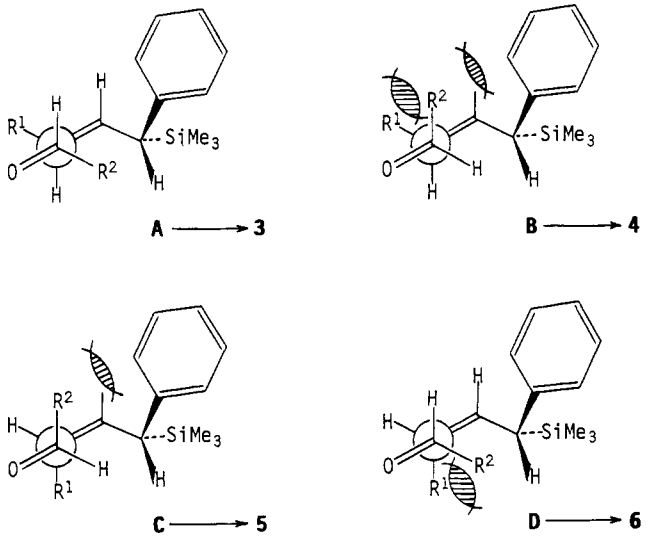
Scheme II



transition state[7] is proposed on the basis of the anti stereochemistry established for the S_E' reaction of allylsilanes.[3,8] In the reaction of the (*E*)-allylsilanes, the transition state A where the aldehyde is attacked on its *re* face leading to the alcohol **3** is sterically much favored over the diastereomeric transition state B, which suffers steric repulsion between the alkyl group R^2 on the aldehyde and R^1 on the allylsilane (gauche interaction) and also steric repulsion between R^2 and the phenyl group on the allylsilane.[9] In case of the (*Z*)-allylsilanes, the steric repulsions between R^1 and R^2 and between R^2 and the phenyl make both the diastereomeric transition states C and D less favorable. When R^2 is *t*-Bu, the gauche interaction is more decisive, and the alcohols **5** are produced via C. On the other hand, when R^2 is smaller (*i*-Pr or Me), the two kinds of steric repulsions have competitive effects on the stereoselection, leading to both **5** and **6** in comparable amounts.

Acknowledgment. We thank the Ministry of Education, Japan, for Grant-in-Aid for Scientific Research (No. 00547080), Hokko Chemical Industry Co., Ltd., and Shin-etsu Chemical Industry Co., Ltd., for partial financial support of this work.

Registry No. (*R*)-(*E*)-**1a**, 82570-93-2; (*R*)-(*Z*)-**1a**, 82570-94-3; (*R*)-(*E*)-**1b**, 82537-20-0; (*R*)-(*Z*)-**1b**, 82537-21-1; **2a**, 630-19-3; **2b**, 78-84-2; **2c**, 75-07-0; **3a**, 82545-33-3; **3b**, 82545-34-4; **3c**, 82545-35-5; **3d**, 82545-36-6; **4a**, 82545-37-7; **4b**, 82545-38-8; **4c**, 82545-39-9; **4d**, 82545-40-2; **5a**, 82545-41-3; **5b**, 82545-42-4; **5c**, 82545-43-5; **5d**, 82545-44-6; **6a**, 82545-45-7; **6b**, 82545-46-8; **6c**, 82545-47-9; **6d**, 82545-48-0; **7a**, 82545-49-1; **7b**, 82545-50-4; **7c**, 473-86-9; **7d**, 82545-51-5; **8a**, 82545-52-6; **8b**, 82545-53-7; **8c**, 34293-67-9; **8d**, 82545-54-8.

Supplementary Material Available: ^1H NMR spectra of the homoallylic alcohols (1 page). Ordering information is given on any current masthead page.

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(9) The important role of the steric repulsion between R^2 and the phenyl in differentiating the enantiotopic faces of aldehydes has been observed in the enantioselective allylation with (*R*)-3-phenyl-3-(trimethylsilyl)propene where the *re* face of the aldehydes is attacked with high selectivity (~95%). Full details will be reported shortly.

Stereocontrolled Total Synthesis of (±)-Coriamyrtin

Kiyoshi Tanaka, Fumiaki Uchiyama, Kiyoshi Sakamoto, and Yasuo Inubushi*

Faculty of Pharmaceutical Sciences, Kyoto University Sakyo-ku, Kyoto, Japan

Received May 12, 1982

Coriamyrtin (**1**), one member of picrotoxane sesquiterpenes, was first isolated in 1864 from the European *Coriaria* species, *Coriaria myrtifolia*,[1a] and was later found to be the major constituent of Japanese-grown *Coriaria japonica*.[1b] Its characteristic structure of two vicinal oxirane rings on the picrotoxane skeleton was confirmed on the basis of degradative and spectroscopic evidence.[2] The central nervous system stimulant activity of coriamyrtin[3] has been known to be nearly identical with that of picrotoxinin (**2**), which is used as an investigative tool in neuroscience. Despite the unique structures and quite interesting physiological activities of these sesquiterpenes, there was no report on the total synthesis of any member of picrotoxane sesquiterpenes[4] until the elegant total synthesis of picrotoxinin[5] in 1979 and picrotin[6] in 1980 were reported by Corey and Pearce. We describe herein a stereocontrolled total synthesis of (±)-coriamyrtin and a general route for the construction of the picrotoxane skeleton.

The basic synthetic plan came from the retrosynthetic analysis of **1**, which involves the disconnections as illustrated in Scheme I. On the basis of this analysis, our synthesis was undertaken starting from readily available protoanemonin (**5**)[7] and 2-methyl-1,3-cyclopentanedione (**6**). 1,6-Addition of **6** to **5** (Scheme II) gave **4**[8] in 13% yield.[9] The Grignard reaction of **4** with isopropenylmagnesium bromide and the subsequent internal aldol reaction provided two lactones, **7** (mp 148 °C) and **8** (mp 153 °C) in an 8:1 ratio and in 95% yield. The equatorial orientation of the isopropenyl of the two products was indicated by the ^1H NMR ($CDCl_3$) spectra, which revealed coupling of three vicinal protons at C_3, C_4, and C_5 with *J* values of 0–0.5 Hz. These observations indicated the undesired stereostructures of these compounds. The stereostructural assignments of the two compounds will be reported separately.[10] Methanolysis of **4** gave a separable mixture of **9** (mp 66 °C) and **10**[11] (oil) in a 1:1 ratio and in 88% yield. At this stage of investigation, the stereostructures of **9** and **10** could not be specified. The conclusive evidence for the stereostructure of **9** will be given by the stereostructural establishment of **13** and **14** (vide infra, Scheme III). Because of the trans relationship between the acrylic ester side

(1) (a) Riban, M. J. *Bull. Soc. Chim. Fr.* **1864**, *1*, 87; **1867**, *7*, 79. (b) Kariyone, T.; Sato, T. *Yakugaku Zasshi* **1930**, *50*, 106; **1930**, *50*, 659.

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(8) All new compounds were fully characterized spectroscopically and by combustion and/or high-resolution mass spectral analyses. The complete data will appear in a full paper.

(9) The poor yield was due to the dimerizing nature of **5**, but this was not a serious obstracle to the present synthesis since **5** is readily prepared from levulinic acid on a rather large scale.

(10) Conversion of **7** into the desired **3** was achieved, but this route was abandoned because of the long steps and poor yield. Details of the experiments will be treated when a full account of the work is published.

(11) Equilibration of **10** with 1% HCl in dry methanol provided **9** in 35% yield together with 49% of the recovered **10**, and hydrolysis of **10** with HCl–MeOH–H_2O regenerated **4** in 75% yield. The undesired product **10**, therefore, was recycled along the synthetic route.

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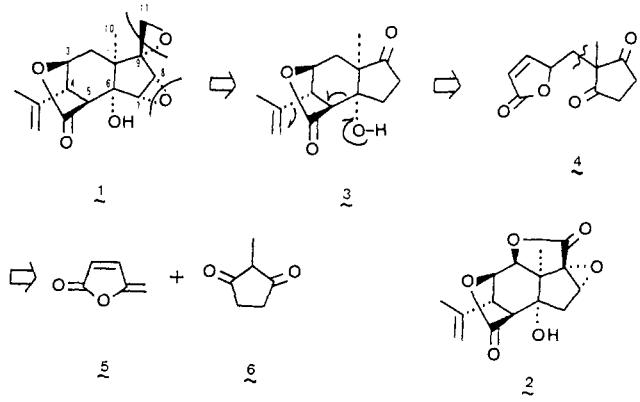
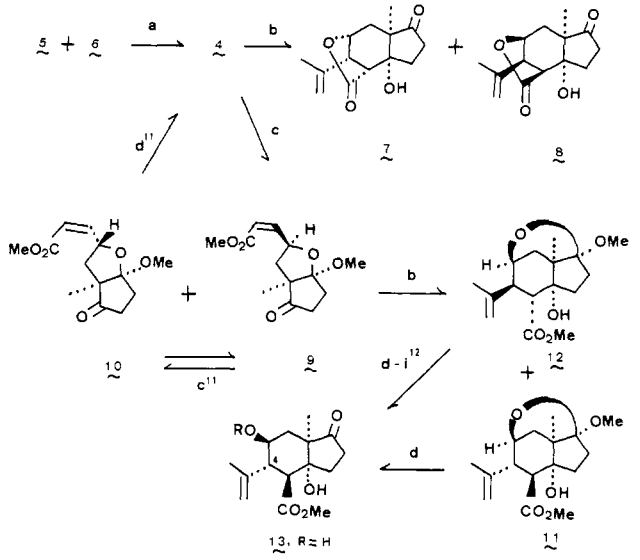
Scheme I. Retrosynthetic Analysis of 1



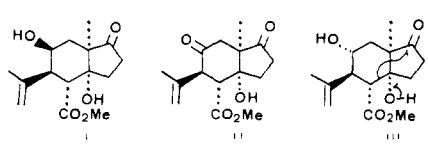
Scheme II. Construction of the Picrotoxan Carbon Skeleton 13[a]



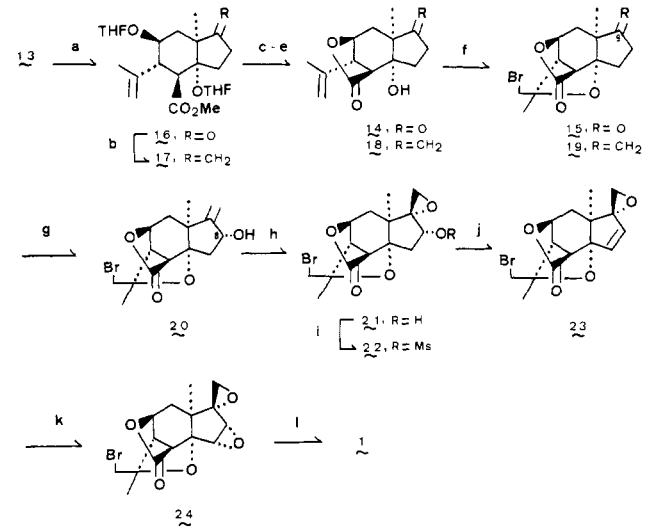
[a] Key: (a) NaOH, EtOH, 0–5 °C, 1 week, in the dark; (b) isopropenylmagnesium bromide, CuI, THF, −50 °C, 2 h; (c) 1% HCl, dry MeOH, room temperature, 60 h; (d) aq HCl, MeOH, overnight; (e) CrO_3-H_2SO_4, 0 °C; (f) $NaBH_4$, *i*-PrOH, −30 to −50 °C; (g) Ac_2O, pyr; (h) *t*-BuOK, 2:1 THF-DMF, room temperature, 12 h; (i) NaOMe, MeOH.

chain and the angular methyl in **9**, compound **13**, having the desired stereostructure, will be obtained through the application of the Grignard reaction to **9**, followed by hydrolysis of its product. The Grignard reaction of **9** with isopropenylmagnesium bromide provided **11** (mp 140 °C) and **12**[12] (mp 101–102 °C) in a 4:3 ratio in 84% yield. Acid hydrolysis of **11** gave the hydroxy ester (**13**, R = H) in 98% yield. The desired stereostructure of **13** and the equatorial orientation of hydroxyl, isopropenyl, and carbomethoxyl functions was indicated by the ^1H NMR ($CDCl_3$) spectrum, which revealed coupling of the double of doublets signal of the C_4–H at δ 2.49 with *J* values of 13 and 10 Hz. Basic hydrolysis of **13**,

(12) Acid hydrolysis of **12** provided i in 97 yield. Jones oxidation of i gave ii, which on reduction with $NaBH_4$ provided the hydroxy ester iii in 25% yield together with 28% of i, and the latter was recycled. Acetylation of iii, followed by treatment with *t*-BuOK gave the acetate (**13**, R = Ac) in 53% yield through the retroaldol cleavage and the subsequent internal aldol reaction as shown in formula iii. The base-catalyzed deacetylation of the acetate (**13**, R = Ac) gave the desired compound (**13**, R = H) in 82% yield. The undesired product **12**, which resulted from the Grignard reaction of **9**, was useful along the synthetic route via i, ii, iii, and **13** (R = Ac).



Scheme III. Completion of the Synthesis of (±)-Coriamyrtin (1)[a]



[a] Key: (a) 3 equiv of dihydrofuran, PPTS (catalytic), CH_2Cl_2, reflux, 3 h; (b) 1.5 equiv of $Ph_3P^+CH_3Br^-$, *t*-AmOK, *t*-AmOH, toluene, reflux, 4 h; (c) oxalic acid, aq MeOH; (d) 1 N NaOH, MeOH, reflux, 3 h; (e) 5 equiv of 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, reflux, 8 h; (f) 1.1 equiv of NBS, THF, 10 min; (g) *t*-BuOOH, SeO_2, CH_2Cl_2, room temperature, 30 h; (h) *t*-BuOOH, $VO(acac)_2$, benzene, room temperature, 4 h; (i) MsCl, DMAP, pyr, 0 °C, 2.5 h; (j) DBU, toluene, reflux, 35 h; (k) MCPBA (excess), Na_2HPO_4, CH_2Cl_2, reflux, 10 days; (l) Zn-Cu couple, NH_4Cl, EtOH, H_2O, reflux, 1.5 h.

followed by lactonization[13] gave the lactone **14** in 43% yield from **13**, and treatment of **14** with NBS[5] provided the bromo ether **15** in 87% yield. Formation of the bromo ether proved chemically the correctness of the stereochemical assignments of **11**, **13**, and **14**. Because of the intense steric crowding, all attempts to introduce a C_1 unit at the C_9 carbonyl of **15** using a variety of approaches were unsuccessful.

Protection of the two hydroxyls of **13** with tetrahydrofuranyl groups gave **16** in 92% yield, which was subjected to the Wittig reaction under Conia's condition[14] to give the exomethylenic compound **17** in 72% yield. Acid hydrolysis of **17** and lactonization in the same manner as **13** afforded the lactone **18** in 55% yield. NBS treatment of **18** in the same manner as **14** afforded the bromo ether **19** in 98% yield. Allylic oxidation of **19** by the Sharpless' procedure[15] gave stereospecifically the allylic alcohol **20** in 48% yield together with 47% of the recovered **19**. The α configuration of the hydroxyl group of **20** was suggested by the ^1H NMR ($CDCl_3$) spectrum, which revealed the downfield shift of the angular methyl signal of **20** (δ 1.24) compared with that of **19** (δ 0.96). Epoxidation of **20** yielded **21** in 64% yield, which was mesylated to give the mesylate **22** in 98% yield. When refluxed in toluene with DBU, **22** yielded the highly *labile* olefin **23** under acidic or even neutral condition in 98% yield. Epoxidation of **23** provided stereospecifically (±)-bromocoriamyrtin (**24**) in 3% yield. Synthetic bromocoriamyrtin and that derived from natural coriamyrtin exhibited indentical IR ($CHCl_3$), ^1H NMR ($CDCl_3$), and mass spectra and showed identical TLC, GLC, and HPLC behavior. Finally, reductive debromination of **24** gave (±)-coriamyrtin (**1**) (mp 224–225 °C) in 58% yield. Synthetic (±)-coriamyrtin and natural **1** exhibited identical IR ($CHCl_3$) and ^1H NMR ($CDCl_3$) spectra and both showed identical TLC and

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GLC behavior. The stereocontrolled total synthesis of coriamyrtin is now completed through 15 steps from **5** and **6**, and all isomeric products arising in some synthetic steps were useful along the synthetic route. The information accumulated during the present synthesis will open the way to the synthesis of the other members of picrotoxanes possessing two vicinal oxirane rings.

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Supplementary Material Available: Spectral data and physical constants for **1**, **4**, and **7–24** (6 pages). Ordering information is given on any current masthead page.

Enantiomeric Selectivity in Binding Tris(phenanthroline)zinc(II) to DNA

Jacqueline K. Barton,* J. J. Dannenberg, and Adrienne L. Raphael

City University of New York, Hunter College
New York, New York 10021

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Intercalation into DNA, where planar aromatic cations insert between adjacent base pairs,[1] is an important mode of drug binding to nucleic acids and may be involved in protein–nucleic acid recognition.[2-4] Metallointercalation reagents have been proven as valuable probes of this binding mode.[5-7] X-ray fiber diffraction analysis[8] of a terpyridylplatinum(II) complex intercalated into DNA yielded evidence in strong support of neighbor-excluded drug binding at saturation and additionally, along with the single-crystal study of the terpyridylplatinum(II) complex bound to dCpG,[9] has been useful in establishing structural characteristics at the intercalation site. Again with use of square-planar platinum complexes, the stereochemical requirement for ligand planarity was nicely demonstrated in a comparative examination of the intercalators $(phen)Pt(en)^{2+}$ and $(bipy)Pt(en)^{2+}$ and the nonintercalative complex $(py)_2Pt(en)^{2+}$.[10] We find that the tetrahedral complexes $(phen)ZnCl_2$ and $(phen)_2Zn^{2+}$ as well as the octahedrally coordinated $(phen)_3Zn^{2+}$ also bind to DNA by intercalation (phen = 1,10-phenanthroline). Moreover since the tris(phenanthroline)zinc(II) complex contains a chiral center, we have examined and report here a stereoselective preference in its binding to the right-handed DNA helix.

Strong evidence for intercalation may be obtained by examining the effects of increasing drug concentrations on the mobility of supercoiled DNA in a gel electrophoresis experiment.[11] Duplex unwinding and lengthening are needed to accommodate intercalative stacking. Because of the topological constraints on a closed circle, this duplex unwinding yields a corresponding alteration in superhelicity and, in so doing, an amplified effect on the electrophoretic mobility of the DNA. A mixture of closed and nicked circular pM2 DNAs was electrophoresed through cylindrical 1% agarose gels containing increasing concentrations of either $Zn(phen)Cl_2$, $Zn(phen)_2^{2+}$, or $Zn(phen)_3^{2+}$.[12,13] Figure 1 shows a plot of the relative mobilities of nicked and closed circular DNAs after electrophoresis. Interestingly, a migration pattern that is reminiscent of ethidium intercalation is seen in the presence of each zinc complex. Initially, with low drug concentrations, the mobility of the supercoiled DNA diminishes. As the duplex unwinds to accommodate binding, the negative supercoils are released and the polymer becomes more flexible. At the minimum migration point, the nicked and closed circles comigrate since no supercoils remain. As the concentration of the reagent is increased further, the duplex unwinds more, leading to positive supercoiling and a more compact polymer of increased mobility. In contrast to those of covalent unwinding agents,[14] this interaction is reversible. DNA incubated with the zinc complexes for 2 h at 37 °C and electrophoresed through gels that do not contain these complexes show mobilities identical with DNA that had not been incubated with the zinc reagents. Also no detectable nicking as a function of incubation was evident.

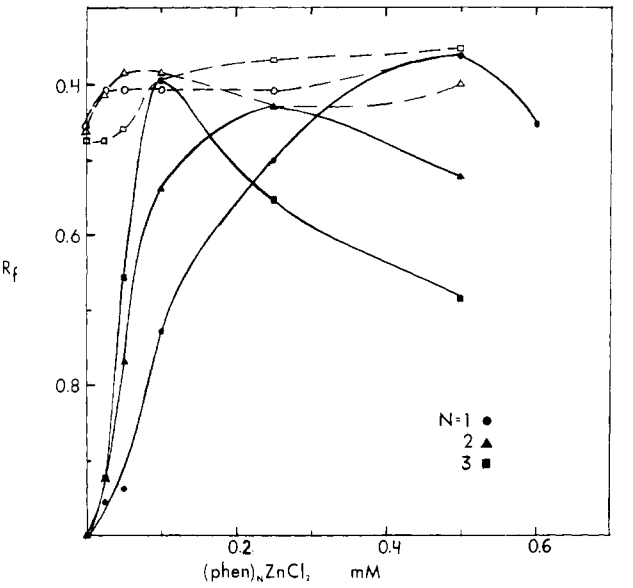

Figure 1. Relative mobilities (R_f) of closed (—) and nicked (---) circular pM2 DNAs in the presence of increasing concentrations of added $Zn(phen)Cl_2$ (●, ○), $Zn(phen)_2Cl_2$ (▲, △), and $Zn(phen)_3Cl_2$ (■, □), respectively. DNA samples (0.3 μg) were electrophoresed through 1% agarose cylinder gels containing 50 mM Tris acetate, 20 mM sodium acetate, 18 mM sodium chloride, as well as the added zinc reagent, at pH 7.0. Gels were stained with ethidium after electrophoresis at 30 V for 3 h, and mobilities were determined. Gel photographs are given in Figure 1S as supplementary material.

Some additional features of this experiment are noteworthy. In the presence of phenanthroline alone, at concentrations of 2.5–5.0 mM, there is only slight retardation of the superhelical DNA mobility. Since in this concentration range phenanthroline, which is neutral at pH 7.0, does not intercalate, the dissociation of a phenanthroline ligand from the metal center cannot lead to the unwinding observed. The unwinding effects also do not appear to be the result of direct metal coordination to the DNA. Coordination sites are not available in $Zn(phen)_3^{2+}$, yet with this reagent unwinding is apparent at low concentrations. Indeed, as can be seen in Figure 1, the comigration points of the nicked and

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(13) The zinc complexes were prepared in aqueous solution by stoichiometric addition and then isolated from high NaCl solution. The chloride salts were analyzed (percent) for zinc content as follows: $(phen)ZnCl_2$, Zn = 21.43, calcd = 20.65; $(phen)_2ZnCl_2$, Zn = 13.42, calcd = 13.16; $(phen)_3ZnCl_2$, Zn = 9.72, calcd = 9.66.
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