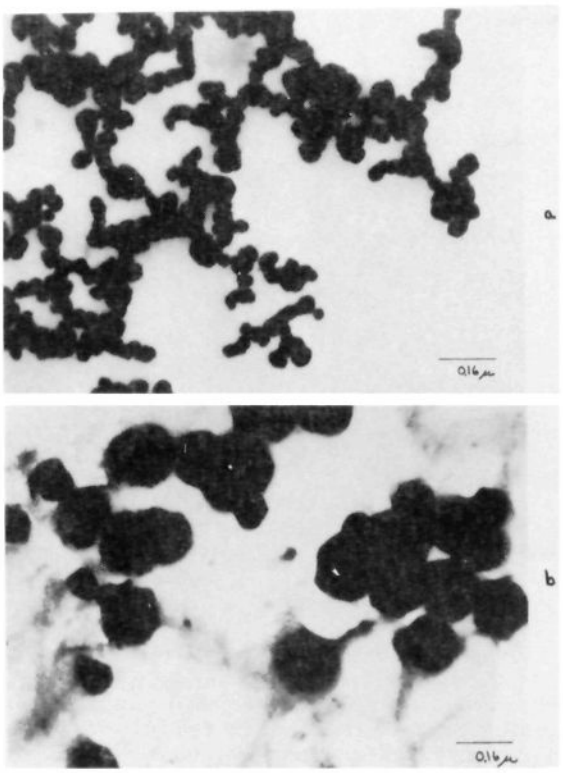

Figure 1. Electron micrograph of a preparation of (a) (top) DMPC:Pd. The particles are approximately 400 Å in diameter and form chains of metal particles. (b) (bottom) DMPC/DODAB:Ni. The stability of the nickel vesicles increased if a reducing agent was entrapped within the vesicles before metal was deposited on the surface. This was achieved if sonication to form the vesicles was carried out in a solution of sodium hypophosphite. The particles appeared as large spheres approximately 1500 Å in diameter.

were successfully used to support catalytic Pd(0) and then form nickel particles by electroless plating (Figure 1b).

The addition of tetrachloropalladate to the unsaturated phospholipid DOPC resulted in the slow formation of Pd(0). This reaction took place in the absence of any added reducing agent. If a Pt(II) salt, tetrachloroplatinate, was added to a sample of DOPC, the solution darkened even more rapidly. These observations indicate that the metal is forming a new complex with the olefin in the phospholipid membrane. The reaction of Pd(II) with olefins in the presence of water is known to rapidly decompose to form aldehydes and Pd(0).[11]

This demonstration of the metalization of both saturated and unsaturated lipid vesicles raises several interesting questions that are currently being explored. These include the following: the nature of the coordination between Pd(II) and the vesicles, the location of the catalytic Pd(0) in both saturated and unsaturated vesicles, and the nature of the deposited metal particles on the saturated vesicles (i.e., is the particle a thin shell of metal associated with most of the vesicle surface or a solid particle that is loosely adhering to the original vesicle surface).

Acknowledgment. We thank Lee Brady (ASD) for the electron microscopy.

Registry No. DMPC, 18194-24-6; DODAB, 3700-67-2; DMAB, 74-94-2; $NiCl_2$, 7718-54-9; $CoCl_2$, 7646-79-9; $CuCl_2$, 7447-39-4; NaH_2PO_2, 7681-53-0; Ni, 7440-02-0; Co, 7440-48-4; Cu, 7440-50-8; dilauroyl PC, 18285-71-7; dioleoyl PC, 10015-85-7; tetrachloropalladate, 14349-67-8; palladium, 7440-05-3; sodium tetrachloropalladate, 13820-53-6; sodium gluconate, 527-07-1; ammonium hydroxide, 1336-21-6.

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Extremely Short Chiral Synthesis of Bicyclic Alkaloids Having a Nitrogen Atom Ring Juncture

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Bicyclic alkaloids having pyrrolizidine, indolizidine, and quinolizidine skeletons are widely distributed in various plant families.[2] The tumor inhibitory activities of the pyrrolizidine alkaloids have been recognized for the past few decades,[2-4] and there have been a large number of reports on their total syntheses.[5-7] However, the syntheses of optically active pyrrolizidine alkaloids have mostly been performed by employing the chiral building block converted from L-proline derivatives,[7a-f] (*R*)- or (*S*)-malic acid,[7g-m] and carbonhydrates,[7n-p] respectively. Most of the previous chiral syntheses take roundabout ways in spite of their simple structures.

We disclose a new general method for extremely short chiral synthesis of the bicyclic alkaloids having a nitrogen atom ring juncture.[8] Equation 1 shows the synthetic sequence via a highly

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Table I. Highly Diastereoselective Alkylation of Chiral Tin(II) Enolates **2** onto Compounds **3**[a]

product **4**	diastrmer excess[b]	isoltd yield[c]	mp, °C	$[\alpha]^{22}_{D}$[g] (*c*) in $CHCl_3$
4a	≥97%	64%	163–164[d]	+447.2 (0.25)
4b	≥93%	72%	142–143.5[e]	+416.3 (0.33)[f]
4c	≥95%	57%	126.5–127.5[e]	+407.8 (0.40)
4d	≥93%	73%	oil	+344.6 (0.57)

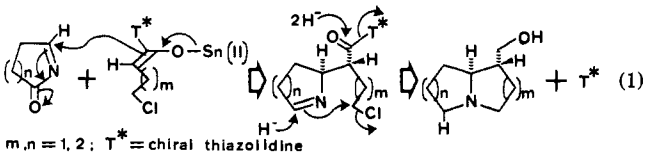
[a] A ca. 9:1 mixture of **3** (n = 1, 2) and the corresponding 5- or 6-ethoxy compound was employed. [b] Checked by HPLC analysis. [c] Calculated based on **1**. [d] Recrystallized from $CHCl_3$–hexane. [e] Recrystallized from CH_2Cl_2–hexane. [f] Recorded at 14 °C. [g] $[\alpha]^{22}_{D}$ is measured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

Table II. Reductive Annulation of Compounds **4a–d**[a]

substrate	product (yield)	byproduct (yield)	$[\alpha]^{22}_{D}$[d] (*c*) in EtOH
4a	**6a** (44%)	**7a** (10%)	**6a**, −13.7 (1.22)[c]
4b	**6b** (41%)	**7b** (22%)	**6b**, −25.9 (1.16)
4c	**6c** (69%)	**7c** (trace)	**6c**, −53.4 (1.18)
4d	**6d** (61%)[b]	**7d** (18%)	**6d**, −30.5 (0.84)

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

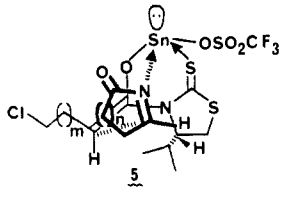
diastereoselective alkylation[9] to the cyclic acyl imines followed by reductive annulation of the resultant cyclic imines.[10]



(1)

To a THF solution of tin(II) enolate **2**, prepared from tin(II) trifluoromethanesulfonate (2 mol equiv), *N*-ethylpiperidine (2.2 mol equiv), and 3-ω-chloroacyl-4(*S*)-isopropyl-1,3-thiazolidine-2-thiones (**1**), was added at −5 °C a solution of 5-acetoxy-2-pyrrolidinone[11] (**3**, n = 1) (1.5 mol equiv) or 6-acetoxy-2-piperidinone[11] (**3**, n = 2) (1.5 mol equiv) in THF. After stirring at −5 to 0 °C for 2 h, the reaction mixture was treated as usual to give the corresponding major product **4a–d** in a highly diastereoselective manner [≥93–≥97% diastereomer excess (de), Scheme I and Table I]. Pure compounds **4a–d** were readily obtained by their chromatographic separation on a silica gel column in 57–73% yields.

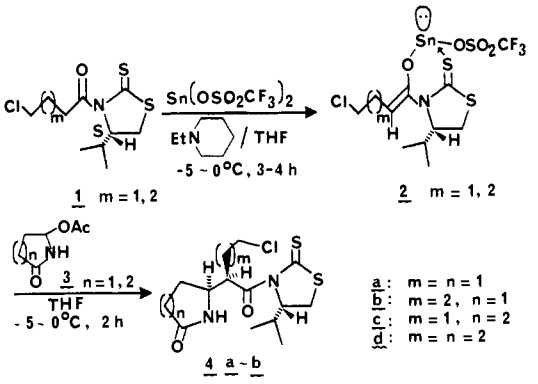
The absolute configuration of compounds **4a** and **4d** was established by their chemical conversion to (−)-trachelanthamidine (**6a**)[7a] or (−)-epilupinine (**6d**),[6i] respectively (vide infla). The stereochemistry of compounds **4b** and **4c** was tentatively assigned on the basis of the similar mechanistic consideration of **5** to that



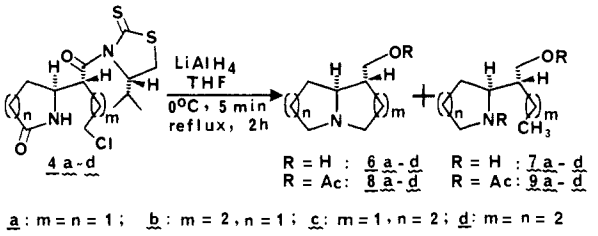
5

for **4a** and **4d**. A six-membered chelated transition state **5** can be used for rationalization of the stereochemical results, regardless of the ring size (n = 0–2 in **5**) of the cyclic acyl imines.[9]

Scheme I



Scheme II



Sebsequently, we designed a one-pot and one-reagent ($LiAlH_4$) synthesis of the chiral bicyclic alkaloids **6** from **4**.[12,13] Thus, ω-halolactams **4a–d** were treated with a small excess of $LiAlH_4$ (4 mol equiv) in THF, first at 0 °C for 5 min to reduce the active amide moiety[14] without epimerization at the active methine carbon and then under reflux for 2 h to achieve the reductive annulation. After the usual workup and separation of the crude products by preparative thin-layer chromatography [silica gel, $CHCl_3$–MeOH–Et_3N = 1:1:1 (for **6a**) or 4:2:1 (for **6b–d**)], the desired bicyclic products **6a–d** (41–69% yields) were directly furnished together with the corresponding hydrogenolysis byproducts **7a–d** (Scheme II and Table II). No O-cyclization product, which had been anticipated, was isolated from the reaction mixture.

For the confirmation of hydroxyl and/or imino group(s) in the molecule, compounds **6a–d** and **7a–d** were acetylated giving the corresponding monoacetyl derivatives **8a–d** or diacetyl derivatives **9a–d** in good yields (70–80%). The synthesized compound **6a** [≥99% optically pure (op) based on the reported data:[15] $[\alpha]_D$ −13.8° (*c* 1.28, EtOH)] proved to be (−)-trachelanthamidine by comparison of its physical data with those for the authentic compound.[7a] Compound **6d** was confirmed to be (−)-epilupinine in similar manner.[6i,16] We attempted to synthesize naturally occurring (+)-epilupinine (**10**) according to our new method. Similar chiral alkylation to compound **3** (n = 2) utilizing 4-(*R*)-isopropyl-1,3-thiazolidine-2-thione [4(*R*)-IPTT] gave the antipodal compound [≥93% de, $[\alpha]^{22}_{D}$ −362.6° (*c* 0.58, $CHCl_3$] of **4d** in 73% yield. The subsequent reductive annulation afforded (+)-epilupinine (**10**) [mp 78-79 °C (hexane); $[\alpha]^{22}_{D}$ +31.2° (*c* 0.86, EtOH), ≥97% op based on the literature data:[16] mp 76–78 °C (petroleum ether); $[\alpha]^{17}_{D}$ +32° (*c* 1.49, EtOH)] in 59% yield together with the byproduct **11** in 17% yield.[17] This is the first

(9) Our recent successful work on the chiral alkylation to 4-acetoxy-2-azetidinones, see: (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. *Perspective in the Organic Chemistry of Sulfur*; Zwanenburg, B., Klunder, A. J. H., Eds.; Elsevier: Amsterdam, 1987; p 57.

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

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(12) Cf. Rodewald, W. J.; Morzycki, J. W. *Tetrahedron Lett.* **1978**, 1077.

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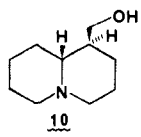
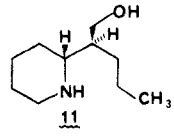
example of a chiral synthesis of (+)-epilupinine.



10



11

We succeeded in developing an extremely short chiral synthesis of the bicyclic alkaloids involving pyrrolizidine, indolizidine, and quinolizidine skeletons. This new method should be applicable to large-scale synthesess of various man-designed anticancer agents.

Selective Hydride-Mediated Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds Using $[(Ph_3P)CuH]_6$

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Hydride-mediated conjugate reduction of α,β-unsaturated carbonyl compounds remains an active area of organic research. By analogy of dialkyl cuprate conjugate addition reactions, in situ generation of unstable copper(I) hydride "ate" complexes have figured prominently in these efforts.[2] In addition, other hydride sources have been used,[3] including several anionic transition-metal hydrido complexes.[4] Despite some success as selective alternatives to catalytic hydrogenation, hydrosilation,[5] and dissolving metal reduction, these methods suffer from, inter alia, significant problems in scope, functional group compatibility, and/or reproducibility.

We wish to report that the stable, well-characterized copper(I) hydride cluster $[(Ph_3P)CuH]_6$[6-9] (1) is generally effective for the selective conjugate hydride addition to α,β-unsaturated carbonyl compounds. This mild hydride donor is chemically compatible with added chlorotrimethylsilane, affording an efficient procedure for reductive silylation. Additionally, due to the unusual ability of copper(I) alkoxide complexes to promote heterolytic activation of molecular hydrogen,[7,10,11] this conjugate reduction can potentially be made *catalytic* in the hydride reagent.[12]

For the stoichiometric conjugate reduction, the reaction is best conducted in benzene or toluene under inert atmosphere at room temperature. All 6 hydride equiv per cluster are delivered to the organic substrate.[13] No 1,2-reduction of the carbonyl moiety has been observed, even under prolonged reaction time in the presence of excess hydride reagent. The hydridic character of the conjugate reduction is strongly suggested both by substrate selectivity and deuterium labeling studies. The copper hydride hexamer is completely inert toward a variety of alkenes unactivated toward hydride attack, including, significantly, 1,1-diphenylethylene.[14] Conjugate reduction of 2-cyclohexenone by the deuteriated complex $[(Ph_3P)CuD]_6$[7] yielded cyclohexanone specifically labeled in the 3-position as determined by ^2H NMR.

Although it is presumed that the reaction proceeds via a copper(I) enolate intermediate, direct formation of the product ketone is observed spectroscopically in reactions run at room temperature under inert atmosphere in sealed NMR tubes.[15] We have as yet been unable to unambiguously determine the source of the quenching hydrogen atom in these reactions. Independent synthesis and characterization of copper enolate complexes is currently under investigation.

For substrates sensitive to base-catalyzed aldol condensations, decomposition of the unstable intermediate leads to significant byproduct formation. These undesirable side reactions are completely suppressed by conducting the reaction in the presence of added water.[16] While the copper hydride hexamer is indefinitely

(1) Address correspondence to this author.

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(3) (a) H_2AlI (from 4 CuI:1 $LiAlH_4$): Ashby, E. C.; Lin, J. J. *Tetrahedron Lett.* **1975**, 4453. Ashby, E. C.; Lin, J. J.; Kovar, R. *J. Org. Chem.* **1976**, *41*, 1939. (b) Li and K selectrides: Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194. (c) NaTeH: Ramasamy, K.; Kalyanasundaram, S. K.; Shanmugam, P. *Synthesis* **1978**, 545. Yamashita, M.; Kato, Y.; Suemitsu, R. *Chem. Lett.* **1980**, 847; (d) $(n\text{-}Bu)_3SnH$: Brimage, D. R. G.; Davidson, R. S.; Lambeth, P. F. *J. Chem. Soc. C* **1971**, 1241.

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