Diastereoselective Synthesis of Substituted Tetrahydroquinoline-4-carboxylic Esters by a Tandem Reduction−Reductive Amination Reaction

Richard A. Bunce,* Derrick M. Herron,[1] Lara B. Johnson, and Sharadsrikar V. Kotturi

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74078-3071

rab@okstate.edu

Received December 20, 2000

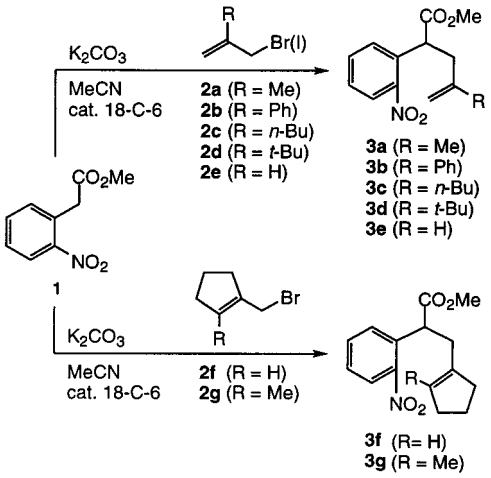
A diastereoselective synthesis of 1-methyl-2-alkyl- and 2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylic esters has been developed from methyl (2-nitrophenyl)acetate (**1**). The method involves alkylation of **1** with an allylic halide, ozonolysis of the double bond, and catalytic hydrogenation. The final hydrogenation initiates a tandem sequence involving (1) reduction of the aromatic nitro group, (2) condensation of the aniline or hydroxylamine[8] nitrogen with the side chain carbonyl, (3) reduction of the resulting nitrogen intermediate, and (4) reductive amination of the tetrahydroquinoline with formaldehyde produced in the ozonolysis to give a methyl (±)-1-methyl-2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylate. Removal of the formaldehyde prior to hydrogenation gives the simple (±)-2-alkyl derivatives. The products are isolated in high yield as single diastereomers having the C-2 alkyl group cis to the C-4 carboxylic ester. The reaction has been extended to the synthesis of tricyclic structures with similar high diastereoselection.

Introduction

The tetrahydroquinoline nucleus is found in a wide range of biologically active compounds[2] and is an important building block for more complex natural products. Previous work from this laboratory described a tandem reduction−Michael addition reaction for the synthesis of tetrahydroquinoline-2-acetic esters.[3] In the current study, we have investigated the reduction-reductive amination[4] of several methyl (2-nitrophenyl)acetate derivatives to give 1,2,3,4-tetrahydroquinoline-4-carboxylic esters and found that the reaction occurs with remarkable selectivity. We report here a diastereoselective synthesis of (±)-1-methyl-2-alkyl- and (±)-2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylic esters using this tandem reaction strategy.

Synthesis of the Cyclization Substrates. Cyclization substrates **3a**−**g** were prepared by alkylation of methyl (2-nitrophenyl)acetate (**1**)[5] with allylic halides **2a**−**g**, respectively. This reaction was most easily carried out using potassium carbonate in dry acetonitrile containing catalytic 18-crown-6 (Scheme 1).[6] The yields ranged from 56 to 93%. The use of nitroaromatic precursors had the advantage of permitting the synthesis of starting compounds without interference from basic nitrogen.

Scheme 1



Results and Discussion

Our initial experiments focused on attempts to carry out an ozonolysis-reduction-reductive amination sequence without isolation of any intermediates. Treatment of methyl (±)-4-methyl-2-(2-nitrophenyl)-4-pentenoate (**3a**) with ozone in methanol[7] at −78 °C followed immediately by hydrogenation at 4 atm over 5% Pd/C gave methyl (±)-1,2-dimethyl-1,2,3,4-tetrahydroquinoline-4-carboxy-

(1) Undergraduate research participant, 1999−2001.

(2) See, for example: (a) Kohno, Y.; Kojima, E. European Patent, EP 403, 980; *Chem. Abstr.* **1990**, *114*, 207056r. (b) Nagata, R.; Tanno, N.; Kodo, T.; Ae, N.; Yamaguchi, H.; Nishimura, T.; Antoku, F.; Tatsuno, T.; Kato, T.; Tanaka, Y.; Nakamura, M.; Ogita, K.; Yoneda, Y. *J. Med. Chem.* **1994**, *37*, 3956−3968. (c) Guarna, A.; Occhiato, E. G.; Scarpi, D.; Tsai, R.; Danza, G.; Comerci, A.; Mancina, R.; Serio, M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2871−2876.

(3) Bunce, R. A.; Herron, D. M.; Ackerman, M. L. *J. Org. Chem.* **2000**, *65*, 2847−2850.

(4) Earlier uses of the reduction−reductive amination sequence on nitroaromatics have appeared, but few cases have used catalytic hydrogenation. See, for example: (a) Rylander, P. N. *Hydrogenation Methods*; Academic Press: New York, 1985; pp 82−93. (b) Artico, M.; DeMartino, G.; Filacchioni, G.; Giuliano, R. *Farmaco, Ed. Sci.* **1969**, *24*, 276−284; *Chem Abstr.* **1970**, *70*, 96775a.

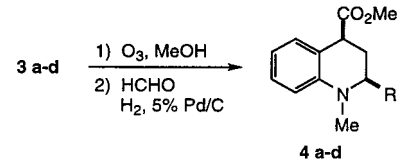
(5) Commercially available 2-nitrophenylacetic acid was esterified using MeOH/HCl (g); see: Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman: New York, 1989; p 700.

(6) Makosza, M.; Tyrala, A. *Synth. Commun.* **1986**, *16*, 419−423.

(7) (a) Bunce, R. A.; Pierce, J. D. *Org. Prep. Proced. Int.* **1987**, *19*, 67−71. (b) See ref 3.

10.1021/jo001761n CCC: $20.00
Published on Web 03/16/2001

Scheme 2



4 a-d

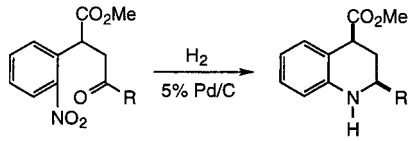
substrate	R	product	yield (%)
3a	Me	**4a**	80
3b	Ph	**4b**	73
3c	*n*-Bu	**4c**	76
3d	*t*-Bu	**4d**	74

late (**4a**) in 36% yield. This process involves (1) reduction of the aromatic nitro group, (2) condensation of the aniline or hydroxylamine[8] nitrogen with the side chain carbonyl, (3) reduction of the resulting nitrogen intermediate and (4) reductive amination of the tetrahydroquinoline with formaldehyde produced in the ozonolysis. The initial modest yield was readily increased to 80% by addition of excess aqueous formaldehyde (3−4 equiv) prior to the hydrogenation. NMR analysis of the product indicated that the reaction had yielded exclusively the diastereomer having the C-2 methyl group cis to the C-4 carboxylic ester;[9] none of the trans isomer was detected by ^{1}H NMR. This diastereoselectivity presumably results from steric hindrance created by the ester group which directs the hydrogenation to the opposite face of the molecule. The reaction was applied to substrates **3b**−**d** to give products **4b**−**d**, respectively, in 73−76% yield (Scheme 2). Interestingly, reduction of the phenyl ketone[10] in **3b** did not compete significantly with the tandem reaction sequence.

It was also possible to generate compounds without alkyl substitution at nitrogen. This variant required removal of the formaldehyde produced in the ozonolysis reaction prior to reduction. To accomplish this, the crude ozonolysates from **3a**−**d** in methanol were treated with *p*-toluenesulfonic acid (*p*-TsOH) before workup to afford ketones **5a**−**d** in 89−95% yield.[11] Catalytic hydrogenation of **5a**−**d** then gave the methyl (±)-*cis*-2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylates **6a**−**d**, respectively, in 93−99% yield (Scheme 3).

In substrate **3e**, where the ozonolysis produced an aldehyde, it was necessary to modify the procedure in order to obtain high yields of the heterocycle. Following ozonolysis in methanol, treatment with *p*-TsOH gener-

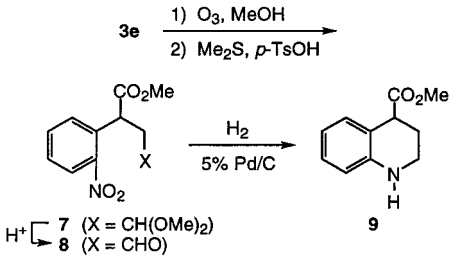
Scheme 3



5a-d 6 a-d

substrate	R	product	yield (%)
5a	Me	**6a**	98
5b	Ph	**6b**	97
5c	*n*-Bu	**6c**	99
5d	*t*-Bu	**6d**	93

Scheme 4



ated the aldehyde dimethyl acetal **7**. This compound was more easily isolated from the ozonolysate than the aldehyde.[12] To continue the sequence, **7** was treated with 3% aqueous $HClO_4$ in THF (1:1 v/v)[12] until TLC indicated complete conversion to the aldehyde **8**. Neutralization and workup, followed by catalytic hydrogenation, then afforded methyl (±)-1,2,3,4-tetrahydroquinoline-4-carboxylate **9** in 88% overall yield (Scheme 4).

This procedure was further extended to the synthesis of 2,3,4,4a,5,6-hexahydro-1*H*-benzo[*c*]quinolizine-6-carboxylic esters **12** and **14** from **3f** and **3g**, respectively.[13] For **3f**, ozonolysis followed by treatment with *p*-TsOH gave the keto acetal **10**. Hydrolysis of the acetal using 3% aqueous $HClO_4$ in THF regenerated the aldehyde **11**, and hydrogenation afforded the angular-fused tricyclic product **12** in 65% overall yield. In accordance with the simpler systems, the ring methylene was cis to the ester group in the final product. In the case of **3g**, a similar sequence gave the expected angular-fused product **14** as a single diastereomer in 60% overall yield along with minor amounts of the linear-fused product **15** (6%) and the single-cyclization product **16** (2%) (Scheme 5). A NOESY spectrum[14] of **14** established the cis relationship of the ester group, the ring methylene and the methyl substituent through correlation of H_a and H_c with H_b which are nearly 1,3-diaxial to each other. Thus, the ester

(8) There is substantial evidence to suggest that the primary reaction pathway does not involve the aniline, but rather a hydroxylamine; see: Emerson, W. S.; Uraneck, C. A. *J. Am. Chem. Soc.* **1941**, *63*, 749−751. The aniline may also be involved, but to a much lesser extent.

(9) Similar selectivity has been previously observed in hydrogenations of substituted quinolines, see Carling, R. W.; Leeson, P. D.; Moseley, A. M.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R. *J. Med. Chem.* **1992**, *35*, 1942−1953.

(10) (a) Rylander, P. N. *Catalytic Hydrogenation in Organic Syntheses*; Academic Press: New York, 1979; pp 100−102. (b) Hudlicky, M. *Reductions in Organic Chemistry*, 2nd ed.; American Chemical Society: Washington, DC, 1996; pp 155−156. (c) Reduction of the phenyl ketone was the major reaction path when a similar reductive ring closure was attempted with a nitroalkane precursor, Bunce, R. A.; Moore, J. D. Unpublished results.

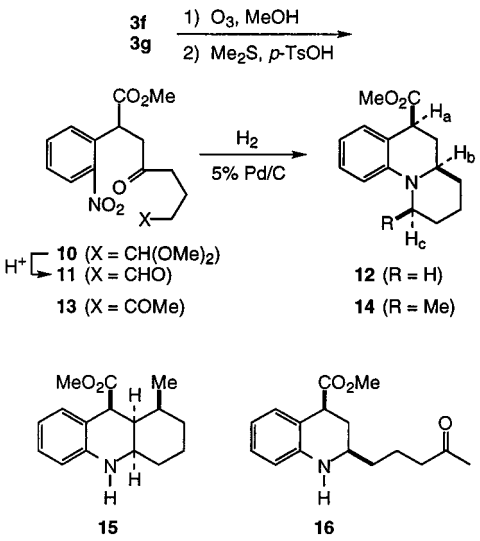
(11) Similar results were achieved by alkylating **1** with chloroacetone under the same reaction conditions (K_2CO_3, 18-C-6, MeCN, 40−50 °C), but the yield was only 56%. Beyond the lower yield, two other factors limited this approach: (1) the α-chloroketones were less readily available, and (2) phenacyl chloride derivatives failed to give the desired alkylation products.

(12) Hudlicky, T.; Ranu, B. C.; Naqvi, S. M.; Srnak, A. *J. Org. Chem.* **1985**, *50*, 123−127.

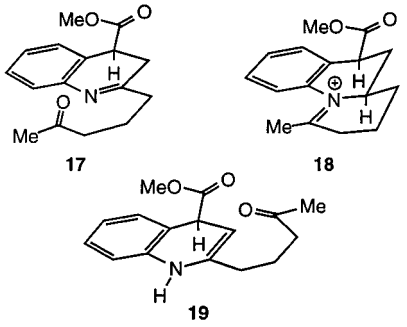
(13) Reductive aminations have been used previously in double ring closures, but from amines and ammonium salts using $NaCNBH_3$; see: (a) Borch, R. F.; Ho, B. C. *J. Org. Chem.* **1977**, *42*, 1225−1227. (b) Jones, T. H.; Franko, J. B.; Blum, M. S.; Fales, H. M. *Tetrahedron Lett.* **1980**, *21*, 789−792. (c) Jones, T. H.; Blum, M. S.; Fales, H. M.; Thompson, C. R. *J. Org. Chem.* **1980**, *45*, 4778−4780. (d) Stevens, R. V.; Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 102−103 and 103−104. (e) Kawaguchi, M.; Ohashi, J.; Kawakami, Y.; Yamamoto, Y.; Oda, J. *Synthesis* **1985**, 701−703. (f) Fray, A. H.; Augeri, D. J.; Kleinman, E. F. *J. Org. Chem.* **1988**, *53*, 896−899. (g) Shawe, T. T.; Sheils, C. J.; Gray, S. M.; Conard, J. L. *J. Org. Chem.* **1994**, *59*, 5841−5842.

(14) Neuhaus, D.; Williamson, M. P. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH: New York, 1989; pp 253−306.

Scheme 5



Scheme 6



group serves to direct the hydrogenation for both reductive aminations (via **17** and **18**)[15] in the sequence that gives **14** (Scheme 6).

One final observation on the reduction-double reductive amination process was that a relatively large amount of catalyst was needed. During our experiments to optimize the reaction of **13**, efficiency was lost when less than 20 wt % of catalyst was used. As the reaction proceeds, the catalyst is apparently deactivated[16] such that it promotes competitive formation of **15** and **16**. Product **15** (structure confirmed by NOESY) results from tautomerization of the initial imine **17** to the enamine **19**[17] which adds to the side chain ketone (Scheme 6). Compound **16** results from reduction of the nitro group followed by a single ring closure. These side products were formed in variable quantities depending on the reaction scale and the amount of catalyst used. When sufficient catalyst was present, however, **15** and **16** totaled less than 10% of the product.

Conclusion

A new synthetic approach to (±)-1-methyl-2-alkyl- and (±)-2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylic esters has been developed. The key step of the synthesis is a tandem reaction sequence triggered by reduction of the aromatic nitro group in an α-substituted methyl (2-nitrophenyl)acetate derivative. In substrates where the α-substituent incorporates a ketone at C-2, reduction of the final iminium intermediate[15] is highly diastereoselective, giving products derived from hydrogen addition to the molecular face opposite the ester group. This results in a cis relationship between the C-2 alkyl and the C-4 ester group in the product heterocycle. The method has been extended to the closure of fused tricyclic structures by a reduction-double reductive amination with similar high diastereoselection. We are continuing our work to explore asymmetric induction as well as other substitution patterns in this reaction.

Experimental Section

Commercial reagents and solvents were used as received. Potassium carbonate was ground to a fine powder, dried under vacuum at 120 °C for 24 h and stored in an oven at 120 °C. The allylic halides were prepared by the following methods: 3-iodo-2-methylpropene (**2a**) was prepared by treating commercial 3-chloro-2-methylpropene with NaI in acetone; 3-bromo-2-phenylpropene (**2b**)[18] and 3-bromo-2-*tert*-butylpropene (**2d**)[19] were prepared by literature procedures; 3-bromo-2-butylpropene (**2c**) was prepared by addition of HBr to 1-hexyne,[20] Grignard reaction with HCHO (g), and treatment with PBr_3 (38% overall yield); 3-bromo-propene (**2e**) was commercial; 1-(bromomethyl)-1-cyclopentene (**2f**) was prepared from 1-cyclopentene-1-carboxaldehyde[21a] by reduction with $LiAlH_4$ followed by treatment with PBr_3[21b] (70% overall yield); 1-(bromomethyl)-2-methyl-1-cyclopentene (**2g**) was prepared from 2-methyl-1-cyclopentene-1-carboxaldehyde[22a] using the literature procedure.[22b]

All reactions were run under dry N_2 in oven-dried glassware. The HCl (0.2, 1, and 6 M), NaOH (0.2 and 1 M), $NaHCO_3$ (saturated), and NaCl (saturated) used in various procedures refer to aqueous solutions. Reactions were monitored by TLC on silica gel GF plates or capillary GC (SE-30 column, 6 m × 0.25 mm i.d., 0.25 μm film thickness) with FI detection programmed between 50 and 300 °C. Preparative separations were performed using flash column chromatography[23] on silica gel (grade 62, 60−200 mesh) mixed with Sylvania no. 2282 UV-active phosphor or PTLC on 20-cm × 20-cm silica gel GF plates; band elution was monitored using a hand-held UV lamp. Melting points were uncorrected. IR spectra were run as thin films on NaCl disks and were referenced to polystyrene. ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 and 75 MHz, respectively, and were referenced to internal $(CH_3)_4Si$. NOESY spectra were recorded at 400 MHz. High-resolution mass spectra (HRMS, EI/DP) were obtained at 70 eV.

Representative Procedure for Alkylation of Methyl (2-Nitrophenyl)acetate: Methyl (±)-4-Methyl-2-(2-nitrophenyl)-4-pentenoate (3a). The general procedure of Makosza and Tyrala was used.[6] To a stirred solution of 1.95 g (10.0 mmol) of **1** in 50 mL of dry MeCN was added 11.6 g (84.1 mmol) of anhydrous K_2CO_3 and 15 mg of 18-crown-6. To the

(15) Imine and iminium intermediates are pictured in Scheme 6, but the reaction may actually involve hydroxylamine or enamine structures; see ref 8.

(16) (a) Freifelder, M. *Practical Catalytic Hydrogenation Techniques and Applications*; Wiley-Interscience: New York, 1971; pp 39−47. (b) See ref 10b, p 12.

(17) A double bond-migrated enamine has been isolated from a similar substrate in one of our other projects: Bunce, R. A. Unpublished results.

(18) Zimmerman, H. E.; Bunce R. A. *J. Org. Chem.* **1982**, *47*, 3377−3396.

(19) Dauben, W. G.; Cogen, J. M.; Ganzer, G. A.; Behar, V. *J. Am. Chem. Soc.* **1991**, *113*, 5817−5824.

(20) Cousseau, J. *Synthesis* **1980**, 805−806.

(21) (a) Preparation of 1-cyclopentene-1-carboxaldehyde: Brown, J. B.; Henbest, H. B.; Jones, E. R. H. *J. Chem. Soc.* **1950**, 3634−3641. (b) Conversion to the bromide: adapted from Borowiecki, L.; Kazubski, A. *Pol. J. Chem.* **1978**, *52*, 1447−1455.

(22) (a) Preparation of 2-methyl-1-cyclopentene-1-carboxaldehyde: See ref 12. (b) Conversion to the bromide: Ziegler, F. E.; Nangia, A.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 3987−3991.

(23) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

resulting blue mixture was added a solution of 2.18 g (12.0 mmol) of **2a** in 5 mL of MeCN. The reaction was stirred at reflux for 8 h, then cooled to room temperature. The solids were removed by filtration and the filtrate was concentrated under vacuum. The remaining oil was purified by flash chromatography on a 30 cm × 2 cm silica gel column eluted with increasing concentrations of ether in hexanes to give 2.28 g (9.19 mmol, 92%) of **3a** as a light yellow oil. The spectral and analytical data matched those reported previously.[3]

Methyl (±)-4-phenyl-2-(2-nitrophenyl)-4-pentenoate (3b): 1.05 g (3.38 mmol, 56%); IR 1744, 1635, 1530, 1352 cm^{-1}; ^1H NMR δ 7.88 (d, J = 8.0 Hz, 1 H), 7.53 (t, J = 7.7 Hz, 1 H), 7.41−7.24 (complex, 7 H), 5.19 (s, 1 H), 4.94 (s, 1 H), 4.29 (dd, J = 8.3, 6.6 Hz, 1 H), 3.63 (s, 3 H), 3.53 (dd, J = 13.7, 6.6 Hz, 1 H), 3.03 (dd, J = 13.7, 8.3 Hz, 1 H); ^{13}C NMR δ 172.5, 149.6, 145.1, 139.9, 132.9 (2), 131.1, 128.4, 128.2, 127.8, 126.2, 124.8, 115.4, 52.2, 46.0, 38.2; HRMS m/z calcd for $C_{18}H_{17}NO_4$ 311.1157, found 311.1154.

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.45; H, 5.47. Found: C, 69.66; H, 5.48.

Methyl (±)-4-butyl-2-(2-nitrophenyl)-4-pentenoate (3c): 1.52 g (5.22 mmol, 84%); IR 1744, 1646, 1532, 1354 cm^{-1}; ^1H NMR δ 7.87 (d, J = 7.8 Hz, 1 H), 7.57 (m, 2 H), 7.41 (m, 1 H), 4.75 (s, 1 H), 4.66 (s, 1 H), 4.47 (dd, J = 8.0, 7.1 Hz, 1 H), 3.67 (s, 3 H), 2.87 (dd, J = 14.7, 8.0 Hz, 1 H), 2.54 (dd, J = 14.7, 7.1 Hz, 1 H), 2.00 (t, J = 7.3 Hz, 2 H), 1.42 (complex, 4 H), 0.89 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 172.9, 149.4, 145.9, 133.1, 132.9, 129.9, 128.1, 124.7, 111.7, 52.3, 44.5, 39.1, 35.5, 29.8, 22.3, 13.9; HRMS m/z calcd for $C_{16}H_{21}NO_4$ 291.1470, found 291.1470.

Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.98; H, 7.22. Found: C, 66.09; H, 7.25.

Methyl (±)-4-*tert*-butyl-2-(2-nitrophenyl)-4-pentenoate (3d): 1.48 g (5.09 mmol, 82%); IR 1745, 1645, 1530, 1353 cm^{-1}; ^1H NMR δ 7.87 (d, J = 7.8 Hz, 1 H), 7.58 (m, 2 H), 7.42 (m, 1 H), 4.89 (s, 1 H), 4.57 (s, 1 H), 4.56 (m, 1 H), 3.67 (s, 3 H), 2.93 (dd, J = 16.4, 8.0 Hz, 1 H), 2.56 (dd, J = 16.4, 7.4 Hz, 1 H), 1.04 (s, 9 H); ^{13}C NMR δ 173.0, 153.9, 149.5, 133.4, 132.9, 129.8, 128.1, 124.7, 107.7, 50.3, 44.7, 36.2, 34.3, 29.0 (3); HRMS m/z calcd for $C_{16}H_{21}NO_4$ 291.1470, found 291.1468.

Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.98; H, 7.22. Found: C, 66.17; H, 7.23.

Methyl (±)-(2-nitrophenyl)-4-pentenoate (3e): 2.18 g (9.28 mmol, 93%); the spectral and analytical data matched those reported previously.[3]

Methyl (±)-3-(1-cyclopentenyl)-2-(2-nitrophenyl)propanoate (3f): 2.74 g (9.96 mmol, 76%); IR 1737, 1654, 1530, 1353 cm^{-1}; ^1H NMR δ 7.86 (d, J = 8.1 Hz, 1 H), 7.57 (dd, J = 4.9, 1.1 Hz, 2 H), 7.40 (m, 1 H), 5.29 (m, 1 H), 4.45 (t, J = 7.4 Hz, 1 H), 3.67 (s, 3 H), 2.93 (dd, J = 15.5, 7.6 Hz, 1 H), 2.61 (dd, J = 15.5, 7.2 Hz, 1 H), 2.25−2.17 (complex, 4 H), 1.80 (quintet, J = 7.3 Hz, 2 H); ^{13}C NMR δ 173.0, 149.4, 140.5, 133.3, 132.8, 129.8, 128.0, 126.7, 124.6, 52.3, 44.7, 35.0, 34.5, 32.5, 23.4; HRMS m/z calcd for $C_{15}H_{17}NO_4$ 275.1157, found 275.1154.

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.45; H, 6.18. Found: C, 65.69; H, 6.22.

Methyl (±)-3-(2-methyl-1-cyclopentenyl)-2-(2-nitrophenyl)propanoate (3g): 3.91 g (13.5 mmol, 82%); IR 1738, 1530, 1353 cm^{-1}; ^1H NMR δ 7.85 (d, J = 8.0 Hz, 1 H), 7.56 (dd, J = 4.9, 1.2 Hz, 2 H), 7.40 (m, 1 H), 4.38 (dd, J = 8.5, 6.6 Hz, 1 H), 3.68 (s, 3 H), 2.85 (dd, J = 13.5, 6.6 Hz, 1 H), 2.61 (dd, J = 13.5, 8.5 Hz, 1 H), 2.22−2.10 (complex, 4 H), 1.68 (m, 2 H), 1.36 (s, 3 H); ^{13}C NMR δ 173.1, 149.5, 135.4, 133.5, 132.7, 130.6, 130.3, 127.9, 124.5, 52.3, 44.6, 38.3, 35.7, 32.4, 21.6, 13.5; HRMS m/z calcd for $C_{16}H_{19}NO_4$ 289.1314, found 289.1313.

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.44; H, 6.57. Found: C, 66.71; H, 6.60.

Representative Preparation of 1-Methyl Tetrahydroquinoline-4-carboxylic Esters: Methyl (±)-(2*R*,4S)-1,2-Dimethyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (4a).** A solution of 500 mg (2.01 mmol) of **3a** in 125 mL of MeOH was ozonized until TLC indicated complete consumption of starting material.[7] The crude ozonolysate was transferred to a stainless steel pressure vessel, 0.50 mL of 37% aqueous HCHO (202 mg, 6.72 mmol of HCHO) and 125 mg of 5% Pd/C were added, and the mixture was shaken in a Parr apparatus under 4 atm of H_2 at 30 °C for 4 h. The reaction was concentrated, diluted with ether and filtered through a pad of Celite® topped with a layer of anhydrous $MgSO_4$ to separate the catalyst. Removal of the ether gave a yellow oil that was flash chromatographed on a 30 cm × 2 cm silica gel column eluted with increasing concentrations of ether in hexane. The major band afforded 352 mg (1.61 mmol, 80%) of **4a** as a light yellow oil: IR 1744 cm^{-1}; ^1H NMR δ 7.15 (tm, J = 7.4 Hz, 1 H), 6.99 (dm, J = 7.4 Hz, 1 H), 6.65 (td, J = 7.4, 1.2 Hz, 1 H), 6.62 (d, J = 7.4 Hz, 1 H), 3.79 (t, J = 6.4 Hz, 1 H), 3.74 (s, 3 H), 3.40 (sextet, J = 5.9 Hz, 1 H), 2.88 (s, 3 H), 2.26 (m, 2 H), 1.13 (d, J = 6.5 Hz, 3 H); ^{13}C NMR δ 174.8, 145.5, 129.1, 128.2, 119.1, 116.0, 111.9, 52.9, 52.0, 41.9, 36.5, 32.7, 18.5; HRMS m/z calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1257.

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.23; H, 7.76; N, 6.39. Found: C, 71.51; H, 7.80; N, 6.42.

Methyl (±)-(2*S*,4S)-1-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (4b):** 330 mg (1.17 mmol, 73%); IR 1744 cm^{-1}; ^1H NMR δ 7.34−7.18 (complex, 6 H), 6.97 (d, J = 7.4 Hz, 1 H), 6.75 (d, J = 7.4 Hz, 1 H), 6.70 (t, J = 7.4 Hz, 1 H), 4.43 (dd, J = 7.6, 4.8 Hz, 1 H), 3.85 (dd, J = 8.1, 5.3 Hz, 1 H), 3.42 (s, 3 H), 2.80 (s, 3 H), 2.56 (dt, J = 13.3, 8.1 Hz, 1 H), 2.40 (dt, J = 13.3, 5.3 Hz, 1 H); ^{13}C NMR δ 173.8, 146.1, 142.5, 128.7, 128.5, 128.4, 127.2, 126.9, 119.5, 116.2, 111.6, 62.4, 51.8, 42.6, 37.8, 34.3; HRMS m/z calcd for $C_{18}H_{19}NO_2$ 281.1416, found 281.1415.

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.76; N, 4.98. Found: C, 76.59; H, 6.82; N, 4.90.

Methyl (±)-(2*R*,4S)-2-butyl-1-methyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (4c):** 341 mg (1.31 mmol, 76%); IR 1744 cm^{-1}; ^1H NMR δ 7.14 (tm, J = 7.4 Hz, 1 H), 6.96 (dm, J = 7.4 Hz, 1 H), 6.64 (td, J = 7.4, 1.2 Hz, 1 H), 6.59 (d, J = 7.5 Hz, 1 H), 3.74 (t, J = 6.3 Hz, 1 H), 3.73 (s, 3 H), 3.24 (m, 1 H), 2.91 (s, 3 H), 2.37 (dt, J = 13.6, 5.8 Hz, 1 H), 2.20 (ddd, J = 13.6, 6.3, 3.9 Hz, 1 H), 1.59 (m, 1 H), 1.36−1.19 (complex, 5 H), 0.88 (t, J = 6.6 Hz, 3 H); ^{13}C NMR δ 174.9, 145.4, 129.2, 128.2, 118.9, 115.7, 111.7, 58.0, 52.0, 41.6, 37.4, 31.4, 29.0, 27.8, 22.9, 14.1; HRMS m/z calcd for $C_{16}H_{23}NO_2$ 261.1729, found 261.1728.

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.81; N, 5.36. Found: C, 73.78; H, 8.85; N, 5.33.

Methyl (±)-(2*S*,4S)-2-*tert*-butyl-1-methyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (4d):** 332 mg (1.27 mmol, 74%); IR 1744 cm^{-1}; ^1H NMR δ 7.14 (tm, J = 8.0 Hz, 1 H), 6.85 (dm, J = 7.6 Hz, 1 H), 6.72 (t, J = 7.8 Hz, 1 H), 6.68 (dd, J = 7.4, 1.1 Hz, 1 H), 3.82 (s, 3 H), 3.53 (dd, J = 12.0, 3.8 Hz, 1 H), 3.11 (s, 3 H), 3.04 (dd, J = 10.0, 7.7 Hz, 1 H), 2.34 (ddd, J = 13.4, 7.7, 3.8 Hz, 1 H), 2.03 (ddd, J = 13.4, 12.0, 10.0 Hz, 1 H), 0.91 (s, 9 H); ^{13}C NMR δ 174.4, 149.1, 127.8, 127.5, 124.5, 117.9, 117.3, 67.6, 51.8, 44.8, 42.8, 38.3, 32.2, 27.6 (3); HRMS m/z calcd for $C_{16}H_{23}NO_2$ 261.1729, found 261.1725.

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.81; N, 5.36. Found: C, 73.51; H, 8.84; N, 5.51.

Representative Ozonolysis Procedure for the Preparation of Nitro Ketones: Methyl (±)-2-(2-Nitrophenyl)-4-oxopentanoate (5a). A solution of 1.25 g (5.02 mmol) of **3a** in 125 mL of MeOH was ozonized at −78 °C until TLC indicated complete consumption of starting material. Excess ozone was purged with a stream of dry N_2 and 5.08 g (6.00 mL, 84.9 mmol) of dimethyl sulfide was added. The mixture was warmed to 0 °C and 200 mg of *p*-TsOH was added.[3] The solution was stirred at 0 °C for 1 h, then warmed to room temperature and stirred for 8 h. The reaction was concentrated, diluted with ether, washed with $NaHCO_3$ (2×) and NaCl (1×) and dried ($MgSO_4$). Removal of the ether gave a yellow oil that was flash chromatographed on a 30 cm × 2 cm silica gel column eluted with increasing concentrations of ether in hexanes. The major band afforded 1.18 g (4.70 mmol, 94%) of **5a** as a light yellow oil. IR 1742, 1715, 1528, 1353 cm^{-1}; ^1H NMR δ 7.97 (d, J = 8.0 Hz, 1 H), 7.58 (t, J = 7.7 Hz, 1 H), 7.44 (m, 2 H), 4.69 (dd, J = 8.2, 4.8 Hz, 1 H), 3.66 (s, 3 H), 3.48 (dd, J = 18.1, 8.2 Hz, 1 H), 2.87 (dd, J = 18.1, 4.8 Hz, 1 H), 2.20 (s, 3 H); ^{13}C NMR δ 205.2, 172.2, 149.4, 133.5 (2),

131.0, 128.5, 125.2, 52.5, 46.3, 42.7, 29.8; HRMS *m/z* calcd for $C_{12}H_{13}NO_5$ 251.0793, found 251.0791.

Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.18. Found: C, 57.59; H, 5.23.

Methyl (±)-2-(2-nitrophenyl)-4-oxo-4-phenylpentanoate (5b): mp 80−82 °C; 1.41 g (4.50 mmol, 89%); IR 1746, 1687, 1530, 1353 cm^{-1}; ^1H NMR δ 7.98 (m, 3 H), 7.57 (m, 3 H), 7.46 (m, 3 H), 4.91 (dd, J = 7.8, 5.1 Hz, 1 H), 4.03 (dd, J = 18.1, 7.8 Hz, 1 H), 3.69 (s, 3 H), 3.47 (dd, J = 18.1, 5.1 Hz, 1 H); ^{13}C NMR δ 196.7, 172.4, 149.3, 136.2, 133.5 (2), 133.4, 131.0, 128.6, 128.5, 128.1, 125.2, 52.6, 42.8, 42.0; HRMS *m/z* calcd for $C_{17}H_{15}NO_5$ 313.0950, found 313.0948.

Anal. Calcd for $C_{17}H_{15}NO_5$: C, 65.18; H, 4.79. Found: C, 65.50; H, 4.84.

Methyl (±)-2-(2-nitrophenyl)-4-oxooctanoate (5c): 1.04 g (3.55 mmol, 95%); IR 1744, 1715, 1527, 1354 cm^{-1}; ^1H NMR δ 7.97 (d, J = 8.1 Hz, 1 H), 7.58 (t, J = 7.7 Hz, 1 H), 7.45 (d, J = 7.8 Hz, 1 H), 7.44 (t, J = 7.3 Hz, 1 H), 4.70 (dd, J = 8.4, 4.8 Hz, 1 H), 3.66 (s, 3 H), 3.44 (dd, J = 18.1, 8.4 Hz, 1 H), 2.85 (dd, J = 18.1, 4.8 Hz, 1 H), 2.45 (m, 2 H), 1.57 (quintet, J = 7.3 Hz, 2 H), 1.30 (sextet, J = 7.4 Hz, 2 H), 0.89 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 207.8, 172.3, 148.7, 133.5 (2), 131.0, 128.4, 125.2, 52.5, 45.4, 42.7, 42.4, 25.8, 22.2, 13.8; HRMS *m/z* calcd for $C_{15}H_{19}NO_5$ 293.1263, found 293.1260.

Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.43; H, 6.48. Found: C, 61.75; H, 6.54.

Methyl (±)-5,5-dimethyl-2-(2-nitrophenyl)-4-oxohexanoate (5d): 2.18 g (7.44 mmol, 92%); IR 1744, 1712, 1530, 1353 cm^{-1}; ^1H NMR δ 7.96 (d, J = 8.1 Hz, 1 H), 7.57 (t, J = 7.6 Hz, 1 H), 7.45 (d, J = 7.7 Hz. 1 H), 7.44 (t, J = 7.3 H, 1 H), 4.66 (dd, J = 8.5, 4.8 Hz, 1 H), 3.66 (s, 3 H), 3.48 (dd, J = 18.1, 8.5 Hz, 1 H), 2.96 (dd, J = 18.1, 4.8 Hz, 1 H), 1.15 (s, 9 H); ^{13}C NMR δ 212.7, 172.5, 148.7, 133.6, 133.4, 130.7, 128.4, 125.2, 52.4, 44.0, 42.8, 40.3, 26.3 (3); HRMS *m/z* calcd for $C_{15}H_{19}NO_5$ 293.1263, found 293.1262.

Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.43; H, 6.48. Found: C, 61.69; H, 6.52.

Representative Preparation of Tetrahydroquinoline-4-carboxylic Esters: **Methyl (±)-(2*R**,4*S**)-2-Methyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (6a).** A solution of 750 mg (2.99 mmol) of **5a** in 125 mL of MeOH containing 100 mg of 5% Pd/C was shaken under 4 atm of H_2 at 30 °C for 2.5 h. The solvent was removed, the residue was diluted with ether, and the solution was filtered through a pad of Celite topped with a layer of anhydrous $MgSO_4$ to separate the catalyst. Concentration under vacuum gave 600 mg (2.93 mmol, 98%) of **6a** as a light yellow oil that crystallized on standing at −20 °C. This solid was triturated with 3% ether in hexane to give **6a** as an off-white powder: mp 82−84 °C; IR 3395, 1737 cm^{-1}; ^1H NMR δ 7.01 (t, J = 8.1 Hz, 1 H), 6.97 (d, J = 7.7 Hz, 1 H); 6.64 (t, J = 7.6 Hz, 1 H), 6.50 (d, J = 8.1 Hz, 1 H), 3.96 (dd, J = 12.0, 5.9 Hz, 1 H), 3.76 (br s, 1 H), 3.76 (s, 3 H), 3.41 (m, 1 H), 2.15 (ddd, J = 12.8, 5.9, 2.6 Hz, 1 H), 1.95 (dt, J = 22.9, 12.8 Hz, 1 H), 1.23 (d, J = 6.3 Hz, 3 H); ^{13}C NMR δ 175.0, 144.7, 128.1, 127.3, 117.9, 117.6, 114.7, 52.0, 46.3, 43.9, 34.4, 22.3; HRMS *m/z* calcd for $C_{12}H_{15}NO_2$ 205.1103, found 205.1104.

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.24; H, 7.32; N, 6.83. Found: C, 70.29; H, 7.33; N, 6.76.

Methyl (±)-(2*S,4*S**)-2-phenyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (6b):** 619 mg (2.32 mmol, 97%); mp 75−78 °C; IR 3395, 1736 cm^{-1}; ^1H NMR δ 7.45−7.27 (complex, 5 H), 7.07 (t, J = 8.1 Hz, 1 H), 7.03 (d, J = 7.7 Hz, 1 H), 6.72 (t, J = 7.7 Hz, 1 H), 6.57 (d, J = 8.1 Hz, 1 H), 4.42 (dd, J = 10.2, 3.7 Hz, 1 H), 4.11 (dd, J = 11.1, 6.5 Hz, 1 H), 4.10 (br s, 1 H), 3.71 (s, 3 H), 2.36 (m, 2 H); ^{13}C NMR δ 174.5, 144.7, 143.2, 128.7, 128.3, 128.1, 127.9, 126.7, 117.8, 117.7, 114.9, 55.7, 52.0, 44.1, 35.2; HRMS *m/z* calcd for $C_{17}H_{17}NO_2$ 267.1259, found 267.1259.

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.40; H, 6.37; N, 5.24. Found: C, 76.33; H, 6.34; N, 5.29.

Methyl (±)-(2*R,4*S**)-2-butyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (6c):** 625 mg (2.53 mmol, 99%); mp 53−54 °C; IR 3393, 1736 cm^{-1}; ^1H NMR δ 7.02 (t, J = 8.1 Hz, 1 H), 6.96 (d, J = 7.7 Hz, 1 H), 6.64 (t, J = 7.6 Hz, 1 H), 6.51 (d, J = 8.0 Hz, 1 H), 3.94 (dd, J = 11.8, 5.7 Hz, 1 H), 3.80 (br s, 1 H), 3.76 (s, 3 H), 3.26 (m, 1 H), 2.21 (ddd, J = 12.6, 5.7, 2.5 Hz, 1 H), 1.94 (dt, J = 23.6, 11.0 Hz, 1 H), 1.52 (m, 2 H), 1.38 (m, 4 H), 0.93 (t, J = 6.9 Hz, 3 H); ^{13}C NMR δ 175.0, 144.6, 128.1, 127.9, 118.1, 117.4, 114.7, 52.0, 50.7, 43.9, 36.1, 32.5, 27.6, 22.7, 14.0; HRMS *m/z* calcd for $C_{15}H_{21}NO_2$ 247.1572, found 247.1571.

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.87; H, 8.50; N, 5.67. Found: C, 73.06; H, 8.52; N, 5.72.

Methyl (±)-(2*S,4*S**)-2-*tert*-butyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (6d):** 588 mg (2.38 mmol, 93%); mp 76−79 °C; IR 3381, 1736 cm^{-1}; ^1H NMR δ 7.02 (t, J = 8.0 Hz, 1 H), 6.93 (d, J = 7.7 Hz, 1 H), 6.62 (t, J = 7.6 Hz, 1 H), 6.53 (d, J = 8.1 Hz, 1 H), 3.93 (dd, J = 12.5, 5.3 Hz, 1 H), 3.84 (br s, 1 H), 3.78 (s, 3 H), 3.00 (dd, J = 11.5, 2.3 Hz, 1 H), 2.20 (ddd, J = 12.5, 5.3, 2.3 Hz, 1 H) 1.93 (dt, J = 24.0, 11.5 Hz, 1 H), 0.98 (s, 9 H); ^{13}C NMR δ 175.2, 145.2, 127.9, 127.7, 118.2, 117.3, 114.8, 59.8, 52.0, 44.4, 33.3, 27.7, 25.8 (3); HRMS *m/z* calcd for $C_{15}H_{21}NO_2$ 247.1572, found 247.1568.

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.87; H, 8.50; N, 5.67. Found: C, 73.08; H, 8.53; N, 5.65.

Methyl (±)-1,2,3,4-Tetrahydroquinoline-4-carboxylate (9). A solution of 1.50 g (6.38 mmol) of **3e** in 150 mL of MeOH was treated with ozone, dimethyl sulfide and *p*-TsOH as described for the preparation of **5a**. The reaction was concentrated, diluted with ether, washed with $NaHCO_3$ (2×) and NaCl (1×) and dried ($MgSO_4$). Evaporation of the ether gave acetal **7** contaminated with a small amount of aldehyde **8**. This mixture was dissolved in 75 mL of THF and 75 mL of 3% aqueous $HClO_4$ was added dropwise at 0 °C.[12] The solution was stirred at 0 °C for 1 h and at room temperature for 6 h, then extracted with CH_2Cl_2 (2×). The organic layer was washed with $NaHCO_3$ (2×) and NaCl (1×), dried ($MgSO_4$) and concentrated under vacuum to give 1.48 g (6.24 mmol, 98%) of **8**. This compound was used without further purification: IR 2846, 2733, 1744, 1729, 1527, 1354 cm^{-1}; ^1H NMR δ 9.80 (s, 1 H), 8.00 (dd, J = 7.8, 1.4 Hz, 1 H), 7.58 (td, J = 7.7, 1.4 Hz, 1 H), 7.47 (m, 2 H), 4.76 (dd, J = 8.1, 5.1 Hz, 1 H), 3.65 (s, 3 H), 3.55 (dd, J = 18.7, 8.1 Hz, 1 H), 2.97 (dd, J = 18.7, 5.1 Hz, 1 H); ^{13}C NMR δ 198.5, 171.8, 148.7, 133.6, 132.9, 130.9, 128.7, 125.4, 52.7, 46.6, 41.4; HRMS *m/z* calcd for $C_{11}H_{11}NO_5$ 237.0637, found 237.0636.

To a solution of 550 mg (2.32 mmol) of **8** in 150 mL of MeOH was added 125 mg of 5% Pd/C, and the mixture was shaken under 4 atm of H_2 at 30 °C for 8 h. The solvent was removed, the residue was diluted with ether, and the solution was filtered through a pad of Celite topped with a layer of anhydrous $MgSO_4$ to separate the catalyst. Concentration under vacuum gave 400 mg (2.09 mmol, 90%) of **9** as a light yellow oil: IR 3403, 1729 cm^{-1}; ^1H NMR δ 7.10 (d, J = 7.8 Hz, 1 H), 7.02 (t, J = 8.0 Hz, 1 H), 6.63 (t, J = 7.8 Hz, 1 H), 6.51 (d, J = 8.0 Hz, 1 H), 3.78 (t, J = 4.8 Hz, 1 H), 3.71 (s, 3 H), 3.69 (br s, 1 H), 3.43 (td, J = 11.0, 3.2 Hz, 1 H), 3.27 (dt, J = 11.5, 4.8 Hz, 1 H), 2.27 (m, 1 H), 2.00 (m, 1 H); ^{13}C NMR δ 174.9, 144.5, 130.3, 128.1, 117.0 (2), 114.8, 52.0, 41.5, 38.7, 24.4; HRMS *m/z* calcd for $C_{11}H_{13}NO_2$ 191.0946, found 191.0943.

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.11; H, 6.81; N, 7.32. Found: C, 69.29; H, 6.85; N, 7.41.

Methyl (±)-(4a*R,6*S**)-2,3,4,4a,5,6-Hexahydro-1*H*-benzo[*c*]quinolizine-6-carboxylate (12).** A solution of 600 mg (2.18 mmol) of **3f** in 150 mL of MeOH was treated with ozone, dimethyl sulfide and *p*-TsOH as described for the preparation of **5a**. The reaction was concentrated, diluted with ether, washed with $NaHCO_3$ (2×) and NaCl (1×) and dried ($MgSO_4$). Evaporation of the ether gave acetal **10** contaminated with a small amount of aldehyde **11**. This mixture was dissolved in 40 mL of THF and 40 mL of 3% aqueous $HClO_4$ was added dropwise at 0 °C. Stirring was continued for 1 h at 0 °C and at room temperature for 3 h. Workup, as above, afforded 626 mg (2.04 mmol, 94%) of **11**. This compound was used without further purification: IR 2840, 2733, 1744, 1730, 1530, 1353 cm^{-1}; ^1H NMR δ 9.75 (t, J = 1.4 Hz, 1 H), 7.97 (dd, J = 8.0, 1.2 Hz, 1 H), 7.59 (td, J = 7.4, 1.4 Hz, 1 H), 7.45 (m, 2 H), 4.71 (dd, J = 8.8, 4.5 Hz, 1 H), 3.65 (s, 3 H), 3.42 (dd, J = 17.9, 8.8 Hz, 1 H), 2.82 (dd, J = 17.9, 4.5 Hz, 1 H), 2.66−2.43 (complex, 4 H), 1.92 (quintet, J = 7.0 Hz, 2 H); ^{13}C NMR δ 206.6, 201.7,

172.1, 148.5, 133.5, 133.2, 130.8, 128.4, 125.2, 52.4, 45.3, 42.7, 41.2, 30.2, 15.9; HRMS *m*/*z* calcd for $C_{15}H_{17}NO_6$ 307.1055, found 307.1052.

To a solution of 550 mg (1.79 mmol) of **11** in 150 mL of MeOH was added 125 mg of 5% Pd/C, and the mixture was hydrogenated as described for the preparation of compound **9**. Workup gave a light yellow oil that crystallized on standing. Recrystallization from pentane afforded 303 mg (1.24 mmol, 69%) of **12** as light yellow crystals: mp 68−70 °C; IR 1744 cm^{-1}; ^1H NMR δ 7.13 (tm, J = 7.7 Hz, 1 H), 6.96 (dm, J = 7.7 Hz, 1 H), 6.85 (d, J = 8.1 Hz, 1 H), 6.69 (t, J = 8.1 Hz, 1 H), 3.91 (m, 2 H), 3.74 (s, 3 H), 2.85 (m, 1 H), 2.56 (td, J = 12.2, 2.7 Hz, 1 H), 2.16 (m, 2 H), 1.77 (m, 3 H), 1.64 (m, 1 H), 1.39 (m, 2 H); ^{13}C NMR δ 174.9, 146.9, 128.1 (2), 121.5, 117.8, 113.4, 55.4, 52.0, 47.9, 43.9, 34.0, 33.5, 25.8, 24.0; HRMS *m*/*z* calcd for $C_{15}H_{19}NO_2$ 245.1416, found 245.1418.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.47; H, 7.76; N, 5.71. Found: C, 73.66; H, 7.79; N, 5.76.

Methyl (±)-(1*R,4a*R**,6*S**)-1-Methyl-2,3,4,4a,5,6-hexahydro-1*H*-benzo[*c*]quinolizine-6-carboxylate (14).** A solution of 1.00 g (3.46 mmol) of **3g** in 150 mL of MeOH was treated with ozone, dimethyl sulfide, and *p*-TsOH as described for the preparation of **5a**. Workup gave an oil that was flash chromatographed on silica gel using increasing concentrations of ether in hexane. The main band afforded 1.06 g (3.30 mmol, 95%) of **13** as a yellow oil that crystallized on standing: mp 47−48 °C; IR 1744, 1715, 1530, 1353 cm^{-1}; ^1H NMR δ 7.97 (dd, J = 8.0, 1.5 Hz, 1 H), 7.59 (td, J = 7.5, 1.5 Hz, 1 H), 7.44 (m, 2 H), 4.70 (dd, J = 8.8, 4.5 Hz, 1 H), 3.66 (s, 3 H), 3.42 (dd, J = 17.9, 8.8 Hz, 1 H), 2.82 (dd, J = 17.9, 4.5 Hz, 1 H), 2.62−2.41 (complex, 4 H), 2.13 (s, 3 H), 1.86 (quintet, J = 7.0 Hz, 2 H); ^{13}C NMR δ 208.3, 207.1, 172.2, 148.6, 133.5, 133.3, 130.8, 128.4, 125.2, 52.5, 45.3, 42.7, 42.2, 41.3, 29.9, 17.5; HRMS *m*/*z* calcd for $C_{16}H_{19}NO_6$ 321.1212, found 321.1208.

To a solution of 500 mg (1.56 mmol) of **13** in 150 mL of MeOH was added 125 mg of 5% Pd/C and the mixture was hydrogenated as described for the preparation of compound **9**. Workup gave a light yellow oil that was purified by PTLC using 50% ether in hexane. The main band afforded 256 mg (0.99 mmol, 63%) of **14** as a colorless oil that crystallized on standing: mp 37−38 °C; IR 1744 cm^{-1}; ^1H NMR δ 7.13 (t, J = 7.5 Hz, 1 H), 6.97 (d, J = 7.5 Hz, 1 H), 6.67 (m, 2 H), 3.84 (dd, J = 9.5, 5.8 Hz, 1 H), 3.71 (s, 3 H), 3.53 (m, 1 H), 3.19 (m, 1 H), 2.17−1.94 (complex, 3 H), 1.80 (m, 2 H), 1.65 (m, 1 H), 1.57 (m, 2 H), 1.23 (d, J = 6.3 Hz, 3 H); ^{13}C NMR δ 175.0, 146.4, 127.8, 127.4, 123.3, 116.9, 112.7, 52.3, 51.9, 49.9, 44.2, 35.1, 31.1, 29.5, 20.9, 18.0; HRMS *m*/*z* calcd for $C_{16}H_{21}NO_2$ 259.1572, found 259.1571.

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.13; H, 8.11; N, 5.41. Found: C, 74.36; H, 8.15; N, 5.39.

Two other minor bands from the PTLC plate gave the following compounds:

Methyl (±)-(8*S,8a*R**,9*S**,10a*R**)-8-methyl-5,6,7,8,8a,9,10,10a-octahydroacridine-9-carboxylate (15):** 24 mg (0.093 mmol, 6%); mp 91−93 °C; IR 3374, 1730 cm^{-1}; ^1H NMR δ 7.15 (dm, J = 7.7 Hz, 1 H), 7.02 (tm, J = 7.7 Hz, 1 H), 6.65 (dt, J = 7.6, 1.2 Hz, 1 H), 6.53 (dd, J = 8.0, 1.2 Hz, 1 H), 3.69 (s, 3 H), 3.58 (d, J = 9.8 Hz, 1 H), 3.38 (br s, 1 H), 2.73 (td, J = 10.6, 3.9 Hz, 1 H), 1.93 (q, J = 10.0 Hz, 1 H), 1.87 (m, 1 H), 1.78 (m, 1 H), 1.67 (dm, J = 12.8 Hz, 1 H), 1.43 (tm, J = 9.4 Hz, 1 H), 1.40−1.09 (complex, 3 H), 0.93 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 176.0, 145.2, 127.7, 127.6, 119.6, 118.2, 115.0, 54.5, 52.0, 48.8, 47.7, 37.6, 35.4, 33.1, 23.9, 18.8; HRMS *m*/*z* calcd for $C_{16}H_{21}NO_2$ 259.1573, found 259.1576.

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.13; H, 8.11; N, 5.41. Found: C, 74.35; H, 8.14; N, 5.34.

Methyl (±)-(2*R,4*S**)-2-(4-oxopentyl)-1,2,3,4-tetrahydroquinoline-4-carboxylate (16):** 9 mg (0.033 mmol, 2%); mp 74−76 °C; IR 3388, 1740 cm^{-1}; ^1H NMR δ 7.02 (tm, J = 7.7 Hz, 1 H), 6.96 (dm, J = 7.7 Hz, 1 H), 6.64 (dt, J = 7.7, 1.2 Hz, 1 H), 6.52 (dd, J = 8.0, 1.2 Hz, 1 H), 3.93 (dd, J = 11.7, 5.8 Hz, 1 H), 3.76 (s, 3 H), 3.69 (dd, J = 10.5, 4.4 Hz, 1 H), 3.26 (m, 1 H), 2.50 (t, J = 7.1 Hz, 1 H), 2.20 (dd, J = 5.8, 2.6 Hz, 1 H), 2.16 (m, 1 H), 2.15 (s, 3 H), 1.98 (quintet, J = 11.7 Hz, 1 H), 1.74 (m, 2 H), 1.52 (m, 2 H); ^{13}C NMR δ 208.5, 174.9, 144.5, 128.1, 128.0, 118.1, 117.6, 114.8, 52.0, 50.4, 43.7, 43.3, 35.7, 32.3, 30.0, 19.3; HRMS *m*/*z* calcd for $C_{16}H_{21}NO_3$ 275.1521, found 275.1522.

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.82; H, 7.63; N, 5.09. Found: C, 70.11; H, 7.67; N, 5.18.

Acknowledgment. We thank the NIH (GM54256) for support of this research. We also to acknowledge Professor E. J. Eisenbraun for a generous sample of 2,3,3-trimethyl-1-butene used to prepare **2d**. Funds for the 300 and 400 MHz NMR spectrometers of the Oklahoma Statewide Shared NMR Facility were provided by NSF (BIR-9512269), the Oklahoma State Regents for Higher Education, the W. M. Keck Foundation, and Conoco, Inc. Partial support for our mass spectrometer by the NIH and the Oklahoma Center for the Advancement of Science and Technology is also appreciated.

Supporting Information Available: ^1H NMR, ^{13}C NMR, COSY-45 and NOESY spectra for compounds **14** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001761N