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Generation Of Molecular Complexity From Cyclooctatetraene: Synthesis Of A Protected 2-(3′-Carboxy-2′-Benzoylcyclopentyl)Glycine

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Abstract  
Synthesis of a protected 2-(3′-carboxycyclopentyl)glycine rac-11, possessing four contiguous chiral carbons, was accomplished in six steps (20% yield) from the hydrocarbon cyclooctatetraene.
Synthesis of a protected 2-(3’-carboxycyclopentyl)glycine rac-11, possessing four contiguous chiral carbons, was accomplished in six steps (20% yield) from the hydrocarbon cyclooctatetraene.

The use of the simple hydrocarbon cyclooctatetraene (1) as a starting material for synthesis has experienced a rebirth in the last five years, as exemplified by its use in the synthesis of aminocyclitols,\(^1\)a bis-homoconduritols,\(^1\)b bis-homoinositol,\(^1\)c pentacycloamoxamic acid methyl ester,\(^1\)d the polyene segment of roxaticin,\(^1\)e and cyclooctitols.\(^1\)f Tricarbonyl(cyclooctatetraene)iron 2, readily prepared from 1,\(^2\) undergoes reaction with electrophiles to give a wide variety of cationic iron complexes\(^3\) (Scheme 1). Protonation\(^3(a),\) 3(b) of 2 or its (CO)\(_2\)PPh\(_3\) ligated analog affords (bicyclo[5.1.0]octadienyl)Fe(CO)\(_2\)L\(^+\) cations 3.

We have previously demonstrated the applicability of cation 3b for the synthesis of the naturally occurring CCG-III (4).\(^4\) In contrast, Friedel–Crafts acylation of 2, followed by anion metathesis, gave (bicyclo[3.2.1]octadienyl)Fe(CO)\(_3\) cations 5/6.\(^3(c)\) The structural assignment of the 8-acyl substituted cation (5) was eventually confirmed by X-ray crystal structure.\(^5\) In comparison to the extensive examination of (cyclohexadienyl)- and (cycloheptadienyl)-iron(1+) cations,\(^6,\) 7 the reactivity of bicyclic cations 5/6 with nucleophiles has been considerably less studied.\(^3(c),\) 8 As part of our growing interest in the generation of molecular complexity from hydrocarbons,\(^4\) we herein report on the reactivity of cation 6 and the synthesis of a protected 2-(3-carboxycyclopentyl)glycine from 1.

The reaction of 6 with BH\(_4\)- gave a mixture of diene complex 7a and the free ligand 8a; decomposition of this mixture by irradiation with a medium pressure Hg lamp in acetic acid solution gave only 8a (Table 1). In a similar fashion, reaction of 6 with MeLi/CuBr, followed by decomplexation, gave 8b albeit in attenuated yield. In comparison, reaction of 6 with triphenylphosphine, dimethyl malonate, dimethyl allylmalonate, or phthalimide gave diene complexes 7c–f in good isolated yield. Decomplexation of 7d or 7f gave the 4-substituted-8-benzoylbicyclo[3.2.1]octa-2,6-dienes 8d/f, respectively.\(^9\) The structural assignments for 8a, b, d, and f were based on their \(^1\)H NMR spectral data. In particular, the signals for H1, H2, H3, H6, and H7 appear at \(\delta 3.1–3.4\).
(dd), 6.2–6.5 (ddd), 5.2–5.5 (dd), 5.6–6.0 (dd), and 6.1–6.35 (dd) ppm, respectively. Furthermore, the structures of 8a and 7c were corroborated by X-ray diffraction analysis (Fig. 1).10

![Molecular representations of 8a (left) and 7c (right, PF6- omitted).](image)

Table 1. Nucleophilic addition to (8-benzoylbicyclo[3.2.1]octa-3,6-dien-2-yl) Fe(CO)3+

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Nu</th>
<th>Products (isolated yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaBH4</td>
<td>H</td>
<td>7a (—)</td>
</tr>
<tr>
<td>MeLi/CuBr</td>
<td>Me</td>
<td>7b (—)</td>
</tr>
<tr>
<td>PPh3+PF6-</td>
<td>PPh3+PF6-</td>
<td>7c (85)</td>
</tr>
<tr>
<td>NaCH(CO2Me)2</td>
<td>CH(CO2Me)2</td>
<td>7d (98)</td>
</tr>
<tr>
<td>NaC(allyl)(CO2Me)2</td>
<td>C(allyl)(CO2Me)2</td>
<td>7e (95)</td>
</tr>
<tr>
<td>K+−NPhth</td>
<td>NPhth</td>
<td>7f (82–89)</td>
</tr>
</tbody>
</table>

a The (diene)Fe(CO)3 complex 7a was decomposed by irradiation with a medium pressure Hg lamp in acetic acid solution.

Nucleophilic addition to C2/C4 of 6 is opposite to the predicted regioselectivity from the ‘Green–Mingos–Davies rules’11 for nucleophilic addition to cationic polyenyl–metal complexes, (i.e., ‘even’ polyenyl ligands in preference to ‘odd’ polyenyl ligands). The observed regioselectivity can be rationalized on the basis of steric hindrance for attack at C6/C7 due to the pendant C8 benzoyl group. Incorporation of non-proteinogenic amino acids or peptide isosteres into proteins or small peptides is of interest due to an increase in proteolytic resistance of the modified protein and/or conformational rigidity imparted due to the structure of the unusual amino acid.12 Recently, Pellegrino reported the synthesis of 2-(3′-carboxycyclopentyl)-glycines 9a/b as conformationally restricted analogs, the naturally occurring, but rare, amino acids 2-aminoadipic acid and 2-aminopimelic acid.13 It was envisioned that bicyclo[3.2.1]octa-2,6-diene 8f could be elaborated into a derivative of 9a. To this end, selective reduction of C6–C7 double bond of 8f with H2 (balloon pressure, RhCl(PPh3)3, 45 min) cleanly gave
mono-olefin 10 (Scheme 2). Use of greater pressure (50 psi) or longer reaction times leads to partial reduction of the C2–C3 olefin. The greater reactivity of the C6–C7 olefin in a bicyclo[3.2.1]octa-2,6-diene system, toward oxidation, reduction, or addition, compared to the C2–C3 olefin is well documented. This selectivity is generally attributed to the greater strain inherent in the C6–C7 olefin compared to the C2–C3 olefin. Sharpless oxidation (RuCl3/I2O4) of 10, followed by Fisher esterification gave diester 11. The structural assignment for 11 was tentatively based on its NMR spectral data. In particular, the doublet for H8 appears at δ 4.95, while the two methyl esters singlets appear at δ 3.62 and 3.44 ppm. This structural assignment was also corroborated by X-ray diffraction analysis of 11 (Fig. 2).

In summary, (8-benzoylbicyclo[3.2.1]octa-3,6-dien-2-yl)Fe(CO)3+ cation 6 reacts with a variety of nucleophiles by attack at the η3-allyl fragment to generate diene complexes 7. This reactivity was utilized in a short synthesis of the protected amino acid analog 11, possessing four contiguous chiral centers, from the simple hydrocarbon cyclooctatetraene.

Acknowledgments
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References and notes


9 To a solution of 7f (50 mg, 0.10 mmol) in methanol was added CAN (109 mg, 0.200 mmol) in one portion. The reaction mixture was stirred for 1 h and then water (10 mL) was added and the mixture extracted with ethyl acetate. The combined organic extracts were dried (MgSO4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO2, hexane–ethyl acetate = 5:1) to afford 8f as a colorless solid (35 mg, 99%): mp 130–132 °C; 1H NMR (CDCl3) δ 7.88 (m, 4H), 7.76 (m, 2H), 7.45 (m, 1H), 7.36 (m, 2H), 6.51 (ddd, J = 2.6, 6.8, 9.6 Hz, 1H), 6.35 (dd, J = 3.0, 5.6 Hz, 1H), 5.99 (dd, J = 3.0, 5.6 Hz, 1H), 5.43 (ddd, J = 2.0, 3.0, 9.5 Hz, 1H), 4.78 (s, 1H), 4.72 (dt, J = 1.2, 2.7 Hz, 1H), 3.38 (dd, J = 2.9, 6.7 Hz, 1H), 3.04 (m, 1H); 13C NMR (CDCl3) δ 200.8, 168.6, 140.9, 136.5, 136.2, 134.5, 132.9, 131.9, 129.0, 128.7, 128.5, 123.8, 123.5, 56.2, 49.7, 47.7, 42.7. FAB-HRMS m/z 356.1290 (calcd for C23H18NO3 (M+H+) m/z 356.1287).

10 The crystallographic data has been deposited with the CCDC for compounds 8a (CCDC 644516), 7c (CCDC 644515) and 11 (CCDC 644517), respectively. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB1 2EZ, UK; fax: +44 (1223)336033; e-mail: deposit@ccdc.ccdc.cam.ac.uk.


14 To a solution of 8f (90 mg, 0.25 mmol) in ethanol (10 mL) was added RhCl(PPh3)3 (135 mg, 0.146 mmol). The mixture was stirred under a balloon of H2 for 1 h. The mixture was concentrated and the residue was purified by column chromatography (SiO2, hexane–ethyl acetate = 5:1) to afford 10 as a colorless solid (88 mg, 98%): 1H NMR (CDCl3) δ 7.95 (m, 2H), 7.84 (m, 2H), 7.71 (m, 2H), 7.51 (m, 1H), 7.41 (m, 2H), 7.31 (m, 2H), 7.11 (m, 2H), 6.51 (m, 2H), 6.39
(ddd, J = 2.1, 6.9, 9.4 Hz, 1H), 5.61 (ddd, J = 1.6, 3.9, 9.3 Hz, 1H), 4.64 (ddd, J = 2.0, 2.7, 4.5 Hz, 1H), 4.41 (s, 1H), 2.94 (br t, J = 5.8 Hz, 1H), 2.77 (d, J = 8.1 Hz, 1H), 2.30 (m, 1H), 1.67 (m, 2H), 1.51 (m, 1H); 13C NMR (CDCl3) δ 201.8, 168.9, 137.9, 136.2, 134.3, 133.0, 132.0, 128.8, 128.7, 123.4, 122.0, 56.5, 50.5, 42.2, 40.3, 31.3, 27.9. FAB-HRMS m/z 358.1455 (calcd for C23H20NO3 (M+H+) m/z 358.1443).


17 To a solution of 10 (100 mg, 0.280 mmol) and NaIO₄ (478 mg, 2.23 mmol) in CCl₄ (2.5 mL), CH₃CN (2.5 mL), and water (4 mL) was added RuCl₃·3H₂O (85 mg, 0.33 mmol). After stirring at room temperature for 3 h, ethyl acetate (15 mL) and brine (10 mL), and water (25 mL) were added to the dark solution. The pink organic phase was separated, and the aqueous phase extracted several times with ethyl acetate. The organic extracts were combined, dried (MgSO₄), and concentrated. The residue was dissolved in methanol (10 mL), and concentrated H₂SO₄ (~5 drops) was added. The mixture was heated to reflux for 12 h, then concentrated to ~5 mL by rotary evaporation. The solution was diluted with ethyl acetate (25 mL) and washed with water several times. The organic layer was dried (MgSO₄), and concentrated in vacuo. The residue was purified by chromatography (SiO₂, hexanes-ethyl acetate = 10:1) to give 11 as a colorless crystalline solid (100 mg, 79%): mp 125–127 °C; ¹H NMR (CDCl₃) δ 8.04 (m, 2H), 7.87 (m, 2H), 7.75 (m, 2H), 7.57 (m, 1H), 7.48 (m, 2H), 4.95 (d, J = 9.6 Hz, 1H), 4.39 (dd, J = 5.3, 6.5 Hz, 1H), 3.78 (m, J = 1H), 3.62 (s, 3H), 3.44 (s, 3H), 2.91 (m, 1H), 2.01–1.92 (m, 3H), 1.54 (m, 1H); ¹³C NMR (CDCl₃) δ 200.7, 175.3, 169.2, 167.8, 136.7, 134.5, 133.4, 131.9, 128.9, 128.8, 123.9, 55.0, 52.7, 52.5, 52.4, 49.6, 42.0, 29.9, 29.8. FAB-HRMS m/z 450.1546 (calcd for C₂₅H₂₄NO₇ (M+H⁺) m/z 450.1553).