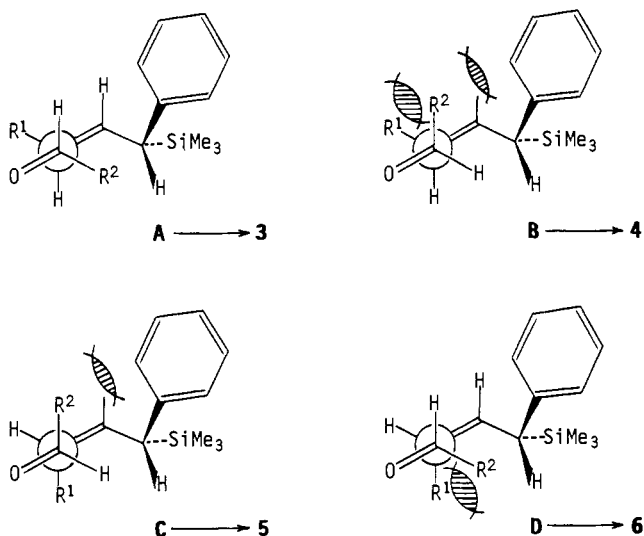


Scheme II



transition state<sup>7</sup> is proposed on the basis of the anti stereochemistry established for the  $S_E'$  reaction of allylsilanes.<sup>3,8</sup> 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.<sup>9</sup> 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 stereo-selection, 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:** <sup>1</sup>H NMR spectra of the homoallylic alcohols (1 page). Ordering information is given on any current masthead page.

(7) (a) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248. (b) Noyori, R.; Nishida, I.; Sakata, J. *Ibid.* **1981**, *103*, 2106. (c) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *Ibid.* **1980**, *102*, 7107. (d) Chérest, M.; Felkin, H.; Frajerman, C. *Tetrahedron Lett.* **1971**, 379 and their previous papers cited therein.

(8) The erythro selectivity of the (*E*)-allylsilanes may also support the linear transition state and reject the cyclic transition state. See ref 1 and 7. See also: (a) Hoffmann, R. W.; Zeiss, H.-J. *J. Org. Chem.* **1981**, *46*, 1309. (b) Yamaguchi, M.; Mukaiyama, T. *Chem. Lett.* **1980**, 993. (c) Hiyama, T.; Kimura, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1037. (d) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 3229. (e) Yamamoto, Y.; Maruyama, K. *Tetrahedron Lett.* **1981**, *22*, 2895 and references cited therein.

(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*,<sup>1a</sup> and was later found to be the major constituent of Japanese-grown *Coriaria japonica*.<sup>1b</sup> Its characteristic structure of two vicinal oxirane rings on the picrotoxane skeleton was confirmed on the basis of degradative and spectroscopic evidence.<sup>2</sup> The central nervous system stimulant activity of coriamyrtin<sup>3</sup> 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<sup>4</sup> until the elegant total synthesis of picrotoxinin<sup>5</sup> in 1979 and picrotin<sup>6</sup> 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**)<sup>7</sup> and 2-methyl-1,3-cyclopentanone (**6**). 1,6-Addition of **6** to **5** (Scheme II) gave **4**<sup>8</sup> in 13% yield.<sup>9</sup> 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 <sup>1</sup>H NMR (CDCl<sub>3</sub>) spectra, which revealed coupling of three vicinal protons at C<sub>3</sub>, C<sub>4</sub>, and C<sub>5</sub> 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.<sup>10</sup> Methanolysis of **4** gave a separable mixture of **9** (mp 66 °C) and **10**<sup>11</sup> (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.

(2) Okuda, T.; Yoshida, T. *Tetrahedron Lett.* **1964**, 439; **1965**, 4191.

(3) For a review of the chemistry, biosynthesis, and physiology of picrotoxane sesquiterpenes and related substances, see: Porter, L. A. *Chem. Rev.* **1967**, *67*, 441.

(4) For the synthesis of dendrobine, an alkaloid in the same general structural class, see: (a) Yamada, K.; Suzuki, M.; Hayakawa, A.; Nakamura, H.; Nagase, H.; Hirata, Y. *J. Am. Chem. Soc.* **1972**, *94*, 8278. (b) Inubushi, Y.; Kikuchi, T.; Ibuka, T.; Tanaka, K.; Saji, I.; Tokane, K. *J. Chem. Soc., Chem. Commun.* **1972**, 1252; *Chem. Pharm. Bull.* **1974**, *22*, 349. (c) Kende, A.; Bentley, J.; Mader, R.; Ridge, D. *J. Am. Chem. Soc.* **1974**, *96*, 4332. (d) Borch, R. F.; Evans, A. J.; Wade, J. *J. Am. Chem. Soc.* **1975**, *97*, 6282 (epidendrobine). (e) Roush, W. R. *Ibid.* **1978**, *100*, 3599.

(5) Corey, E. J.; Pearce, H. L. *J. Am. Chem. Soc.* **1979**, *101*, 5841.

(6) Corey, E. J.; Pearce, H. L. *Tetrahedron Lett.* **1980**, 1823.

(7) (a) Asahina, Y.; Fujita, A. *Yakugaku Zasshi* **1915**, *396*, 81. (b) Grundmann, C.; Kober, E. *J. Am. Chem. Soc.* **1955**, *77*, 2332.

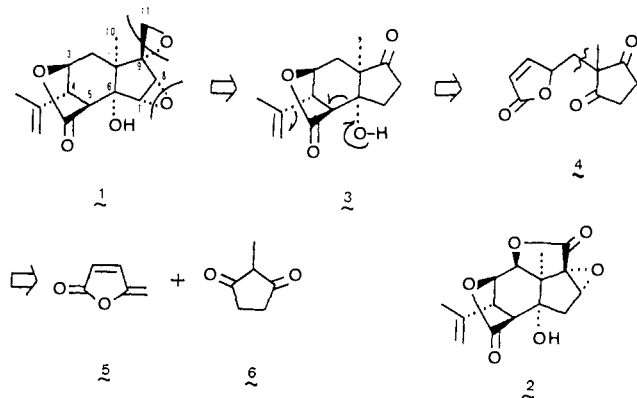
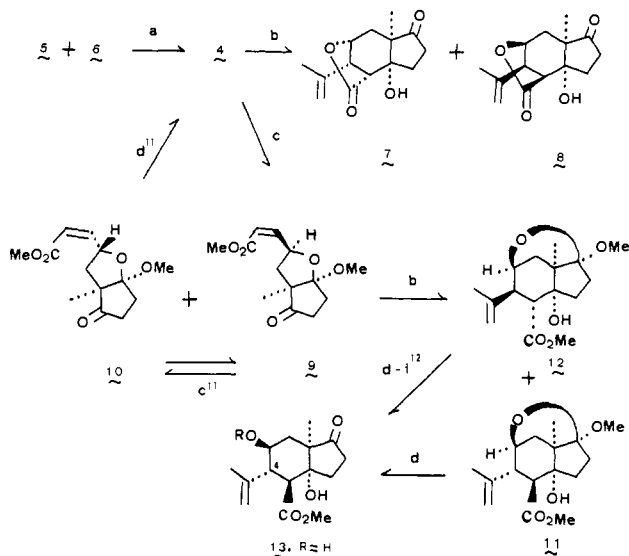
(8) All new compounds were fully characterized spectroscopically and by combustion and/or high-resolution mass spectral analyses. The complete data will appear in a full paper.

(9) The poor yield was due to the dimerizing nature of **5**, but this was not a serious obstacle 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<sub>2</sub>O regenerated **4** in 75% yield. The undesired product **10**, therefore, was recycled along the synthetic route.

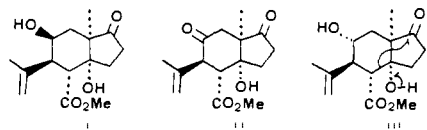
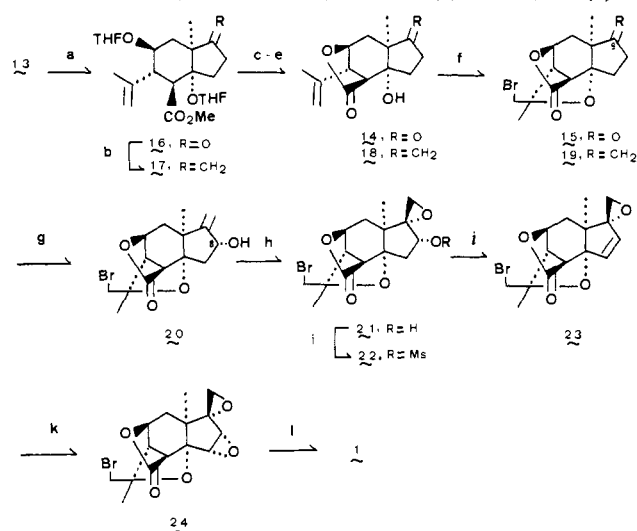
Scheme I. Retrosynthetic Analysis of 1

Scheme II. Construction of the Picrotoxan Carbon Skeleton 13<sup>a</sup>

<sup>a</sup> 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<sub>3</sub>–H<sub>2</sub>SO<sub>4</sub>, 0 °C; (f) NaBH<sub>4</sub>, *i*-PrOH, –30 to –50 °C; (g) Ac<sub>2</sub>O, 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<sup>12</sup> (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 <sup>1</sup>H NMR (CDCl<sub>3</sub>) spectrum, which revealed coupling of the double of doublets signal of the C<sub>4</sub>–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<sub>4</sub> 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)<sup>a</sup>

<sup>a</sup> Key: (a) 3 equiv of dihydrofuran, PPTS (catalytic), CH<sub>2</sub>Cl<sub>2</sub>, reflux, 3 h; (b) 1.5 equiv of Ph<sub>3</sub>P<sup>+</sup>CH<sub>2</sub>Br<sup>-</sup>, *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<sub>3</sub>N, toluene, reflux, 8 h; (f) 1.1 equiv of NBS, THF, 10 min; (g) *t*-BuOOH, SeO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 30 h; (h) *t*-BuOOH, VO(acac)<sub>2</sub>, benzene, room temperature, 4 h; (i) MsCl, DMAP, pyr, 0 °C, 2.5 h; (j) DBU, toluene, reflux, 35 h; (k) MCPBA (excess), Na<sub>2</sub>HPO<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, reflux, 10 days; (l) Zn–Cu couple, NH<sub>4</sub>Cl, EtOH, H<sub>2</sub>O, reflux, 1.5 h.

followed by lactonization<sup>13</sup> gave the lactone 14 in 43% yield from 13, and treatment of 14 with NBS<sup>5</sup> provided the bromo ether 15 in 87% yield. Formation of the stereochemical assignments of 11, 13, and 14. Because of the intense steric crowding, all attempts to introduce a C<sub>1</sub> unit at the C<sub>9</sub> 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<sup>14</sup> to give the exomethylene 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<sup>15</sup> 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 <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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 identical IR (CHCl<sub>3</sub>), <sup>1</sup>H NMR (CDCl<sub>3</sub>), 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<sub>3</sub>) and <sup>1</sup>H NMR (CDCl<sub>3</sub>) spectra and both showed identical TLC and

(13) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* 1979, 52, 1989. (b) When Ac<sub>2</sub>O or ClCO<sub>2</sub>Me was used for this lactonization, acetylation or carbomethoxylation of C<sub>9</sub>-OH occurred to some extent.

(14) (a) Conia, J. M.; Limasset, J. C. *Bull. Soc. Chim. Fr.* 1967, 1936. Provin, J.; Leyendecker, F.; Conia, J. M. *Tetrahedron Lett.* 1975, 4053. Show, S. R.; McMorris, T. C. *J. Org. Chem.* 1979, 44, 3076. (b) The Wittig reaction using dimethylsulfinyl anion or *n*-BuLi as a base recovered only the starting material.

(15) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* 1977, 99, 5526.

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.

**Acknowledgment.** We are grateful to Professor T. Okuda, Faculty of Pharmaceutical Sciences, Okayama University, for supplying an authentic sample of natural coriamyrtin.

**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

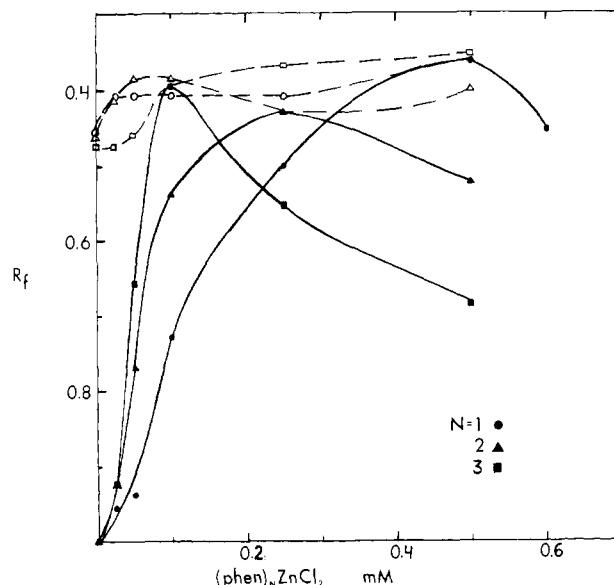
Jacqueline K. Barton,\* J. J. Dannenberg, and  
Adrienne L. Raphael

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

Received May 24, 1982

Intercalation into DNA, where planar aromatic cations insert between adjacent base pairs,<sup>1</sup> is an important mode of drug binding to nucleic acids and may be involved in protein-nucleic acid recognition.<sup>2-4</sup> Metallointercalation reagents have been proven as valuable probes of this binding mode.<sup>5-7</sup> X-ray fiber diffraction analysis<sup>8</sup> 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,<sup>9</sup> 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)<sup>2+</sup> and (bipy)Pt(en)<sup>2+</sup> and the nonintercalative complex (py)<sub>2</sub>Pt(en)<sup>2+</sup>.<sup>10</sup> We find that the tetrahedral complexes (phen)ZnCl<sub>2</sub> and (phen)<sub>2</sub>Zn<sup>2+</sup> as well as the octahedrally coordinated (phen)<sub>3</sub>Zn<sup>2+</sup> 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.<sup>11</sup> 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



**Figure 1.** Relative mobilities ( $R_f$ ) of closed (—) and nicked (---) circular pM2 DNAs in the presence of increasing concentrations of added Zn(phen)Cl<sub>2</sub> (●, ○), Zn(phen)<sub>2</sub>Cl<sub>2</sub> (▲, △), and Zn(phen)<sub>3</sub>Cl<sub>2</sub> (■, □), 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.

circular pM2 DNAs was electrophoresed through cylindrical 1% agarose gels containing increasing concentrations of either Zn(phen)Cl<sub>2</sub>, Zn(phen)<sub>2</sub><sup>2+</sup>, or Zn(phen)<sub>3</sub><sup>2+</sup>.<sup>12,13</sup> 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,<sup>14</sup> 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.

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)<sub>3</sub><sup>2+</sup>, 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

(1) Lerman, L. S. *J. Mol. Biol.* **1961**, *3*, 18.

(2) Berman, H. M.; Young, P. R. *Ann. Rev. Biophys. Bioeng.* **1981**, *10*, 87.

(3) Coleman, J. E.; Armitage, I. M. *Biochemistry* **1978**, *17*, 5038.

(4) Maurizot, J. C.; Boubault, G.; Helene, C. *Biochemistry* **1978**, *17*, 5038.

(5) Lippard, S. J. *Acc. Chem. Res.* **1978**, *11*, 211.

(6) Jennette, K. W.; Lippard, S. J.; Vassiliades, G. A.; Bauer, W. R. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 3839.

(7) Howe-Grant, M.; Lippard, S. J. *Biochemistry* **1979**, *18*, 5762.

(8) Bond, P. J.; Langridge, R.; Jennette, K. W.; Lippard, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 4825.

(9) Wang, A. H.-J.; Nathans, J.; van der Marel, G.; van Boom, J. H.; Rich, A. *Nature (London)* **1978**, *276*, 471.

(10) Lippard, S. J.; Bond, P. J.; Wu, K. C.; Bauer, W. R. *Science (Washington, D.C.)* **1976**, *194*, 726.

(11) Waring, M. J. *J. Mol. Biol.* **1966**, *54*, 247. Espejo, R. T.; Lebowitz, J. *Anal. Biochem.* **1976**, *72*, 95.

(12) Reimann, C. W.; Block, S.; Perloff, A. *Inorg. Chem.* **1966**, *5*, 1185. Inskip, R. G. *J. Inorg. Nucl. Chem.* **1962**, *24*, 763. Brandt, W. W.; Dwyer, F. P.; Gyarfás, E. C. *Chem. Rev.* **1954**, *54*, 959 and references therein.

(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<sub>2</sub>, Zn = 21.43, calcd = 20.65; (phen)<sub>2</sub>ZnCl<sub>2</sub>, Zn = 13.42, calcd = 13.16; (phen)<sub>3</sub>ZnCl<sub>2</sub>, Zn = 9.72, calcd = 9.66.

(14) Cohen, G. L.; Bauer, W. R.; Barton, J. K.; Lippard, S. J. *Science (Washington, D.C.)* **1979**, *203*, 1014.