(Brinkmann Instrument Co.) or a PAR 170 system (Princeton Applied Research).

In general, 100–500 mg of substrate was added to a stirred, preequilibrated, preelectrolyzed (+1.0 V), deoxygenated cell containing 120 mL of supporting electrolyte. (A solution of 9.56 g of KH_2PO_4 and 1.69 g of K_2HPO_4 dissolved in 500 mL of H_2O and diluted with 500 mL of MeOH was used for all oxidations except that of **8**. The electrolyte had a pH of 7.0 at 25 °C.) In some cases, warming was necessary to dissolve the substrate. The anode potential was increased until a current of 20–50 mA above the background was obtained, and the reactions were terminated when the current dropped back to near the background or when TLC showed the absence of starting material. The contents were then removed from the cell, and the felt anode was ground up in a Waring blender under MeOH. The blender contents were filtered, and the graphite fibers were washed with more MeOH. The combined cell contents and anode washings were evaporated to dryness, dissolved in 50 mL of H_2O, basified to a pH of 12 with 4 N NaOH, and extracted with ether. The ether extracts were washed (H_2O), dried (Na_2SO_4), and processed as described in each case.

Oxidation of 3. Compound **3** (100 mg) was oxidized for 19 h at +0.7 V with an initial current of 61 mA. Evaporation of the ether extract yielded 50 mg (75%) of **9**, mp 233–236 °C (lit.[45] mp 238 °C). The pH of the aqueous layer from the ether extraction was adjusted to 5 with concentrated HCl, and the solution was evaporated to dryness. The residue was dissolved in MeOH, filtered to remove salts, concentrated to about 1 mL, and separated by preparative TLC on four 1-mm layers to give 20 mg (23%) of **6** which was identical with the synthetic sample.

Oxidation of 4. Compound **4** (200 mg) was oxidized for 6 h at +0.8 V with an initial current of 32 mA. Evaporation of the ether extract gave 96 mg of crude product which was separated by preparative TLC (as described for **3**) to yield 67 mg (42%) of **7** and 22 mg (14%) of **9**.

Oxidation of 5. The 1*S*,3*S* isomer of **5** (200 mg) was oxidized for 5 h at +0.9 V with an initial current of 27 mA. Evaporation of the ether extract gave 95 mg (60%) of **9**. In a similar manner, oxidation of the 1*R*,3*S* isomer yielded 40 mg (25%) of **9**.

Oxidation of 6. Compound **6** (250 mg) was oxidized for 3 h at +0.9 V with an initial current of 26 mA. Evaporation of the ether layer yielded 100 mg (50%) of **9**.

Oxidation of 8. Compound **8** (300 mg) was oxidized for 5.5 h at +0.16 V in 120 mL of 0.1 M NaOMe in MeOH at an initial current of 22 mA. The solution was neutralized with concentrated HCl, evaporated to dryness, dissolved in 25 mL of MeOH, filtered to remove salts, evaporated to dryness, and separated by preparative TLC to give 37 mg of starting material and 30 mg (10%) of **9**. Overoxidation was apparent since much of the product remained at the base line of the chromatograms.

Oxidation of 10. The 1*R*,3*S* isomer of **10** (200 mg) was oxidized for 5 h at +0.7 V with an initial current of 22 mA. Evaporation of the ether extract yielded 73 mg (52%) of **9**.

Oxidation of 11. Compound **11** (250 mg) was oxidized for 5 h at +0.7 V with an initial current of 56 mA. Evaporation of the ether layer gave 151 mg (75%) of 1-(hydroxymethyl)-β-carboline, mp 228–229 °C, after recrystallation from acetone and sublimation (lit.[46] mp 228–230 °C).

Oxidation of 12. Compound **12** (200 mg) was oxidized for 5 h at +1.0 V with an initial current of 30 mA. Evaporation of the ether extract gave 53 mg (35%) of β-carboline as a light brown crystalline solid, mp 194–195 °C (lit.[47] mp 194–195 °C).

Dimerization of Tetrahydrocarbazole to 18. Recrystallized tetrahydrocarbazole (250 mg) was oxidized for 1.5 h at +0.7 V in 120 mL of 0.1 M $LiClO_4$ in CH_3CN–H_2O (9:1) with an initial current of 44 mA. The reaction mixture was basified to pH 12 with 4 N NaOH and evaporated to near dryness. The residue was partitioned between H_2O and $CHCl_3$. The $CHCl_3$ layer was washed (H_2O), dried (Na_2SO_4), and evaporated to yield 244 mg (98%) of a light brown oil which was homogeneous by TLC. The oil was treated with 2–3 mL of acetone and cooled to −10 °C whereupon 150 mg of **18** crystallized; mp 223–228 °C (lit.[19] mp 223–225 °C).

Acknowledgment. We thank Dr. Thomas Leipert for measuring the ^{13}C NMR spectra and the NSF (Grant No. CHE-76-05739) for help in purchasing the Bruker NMR instrument. We also appreciate the help and cooperation of Professor S. J. Huang of this department.

Registry No. 1, 6912-86-3; **2**·HCl, 343-94-2; **3**, 18070-61-6; **4**, 6543-83-5; (1*S*,3*S*)-**5**, 40678-46-4; (1*R*,3*S*)-**5**, 42438-72-2; (*S*)-**6**, 39537-10-5; **7**, 525-41-7; **8**, 2506-10-7; **9**, 486-84-0; (1*R*,3*S*)-**10**, 73246-29-4; (1*S*,3*S*)-**10**, 73198-01-3; **11**, 73198-02-4; **12**, 6052-68-2; **13**, 16502-01-5; **14**, 58100-29-1; **15**, 6649-98-5; **16**, 73198-03-5; **17**, 73198-04-6; **18**, 52784-14-2; pyruvic acid, 127-17-3; acetaldehyde, 75-07-0; acetyl chloride, 75-36-5; α-hydroxyacetone, 116-09-6; glycolaldehyde, 141-46-8; glyoxylic acid, 298-12-4; 1,2,3,4-tetrahydro-β-carboline-1,3-dicarboxylic acid, 59132-30-8; acetone, 67-64-1; 2-oxoglutaric acid, 328-50-7; L-tryptophan methyl ester hydrochloride, 7524-52-9; 1-(hydroxymethyl)-β-carboline, 21236-66-8; tetrahydrocarbazole, 942-01-8; indole, 120-72-9; β-carboline, 244-63-3.

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Use of Organoiron Complexes in β-Lactam Synthesis. Preparation of 2-Methylcarbopenam

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A short synthesis of a 2-methylcarbopenam (**9**), employing organoiron complexes as intermediates, is described. Allylacetone is transformed to the π-complex **1**, and this on treatment with ammonia is converted to the pyrroline complex **2**. Reduction with sodium borohydride affords a mixture of stereoisomeric pyrrolidine complexes, only one of which is transformed to a chelate complex (**8**). Oxidation of the chelate with silver oxide gives the carbopenam as a single stereoisomer (**9**).

As part of a program designed to examine a range of synthetic applications for complexes of the $CpFe(CO)_2$ radical (hereafter designated by the symbol Fp), we recently reported a new sequence for the synthesis of β-lactams based on the addition of a primary amine to Fp-(olefin) cations and subsequent oxidative lactamization of

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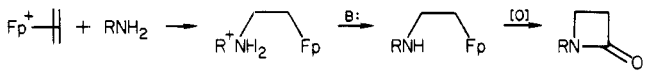
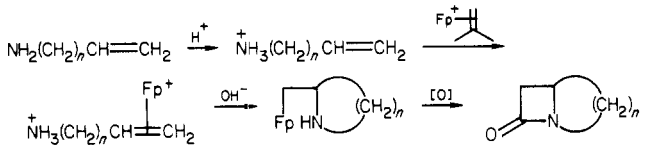
an intermediate β-aminoalkyl Fp complex (eq 1).[1]



(1)

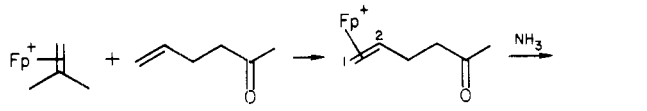
This scheme was also extended to the synthesis of bicyclic β-lactams, by the use of ω-amino olefins as starting materials (eq 2; n = 3, 4).



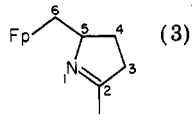
(2)

Current interest in fused-ring β-lactams, especially those of the carbopenem class,[2] prompted us to examine some further elaborations of the above sequence, especially those which would dispense with the need to preform the amino olefin ligand and make use instead of other more easily accessible starting materials. The present paper reports on some model reactions directed to this end.

We considered that introduction of nitrogen in an alkyl Fp chain and formation of a suitably positioned pyrroline ring might be accomplished in essentially one step by the use of a keto or aldehydo olefin as starting material. Accordingly, the readily available 5-hexen-2-one[3] was converted in high yield to the corresponding Fp(olefin)BF_4 complex 1 by exchange with Fp(isobutylene)BF_4.[4] No competitive complexation of the Fp group with the carbonyl function is observed in this reaction, since the oxygen atom is not sufficiently basic to interfere in the exchange reaction.[5] The cation 1 is a stable, yellow, crystalline substance, easily handled in air. When ammonia gas is passed over a methylene chloride solution of this salt at room temperature, it is rapidly and cleanly converted to the pyrroline complex 2 (eq 3).



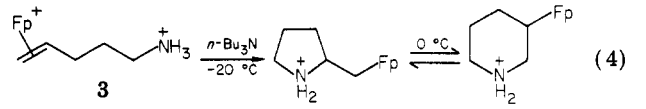
1



(3)

2

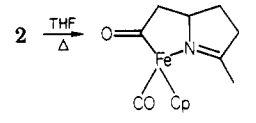
The structure is supported by its NMR spectrum which exhibits a one-proton, low-field multiplet for H-5 and a high-field, two-proton multiplet characteristic of the $FpCH_2$ group. Kinetic preference for the formation of five-membered rings compared with six-membered rings is well precedented in classical cyclization reactions,[6] but in the present context preferential addition of nitrogen to C-2 in 2 would in any event be anticipated, since this is the generally observed course of addition of amines to monoalkylated olefins.[7] An excellent illustration of this is provided by the reaction of the 4-pentenylammonium dication 3, which on deprotonation gives the pyrrolidine complex 4 as the exclusive product. At 0 °C this substance is equilibrated with the isomeric piperidine complex 5[8] (eq 4).



3 4 5

(4)

The pyrroline complex 2 is readily transformed to the chelate complex 6 on heating in THF solution (eq 5). The

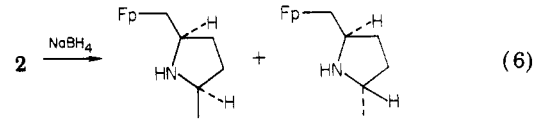


6

(5)

reaction may be conveniently followed by observing the loss of IR carbonyl absorptions at 2010 and 1937 cm^{-1} and the appearance of a new band at 1916 cm^{-1} characteristic of the carbonyl ligand in the chelate. The chelation reaction creates a new chiral center at the iron atom, and this step is evidently nonstereospecific since the product is obtained as an almost equal mixture of diastereomers.

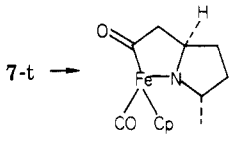
Preliminary experiments designed to close 6 to a carbopenem system, through oxidation under basic conditions, have not been successful. The chelate also resists reduction with sodium borohydride, but the nonchelated pyrroline complex 2 is smoothyl reduced with this reagent in ethanol solution to a 1:1 mixture of diastereomeric pyrrolidine complexes 7 (eq 6).



7-c 7-t

(6)

When this product mixture is heated in acetonitrile solution, it is transformed to a single stereoisomeric chelate (30%). The failure of both isomers to undergo chelation is not surprising, since molecular models show that a chelate derived from 7-c has the methyl group within the fold of the bicyclic system and consequently forces it to interact strongly with either the cyclopentadiene ring or a carbonyl ligand. The product is accordingly assigned structure 8 (eq 7).



8

(7)

Oxidation of the diastereomeric pyrrolidine complexes 7 with silver oxide in THF gave only a trace of β-lactam product. However, similar treatment of the chelate 8 afforded the bicyclic lactam 9 (eq 8) in 72% yield, together with a small amount of ferrocene.[9]

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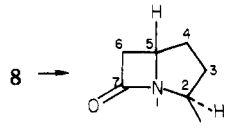
(9) We are indebted to Professor T. Durst for sending us spectral data for this compound, prepared recently by him by cyclization of 4-(3′-butenyl)azetidin-2-one with mercuric acetate followed by sodium borohydride reduction.[10]



(8)

9

The relative configurations at C-2 and C-5 in **9** follow from the stereochemistry assigned to **8**, which would be expected to remain unchanged in the course of lactamization.[11] It is of interest to note that the stereochemical constraints of the chelation reaction selectively lead to a carbopenam system in which the relative configurations of the substituent at C-2 and H-5 are those found in the corresponding positions of the natural β-lactam antibiotics. Although only one of the two diastereomeric pyrrolidine complexes is capable of conversion to a chelate and thence to β-lactam, it may be possible to overcome this difficulty for C-2 carboxyl substituted analogues of **7** by carrying out the chelation reaction under base-catalyzed equilibration conditions.

Work is in progress on further elaborations of this synthetic scheme.

Experimental Section

Preparation of Fp(η^2-5-hexen-2-one)BF_4 (1). Fp(isobutene)BF_4[4] (8.32 g, 26 mmol) was dissolved in 250 mL of methylene chloride in a flask fitted with a septum cap and a reflux condenser. As the temperature of the solution was slowly raised, 5-hexen-2-one (6 mL, 52 mmol) was added by syringe, and the resulting orange solution was maintained at reflux for 4 h. Slow addition of ether to the cooled solution precipitated a light orange solid, which was collected and washed thoroughly with ether. Recrystallization from nitromethane–ether afforded 8.21 g (87%) of product as a light yellow crystalline solid: NMR (CD_3NO_2) δ 5.69 (s, 5, Cp), 5.13 (m, 1, CH=), 3.95 (d, 1, J = 8 Hz, cis CH_2=), 3.53 (d, 1, J = 15 Hz, trans CH_2=), 2.75 (m, 4, CH_2CH_2), 2.14 (s, 3, CH_3); IR (CH_3CN) 2085, 2045, 1715 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}BF_4FeO_3$: C, 43.14; H, 4.18. Found: C, 42.68; H, 4.17.

Preparation of 2-Methyl-5-[Fp(methyl)]-1-pyrroline (2). Complex **1** (1.8 g, 5 mmol) was dissolved in 45 mL of methylene chloride in a Schlenk flask. Ammonia gas was slowly passed over the orange solution, which turned a deep reddish color while being stirred for 2 h at room temperature. Ether (50 mL) was then added, and the resulting mixture was filtered through a small volume of Celite and concentrated in vacuo to a viscous red oil. The crude product was chromatographed on basic alumina. Elution with ether–methylene chloride (1:1) afforded 0.93 g (68%) of a red orange oil: NMR ($CDCl_3$) δ 4.79 (s, 5, Cp), 3.88 (m, 1, CH), 2.6–1.9 (m, 4, CH_2CH_2), 1.99 (s, 3, CH_3), 1.6–1.1 (m, 2, $FpCH_2$); ^{13}C NMR ($CDCl_3$) 217.6 (CO), 171.7 (C=N), 85.4 (Cp), 79.4 (C—N), 39.2, 32.6 (CH_2CH_2), 19.9 (CH_3), 8.8 ($FpCH_2$); IR (CH_2Cl_2) 2010, 1937, 1640 cm^{-1}.

Transformation of 2 to the Chelate Complex 6. The pyrroline complex (0.93 g, 3.4 mmol) was dissolved in 25 mL of THF, and 3 drops of tri-*n*-butylphosphine was added by syringe. The solution was heated at 60 °C for 19 h, with stirring, and then allowed to cool. Concentration of the solution in vacuo left a thick red oil, which was chromatographed on neutral alumina. Elution with ether yielded a small amount of dicarbonylcyclopentadienyliron dimer (Fp_2). Continued elution with ether–methylene chloride (1:1) afforded 0.79 g (85%) of a thick red-orange oil as a 55:45 mixture of diastereomers: NMR ($CDCl_3$) δ 4.51 and 4.45 (s, 5, Cp), 3.90 (m, 1, CH), 2.27 and 2.15 (2 d, J = 1 Hz, CH_3), 3.0–1.5 (several m, 9, CH_3, CH_2); IR (CH_2Cl_2) 1916, 1611 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}FeNO_2$: C, 57.17; H, 5.54; N, 5.13. Found: C, 55.90; H, 5.59; N, 4.91.

Reduction of Complex 2. The pyrroline complex **2** (0.545 g, 2 mmol) was dissolved in 15 mL of absolute ethanol. Sodium borohydride (76 mg, 2 mmol) was added, and the orange solution was stirred for 1 h at room temperature. After cooling to 0 °C, the reaction mixture was treated with 5 mL of water and then concentrated to approximately one-third of its volume in vacuo. An additional 5 mL of water was added, and the mixture was then neutralized with HCl and extracted three times with 15-mL portions of methylene chloride. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of solvent left a red oil which was chromatographed on basic alumina. (In subsequent experiments, the crude product was used in further synthetic transformations without chromatography since considerable decomposition takes place on the column.) Elution with ether yielded a small amount of Fp_2, and continued elution with methylene chloride–methanol (9:1) gave 0.29 g (52%) of **7** as an orange oil, shown by NMR spectroscopic analysis to be a 1:1 mixture of two diastereomers: NMR ($CDCl_3$) δ 4.79 and 4.74 (2 s, 5, Cp), 3.1, 1.9, 1.2 (3 m, CH, CH_2CH_3), 1.16 and 0.99 (2 d, J = 7 Hz, CH_3); IR (CH_2Cl_2) 2010, 1942 cm^{-1}.

Anal. Calcd for $C_{13}H_{17}FeNO_2$: C, 56.75; H, 6.23; N, 5.09. Found: C, 57.57; H, 7.08; N, 4.82.

Conversion of Complex 7 to the Chelate 8. The pyrroline complex **2** (3.26 g, 12 mmol) was reduced as described above. After workup, 2.68 g of the crude pyrrolidine complex **7** was obtained, which showed no remaining C=N IR absorption. This material was dissolved in 30 mL of acetonitrile, and three drops of tri-*n*-butylphosphine was added by syringe. The solution was stirred at 65 °C for 7.5 h, cooled and concentrated in vacuo. The crude product, obtained as a dark red oil, was chromatographed on neutral alumina. Ether eluted Fp_2 followed by the chelate **8** which was eluted as a bright orange band. Evaporation of solvent left 0.81 g (30%) of **8** as a red oil which crystallized on standing: NMR ($CDCl_3$) δ 4.48 (s, 5, Cp); IR (CH_2Cl_2) 1907, 1610 cm^{-1}.

Conversion of Chelate 8 to *r*-5*H*,*c*-2-Methyl-7-oxo-1-azabicyclo[3.2.0]heptane (9). The chelate **8** (0.26 g, 0.98 mmol) was dissolved in 20 mL of THF. Freshly prepared Ag_2O (0.57 g, 2.45 mmol) was added with rapid stirring. The reaction flask was covered to protect it from light, and the mixture was stirred at room temperature for 2 h. Insoluble solids were then removed by centrifugation and washed with 5 mL of THF. The combined supernatant and washings were concentrated in vacuo to a reddish oil. Ether was added, and the solution was filtered through glass wool to remove insoluble material. Solvent was removed, and the residue was chromatographed on neutral alumina. Petroleum ether (bp 30–60 °C) eluted a yellow crystalline fraction identified as ferrocene. Continued elution with ether afforded 88 mg (72%) of product as a pale yellow oil: NMR ($CDCl_3$) δ 1.46 (d, 3, J = 7 Hz, CH_3), 3.13 (dd, 1, J = 16, 5 Hz, cis H-6), 2.59 (dd, 1, J = 16, 2.5 Hz, trans H-6), 3.8–3.2 and 2.5–1.5 (unresolved m); ^{13}C NMR ($CDCl_3$) 189.7 (CO), 56.6, 52.6 (C–N–C), 42.4, 38.8 (CH_2-CH_2), 29.6 (CH_2CO), 17.5 (CH_3); IR (CH_2Cl_2) 1760 cm^{-1}.

Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.08; H, 8.79; N, 11.12.

Acknowledgment. We thank the National Institutes of Health for the support of this work (Grant No. GM-16395).

Registry No. 1, 73274-72-3; 2, 73274-73-4; 6 (isomer 1), 73274-74-5; 6 (isomer 2), 73307-16-1; *cis*-7, 73274-75-6; *trans*-7, 73307-17-2; 8, 73274-76-7; 9, 73274-51-8; Fp(isobutene)BF_4, 32756-78-8; 5-hexen-2-one, 109-49-9.

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