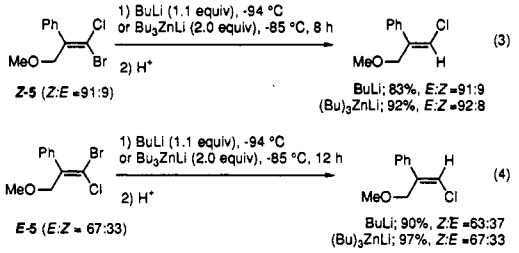
geminal position seems to render the phenyl group to rotate, resulting in reduction of its effective size against the syn bromine atom.

Judging from similar trends in stereoselectivity among **1a**, **1b**, and **1c** as well as the nonselective reaction of the (benzyloxy)methyl (BOM) derivatives **1f**, a directing effect of a metal chelation is not necessarily a major factor in the kinetically controlled reactions.[15]

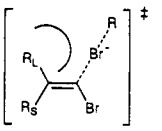
Four possible mechanisms have been proposed for the halogen/metal exchange reactions:[16] (1) a stepwise process initiated by a single electron transfer, (2) a four-centered process, (3) formation of an ate complex, and (4) an S_N2 reaction. Reaction of the pathway invoked for a single electron-transfer mechanism is less likely in the present carbenoid formation for the following reasons. Such mechanism involves a radical intermediate which could undergo *E,Z*-isomerization, at least partially, in the course of reaction.[17,18] The results of lithium and zincate carbenoid formation from (*E*)- and (*Z*)-bromochloroalkene **5**[19] (eq 3) clearly demonstrate that both BuLi and $(Bu)_3ZnLi$ undergo exchange reaction stereospecifically with retention



(14) Lipton, M.; Still, W. C. *J. Comput. Chem.* **1988**, *9*, 343.
(15) (a) Lau, K. S. Y.; Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595. (b) Meyers, A. I.; Spohn, R. F. *J. Org. Chem.* **1985**, *50*, 4872.
(16) (a) Review; Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1 and references cited therein. (b) Beak, P.; Allen, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 3420.
(17) A rate between 10^8 and 10^{10} s^{-1} at −170 °C was reported for the isomerization of propen-2-yl: Fessenden, R. W.; Schuler, R. H. *J. Chem. Phys.* **1963**, *39*, 2147.
(18) Walborsky, H. M. *Acc. Chem. Res.* **1990**, *23*, 286.
(19) **5** was prepared by the reaction of lithium carbenoid **2a** with $ClCF_2CCl_2F$.

of the configuration of the carbenoid carbon. Moreover, $(t\text{-Bu})_3ZnLi$ which should be a better electron donor in comparison with $(Bu)_3ZnLi$ exhibited a lower reactivity in the Br/Zn exchange reaction: The reaction of **1a** was $(t\text{-Bu})_3ZnLi$ at −85 °C in THF for 5 min gave **4a** (*E*:*Z* = 92:8) in 29% yield together with recovery of **1a** (68%).

The observation of the higher reactivities of the more hindered bromine atom is not compatible with a sterically demanding four-centered transition-state model. The selectivities are most reasonably explained by a linear transition state **6** of either an ate complex[20] or S_N2[21] reaction where strain relief due to elongation of the carbon–bromine bond is expected in the reaction at the more hindered bromine atom.



6

Acknowledgment. This work was supported partially by grants from the Ministry of Education, Science, and Culture, Japanese Government [Grant-in-Aid for Scientific Research on Priority Areas No. 03233216 (Unusual Valency) and Grant-in-Aid for Scientific Research Relating to JSPS Fellowships for Japanese Junior Scientist (for T.K.)] and from the Japan Science Society [Sasakawa Scientific Research Grant (for T.K.)].

Supplementary Material Available: General experimental procedures and characterization data of new compounds including NOESY spectra of (*E*)- and (*Z*)-bromoalkenes derived from **1a–d** (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(20) (a) Reich, H. J.; Philips, N. H.; Reich, I. L. *J. Am. Chem. Soc.* **1985**, *107*, 4101. (b) Reich, H. J.; Green, D. P.; Philips, N. H. *Ibid.* **1989**, *111*, 3444.
(21) Farnham, W. B.; Calabrese, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 2449.

Enantiopure 2,3-Dihydro-4-pyridones as Synthetic Intermediates. Asymmetric Syntheses of the Quinolizidine Alkaloids (+)-Myrtine, (−)-Lasubine I, and (+)-Subcosine I†

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Summary: The first asymmetric syntheses of three quinolizidine alkaloids, (+)-myrtine, (−)-lasubine I, and (+)-subcosine I, were accomplished with a high degree of stereocontrol from readily available 4-methoxy-3-(triisopropylsilyl)pyridine in three, four, and five steps, respectively.

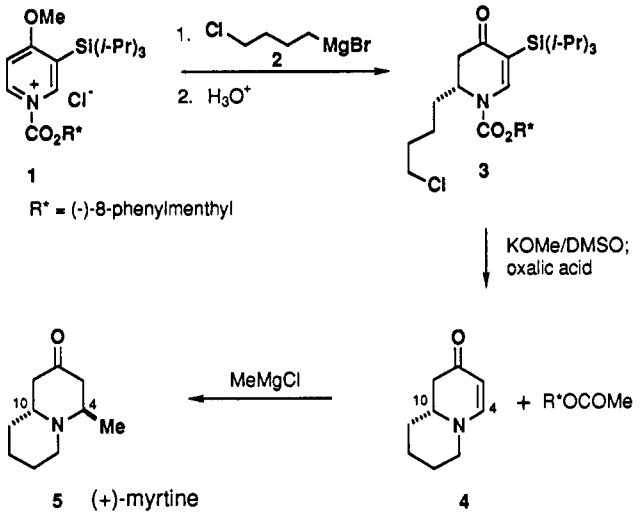
The indolizidine and quinolizidine skeletons comprise the backbone of many biologically and structurally interesting alkaloids.[1] We have been exploring methods for the enantioselective preparation of these ring systems via chiral 1-acyl-2,3-dihydro-4-pyridone intermediates. Using this strategy, we recently accomplished short, enantioselective syntheses of the indolizidine alkaloids (+)-elaeokanine A and (+)-elaeokanine C.[2] In this paper we report a three-step preparation of the quinolizidine alkaloid (+)-myrtine and the first asymmetric syntheses of the

† Dedicated to Professor A. I. Meyers on the occasion of his 60th birthday.

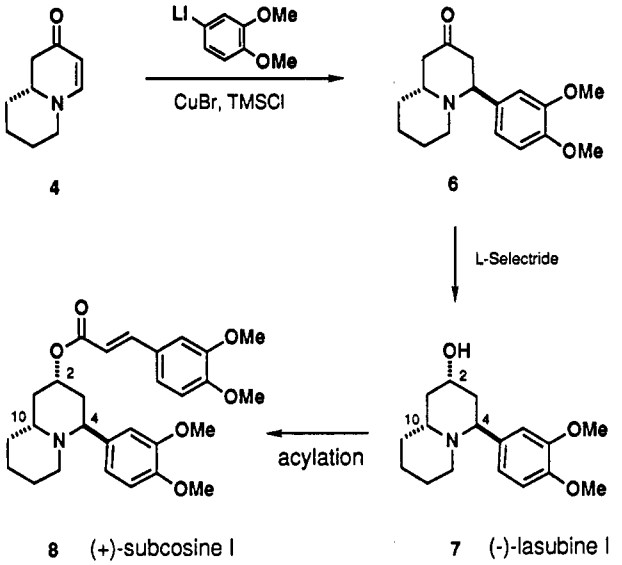
(1) Elbein, A. D.; Molyneus, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1987; Vol. 5, Chapter 1.
(2) Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* **1991**, *113*, 6672.

0022-3263/92/1957-5807$03.00/0

Scheme I



Scheme II



Lythraceae alkaloids (−)-lasubine I and (+)-subcosine I.

The myrtine synthesis was carried out as shown in Scheme I. Reaction of chiral 1-acylpyridinium salt **1**, prepared in situ from 4-methoxy-3-(triisopropylsilyl)-pyridine and the chloroformate of (−)-8-phenylmenthol,[3] with Grignard reagent **2**[4,5] in THF/toluene at −78 °C gave the dihydropyridone **3** in 77% yield and 86% de. The major diastereomer resulting from addition of an aliphatic Grignard reagent to chiral 1-acyl salt **1** is known to possess the *R* configuration at C-2 of the dihydropyridone ring.[3] After purification by chromatography (silica gel, 5% EtOAc/hexane), diastereomerically pure **3** (mp 108–110 °C, 71% yield) was treated with potassium methoxide in DMSO (4 equiv, room temperature, 2 h) to effect concomitant removal of the chiral auxiliary and cyclization. Workup with oxalic acid and purification (silica gel, 50–95% EtOAc/hexane) provided a 90% yield of the quinolizidinone **4** as a clear oil [$[\alpha]^{22}_D$ −146.0° (*c* 0.89, $CHCl_3$)]. The chiral auxiliary, (−)-8-phenylmenthol, was recovered via its methyl carbonate in 95% yield. The enantiomeric purity of **4** was determined to be >99% by chiral column HPLC analysis.[6]

The quinolizidinone **4** has considerable potential as a chiral building block for various alkaloids having the *cis*-quinolizidine skeleton, since stereoelectronically preferred axial 1,4-addition of a nucleophile to the enone of **4** leads to a product containing a trans C-4, C-10 hydrogen relationship. Reaction of **4** with methylmagnesium chloride in benzene at room temperature[7] gave a 55% yield of *cis*-quinolizidine alkaloid (+)-myrtine (**5**) as a clear oil [$[\alpha]^{28}_D$ +19.3° (*c* 1.95, $CHCl_3$) (lit.[7] $[\alpha]_D$ +11.3° (*c* 2.7, $CHCl_3$))]. Although optically enriched (+)-myrtine has been prepared through the Mannich condensation of resolved (*R*)-pelletierine and by resolution of the racemate,[7] our three-step procedure represents the first asymmetric synthesis of this alkaloid.[8]

Many of the alkaloids from the Lythraceae family possess a *cis*-quinolizidine ring system.[9] Our interest in establishing **4** as an attractive chiral building block for alkaloid synthesis prompted us to investigate the syntheses of two Lythraceae alkaloids, (−)-lasubine I (**7**) and (+)-subcosine I (**8**). A short, enantioselective preparation of these alkaloids was carried out as depicted in Scheme II. Addition of **4** to a mixture of (3,4-dimethoxyphenyl)lithium, cuprous bromide, and chlorotrimethylsilane gave a 53% yield of *trans*-piperidone **6** as a clear oil[10] [$[\alpha]^{23}_D$ +10.8° (*c* 1.31, $CHCl_3$); ee[6] >99%]. Stereoselective reduction of **6** with L-Selectride[11] provided (−)-lasubine I (**7**) in 74% yield as a pale yellow oil [ee[6] >97%, $[\alpha]^{23}_D$ −7.03° (*c* 0.37, MeOH); lit.[12] $[\alpha]^{23}_D$ −8.8° (*c* 0.34, MeOH)]. Acylation of **7** with 3,4-dimethoxycinnamic anhydride[13] (pyridine, DMAP, reflux, 3 h) gave a 62% yield of (+)-subcosine I (**8**); [$[\alpha]^{26}_D$ +93.6° (*c* 0.14, MeOH) (lit.[12] $[\alpha]^{23}_D$ +68.0° (*c* 0.20, MeOH))].[14,15]

Although several racemic preparations have been reported,[9] our work represents the first asymmetric syntheses of alkaloids in the Lythraceae family. The synthetic approach is highly stereoselective and efficient, allowing (−)-lasubine I and (+)-subcosine I to be prepared from readily available 4-methoxy-3-(triisopropylsilyl)pyridine[3] in four and five steps, respectively. These asymmetric syntheses have established the absolute stereochemistry in alkaloids **7** and **8** as 2*S*,4*S*,10*R*. The basic strategy should be amenable to the asymmetric synthesis of numerous other quinolizidine and indolizidine alkaloids.

(3) Comins, D. L.; Goehring, R. R.; Joseph, S. P.; O'Connor, S. *J. Org. Chem.* **1990**, *55*, 2574.

(4) Bernady, K. F.; Poletto, J. F.; Nocera, J.; Mirando, P.; Schaub, R. E.; Weiss, M. J. *J. Org. Chem.* **1980**, *45*, 4702. The best results were obtained by preparing the Grignard reagent from the organolithium[5] and $MgBr_2$.

(5) Meyers, A. I.; Licini, G. *Tetrahedron Lett.* **1989**, *30*, 4049.

(6) The enantiomeric purity was determined by HPLC using a Chiralcel OJ column (J. T. Baker, Inc., Phillipsburg, NJ).

(7) Racemic **4** has been converted to (±)-myrtine in this manner; see: Slosse, P.; Hotelé, C. *Tetrahedron Lett.* **1979**, *20*, 4587; *Tetrahedron* **1981**, *37*, 4287.

(8) For racemic syntheses of myrtine, see: (a) Gelas-Mialhe, Y.; Gramain, J.-C.; Louvet, A.; Remuson, R. *Tetrahedron Lett.* **1992**, *33*, 73. (b) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1989**, *30*, 5053 and references cited therein.

(9) For reviews on the Lythraceae alkaloids, see: (a) Gollebbiewski, W. M.; Wrobel, J. T. In *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic: New York, 1981; Vol. 18, Chapter 4. (b) Fuji, K. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic: New York, 1989; Vol. 35, Chapter 3.

(10) The crude product contained approximately 10% of the cis isomer as determined by ^1H NMR.

(11) For discussion on the L-Selectride reduction of aryl quinolizidones of the type **6**, see: Rother, A.; Schwarting, A. E. *Lloydia* **1975**, *38*, 477.

(12) Fuji, K.; Yamada, T.; Fujita, E.; Murata, H. *Chem. Pharm. Bull.* **1978**, *26*, 2515.

(13) Iida, H.; Tanaka, M.; Kibayashi, C. *J. Org. Chem.* **1984**, *49*, 1909.

(14) The spectral properties of (−)-**7** and (+)-**8** were in agreement with reported data.[9,13]

(15) All new compounds were spectroscopically characterized and furnished satisfactory elemental analyses (C, H, N ±0.4%). Details are provided in the supplementary material.

Acknowledgment. We gratefully acknowledge support of this work by the National Institutes of Health (Grant GM 34442).

Supplementary Material Available: Experimental details for the preparation of 3–8 and physical data for 3–8 (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Carbometalation of Cyclopropenes. Stereoselective Synthesis of Divinyl Ketone Acetals by 1,5-Hydrogen Migration of Vinylcyclopropanes

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Department of Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan
Received June 8, 1992

Summary: Stereoselective vinylcupration of a cyclopropenone acetal (1), followed by in situ electrophilic trapping with an alkylating agent, affords a cis-substituted vinylcyclopropane 2, which stereoselectively rearranges to the acetal of a cross-conjugate dienone 3 upon thermolysis at 60–160 °C.

Conversion of a *cis*-1-alkyl-2-vinylcyclopropane to a 1,4-diene through a 1,5-sigmatropic hydrogen migration has long attracted the attention of organic chemists.[1] Synthetically, however, this reaction is strategically unattractive, since there are few efficient synthetic routes to the starting cis-substituted cyclopropane. We report that stereospecific addition of a vinyl cuprate to a cyclopropene 1 provides a highly effective synthetic entry to the required *cis*-1-alkyl-2-vinylcyclopropane structure 2. The mechanism of the carbocupration and the electrophilic trapping[2] secure the necessary cis-stereochemistry, and mild thermolysis of the cyclopropane 2 produces the diene 3 in two steps from 1 in overall yield of 70–90% (Scheme I). Stereoelectronic and steric control in the transition state of the 1,5-hydrogen migration resulted in excellent stereoselectivity with respect to *both* of the two newly formed double bonds in 3.

The cyclopropene 1 is a stable compound and is available in two steps from 1,3-dichloroacetone on a multigram scale.[3] The use of 1 as a cyclopropene substrate is of particular synthetic benefit,[4] since the product is the acetal of a cross-conjugated dienone (4)—a useful synthetic intermediate, e.g., for Nazarov synthesis of cyclopentenones.[5] Efficiency of the vinylcupration/alkyl trapping sequence (1 to 2) was examined first, and the results are shown in columns 2–4 in Table I. The reaction tolerates a variety of cuprate structures which can be used in nearly equi-

Scheme I

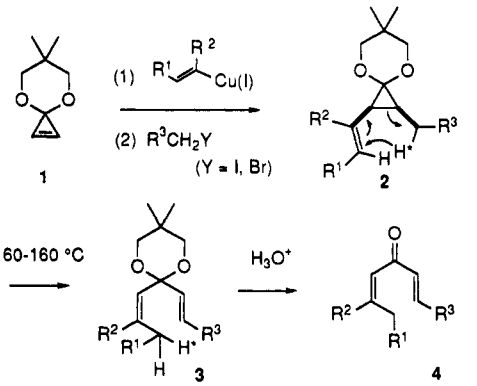
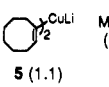
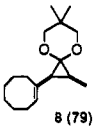
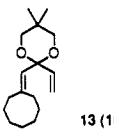
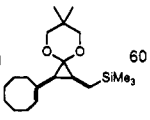
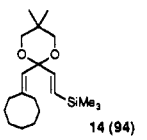
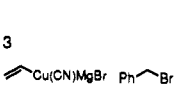
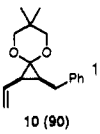
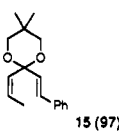
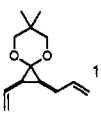
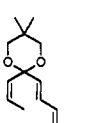
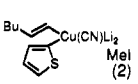
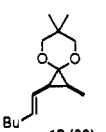
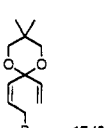


Table I. Vinylcupration and Rearrangement[a]

entry	cuprate (equiv)	R^3CH_2X (equiv)	3 (%yield)	rearrngt condns	4 (%yield)
1		MeI (5)	 8 (79)	120 °C, 11 h	 13 (100)
	5 (1.1)				
2		Me_3SiCH_2I (5)	 9 (84)	60 °C, 54 h	 14 (94)
3		(1.1)	 10 (90)	100 °C, 60 h	 15 (97)
	6 (1.1)				
4		(2)	 11 (68)	100 °C, 29 h	 16 (96)
5		MeI (2)	 12 (89)	160 °C, 70 h	 17 (92)
	7 (1.2)				

[a] The rearrangement was carried out in either benzene, toluene, or mesitylene depending on the required reaction temperature (in some cases, in the presence of BSA). All yields are based on pure isolated product. All olefins in the table are of at least 97% stereochemical purity as determined by ^1H NMR and/or capillary GC analyses.

(1) (a) Ellis, R. J.; Frey, H. M. *J. Chem. Soc., Suppl. 1* **1964**, 5578. Ellis, R. J.; Frey, H. M. *Proc. Chem. Soc., London* **1964**, 221. Roth, W. R.; Konig, J. *Liebigs Ann. Chem.* **1965**, *688*, 28. Glass, D. S.; Boikess, R. S.; Winstein, S. *Tetrahedron Lett.* **1966**, 999. (b) Berson, J. A. *Acc. Chem. Res.* **1991**, *24*, 215. Parziale, P. A.; Berson, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 1650. Getty, S. J.; Berson, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 4607. Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187.

(2) (a) Nakamura, E.; Isaka, M.; Matsuzawa, S. *J. Am. Chem. Soc.* **1988**, *110*, 1297. (b) Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1990**, *112*, 7248.

(3) (a) Isaka, M.; Matsuzawa, S.; Yamago, S.; Ejiri, S.; Miyachi, Y.; Nakamura, E. *J. Org. Chem.* **1989**, *54*, 4727. (b) Isaka, M.; Ando, R.; Morinaka, Y.; Nakamura, E. *Tetrahedron Lett.* **1991**, *32*, 1339. (c) Isaka, M.; Ejiri, S.; Nakamura, E. *Tetrahedron Symposium-in-Print* **1992**, *48*, 2045.

(4) (a) The present sequence may also be applicable to simple cyclopropenes. Cf. Nakamura, E.; Isaka, M. *Organomet. News* **1990**, 194. Moiseenkov, A. M.; Czeskis, B. A.; Semenovsky, A. V. *J. Chem. Soc., Chem. Commun.* **1982**, 109. Lukina, M. Yu.; Rudashevskaya, T. Yu.; Nesmeyanova, O. A. *Dokl. Akad. Nauk SSSR.* **1970**, *190*, 1109. Lehmkuhl, H.; Mehler, K. *Liebigs Ann. Chem.* **1982**, 2244. Stoll, A. T.; Negishi, E.-i. *Tetrahedron Lett.* **1985**, *26*, 5761. (b) We have found that spiro[2.5]oct-1-ene, an all-carbon congener of 1, also serves as a good acceptor of dialkylcuprates.

(5) Reviews: Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429. Denmark, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 751–784.

0022-3263/92/1957-5809$03.00/0