Diastereoselective Synthesis of Trisubstituted Cyclopentane- and Cyclohexanecarboxylic Acid Derivatives Mediated by Iron Tricarbonyl

Ming-Chang P. Yeh,* L.-W. Chuang, and C.-H. Ueng

Department of Chemistry, National Taiwan Normal University, 88 Section 4, Ding-Jou Road, Taipei, Taiwan 117, ROC

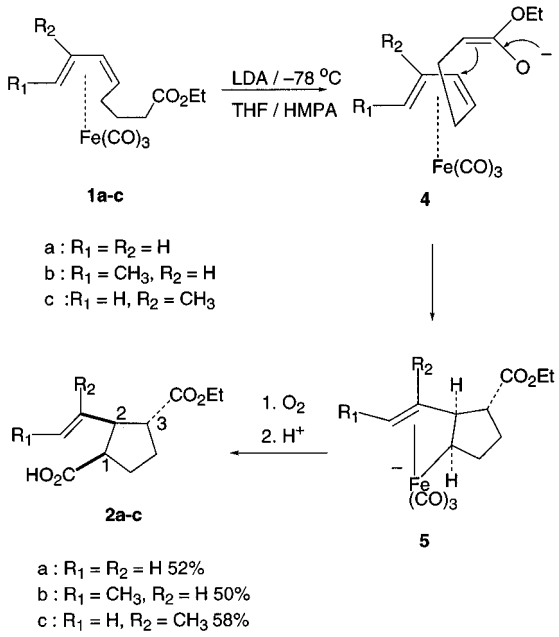
Received December 4, 1995

The stereoselective construction of highly functionalized five- and six-membered rings is an important synthetic goal since such ring skeletons are present in numerous natural products of biological interest.[1,2] Recently, we have shown that intramolecular cyclization of (η^4-diene)$Fe(CO)_3$ complexes bearing functionalized side chains at the terminal position of the diene ligands furnished bicyclo[3.3.0]octane and -[4.3.0]nonane ring units in the presence of carbon monoxide.[3] We have now demonstrated that this methodology can be applied toward highly diastereoselective synthesis of trisubstituted cyclopentane- and cyclohexanecarboxylic acid derivatives by treatment of carboester functionalized (η^4-diene)Fe$(CO)_3$ complexes with lithium diisopropylamide (LDA) followed by *in situ* oxidation with molecular oxygen.

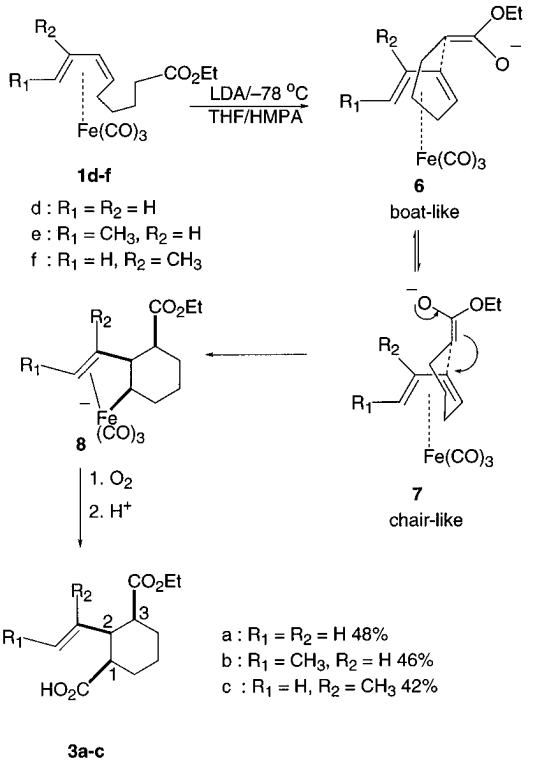
Results and Discussion

Reaction of complex **1a** (Scheme 1), obtained by nucleophilic addition of the zinc−copper reagent of ethyl 3-iodopropionate to (η^5-pentadienyl)$Fe(CO)_3$ cation salt,[3] with 1.2 equiv of LDA followed by quenching the reaction mixture with 1 atm of oxygen provided the trisubstituted cyclopentanecarboxylic acid derivative **2a** (in 52% yield) (Scheme 1). It is important to note that three new contiguous stereogenic centers are created with extreme diastereoselectivity. The product of the relative stereochemistry as shown was isolated as a single diastereomer. Under the same reaction conditions, intramolecular cyclization/oxidation of complexes **1b** and **1c** afforded trisubstituted cyclopentanecarboxylic acid derivatives **2b** (50%) and **2c** (58%), respectively, as the sole cyclized product in each case (Scheme 1). The relative stereochemistry of **2a**−**c** were assigned as the same 1,2−*cis*, 2,3−*trans* relationship on the basis of their close chemical shift values and similar coupling patterns of the protons at the C-2 position in their ^1H NMR spectra. Moreover, molecular modeling indicates that the dihedral angles for H_2-H_3 and H_2-H_1 of **2c** are 173° and 40°, respectively. The observed 10.3 Hz for J_{23} and 8.3 Hz for J_{12} therefore are consistent with the stereochemistry depicted.[4] The stereochemical assignments of **2a**,**b** was ultimately secured by X-ray diffraction analysis of **2c**.[9] The stereochemical course is consistent an anti, *si*−face addition of enolate **4** at the internal C-3 position of the diene ligand to give homoallyl intermediate **5** (Scheme 1). None of the product arising from *re*−face approach of enolate **4** has been found. Oxidation of the postulated homoallyl anion intermediate **5** with oxygen led to the formation of trisubstituted cyclopentane derivatives **2a**−**c** of correct stereochemistry.[5]

Scheme 1



Scheme 2



(1) For five-membered ring see: (a) Trost, B. M.; Romero, D. L.; Rise, F. *J. Am. Chem. Soc.* **1994**, *116*, 4268. (b) Taber, D. F.; You, K. K. *J. Am. Chem. Soc.* **1995**, *117*, 5757. (c) Ramaiah, M. *Synthesis*, **1984**, 529. (d)Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry*; Springer: New York, 1987. (e) Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 141. (f) Pauson, P. L.; Khand, I. U. *Ann. N. Y. Acad. Sci.* **1977**, *295*, 2.

(2) For six-membered ring see: (a) Molander, G. A.; Nichols, P. J. *J. Am. Chem. Soc.* **1995**, *117*, 4415. (b) Stork, G.; Chan, T. Y.; Breault, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7578.

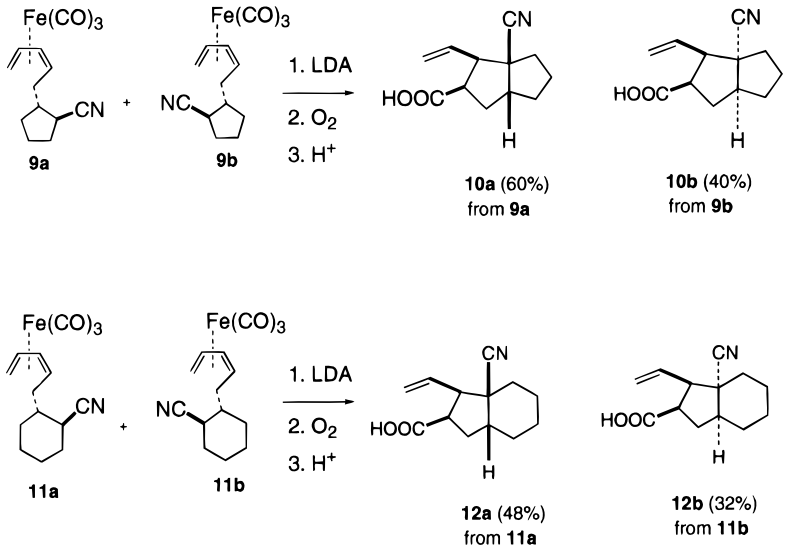
(3) Yeh, M. C. P.; Sheu, B. A.; Fu, H. W.; Tau, S. I.; Chuang, L. W. *J. Am. Chem. Soc.* **1993**, *115*, 5941.

(4) A coupling constant of 8.0-Hz for *cis* protons in the five-membered ring is reported with a dihedral angle of 43°. Trost, B. M.; Romero, D. L.; Rise, F. *J. Am. Chem. Soc.* **1995**, *116*, 4268.

(5) The generation of carboxylic acid derivatives via oxidation of iron−carbon bonds is also proposed for alkylation and bromination of the tetracarbonyliron dianion (known as the Collman reagent). Collman, J. P. *Acc. Chem. Res.* **1975**, *8*, 342.

S0022-3263(95)02148-7 CCC: $12.00

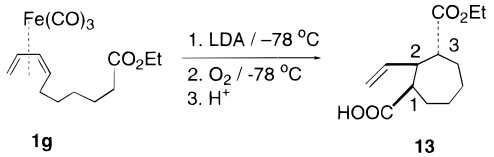
Scheme 3



Increasing the tether length by one with complexes **1d**−**f** (Scheme 2) led to the trisubstituted cyclohexanecarboxylic acid derivatives **3a**−**c** as the only diastereomer in each case in moderate yields. However, the relative stereochemistry of **3a**−**c** was assigned as 1,2-*cis*, 3,4-*cis* on the basis of the X-ray diffraction analysis[9] of **3a** and the ^{1}H NMR spectrum of **3c**. The hydrogen shift of 3.34 in **3c** exhibited as a doublet of doublets was assigned to H_2. The observed coupling constants of H_1−H_2 (J_{12}) and H_2−H_3 (J_{23}) of 5.3 and 4.4 Hz demands the *cis*, *cis* relationship in a six-membered ring. The origin of different stereocontrols for the formation of trisubstituted five- and six-membered ring carboxyxlic acid derivatives was suggested as follow. As stated previously, the trisubstituted cyclopentanecarboxylic acid derivatives **2a**−**c** presumably resulted from the anti, *si*−face addition of enolate **4** at the internal position (C-3) of the diene ligand (Scheme 1). However, anti addition of the *si*−face of the enolate in complexes **1d**−**f** with a longer carbon side chain would result in the formation of a boatlike transition state **6** (Scheme 2). Under such circumstances, the alternative chairlike transition state derived from anti addition of the *re*−face of enolate **7** may be favorable and would lead to *cis*, *cis* stereochemistry of cyclohexanecarboxylic derivatives **3a**−**c** after oxidation and hydrolysis of the incipient anion **8**.

This addition/oxidation sequence can be extended to cyclic substrates. Addition of 2-cyano zinc−copper reagent of the cyclopentane derivative[6] to (η^5-pentadienyl)-$Fe(CO)_3$ cation salt produced the cyclic precursors **9a** and **9b** (Scheme 3) as an unseparable diastereomeric mixture in 1:1 ratio. Intramolecular cyclization/oxidation of the mixture of **9a** and **9b** furnished fused bicyclo[3.3.0]-octanecarboxylic acid derivatives **10a** (60% yield from **9a**) and **10b** (40% yield from **9b**). Diastereomers **10a** and **10b** can be easily separated by column chromatography. The relative stereochemistry in **10a** is confirmed to be all *exo* by X-ray diffraction analysis.[9] The substituents in the ring junctions (i.e., CN and H) in **10b** were assigned *trans* (to olefin and carboxylic acid groups) in view of the anti addition of the cyano-stabilized carbanion at the internal position of the diene ligand of **9b**. Under the same reaction conditions, intramolecular cyclization of the diastereomeric mixture of **11a** and **11b** afforded bicyclo[4.3.0]nonanecarboxylic acid **12a** (48% yield from **11a**) and **12b** (32% yield from **11b**) (Scheme 3). The relative stereochemistry of **12a** and **12b** were assigned by direct correlation of their ^{13}C chemical shifts with those of **10a** and **10b**. The relative upfield shift of the cyano group in **10a** (δ 123.8) as compared with that of **10b** (δ 126.1) is presumably due to the shielding effect exerted by both the carbonyl of the carboxylic acid and the olefin group. Thus, the diastereomer with an upfield shift (δ 122.4) of the cyano group was assigned as the all *cis* isomer **12a**. On the other hand, the isomer with the downfield shift (δ 123.4) of the cyano group was assigned as **12b** with the *endo* vinyl and carboxyl substituents. Moreover, intramolecular cyclization/oxidation of the (η^4-diene)$Fe(CO)_3$ complex **1g** with an even longer side chain furnished trisubstituted cycloheptanecarboxylic acid derivatives **13** as the only diastereomer in 56% yield (Scheme 4). The relative stereochemistry of **13** was tentatively assigned as 1,2-*cis*, 2,3-*trans* on the basis of ^{1}H−^{1}H decoupling experiments. The proton shift at δ 5.82 (multiplet) was assigned as the internal vinyl hydrogen, and the peak at δ 3.15 (triplet of doublets) was assigned as the hydrogen at C-2. Irradiation of the peak at δ 5.82 caused the proton signal at C-2 collapse to a doublet of doublets. The coupling constant of 9.4 and 4.8 Hz suggests the *trans, cis* stereochemistry in a trisubstituted cycloheptane ring system.[7] The *cis* relative stereochemistry of H_1 and H_2 is fixed according to the reaction pathway proposed. The stereochemistry for H_2 and H_3 is therefore assigned as *trans*.

Scheme 4



In conclusion, we have provided an effective method for the formation of trisubstituted five- and six-membered

(6) Majid, T. H.; Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 5069.

(7) Coupling constants of 8.4, 8.0 Hz were observed for a *cis, cis* trisubstituted cycloheptane. See : Lautens, M.; Kumanovic, S. *J. Am. Chem. Soc.* **1995**, *117*, 1954.

carboxylic acid derivatives which invokes the intramolecular cyclization/oxidation of (η^4-diene)$Fe(CO)_3$ complexes bearing a functionalized side chain. The ability to achieve the exclusive diastereocontrol in all cases may have further applications. Specifically, the preparation of even more densely substituted templates for natural product synthesis would be expected to demonstrate still higher levels of stereocontrol.

Experimental Section

General. All reactions were run under a nitrogen atmosphere in oven-dried glassware unless otherwise indicated. Anhydrous solvents or reaction mixtures were transferred via an oven-dried syringe or cannula. Diethyl ether (ether) and tetrahydrofuran (THF) were distilled under nitrogen from a deep blue sodium benzophenone ketyl solution. Complexes **1a**−**g** were synthesized by addition of the corresponding functionalized zinc−copper reagents to (η^5-cyclopentadienyl)$Fe(CO)_3$ cations according to the procedure in ref 3.

Instrumentation. Flash column chromatography, following the method of Still,[8] was carried out with E. Merck 230−400 mesh silica gel using the indicated solvents. Analytical thin-layer chromatography was performed with silica gel 60 F_{254} plastic plates of 0.2-mm thickness. The term "concentration" refers to the removal of solvent with an aspirator pump. The term "under nitrogen" implies that the apparatus was evacuated (oil pump) and then filled with nitrogen three times. Melting points were determined in open capillaries apparatus and are uncorrected. NMR spectra were recorded at 400 MHz for ^{1}H NMR and 100.4 MHz for ^{13}C NMR. Mass spectra were acquired on a JMS-D 100 spectrometer at an ionization potential of 70 eV and are reported as mass/charge (*m*/*z*) with percent relative abundance. High-resolution mass spectra were obtained with an AEI MS-9 double-focusing mass spectrometer and a JMS-HX 110 spectrometer in the Department of Chemistry, Central Instrument Center, Taichung.

Synthesis of Complexes 9a and 9b. A solution of 2-cyanocyclopentane zinc−copper reagent[6] (15 mmol) in 20 mL of THF was added to a stirred suspension of the (η^5-cyclopentadienyl)$Fe(CO)_3$ cation salt (5 mmol) in 5 mL of THF at 5 °C under nitrogen. A homogeneous solution was obtained after the reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was then quenched with saturated aqueous ammonium chloride solution at 0 °C and was diluted with 100 mL of 50% ethyl acetate/hexanes. The resultant solution was washed with water (100 mL × 3) and brine (100 mL × 3), dried over anhydrous magnesium sulfate (10 g), and concentrated to give the crude mixture. The crude mixture was purified via flash column chromatograpy (silica gel, 1:20 ethyl acetate/hexanes) to give **9a** and **9b** (1.1 g, 3.9 mmol, 79%) as an unseparable mixture: IR (CH_2Cl_2) 3059, 2971, 2238, 2049, 1981, 1620, 1453, 1381, 1101, 912, 876, 851 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 (m, 2H), 5.34 (m, 2H), 2.53 (m, 2H), 2.25 (m, 2H), 2.08−2.00 (m, 4H), 1.98−1.71 (m, 12H), 1.64 (m, 2H), 1.41 (m, 1H), 1.22 (m, 1H), 1.09 (m, 1H), 0.96 (m, 1H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 210.8, 122.9, 122.6, 90.9, 90.8, 87.4, 87.1, 56.7, 56.5, 48.5, 48.3, 40.9, 40.8, 34.1, 33.6, 33.5, 31.8, 31.2, 30.8, 30.7, 24.2, 23.8; MS (EI) *m*/*z* (rel intensity) 273 (M^+ − CO, 5), 245 (98), 217 (100), 214 (48), 189 (5), 163 (6), 161 (10), 148 (11), 134 (12), 92 (7), 67 (14), 54 (17); HRMS (EI) calcd for $C_{13}H_{15}FeNO_2$ (M^+ − CO) 273.0448, found 273.0447.

Synthesis of Complexes 11a and 11b. A solution of 2-cyanocyclohexane zinc−copper reagent[6] (15 mmol) in 20 mL of THF was added to a stirred suspension of the (η^5-cyclopentadienyl)$Fe(CO)_3$ cation salt (5 mmol) in 5 mL of THF at 5 °C under nitrogen. A homogeneous solution was obtained after the reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was then quenched with saturated aqueous ammonium chloride solution at 0 °C and was diluted with 100 mL of 50% ethyl acetate/hexanes. The resultant solution was washed with water (100 mL × 3) and brine (100 mL × 3), dried over anhydrous magnesium sulfate (10 g), and concentrated to give the crude mixture. The crude mixture was purified via flash column chromatograpy (silica gel, 1:20 ethyl acetate/hexanes) to give **11a** and **11b** (1.2 g, 3.8 mmol, 76%) as an unseparable mixture: IR (CH_2Cl_2) 3061, 3054, 2988, 2940, 2236, 2049, 1975, 1620, 1449, 1364, 1271, 1223, 1107, 895 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (m, 2H), 5.24 (m, 2H), 2.78 (m, 2H), 2.35 (m, 2H), 1.88 (m, 2H), 1.78 (m, 2H), 1.65 (m, 4H), 1.57 (m, 4H), 1.46−1.39 (m, 8H), 1.36 (m, 2H), 1.22 (m, 2H), 0.96 (m, 2H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 210.9, 121.9, 91.0, 90.8, 87.4, 87.3, 55.7, 55.5, 43.0, 41.6, 41.5, 40.9, 34.2, 34.1, 33.8, 33.5, 30.4, 30.0, 29.7, 29.4, 24.8, 24.7, 24.6, 24.0, 22.6, 22.0, 14.0; MS (EI) *m*/*z* (rel intensity) 287 (M^+, 6), 259 (80), 231 (100), 229 (46), 203 (6), 153 (29), 147 (28), 133 (71), 123 (26), 109 (17), 67 (29), 56 (40); HRMS (EI) calcd for $C_{14}H_{17}FeNO_2$ (M^+) 287.0604, found 287.0611.

General Procedure for Intramolecular Nucleophilic Addition of (η^4-Diene)$Fe(CO)_3$ Complexes Followed by Oxidation. In a typical procedure, to a solution of diisopropylamine (0.48 mL, 3.4 mmol) in 5.0 mL of THF under nitrogen at −78 °C was added rapidly, neat, via syringe, a solution of *n*-butyllithium (2.4 mL, 3.4 mmol, 1.6 M) in hexane followed by addition of 0.60 mL of hexamethylphosphoramide. The reaction mixture was stirred at −78 °C for 20 min. A solution of a diene−iron complex (**1a**−**g**, **9a,b**, **11a,b**, 2.8 mmol) in 3.0 mL of THF was added dropwise via syringe. The mixture was stirred at −78 °C for 2 h. With the solution at −78 °C, oxygen was added to the system via a syringe needle and was pressurized to *ca*. 2 psig (always keeping a positive pressure on the system) as measured by a regulator at the O_2 cylinder. The O_2 pressure was then released via an additional needle, and the O_2 was allowed to flow through the system for 20 s. The gas exit needle was removed, and the closed system was pressurized to *ca*. 14 psig with O_2. The reaction mixture was allowed to stir at −78 °C under O_2 for 30 min. After this time, the O_2 needle was removed, and the reaction mixture was quenched with trifluoroacetic acid (5.0 mol equiv) via a syringe needle and was stirred at −78 °C for 0.5 h. After this time, the reaction mixture was diluted with a mixture of ethyl acetate/hexanes (1/2, 100 mL). The resultant solution was washed with water (100 mL × 3) and brine (100 mL × 3), dried over anhydrous magnesium sulfate (10 g), and concentrated to give the crude mixture.

(1*R,2*R**,3*R**)-3-Carbethoxy-2-vinylcyclopentanecarboxylic Acid (2a)**. The crude mixture from intramolecular cyclization of complex **1a** (0.87 g, 2.80 mmol) followed by oxidation of the reaction with oxygen (14 psi) was purified via flash column chromatography (silica gel, 20% ethyl acetate/hexanes) to give **2a** (0.31 g, 1.46 mmol, 52%) as a colorless liquid: IR (CH_2Cl_2) 3692, 3056, 2986, 1726, 1605, 1424, 1279, 1157, 895 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (td, J = 17.1, 10.3 Hz, 1H), 5.15 (d, J = 17.1 Hz, 1H), 5.09 (d, J = 10.3 Hz, 1H), 4.13 (m, 2H), 3.10 (m, 2H), 2.93 (ddd, J = 16.6, 8.3, 3.5 Hz, 1H), 2.22 (m, 1H), 2.03 (m, 2H), 1.91 (m, 1H), 1.25 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 180.3, 175.4 , 135.7, 117.3, 60.6, 50.7, 48.7, 48.4, 28.9, 27.8, 14.1; MS *m*/*z* (rel intensity) 211 (M^+ − 1, 2), 194 (45), 167 (26), 166 (48), 138 (46), 121 (18), 111 (15), 93 (100), 91 (37), 77 (26), 55 (28); HRMS (70 eV) *m*/*z* calcd for $C_{10}H_{15}O_2$ (M^+ − COOH) 167.1068, found 167.1071.

(1*R,2*R**,3*R**)-3-Carbethoxy-2-[(*E*)-1-propenyl]cyclopentanecarboxylic Acid (2b)**. The crude mixture from intramolecular cyclization of complex **1b** (0.74 g, 2.29 mmol) followed by oxidation of the reaction with oxygen (14 psi) was purified via flash column chromatography (silica gel, 20% ethyl acetate/hexanes) to give **2b** (0.26 g, 1.15 mmol, 50%) as a colorless liquid: IR (CH_2Cl_2) 3690, 3050, 2986, 1725, 1607, 1424, 1377, 1279, 1194, 1034, 968 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (dq, J = 15.1, 7.3 Hz, 1H), 5.40 (dd, J = 15.1, 6.8 Hz, 1H), 4.13 (m, 2H), 3.03 (m, 2H), 2.88 (ddd, J = 16.6, 8.3, 3.5 Hz, 1H), 2.17 (m, 1H), 2.00 (m, 2H), 1.89 (m, 1H), 1.65 (dd, J = 6.4, 1.5 Hz, 3H), 1.24 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 180.3, 175.4, 128.4, 128.3, 60.4, 50.1, 49.0, 48.8, 28.9, 27.9, 27.9, 17.9, 14.2; MS *m*/*z* (rel intensity) 226 (M^+, 2), 208 (100), 193 (18), 181 (45), 180 (61), 165 (19), 99 (24), 98 (70), 83 (17), 61 (24), 57 (97), 56 (55); HRMS (EI) *m*/*z* calcd for $C_{12}H_{18}O_4$ 226.1200, found 226.1198.

(1*R,2*R**,3*R**)-3-Carbethoxy-2-(2-propenyl)cyclopentanecarboxylic Acid (2c)**. The crude mixture from intramolecular cyclization of complex **1c** (0.72 g, 2.24 mmol) followed

(8) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(9) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

by oxidation of the reaction with oxygen (14 psi) was purified via flash column chromatography (silica gel, 20% ethyl acetate/hexanes) to give **2c** (0.29 g, 1.30 mmol, 58%) as a colorless solid: mp 115−116 °C; IR (CH_2Cl_2) 3692, 3050, 2986, 1726, 1605, 1424, 1275, 1157, 911, 893 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.84 (s, 1H), 4.79 (s, 1H), 4.13 (m, 2H), 3.21−3.13 (m, 2H), 3.03 (dd, J = 10.3, 8.7 Hz, 1H), 2.27 (m, 1H), 2.04 (m, 2H), 1.86 (m, 1H), 1.80 (s, 3H), 1.24 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 180.4, 175.5 , 142.5, 111.5, 60.5, 53.8, 47.7, 45.8, 29.1, 27.6, 23.0, 14.2; MS (70 eV) *m/z* (rel intensity) 227 ($M^+ + 1$, 18), 209 (95), 193 (22), 182 (56), 180 (100), 165 (36), 152 (91), 134 (31), 107 (82), 91 (16), 79 (33), 55 (10). Anal. Calcd for $C_{12}H_{18}O_4$ C, 63.70; H, 8.02. Found: C, 63.55; H, 8.07.

(1*R,2*R**,3*S**)-3-Carbethoxy-2-vinylcyclohexanecarboxylic Acid (3a)**. The crude mixture from intramolecular cyclization of complex **1d** (0.75 g, 2.33 mmol) followed by oxidation of the reaction with oxygen (14 psi) was purified via flash column chromatography (silica gel, 20% ethyl acetate/hexanes) to give **3a** (0.25 g, 1.11 mmol, 48%) as a colorless solid: mp 90−91 °C; IR (CH_2Cl_2) 3063, 2984, 1711, 1605, 1422, 1375, 1277, 1136, 1038, 993 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.86 (dt, J = 16.6, 10.2 Hz, 1H), 5.11 (d, J = 16.6 Hz, 1H), 5.08 (d, J = 10.2 Hz, 1H), 4.09 (m, 2H), 3.26 (dt, J = 10.2, 5.0 Hz, 1H), 2.62−2.57 (m, 2H), 1.93 (m, 1H), 1.77 (m, 2H), 1.63 (m, 2H), 1.27 (m, 1H), 1.23 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 179.5, 173.4, 132.0, 119.5, 60.3, 47.0, 46.9, 43.4, 24.0, 22.1, 21.8, 14.2; MS *m/z* (rel intensity) 226 (M^+, 21), 181 (48), 180 (58), 162 (20), 152 (42), 134 (25), 127 (21), 107 (100), 91 (21), 79 (62), 67 (24). Anal. Calcd for $C_{12}H_{18}O_4$ C, 63.7; H, 8.02. Found: C, 63.27; H, 7.99.

(1*R,2*R**,3*S**)-3-Carbethoxy-2-[(*E*)-1-propenyl]cyclohexanecarboxylic Acid (3b)**. The crude mixture from intramolecular cyclization of complex **1e** (1.04 g, 3.00 mmol) followed by oxidation of the reaction with oxygen (14 psi) was purified via flash column chromatography (silica gel, 20% ethyl acetate/hexanes) to give **3b** (0.46 g, 1.38 mmol, 46%) as a colorless solid: mp 94−95 °C; IR (CH_2Cl_2) 3395, 3065, 2948, 1728, 1605, 1451, 1314, 1263, 1260, 1250, 1109, 909 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.51 (m, 2H), 4.09 (m, 2H), 3.23 (dd, J = 8.5, 4.3 Hz, 1H), 2.59−2.50 (m, 2H), 1.91 (m, 1H), 1.75 (dt, J = 12.8, 4.2 Hz, 1H), 1.62 (m, 2H), 1.60 (d, J = 5.5 Hz, 3H), 1.26 (m, 1H), 1.21 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 179.6, 173.5, 130.1, 124.1, 60.1, 47.1, 47.0, 42.3, 24.0, 22.0, 21.8, 18.0, 14.2; MS *m/z* (rel intensity) 240 (M^+, 37), 222(11), 194 (55), 176 (100), 166 (18), 148 (22), 131 (42), 121 (59), 107 (8), 93 (25), 91 (28), 79 (82), 77 (27), 67 (16), 55 (78). Anal. Calcd for $C_{13}H_{20}O_4$ C, 64.98; H, 8.39. Found: C, 64.77; H, 8.36.

(1*R,2*R**,3*S**)-3-Carbethoxy-2-(2-propenyl)cyclohexanecarboxylic Acid (3c)**. The crude mixture from intramolecular cyclization of complex **1f** (0.73 g, 2.17 mmol) followed by oxidation of the reaction with oxygen (14 psi) was purified via flash column chromatography (silica gel, 20% ethyl acetate/hexanes) to give **3c** (0.22 g, 0.91 mmol, 42%) as a colorless solid: mp 85−86 °C; IR (CH_2Cl_2) 3694, 3063, 2986, 2307, 1728, 1605, 1424, 1279, 926 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 4.88 (s, 1 H), 4.86 (s, 1 H), 4.10 (q, J = 7.3 Hz, 2 H), 3.34 (dd, J = 5.3, 4.4 Hz, 1H), 2.69−2.61 (m, 2H), 1.91 (m, 1H), 1.82 (m, 2H), 1.79 (s, 3H), 1.78 (m, 1H), 1.38−1.22 (m, 2H), 1.24 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 179.6, 173.7, 143.3, 116.5, 60.2, 46.6, 46.5, 43.8, 25.7, 23.6, 22.7, 22.5, 14.1; MS *m/z* (rel intensity) 240 (M^+, 30), 222 (25), 195 (58), 194 (100), 180 (12), 179 (10), 176 (17), 167 (19), 166 (47), 153 (13), 100 (39), 99 (76), 97 (52), 81 (15), 72 (20), 71 (68), 70 (28), 64 (17), 61 (13), 57 (42); HRMS (EI) *m/z* calcd for $C_{13}H_{20}O_4$ 240.1356, found 240.1359.

(1*S,2*R**,3*R**,5*R**)-1-Cyano-2-vinylbicyclo[3.3.0]octane-3-carboxylic Acid (10a)**. The crude mixture from intramolecular cyclization of complexes **9a** and **9b** (0.73 g, 2.40 mmol) followed by oxidation of the reaction with oxygen (14 psi) was purified via flash column chromatography (silica gel, 20% ethyl acetate/hexanes) to give **10a** (0.15 g, 0.72 mmol, 60% from **9a**) as a colorless solid and **10b** (0.10 g, 0.48 mmol, 40% from **9b**) as a colorless solid. **10a:** mp 161−162 °C; IR (CH_2Cl_2) 3378, 3061, 2990, 2986, 2234, 1611, 1279, 1258, 1136, 937 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.94 (dt, J = 17.0, 10.2 Hz, 1H), 5.26 (d, J = 10.2 Hz, 1H), 5.25 (d, J = 17.0 Hz, 1H), 3.15 (m, 1H), 3.05 (dd, J = 6.9, 6.8 Hz, 1H), 2.72 (dd, J = 10.2, 9.8 Hz, 1H), 2.40 (m, 1H), 2.16 (dd, J = 12.7, 6.3 Hz, 1H), 2.03 (m, 1H), 1.79−1.71 (m, 3H), 1.52 (m, 1H), 1.44 (m, 1H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 177.7, 133.5, 123.8, 119.8, 56.0, 51.4, 49.7, 48.7, 39.8, 34.2, 34.1, 25.6; MS *m/z* (rel intensity) 205 (M^+, 16), 188 (12), 178 (14), 164 (55), 160 (63), 158 (28), 133 (100), 119 (41), 105 (33), 91 (66), 77 (61), 65 (71).

(1*R,2*R**,3*R**,5*S**)-1-Cyano-2-vinylbicyclo[3.3.0]octane-3-carboxylic Acid (10b)**: mp 87−88 °C; IR (CH_2Cl_2) 3378, 3059, 2990, 2230, 1607, 1267, 1256, 1136, 897 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.63 (dt, J = 16.6, 10.3 Hz, 1H), 5.26 (d, J = 16.6 Hz, 1H), 5.24 (d, J = 10.2 Hz, 1H), 3.33−3.24 (m, 2H), 2.94 (m, 1H), 2.21 (m, 1H), 2.06−1.71 (m, 6H), 1.63 (m, 1H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 177.5, 131.7, 126.1, 121.1, 55.0, 51.5, 50.3, 49.8, 34.4, 33.3, 32.1, 26.9; MS *m/z* (rel intensity) 205 (M^+, 21), 187 (18), 163 (45), 160 (80), 158 (37), 133 (100), 118 (49), 91 (52), 77 (39), 67 (53), 65 (38). Anal. Calcd for $C_{12}H_{15}NO_2$ C, 70.22; H, 7.37; N, 6.82. Found: C, 70.00; H, 7.07; N, 6.55.

(1*S,6*R**,8*R**,9*R**)-1-Cyano-9-vinylbicyclo[4.3.0]nonane-8-carboxylic Acid (12a).** The crude mixture from intramolecular cyclization of complexes **11a** and **11b** (0.71 g, 2.25 mmol) followed by oxidation of the reaction with oxygen (14 psi) was purified via flash column chromatography (silica gel, 20% ethyl acetate/hexanes) to give **12a** (0.12 g, 0.54 mmol, 48% from **11a**) as a colorless solid and **12b** (0.08 g, 0.36 mmol, 32% from **11b**) as a colorless solid. **12a**: mp 200−201 °C; IR (CH_2Cl_2) 3380, 3063, 2986, 2307, 1605, 1424, 1258, 1152, 932 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (dt, J = 16.6, 10.3 Hz, 1H), 5.26 (d, J = 10.3 Hz, 1H), 5.22 (d, J = 16.6 Hz, 1H), 3.32 (dd, J = 10.3, 9.8 Hz, 1H), 2.95 (t, J = 10.3 Hz, 1H), 2.63 (m, 1H), 2.41 (dt, J = 14.2, 6.9 Hz, 1H), 1.84 (m, 2H), 1.74 (m, 1H), 1.59−1.49 (m, 6H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 177.7, 133.3, 122.4, 120.4, 53.8, 47.2, 45.5, 41.6, 30.3, 29.4, 25.1, 21.8, 20.6; MS *m/z* (rel intensity) 219 (M^+, 22), 192 (24), 179 (13), 178 (55), 175 (13), 174 (58), 173 (29), 172 (22), 159 (11), 98 (17), 97 (100), 96 (40), 95 (13), 83 (46), 82 (17), 81 (15), 71 (33), 69 (22), 67 (16), 58 (25); HRMS (EI) *m/z* calcd for $C_{13}H_{17}NO_2$ 219.1255, found 219.1264.

(1*R,6*S**,8*R**,9*R**)-1-Cyano-8-carboxy-9-vinylbicyclo[3.3.0]-nonane (12b)**: mp 137−138 °C; IR (CH_2Cl_2) 3380, 3052, 2988, 2307, 1746, 1605, 1424, 1252, 1148, 932, 922 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.71 (dt, J = 17.1, 9.8 Hz, 1H), 5.37 (d, J = 17.1 Hz, 1H), 5.27 (d, J = 9.8 Hz, 1H), 3.22 (m, 2H), 2.42 (m, 1H), 2.31 (td, J = 12.7, 6.4 Hz, 1H), 1.97 (m, 1H), 1.83−1.48 (m, 8H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 179.1, 131.0, 123.4, 121.1, 55.6, 46.3, 44.9, 43.5, 30.5, 25.4, 23.9, 22.8, 19.4; MS *m/z* (rel intensity) 219 (M^+, 37), 201 (27), 192 (73), 190 (12), 178 (17), 175 (24), 174 (100), 173 (96), 172 (36), 164 (15), 163 (41), 158 (18), 97 (96), 96 (33), 82 (31), 81 (27), 71 (33), 68 (42), 58 (56); HRMS (EI) *m/z* calcd for $C_{13}H_{17}NO_2$ 219.1255, found 219.1262.

(1*R,2*R**,3*R**)-3-Carbethoxy-2-vinylcycloheptanecarboxylic Acid (13)**. The crude mixture from intramolecular cyclization of complex **1g** (0.95 g, 2.59 mmol) followed by oxidation of the reaction with oxygen (14 psi) was purified via flash column chromatography (silica gel, 20% ethyl acetate/hexanes) to give **13** (0.35 g, 1.45 mmol, 56%) as a colorless liquid: IR (CH_2Cl_2) 3690, 3057, 2932, 1726, 1640, 1422, 1375, 1281, 1034, 995 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (dt, J = 17.1, 9.3 Hz, 1H), 5.05 (d, J = 17.1 Hz, 1H), 5.02 (d, J = 9.3 Hz, 1H), 4.12 (q, J = 6.8 Hz, 2H), 3.09 (td, J = 9.3, 4.4 Hz, 1H), 2.88 (m, 1H), 2.65 (m, 1H), 1.93 (m, 1H), 1.79 (m, 5H), 1.46 (m, 2H), 1.24 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 180.3, 175.7, 138.0, 116.8, 60.4, 49.0, 47.5, 46.4, 29.1, 28.0, 27.5, 26.1, 14.2; MS *m/z* (rel intensity) 240 (M^+, 2), 222 (42), 194 (84), 176 (13), 166 (27), 148 (52), 137 (10), 122 (18), 120 (100), 105 (25), 93 (45), 91 (51), 79 (72), 67 (39), 55 (57); HRMS (EI) *m/z* calcd for $C_{13}H_{20}O_4$ (M^+) 240.1356, found 240.1360.

Acknowledgment. Support for this research from the National Science Council (82−0208-M-003-006) of the Republic of China is gratefully acknowledged.

Supporting Information Available: ^1H NMR and ^{13}C NMR spectra of **2a**,**c**, **3a**,**c**, **12a**,**b**, and **13** and ORTEP diagrams of **2c**, **3a**, and **10a** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO952148K