Articles

Highly Diastereoselective Alkylation of Chiral Tin(II) Enolates onto Cyclic Acyl Imines. An Efficient Asymmetric Synthesis of Bicyclic Alkaloids Bearing a Nitrogen Atom Ring Juncture

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Asymmetric alkylation onto 5-acetoxy-2-pyrrolidinone (**5**, $n = 1$) in THF employing chiral tin(II) enolates **4a,b,e,f** obtained from treatment of the corresponding 3-acyl-4(*S*)- or -4(*R*)-isopropyl-1,3-thiazolidine-2-thiones **3a,b,e,f** with $Sn(OSO_2CF_3)_2$ and *N*-ethylpiperidine in THF afforded the corresponding C(5)-alkylated 2-pyrrolidinones **6**, **7**, **12**, and **13** in 67–92% yields and in a highly diastereoselective manner [91–97% diastereomer excess (de)]. Similar alkylation of **4e** onto 6-acetoxy-2-piperidinone (**5**, $n = 2$) gave the C(6)-alkylated 2-piperidinone **14** in 63% yield and in 96% de. Complete enolization of **3c,d,g** was achieved by employing 2 mol equiv of $Sn(OSO_2CF_3)_2$ and 2.2 mol equiv of *N*-ethylpiperidine at −5 to 0 °C in THF. Subsequently, diastereoselective alkylation onto cyclic acyl imines derived from **5** ($n = 1$ and 2) in situ using the tin(II) enolates **4c,d,g** gave the chiral alkylated lactams **8–11** and **15** in 57–73% yields and in 91–98% de. A six-membered chelated transition state (e.g., **16**) is proposed for the highly diastereoselective alkylation with various chiral tin(II) enolates onto **5** ($n = 1$ and 2). Simplified reductive annulation of **8–11** and **15** with $LiAlH_4$ proceeded smoothly to furnish optically pure (−)-trachelanthamidine (**17a**), two kinds of indolizidine type compounds **17b,c**, (−)-epilupinine (**17d**), and (+)-epilupinine (**21**) together with the corresponding hydrogenolysis products **19a–d** and **23**, respectively. Chiral lactam **6** was readily converted to carboxylic acid **26**, the synthetic precursor of (*S*)-homoproline **27**, and the chiral diester **31**, which could be exploited for the asymmetric synthesis of various chiral pyrrolizidine alkaloids via **32**.

Bicyclic alkaloids possessing pyrrolizidine,[2] indolizidine,[3] and quinolizidine[3] skeletons are widely represented in various plant families,[4] and the tumor inhibitory activities of the pyrrolizidine alkaloids have been recognized for the past few decades.[4,5] The diversity that pyrrolizidine alkaloids exhibit in both their structures and biological activities has stimulated a great deal of interest in accomplishing the total syntheses of these compounds.[6] However, the synthesis of optically active pyrrolizidine alkaloids has been a recent development, dating only from the beginning of the past decade.[7] Most of the asymmetric syntheses of pyrrolizidine alkaloids published have been effected by employing chiral building blocks converted from L-proline derivatives, (*R*)- or (*S*)-malic acid, and carbohydrates, respectively. The roundabout ways used in the asymmetric synthesis of pyrrolizidine alkaloids usually affect the efficiency of the synthetic routes, resulting in low overall yields. The deficiency of good synthetic routes to pyrrolizidine alkaloids also gives rise to the problem of low selectivity when diastereomers are formed. In a recent preliminary communication,[7] we reported an efficient and general asymmetric synthesis of pyrrolizidine–, indolizidine–, and quinolizidine–alkaloid ring systems based on a highly diastereoselective alkylation of chiral tin(II) enolates onto cyclic acyl imines. Here, we describe the details of the simple construction procedure for these 1-azabicyclic alkaloidal skeletons and related asymmetric induction methods.

Results and Discussion

4(*S*)- or 4(*R*)-isopropyl-1,3-thiazolidine-2-thione (4(*S*)- or 4(*R*)-IPTT), **1** or **2**, first prepared by us,[8] has been used as an excellent chiral auxiliary in various chiral recognition capacities.[7-9] Typically, the tin(II) enolates derived from

(1) (a) Kyoto University. (b) Japanese Foundation for Cancer Research. (c) Osaka University of Pharmaceutical Sciences.

(2) Reviews for pyrrolizidine alkaloids, see: (a) Bull, L. B.; Culvenor, C. C. J.; Dick, A. T. *The Pyrrolizidine Alkaloids*; North-Holland: Amsterdam, 1968. (b) Wróbel, J. T. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26, Chapter 7.

(3) Reviews for indolizidine alkaloids see: (a) Howard, A. S.; Michael, J. P. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 28, Chapter 3. (b) Grundon, M. F. *Nat. Prod. Rep.* **1985**, 2, 235, and earlier references in this series.

(4) Zalkow, L. H.; Bonetti, S.; Gelbaum, L. T.; Gordon, M. M.; Patil, B. B.; Shani, A. *J. Nat. Prod.* **1979**, *42*, 603, and references therein.

(5) (a) Zalkow, L. H.; Glinski, J. A.; Gelbaum, L. T.; Fleischmann, T. J.; Mcgowan, L. S.; Gordon, M. M. *J. Med. Chem.* **1985**, *28*, 687, and references therein. (b) A review in Japanese: Chemistry of Pyrrolizidine Alkaloids; Furuya, T.; Hikichi, M. *J. Synth. Org. Chem. Jpn.* **1977**, *35*, 653. (c) Suffness, M.; Cordell, G. A. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 28, pp 21–38.

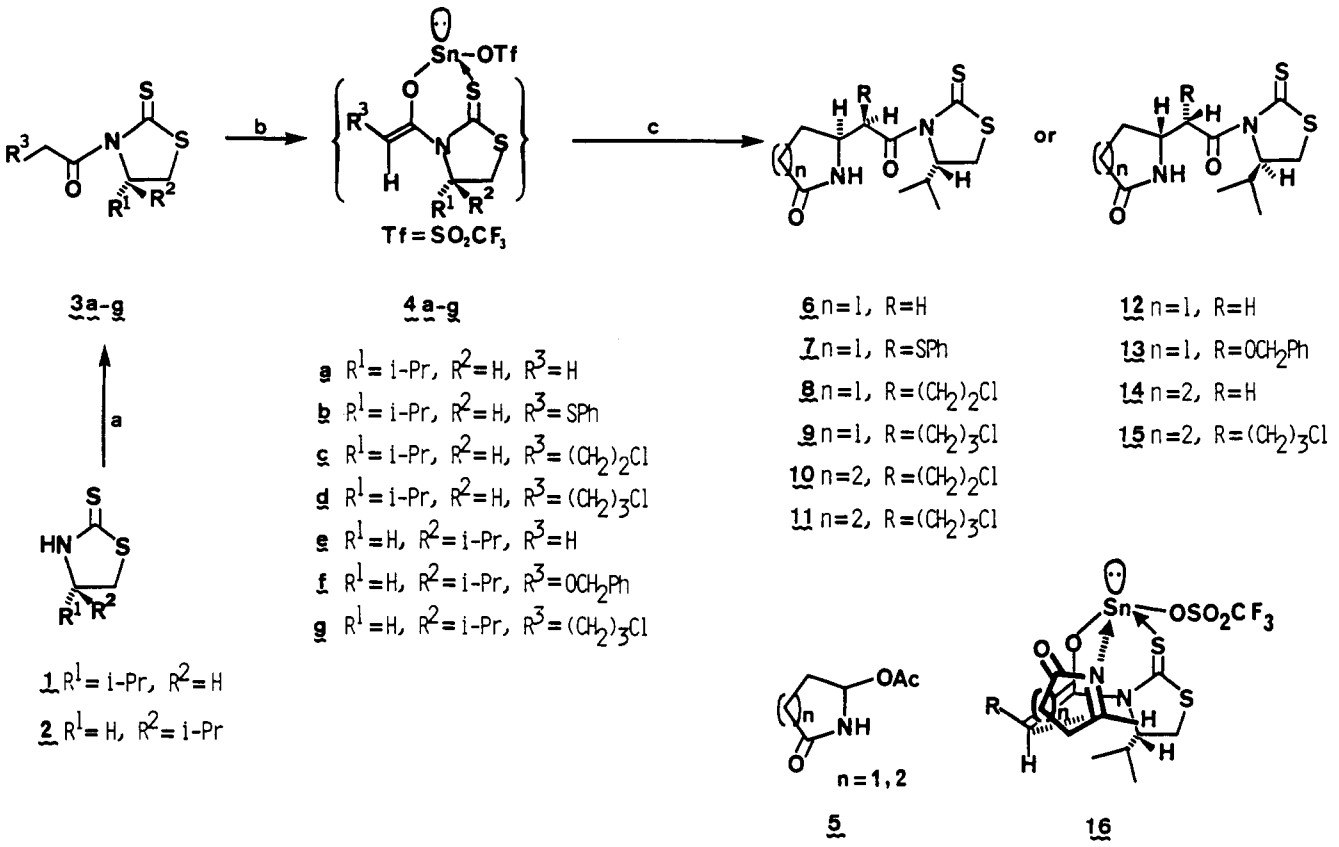
(6) (a) Stevens, R. V. In *The Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley: New York, 1977; Vol. 3, p 439. (b) For recent review papers of pyrrolizidine alkaloids, see: Robins, D. *J. Nat. Prod. Rep.* **1986**, *3*, 297, and earlier papers in this series. (c) Ikeda, M.; Sato, T.; Ishibashi, H. *Heterocycles* **1988**, *27*, 1465.

(7) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Am. Chem. Soc.* **1988**, *110*, 289, and references therein.

(8) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391.

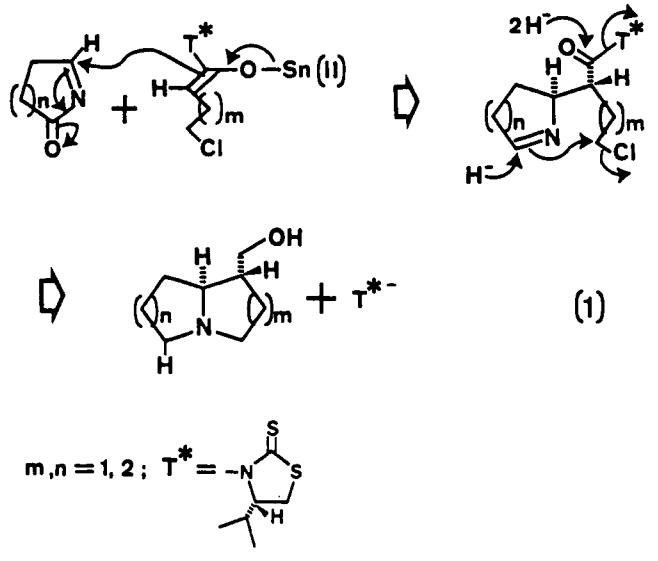
0022-3263/90/1955-1148$02.50/0

Scheme I[a]



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

3-acyl-4(*S*)-IPTTs have been successfully exploited in highly diastereoselective alkylations onto 4-acetoxy-2-azetidinones[9a,b,f] and α,β-unsaturated aldehydes.[8] Equation 1 shows a two-step sequence for the chiral synthesis of



(1)

bicyclic alkaloids bearing a nitrogen atom ring juncture. It consists of a highly diastereoselective alkylation of chiral tin(II) enolates onto cyclic acyl imines[10] followed by reductive annulation of the resultant cyclic imines.[11]

5-Acetoxy-2-pyrrolidinone (**5**, $n = 1$)[12] or 6-acetoxy-2-piperidinone (**5**, $n = 2$)[13] was considered to be a suitable precursor for the desired cyclic acyl imine as represented

Table I. Preparation of Compounds 3

entry	compd	method[a]	compd[b]	isolated yield, %	$[\alpha]^{22}_D$[d] (*c*) in $CHCl_3$
1	1	A	**3a**[8,9g]	94	+448.9 (0.51)
2	1	B	**3b**[c]	88	+315.8 (0.60)[e]
3	1	A	**3c**	95	+366.5 (0.57)[g]
4	1	A	**3d**	96	+348.9 (0.72)
5	2	A	**3e**	100	−442.1 (0.62)
6	2	A	**3f**[9b]	94	−254.9 (0.65)[g]
7	2	A	**3g**	96	−342.0 (0.64)[f]

[a] Method A: prepared by reaction of 4(*S*)- or 4(*R*)-IPTT sodium salt with the corresponding acyl chloride in THF at room temperature. Method B: prepared by dehydrative condensation between 4(*S*)-IPTT and the carboxylic acid in the presence of DCC–DMAP in CH_2Cl_2 at room temperature. [b] Yellow oil. [c] Yellow prisms, mp 80.5–81.5 °C (recrystallized from Et_2O–hexane). [d] $[\alpha]^{22}_D$ is measured in degrees. [e] Recorded at 25 °C. [f] Recorded at 23 °C. [g] Recorded at 18 °C.

(9) (a) Nagao, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 4673. (b) Nagao, Y.; Kumagai, T.; Abe, T.; Ochiai, M.; Taga, T.; Machida, K.; Inoue, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 602. (c) Nagao, Y.; Hagiwara, Y.; Hasegawa, Y.; Ochiai, M.; Inoue, T.; Shiro, M.; Fujita, E. *Chem. Lett.* **1988**, 381. (d) Nagao, Y.; Hagiwara, Y.; Tohjo, T.; Hasegawa, Y.; Ochiai, M.; Shiro, M. *J. Org. Chem.* **1988**, *53*, 5983. (e) Nagao, Y.; Dai, W.-M.; Ochiai, M. *Tetrahedron Lett.* **1988**, *29*, 6133. (f) Nagao, Y.; Abe, T.; Shimizu, H.; Kumagai, T.; Inoue, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 821. (g) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Shiro, M. *J. Org. Chem.* **1989**, *54*, 5211.

(10) For chiral α-amidoalkylation of optically active *N*-acyliminium with achiral nucleophiles, see: Wanner, K. T.; Kartner, A. *Heterocycles* **1987**, *26*, 921.

(11) (a) Rodewald, W. J.; Morzycki, J. W. *Tetrahedron Lett.* **1978**, 1077. (b) House, H. O. *Morden Synthetic Reactions*, 2nd ed.; W. A. Benjamin: CA, 1977; p 79.

(12) Nagasaka, T.; Abe, M.; Ozawa, N.; Kosugi, Y.; Hamaguchi, F. *Heterocycles* **1983**, *20*, 985.

(13) Prepared from 6-ethoxy-2-piperidinone, see: Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

Table II. Highly Diastereoselective Alkylation of Compounds 5 with Chiral Tin(II) Enolates 4

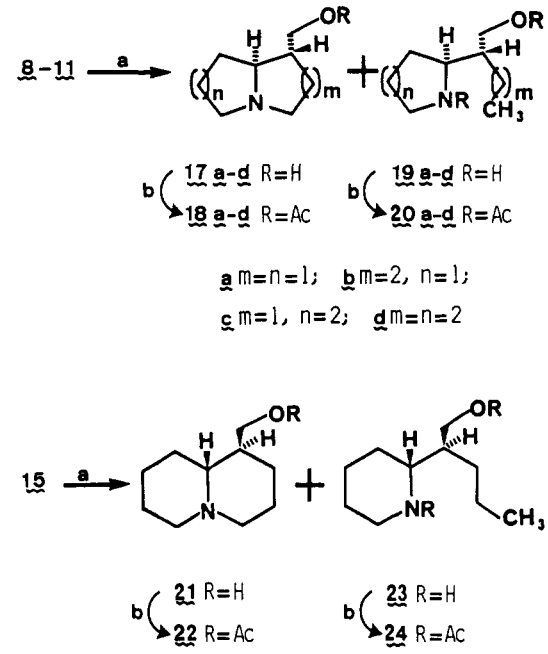
entry	enolate	compd 5[a]	product	isolated yield,[b] %	diastrmer excess,[c] %	mp, °C	$[\alpha]^{22}_D$[h] (c) in $CHCl_3$
1	**4a**, R^3 = H	n = 1	**6**	67	94	oil	+356.9 (1.11)
2	**4b**, R^3 = SPh	n = 1	**7**	92	91	138–140[d]	+366.8 (0.44)[i]
3	**4c**, R^3 = $(CH_2)_2Cl$	n = 1	**8**	64	98	163–164[e]	+447.2 (0.25)
4	**4d**, R^3 = $(CH_2)_3Cl$	n = 1	**9**	72	97	142–143.5[f]	+416.3 (0.33)[j]
5	**4c**, R^3 = $(CH_2)_2Cl$	n = 2	**10**	57	95	126.5–127.5[f]	+407.8 (0.40)
6	**4d**, R^3 = $(CH_2)_3Cl$	n = 2	**11**	73	91	97–98[g]	+344.6 (0.57)
7	**4e**, R^3 = H	n = 1	**12**	66	94	oil	−359.3 (1.06)
8	**4f**, R^3 = OCH_2Ph	n = 1	**13**	78	97	149–150[e]	−405.6 (0.25)
9	**4e**, R^3 = H	n = 2	**14**	63	96	138.5–139.5[g]	−393.3 (0.15)[j]
10	**4g**, R^3 = $(CH_2)_3Cl$	n = 2	**15**	73	91	oil	−362.6 (0.58)

[a] A ca. 9:1 mixture of **5** (n = 1, 2) and the corresponding 5- or 6-ethoxy compound was employed. [b] Calculated based on **3**. [c] Checked by HPLC analysis (see Experimental Section). [d] Recrystallized from Et_2O–hexane. [e] Recrystallized from $CHCl_3$–hexane. [f] Recrystallized from CH_2Cl_2–hexane. [g] Recrystallized from EtOAc–hexane. [h] $[\alpha]^{22}_D$ is measured in degrees. [i] Recorded at 25 °C. [j] Recorded at 14 °C.

in eq 1. Thus, the alkylations of 5-acetoxy-2-pyrrolidinone and 6-acetoxy-2-piperidinone with chiral tin(II) enolates **4** were carried out (Scheme I). 3-Acyl-4(*S*)- or 3-acyl-4(*R*)-IPTT derivatives **3a**[8,9g] and **3c–g** were readily prepared in 94–100% yields by reaction of 4(*S*)- or 4(*R*)-IPTT sodium salt, derived from **1** or **2** and NaH in THF, with the corresponding acyl chloride (method A). Compound **3b** was obtained through dehydrative condensation between **1** and (phenylthio)acetic acid in the presence of DCC and DMAP in CH_2Cl_2 in 88% yield (method B, Table I). Reaction of tin(II) enolate **4a**,[8,9a,g] formed by treatment of **3a** with tin(II) trifluoromethanesulfonate (1.3 mol equiv)[14] and *N*-ethylpiperidine (1.5 mol equiv)[14] in THF (−50 to −40 °C, 3 h),[9a] with 5-acetoxy-2-pyrrolidinone (**5**, n = 1, 1.5 mol equiv) in THF (−5 to 0 °C, 2 h) gave the C(5)-alkylation product **6** in 67% yield and in a very highly diastereoselective manner [94% diastereomer excess (de), Scheme I and entry 1 in Table II]. The antipodal compound of **6**, **12**, was similarly obtained from tin(II) enolate **4e** and 5-acetoxy-2-pyrrolidinone. Reaction of the tin(II) enolates **4b** and **4f** generated from 3-(heteroatom-substituted acetyl)-4(*S*)- [or 4(*R*)]-IPTT (**3b,f**) by treatment with tin(II) trifluoromethanesulfonate (1.3 mol equiv) and *N*-ethylpiperidine (1.5 mol equiv) in THF (−78 °C, 30 min),[9b] with 5-acetoxy-2-pyrrolidinone (**5**, n = 1, 1.5 mol equiv) in THF (−5 to 0 °C, 2 h) afforded the corresponding C(5)-alkylation products **7** and **13** in 92% and 78% yields and in 91% and 97% de, respectively (Scheme I and entries 2 and 8 in Table II). Similar diastereoselective alkylation onto 6-acetoxy-2-piperidinone (**5**, n = 2, 1.5 mol equiv) with chiral tin(II) enolate **4e** furnished C(6)-alkylation product **14** in 63% yield and in 96% de (Scheme I and entry 9 in Table II). Encouraged by our success in the asymmetric alkylations mentioned above, we attempted the alkylations employing chiral tin(II) enolates **4c** and **4d**, which were required for the syntheses of our target compounds, as depicted in eq 1. When the enolization conditions used for compound **3a** were adopted for 3-ω-chloroacyl-4(*S*)-IPTT derivatives **3c** and **3d**, the alkylations onto 5-acetoxy-2-pyrrolidinone (**5**, n = 1) or 6-acetoxy-2-piperidinone (**5**, n = 2) were found to be inefficient, resulting in lower conversions of **3c** and **3d** to the desired alkylation products. After several trials, it was found that the tin(II) enolates **4c** and **4d** could be efficiently generated by employing 2 mol equiv of tin(II) trifluoromethanesulfonate and 2.2 mol equiv of *N*-ethylpiperidine in THF at −5 to 0 °C for 3–4 h. Thus, the alkylations of 5-acetoxy-2-pyrrolidinone (1.5 mol equiv) and 6-acetoxy-2-piperidinone (1.5 mol equiv) with **4c** and **4d** in THF (−5 to 0 °C, 2 h) afforded the corresponding

(14) Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1983**, 297.

Scheme II[a]

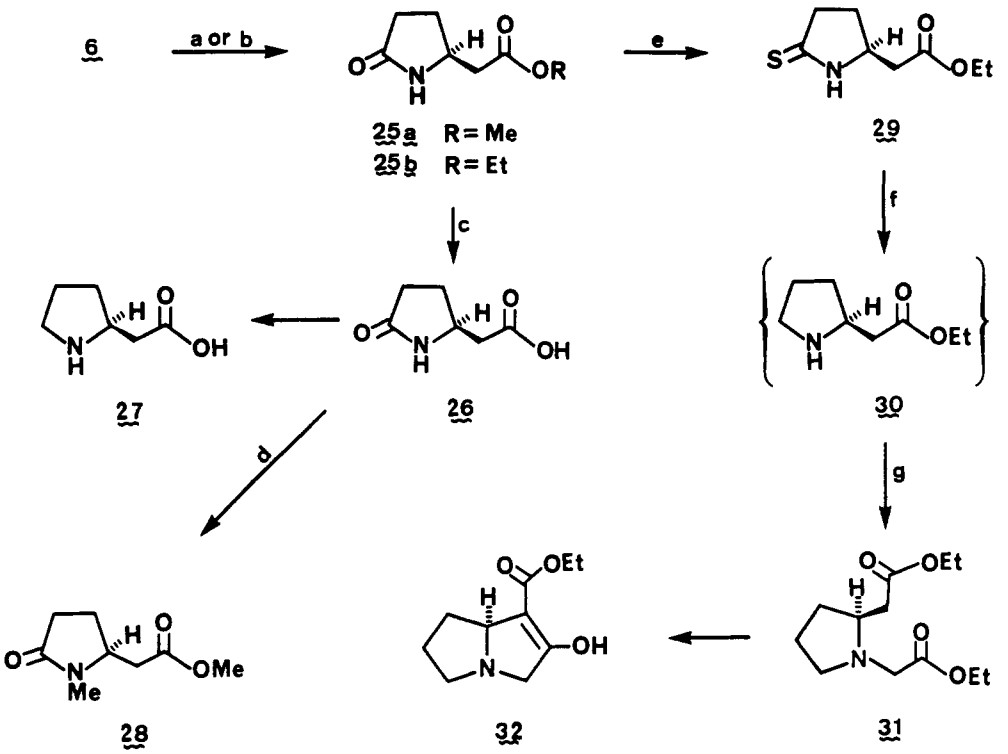


[a] a, $LiAlH_4$, THF, 0 °C, 5 min then reflux, 2 h. b, $AcCl/Et_3N$, THF, room temperature.

C(5)- and C(6)-alkylation products **8–11** in 57–73% yields and in 91–98% de, respectively (Scheme I and entries 3–6 in Table II). The antipodal compound of **11**, **15**, was also obtained from the alkylation of 6-acetoxy-2-piperidinone with tin(II) enolate **4g** in the same manner. In all cases, the optically pure major alkylation products **6–15** were readily obtained through chromatographic separation on a silica gel column. The absolute configurations of compounds **6**, **8**, **11**, and **14** were established following chemical conversion to the compounds (*S*)-(+)-5-oxo-2-pyrrolidineacetic acid (**26**), (−)-trachelanthamidine (**17a**), (−)-epilupinine (**17d**), and (*R*)-(−)-6-oxo-2-piperidineacetic acid (**36b**), respectively (vide infra). The stereochemistry of compounds **7**, **9**, **10**, and **13** was tentatively assigned on the basis of the similarity of mechanistic considerations for **16** to those for the compounds mentioned above. The six-membered chelated transition state **16** can be invoked to rationalize the stereochemical outcome, regardless of the ring size (n = 0–2 in **16**) of the cyclic acyl imines.[7,9a,b,f]

Subsequently, we designed a much simplified reductive annulation of **8–11** by employing $LiAlH_4$ to afford the chiral bicyclic alkaloids **17a–d** (eq 1 and Scheme II). Thus, the optically pure alkylation products **8–11** were treated with 4 mol equiv of $LiAlH_4$ in THF, first at 0 °C

Scheme III[a]



[a] a, K_2CO_3, MeOH, room temperature, 30 min (**6** → **25a**, 95%); b, K_2CO_3, EtOH, room temperature, 12 h (**6** → **25b**, 77%); c, 3 N NaOH–MeOH, room temperature, 18 h (**25a** → **26**, 64%); d, NaH–MeI, DMF, room temperature, 6 h; CH_2N_2 (49%); e, Lawesson's reagent, toluene, 105 °C, 1 h (**25b** → **29**, 87%); f, Et_3OBF_4, CH_2Cl_2, room temperature, 3 h; $NaBH_3CN$, MeOH–AcOH (92:8), room temperature, 3 h; g, $BrCH_2CO_2Et$, EtOH, Na_2CO_3, room temperature, 20.5 h (**29** → **31**, 83%).

Table III. Reductive Annulation of Compounds 8–11 and 15[a]

entry	substrate	product (yield, %)	byproduct (yield, %)	$[\alpha]^{22}_D$[d] (c) in EtOH
1	8	**17a** (44)	**19a** (10)	**17a**, −13.7 (1.22)[e]
2	9	**17b** (41)	**19b** (22)	**17b**, −25.9 (1.16)
3	10	**17c** (69)	**19c** (tr)	**17c**, −53.4 (1.18)
4	11	**17d** (61)[b]	**19d** (18)	**17d**, −30.5 (0.84)
5	15	**21** (59)[c]	**23** (17)	**21**, +31.2 (0.86)

[a] The auxiliary 4(*S*)- or 4(*R*)-IPTT was recovered in 70–90% yields in all cases. [b] Colorless needles (mp 76–76.5 °C) from hexane. [c] Colorless needles (mp 78–79 °C) from hexane. [d] $[\alpha]^{22}_D$ is measured in degrees. [e] Recorded at 20 °C.

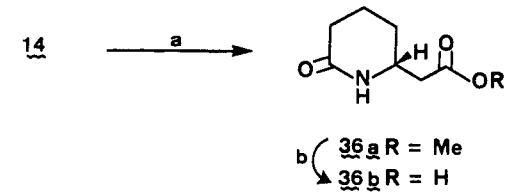
for 5 min to reduce the active amide moiety[15] without epimerization at the active methine carbon and then under reflux for 2 h to achieve the reductive annulation. The desired bicyclic products **17a–d** were furnished directly, together with the corresponding hydrogenolysis byproducts **19a–d** (Scheme II and Table III). No O-cyclization product, which had been anticipated was isolated from the reaction mixture. To confirm the presence of hydroxy and/or imino group(s) in the molecule, compounds **17a–d** and **19a–d** were acetylated with $AcCl/Et_3N$, giving the corresponding monoacetyl derivatives **18a–d** and diacetyl derivatives **20a–d** in good yields (70–80%), respectively. Similarly, the asymmetric alkylation product **15** was converted to **21** by reductive annulation together with the hydrogenolysis byproduct **23** (Scheme II and entry 5 in Table III). The synthesized compound **17a** {≥99% optically pure (op) based on the reported data:[16] $[\alpha]_D$ −13.8° (*c* 1.28, EtOH)} proved to be (−)-trachelanthamidine, as evidenced by a comparison of its physical data with those of the authentic compound. Compounds **17d** and **21** were confirmed to be (−)- and (+)-epilupinine in a similar manner {(+)-epilupinine (**21**), 97% op based on the literature data:[17] mp 76–78 °C (petroleum ether), $[\alpha]^{17}_D$ +32° (*c* 1.49, EtOH)}. Thus, this work presents the first example of an asymmetric synthesis of naturally occurring (+)-epilupinine.

The asymmetric alkylation product **6** also proved to be a very useful intermediate for 7aα-pyrrolizidine alkaloid synthesis as shown in Scheme III. Treatment of **6** with solid K_2CO_3 in absolute MeOH at room temperature for 30 min afforded the methyl ester **25a** in 95% yield. Saponification of **25a** yielded (*S*)-(+)-5-oxo-2-pyrrolidineacetic acid (**26**)[18] in 64% yield. Methylation of compound **26** gave the known compound **28** in 49% unoptimized yield. Thus, the absolute configuration of C(5) in compound **6** was established to be *S*. Compound **26** has been converted,[19] by its treatment with Et_3OBF_4 followed by reduction with $NaBH_4$, to (*S*)-homoproline (**27**), which has been used as a chiral catalyst in an asymmetric aldol cyclization.[20] As reported by Rüeger and Benn,[21a] the chiral

(15) This reduction can be readily monitored by the disappearance of the original yellow color of the solution. Cf.: Nagao, Y.; Kawabata, K.; Seno, K.; Fujita, E. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2470.

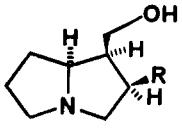
(16) Tsuda, Y.; Marion, L. *Can. J. Chem.* **1963**, *41*, 1919.
(17) White, E. P. *N. Z. J. Sci. Technol.* **1951**, *33B*, 50.
(18) Wakabayashi, T.; Kato, Y.; Watanabe, K. *Chem. Lett.* **1976**, 1283. This compound has recently been used for the synthesis of γ-lactam antibiotics; see: Allen, N. E.; Boyd, D. B.; Campbell, J. B.; Deeter, J. B.; Elzey, T. K.; Foster, B. J.; Hatfield, L. D.; Hobbs, J. N., Jr.; Hornback, W. J.; Hunden, D. C.; Jones, N. D.; Kinnick, M. D.; Morin, J. M., Jr.; Munroe, J. E.; Swartzendruber, J. K.; Vogt, D. G. *Tetrahedron* **1989**, *45*, 1905.
(19) Wakabayashi, T.; Watanabe, K.; Kato, Y. *Synth. Commun.* **1977**, *7*, 239.
(20) Buchschacher, P.; Cassal, J.-M.; Furst, A.; Meier, W. *Helv. Chim. Acta* **1977**, *60*, 2747.
(21) (a) Rüeger, H.; Benn, M. *Heterocycles* **1982**, *19*, 1677. (b) Rüeger, H.; Benn, M. *Heterocycles* **1983**, *20*, 235.

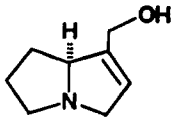
Scheme IV[a]



[a] a, K_2CO_3, MeOH, room temperature, 30 min (14 → **36a**, 88%); b, 2% NaOH–MeOH, room temperature, 5 h (**36a** → **36b**, 63%).

diester **31** has been prepared by N-alkylation of ethyl (*S*)-2-pyrrolidinylacetate (**30**), obtained via two different homologation methods from L-proline, with ethyl bromoacetate. The chiral diester **31** has been cyclized under equilibrium control conditions to form **32**, which has been used as a common intermediate in the synthesis of optically active 7aα-pyrrolizidine alkaloids such as (−)-trachelanthamidine (**17a**),[21a] (−)-isoretronecanol (**33**),[21a]





33 R= H

34 R= OH

35

(−)-supinidine (**35**),[21a] and (−)-petasinecine (**34**).[21b] We also succeeded in preparing the chiral diester **31** from **6** (Scheme III). Alcoholysis of **6** in the presence of solid K_2CO_3 in absolute EtOH afforded the ethyl ester **25b** in 77% yield. Treatment of **25b** with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphatane 2,4-disulfide (Lawesson's reagent)[22] in hot toluene furnished the thiolactam **29** in 87% yield. Reductive removal of the thiocarbonyl group in **29** was achieved by following the known procedures[23] to produce ethyl (*S*)-2-pyrrolidinylacetate (**30**) which, without isolation, was treated with ethyl bromoacetate in the presence of solid Na_2CO_3 in EtOH to afford the known chiral diester **31**[21a] in 83% yield from **29**. The spectral data of compound **31** were identical with those of the authentic sample. Thus, we have established a new efficient synthetic route to optically active 7aα-pyrrolizidine alkaloids. It is obvious that the chiral alkylation product **12** is available for the synthesis of 7aβ-pyrrolizidine alkaloids by the same procedures as those described above.

The absolute configuration of C(6) in the chiral alkylation product **14** was unequivocally established to be *R* by its conversion to (*R*)-(−)-6-oxo-2-piperidineacetic acid (**36b**, Scheme IV). Methanolysis of **14** in the presence of solid K_2CO_3 in absolute MeOH at room temperature gave the methyl ester **36a** in 88% yield. Saponification of **36a** in 2% NaOH–MeOH at room temperature for 5 h afforded the carboxylic acid **36b** {mp 131.5–133.5 °C (from $CHCl_3$–EtOAc), $[\alpha]^{25}_D$ −19.7° (*c* 0.38, EtOH)} in 63% yield. The known (*S*)-(+)-6-oxo-2-piperidineacetic acid {mp 132–134 °C, $[\alpha]^{24}_D$ +11.3° (*c* 1, EtOH), ≤64% ee} has been reported and used for the synthesis of (*S*)-(−)-sedamine and (*S*)-(−)-allosedamine.[24] Thus, our synthesized compound **36b** was determined to be the antipodal compound of (*S*)-(+)-6-oxo-2-piperidineacetic acid.

Conclusions

We have succeeded in developing an extremely short asymmetric synthesis of the 1-azabicyclic alkaloids involving pyrrolizidine, indolizidine, and quinolizidine skeletons. The key reaction used is a novel asymmetric alkylation of chiral tin(II) enolates of various 3-acyl-4(*S* or *R*)-IPTTs onto cyclic acyl imines. This particularly mild alkylation procedure is highly general, exhibits high diastereoselectivity, and allows prediction of the absolute stereochemistry of the alkylation products. The alkylation products so obtained are synthetically useful both as important intermediates for the synthesis of bicyclic alkaloids and other nitrogen-containing natural products and as potential chiral auxiliaries for asymmetric reactions.

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 JMN-FX 100 spectrometer (100 MHz) or a JEOL JMN-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 JMN-FX 100 spectrometer (25 MHz); signals are given in ppm with $CHCl_3$ 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 × 20 cm × 20 cm). Flash column chromatography was carried out on E. Merck silica gel (60, particle size 230–400 mesh). "Workup" indicates drying over anhydrous Na_2SO_4, filtration, and concentration in vacuo. THF and toluene were distilled from sodium benzophenone ketyl under N_2. *N*-Ethylpiperidine, Et_3N, DMF, and CH_2Cl_2 were distilled from CaH_2. Absolute MeOH and EtOH were obtained by treatment with sodium metal followed by distillation under N_2. All other reagents were used as purchased. 4(*S*)- and 4(*R*)-isopropyl-1,3-thiazolidine-2-thione [4(*S*)- or 4(*R*)-IPTT] were prepared according to our reported method.[8] Tin trifluoromethanesulfonate was prepared according to the literature procedures.[25] 5-Acetoxy-2-pyrrolidinone was obtained through a known procedure.[12]

Preparation of Compounds 3. Method A. To a suspension of 60% NaH (0.546 g, 13.64 mmol) in dry THF (10 mL) at 0 °C was added a solution of 4(*S*)- or 4(*R*)-IPTT (**1** or **2**, 2.00 g, 12.40 mmol) in dry THF (10 mL). The mixture was stirred at 0 °C for 10 min, and acyl chloride (13.64 mmol) was injected into the solution, which was stirred at 0 °C for 10 min and then at room temperature for 1–1.5 h. Hydrochloric acid (5%) was added, and the mixture was extracted with EtOAc, washed with brine, and worked up. The crude product was purified by flash column chromatography (elution with 10% EtOAc in hexane for **3a,c,e,f**, or with 17% Et_2O in hexane for **3d,g**) to afford the corresponding product **3**.

3-Acetyl-4(*S*)-isopropyl-1,3-dithiazolidine-2-thione (3a): Compound **3a** was prepared according to the reported method.[8,9g]

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(23) (a) Niwa, H.; Miyachi, Y.; Okamoto, O.; Uosaki, Y.; Yamada, K. *Tetrahedron Lett.* **1986**, *27*, 4605. (b) Niwa, H.; Okamoto, O.; Miyachi, Y.; Uosaki, Y.; Yamada, K. *J. Org. Chem.* **1987**, *52*, 2941.

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(25) (a) Batchelor, R. J.; Ruddick, J. N. R.; Sams, J. R.; Aubke, F. *Inorg. Chem.* **1977**, *16*, 1414. (b) Iwasawa, N.; Mukaiyama, T. *J. Synth. Org. Chem. Jpn.* **1986**, 71.

3-(4-Chlorobutyryl)-4(*S*)-isopropyl-1,3-thiazolidine-2-thione (3c): 95% yield from **1** and 4-chlorobutyryl chloride as a yellow oil; IR ($CHCl_3$) 1690, 1360, 1313, 1255, 1164, and 1140 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.97 and 1.06 (6 H, d, J = 7.0 Hz), 2.00–2.56 (3 H, m), 3.03 (1 H, dd, J = 1.5, 11.2 Hz), 3.39 (1 H, dd, J = 7.1, 11.0 Hz), 3.44–3.70 (4 H, m), 5.16 (1 H, ddd, J = 1.5, 6.3, 7.8 Hz); MS, m/z 265 (M^+), 230, 202, 162, 118 (100), 105; HRMS calcd for $C_{10}H_{16}NOS_2Cl$ MW 265.0362, found m/z 265.0363 (M^+). Anal. Calcd for $C_{10}H_{16}NOS_2Cl$: C, 45.18; H, 6.07; N, 5.27. Found: C, 45.05; H, 6.03; N, 5.75.

3-(5-Chlorovaleryl)-4(*S*)-isopropyl-1,3-thiazolidine-2-thione (3d): 96% yield from **1** and 5-chlorovaleryl chloride as a yellow oil; IR ($CHCl_3$) 1690, 1360, 1310, 1275, 1255, and 1160 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.97 and 1.06 (6 H, d, J = 7.0 Hz), 1.68–1.96 (4 H, m), 2.12–2.56 (1 H, m), 3.02 (1 H, dd, J = 1.4, 11.5 Hz), 3.52 (1 H, dd, J = 8.0, 11.5 Hz), 3.12–3.68 (4 H, m), 5.17 (1 H, m); MS, m/z 279 (M^+), 244, 202, 162, 118, 91, 55 (100); HRMS calcd for $C_{11}H_{18}NOS_2Cl$ MW 279.0518, found m/z 279.0535 (M^+). Anal. Calcd for $C_{11}H_{18}NOS_2Cl$: C, 47.21; H, 6.48; N, 5.01. Found: C, 47.47; H, 6.57; N, 5.13.

3-Acetyl-4(*R*)-isopropyl-1,3-thiazolidine-2-thione (3e): 100% yield from **2** and acetyl chloride as a yellow oil. Spectral data of **3e** were identical with those of its enantiomer **3a** except for the optical rotation. Anal. Calcd for $C_8H_{13}NOS_2$: C, 47.26; H, 6.44; N, 6.89. Found: C, 47.29; H, 6.37; N, 7.01.

3-((Benzyloxy)acetyl)-4(*R*)-isopropyl-1,3-thiazolidine-2-thione (3f): 94% yield from **2** and (benzyloxy)acetyl chloride as a yellow oil; IR ($CHCl_3$) 1705, 1365, 1260, 1175, and 1110 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.98 and 1.05 (6 H, d, J = 7.0 Hz), 2.20–2.54 (1 H, m), 3.04 (1 H, dd, J = 1.5, 11.5 Hz), 3.57 (1 H, dd, J = 7.8, 11.7 Hz), 4.64 (2 H, s), 4.97 and 5.04 (2 H, ABq, J = 16.5 Hz), 5.16 (1 H, m), 7.28–7.48 (5 H, m); MS, m/z 309 (M^+), 218, 203, 162, 118, 91 (100); HRMS calcd for $C_{15}H_{19}NO_2S_2$ MW 309.0857, found m/z 309.0850 (M^+). Anal. Calcd for $C_{15}H_{19}NO_2S_2$: C, 58.22; H, 6.19; N, 4.53. Found: C, 57.86; H, 6.09; N, 5.04.

3-(5-Chlorovaleryl)-4(*R*)-isopropyl-1,3-thiazolidine-2-thione (3g): 96% yield from **2** and 5-chlorovaleryl chloride as a yellow oil. Spectral data of **3g** were identical with those of its enantiomer **3d** except for the optical rotation. Anal. Calcd for $C_{11}H_{18}NOS_2Cl$: C, 47.21; H, 6.48; N, 5.01. Found: C, 47.20; H, 6.30; N, 5.12.

Method B. 3-((Phenylthio)acetyl)-4(*S*)-isopropyl-1,3-thiazolidine-2-thione (3b): To a mixture of **1** (1.38 g, 8.55 mmol) and (phenylthio)acetic acid (2.16 g, 12.83 mmol) in dry CH_2Cl_2 (20 mL) precooled at 0 °C was added a solution of DCC (2.64 g, 12.83 mmol) and DMAP (0.156 g, 1.28 mmol) in dry CH_2Cl_2 (20 mL). The whole mixture was stirred at room temperature for 11 h. The precipitate was filtered off through Celite, and the filtrate was condensed and purified by flash column chromatography (elution with 14% EtOAc in hexane) to give 2.34 g (88%) of **3b** as yellow prisms: IR ($CHCl_3$) 1685, 1580, 1288, 1155, and 1140 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.96 and 1.04 (6 H, d, J = 7.0 Hz), 2.16–2.52 (1 H, m), 3.01 (1 H, dd, J = 1.5, 11.7 Hz), 3.49 (1 H, dd, J = 8.3, 11.7 Hz), 4.70 (2 H, s), 5.10 (1 H, ddd, J = 1.5, 6.4, 7.8 Hz), 7.16–7.52 (5 H, m); MS, m/z 311 (M^+), 226, 202 (100), 162, 150, 123, 118, 105, 69; HRMS calcd for $C_{14}H_{17}NOS_3$ MW 311.0488, found m/z 311.0494 (M^+). Anal. Calcd for $C_{14}H_{17}NOS_3$: C, 53.98; H, 5.50; N, 4.50. Found: C, 54.19; H, 5.43; N, 4.48.

6-Acetoxy-2-piperidinone (5, *n* = 2): A solution of 6-ethoxy-2-piperidinone[13] (2.0 g) in acetic acid (70 mL) was stirred at 30 °C for 24 h and then under slightly reduced pressure at 30 °C for another 24 h. Acetic acid was carefully removed in vacuo below 40 °C (water bath temperature) to give an oily residue. Diethyl ether (100 mL) was added to the oily residue, and the precipitate was collected by filtration to afford 1.06 g of 6-acetoxy-2-piperidinone (ca. 90% pure by ^1H NMR analysis). The filtrate was condensed to give 0.955 g of an oily residue that contained mainly 3,4-dihydro-2-pyridone[13] from 6-acetoxy-2-piperidinone by elimination of acetic acid; IR ($CHCl_3$) 3400, 1725, 1675, 1660 (sh), 1235, 1190, and 990 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.48–2.20 (4 H, m), 2.07 (3 H, s), 2.20–2.60 (2 H, m), 5.80 (1 H, m), 6.96 (1 H, br s).

General Procedure for Generation of Chiral Tin(II) Enolate 4. Method A (for Enolates 4a,e). Tin(II) trifluoromethanesulfonate (0.90 g, 2.16 mmol) was dissolved in dry THF (5 mL) under argon atmosphere at room temperature. To the solution cooled at −50 °C in a dry ice–acetonitrile bath was added successively *N*-ethylpiperidine (0.34 mL, 2.49 mmol) and 3-acetyl-4(*S*)-IPTT (**3a**, 0.338 g, 1.66 mmol) in dry THF (1.5 mL), and the mixture was then stirred for 3 h between −50 and −40 °C to form the tin(II) enolate **4a**.

Method B (for Enolates 4c,d,g). Tin(II) trifluoromethanesulfonate (2.16 g, 5.18 mmol) was dissolved in dry THF (10 mL) under argon atmosphere at room temperature. To the solution cooled at −5 °C in an ice–brine bath was added successively *N*-ethylpiperidine (0.79 mL, 5.70 mmol) and 3-(5-chlorovaleryl)-4(*S*)-IPTT (**3d**) (0.728 g, 2.60 mmol) in dry THF (4 mL), and the mixture was then stirred for 4 h between −5 and 0 °C to form the tin(II) enolate **4d**.

Method C (for Enolates 4b,f). Tin(II) trifluoromethanesulfonate (1.31 g, 3.14 mmol) was dissolved in dry THF (7 mL) under argon atmosphere at room temperature. To the solution cooled at −78 °C in a dry ice–acetone bath was added successively 3-[(benzyloxy)acetyl]-4(*R*)-IPTT (**3f**, 0.749 g, 2.42 mmol) in dry THF (5 mL) and *N*-ethylpiperidine (0.50 mL, 3.63 mmol), and the mixture was stirred at −78 °C for 30 min to form the tin(II) enolate **4f**.

General Procedure for Alkylation of Compound 5 (*n* = 1, 2) with Chiral Tin(II) Enolate 4. To the tin(II) enolate **4** (2.0 mmol), prepared from **3** as described above, was added a ca. 1.0 M solution of 5-acetoxy-2-pyrrolidinone (**5**, n = 1, 3.0 mmol) or a ca. 0.8 M solution of 6-acetoxy-2-piperidinone (**5**, n = 2, 3.0 mmol) in dry THF at −5 °C, and the mixture was then stirred for 2 h between −5 and 0 °C. The reaction mixture was poured into a mixture of phosphate buffer solution (pH 7.0, 50 mL) and EtOAc (50 mL) with vigorous stirring. After the precipitate was filtered off through Celite and washed with EtOAc (3 × 50 mL), the combined filtrate was washed with brine and then submitted to workup to provide a crude product. A sample of the crude product was submitted to HPLC analysis[26] (column, Diasil 5C 18 4.6 mm i.d. × 25 cm; eluent, CH_3CN–H_2O = 9:1; flow rate, 1.0 mL/min; detection, UV 305 nm) to determine diastereomeric excess (see Table II). Flash column chromatography of the crude product (elution with 33% EtOAc in $CHCl_3$ for compounds **7**, **9–11**, and **15**, 50% EtOAc in $CHCl_3$ for compounds **8**, **13**, and **14**, or 67% EtOAc in $CHCl_3$ for compounds **6** and **12**) afforded the pure products **6–15**[27] (see Table II). Data for compounds **6–15** are reported as follows.

3-((5-Oxo-2(*S*)-pyrrolidinyl)acetyl)-4(*S*)-isopropyl-1,3-thiazolidine-2-thione (6): yellow oil; IR ($CHCl_3$) 3340, 1690 (br), 1255, and 1175 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.98 and 1.06 (6 H, d, J = 6.8 Hz), 1.68–2.08 (1 H, m), 2.18–2.60 (4 H, m), 3.04 (1 H, dd, J = 1.5, 11.5 Hz), 3.18 (1 H, dd, J = 9.8, 17.8 Hz), 3.57 (1 H, dd, J = 8.0, 11.5 Hz), 3.78 (1 H, dd, J = 3.5, 17.8 Hz), 3.96–4.28 (1 H, m), 5.20 (1 H, ddd, J = 1.5, 6.0, 8.0 Hz), 6.28 (1 H, br s); MS, m/z 286 (M^+), 253, 161, 149, 118, 84; HRMS calcd for $C_{12}H_{18}N_2O_2S_2$ MW 286.0808, found m/z 286.0808 (M^+). Anal. Calcd for $C_{12}H_{18}N_2O_2S_2$: C, 50.32; H, 6.33; N, 9.78. Found: C, 50.46; H, 6.48; N, 9.19.

3-(2(*R*)-(5-Oxo-2(*S*)-pyrrolidinyl)(phenylthio)acetyl)-4-(*S*)-isopropyl-1,3-thiazolidine-2-thione (7): yellow needles;

(26) For assignment of the peaks due to the related diastereomers on the HPLC chart, each corresponding authentic diastereomeric mixture of the alkylation products was prepared as follows: The pure compounds **6–11**, **13**, and **14** were subjected to alkaline hydrolysis in 10% KOH–MeOH (1:2) at room temperature for 10–60 min to give the corresponding carboxylic acids with racemization at the α position of the carboxy group in the cases of compounds **7–11** and **13**. Then, dehydrative condensation of the carboxylic acids with racemic IPTT in the presence of DCC–DMAP in CH_2Cl_2 at room temperature furnished each corresponding diastereomeric mixture of the 3-acyl-4-IPTT amides, respectively. These samples were submitted to HPLC analysis for calculation of the diastereomeric excess of each major alkylation product.

(27) The isolated compounds **6–15** were checked for diastereomeric purity by HPLC analysis.

(28) After our asymmetric synthesis, a new indolizidine alkaloid, tashiromine, has very recently been isolated from the fresh stems of *Maackia tashiroi* (Leguminosae) together with seven lupin alkaloids including (+)-epilupinine. However, the absolute stereochemistry of the natural tashiromine still remains unknown; see: Kubo, H.; Ohmiya, S.; Otomasu, H.; Saito, K.; Murakoshi, I., presented at the 109th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, Japan, Apr 4–6, 1989; abstr papers III, p 225.

IR ($CHCl_3$) 3425, 1688 (br), 1580, 1245, and 1160 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.93 and 1.02 (6 H, d, J = 7.0 Hz), 2.00–2.60 (5 H, m), 2.94 (1 H, dd, J = 1.0, 11.5 Hz), 3.22 (1 H, dd, J = 7.0, 11.5 Hz), 4.00–4.28 (1 H, m), 4.75 (1 H, br t, J = 7.0 Hz), 6.22 (1 H, d, J = 7.3 Hz), 7.18–7.60 (5 H, m); MS, m/z 395 (M^+ + 1), 361, 310, 285, 202, 161, 150, 118, 84 (100), 59. Anal. Calcd for $C_{18}H_{22}N_2O_2S_3$: C, 54.79; H, 5.62; N, 7.10. Found: C, 54.88; H, 5.61; N, 7.09.

3-(2(*R*)-(5-Oxo-2(*S*)-pyrrolidinyl)-4-chlorobutyryl)-4-(*S*)-isopropyl-1,3-thiazolidine-2-thione (8): yellow needles; IR ($CHCl_3$) 3420, 3350, 1685 (br), 1360, 1300, 1246, 1175, and 1150 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.97 and 1.07 (6 H, d, J = 6.8 Hz), 1.80–2.52 (7 H, m), 3.05 (1 H, dd, J = 1.0, 11.5 Hz), 3.36–3.76 (3 H, m), 4.04–4.28 (1 H, m), 5.00–5.22 (2 H, m), 6.28 (1 H, br s); MS, m/z 348 (M^+), 315, 264, 162, 110, 84 (100). Anal. Calcd for $C_{14}H_{21}N_2O_2S_2Cl$: C, 48.19; H, 6.07; N, 8.03. Found: C, 47.92; H, 5.99; N, 7.98.

3-(2(*R*)-(5-Oxo-2(*S*)-pyrrolidinyl)-5-chlorovaleryl)-4-(*S*)-isopropyl-1,3-thiazolidine-2-thione (9): yellow needles; IR ($CHCl_3$) 3425, 3365, 1688 (br), 1245, 1172, and 1156 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.97 and 1.06 (6 H, d, J = 6.8 Hz), 1.56–2.56 (9 H, m), 3.05 (1 H, br d, J = 11.2 Hz), 3.40–3.68 (3 H, m), 3.96–4.24 (1 H, m), 4.90–5.08 (1 H, m), 5.14 (1 H, br t, J = 7.0 Hz), 6.34 (1 H, br s); MS, m/z 362 (M^+), 329, 278, 173, 162, 118, 110, 84 (100). Anal. Calcd for $C_{15}H_{23}N_2O_2S_2Cl$: C, 49.64; H, 6.39; N, 7.72. Found: C, 49.52; H, 6.25; N, 7.65.

3-(2(*R*)-(6-Oxo-2(*S*)-piperidinyl)-4-chlorobutyryl)-4-(*S*)-isopropyl-1,3-thiazolidine-2-thione (10): yellow needles; IR ($CHCl_3$) 3355, 1652 (br), 1246, 1177, and 1150 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.96 and 1.06 (6 H, d, J = 6.8 Hz), 1.50–2.16 (5 H, m), 2.16–2.60 (4 H, m), 3.04 (1 H, dd, J = 1.0, 11.5 Hz), 3.30–3.74 (3 H, m), 3.80–4.02 (1 H, m), 4.93 (1 H, ddd, J = 2.3, 3.3, 10.5 Hz), 5.07 (1 H, br t, J = 7.0 Hz), 6.34 (1 H, br s); MS, m/z 362 (M^+), 329, 264, 173, 161, 124, 118 (100), 98. Anal. Calcd for $C_{15}H_{23}N_2O_2S_2Cl$: C, 49.64; H, 6.39; N, 7.72. Found: C, 49.72; H, 6.40; N, 7.69.

3-(2(*R*)-(6-Oxo-2(*S*)-piperidinyl)-5-chlorovaleryl)-4(*S*)-isopropyl-1,3-thiazolidine-2-thione (11): yellow oil; IR ($CHCl_3$) 3370, 1723, 1650, 1240, 1172, 1160, and 1148 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.99 and 1.09 (6 H, d, J = 6.8 Hz), 1.50–2.16 (7 H, m), 2.16–2.68 (4 H, m), 3.09 (1 H, dd, J = 1.0, 11.0 Hz), 3.40–3.70 (3 H, m), 3.72–3.98 (1 H, m), 4.76–4.98 (1 H, m), 5.16 (1 H, br t, J = 7.0 Hz), 6.36 (1 H, br s); MS, m/z 376 (M^+), 343, 320, 278, 243, 187, 161, 118, 98 (100); HRMS calcd for $C_{16}H_{25}N_2O_2S_2Cl$ MW 376.1051, found m/z 376.1054 (M^+). Anal. Calcd for $C_{16}H_{25}N_2O_2S_2Cl$: C, 50.98; H, 6.68; N, 7.43. Found: C, 51.02; H, 6.74; N, 7.43.

3-((5-Oxo-2(*R*)-pyrrolidinyl)acetyl)-4(*R*)-isopropyl-1,3-thiazolidine-2-thione (12): yellow oil. Spectral data of **12** were identical with those of its enantiomer **6** except for the optical rotation. Anal. Calcd for $C_{12}H_{18}N_2O_2S_2$: C, 50.32; H, 6.33; N, 9.78. Found: C, 50.37; H, 6.38; N, 9.46.

3-(2(*S*)-(5-Oxo-2(*R*)-pyrrolidinyl)(benzyloxy)acetyl)-4-(*R*)-isopropyl-1,3-thiazolidine-2-thione (13): yellow needles; IR ($CHCl_3$) 3425, 1688 (br), 1359, 1245, and 1170 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.90 and 0.99 (6 H, d, J = 6.8 Hz), 2.00–2.52 (5 H, m), 2.88 (1 H, dd, J = 1.5, 11.5 Hz), 3.17 (1 H, dd, J = 7.8, 11.2 Hz), 3.96–4.20 (1 H, m), 4.48 and 4.68 (2 H, ABq, J = 12.2 Hz), 4.81 (1 H, m), 5.92 (1 H, br s), 6.08 (1 H, d, J = 5.4 Hz), 7.34 (5 H, s); MS, m/z 392 (M^+), 359, 320, 301, 284, 218, 162, 118, 91 (100); HRMS calcd for $C_{19}H_{24}N_2O_3S_2$ MW 392.1219, found m/z 392.1214 (M^+). Anal. Calcd for $C_{19}H_{24}N_2O_3S_2$: C, 58.14; H, 6.16; N, 7.14. Found: C, 58.13; H, 6.19; N, 7.25.

3-((6-Oxo-2(*R*)-piperidinyl)acetyl)-4(*R*)-isopropyl-1,3-thiazolidine-2-thione (14): yellow prisms; IR ($CHCl_3$) 3375, 1675, 1643, and 1172 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.98 and 1.07 (6 H, d, J = 7.0 Hz), 1.40–2.16 (4 H, m), 2.16–2.56 (3 H, m), 3.04 (1 H, dd, J = 1.0, 11.2 Hz), 3.21 (1 H, dd, J = 10.3, 18.1 Hz), 3.58 (1 H, dd, J = 7.8, 11.2 Hz), 3.65 (1 H, dd, J = 2.9, 18.1 Hz), 3.80–4.16 (1 H, m), 5.16 (1 H, ddd, J = 1.0, 6.5, 7.5 Hz), 6.45 (1 H, br s); MS, m/z 300 (M^+), 267, 202, 161, 118, 111, 98 (100), 83; HRMS calcd for $C_{13}H_{20}N_2O_2S_2$ MW 300.0996, found m/z 300.1010 (M^+). Anal. Calcd for $C_{13}H_{20}N_2O_2S_2$: C, 51.97; H, 6.71; N, 9.32. Found: C, 51.92; H, 6.56; N, 9.29.

3-(2(*S*)-(6-Oxo-2(*R*)-piperidinyl)-5-chlorovaleryl)-4(*R*)-isopropyl-1,3-thiazolidine-2-thione (15): yellow oil. Spectral data of **15** were identical with those of its enantiomer **11** except for the optical rotation. Anal. Calcd for $C_{16}H_{25}N_2O_2S_2Cl$: C, 50.98; H, 6.68; N, 7.43. Found: C, 51.24; H, 6.82; N, 7.20.

General Procedure for Reductive Annulation of Compounds 8–11 and 15. (–)-Trachelanthamidine (17a) and 2-(*S*)-(1-hydroxy-2(*R*)-butyl)pyrrolidine (19a): To a suspension of $LiAlH_4$ (71 mg, 1.87 mmol) in dry THF (4 mL) cooled at 0 °C under N_2 was added a yellow solution of compound **8** (163 mg, 0.467 mmol) in dry THF (4 mL). The original yellow color of the solution immediately disappeared. After stirring at 0 °C for 5 min, the mixture was heated under reflux for 2 h. The reaction mixture was recooled to 0 °C and diluted with Et_2O (10 mL). The etheral mixture was successively treated with 68 μL of water, 68 μL of 3 N aqueous NaOH solution, and 97 μL of water and then stirred at room temperature for 30 min. The resultant precipitate was filtered off through Celite and washed with 10% Et_3N in THF (4 × 25 mL). The combined filtrate was dried over anhydrous Na_2SO_4, and the solvent was removed to give a crude product (158 mg), which was submitted to preparative TLC developing with $CHCl_3$–MeOH–Et_3N (1:1:1) to afford 29 mg (44%) of (–)-trachelanthamidine (**17a**) and 6.8 mg (10%) of the byproduct **19a**. **17a**: pale yellow oil; IR ($CHCl_3$) 3320, 3100, 1448, 1090, and 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50–2.04 (7 H, m), 2.52 (1 H, dt, J = 5.86, 9.76 Hz), 2.59 (1 H, dt, J = 10.74, 6.35 Hz), 2.96 (1 H, dt, J = 10.74, 6.35 Hz), 3.14 (1 H, ddd, J = 3.42, 6.84, 10.26 Hz), 3.22 (1 H, dd, J = 6.35, 13.67 Hz), 3.59 (2 H, dd, J = 0.98, 6.35 Hz), 4.00 (1 H, br s, exchangeable by D_2O); MS, m/z 141 (M^+), 124, 110, 83, 82, 55; HRMS calcd for $C_8H_{15}NO$ MW 141.1165, found m/z 141.1167 (M^+). **19a**: pale yellow oil; IR ($CHCl_3$) 3350 (br) cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.96 (3 H, t, J = 6.0 Hz), 1.10–1.44 (2 H, m), 1.52–2.40 (7 H, m), 3.08–3.36 (1 H, m), 3.52–3.94 (2 H, m), 5.50–6.20 (2 H, br s, exchangeable by D_2O); MS, m/z 143 (M^+), 70 (100). Preparative TLC for compounds **17b–d**, **19b**, **19d**, **21**, and **23** was done on silica gel plates using $CHCl_3$–MeOH–Et_3N (4:2:1) for developing.

(5*R*,6*S*)-1-Aza-5-(hydroxymethyl)bicyclo[4.3.0]nonane ((–)-tashiromine[28]) (17b): pale yellow oil; IR ($CHCl_3$) 3630, 3350, 3320, 1460, 1440, 1162, 1085, and 1030 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.84–2.46 (13 H, m), 2.96–3.26 (2 H, m), 3.46 (1 H, dd, J = 5.8, 10.5 Hz), 3.66 (1 H, dd, J = 4.3, 10.5 Hz); ^{13}C NMR (25 MHz, $CDCl_3$) δ 20.8, 25.2, 27.7, 29.1, 44.6, 52.8, 54.2, 65.5, 66.5; MS, m/z 155 (M^+), 154, 138, 124, 97, 96, 83, 69; HRMS calcd for $C_9H_{17}NO$ MW 155.1305, found m/z 155.1304 (M^+).

(4*R*,5*S*)-1-Aza-7-(hydroxymethyl)bicyclo[4.3.0]nonane (17c): pale yellow oil; IR ($CHCl_3$) 3625, 3350, 3200 (sh), 1450, 1440, and 1080 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.05–2.36 (12 H, m), 2.80–3.38 (3 H, m, one of them is exchangeable by D_2O), 3.63 (2 H, d, J = 5.0 Hz); ^{13}C NMR (25 MHz, $CDCl_3$) δ 24.3, 25.2, 25.4, 30.4, 46.1, 53.1, 53.4, 64.6, 67.4; MS, m/z 155 (M^+), 154, 138, 124, 97, 96, 69; HRMS calcd for $C_9H_{17}NO$ MW 155.1315; found m/z 155.1316 (M^+).

(–)-Epilupinine (17d): colorless needles; IR ($CHCl_3$) 3615, 3325 (sh), 3150, 1465, 1440, 1108, and 1085 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.96–2.24 (15 H, m), 2.68–2.98 (2 H, m), 3.52 (1 H, dd, J = 4.8, 11.0 Hz), 3.68 (1 H, dd, J = 3.3, 11.0 Hz); MS, m/z 169 (M^+), 168, 152 (100), 138, 124, 97, 83. Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.27. Found: C, 70.58; H, 11.19; N, 8.20.

(+)-Epilupinine (21): colorless needles. Spectra data of **21** were identical with those of its enantiomer **17d** except for the optical rotation. Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.27. Found: C, 70.87; H, 11.44; N, 8.19.

2(*S*)-(1-Hydroxy-2(*R*)-pentyl)pyrrolidine (19b): pale yellow oil; IR ($CHCl_3$) 3300 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.91 (3 H, t, J = 6.5 Hz), 1.06–2.44 (9 H, m), 2.88–4.12 (5 H, m), 4.56–5.24 (2 H, s, exchangeable by D_2O); MS, m/z 157 (M^+), 70 (100).

2(*S*)-(1-Hydroxy-2(*R*)-pentyl)piperidine (19d): pale yellow oil; IR ($CHCl_3$) 3300 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.90 (3 H, t, J = 6.5 Hz), 1.02–2.05 (11 H, m), 2.05–3.80 (5 H, m), 4.00–4.70 (2 H, br s, exchangeable by D_2O); MS, m/z 171 (M^+), 141, 112, 98, 84 (100), 83, 70; HRMS calcd for $C_{10}H_{21}NO$ MW 171.1612, found m/z 171.1610 (M^+).

2(*R*)-(1-Hydroxy-2(*S*)-pentyl)piperidine (23): pale yellow oil. Spectral data of **23** were identical with those of its enantiomer **19d**.

General Procedure for Acetylation of Compounds 17a–d, 19a,b,d, 21, and 23. To a solution of the substrate in dry THF (ca. 0.1 M) cooled at 0 °C was added acetyl chloride (3 mol equiv for **17a–d** and **21**; 4 mol equiv for **19a,b,d**, and **23**) and triethylamine (3 mol equiv for **17a–d** and **21**; 4 mol equiv for **19a,b,d** and **23**) followed by stirring at room temperature for 4–24 h. The reaction mixture was diluted with EtOAc, and the resultant precipitate was filtered off through Celite. The filtrate was condensed to give a crude product, which was purified by preparative TLC ($CHCl_3$–MeOH–Et_3N (5:1:1) for **18a**; $CHCl_3$–EtOAc–Et_3N (4:1:1) for **18b,c**; $CHCl_3$–EtOAc–Et_3N (10:1:1) for **18d** and **22**; $CHCl_3$–CH_3COCH_3 (5:1) for **20a,b,d and 24**) to afford the corresponding monoacetyl and diacetyl derivatives in 70–80% yields, respectively.

(4*R*,5*S*)-1-Aza-4-(acetoxymethyl)bicyclo[3.3.0]octane (18a): pale yellow oil; IR ($CHCl_3$) 1735, 1365, 1230 (br), 1035, and 905 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.36–2.10 (7 H, m), 2.06 (3 H, s), 2.40–2.74 (2 H, m), 2.86–3.38 (3 H, m), 4.02 (1 H, dd, J = 6.4, 11.0 Hz), 4.16 (1 H, dd, J = 6.4, 11.0 Hz); MS, m/z 183 (M^+), 149, 124, 83, 60, 44; HRMS calcd for $C_{10}H_{17}NO_2$ MW 183.1256, found m/z 183.1255 (M^+).

(5*R*,6*S*)-1-Aza-5-(acetoxymethyl)bicyclo[4.3.0]nonane (18b): pale yellow oil; IR ($CHCl_3$) 1725, 1365, 1240 (br), 1220 (sh), and 1035 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.80–2.66 (12 H, m), 2.06 (3 H, s), 2.92–3.24 (2 H, m), 3.80–4.20 (2 H, m); MS, m/z 197 (M^+), 138, 122, 97, 40; HRMS calcd for $C_{11}H_{19}NO_2$ MW 197.1399, found m/z 197.1395 (M^+).

(4*R*,5*S*)-1-Aza-7-(acetoxymethyl)bicyclo[4.3.0]nonane (18c): pale yellow oil; IR ($CHCl_3$) 1730, 1373, 1365, 1240, 1220 (sh), and 1035 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.06–2.64 (12 H, m), 2.06 (3 H, s), 2.94–3.20 (2 H, m), 3.96–4.18 (2 H, m); MS, m/z 197 (M^+), 196, 154, 138, 97; HRMS calcd for $C_{11}H_{19}NO_2$ MW 197.1414, found m/z 197.1413 (M^+).

(5*R*,6*S*)-1-Aza-5-(acetoxymethyl)bicyclo[4.4.0]decane (18d): pale yellow oil; IR ($CHCl_3$) 1730, 1365, 1240, 1220 (sh), 1113, and 905 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.90–2.32 (14 H, m), 2.06 (3 H, s), 2.68–2.94 (2 H, m), 3.84–4.26 (2 H, m); MS, m/z 211 (M^+), 152, 149, 110, 97; HRMS calcd for $C_{12}H_{21}NO_2$ MW 211.1550, found m/z 211.1544 (M^+).

(5*S*,6*R*)-1-Aza-5-(acetoxymethyl)bicyclo[4.4.0]decane (22): pale yellow oil. Spectral data of **22** were identical with those of its enantiomer **18d**.

1-Acetyl-2(*S*)-(1-acetoxy-2(*R*)-butyl)pyrrolidine (20a): pale yellow oil; IR ($CHCl_3$) 1725 and 1620 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.98 (3 H, t, J = 7.0 Hz), 1.10–1.50 (2 H, m), 1.76–2.60 (7 H, m), 2.04 (3 H, s), 2.06 (3 H, s), 3.30–3.60 (1 H, m), 3.94–4.30 (2 H, m); MS, m/z 227 (M^+), 208, 193, 158, 112, 70, 44 (100); HRMS calcd for $C_{12}H_{21}NO_3$ MW 227.1523, found m/z 227.1522 (M^+).

1-Acetyl-2(*S*)-(1-acetoxy-2(*R*)-pentyl)pyrrolidine (20b): pale yellow oil; IR ($CHCl_3$) 1725, 1625, 1240, and 1035 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.94 (3 H, t, J = 6.4 Hz), 1.04–1.60 (3 H, m), 1.72–2.70 (6 H, m), 2.04 (3 H, s), 2.06 (3 H, m), 3.20–3.60 (3 H, m), 3.92–4.12 (2 H, m); MS, m/z 241 (M^+), 213, 181, 112, 70; HRMS calcd for $C_{13}H_{23}NO_3$ MW 241.1649, found m/z 241.1648 (M^+).

1-Acetyl-2(*S*)-(1-acetoxy-2(*R*)-pentyl)piperidine (20d): pale yellow oil; IR ($CHCl_3$) 1730, 1630, 1230, and 1030 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.90 (3 H, t, J = 6.0 Hz), 1.04–2.00 (11 H, m), 2.08 (3 H, s), 2.11 (3 H, s), 2.88–3.20 (1 H, m), 3.50–3.86 (1 H, m), 4.04–4.20 (2 H, m), 4.46–4.84 (1 H, m); MS, m/z 255 (M^+), 240, 212, 152, 126 (100), 84; HRMS calcd for $C_{14}H_{25}NO_3$ MW 255.1853, found m/z 255.1859 (M^+).

1-Acetyl-2(*R*)-(1-acetoxy-2(*S*)-pentyl)piperidine (24): pale yellow oil. Spectral data of **24** were identical with those of its enantiomer **20d**.

Methyl (*S*)-5-oxo-2-pyrrolidineacetate (25a): A mixture of **6** (0.667 g, 2.33 mmol) and K_2CO_3 (0.20 g, 1.45 mmol) in absolute MeOH (30 mL) was stirred at room temperature for 30 min (the original yellow color of the solution disappeared). The solid was filtered off through Celite, and the filtrate was condensed in vacuo to give a residue. Flash column chromatography (elution with 67% EtOAc in $CHCl_3$) of the residue yielded 0.347 g (95%) of **25a** as colorless prisms: mp 64–64.5 °C (recrystallized from Et_2O); $[\alpha]^{21}_D$ +21.1° (*c* 0.54, EtOH); IR ($CHCl_3$) 3425, 1730, 1690, and 1078 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.60–2.00 (1 H, m), 2.16–2.68 (5 H, m), 3.71 (3 H, s), 3.86–4.18 (1 H, m), 6.38 (1 H, br s); MS, m/z 157 (M^+), 129, 115, 84 (100), 55, 41. Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.43; H, 7.10; N, 9.07.

Ethyl (*S*)-5-oxo-2-pyrrolidineacetate (25b): A mixture of **6** (0.576 g, 2.01 mmol) and K_2CO_3 (0.60 g, 4.34 mmol) in absolute EtOH (10 mL) was stirred at room temperature for 12 h (the original yellow color of the solution disappeared). The solid was filtered off through Celite, and the filtrate was condensed in vacuo to give a residue. Flash column chromatographic separation (elution with 20% acetone in CH_2Cl_2) of the residue yielded 0.265 g (77%) of **25b** as a colorless oil: $[\alpha]^{25}_D$ +14.8° (*c* 1.06, EtOH); IR ($CHCl_3$) 3420, 1720, 1685, and 1080 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.27 (3 H, t, J = 7.0 Hz), 1.50–2.00 (1 H, m), 2.00–2.68 (5 H, m), 3.80–4.00 (1 H, m), 4.17 (2 H, q, J = 7.0 Hz), 6.45 (1 H, br s); MS, m/z 171 (M^+), 143, 84; HRMS calcd for $C_8H_{13}NO_3$ MW 171.0911, found m/z 171.0914 (M^+). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.20; H, 7.64; N, 8.40.

(*S*)-5-Oxo-2-pyrrolidineacetic acid (26): A mixture of **25a** (120 mg, 0.76 mmol) in MeOH (1.5 mL) and 3 N aqueous NaOH (1.5 mL) was stirred at room temperature for 18 h. The reaction mixture was acidified with 5% HCl, and the solvent was completely removed. Extraction of the residue with CH_2Cl_2, followed by removal of the solvent gave 70 mg (64%) of **26** as colorless prisms: mp 100.5–101.5 °C (recrystallized from $CHCl_3$–EtOAc); $[\alpha]^{21}_D$ +21.6° (*c* 0.41, EtOH) [lit.[18] mp 103–105 °C; $[\alpha]^{26}_D$ +17.6° (EtOH)]; IR ($CHCl_3$) 3290, 2500 (br), 1920 (br), 1700 (br), 1670 (sh), and 1650 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.50–2.00 (1 H, m), 2.08–2.82 (5 H, m), 3.90–4.24 (1 H, m), 7.94 (2 H, br s); MS, m/z 143 (M^+), 115, 84 (100), 55, 41. Anal. Calcd for $C_6H_9NO_3$: C, 50.35; H,6.34; N, 9.79. Found: C, 50.02; H, 6.29; N, 9.73.

Methyl (*S*)-1-methyl-5-oxo-2-pyrrolidineacetate (28): To a suspension of 60% NaH (33 mg, 0.81 mmol) in dry DMF (0.5 mL) was added a solution of **26** (58 mg, 0.405 mmol) in dry DMF (0.5 mL) at 0 °C followed by stirring at room temperature for 20 min. Methyl iodide (76 μL, 1.22 mmol) was added, and the mixture was stirred at room temperature for 6 h. The reaction mixture was acidified with 5% HCl and evaporated in vacuo to give a residue, which was extracted with $CHCl_3$. After evaporation of the $CHCl_3$ extract, the crude product was treated with CH_2N_2 in ether. Preparative TLC of the crude methyl ester and development with 20% acetone in $CHCl_3$ afforded 34.1 mg (49%) of **28** as a colorless oil: $[\alpha]^{22}_D$ −40.0° (*c* 1.14, EtOH) [lit.[18] $[\alpha]^{23}_D$ −40.1° (EtOH)]; IR ($CHCl_3$) 1730 and 1675 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.60–2.00 (1 H, m), 2.16–2.72 (5 H, m), 2.81 (3 H, s), 3.72 (3 H, s), 3.80–4.08 (1 H, m); MS, m/z 171 (M^+), 128, 98 (100), 70, 53; HRMS calcd for $C_8H_{13}NO_3$ MW 171.0867, found m/z 171.0914 (M^+). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.09; H, 7.58; N, 8.40.

Ethyl (*S*)-5-thioxo-2-pyrrolidineacetate (29): To a solution of **25b** (0.20 g, 1.17 mmol) in dry toluene (3 mL) was added 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphatane 2,4-disulfide (0.251 g, 0.62 mmol), and the mixture was then refluxed for 1 h under argon atmosphere. Removal of the solvent and flash column chromatography of the residue using 33% EtOAc in hexane gave 0.19 g (87%) of **29** as a pale yellow oil: $[\alpha]^{25}_D$ +91.6° (*c* 0.74, $CHCl_3$); IR ($CHCl_3$) 3375, 1720, 1495, and 1015 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.28 (3 H, t, J = 7.0 Hz), 1.60–2.14 (1 H, m), 2.24–2.78 (3 H, m), 2.80–3.10 (2 H, m), 4.00–4.50 (3 H, m), 8.58 (1 H, br s); MS, m/z 187 (M^+), 115, 100 (100); HRMS calcd for $C_8H_{13}NO_2S$ MW 187.0673, found m/z 187.0675 (M^+). Anal. Calcd for $C_8H_{13}NO_2S$: C, 51.31; H, 7.00; N, 7.48. Found: C, 51.36; H, 6.95; N, 7.78.

Ethyl (*S*)-1-((ethoxycarbonyl)methyl)-2-pyrrolidineacetate (31): To a solution of Et_3OBF_4 (207 mg, 1.09 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C was added **29** (157 mg, 0.838 mmol) in dry CH_2Cl_2 (3 mL) followed by stirring at 0 °C for 5 min and then at room temperature for 3 h. The reaction mixture was recooled to 0 °C, a solution of 95% $NaBH_3CN$ (222 mg, 3.35 mmol) in MeOH (2.3 mL) and AcOH (0.2 mL) was added, and the mixture was stirred at 0 °C for 1 h and then at room temperature for another 2 h. After removal of the solvent, the residue was dissolved in EtOH (20 mL), and Na_2CO_3 (0.5 g) and ethyl bromoacetate (0.14 mL, 1.26 mmol) were added. The mixture was

stirred at room temperature for 20.5 h and then diluted with CH_2Cl_2. The solid was filtered off through Celite and the filtrate was condensed to give a crude product. Flash column chromatography (elution with 20% EtOAc in CH_2Cl_2) afforded 170 mg (83%) of **31** as a colorless oil: $[\alpha]^{25}_D$ -58.0° (*c* 1.21, $CHCl_3$) [lit.[21a] $[\alpha]^{25}_D$ -56.9° (*c* 1.13, $CHCl_3$)]; IR ($CHCl_3$) 1720, 1180, and 1020 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.26 (3 H, t, *J* = 7.0 Hz), 1.27 (3 H, t, *J* = 7.0 Hz), 1.44-2.70 (8 H, m), 2.88-3.32 (1 H, m), 3.26 and 3.53 (2 H, ABq, *J* = 17.1 Hz), 4.13 (2 H, q, *J* = 7.0 Hz), 4.18 (2 H, q, *J* = 7.0 Hz); MS, *m/z* 243 (M^+), 170, 156, 128; HRMS calcd for $C_{12}H_{21}NO_4$ MW 243.1489, found *m/z* 243.1495 (M^+). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.36; H, 8.65; N, 5.94.

Methyl (*R*)-6-oxo-2-piperidineacetate (36a): A mixture of **14** (151 mg, 0.50 mmol) and K_2CO_3 (35 mg, 0.25 mmol) in absolute MeOH (4 mL) was stirred at room temperature for 30 min (the original yellow color of the solution disappared). The solid was filtered off through Celite, and the filtrate was condensed in vacuo to give a residue. Preparative TLC (elution with 33% acetone in $CHCl_3$) of the residue yielded 75 mg (88%) of **36a** as colorless prisms: mp 87-88 °C (recrystallized from Et_2O); $[\alpha]^{21}_D$ -14.1° (*c* 0.41, EtOH); IR ($CHCl_3$) 3375, 1725, 1653, and 1078 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.20-2.10 (4 H, m), 2.20-2.58 (4 H, m), 3.71 (3 H, s), 3.60-4.00 (1 H, m), 6.32 (1 H, br s); MS, *m/z* 171 (M^+), 143, 115, 98 (100), 55. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.22; H, 7.71; N, 8.26.

(*R*)-6-Oxo-2-piperidineacetic acid (36b): A solution of **36a** (34.5 mg, 0.202 mmol) in MeOH (0.5 mL) and 2% aqueous NaOH (0.5 mL) was stirred at room temperature for 5 h. The reaction mixture was acidified with 5% HCl, and the solvent was completely removed. Extraction of the residue with $CHCl_3$, washing with brine, and the usual workup gave 20 mg (63%) of **36b** as colorless needles: mp 131.5-133.5 °C (recrystallized from $CHCl_3$-EtOAc); $[\alpha]^{25}_D$ -19.7° (*c* 0.38, EtOH) [lit.[24] (*S*)-form (≤64% ee) mp 132-134 °C; $[\alpha]^{24}_D$ +11.3° (*c* 1, EtOH)]; IR ($CHCl_3$) 3280, 2450 (br), 1930 (br), 1705 (br), and 1620 (br) cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.14-2.20 (4 H, m), 2.20-2.76 (4 H, m), 3.80-4.16 (1 H, m), 7.20-8.10 (1 H, br s), 8.26 (1 H, br s); MS, *m/z* 157 (M^+), 139, 129, 101, 98, 70, 55 (100).

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Registry No. 1, 76186-04-4; **2**, 110199-16-1; **3a**, 101979-45-7; **3b**, 124201-69-0; **3c**, 111975-21-4; **3d**, 111975-22-5; **3e**, 121929-87-1; **3f**, 121929-88-2; **3g**, 124201-70-3; (±)-**5** *n* = 1, 111975-27-0; (±)-**5** *n* = 2, 111975-28-1; **6**, 121929-83-7; **7**, 124201-72-5; **8**, 111975-23-6; **9**, 111975-24-7; **10**, 111975-25-8; **11**, 111975-26-9; **12**, 121929-84-8; **13**, 121929-85-9; **14**, 124201-73-6; **15**, 112065-91-5; **17a**, 526-64-7; **17b**, 111975-29-2; **17c**, 111975-30-5; **17d**, 112065-89-1; **18a**, 62912-97-4; **18b**, 111975-35-0; **18c**, 111975-36-1; **18d**, 112065-90-4; **19a**, 111975-31-6; **19b**, 111975-32-7; **19d**, 111975-34-9; **20a**, 111975-37-2; **20b**, 111975-38-3; **20d**, 111975-40-7; **21**, 486-71-5; **22**, 71657-68-6; **23**, 111975-41-8; **24**, 124201-74-7; **25a**, 67036-44-6; **25b**, 124201-75-8; **26**, 61884-75-1; **28**, 61884-76-2; **29**, 124201-76-9; **31**, 83455-90-7; **36a**, 67036-45-7; **36b**, 65084-15-3; (±)-6-ethoxy-2-piperidinone, 124201-71-4; 3,4-dihydro-2-pyridone, 57147-25-8.

General Method for the Synthesis of Bridged Indole Alkaloids. Nucleophilic Addition of Indoleacetic Ester Enolates to *N*-Alkylpyridinium Salts

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A short route to tetracyclic ring substructures of C-mavacurine, *Strychnos*, and akuammiline-type alkaloids, based on the addition of methyl 1-, 2-, or 3-indoleacetate anions to *N*-alkylpyridinium salts followed by acid cyclization of the resultant 1,4-dihydropyridines, is reported. Further stereoselective elaboration of the C-20 (*E*)-ethylidene substituent results in the synthesis of the indole alkaloid vinoxine (**7b**) and of 4-ethylidenehexahydro-1,5-methanoazocino[4,3-*b*]- and -[3,4-*b*]indoles **14-17**, **32**, and **35**. Some mechanistic aspects concerning the regiochemistry of the nucleophilic addition to the pyridinium ring are discussed.

The development of general methods for the synthesis of indole alkaloids has been a longtime goal for organic synthesis chemists.[1] The main group of indole alkaloids biogenetically derives from tryptophan and secologanin,[2] geissoschizine being a key early intermediate: oxidative cyclization between C-16[3] and the indole 3-position (C-7) gives formylstrictamine, from which the alkaloids of the akuammiline group are formed; similarly, oxidative ring closure between C-16 and the indole nitrogen affords the alkaloids of the C-mavacurine group. The hydrolytic cleavage of the tryptamine bridge would explain the formation of the tetracyclic alkaloid vinoxine. A skeletal rearrangement (cleavage of C-7/C-16 and C-2/C-3 bonds and formation of C-3/C-7 and C-2/C-16 bonds) interconnects formylstrictamine with *Strychnos* alkaloids (Scheme I).

Despite their apparent skeletal dissimilarity, the indole alkaloids of the C-mavacurine, *Strychnos*, and akuammiline groups have some common structural features due to their common biogenetic origin: (i) an oxidized one-carbon substituent at C-16 (lost in some cases), (ii) a two-carbon chain, usually an *E*-configurated ethylidene, at C-20, (iii) a tryptamine C-5/C-6 unit connecting the indole 3-position and the piperidine nitrogen, (iv) a bond linking indole and piperidine rings, the latter by an α-carbon, and (v) a cis-2,4-disubstituted piperidine ring in-

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