10-2007

Generation of molecular complexity from cyclooctatetraene: synthesis of a protected 2-(3'-carboxy-2'-benzoylcyclopentyl)glycine

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Tetrahedron Letters, Vol. 48, No. 44 (October 29, 2007): 7849-7852. DOI.

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

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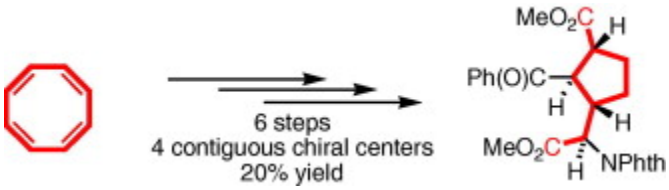
Abstract

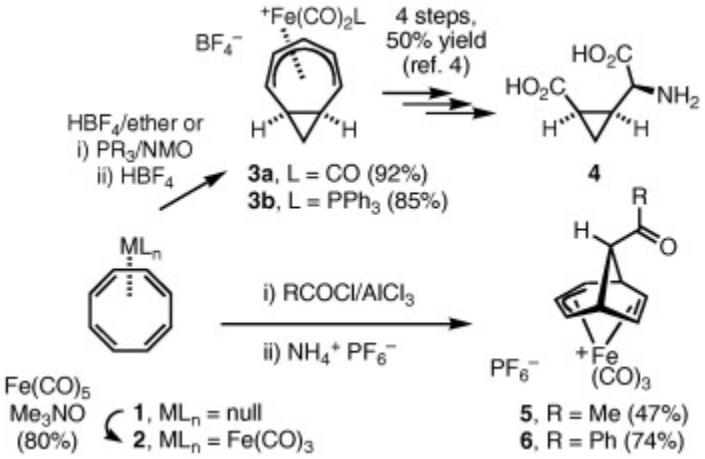
Synthesis of a protected 2-(3'-carboxycyclopentyl)glycine *rac*-**11**, possessing four contiguous chiral carbons, was accomplished in six steps (20% yield) from the hydrocarbon cyclooctatetraene.

Graphical 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.



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,[1a] bis-homoconduritols,[1b] bis-homoinositol,[1c] pentacycloanammoxic acid methyl ester,[1d] the polyene segment of roxaticin,[1e] and cyclooctitols.[1f] 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 $(CO)_2PPh_3$ ligated analog affords (bicyclo[5.1.0]octadienyl)$Fe(CO)_2L^+$ 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**.[3c] 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**.



Scheme 1.

The reaction of **6** with BH4- 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 δ 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]

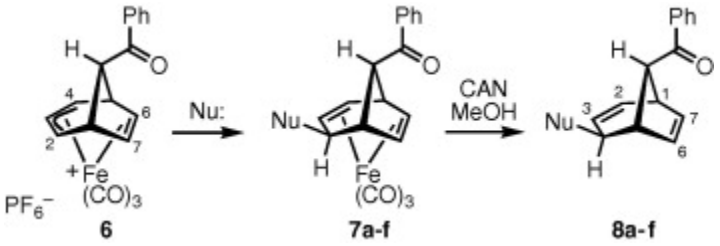


Table 1. Nucleophilic addition to (8-benzoylbicyclo[3.2.1octa-3,6-dien-2-yl) Fe(CO)3+

Nucleophile	Nu	Products (isolated yield, %)	
$NaBH_4$	H	7a (—)	8a (41)[a]
MeLi/CuBr	Me	7b (—)	8b (23)
PPh_3	PPh3+PF6-	7c (85)	—
$NaCH(CO_2Me)_2$	$CH(CO_2Me)_2$	7d (98)	8d (99)
$NaC(allyl)(CO_2Me)_2$	$C(allyl)(CO_2Me)_2$	7e (95)	—
$K^{+-}NPhth$	NPhth	7f (82–89)	8f (87–99)

a The (diene)$Fe(CO)_3$ complex **7a** was decomposed by irradiation with a medium pressure Hg lamp in acetic acid solution.

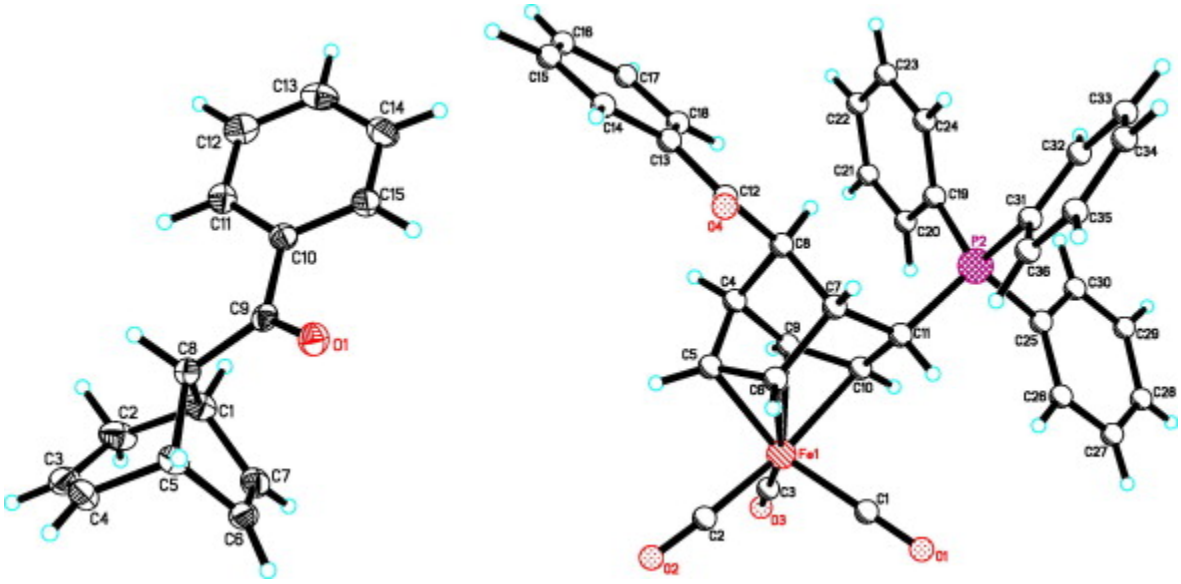
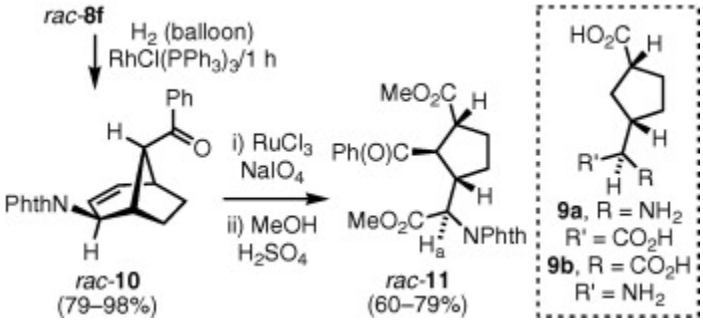


Figure 1. Molecular representations of **8a** (left) and **7c** (right, PF6- omitted).

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 H_2 (balloon pressure, $RhCl(PPh_3)_3$, 45 min) cleanly gave

mono-olefin **10** (Scheme 2).[14] 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.[15] This selectivity is generally attributed to the greater strain inherent in the C6–C7 olefin compared to the C2–C3 olefin.[15d] Sharpless oxidation ($RuCl_3$/IO4-)[16] of **10**, followed by Fisher esterification gave diester **11**.[17] The structural assignment for **11** was tentatively based on its NMR spectral data. In particular, the doublet for H_a 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).[10]



Scheme 2.

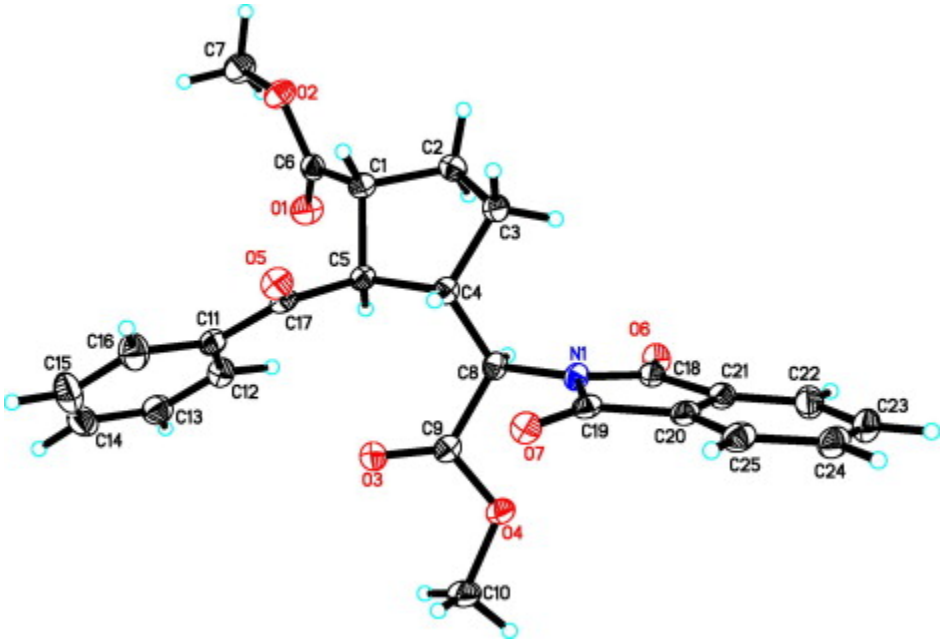


Figure 2. Molecular representation of **11**.

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 η^3-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

This work was supported by the National Science Foundation (CHE-0415771) and NSF instrumentation grants (CHE-0521323). High-resolution mass spectra were obtained at the University of Nebraska—Center for Mass Spectrometry.

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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 ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane–ethyl acetate = 5:1) to afford **8f** as a colorless solid (35 mg, 99%): mp 130–132 °C; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{23}H_{18}NO_3$ ($M+H^+$) *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/retreiving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB12 1EZ, UK; fax: +44 (1223)336033; e-mail: deposit@ccdc.ccdc.cam.ac.uk.

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14 To a solution of **8f** (90 mg, 0.25 mmol) in ethanol (10 mL) was added $RhCl(PPh_3)_3$ (135 mg, 0.146 mmol). The mixture was stirred under a balloon of H_2 for 1 h. The mixture was concentrated and the residue was purified by column chromatography (SiO_2, hexane–ethyl acetate = 5:1) to afford **10** as a colorless solid (88 mg, 98%): ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 2H), 7.84 (m, 2H), 7.71 (m, 2H), 7.51 (m, 1H), 7.41 (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); ^{13}C NMR ($CDCl_3$) 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 $C_{23}H_{20}NO_3$ ($M+H^+$) *m/z* 358.1443).

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17 To a solution of **10** (100 mg, 0.280 mmol) and $NaIO_4$ (478 mg, 2.23 mmol) in CCl_4 (2.5 mL), CH_3CN (2.5 mL), and water (4 mL) was added $RuCl_3 \cdot 3H_2O$ (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 ($MgSO_4$), and concentrated. The residue was dissolved in methanol (10 mL), and concentrated H_2SO_4 (~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 ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography (SiO_2, hexanes-ethyl acetate = 10:1) to give **11** as a colorless crystalline solid (100 mg, 79%): mp 125–127 °C; ^{1}H NMR ($CDCl_3$) 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, 1H), 3.62 (s, 3H), 3.44 (s, 3H), 2.91 (m, 1H), 2.01–1.92 (m, 3H), 1.54 (m, 1H); ^{13}C NMR ($CDCl_3$) 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 $C_{25}H_{24}NO_7$ ($M+H^+$) *m/z* 450.1553).