Divergent Reactivity in Tandem Reduction–Michael Ring Closures of Five- and Six-Membered Cyclic Enones

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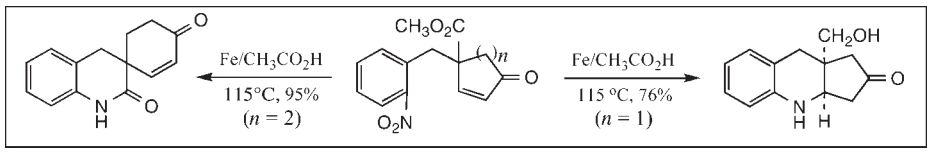

In this study, methyl (±)-1-(2-nitrobenzyl)-4-oxo-2-cyclohexene-1-carboxylate and methyl (±)-(2-nitrobenzyl)-4-oxo-2-cyclopentene-1-carboxylate were prepared and subjected to reductive cyclization under dissolving metal conditions. The two reactants showed divergent behavior with the six-ring substrate reacting at the ester carbonyl and the five-ring substrate closing on the enone double bond. The difference in reactivity is attributed to the conformational flexibility, relative reactivity, and steric environment of C4-substituted six- and five-membered cyclic enones.

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INTRODUCTION

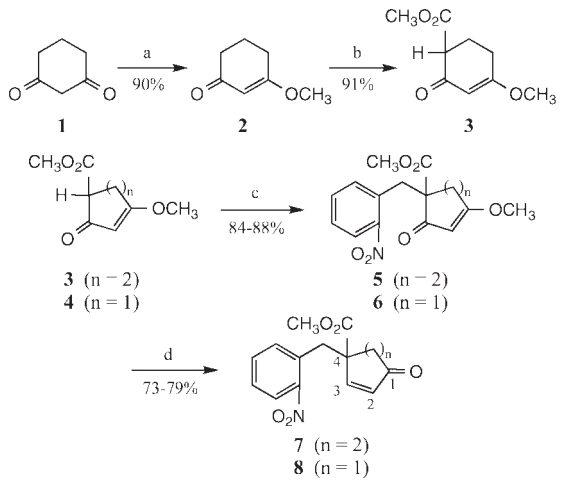
The reductive cyclization of 2-nitrobenzyl ketones under dissolving metal conditions is well established as a route to the synthesis of indoles [1,2]. Earlier work from our laboratory studied a tandem reduction–Michael addition variant of this reaction as a route to the synthesis of 1,2,3,4-tetrahydroquinoline-2-acetic esters [3], and we have recently used this reaction to synthesize 1,2,3,9-tetrahydro-4*H*-carbazol-4-one [4]. In this investigation, we sought to expand the scope of the tandem reduction–Michael sequence to access functionalized linear-fused tricyclic systems. For this study, we prepared six- and five-membered cyclic enones substituted at C4 by a methyl ester and a 2-nitrobenzyl group, and subjected each to mild reduction using iron in acetic acid. To our surprise, divergent reactivity was observed from the cyclohexenone and cyclopentenone substrates, resulting in two relatively uncommon ring systems. In addition, a mechanistically novel competitive ester reduction process was observed. Thus, we report our findings in this area.

RESULTS AND DISCUSSION

The syntheses of our cyclization substrates are summarized in Scheme 1. Ketoester **3** was prepared from 1,3-cyclohexanedione (**1**) by Lewis acid-catalyzed enol ether formation to give **2** [5] followed by kinetic deprotonation [6] and reaction with methyl cyanoformate [7]. In this case, we found that methyl cyanoformate gave better yields of the ketoester than methyl chloroformate with easier purification of the product. Ketoester **4** was prepared as previously described [8]. Alkylation of **3** and **4** with 2-nitrobenzyl bromide [9] using potassium carbonate and catalytic 18-crown-6 in acetonitrile under anhydrous conditions [10] gave products **5** and **6**, respectively. Reduction of the enone carbonyls in **5** and **6** with sodium borohydride in the presence of cerium(III) chloride [11], followed by treatment with aqueous acid resulted in 1,3-carbonyl transposition to give substrates **7** and **8**.

The results of our reduction-cyclization study are outlined in Scheme 2. In each case, the reaction was

Scheme 1 [a]



[a] Key: (a) CH_3OH, $CeCl_3 \cdot 7H_2O$-SiO_2, 22°C; (b) *i*. $LiN(i\text{-}C_3H_7)_2$, tetrahydrofuran, −78°C; *ii*. CH_3O_2CCN, −78°C → 22°C; (c) K_2CO_3, 18-crown-6, CH_3CN, 2-nitrobenzyl bromide, 82°C; (d) *i* $NaBH_4$, $CeCl_3 \cdot 7H_2O$, CH_3OH, 22 °C; *ii*. 3 M HCl.

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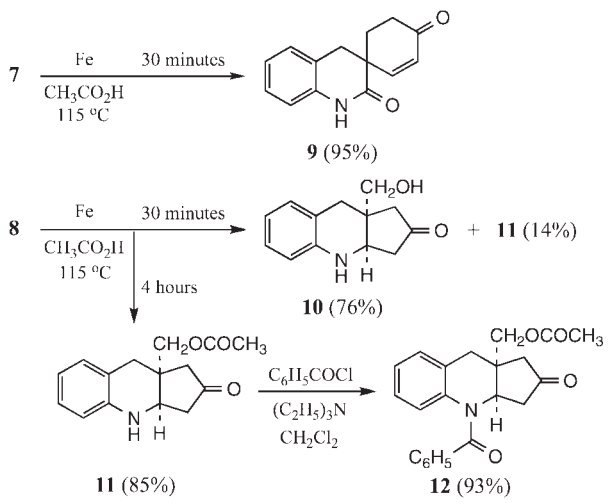
Scheme 2



complete in 30 min and led predominantly to a single product. For cyclohexenone **7**, the expected reduction-Michael addition was not observed, but instead, reduction of the nitro group was followed by addition of the aniline nitrogen to the ester to give the spiro-fused 3,4-dihydro-2(1*H*)-quinolinone derivative **9** in 95% yield. For cyclopentenone **8**, the reduction–Michael sequence proceeded as planned, but was accompanied by reduction of the ester to afford **10** in 76% yield. Extended reaction times (4 h) led to further acylation of the primary alcohol in **10** to give **11**. The *cis* stereochemistry

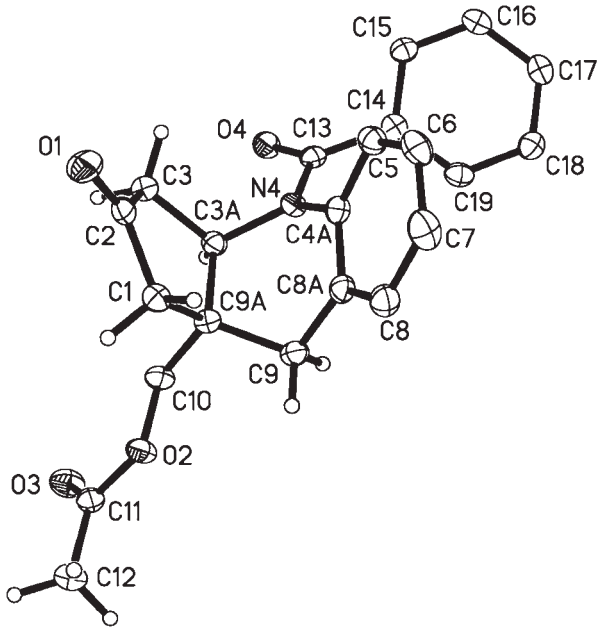
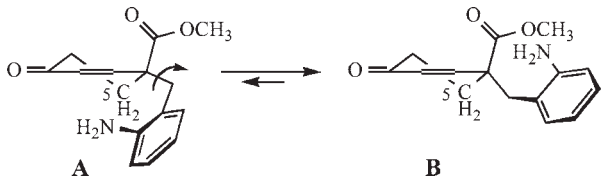


Figure 1. Molecular structure of compound **12**, with thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms on C10 and on the aromatic rings have been removed for clarity.

Scheme 3



of the ring junction was confirmed by the conversion of **11** to its solid *N*-benzoyl derivative **12** and single crystal X-ray analysis (Fig. 1).

Examination of molecular models provides some insight into the observed difference in reactivity. Following reduction of the nitro function in **7**, alignment of the amino group for addition to the enone would result in steric repulsion between the C5 methylene of the cyclohexenone and the aromatic ring as in **A** (Scheme 3). Rotation about the benzylic bond to minimize this interaction would then lead to conformation **B**, which is more prone to react at the ester carbonyl. By comparison, similar steric interference is not present in cyclopentenone **8**. Furthermore, the five-membered cyclic enone should be more reactive due to strain. Eclipsing interactions that develop in the five-membered ring of **10** during addition should not significantly deter cyclization since the starting enone also possesses considerable torsional strain. The eclipsing in the cyclized product is clearly visible in the X-ray structure of **12** (Fig. 1).

The preference for the *cis* stereochemistry of the ring junction in **10** is in accord with both strain and stereoelectronic considerations. The *cis*-fused stereochemistry would be expected based on strain arguments, with the *cis*-fused ring junction preferred over the more strained *trans* [12]. Stereoelectronically, it is well established that the *cis*-fused isomer is strongly favored in nucleophilic ring closures on pre-existing rings via an axial attack that permits a chair-like transition state [13]. Although, a true chair transition state is not possible due to the aromatic sp^2 carbons, pseudoaxial attack would still be expected to afford a *cis* product.

The reduction of the ester group in **8** is also an interesting observation. The reduction is analogous to the classical Bouveault-Blanc reaction [14], but would not be expected to occur with iron as the electron source [15]. In our substrates, the α,β-unsaturated ketone is the functional group most susceptible to reduction under dissolving metal conditions [16], and we believe that this moiety is the key to reduce the ester.

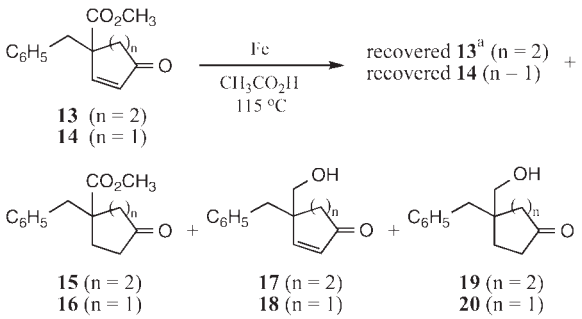
To explore this process without interference from the amino group, methyl (±)-1-benzyl-4-oxo-2-cyclohexene-1-carboxylate (**13**) and methyl (±)-1-benzyl-4-oxo-2-cyclopentene-1-carboxylate (**14**) were prepared using the method described for the nitro-bearing substrates. Treatment of **13** with iron in acetic acid for 24 h yielded a

33:67 mixture (by NMR) of starting material **13** and the double bond reduction product **15**. This ratio varied little with longer reaction times or increased amounts of iron. Similar reaction of **14** gave more interesting results, and the reaction was considerably faster. Exposure of **14** to iron in refluxing acetic acid gave nearly complete conversion to alcohol **18** in 15 min. Prolonged treatment (2 h) under the same conditions gave a 67:33 mixture (by NMR) of **18**:**20**, as the acetates, in 95% yield. These results are summarized in Scheme 4.

Mechanistically, the reduction of **13** and **14** is initiated by protonation of the enone carbonyls followed by the addition of two electrons to each conjugated system [16] to give anions **21** and **22**, respectively (Scheme 5). In **21**, the six-membered ring is conformationally flexible making the ester at C4 less accessible to attack by the anionic center at C3. Thus, protonation and tautomerization occur to give **15**. In the more rigid structure **22**, the C3 anion is closer to the C4 ester and cyclization occurs to afford the strained cyclopropanone hemiketal **23**. Under the acidic conditions of the reaction, **23** would undergo rapid proton and enol-assisted three-ring opening [17], as in **24**, followed by the loss of methanol to give aldehyde **25**. Further reduction of **25** would then afford alcohol **18** and, eventually, **20**.

The systems resulting from these ring closures have minimal precedent in the literature. The 3,3-dialkyl-3,4-dihydro-2(1*H*)-quinolinone scaffold of **9** is found in some antidepressants [18], but spiro-fused compounds have not been extensively investigated [19]. The 2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]quinoline system has been reported [20] and is known to exhibit some antipsychotic activity [21], but structures with the functional group arrangement of **10** are unknown.

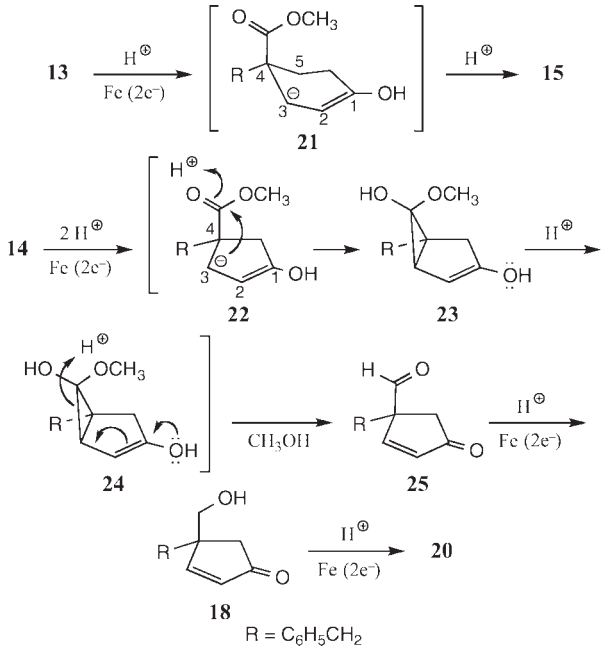
Scheme 4



Substrate	time (hours)	13	15	17	19
13 (n = 2)	24	33	67	0	0
		14	**16**	**18**	**20**
14 (n = 1)	0.25	10[b]	0	72[b]	trace
	2	0	0	67[c]	33[c]

[a] Percentages listed are from the ^{1}H NMR. [b] Isolated yields. [c] Products detected were the acetates of the indicated alcohols.

Scheme 5



CONCLUSIONS

Divergent behavior has been observed in the dissolving metal reduction–Michael reaction of two substrates differing only in the size of the ring incorporating the Michael acceptor. The disparate reaction pathways can be attributed to the differences in strain and steric environment of the enone acceptor as well as the alignment of the reacting functionality in the two systems. The reaction is clean and offers an efficient route to a relatively rare ring skeleton from each substrate. The reduction of the ester functionality in the five-membered ring substrate is novel and likely involves the participation of the enone moiety.

EXPERIMENTAL

Commercial reagents and solvents were used as received. Tetrahydrofuran was dried over potassium hydroxide pellets and distilled from lithium aluminum hydride before use. The hydrochloric acid (3*M*), ammonium chloride (saturated), sodium bicarbonate (saturated), and sodium chloride (saturated) used in workup procedures refer to aqueous solutions. All reactions were run under dry nitrogen in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech 21521). Preparative separations were performed using flash column chromatography [22] on silica gel (grade 62, 60–200 mesh) mixed with ultraviolet-

active phosphor (Sorbent Technologies No. UV-5) or thin layer chromatography on 20 cm × 20 cm silica gel GF plates (Analtech 02015); band elution was monitored using a hand-held ultraviolet lamp. Hexanes used in chromatography had a boiling range of 65–70°C. Melting points were uncorrected. Infrared spectra were run as thin films on sodium chloride disks and were referenced to polystyrene. ^{1}H- and ^{13}C-NMR spectra were measured in deuteriochloroform at 300 MHz and 75 MHz, respectively, using tetramethylsilane as the internal standard; coupling constants (J) are reported in Hertz. Low-resolution mass spectra (electron impact/direct probe) were run at 30 eV.

3-Methoxy-2-cyclohexen-1-one (2). The procedure of Sabitha *et al*. [5] was modified. A mixture of 20.0 g of silica gel (Alfa-Aesar, 220–440 mesh) and 3.60 g (9.60 mmoles) of cerium(III) chloride heptahydrate in 60 mL of dry acetonitrile was stirred for 12 h at 22°C. The acetonitrile was removed under vacuum and a solution of 5.00 g (44.6 mmoles) of **1** in 20 mL of methanol was added. The mixture was stirred for 72 h at 22°C and filtered with ethyl acetate. The filtrate was concentrated under reduced pressure, and the crude product was purified by flash chromatography on a 30 cm × 2.5 cm silica gel column eluted with 50% ethyl acetate in hexanes to give 3.70 g (90%) of **2** as a colorless oil. IR: 1671, 1645, 1605 cm^{-1}; ^{1}H-NMR: δ 5.37 (s, 1H), 3.70 (s, 3H), 2.42 (t, 2H, J = 6.4), 2.35 (t, 2H, J = 6.9), 1.98 (quintet, 2H, J = 6.6); ^{13}C-NMR: δ 199.4, 178.4, 102.1, 55.4, 36.5, 28.6, 21.0.

Methyl (±)-4-methoxy-2-oxo-3-cyclohexene-1-carboxylate (3). To a stirred solution of 2.88 g (4.00 mL, 28.6 mmoles) of diisopropylamine in 30.0 mL of tetrahydrofuran at −78°C, was slowly added 17.0 mL of 1.75*M* *n*-butyllithium in hexanes (30.0 mmoles). After 30 min, a solution of 3.00 g (23.8 mmoles) of **2** in 20.0 mL of tetrahydrofuran was added dropwise and stirring was continued at −78°C for 30 min. A solution of 3.40 g (40.0 mmoles) of methyl cyanoformate in 10 mL of tetrahydrofuran was then added dropwise and the reaction was stirred for 1 h at −78°C. The reaction mixture was slowly warmed to 22°C, stirred for 30 min, cautiously added to saturated ammonium chloride and extracted with ether. The ether extracts were washed with saturated sodium bicarbonate (one time), water (one time), and saturated sodium chloride (one time), and then dried (magnesium sulfate) and concentrated under vacuum. The crude product was purified by flash chromatography on a 100 cm × 2.5 cm silica gel column eluted with 30% ethyl acetate in hexanes to give 0.60 g (20%) of **2** and 3.20 g (73%) of **3**. The yield of **3** was 91% based on recovered starting material. IR: 1740, 1656, 1606 cm^{-1}; ^{1}H-NMR: δ 5.41 (s, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.35 (dd, 1H, J = 9.2, 5.3), 2.57 (m, 1H), 2.46 (m, 1H), 2.36 (m, 1H), 2.17 (m, 1H); ^{13}C-NMR: δ 193.5, 178.4, 170.6, 101.6, 55.8, 52.2, 52.0, 27.0, 24.0; ms: m/z 184 (M^+); *Anal*. Calcd. for $C_9H_{12}O_4$: C, 58.70; H, 6.52. Found: C, 58.77; H, 6.55.

Methyl (±)-4-methoxy-2-oxo-3-cyclopentene-1-carboxylate (4). This compound was prepared by the method of Fuchs and McGarrity [8]. The spectral data matched those reported.

Representative procedure for alkylation of 3 with 2-nitrobenzyl bromide: Methyl (±)-4-methoxy-1-(2-nitrobenzyl)-2-oxo-3-cyclohexene-1-carboxylate (5). The general procedure of Makosza and Tyrala [10] was used. A 100-mL three-necked, round-bottomed flask equipped with an addition funnel, a reflux condenser, and a magnetic stir bar was charged with 35 mL of dry acetonitrile, 4.87 g (35.2 mmoles) of anhydrous potassium carbonate, and 10 mg of 18-crown-6. Stirring was initiated and a solution of 2.16 g (11.7 mmoles) of **3** in 10 mL of acetonitrile was added dropwise at 22°C. The resulting blue solution was stirred for 10 min and a solution of 2.80 g (13.0 mmoles) of 2-nitrobenzyl bromide [9] in 10 mL of acetonitrile was added dropwise. The reaction was refluxed for 18 h at which time thin layer chromatography indicated complete consumption of **3**. The crude reaction mixture was cooled, diluted with ether, vacuum filtered, and concentrated under vacuum. The resulting dark yellow oil was purified by flash chromatography on a 100 cm × 2.5 cm silica gel column eluted with 20–30% ether in hexanes to give 3.30 g (88%) of **5** as a light yellow oil. IR: 1729, 1660, 1609, 1526, 1384, 1350 cm^{-1}; ^{1}H-NMR: δ 7.82 (dd, 1H, J = 8.2, 6.6), 7.47 (td, 1H, J = 7.5, 1.5), 7.36 (td, 1H, J = 7.9, 1.6), 7.35 (d, 1H, J = 7.0), 5.41 (d, 1H, J = 1.5), 3.87 (d, 1H, J = 14.1), 3.68 (s, 3H), 3.67 (s, 3H), 3.57 (d, 1H, J = 14.1), 2.59 (m, 1H), 2.39 (m, 1H), 2.27 (m 1H), 1.77 (m, 1H); ^{13}C-NMR: δ 193.9, 177.7, 171.1, 150.9, 133.4, 133.3, 131.5, 127.9, 124.7, 101.9, 57.0, 55.8, 52.7, 34.7, 28.3, 26.3; ms: m/z 319 (M^+). *Anal*. Calcd. for $C_{16}H_{17}NO_6$: C, 60.19; H, 5.33; N, 4.39. Found: C, 60.29; H, 5.36; N, 4.35.

Methyl (±)-4-methoxy-1-(2-nitrobenzyl)-2-oxo-3-cyclopentene-1-carboxylate (6). This compound (3.00 g, 84%) was obtained as a light yellow oil. IR: 1740, 1699, 1596, 1526, 1359 cm^{-1}; ^{1}H-NMR: δ 7.86 (dd, 1H, J = 8.1, 1.5), 7.47 (td, 1H, J = 7.5, 1.5), 7.38 (td, 1H, J = 7.9, 1.6), 7.35 (dd, 1H, J = 7.7, 1.5), 5.26 (t, 1H, J = 1.1), 3.80 (s, 3H), 3.75 (d, 1H, J = 14.6), 3.75 (s, 3H), 3.52 (d, 1H, J = 14.6), 3.17 (dd, 1H, J = 17.9, 1.1), 2.48 (dd, 1H, J = 17.9, 1.1); ^{13}C-NMR: δ 200.3, 191.0, 170.8, 150.5, 132.7, 132.2, 131.4, 128.0, 124.7, 102.0, 59.8, 59.1, 53.1, 37.0, 33.7; ms: m/z 305 (M^+). *Anal*. Calcd. for $C_{15}H_{15}NO_6$: C, 59.02; H, 4.92; N, 4.59. Found: C, 59.13; H, 4.96; N, 4.53.

Representative procedure for 1,3-carbonyl tranposition: Methyl (±)-1-(2-nitrobenzyl)-4-oxo-2-cyclohexene-1-carboxylate (7). The procedure of Luche was modified [11]. A 250-mL three-necked, round-bottomed flask equipped with a reflux condenser and a magnetic stir bar was charged with 20 mL of methanol followed by 4.60 g (12.4 mmoles) of cerium(III) chloride heptahydrate. The mixture was stirred for 10 min and a solution of 2.50 g (7.84 mmoles) of **5** in 10 mL of methanol was added dropwise. After 5 min, 1.25 g (32.9 mmoles) of sodium borohydride was added in small portions over a period of 20 min. (Note: Frothing is a problem if the added portions of sodium borohydride are too large). The reaction mixture was stirred for 15 min at which time 12 mL of 3*M* hydrochloric acid was added. After 20 min, the mixture was concentrated under vacuum to one-third its volume and extracted with ether (three times). The combined ether extracts were washed with water (three times) and saturated sodium chloride (one time), then dried (magnesium sulfate) and concentrated under vacuum. The resulting dark brown liquid was purified by flash chromatography on a 50 cm × 2.5 cm silica gel column eluted with 20–30% ether in hexanes to give 1.78 g (79%) of **7** as thick yellow oil. IR: 1732, 1685, 1609, 1528, 1351 cm^{-1}; ^{1}H-NMR: δ 7.92 (dd, 1H, J = 8.1, 1.5), 7.55 (td, 1H, J = 7.5, 1.3), 7.43 (td, 1H, J = 8.1, 1.5), 7.27 (dd, 1H, J = 7.7, 1.5), 6.82 (d, 1H, J = 10.4), 6.02 (d, 1H, J = 10.4),

3.70 (s, 3H), 3.66 (d, 1H, J = 13.8), 3.50 (d, 1H, J = 13.8), 2.45 (m, 2H), 2.36 (m, 1H), 2.06 (m, 1H); ^{13}C-NMR: δ 197.8, 172.8, 150.2, 149.0, 133.0, 132.7, 130.3, 129.7, 128.5, 125.2, 52.8, 48.6, 39.5, 34.4, 30.9; ms: m/z 289 (M^+). *Anal*. Calcd. for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.19; N, 4.84. Found: C, 62.40; H, 5.24; N, 4.76.

Methyl (±)-1-(2-nitrobenzyl)-4-oxo-2-cyclopentene-1-carboxylate (8). This compound (1.65 g, 73%) was obtained as yellow crystals, mp 103–105°C. IR: 1712, 1679, 1608, 1526, 1352 cm^{-1}; ^{1}H-NMR: δ 7.86 (dd, 1H, J = 8.2, 1.3), 7.52 (td, 1H, J = 7.5, 1.3), 7.47 (d, 1H, J = 5.7), 7.39 (td, 1H, J = 8.1, 1.5), 7.29 (dd, 1H, J = 7.7, 1.5), 6.08 (d, 1H, J = 5.7), 3.65 (s, 3H), 3.50 (d, 1H, J = 13.7), 3.17 (d, 1H, J = 13.7), 2.36 (d, 1H, J = 18.7), 2.18 (d, 1H, J = 18.7); ^{13}C-NMR: δ 208.7, 167.3 (2C), 150.1, 134.9, 133.4, 132.6, 131.2, 128.1, 125.0, 67.7, 52.3, 42.6, 36.5; ms: m/z 275 (M^+). *Anal*. Calcd. for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.73; N, 5.09. Found: C, 61.13; H, 4.74; N, 5.09.

(±)-1′,4′-Dihydrospiro[2-cyclohexene-1,3′(2′*H*)-quinoline]-2′,4-dione (9). The procedure of Bunce *et al*. was used [1]. A mixture of 500 mg (1.73 mmoles) of **7**, 25 mL of acetic acid, and 773 mg (13.8 mmoles, 8.0 equiv) of iron powder (>100 mesh) was heated with stirring at 115°C (oil bath) until thin layer chromatography indicated complete consumption of starting material (*ca*. 30 min). The reaction mixture was cooled, diluted with 50 mL of water, and extracted with ether (three times). The combined ether layers were washed with water (one time), saturated sodium bicarbonate (three times), saturated sodium chloride (one time), then dried (magnesium sulfate) and concentrated under vacuum to give 373 mg (95%) of **9** as a pale white solid, mp 212–215°C. IR: 3195, 1667 cm^{-1}; ^{1}H-NMR: δ 8.69 (br s, 1H), 7.21 (complex, 2H), 7.05 (td, 1H, J = 7.5, 1.3), 6.82 (obscured, 1H) 6.81 (d, 1H, J = 10.3), 6.14 (d, 1H, J = 10.3), 3.13 (d, 1H, J = 15.9), 2.99 (d, 1H, J = 15.9), 2.73 (ddd, 1H, J = 17.1, 8.4, 4.9), 2.49 (ddd, 1H, J = 17.1, 8.4, 4.9), 2.34 (ddd, 1H, J = 13.4, 8.4, 4.9), 1.98 (ddd, 1H, J = 13.4, 8.4, 4.9); ^{13}C-NMR: δ 198.2, 172.1, 148.9, 136.1, 130.7, 128.6, 128.2, 123.7, 121.1, 115.2, 42.6, 36.6, 33.6, 29.4; ms: m/z 227 (M^+). *Anal*. Calcd. for $C_{14}H_{13}NO_2$: C, 74.01; H, 5.73; N, 6.17. Found: C, 74.00; H, 5.71; N, 6.20.

(±)-(3a*R, 9a*R**)-9a-Hydroxymethyl-1,3,3a,4,9,9a-hexahydro-2*H*-cyclopenta[*b*]quinolin-2-one (10).** The procedure used to prepare **9** was followed using 200 mg (0.73 mmoles) of **8** and 325 mg (5.84 mmoles) of iron powder in 12 mL of acetic acid. After 30 min at 115°C, workup and preparative thin layer chromatography using 40% ether in hexanes gave 120 mg (76%) of **10** as a light yellow oil. IR: 3395, 1733 cm^{-1}; ^{1}H-NMR: δ 7.01 (td, 1H, J = 7.3, 1.2), 6.98 (dd, 1H, J = 7.5, 0.8), 6.64 (td, 1H, J = 7.3, 1.2), 6.48 (dd, 1H, J = 7.9, 0.8), 3.92 (br s, 1H), 3.94 (t, 1H, J = 6.4), 3.59 (d, 1H, J = 10.9), 3.55 (d, 1H, J = 10.9), 2.74 (d, 1H, J = 16.7), 2.69 (obscured, 2H), 2.65 (d, 1H, J = 16.7), 2.37 (d, 1H, J = 18.7), 2.17 (dd, 1H, J = 18.7, 1.6), 2.20 (m, 1H); ^{13}C-NMR: δ 216.6, 141.7, 129.6, 127.4, 117.5, 117.4, 113.4, 66.6, 52.0, 46.4, 45.9, 41.3, 31.3; ms: m/z 217 (M^+). *Anal*. Calcd. for $C_{13}H_{15}NO_2$: C, 71.89; H, 6.91; N, 6.45. Found: C, 71.96; H, 6.95; N, 6.40. This reaction also gave 26 mg (14%) of compound **11**.

(±)-(3a*R, 9a*R**)-9a-Acetoxymethyl-1,3,3a,4,9,9a-hexahydro-2*H*-cyclopenta[*b*]quinolin-2-one (11).** The procedure used to prepare **9** was followed using 500 mg (1.82 mmoles) of **8** and 812 mg (14.6 mmoles) of iron powder in 30 mL of acetic acid. After 4 h at 115°C, workup and flash chromatography on a 25 cm × 2 cm silica gel column using 15% ether in hexanes gave 400 mg (85%) of **10** as a tan oil. IR: 3394, 1740 cm^{-1}; ^{1}H-NMR: δ 7.05 (m, 2H), 6.66 (td, 1H, J = 7.5, 1.3), 6.50 (dd, 1H, J = 7.8, 0.8), 4.10 (br s, 1H), 4.08 (d, 1H, J = 11.4), 4.02 (d, 1H, J = 11.4), 3.92 (t, 1H, J = 6.4), 2.80 (d, 1H, J = 16.5), 2.70 (d, 1H, J = 16.5), 2.70 (m, 1H), 2.27 (m, 2H), 2.21 (dd, 1H, J = 5.4, 1.1), 2.06 (s, 3H); ^{13}C-NMR: δ 214.9, 170.8, 141.4, 129.7, 127.6, 117.7, 116.8, 113.5, 67.6, 52.4, 46.3, 46.0, 39.6, 31.5, 20.8; ms: m/z 259 (M^+). *Anal*. Calcd. for $C_{15}H_{17}NO_3$: C, 69.50; H, 6.56; N, 5.41. Found: C, 69.52; H, 6.55; N, 5.39.

(±)-(3a*R, 9a*R**)-9a-Acetoxymethyl-4-benzoyl-1,3,3a,4,9,9a-hexahydro-2*H*-cyclopenta[*b*]quinolin-2-one (12).** To a stirred solution of 200 mg (0.77 mmoles) of **11** and 85.6 mg (0.85 mmoles) of triethylamine in 20 mL of dichloromethane, a solution of 120 mg (0.85 mmoles) of benzoyl chloride in 1 mL of dichloromethane was slowly added over a period of 5 min. The reaction mixture was stirred at 22°C for 2 h at which time thin layer chromatography confirmed the absence of starting material. The reaction mixture was poured into cold water and the dichloromethane layer was separated. The organic phase was washed with cold water (two times), dried (magnesium sulfate) and concentrated under vacuum. The resulting residue was passed through a small plug of silica gel with 30% ether in hexanes to give 260 mg (93%) of **12** as a light yellow solid, mp 108–110°C. IR: 1744, 1643 cm^{-1}; ^{1}H-NMR: δ 7.38–7.21 (complex, 6H), 7.07 (td, 1H, J = 7.5, 1.1), 6.93 (t, 1H, J = 7.5), 6.49 (d, 1H, J = 7.9), 5.19 (dd, 1H, J = 9.0, 4.4), 4.28 (d, 1H, J = 10.9), 4.20 (d, 1H, J = 10.9), 3.04 (ddd, 1H, J = 19.4, 9.0, 1.8), 2.94 (d, 1H, J = 14.1), 2.73 (d, 1H, J = 14.1), 2.29 (ddd, 1H, J = 19.4, 4.4, 1.8), 2.20 (dd, 1H, J = 18.5, 1.8), 2.10 (s, 3H), 2.06 (dd, 1H, J = 18.5, 1.8); ^{13}C-NMR: δ 214.1, 170.7, 169.8, 138.1, 134.8, 130.8, 130.6, 129.1, 129.0, 128.1, 127.4, 126.9, 126.1, 71.1, 57.4, 47.9, 45.6, 45.2, 34.6, 20.7; ms: m/z 363 (M^+). *Anal*. Calcd. for $C_{22}H_{21}NO_4$: C, 72.73; H, 5.79; N, 3.86. Found: C, 73.71; H, 5.79; N, 3.88.

X-ray crystallographic analysis of 12. Flat, elongated rods of **12** were obtained by slow diffusion of pentane into an ether solution of the compound. A sample measuring 0.4 mm × 0.4 mm × 0.1 mm, which was cut from a longer rod, was immersed in polyisobutylene and placed in a nylon loop under a nitrogen cold stream. X-ray intensity data were measured at 115(2) K on a Bruker SMART Apex II diffractometer. Graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å, fine-focus sealed tube) was used with the CCD detector placed 6.0 cm from the sample. Data frames were collected in a series of φ and ω scans with 0.5° scan widths and 30-s exposure times. Data integration used the Bruker SAINT software package [23]. Data were corrected for absorption effects using the multiscan technique (SADABS) [24]. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 using the Bruker SHELXTL software suite [25]. Non-hydrogen atoms were assigned anisotropic temperature factors. Hydrogen atoms were placed in calculated positions based on the geometry at carbon (riding model). Refined formula: $C_{22}H_{21}NO_4$, M = 363.40, monoclinic, space group $P2_1/n$, a = 11.1983(2) Å, b = 8.18310(10) Å, c = 19.7453(3) Å, β = 101.7010(10)°, U = 1771.80(5) Å^3, Z = 4, D_c = 1.362 g/cm, μ = 0.094 mm^{-1},

T = 115(2) K, $2\theta_{max}$ = 50.6°, completeness to $2\theta_{max}$ = 100.0%, 13372 total reflections, 3227 independent (R_{int} = 0.0248), 2619 observed [$I > 2\sigma(I)$]. Final $R1$ [$I > 2\sigma(I)$] = 0.0336, $wR2$ (all data) = 0.0833, largest difference peak and hole 0.225 and −0.194 eÅ^{-3}. CCDC 692896 contains the supplementary crystallographic data for compound **12**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Methyl (±)-4-benzyl-2-oxo-3-cyclohexene-1-carboxylate (13). The procedure used to prepare **5** was followed using 1.08 g (5.85 mmoles) of **3** and 1.11 g (6.5 mmoles) of benzyl bromide. Following flash chromatography, 1.52 g (95%) of methyl (±)-1-benzyl-4-methoxy-2-oxo-3-cyclohexene-1-carboxylate was isolated as a white solid, mp 68–70°C. IR: 1729, 1660, 1610 cm^{-1}; ^{1}H-NMR: δ 7.28–7.17 (complex, 3H), 7.14 (m, 2H), 5.41 (d, 1H, J = 1.2), 3.71 (s, 3H), 3.66 (s, 3H), 3.32 (d, 1H, J = 13.7), 3.23 (d, 1H, J = 13.7), 2.63 (m, 1H), 2.29 (m, 2H), 1.80 (m, 1H); ^{13}C-NMR: δ 194.4, 177.8, 171.5, 136.5, 130.4, 128.1, 126.7, 101.9, 56.9, 55.7, 52.4, 40.0, 28.1, 26.3; ms (30 eV): m/z 274 (M^+); *Anal*. Calcd. for $C_{16}H_{18}O_4$: C, 70.07; H, 6.57. Found: C, 70.12; H, 6.59.

Reduction and carbonyl transposition were carried out as described for the preparation of **7** using 1.52 g (5.56 mmoles) of the benzylated product from the earlier procedure. Following flash chromatography, 1.22 g (90%) of **13** was isolated as a colorless oil. IR: 1732, 1682 cm^{-1}; ^{1}H-NMR: δ 7.32–7.22 (complex, 3H), 7.09 (dd, 1H, J = 7.8, 1.8), 6.95 (d, 1H, J = 10.3), 6.02 (d, 1H, J = 10.3), 3.69 (s, 3H), 3.08 (s, 2H), 2.47 (m, 2H), 2.40 (m, 1H), 2.07 (m, 1H); ^{13}C-NMR: δ 198.3, 173.2, 150.3, 135.4, 129.8, 129.2, 128.4, 127.2, 52.3, 49.0, 44.5, 34.5, 30.5; ms: m/z 244 (M^+); *Anal*. Calcd. for $C_{15}H_{16}O_3$: C, 73.77; H, 6.56. Found: C, 73.81; H, 6.60.

Methyl (±)-4-benzyl-2-oxo-3-cyclopentene-1-carboxylate (14). The procedure used to prepare **5** was followed using 0.99 g (5.85 mmoles) of **4** and 1.11 g (6.50 mmoles) of benzyl bromide. Following flash chromatography, 1.46 g (96%) of methyl (±)-1-benzyl-4-methoxy-2-oxo-3-cyclopentene-1-carboxylate was isolated as white solid, mp 96–98°C. IR: 1741, 1699, 1597 cm^{-1}; ^{1}H-NMR: δ 7.27–7.17 (complex, 3H), 7.13 (m, 2H), 5.18 (s, 1H), 3.76 (2s, 6H), 3.30 (d, 1H, J = 14.1), 3.25 (d, 1H, J = 14.1), 3.11 (dd, 1H, J = 17.7, 1.0), 2.61 (dd, 1H, J = 17.7, 1.0); ^{13}C-NMR: δ 200.6, 190.3, 171.0, 136.2, 130.0, 128.2, 126.9, 102.3, 60.1, 59.0, 52.9, 39.1, 36.5; ms: m/z 260 (M^+). *Anal*. Calcd for $C_{15}H_{16}O_4$: C, 69.23; H, 6.15. Found: C, 69.29; H, 6.17.

Reduction and carbonyl transposition were carried out as described for the preparation of **7** using 1.46 g (5.62 mmoles) of the benzylated product from the earlier procedure. Following flash chromatography, 1.16 g (90%) of **14** was isolated as a colorless oil. IR: 1710, 1677 cm^{-1}; ^{1}H-NMR: δ 7.54 (d, 1H, J = 5.7), 7.32–7.20 (complex, 3H), 7.13 (m, 2H), 6.14 (d, 1H, J = 5.7), 3.62 (s, 3H), 2.97 (d, 1H, J = 13.3), 2.84 (d, 1H, J = 13.3), 2.29 (s, 2H); ^{13}C-NMR: δ 209.0, 168.2 (2C), 136.4, 134.7, 130.2, 128.3, 126.8, 67.3, 51.7, 43.0, 41.5; ms: m/z 230 (M^+). *Anal*. Calcd. for $C_{14}H_{14}O_3$: C, 73.04; H, 6.09. Found: C, 73.10; H, 6.12.

Reduction of 13 with iron and acetic acid: Methyl 1-benzyl-4-oxocyclohexane-1-carboxylate (15). The procedure used to prepare **9** was followed using 500 mg (2.05 mmoles) of **13** and 915 mg (16.4 mmoles) of iron powder in 35 mL of acetic acid. After 24 h, workup gave 450 mg of an inseparable 33:67 mixture of **13**:**15**. The spectral data for **15** were: IR: 1727, 1702 cm^{-1}; ^{1}H-NMR: δ 7.36–7.27 (complex, 3H), 7.12 (m, 2H), 3.77 (s, 3H), 2.96 (s, 2H), 2.56–2.33 (complex, 6H), 1.78 (m, 2H); ^{13}C-NMR: δ 210.4, 174.8, 129.4, 128.1, 127.9, 126.6, 51.6, 47.5, 45.6, 38.1, 33.1. The use of more iron and longer reaction times failed to significantly alter this product ratio.

Reduction of 14 with iron and acetic acid: (±)-4-Benzyl-4-hydroxymethyl-2-cyclopenten-1-one (18). The procedure used to prepare **9** was followed using 500 mg (2.17 mmoles) of **14** and 969 mg (17.3 mmoles) of iron powder in 35 mL of acetic acid. After 15 min, workup and preparative thin layer chromatography gave 320 mg (72%) of **18** as a colorless oil. IR: 3416, 1711, 1677 cm^{-1}; ^{1}H-NMR: δ 7.53 (d, 1H, J = 5.7), 7.30–7.21 (complex, 3H), 7.10 (d, 2H, J = 6.8), 6.11 (d, 1H, J = 5.7), 3.60 (d, 1H, J = 10.7), 3.58 (d, 1H, J = 10.7), 2.96 (d, 1H, J = 13.5), 2.81 (d, 1H, J = 13.5), 2.62 (br s, 1H), 2.29 (d, 1H, J = 18.6), 2.26 (d, 1H, J = 18.6); ^{13}C-NMR: δ 209.5, 168.7, 136.3, 134.4, 130.1, 128.2, 126.7, 67.0, 51.8, 42.9, 41.3; ms: m/z 111 (M^+-C_7H_7). *Anal*. Calcd. for $C_{13}H_{14}O_2$: C, 77.23; H, 6.93. Found: C, 77.29; H, 6.97. This reaction also afforded 10% of recovered **14**.

Upon prolonged heating for 2 h, the reaction gave 450 mg of an inseparable 67:33 mixture of **18**:**20** as the acetates. The spectral data for **18** (acetate): IR: 1743, 1715 cm^{-1}; ^{1}H-NMR: δ 7.46 (d, 1H, J = 5.7), 7.33–7.17 (complex, 3H), 7.09 (m, 2H), 6.13 (d, 1H, J = 5.7), 4.17 (d, 1H, J = 10.9), 4.00 (d, 1H, J = 10.9), 2.96 (d, 1H, J = 13.7), 2.84 (d, 1H, J = 13.6), 2.31 (s, 2H), 2.06 (s, 3H); ^{13}C-NMR: δ 207.6, 170.6, 166.7, 135.5, 134.6, 130.0, 128.4, 127.0, 67.7, 49.4, 43.0, 42.0, 20.7. The spectral data for **20** (acetate): 1743 cm^{-1}; ^{1}H-NMR: δ 7.34–7.18 (complex, 3H), 7.10 (m, 2H), 3.98 (d, 1H, J = 11.1), 3.89 (d, 1H, J = 11.1), 2.79 (s, 2H), 2.39–2.21 (complex, 2H), 2.33 (s, 2H), 2.10 (s, 3H), 1.93 (m, 2H); ^{13}C-NMR: δ 217.5, 170.7, 136.6, 130.0, 128.3, 126.7, 68.4, 47.0, 43.6, 42.3, 36.3, 30.2, 20.8.

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