 (1 H, dd, J = 8.5, 11.7 Hz), 4.44 (1 H, dt, J = 8.9, 2.4 Hz), 5.33 (1 H, ddd, J = 1.5, 5.9, 8.5 Hz), 6.79 (2 H, d, J = 7.7 Hz), 6.99 (1 H, t, J = 7.5 Hz), 7.08 (1 H, d, J = 2.0 Hz), 7.20-7.35 (2 H, m); MS *m/z* 392 (M^+), 299, 294, 240, 202, 160, 138, 117, 98 (100); Anal. Calcd for $C_{19}H_{24}N_2O_3S_2$: C, 58.14; H, 6.16; N, 7.14. Found: C, 57.78; H, 5.96; N, 7.10.

3-(2(*S*)-(1-Methyl-5-oxo-2(*S*)-pyrrolidinyl)-4-chlorobutyryl)-4(*R*)-isopropyl-1,3-thiazolidine-2-thione (21): yellow oil as a 78:22 mixture of 21 with a minor diastereomer; IR ($CHCl_3$) 1685 (shoulder), 1670, 1365, 1300, 1240 (br), 1170, 1148, 1110, 1090, and 905 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 and 1.07 (4.68 H, d, J = 6.60 Hz), 1.00 and 1.09 (1.32 H, d, J = 6.60 Hz), 1.63-1.71 (0.78 H, m), 1.85-2.39 (6.22 H, m), 2.86 (0.66 H, s), 2.87 (2.34 H, s), 3.04 (0.22 H, br d, J = 11.74 Hz), 3.05 (0.78 H, br d, J = 11.74 Hz), 3.41-3.50 (1 H, m), 3.53 (0.22 H, dd, J = 8.07, 11.74 Hz), 3.57 (0.78 H, dd, J = 8.07, 11.74 Hz), 3.57-

3.65 (1 H, m), 4.06 (0.22 H, m), 4.37 (0.78 H, m), 5.11 (0.22 H, ddd, J = 3.67, 3.67, 10.27 Hz), 5.24 (0.78 H, br t, J = 7.00 Hz), 5.26 (0.22 H, br t, J = 6.60 Hz), 5.29 (0.78 H, ddd, J = 2.94, 2.94, 11.00 Hz); MS m/z 364 (M^++2), 362 (M^+), 329, 264, 225, 200, 173, 162, 124, 98 (100); HRMS calcd for $C_{15}H_{23}N_2O_2S_2Cl$ MW 362.0885, found m/z 362.0883 (M^+). Anal. Calcd for $C_{15}H_{23}N_2O_2S_2Cl$: C, 49.64; H, 6.39; N, 7.72. Found: C, 49.80; H, 6.33; N, 7.73.

Methyl (*S*)-1-Methyl-5-oxo-2-pyrrolidineacetate (22). To a solution of the 50:50 mixture of 12 and 13 (0.332 g, 1.10 mmol) in absolute MeOH (5 mL) was added solid K_2CO_3 (50 mg) and the mixture was stirred at room temperature for 10 min (the original yellow color of the solution disappeared). The solid was filtered off through Celite and the filtrate was concentrated to give a residue. Flash column chromatographic separation (elution with 50% EtOAc in $CHCl_3$) of the residue furnished 0.16 g (85%) of the known compound 22 in racemic form as a colorless oil. Its spectral data were indentical with the reported ones.[7] 4(*S*)-IPTT (0.124 g, 70%) was recovered.

Conversion of Major Alkylation Products 15-17 to Ethyl (*R*)-1-Methyl-5-oxo-2-pyrrolidineacetate (23). Representative Procedure. To a solution of the 91:9 mixture of 17 (0.40 g, 0.98 mmol) in absolute EtOH (5 mL) was added solid K_2CO_3 (40 mg) and the mixture was stirred at room temperature for 1.5 h (the original yellow color of the solution disappeared). The solid was filtered off through Celite and the filtrate was concentrated to give a residue. Flash column chromatography (elution with EtOAc-hexane-$CHCl_3$ (1:1:2)) of the residue afforded 0.239 g (83%) of the corresponding ethyl ester as a colorless oil. 4(*S*)-IPTT (90 mg, 57%) was recovered. To a solution of the ethyl ester obtained above (0.181 g, 0.617 mmol) in EtOH (5 mL) was added excess Raney nickel (W-2) followed by heating the mixture at 70 ℃ for 1 h (at 80 ℃, overnight for the esters obtained from 15 and 16). Raney nickel was filtered off through Celite and the filtrate was concentrated to give a crude product. Preparative TLC (developing with 20% acetone in $CHCl_3$) of the crude product provided 100 mg (87%) of 23 as a colorless oil: $(\alpha)^{24}_D$ +34.2° (c 1.06, EtOH); IR ($CHCl_3$) 1728, 1675, 1250, 1182, 1113, and 1020 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.28 (3 H, t, J = 7.0 Hz), 1.60-2.78 (6 H, m), 2.82 (3 H, s), 3.80-4.02 (1 H, m), 4.18 (2 H, q, J = 7.0 Hz); MS m/z 185 (M^+), 157, 149, 98, 84, 70; HRMS calcd for $C_9H_{15}NO_3$ MW 185.1030, found m/z 185.1025 (M^+). Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.59; H, 7.90; N, 7.68.

(*R*)-(+)-Ecgoninic acid (24). A solution of 23 (72 mg, 0.389 mmol, $(\alpha)^{24}_D$ +34.2° (c 1.06, EtOH)) in a mixture of 2% NaOH (2 mL) and MeOH (2 mL) was stirred at room temperature for 6 h. The reaction mixture was treated with 5% HCl, extracted with CH_2Cl_2, and then submitted to the usual workup to afford 27 mg (44%) of 24. Recrystallization from CH_2Cl_2 gave colorless crystals: mp 119-120 ℃; $(\alpha)^{26}_D$ +30.5° (c 0.87, EtOH); IR ($CHCl_3$) 3500-2400 (br), 1715, 1673, 1642, 1400, 1300, 1250, 1180, and 1110 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.64-2.72 (6 H, m), 2.84 (3 H, s), 3.76-4.06 (1 H, m), 9.08 (1 H, br s); MS m/z 157 (M^+),

129, 98 (100), 70, 55; HRMS calcd for $C_7H_{11}NO_3$ MW 157.0736, found *m/z* 157.0736 (M^+). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.50; H, 7.07; N, 8.80. (*S*)-(-)-**24**:[10] mp 121-122 °C, $[\alpha]^{23}_D$ -41.6° (EtOH).

N-(2-Hydroxyethyl) Succinimide (**26**). A mixture of succinic anhydride (39.0 g, 0.39 mol) and 2-aminoethanol (25 mL, 0.39 mol) was heated at 200 °C for 2 h and then distilled under vacuum at 200-250 °C (oil bath temperature) to give 50.0 g (90%) of **26** as colorless prisms: bp 160-164 °C/3 mm Hg; mp 61-62 °C (EtOAc-hexane); IR ($CHCl_3$) 3450, 1773, 1698, 1400, 1160, and 1078 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.75 (5 H, br s, one of them is exchangable by D_2O), 3.73 (4 H, br s); MS *m/z* 142 (M^+-1), 125, 124, 113, 100 (100), 84, 55. Anal. Calcd for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.26; H, 6.37; N, 9.64.

N-(2-Acetoxyethyl) Succinimide (**27**). To a solution of **26** (20.0 g, 0.14 mol) in dry THF (400 mL) cooled in an ice-water bath was added successively acetyl chloride (12.9 mL, 0.18 mol) and triethylamine (14 mL, 0.18 mol). The mixture was stirred at room temperature for 4 h and the precipitate was then filtered off through a short silica gel column by elution with EtOAc. The collections were condensed to give a crude product which was distilled under vacuum to afford 22.86 g (88%) of **27** as a pale yellow oil: bp 133-135 °C/0.15 mm Hg; IR ($CHCl_3$) 1775, 1735, 1700, 1388, 1215 (br), 1108, and 1055 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.02 (3 H, s), 2.73 (4 H, s), 3.77 (2 H, t, J = 5.3 Hz), 4.24 (2 H, t, J = 5.3 Hz); MS *m/z* 185 (M^+), 155, 142, 124, 113, 84, 55, 44 (100); HRMS calcd for $C_8H_{11}NO_4$ MW 185.0716, found *m/z* 185.0722 (M^+). Anal. Calcd for $C_8H_{11}NO_4$: C, 51.89; H, 5.99; N, 7.56. Found: C, 52.05; H, 5.88; N, 7.79.

1-(2-Acetoxyethyl)-5-ethoxy-2-pyrrolidinone (**28**). To a solution of **27** (4.0 g, 21.6 mmol) in EtOH (250 mL) cooled in an ice-water bath was added $NaBH_4$ (3.27 g, 86.4 mmol) and the mixture was then stirred at 0 °C for 5 h (at regular intervals of 15 min, 2 drops of 2 N HCl in EtOH were added). The reaction mixture was quenched by gaseous HCl to reach pH 2.0. After stirring at 0 - 10 °C for 3 h, the mixture was treated with 1% KOH in aqueous EtOH to pH 7.0. Removal of the solvent, extraction of the residue with $CHCl_3$ (5 x 100 mL), and evaporation of the extracts provided a crude product. Flash column chromatography (elution with 17% acetone in CH_2Cl_2) of the crude product furnished 3.04 g (65%) of **28** as a colorless oil: IR ($CHCl_3$) 1735, 1690, 1220 (br), 1075, and 1045 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.24 (3 H, t, J = 7.0 Hz), 2.06 (3 H, s), 1.80-2.76 (4 H, m), 3.22-2.92 (4 H, m), 3.98-4.46 (2 H, m), 5.04 (1 H, dd, J = 2.0, 5.2 Hz); MS *m/z* 215 (M^+), 171, 104, 75, 44 (100); HRMS calcd for $C_{10}H_{17}NO_4$ MW 215.1152, found *m/z* 215.1151 (M^+). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.75; H, 7.71; N, 6.73.

1-(2-Acetoxyethyl)-5-acetoxy-2-pyrrolidinone (**29**). To a solution of **28** (2.77 g) in acetic acid (100 mL) was stirred at 30 °C for 24 h and then under slightly reduced pressure for another 24 h. Acetic acid was removed carefully in vacuo below 40 °C (water bath temperature) to provide 3.0 g of **29** as an unstable

yellow oil (ca. 90% pure by ^{1}H NMR analysis): IR ($CHCl_3$) 1735, 1710, 1235, 1195, 1042, and 1008 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 2.06 (3 H, s), 2.09 (3 H, s), 1.92-2.76 (4 H, m), 3.15-4.44 (4 H, m), 6.24-6.38 (1 H, m).

3-((Phenylthio)acetyl)-4(*R*)-isopropyl-1,3-thiazolidine-2-thione (30). Compound 30 was prepared from (phenylthio)acetic acid and 4(*R*)-IPTT (8) by the known procedure described for its enantiomer.[7] Yellow prisms; mp 81-82.5 ℃ (Et_2O-hexane); $[\alpha]^{25}_D$ -301.7° (c 0.65, $CHCl_3$); Anal. Calcd for $C_{14}H_{17}NOS_3$: C, 53.98; H, 5.50; N, 4.50. Found: C, 54.08; H, 5.55; N, 4.45. The other spectral data of 30 were indentical with those of its enantiomer.[7]

Alkylation of Chiral Tin(II) Enolate 31 onto Compound 29. 3-(2(*S*)-(1-(2-Acetoxyethyl)-5-oxo-2(*S*)-pyrrolidinyl)(phenylthio)acetyl)-4(*R*)-isopropyl-1,3-thiazolidine-2-thione (32): The reaction of the enolate 31 with compound 29 was run using the same procedure described above for the alkylation of enolate 10 with compound 11. A diastereomeric ratio (82 : 8 : 7 : 3) of the crude product was determined by the HPLC analysis (column, Diasil 5C 18 ϕ 4.6 mm x 25 cm; eluent, CH_3CN-H_2O (60:40); flow rate, 1.5 mL/min; detection, UV 305 nm). Flash column chromatography (elution with EtOAc-hexane-$CHCl_3$ (1:1:2)) of the crude product afforded the major product 32 (58%, a 91:9 inseparable mixture of 32 and one of the three minor components) as a yellow oil; IR ($CHCl_3$) 1730, 1680, 1235, 1210, 1155, and 1037 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 0.84-1.12 (6 H, m), 1.99 (3 H, s), 2.10-2.86 (6 H, m), 2.88-3.08 (1 H, m), 3.20-3.78 (2 H, m), 3.84-4.55 (3 H, m), 4.66-5.02 (1 H, m), 6.45 (0.91 H, d, J = 3.4 Hz), 6.58 (0.09 H, d, J = 6.5 Hz), 7.16-7.56 (5 H, m); MS *m/z* 481 (M^++1), 449, 373, 341, 338, 277, 202, 185, 170, 128, 93 (100), 87, 75. Anal. Calcd for $C_{22}H_{28}N_2O_4S_3$: C, 54.97; H, 5.87; N, 5.83. Found: C, 54.93; H, 5.94; N, 5.84. The other two minor diastereomers were also isolated in 3% and 2% yields, respectively.

Methyl 2(*RS*)-(1-(2-Hydroxyethyl)-5-oxo-2(*S*)-pyrrolidinyl)(phenylthio)acetate (33). To a solution of 32 (0.723 g, 1.5 mmol) in MeOH (10 mL) was added a 10% aqueous KOH solution (10 mL) at 0 ℃ and the mixture was then stirred at room temperature for 30 min. Quenching the reaction mixture with 5% HCl to reach pH 2.0, extraction with EtOAc, and the usual workup gave a residue which was treated with an etheral solution of CH_2N_2 to provide a crude methyl ester. Flash column chromatography (elution with 25% acetone in CH_2Cl_2) of the crude methyl ester afforded 0.434 g (93%) of 33 (a 60:40 mixture of the epimers at the α position of the ester moiety) as a colorless oil: IR ($CHCl_3$) 3350, 1727, 1670, 1580, 1152, and 905 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 2.08-3.68 (9 H, m), 3.71 (1.2 H, s), 3.75 (1.8 H, s), 3.98-4.38 (2 H, m), 7.20-7.60 (5 H, m); MS *m/z* 309 (M^+), 218, 182, 170, 128 (100), 110, 77, 64; HRMS calcd for $C_{15}H_{19}NO_4S$ MW 309.1017, found *m/z* 309.1009 (M^+). Anal. Calcd for $C_{15}H_{19}NO_4S$: C, 58.23; H, 6.19; N, 4.53. Found: C, 57.88; H, 6.18; N, 4.43.

Methyl 2(*RS*)-(1-(2-Iodoethyl)-5-oxo-2(*S*)-pyrrolidinyl)(phenylthio)acetate (34b). To a solution of 33 (1.065 g, 3.44 mmol) in dry THF (15 mL) was added

successively $MeSO_2Cl$ (0.347 mL, 4.48 mmol) and triethylamine (0.64 mL, 4.48 mmol) at 0 °C and the mixture was then stirred at room temperature for 3 h. The precipitate was filtered off through Celite and the filtrate was concentrated to give a residue. To the residue in dry THF (25 mL) was added solid NaI (2.57 g) and the mixture was then stirred at room temperature for 12 h. Removal of the solvent, addition of water to the residue, extraction with EtOAc (three times), washing with saturated $Na_2S_2O_3$, and the usual workup provided an oily mixture. Flash column chromatographic purification (elution with 50% EtOAc in hexane) of the oily mixture furnished 1.25 g (87%) of **34b** (a 60:40 mixture of the epimers at the α position of the ester moiety) as a pale yellow oil: IR ($CHCl_3$) 1730, 1680, 1580, 1150, and 905 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.12-2.70 (4 H, m), 2.70-3.50 (4 H, m), 3.70 (1.2 H, s), 3.76 (1.8 H, s), 3.87 (0.6 H, d, *J* = 4.3 Hz), 3.95 (0.4 H, d, *J* = 4.3 Hz), 4.08-4.36 (1 H, m), 7.24-7.56 (5 H, m); MS *m/z* 419 (M^+), 238 (100), 210, 155, 149, 112, 83, 55; HRMS calcd for $C_{15}H_{18}NO_3SI$ MW 419.0077, found *m/z* 419.0093 (M^+).

(4*R*,5*S*)-1-Aza-4-phenylthio-4-(methoxycarbonyl)bicyclo[3.3.0]octan-8-one (35). To a solution of diisopropylamine (0.24 mL, 1.69 mmol) in dry THF (7 mL) cooled in a dry ice-acetone bath (-78 °C) was added dropwise a 1.6 M *n*-BuLi solution in hexane (1.06 mL, 1.69 mmol) and the mixture was then stirred at -78 °C for 30 min. To this solution was added dropwise a solution of **34b** (0.646 g, 1.54 mmol) in dry THF (5 mL) followed by stirring at -78 °C for 2 h and then at -30 °C for 3 h. The reaction mixture was quenched by 5% HCl, extracted with EtOAc (three times), and worked up to give a residue. Flash column chromatography (elution with 14% acetone in CH_2Cl_2) of the residue afforded 0.373 g (83%) of **35** as colorless crystals: mp 127-128 °C (EtOAc-hexane); $[\alpha]_D^{18}$ +2.0° (c 0.90, $CHCl_3$); IR ($CHCl_3$) 1725, 1680 (br), 1260, 1205 (shoulder), and 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.06 (1 H, ddd, *J* = 1.5, 7.8, 14.6 Hz), 2.24-2.48 (3 H, m), 2.58-2.76 (2 H, m), 3.17 (1 H, dddd, *J* = 1.5, 1.5, 9.8, 11.2 Hz), 3.59 (1 H, ddd, *J* = 7.8, 10.7, 10.7 Hz), 3.77 (3 H, s), 4.32 (1 H, dd, *J* = 5.4, 8.3 Hz), 7.30-7.47 (5 H, m); ^{13}C NMR (25 MHz, $CDCl_3$) δ 19.8, 33.6, 34.0, 39.9, 52.5, 61.0, 67.0, 129.1, 129.9, 136.8, 171.6, 176.5; MS *m/z* 291 (M^+), 259, 231, 182, 149, 122, 97 (100), 69. Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81. Found: C, 61.70; H, 5.90; N, 4.80.

(4*R*,5*S*)-1-Aza-4-phenylthio-4-(hydroxymethyl)bicyclo[3.3.0]octan-8-one (36). To a suspension of $LiAlH_4$ (40 mg, 1.06 mmol) in dry THF (5 mL) was added **35** (0.309 g, 1.06 mmol) in dry THF (5 mL) at 0 °C followed by stirring at 0 °C for 30 min. Quenching the reaction with 5% HCl, extraction with CH_2Cl_2 (three times), and the usual workup gave 0.249 g (89%) of **36**. An analytic sample of compound **36** was obtained by preparative TLC (developing with 20% acetone in $CHCl_3$) as a colorless oil: IR ($CHCl_3$) 3550-3200 (br), 1670, 1450, 1428, 1405, and 1268 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.76-2.40 (4 H, m), 2.48-2.80 (2 H, m), 3.02-3.80 (3 H, m), 3.55 and 3.77 (2 H, AB q, *J* = 11.5 Hz), 4.22 (1 H, t, *J* = 7.0 Hz), 7.20-7.60 (5 H, m); MS *m/z* 263 (M^+), 246, 232, 162, 154 (100), 136, 110, 97, 84, 69, 55. Anal. Calcd for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.51; N, 5.32. Found: C, 63.44; H,

6.51; N, 5.10.

5(*S*)-1-Aza-4-(acetoxymethyl)bicyclo(3.3.0)oct-3-en-8-one (37). To a solution of 36 (150 mg, 0.57 mmol) in dry CH_2Cl_2 (2 mL) was added 80% MCPBA (136 mg, 0.63 mmol) in dry CH_2Cl_2 (2 mL) at -78 ℃ followed by stirring for 30 min at -78 ℃. Dilution of the reaction mixture with CH_2Cl_2, washing with saturated $Na_2S_2O_3$, $NaHCO_3$, and brine, and the usual workup gave 156.7 mg of a crude sulfoxide. The solution of the crude sulfoxide (156.7 mg) in toluene (10 mL) was heated under reflux for 22 h. Removal of the solvent and flash column chromatography (elution with 33% acetone in CH_2Cl_2) of the residue provided 70.1 mg of a mixture which contained the desired allylic alcohol and the C(1)[12] aldehyde (at δ 9.77 (d, J = 2.5 Hz) in the ^{1}H NMR spectrum)[18] formed from the exo-elimination of phenylsulfinic acid during pyrolysis. To a solution of the mixture (70.1 mg) obtained above in dry CH_2Cl_2 (2 mL) was added successively Ac_2O (93 μL), Et_3N (91 μL), and DMAP (cat.) followed by stirring for 30 min at room temperature. The reaction mixture was diluted with CH_2Cl_2, washed with water, saturated $NaHCO_3$, and brine, and worked up. Flash column chromatographic separation (elution with 14% acetone in CH_2Cl_2) of the residue afforded 42 mg (38% from 36) of 37 as a colorless oil: $[\alpha]^{21}_D$ -58.1° (c 1.43, $CHCl_3$); IR ($CHCl_3$) 1730, 1680, 1642, and 1218 (br) cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.76-2.86 (4 H, m), 2.10 (3 H, s), 3.74 and 4.42 (2 H, AB qm, J = 16.5 Hz), 4.56-4.80 (1 H, m), 4.71 (2 H, br s), 5.82 (1 H, br s); MS m/z 195 (M^+), 193, 149, 133, 122, 106, 80, 55, 43; HRMS calcd for $C_{10}H_{13}NO_3$ MW 195.0925, found m/z 195.0932 (M^+).

(-)-Supinidine (38). To a suspension of $LiAlH_4$ (26 mg, 0.69 mmol) in dry THF (1 mL) was added 37 (27 mg, 0.138 mmol) in dry THF (1 mL) at room temperature and the mixture was then heated under reflux for 80 min. The reaction mixture was quenched successively by 24 μL of water, 24 μL of 3 N aqueous NaOH, and 35 μL of water followed by stirring at room temperature for 30 min. The precipitate was filtered off through Celite with washing the residue by 10% Et_3N in THF. The combined filtrate was evaporated to give 18.6 mg (97%) of 38 as a pale yellow oil: $[\alpha]^{21}_D$ -8.0° (c 0.55, EtOH); IR ($CHCl_3$) 3300, 1113, 1085, 1040, 1005, and 995 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.42-2.16 (4 H, m), 2.56 (1 H, dt, J = 10.4, 6.3 Hz), 3.12 (1 H, dt, J = 10.4, 5.5 Hz), 3.33 and 3.87 (2 H, AB qm, J = 15.0 Hz), 4.18 (3 H, br s), 4.75 (1 H, s, exchangable by D_2O), 5.48 (1 H, br s); MS m/z 140 (M^++1), 139 (M^+), 138, 122, 120, 111, 110, 108, 94, 80 (100); HRMS calcd for $C_8H_{13}NO$ MW 139.1021, found m/z 139.1024 (M^+).

(4*R*, 5*S*)-1-Aza-4-(methoxycarbonyl)bicyclo(3.3.0)octan-8-one (40). To a solution of 35 (0.255 g, 0.875 mmol) in EtOH (5 mL) was added excess Ranyl nickel (W-2) followed by heating at 70 ℃ for 3 h. The reaction mixture was filtered through Celite and the filtrate was evaporated to give a residue. Flash column chromatography (elution with 14% acetone in CH_2Cl_2) of the residue furnished 0.157 g of a mixture of the two C(1) epimers as a colorless oil. The mixture (0.147 g) was dissolved in absolute MeOH (1 mL) to which 28% NaOMe (0.5 mL) was added followed by stirring at room temperature for 5 h. The reaction mixture was

acidified with 5% HCl, extracted with $CHCl_3$, and worked up to provide a residue. Treatment of the residue with an etheral solution of CH_2N_2, removal of the solvent, and the flash column chromatography (elution with 17% acetone in CH_2Cl_2) afforded 120 mg (75% from 35) of 40 as a colorless oil: $[\alpha]^{25}_D$ -58.3° (c 0.65, $CHCl_3$); IR ($CHCl_3$) 1728, 1675, 1280, 1190, and 1170 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.64-2.40 (1 H, m), 2.16-2.96 (6 H, m), 3.04-3.32 (1 H, m), 3.48-3.76 (1 H, m), 3.73 (3 H, s), 4.08 (1 H, dd, J = 7.0, 15.0); ^{13}C NMR (25 MHz, $CDCl_3$) δ 25.6, 30.5, 34.0, 40.5, 48.2, 51.8, 63.9, 172.2, 174.6; MS m/z 183 (M^+), 168, 155, 140, 97, 69, 55; HRMS calcd for $C_9H_{13}NO_3$ MW 183.0899, found m/z 183.0900 (M^+).

Reduction of Compound 40. (4*R*,5*S*)-1-Aza-4-(hydroxymethyl)bicyclo(3.3.0)octan-8-one (41a): To a suspension of $LiAlH_4$ (5.2 mg, 0.136 mmol) in dry THF (1 mL) was added a solution of 40 (24.9 mg, 0.136 mmol) in dry THF (2 mL) at 0 °C and the mixture was then stirred at 0 °C for 30 min. Quenching the reaction with 5% HCl, extraction with CH_2Cl_2, and the usual workup gave a crude product which was submitted to preparative TLC (developing with 50% acetone in CH_2Cl_2) to afford 15.4 mg (72%) of 41a as a colorless oil; $[\alpha]^{25}_D$ -11.9° (c 0.39, $CHCl_3$); IR ($CHCl_3$) 3340 and 1765 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.60-2.94 (8 H, m), 2.98-3.26 (1 H, m), 3.38-3.86 (4 H, m); ^{13}C NMR (25 MHz, $CDCl_3$) δ 26.9, 30.1, 35.0, 40.8, 48.1, 63.6, 65.3, 174.9; MS m/z 156 (M^++1), 155 (M^+), 138, 114, 97 (100), 84, 69, 55; HRMS calcd for $C_8H_{13}NO_3$ MW 155.0928, found m/z 155.0924 (M^+).

Reductive Desulfurization of Compound 36 to Compounds 41a and 42. To a solution of 36 (0.126 g, 0.478 mmol) in EtOH (3 mL) was added excess Raney nickel (W-2) followed by heating for 2 h at 70 °C. The reaction mixture was filtered through Celite and the filtrate was condensed to give a residue which was purified by flash column chromatography (elution with 50% acetone in CH_2Cl_2) to afford 45.5 mg (61%) of a mixture of the major product 42 and the minor component 41a as a colorless oil: ^1H NMR (100 MHz, $CDCl_3$) δ 1.64-2.82 (8 H, m), 2.82-3.28 (1 H, m), 3.30-3.96 (3.3 H, m), 4.12 (0.7 H, dd, J = 8.0, 15.0 Hz); ^{13}C NMR (25 MHz, $CDCl_3$) for compound 42: δ 21.4, 30.1, 34.9, 40.1, 40.6, 61.3, 63.4, 175.1; for compound 41a: δ 26.7, 35.0, 47.9, 63.2, 65.3, (Other signals could not be distinguished from those of compound 42).

Acetylation of Compounds 41a and 42. To a solution of the mixture of 41a and 42 (42 mg, 0.27 mmol) in dry THF (2 mL) was added acetyl chloride (38.5 μL, 0.54 mmol) and triethylamine (75.3 μL, 0.54 mmol) at 0 °C and the mixture was then stirred at room temperature for 3 h. The reaction mixture was diluted with Et_2O and the precipitate was then filtered off through Celite followed by the usual workup to give a residue. Flash column chromatography (elution with 11% acetone in CH_2Cl_2) of the residue furnished 47.4 mg (89%) of the mixture of the acetates 43 and 44 (43:44 = 29:71) as a colorless oil: IR ($CHCl_3$) 1730, 1675, 1230, 1205 (shoulder), and 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.78-1.98 (2 H, m), 2.06 (2.13 H, s), 2.07 (0.87 H, s), 2.08-2.48 (4 H, m), 2.63-2.78 (1 H, m), 3.04 (0.71 H, m), 3.17 (0.29 H, tm, J = 11.2 Hz), 3.55-3.64 (1 H, m), 3.70 (0.29

H, dt, J = 8.8, 7.3 Hz), 4.02 (0.71 H, dd, J = 5.9, 11.2 Hz), 4.04 (0.29 H, dd, J = 7.8, 11.2 Hz), 4.09 (0.71 H, dd, J = 6.8, 11.2 Hz), 4.11 (0.71 H, dd, J = 6.8, 15.1 Hz), 4.20 (0.29 H, dd, J = 5.4, 11.2 Hz); ^{13}C NMR (25 MHz, $CDCl_3$) for compound **43**: δ 20.7, 26.3, 30.3, 34.7, 40.5, 44.8, 64.8, 65.2, 170.8, 174.5; for compound **44**: δ 20.9, 21.4, 30.4, 34.5, 37.9, 40.3, 62.8, 63.4, 170.8, 174.7; MS *m/z* 198 (M$^+$+1), 197 (M$^+$), 169, 155, 138 (100), 110, 97, 84, 69, 55, 43; HRMS calcd for $C_{10}H_{15}NO_3$ MW 197.1056, found *m/z* 197.1057 (M$^+$). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.60; H, 7.52; N, 7.22.

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