$H_2S(O)$), 53.6 ($CHCH_2CH_2$), 54.2 ($S(O)CH_2S$), 173.5 (Glu-COOH and Cys-COOH), 174.4 (C(O)NH); CD spectrum, at 237.5 nm a single positive maximum was observed for an aqueous solution ($\Delta\epsilon$ +17.5, Figure 2). Anal. Calcd for $C_{10}H_{18}N_2O_6S_2 \cdot H_2O$: C, 34.87; H, 5.85; N, 8.13. Found: C, 34.24; H, 6.29; N, 8.06.

For **22**: mp 169-172 °C; ^1H NMR (500 MHz, D_2O, Figure 1)[35] δ 2.07-2.20 (m, 2 H, $CHCH_2CH_2$), 2.27 (s, 3 H, SCH_3), 2.47 (distorted t, J = 7.7 Hz, 2 H, $CHCH_2CH_2$), 3.18 and 3.55 (AB part of ABX spectrum, 8 lines, J_{AX} = 8.6 Hz, J_{BX} = 5.3 Hz, J_{AB} = 13.6 Hz, 2 H, $CHCH_2S(O)$), 3.76 (t, J = 6.1 Hz, 1 H, $CHCH_2CH_2$), 3.91 and 4.11 (ABq, J_{AB} = 13.8 Hz, 2 H, $S(O)CH_2S$), 4.60 (X part of ABX spectrum, 4 lines, $J_{AX} + J_{BX}$ = 14.0 Hz, 1 H, $CHCH_2S(O)$); FAB MS, m/e 327 ($M^+ + 1$); $[\alpha]^{25}_D$ -23° (c 0.2, H_2O); IR (KBr) 1615, 1525, 1020 cm^{-1}; ^{13}C NMR (D_2O) δ 15.6 (SCH_3), 2.57 ($CHCH_2CH_2$), 31.2 ($CHCH_2CH_2$), 49.5 ($CHCH_2S(O)$), 53.0 ($CHCH_2S(O)$), 53.8 ($CHCH_2CH_2$), 54.2 ($S(O)CH_2S$), 173.5 (Glu-COOH), 173.9 (Cys-COOH), 174.9 (C(O)NH); CD spectrum: at 237.5 nm a single negative maximum was observed for an aqueous solution ($\Delta\epsilon$ -9.8, Figure 2).

Acknowledgment. We express our gratitude to the late Professor Rolf Gmelin (Institut für Pharmakognosie und Phytochemie der Freien Universität Berlin) for his kind suggestions at the beginning of this project. We thank Professor G. Höfle (Gesellschaft für Biotechnologische Forschung, Braunschweig, W. Germany) for sending a copy of the ^1H NMR spectrum of γ-glutamylmarasmine and Dr. W. ten Hoeve (University of Groningen, The Netherlands) for help in recording the CD spectra. This research was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO). NMR spectra were recorded at the Dutch National 500/200 MHz-hf-NMR facility at Nijmegen.

Registry No. 1, 106565-95-1; 9, 56-89-3; 10, 106501-49-9; (R_CS_S)-11, 106501-50-2; (R_CR_S)-11, 106501-56-8; 12, 96846-37-6; (R_CS_S)-13, 106501-51-3; (R_CR_S)-13, 106501-57-9; (R_CS_S)-14, 106501-52-4; (R_CR_S)-14, 106501-58-0; 15, 25830-77-7; 16, 106501-53-5; 17, 106565-96-2; 18, 106501-54-6; 19, 106565-97-3; 20, 106501-55-7; 21, 106565-98-4; 22, 106565-99-5; Boc-cystine, 10389-65-8; di-*tert*-butyl pyrocarbonate, 24424-99-5; 2-(trimethylsilyl)ethanol, 2916-68-9.

Utilization of the 1-Ferrocenyl-2-methylpropyl Substituent as a Chiral Auxiliary in the Asymmetric Syntheses of the Benzophenanthridine Alkaloids (+)- and (-)-Corynoline†

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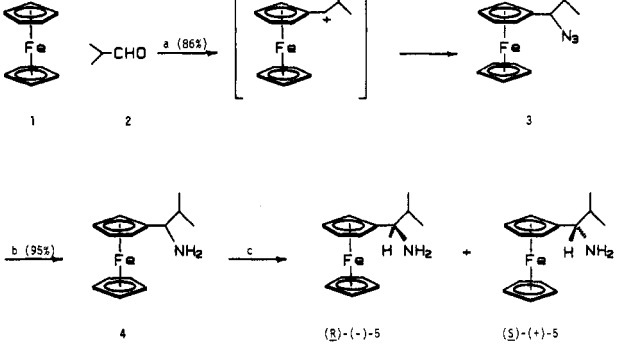
The benzophenanthridine alkaloids (+)- and (-)-corynoline have been synthesized by a route that utilizes the 1-ferrocenyl-2-methylpropyl group as a chiral auxiliary. The key step in the asymmetric synthesis of (+)-corynoline involved the condensation of the Schiff base (*R*)-(-)-**7** with the racemic homophthalic anhydride (±)-**8** to afford (-)-**9** in 81% yield and (-)-**10** in 10% yield. The chiral auxiliary thus influences both the relative and absolute configurations of two asymmetric centers. Removal of the chiral auxiliary under acidic conditions gave (-)-**11**, which was transformed into (+)-corynoline (**16**) by previously established methods. The overall yield of (+)-corynoline from piperonal was 16.5%.

Although (±)-corynoline[1] is the major alkaloid present in *Corydalis incisa*, (+)-corynoline (**16**; Scheme II) has also been detected[2] and isolated[3] from the plant. The absolute configuration of (+)-corynoline has been determined by chemical correlation with (+)-14-*epi*-corynoline,[3] whose absolute configuration has been established by X-ray analysis of the bromoacetate.[4] The CD spectra of the chiral hexahydrobenzo[*c*]phenanthridine alkaloids, including (+)-corynoline, have recently been reinterpreted in terms of revised absolute configurations.[5]

Although several syntheses of racemic hexahydrobenzo[*c*]phenanthridines have been executed,[6] no work has been reported on the asymmetric synthesis of any of the alkaloids of this class. The present report describes the utilization of the 1-ferrocenyl-2-methylpropyl substituent[7] as a chiral auxiliary modifying our previous synthesis of (±)-corynoline[8] for the asymmetric syntheses of (+)-corynoline and also (-)-corynoline.

The chiral amines (*R*)-(-)-**5** and (*S*)-(+)-**5** were prepared as depicted in Scheme I.[9,10] Thus, a mixture of ferrocene (**1**) and isobutyraldehyde (**2**) was treated with fluorosulfonic acid, resulting in the formation of an intermediate cation that was reacted with a solution of sodium azide in triethylamine. The azide **3** was then reduced with lithium aluminum hydride to afford the racemic mixture of amines

Scheme I[a]



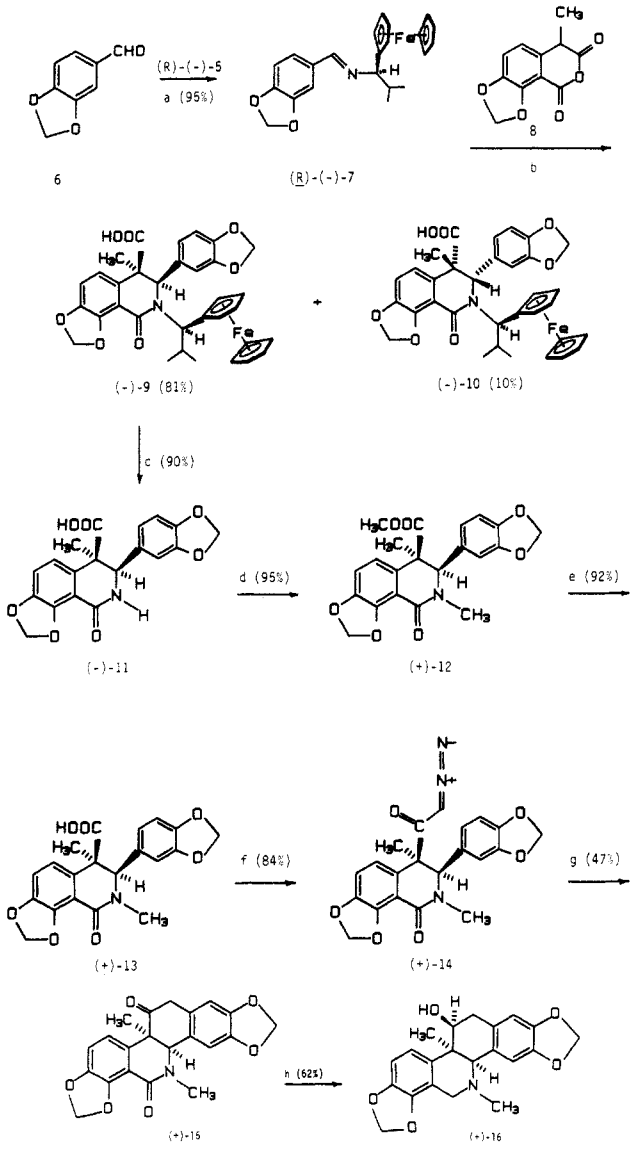
[a] Key: (a) (1) FSO_3H, CCl_3COOH, CH_3COOH, -25 °C (50 min); (2) $CHCl_3$; (3) aqueous NaN_3, Et_3N, -25 °C to room temperature (5 h). (b) $LiAlH_4$, THF, reflux (3.5 h). (c) (+)- and (-)-tartaric acids, MeOH, Et_2O.

† This paper is dedicated to Professor George Büchi on the occasion of his 65th birthday.

(1) Isolation: Tani, C.; Takao, N. *Yakugaku Zasshi* **1962**, *82*, 594. Structure elucidation: Takao, N. *Chem. Pharm. Bull.* **1963**, *11*, 1306. Takao, N. *Chem. Pharm. Bull.* **1963**, *11*, 1312. Kamitani, T.; Honda, T.; Ihara, M.; Shimanouchi, H.; Sasada, Y. *Tetrahedron Lett.* **1972**, 3729.

0022-3263/87/1952-1517$01.50/0

Scheme II[a]



[a] Key: (a) PhH, reflux (72 h). (b) PhH, reflux (84 h). (c) CF_3COOH, $HSCH_2COOH$, room temperature (72 h). (d) KOH, Me_2CO, Me_2SO_4, room temperature (1.5 h). (e) KOH, aqueous Me_2CO, reflux (2 h). (f) (1) $SOCl_2$; (2) CH_2N_2, PhH, alcohol-free Et_2O, −10 °C to room temperature (4 h). (g) CF_3COOH, CH_3NO_2, −20 °C (1.5 h). (h) $LiAlH_4$, THF, reflux (17.5 h).

4, which was resolved with (+)- and (−)-tartaric acids in methanol–ether. The optical purities of the resolved amines (*R*)-(−)- and (*S*)-(+)-**5** were established by ^1H NMR through utilization of the chiral shift reagent tris[3-(heptafluorobutyryl-*d*)-camphorato]europium(III). In the presence of 40 mol % of the shift reagent in $CDCl_3$, the singlets for the unsubstituted ferrocenyl rings in a mixture of (*S*)-(+)- and (*R*)-(−)-**5** were well resolved and appeared at δ 4.76 and 4.64, respectively (see the Experimental Section for details). Spectra of the resolved amines displayed only one of these two singlets.

Table I. Separation of Enantiomers on a Covalent (*R*)-*N*-[(3,5-Dinitrobenzoyl)phenyl]glycine Column[a,b]

compd	hexane–2-propanol mobile phase ratio	flow rate, mL/min	ret time, min
(+)-**12**	5:1	2	15.2
(−)-**12**	5:1	2	16.0
(+)-**14**	9:1	4	34.1
(−)-**14**	9:1	4	36.4
(+)-**16**	39:1	4	19.2
(−)-**16**	39:1	4	17.2

[a] The column was a Bakerbond chiral phase prepacked (*R*)-*N*-[(3,5-dinitrobenzoyl)phenyl]glycine column bonded covalently to aminopropyl silica (5 μm), 4.6 mm i.d. × 25 cm. [b] All of the compounds were detected by UV at 254 nm.

The reaction of piperonal (**6**) with (*R*)-(−)-**5** in refluxing benzene was rather sluggish owing to the hindered nature of the amine (Scheme II). However, excellent yields of the chiral Schiff base (*R*)-(−)-**7** could be obtained provided prolonged reaction times were employed. The reaction of (*R*)-(−)-**7** with (±)-**8**[8] also proved to be relatively slow. Refluxing in benzene for 84 h provided an 81% isolated yield of (−)-**9** accompanied by a 10% isolated yield of (−)-**10**. Intermediate (−)-**9** crystallized directly from the reaction mixture, while (−)-**10** was obtained by chromatographic techniques. The low reactivity of (*R*)-(−)-**7** also reflects steric hindrance by the large 1-ferrocenyl-2-methylpropyl substituent. For example, if the 1-ferrocenyl-2-methylpropyl substituent of (*R*)-(−)-**7** is replaced by a methyl group, the reaction proceeds exothermally at room temperature in a variety of solvents and is complete in a matter of minutes.[8] Replacement of the isopropyl group in (*R*)-(−)-**7** with a *tert*-butyl substituent gave a compound that was completely unreactive with (±)-**8**.

The relative configuration of the substituents at C-3 and C-4 of the isoquinolone ring in the minor isomer (−)-**10** was established by removal of the 1-ferrocenyl-2-methylpropyl substituent to yield (+)-**11**, which compared favorably with (−)-**11** obtained by removal of the chiral auxiliary from (−)-**9**. The relative configuration at C-3 and C-4 in (−)-**11** was proven by its conversion to intermediate (+)-**12** of known relative configuration.[8] Recent observations in our laboratory have indicated that Schiff bases containing bulky substituents on nitrogen predictably react with homophthalic anhydrides to yield isoquinolones in which the aromatic substituent at C-3 and the carboxyl group at C-4 are cis. In the present instance, none of the corresponding trans diastereomers were detected.

The chiral auxiliary in (−)-**9** was removed under acidic conditions in the presence of thioglycolic acid.[7] The resulting intermediate (3*R*,4*R*)-(−)-**11** was dimethylated with dimethyl sulfate under basic conditions to give (3*R*,4*R*)-(+)-**12**. Hydrolysis of the methyl ester yielded the acid (3*R*,4*R*)-(+)-**13**. The assignment of absolute configurations in these synthetic intermediates ultimately rests on their utilization in the synthesis of (+)-corynoline of known absolute configuration.

(2) Takao, N.; Iwasa, K.; Kamigauchi, M.; Sugiura, M. *Chem. Pharm. Bull.* **1976**, *24*, 2859.
(3) Takao, N.; Kamigauchi, M.; Iwasa, K. *Tetrahedron* **1979**, *35*, 1977.
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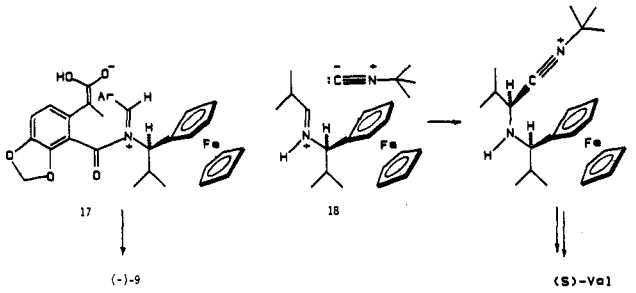
(5) Takao, N.; Kamigauchi, M.; Iwasa, K.; Morita, N. *Arch. Pharm. (Weinheim)* **1984**, *317*, 223.
(6) For a review of the benzophenanthridene alkaloids, including syntheses, see: Šimánek, V. *Alkaloids (N.Y.)* **1985**, *26*, 185.
(7) Urban, R.; Ugi, I. *Angew. Chem., Int. Ed. Eng.* **1975**, *14*, 61.
(8) Cushman, M.; Abbaspour, A.; Gupta, Y. P. *J. Am. Chem. Soc.* **1983**, *105*, 2873.
(9) This procedure was modified from a description of a synthesis of 1-ferrocenyl-2,2-dimethyl-1-propylamine, which was provided to us by Dr. Rudolph Herrmann and Prof. I. Ugi, Technische Universität München. See: Herrmann, R.; Hübener, G.; Siglmüller, F.; Ugi, I. *Justus Liebigs Ann. Chem.* **1986**, 251.
(10) For the absolute configuration assignments, see: Eberle, G.; Lagerlund, I.; Ugi, I.; Urban, R. *Tetrahedron* **1978**, *34*, 977.
(11) Beames, D. J.; Mander, L. N. *Aust. J. Chem.* **1974**, *27*, 1257.

Scheme III



The remaining three steps of the synthesis closely parallel those of our previously reported (±)-corynoline synthesis.[8] Treatment of the acid (3*R*,4*R*)-(+)-**13** with thionyl chloride yielded an acid chloride that was converted to the diazo ketone (3*R*,4*R*)-(+)-**14** with diazomethane. Cyclization of the diazo ketone in the presence of trifluoroacetic acid then afforded the ketone (3*R*,4*R*)-(+)-**15**. Lithium aluminum hydride reduction of (3*R*,4*R*)-(+)-**15** gave (+)-corynoline (**16**), $[\alpha]_D$ +115° (*c* 0.2, $CHCl_3$). (+)-Corynoline has been reported to produce optical rotations of $[\alpha]_D$ +132° (*c* 2.64, $CHCl_3$)[12] and $[\alpha]_D$ 116.4° (*c* 1.7, $CHCl_3$)[3]. The synthesis was also repeated with (*S*)-(+)-**7** to yield (−)-corynoline. The physical properties of all of the intermediates in the preparation of (−)-corynoline were in agreement with expectations based on the (+)-corynoline synthesis. The synthetic (+)- and (−)-corynoline samples, as well as the intermediates (+)- and (−)-**12** and (+)- and (−)-**14**, were determined to be optically pure within the limits of detection by HPLC on a covalent (*R*)-*N*-[(3,5-dinitrobenzoyl)phenyl]glycine column (Table I).[13]

The general method outlined here for the asymmetric synthesis of (+)- and (−)-corynoline should also be applicable to the preparation of a variety of other optically active benzophenanthridine and related alkaloids.[14]

As a final note, it is of interest to compare how the chiral auxiliary influences the stereochemical course of the four-component condensation[7] and the present asymmetric isoquinolone synthesis. Iminolysis of the anhydride **8** by the thermodynamically more stable trans Schiff base (*R*)-(−)-**7** followed by enolization would be expected to produce the hypothetical intermediate **17** (Scheme III).[15] The stereochemical outcome of the reaction is then determined by whether the nucleophilic enolate attacks the "bottom" or "top" side of the iminium ion as drawn in structure **17**. Analysis of the stereochemistry of the major reaction product (−)-**9** shows that it adds preferentially to the bottom of the iminium ion. Although the conformation about the N–C bond of the ferrocenyl substituent in the transition state leading to the product is critical and also unknown, the stereochemical outcome can be rationalized on the basis of the conformation shown, so that the enolate adds preferentially on the same side of the iminium ion as the hydrogen and opposite the bulky ferrocenyl substituent. However, if one assumes a similar conformation for the iminium ion involved in the four-component condensation, the isonitrile adds to the top of the iminium ion **18**,[7] opposite to the nucleophilic addition involved in the isoquinolone synthesis. This probably indicates that the conformations of the chiral auxilliary during the step that determines the stereochemical outcomes are dissimilar in the two reactions.

Experimental Section

All reactions were performed under a nitrogen atmosphere. Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. NMR spectra were recorded on Varian FT-80 80-MHz and XL-200 200-MHz spectrometers in $CDCl_3$ solvent, except where noted. The high-resolution 470-MHz NMR spectra were obtained by using a Nicolet NTC-470 spectrometer and the data accumulated by using 32K free-induction decays. IR spectra were recorded on a Beckman IR-33 spectrophotometer. Microanalyses were performed by the Purdue Microanalytical Laboratory. The mass spectra were determined on a Finnigan 4000 spectrometer using an ionization potential of 70 eV. The chemical ionization mass spectra (CIMS) were obtained by using isobutane as the reagent gas. Fast atom bombardment mass spectra (FABMS) were run on a Kraytos MS50 spectrometer at room temperature using glycerol matrix. Preparative, centrifugally accelerated, radial, thin-layer chromatography was performed on a Harrison Research Model 7924 chromatotron. Optical rotations were measured with a Perkin-Elmer 241 polarimeter.

(±)-1-Ferrocenyl-2-methylpropyl Azide (3). Ferrocene (**1**; 10 g, 53.75 mmol) and isobutyraldehyde (10 mL, 110 mmol) were added to a stirred mixture of trichloroacetic acid (52.28 g) and glacial acetic acid (8.1 mL) at room temperature. The temperature of the reaction mixture was decreased to −25 °C before fluorosulfonic acid (8.1 mL) was added dropwise. The reaction mixture was stirred at −25 °C for 50 min and then diluted with CH_2Cl_2 while the temperature was maintained at −25 °C. A saturated aqueous solution of NaN_3 (25 mL, 17.48 g, 268.8 mmol) was mixed with Et_3N (75 mL) with mechanical stirring and then cooled to −50 °C. The −25 °C CH_2Cl_2 solution was then added dropwise to the −50 °C solution containing the NaN_3. After complete addition, the cooling bath was removed and the reaction was stirred at room temperature for 5 h. The mixture was washed with water (5 × 60 mL) and then dried (Na_2SO_4). The solvent was evaporated to yield the crude product (19 g), which was purified by column chromatography on silica gel (285 g, 60–200 mesh), eluting with hexane. Kugelrohr distillation yielded analytically pure product: 13.0 g (86%); bp 120 °C (0.9 mm); IR (neat) 3090, 2950, 2070 cm^{-1}; NMR (470 MHz) δ 4.19 (s, 5 H), 4.11 (m, 5 H), 1.82 (m, 1 H), 0.86 (d, 3 H, *J* = 6.8 Hz), 0.82 (d, 3 H, *J* = 6.7 Hz); CIMS, *m/e* (relative intensity) 283 (MH^+, 42), 241 (100).

Caution! Dr. R. Herrmann, Technische Universität München, has notified us of an explosion when the temperature reached 100 °C during an attempted distillation of 1-ferrocenyl-2,2-dimethylpropyl azide. In the present instance, the product obtained by evaporation of hexane after column chromatography may be used in the synthesis without compromise in yield.

Anal. Calcd for $C_{14}H_{17}N_3Fe$: C, 59.39; H, 6.05; N, 14.84; Fe, 19.72. Found: C, 59.16; H, 6.13; N, 14.57; Fe, 19.73.

(±)-1-Ferrocenyl-2-methylpropylamine (4). A solution of the azide **3** (22.00 g, 77.74 mmol) in THF (150 mL) was added dropwise to a solution of $LiAlH_4$ (4.40 g, 115.9 mmol) in THF (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then at reflux for 3.5 h. The mixture was cooled to 0 °C and decomposed with water (4.4 mL), 15 % aqueous NaOH (4.4 mL), and finally water (13.2 mL). The mixture was stirred for 15 min and then filtered. The solid was washed with CH_2Cl_2. The organic filtrate was washed with water (3 × 150 mL), dried, and evaporated to give the product: 18.9 g (95%); bp 101.5 °C (0.4 mm) [lit.[10] bp 101.5 (0.4 mm)]; IR ($CHCl_3$) 3350, 2910, 1755, 1550 cm^{-1}; NMR (470 MHz) δ 4.18 (br s, 1 H), 4.14 (s, 5 H), 4.08 (m, 3 H), 3.45 (d, 1 H, *J* = 5.3 Hz), 1.67 (s, 2 H), 1.61 (m, 1 H), 0.83 (d, 3 H, *J* = 6.8 Hz), 0.76 (d, 3 H, *J* = 6.8 Hz); CIMS, *m/e* (relative intensity) 257 (MH^+, 48), 241 (100).

(*R*)-(−)-1-Ferrocenyl-2-methylpropylamine (5). A solution of racemic **5** (4.23 g, 16.5 mmol) in methanol (4.2 mL) was added to a solution of (+)-tartaric acid (2.47 g, 16.5 mmol) in methanol (12.34 mL) at 60 °C. The resulting solution was allowed to cool to room temperature. Ether was added until the solution turned cloudy. The mixture was then allowed to stand at room temperature overnight. The solid was filtered and dissolved in water and the solution basified to pH 10 with 1 N NaOH. The aqueous

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(13) Pirkle, W. H.; House, D. W.; Finn, J. M. *J. Chromatogr.* **1980**, *192*, 143.
(14) For a list of benzophenanthridine alkaloids, see: Krane, B. D.; Fagbule, M. O.; Shamma, M.; Gözler, B. *J. Nat. Prod.* **1984**, *47*, 1.
(15) Cushman, M.; Castagnoli, N., Jr. *J. Org. Chem.* **1971**, *36*, 3404.

solution was extracted with ether (3 × 10 mL). The organic extract was dried (Na_2SO_4) and then evaporated to afford amine with $[\alpha]_D$ -15.6° (c 1, benzene). The procedure was repeated eight times until amine [1.86 g (88%)] having $[\alpha]_D$ -89° (c 1, benzene) was obtained (lit.[9] $[\alpha]_D$ -89.7°).

(*R*)-(-)-*N*-Piperonylidene-1-ferrocenyl-2-methylpropylamine (7). Optically pure (*R*)-(-)-**5** (2.22 g, 8.64 mmol) and piperonal (1.30 g, 8.66 mmol) were dissolved in benzene (35 mL). The reaction mixture was heated at reflux for 72 h in the presence of a Dean–Stark trap. The solvent was evaporated and the residue crystallized from petroleum ether: 3.01 g (90%); mp 83.5–85 °C; $[\alpha]_D$ -319° (c 0.1, benzene); IR (KBr) 3100–3060, 2960–2800, 1635, 1600, 1490, 1480, 1430 cm^{-1}; NMR (470 MHz) δ 8.24 (s, 1 H), 7.52 (s, 1 H), 7.18 (d, 1 H, *J* = 7.9 Hz), 6.85 (d, 1 H, *J* = 7.9 Hz), 6.01 (s, 2 H), 4.34 (br s, 1 H), 4.10 (br s, 1 H), 4.08 (br s, 1 H), 4.06 (br s, 1 H), 3.97 (s, 5 H), 3.69 (d, 1 H, *J* = 5.9 Hz), 1.78 (hex, 1 H, *J* = 6.6 Hz), 0.80 (d, 3 H, *J* = 4.5 Hz), 0.78 (d, 3 H, *J* = 4.5 Hz); CIMS, *m/e* (relative intensity) 389 (MH^+, 40), 241 (100).

Anal. Calcd for $C_{22}H_{23}NO_2Fe$: C, 67.88; H, 5.96; N, 3.60; Fe 14.35. Found: C, 67.62; H, 5.96; N, 3.56; Fe 14.11.

(3*R*,4*R*)-(-)-*N*-[(*R*)-1-Ferrocenyl-2-methylpropyl]-4-carboxy-3,4-dihydro-4-methyl-7,8-(methylenedioxy)-3-[3,4-(methylenedioxy)phenyl]-1(2*H*)-isoquinolone (9). A mixture of racemic anhydride **8** (600 mg, 2.73 mmol) and the Schiff base (*R*)-(-)-**7** (1.10 g, 2.82 mmol) in benzene (30 mL) was heated at reflux for 82 h. The reaction mixture was then stored at 0 °C overnight. The solid precipitate was filtered and washed with cold benzene: 1.34 g (81%); mp 196–198 °C; $[\alpha]_D$ -228° (c 0.1, MeOH); IR (KBr) 3700–2400, 1730, 1630, 1590 cm^{-1}; NMR (CF_3COOD, 470 MHz) δ 7.12 (d, 1 H, *J* = 8.2 Hz), 7.09 (s, 1 H), 7.06 (d, 1 H, *J* = 8.7 Hz), 6.95 (s, 1 H), 6.94 (d, 1 H, *J* = 7.8 Hz), 6.88 (d, 1 H, *J* = 7.9 Hz), 6.35 (m, 1 H), 6.22 (m, 1 H), 6.19 (s, 2 H), 6.01 (s, 1 H), 5.99 (s, 1 H), 5.15 (s, 5 H), 5.00 (m, 1 H), 4.89 (br s, 1 H), 4.43 (m, 1 H), 2.61 (m, 1 H), 1.66 (s, 3 H), 1.56 (d, 3 H, *J* = 6.5 Hz), 1.37 (d, 3 H, *J* = 7.1 Hz); FABMS, *m/e* (relative intensity) 610 (MH^+, 100), 609 (91).

Anal. Calcd for $C_{33}H_{31}NO_7Fe \cdot {}^1/_2H_2O$: C, 64.09; H, 5.22; N, 2.26; Fe, 9.03. Found: C, 63.89; H, 5.07; N, 2.25; Fe, 8.90.

(3*S*,4*S*)-(-)-*N*-[(*R*)-1-Ferrocenyl-2-methylpropyl]-4-carboxy-3,4-dihydro-4-methyl-7,8-(methylenedioxy)-3-[3,4-(methylenedioxy)phenyl]-1(2*H*)-isoquinolone (10). The filtrate from above was subjected to preparative, centrifugally accelerated, radial, thin-layer chromatography on silica gel, eluting with EtOAc–hexane (6:4). The minor isomer was obtained by evaporating the solvent: 160 mg (10%); mp 160–162 °C; $[\alpha]_D$ -315° (c 0.1, MeOH); IR (KBr) 3700–2400, 1720, 1710, 1640, 1625, 1490 cm^{-1}; NMR (CF_3COOD, 470 MHz) δ 7.13 (d, 1 H, *J* = 8.1 Hz), 7.10 (s, 1 H), 7.07 (d, 1 H, *J* = 8.8 Hz), 6.97 (s, 1 H), 6.95 (d, 1 H, *J* = 7.8 Hz), 6.89 (d, 1 H, *J* = 7.9 Hz), 6.36 (m, 1 H), 6.24 (m, 1 H), 6.20 (s, 2 H), 6.02 (s, 1 H), 6.01 (s, 1 H), 5.16 (s, 5 H), 5.02 (m, 1 H), 4.90 (br s, 1 H), 4.45 (m, 1 H), 2.63 (m, 1 H), 1.67 (s, 3 H), 1.57 (d, 3 H, *J* = 6.5 Hz), 1.38 (d, 3 H, *J* = 7 Hz).

(3*R*,4*R*)-(-)-4-Carboxy-3,4-dihydro-4-methyl-7,8-(methylenedioxy)-3-[3,4-(methylenedioxy)phenyl]-1(2*H*)-isoquinolone (11). (-)-**9** (300 mg, 0.49 mmol) was dissolved in CF_3COOH (3 mL). $HSCH_2COOH$ (95%, 0.18 mL, 2.46 mmol) was added dropwise. The solution was stirred at room temperature in the dark for 72 h. The solution was poured into ice water (5 mL), and the mixture was extracted with ether (5 × 10 mL). The combined ether extracts were then washed with water (5 × 30 mL). The solvent was evaporated, and the residue recrystallized from ether-pentane (1:1). The analytical sample was recrystallized by dissolving it in a minimum of MeOH and diluting the solution with ether: 163.4 mg (90%); mp 226–227 °C dec; $[\alpha]_D$ -222° (c 0.1, MeOH); IR (KBr) 3600–2800, 1720, 1710, 1690, 1660, 1620, 1585 cm^{-1}; NMR (CF_3COOD, 470 MHz) δ 7.12 (d, 1 H, *J* = 8.2 Hz), 7.08 (d, 1 H, *J* = 8.2 Hz), 6.96 (s, 1 H), 6.95 (d, 1 H, *J* = 7.6 Hz), 6.89 (d, 1 H, *J* = 8.2 Hz), 6.20 (s, 2 H), 6.01 (s, 1 H), 6.00 (s, 1 H), 4.88 (s, 1 H), 1.66 (s, 3 H); CIMS, *m/e* (relative intensity) 370 (MH^+, 82), 326 (100).

Anal. Calcd for $C_{19}H_{15}NO_7 \cdot {}^1/_2H_2O$: C, 60.31; H, 4.26; N, 3.70. Found: C, 60.29; H, 3.97; N, 3.73.

Conversion of (-)-10 to (+)-11. $HSCH_2COOH$ (95%, 0.042 mL, 0.57 mmol) was added dropwise to a solution of the acid (-)-**10** (70 mg, 0.114 mmol) in CF_3COOH (0.7 mL). The solution was stirred in the dark at room temperature for 72 h. The reaction mixture was then poured into ice water (1.5 mL) and extracted with ether (5 × 4 mL). Evaporation of ether from the extract left a solid residue that was recrystallized from ether–pentane (1:1). The analytical sample was then recrystallized from methanol–ether: 15 mg (35%); mp 226–227 °C dec; $[\alpha]_D$ +222° (c 0.1, MeOH).

(3*R*,4*R*)-(+)-3,4-Dihydro-*N*-methyl-4-(methoxycarbonyl)-4-methyl-7,8-(methylenedioxy)-3-[3,4-(methylenedioxy)phenyl]-1(2*H*)-isoquinolone (12). Powdered KOH (85%, 609.1 mg, 9.2 mmol) was stirred in Me_2CO (10 mL) for 30 min. The acid **11** (525 mg, 1.42 mmol) was added and the mixture stirred for an additional 20 min. Me_2SO_4 (0.546 mL, 5.78 mmol) was then added dropwise and the mixture stirred at room temperature for 1.5 h. The insoluble material was removed by filtration. The acetone was evaporated from the filtrate and the residue crystallized on trituration with water. The solid was filtered and washed with water: 534.5 mg (95%); mp 181–182.5 °C dec; $[\alpha]_D$ +126° (c 0.1, $CHCl_3$); IR ($CHCl_3$) 1730, 1710, 1630, 1585 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 6.87 (d, 1 H, *J* = 8.2 Hz), 6.82 (d, 1 H, *J* = 8.2 Hz), 6.63 (d, 1 H, *J* = 8.1 Hz), 6.49 (d, 1 H, *J* = 8.1 Hz), 6.46 (s, 1 H), 6.18 (d, 1 H, *J* = 1.21 Hz), 6.12 (d, 1 H, *J* = 1.3 Hz), 5.89 (d, 1 H, *J* = 1.4 Hz), 5.87 (d, 1 H, *J* = 1.5 Hz), 4.37 (s, 1 H), 3.44 (s, 3 H), 3.00 (s, 3 H), 1.73 (s, 3 H); CIMS, *m/e* (relative intensity) 398 (MH^+, 100).

(3*R*,4*R*)-(+)-3,4-Dihydro-*N*-methyl-4-carboxy-4-methyl-7,8-(methylenedioxy)-3-[3,4-(methylenedioxy)phenyl]-1-(2*H*)-isoquinolone (13). Powdered KOH (85%, 932.7 mg, 14.1 mmol) and the ester **12** (330 mg, 0.83 mmol) were dissolved in 50% aqueous MeOH (10.56 mL), and the mixture was heated at reflux for 2 h. The solvent was evaporated, and water (10 mL) was used to dissolve the residue. The solution was acidified with 10% H_2SO_4, and the solid precipitate was filtered: 294 mg (92%); mp 238–239 °C dec; $[\alpha]_D$ +137° (c 0.1, MeOH); IR ($CHCl_3$) 3020–2700, 1730, 1700, 1630, 1590 cm^{-1}; NMR (CD_3COCD_3, 200 MHz) δ 7.14 (d, 1 H, *J* = 8.2 Hz), 6.93 (d, 1 H, *J* = 8.2 Hz), 6.67 (s, 2 H), 6.54 (s, 1 H), 6.11 (d, 1 H, *J* = 0.8 Hz), 6.09 (d, 1 H, *J* = 0.8 Hz), 5.92 (d, 1 H, *J* = 1 Hz), 5.90 (d, 1 H, *J* = 1 Hz), 4.64 (s, 1 H), 2.96 (s, 3 H), 1.71 (s, 3 H); CIMS, *m/e* (relative intensity) 384 (MH^+, 100).

(3*R*,4*R*)-(+)-3,4-Dihydro-*N*-methyl-4-(diazoacetyl)-4-methyl-7,8-(methylenedioxy)-3-[3,4-(methylenedioxy)-phenyl]-1(2*H*)-isoquinolone (14). Thionyl chloride (3.5 mL) was added to the acid (+)-**13** (460 mg, 1.20 mmol), and the mixture was stirred at room temperature for 12.5 h. The thionyl chloride was evaporated. Benzene (5 mL) was added to the residue and then evaporated. Benzene (10 mL) was added, and the mixture was cooled on a -10 °C bath before excess diazomethane in alcohol-free ether was added dropwise. The reaction mixture was stirred at room temperature for 4 h. The solvent was evaporated to yield a yellow solid that was recrystallized from MeOH–Ether–petroleum ether: 256 mg (84%); $[\alpha]_D$ +228 (c 0.1, $CHCl_3$); IR ($CHCl_3$) 2970, 2890, 2090, 1630 cm^{-1}; NMR (470 MHz) δ 6.85 (d, 1 H, *J* = 8.1 Hz), 6.66 (d, 1 H, *J* = 7.6 Hz), 6.59 (d, 1 H, *J* = 8.1 Hz), 6.52 (d, 1 H, *J* = 7.6 Hz), 6.51 (s, 1 H), 6.20 (d, 1 H, *J* = 1.2 Hz), 6.15 (d, 1 H, *J* = 1.1 Hz), 5.91 (d, 1 H, *J* = 1.3 Hz), 5.90 (d, 1 H, *J* = 1.3 Hz), 4.58 (s, 1 H), 4.26 (s, 1 H), 2.98 (s, 3 H), 1.66 (s, 3 H); CIMS, *m/e* (relative intensity) 408 (MH^+, 20), 380 (100).

(4b*R*,10b*R*)-(+)-*N*-Methyl-10b-methyl-2,3:7,8-bis(methylenedioxy)-6,11-dioxo-4b,5,6,10b,11,12-hexahydrobenzo[*c*]-phenanthridine (15). The diazo ketone (+)-**14** (62 mg, 0.15 mmol) and trifluoroacetic acid (0.05 mL) were added to nitromethane (0.5 mL), and the mixture was stirred at -20 °C for 1.5 h. $CHCl_3$ (2 mL) was added, and the solvent was then evaporated. Preparative TLC on silica gel using ether–benzene–EtOAc (5:5:2) furnished the pure product: 27.3 mg (47%); mp 175–177 °C; $[\alpha]_D$ +15° (c 0.1, $CHCl_3$); IR ($CHCl_3$) 1700, 1635, 1590, 1490, 1450 cm^{-1}; NMR (470 MHz) δ 6.69 (d, 1 H, *J* = 8.1 Hz), 6.62 (s, 1 H), 6.51 (s, 1 H), 6.47 (d, 1 H, *J* = 8.1 Hz), 6.09 (d, 1 H, *J* = 1.2 Hz), 6.00 (d, 1 H, *J* = 1.3 Hz), 5.90 (s, 2 H), 4.48 (s, 1 H), 3.64 (d, 1 H, *J* = 20.4 Hz), 3.57 (d, 1 H, *J* = 20.5 Hz), 3.31 (s, 3 H), 1.50 (s, 3 H); CIMS, *m/e* (relative intensity) 380 (MH^+, 100).

(+)-Corynoline (16). A mixture of the keto lactam (+)-**15** (15 mg, 0.038 mmol) and $LiAlH_4$ (30 mg, 0.79 mmol) in THF (10 mL) was heated at reflux for 17.5 h. The reaction mixture was cooled to 0 °C and decomposed by addition of water (0.35 mL), 15%

aqueous NaOH (0.35 mL), and finally water (0.35 mL). The mixture was stirred for 15 min and filtered. The aluminates were washed with $CHCl_3$. The combined organic layers were dried and evaporated. Preparative TLC on silica gel, eluting with $CHCl_3$–benzene (12:7) gave pure (+)-corynoline: 9 mg (62%); $[\alpha]_D$ +115° (c 0.2, $CHCl_3$); NMR (470 MHz) δ 6.91 (d, 1 H, J = 8.3 Hz), 6.79 (d, 1 H, J = 8.3 Hz), 6.65 (s, 1 H), 6.63 (s, 1 H), 5.98 (d, 1 H, J = 1.4 Hz), 5.95 (d, 1 H, J = 1.3 Hz), 5.94 (s, 2 H), 4.03 (d, 1 H, J = 15.3 Hz), 3.94 (m, 1 H), 3.44 (d, 1 H, J = 15.3 Hz), 3.28 (br s, 1 H), 3.14 (d, 1 H, J = 17.3 Hz), 3.06 (dd, 1 H, J = 4.4, 17.9 Hz), 2.19 (s, 3 H), 1.12 (s, 3 H); CIMS, m/e (relative intensity) 368 (MH^+, 100); EIMS, m/e (relative intensity) 367 (52), 349 (100), 334 (65), 318 (48), 202 (48), 190 (35), 176 (43), 162 (51).

NMR Experiment with (−)-, (+)-, and (±)-5 and the Chiral NMR Shift Reagent Tris[3-(heptafluorobutyryl)-*d*-camphorato]europium(III). A solution of the shift reagent (14.9 mg) in $CDCl_3$ (80 μL) was added to a solution of racemic **5** (8 mg) in $CDCl_3$ (0.4 mL). The 80-MHz ^1H NMR spectrum showed two singlets for the unsubstituted ferrocenyl rings at δ 4.76 and 4.64. Similar experiments with (*S*)-(+)- and (*R*)-(−)-**5** showed only one of these singlets. The lower field signal corresponds to the (*S*)-(+) enantiomer.

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Registry No. 1, 102-54-5; 2, 78-84-2; (±)-3, 105017-95-6; (±)-4, 53992-88-4; (*R*)-(−)-5, 54053-41-7; (*S*)-(+)-5, 54053-42-8; (±)-5, 53992-88-4; 7, 105502-60-1; (±)-8, 82929-74-6; 9, 105561-83-9; 10, 105502-61-2; 11, 105519-40-2; 12, 105615-71-2; 13, 105615-72-3; 14, 105615-73-4; 15, 105537-44-8; (±)-16, 18797-79-0; (−)-16, 74163-86-3; piperonal, 120-57-0.

Studies on the Total Synthesis of CC-1065: Preparation of a Synthetic, Simplified 3-Carbamoyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole Dimer/Trimer/Tetramer (CDPI Dimer/Trimer/Tetramer) and Development of Methodology for PDE-I Dimer Methyl Ester Formation

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Two synthetic preparations of 3-carbamoyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylic acid (**2b**, CDPI) and the investigation and development of methodology for the preparation of 3-carbamoyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole dimer **3** (CDPI dimer) constituting the simplified and stable PDE-I dimer skeleton possessing the B-DNA minor groove complementary shape of the natural product CC-1065 are detailed. The extension of this methodology to the preparation of 3-carbamoyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole trimer **4** and tetramer **5** (CDPI trimer and tetramer) are described and constitute synthetic, potentially selective, high-affinity, noncovalent B-DNA minor groove binding agents.

CC-1065 (**1**), an antitumor antibiotic isolated from *Streptomyces zelensis*[2] and unambiguously identified by single-crystal X-ray structural analysis,[3] has been shown to possess exceptional, potent in vitro cytotoxic activity,[4] antimicrobial activity,[2] and confirmed, potent in vivo antitumor activity.[2] Recent studies have shown that CC-1065 binds to double-stranded B-DNA in an initial high-affinity, five base-pair sequence-specific (A/GNTTA or AAAAA), nonintercalative fashion along the minor groove[5] and subsequently forms an irreversible covalent adduct.[6] The covalent alkylation of DNA has been shown to proceed by N-3 adenine alkylation on the spiro[cyclopropane-1,1′-cyclohexa-2′,5′-dien]-4′-one (spiro[5.2]octa-2,5-dien-4-one) unit present in the left-hand segment of CC-1065.[6] Consequently, the mechanism of CC-1065 cytotoxicity has been proposed to be derived from overstabilization of the DNA helix and inhibition of the normal unwinding and melting processes necessary for DNA synthesis.[5] The binding specificity and cytotoxicity associated with this agent may

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