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

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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. Recently, we have shown that intramolecular cyclization of \((\eta^4\text{-diene})\text{Fe(CO)}_3\) 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. We have now demonstrated that this methodology can be applied toward highly diastereoselective synthesis of trisubstituted cyclopentane- and cyclohexanecarboxylic acid derivatives by treatment of carbocoster functionalized \((\eta^4\text{-diene})\text{Fe(CO)}_3\) 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 \((\eta^5\text{-pentadienyl})\text{Fe(CO)}_3\) cation salt, with 1.2 equiv of LDA followed by quenching the reaction mixture with 1 atm of oxygen provided the trisubstituted cyclopentane-carboxylic 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 cyclopentane-carboxylic 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 \(^1\text{H} NMR\) spectra. Moreover, molecular modeling indicates that the dihedral angles for H-2-H3 and H-2-H1 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.

The stereochemical assignments of 2a–b were ultimately secured by X-ray diffraction analysis of 2c. 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.


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 H2. The observed coupling constants of H1–H3 (J\(_12\)) and H2–H3 (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 carboxylic acid derivatives was suggested as follows. 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 \((\eta^5\)-pentadienyl)\(
Fe(CO)\)_3 cation salt produced the cyclic precursors 9a and 9b (Scheme 3) as an inseparable 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\(^5\)-dienyl)\(
Fe(CO)\)_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 Hz suggests the trans, cis stereochemistry in a trisubstituted cycloheptane ring system.\(^7\) The cis relative stereochemistry of H3 and H2 is fixed according to the reaction pathway proposed. The stereochemistry for H2 and H3 is therefore assigned as trans.

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


\(^{7}\) 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 \( (\gamma^2\text{-dien})\text{Fe(CO)}_3 \) complexes bearing a functionalized side chain. The ability to achieve the exclusive diastereocore 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 stereocore.

**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-carboxylate reagent to \( (\gamma^2\text{-cyclopentadienyl})\text{Fe(CO)}_3 \) cations according to the procedure in ref 3.

**Instrumentation.** Flash 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 amount of solvent used in the thin-layer spirator 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 \( ^1H \) NMR and 100.4 MHz for \( ^13C \) 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 the HX110 spectrometer in the Department of Chemistry, Central Instrument Service Centre, Taichung.

**Synthesis of Complexes 9a and 9b.** A solution of 2-cyclopentadienylzinc–copper reagent\(^{10} \) (15 mmol) in 20 mL of THF was added to a stirred suspension of the \( (\gamma^1\text{-cyclopentadienyl})\text{Zn} \) cation salt (5 mmol) in 5 mL of THF at 5 °C under nitrogen. A homogenous 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 9a and 9b (1.1 g, 3.9 mmol, 79%) as an unseparable mixture. All reactions were run under a nitrogen atmosphere.

**Synthesis of Complexes 11a and 11b.** A solution of 2-cyclopentadienylzinc–copper reagent\(^{10} \) (15 mmol) in 20 mL of THF was added to a stirred suspension of the \( (\gamma^2\text{-cyclopentadienyl})\text{Fe(CO)}_3 \) cation salt (5 mmol) in 5 mL of THF at 5 °C under nitrogen. A homogenous 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.

**Notes**


(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 10a (0.15 g, 0.72 mmol). 10b (0.08 g, 0.36 mmol) was isolated as a colorless solid.

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**Supporting Information Available:**  
H NMR and 13C 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.

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