(±)-2,3-Dialkyl-1,2,3,4-tetrahydroquinoline-3-carboxylic Esters by a Tandem Reduction-Reductive Amination Reaction

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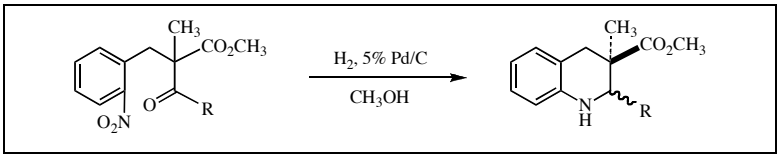
Received October 17, 2006



A series of 2-methyl-2-(2-nitrobenzyl)-substituted β-keto ester derivatives has been subjected to reductive cyclization under hydrogenation conditions to assess the importance of the ester group position on the diastereoselectivity of the process. Hydrogenation over 5% palladium-on-carbon at 4 atmospheres pressure resulted in formation of (±)-2,3-dialkyl-1,2,3,4-tetrahydroquinoline-3-carboxylic esters with a preference for the product isomer having the C2 alkyl *cis* to the C3 ester. The product ratios were synthetically useful (6-16:1), but less than that observed in cyclizations to prepare (±)-2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylic esters. The reduced selectivity in the current reactions has been rationalized in terms of the greater conformational mobility around the ester bearing carbon, which decreases the ability of the ester to sterically influence the addition of hydrogen to the final imine intermediate.

J. Heterocyclic Chem., **44**, 1051 (2007).

INTRODUCTION

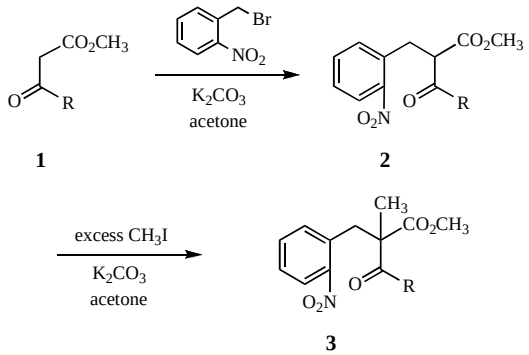
An earlier report from this laboratory disclosed a highly diastereoselective tandem reduction-reductive amination sequence for the synthesis of (±)-2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylic esters from 2-(2-nitrophenyl)-substituted γ-keto esters [2,3]. The selectivity in this reaction was attributed to a steric effect exerted by the ester group on the benzylic carbon, which shields one face of the molecule and directs hydrogen addition from the opposite side to give the *cis* orientation between the C2 and C4 substituents. Placement of the ester on the benzylic (α) carbon was deemed an important factor in the observed selectivity since this carbon is held rigidly planar with the aromatic ring. The current study sought to further explore the limits of this selectivity by (1) moving the ester from the α to the β carbon (relative to the aromatic ring) and (2) introducing a second sterically demanding substituent geminal to the ester. The greater conformational flexibility around the β carbon was expected to decrease the ability of the ester to direct the addition of hydrogen to the final imine intermediate. The further introduction of a geminal methyl substituent, added to preclude potential complications from enol formation, was also expected to impact the product stereochemistry.

The (±)-2-alkyl-3-methyl-1,2,3,4-tetrahydroquinoline-3-carboxylic esters prepared in this study have few documented uses, but analogous compounds lacking the C3 methyl group are well known to have potential as medicinal agents [4,5]. Additionally, the current targets are esters of β-amino acids, which have been investigated for the treatment of several neurological disorders [6]. Access to C3 alkylated derivatives could provide new leads in the search for future drug candidates.

RESULTS AND DISCUSSION

The synthesis of our cyclization substrates is depicted in Scheme 1. β-Keto esters **1a**-**g** [7,8] were sequentially alkylated with 2-nitrobenzyl bromide [9] and methyl iodide. In most cases, potassium carbonate in acetone was used for these reactions, but sodium hydride in dimethylformamide proved superior for the final methylation when R was *t*-C_4H_9 or C_6H_5. To minimize dialkylation, the first reaction of the sequence was carried out using a three-fold excess of the β-keto ester relative to the alkylating agent. For the second alkylation, a three-fold excess of methyl iodide was used to assure complete conversion to the final product. Overall yields for the synthetic sequence ranged from 55-68%.

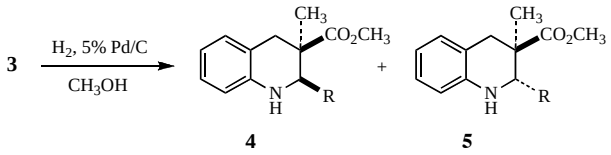
Scheme 1



a (R = CH_3)
b (R = *n*-C_5H_{11})
c (R = $CH_2CH_2C_6H_5$)
d (R = *i*-C_3H_7)
e (R = *c*-C_6H_{11})
f (R = *t*-C_4H_9)
g (R = C_6H_5)

Reductive cyclization of nitro keto esters **3a**-**g** was carried out under 4 atmospheres of hydrogen using 5% palladium-on-carbon as the catalyst. The reaction proceeded smoothly to give the expected *cis*- and *trans*-(±)-2-alkyl-3-methyl-1, 2, 3, 4-tetrahydroquinoline-3-carboxylic esters, **4** and **5**, respectively. Compared with our earlier study describing the preparation of (±)-2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylic esters [2], however, the current cyclizations were less selective, though the products having the C2 alkyl group and the C3 ester *cis* still predominated in synthetically useful ratios of 6-16:1. The two diastereomers were generally separable using preparative thin layer chromatography (Scheme 2).

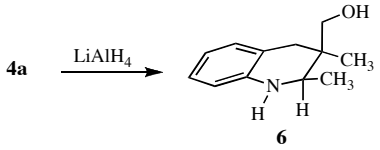
Scheme 2



3		Isolated Yields (%) 4	5	Ratio
a	(R = CH_3)	72	8	9:1
b	(R = C_5H_{11})	72	9	8:1
c	(R = CH_2CH_2Ph)	73	10	7:1
d	(R = *i*-C_3H_7)	78	5	16:1
e	(R = *c*-C_6H_{11})	80	5	16:1
f	(R = *t*-C_4H_9)	67	11	6:1
g	(R = C_6H_5)	77	10	8:1

The stereochemistry of major product was established for **4a** by reduction to amino alcohol **6** and single crystal X-ray analysis**.** The structure of **6** clearly shows a *cis* relationship between the C2 methyl and the C3 hydroxymethyl (derived from the ester). The formation of **6** is illustrated in Scheme 3 and its ORTEP diagram is shown in Figure 1.

Scheme 3



The mechanism of the reaction involves initial reduction of the nitro function to give **7** followed by condensation of the amino group with the side chain ketone to give imine **8**. Further reduction of **8** then leads to a mixture of *cis* and *trans* product isomers. Interestingly, addition of the amino group to the ester is not observed under the conditions used for the cyclization. The modest decrease in selectivity for the current reaction can be ascribed to the increased conformational flexibility around the β carbon giving the ester less control over the stereochemical outcome of the reaction. Since the ester is

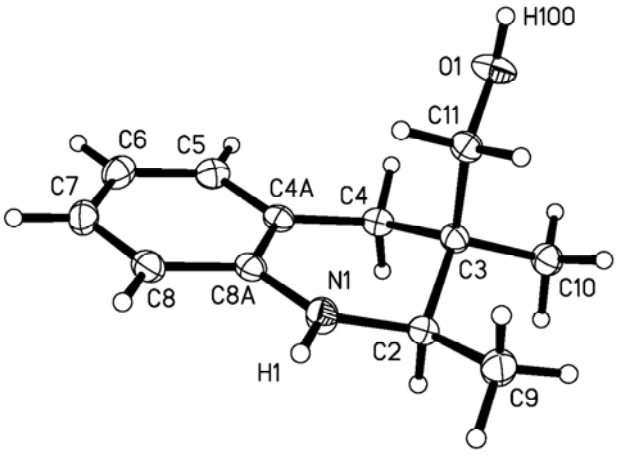
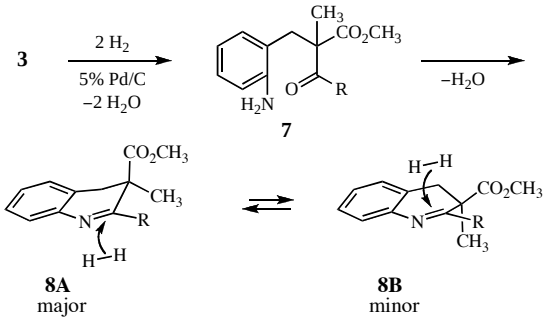


Figure 1. ORTEP diagram of **6** with 50% probability elipsoids.

sterically smaller than the methyl group [10], imine conformation **8A** (ester pseudoaxial) would be expected to predominate over **8B** (see Scheme 4). Addition of hydrogen to **8A** from the least hindered face of the molecule would then lead to the major product having the C2 alkyl *cis* to the C3 ester; similar addition to minor conformation **8B** would give the product having the *trans* arrangement of these two groups. In the current study, placing the ester further from the aromatic ring was expected to significantly lower the selectivity, but the introduction of the sterically larger methyl group geminal to the ester may have partially reversed the effect and allowed the ester to reassert its influence over the final hydrogen addition. Because of these possible competing effects, a further investigation of substrates lacking the C3 methyl group has been carried out [11].

Scheme 4



Though conformation **8A** leading to the *cis* product appears to be significantly favored in all cases, interactions between the alkyl groups at C2 and C3 can cause some erosion of selectivity in the final reduction. When R is a primary alkyl group, the observed product ratio most likely reflects the preference for **8A** over **8B** due to the relative sizes of the C3 substituents since interactions with the C2

alkyl are minimal. Interestingly, the reaction selectivity is highest when R is a secondary alkyl substituent. These groups still have the ability to avoid steric crowding in **8A** by orienting the methine hydrogen toward the C3 methyl [12]; in **8B**, however, a destabilizing 1,3-diaxial-like repulsion between the C3 methyl and one carbon of the secondary alkyl group tends to disfavor this arrangement. With R = *t*-C_4H_9, interaction with the C3 methyl becomes more important [12] and increased amounts of the *trans* products are produced via **8B**. Finally, for R = C_6H_5, the aromatic ring would presumably seek planarity with the conjugated imine double bond causing steric interference between the *ortho* protons and the C3 methyl. As a consequence, slightly more of the reaction should divert through **8B** to give the *trans* product.

CONCLUSION

We have developed an efficient diastereoselective synthetic approach to (±)-2,3-dialkyl-1,2,3,4-tetrahydroquinoline-3-carboxylate esters from readily available β-keto esters. The final reductive cyclization, while not as selective as that observed for the closure of (±)-2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylic esters, still favors the product having a *cis* relationship between the C2 alkyl and the C3 ester group. The slight reduction in selectivity results from the greater conformational flexibility about the β carbon, which diminishes the ability of the ester to direct the orientation of hydrogen addition to the final imine intermediate. The inclusion of a sterically larger methyl substituent geminal to the ester, however, may benefit the selectivity by favoring a conformation that places the ester in a pseudoaxial position where it can control the stereochemical outcome.

EXPERIMENTAL

All reactions (except hydrogenations) were run under dry nitrogen in oven-dried glassware. Potassium carbonate was ground to a fine powder, dried under vacuum at 120° for 24 hours and stored in an oven at 120°. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech 21521) with ultraviolet detection. Preparative separations were performed by one of the following methods: (1) flash column chromatography [13] on silica gel (grade 62, 60-200 mesh) containing ultraviolet-active phosphor (Sorbent Technologies UV-5) packed into quartz columns or (2) preparative thin layer chromatography on 20-cm x 20-cm silica gel GF plates (Analtech 02015). Band elution for both methods was monitored using a hand-held ultraviolet lamp. Hexanes used in chromatography had a boiling range of 65-70°; petroleum ether used in crystallization and trituration procedures had a boiling range of 35-60°. Melting points were uncorrected. Infrared spectra were run as thin films on sodium chloride disks and referenced to polystyrene. ^{1}H and ^{13}C Nuclear magnetic resonance spectra were measured in deuteriochloroform at 300 MHz and 75 MHz, respectively, using tetramethylsilane as the internal standard; coupling constants (J) are given in Hertz. Mass spectra (electron impact/direct probe) were obtained at 70 electron volts.

Keto esters **1b**, **1c** and **1e**, that were not commercially available, were prepared from Meldrum's acid [7] by acylation with the appropriate acid chloride followed by methanolysis using the method of Yonemitsu and co-workers [8].

Representative Procedure for 2-Nitrobenzylation of β-Keto Esters 1a-g: Methyl (±)-2-(2-Nitrobenzyl)-3-oxobutanoate (2a). A solution of 2.50 g, (21.6 mmoles) of methyl acetoacetate was added dropwise to a stirred suspension of 16.6 g (120 mmoles) potassium carbonate in 100 mL of dry acetone. A solution of 1.56 g (7.22 mmoles) of 2-nitrobenzyl bromide [8] in 10 mL of acetone was added dropwise to this solution at room temperature. The reaction was stirred at room temperature for 12-24 hours. The reaction mixture was vacuum filtered through a pad of Celite® and concentrated under reduced pressure. The resulting residue was diluted with ether, washed with aqueous ammonium chloride (three times) and aqueous sodium chloride (one time), and then dried (magnesium sulfate). The compound was concentrated under vacuum and purified by flash chromatography on a 50-cm x 2-cm silica gel column using 5% ether in hexanes to give the following: band 1, 1.48 g of recovered methyl acetoacetate; band 2, 1.34 g (74%) of **2a** as a light yellow oil. ir: 1745, 1718, 1528, 1348 cm^{-1}; ^{1}H nmr: δ 8.00 (dd, 1H, *J* = 8.2, 1.4), 7.53 (ddd, 1H, *J* = 8.5, 7.1, 1.4), 7.42 (d, 1H, *J* = 7.4), 7.41 (td, 1H, *J* = 8.2, 1.6), 4.04 (dd, 1H, *J* = 8.5, 5.7), 3.69 (s, 3H), 3.50 (dd, 1H, *J* = 13.6, 5.7), 3.36 (dd, 1H, *J* = 13.6, 8.5), 2.28 (s, 3H); ^{13}C nmr: δ 201.8, 169.1, 149.2, 133.5, 133.4, 132.9, 128.2, 125.2, 59.5, 52.6, 31.4, 29.8; ms: *m/z* 251 (M^+). *Anal.* Calcd. for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.18; N, 5.58. Found: C, 57.57; H, 5.21; N, 5.51.

Methyl (±)-2-(2-Nitrobenzyl)-3-oxooctanoate (2b). This compound (1.68 g, 76%) was isolated as a light yellow oil. ir: 1745, 1715, 1528, 1348 cm^{-1}; ^{1}H nmr: δ 8.01 (m, 1H), 7.43 (m, 1H), 7.40 (m, 2H), 4.06 (dd, 1H, J = 8.2, 6.0), 3.68 (s, 3H), 3.46 (dd, 1H, J = 13.7, 6.0), 3.38 (dd, 1H, J = 13.7, 8.2), 2.61 (dt, 1H, J = 17.3, 7.3), 2.46 (dt, 1H, J = 17.3, 7.3), 1.54 (quintet, 2H, J = 7.4), 1.24 (m, 4H), 0.86 (t, 3H, J = 6.9); ^{13}C nmr: δ 204.3, 169.1, 149.1, 133.6, 133.5, 133.3, 128.1, 125.2, 58.6, 52.5, 42.8, 31.5, 31.0, 23.0, 22.3, 13.8; ms: *m/z* 307 (M^+). *Anal.* Calcd. for $C_{16}H_{21}NO_5$: C, 62.54; H, 6.84; N, 4.56. Found: C, 62.68; H, 6.89; N, 4.49.

Methyl (±)-2-(2-Nitrobenzyl)-5-phenyl-3-oxopentanoate (2c). This compound (1.89 g, 77%) was isolated as a light yellow oil. ir: 1745, 1715, 1528, 1348 cm^{-1}; ^{1}H nmr: δ 7.98 (dd, 1H, J = 7.9, 1.4), 7.49 (td, 1H, J = 7.6, 1.4), 7.38 (m, 2H), 7.30-7.10 (complex, 5H), 4.03 (dd, 1H, J = 8.2, 6.3), 3.62 (s, 3H), 3.44 (dd, 1H, J = 13.9, 6.3), 3.36 (dd, 1H, J = 13.9, 8.2), 3.04-2.72 (complex, 4H); ^{13}C nmr: δ 203.2, 168.9, 149.0, 140.4, 133.5, 133.4 (2C), 128.5, 128.3, 128.1, 126.2, 125.2, 58.9, 52.5, 44.3, 31.4, 29.4; ms: *m/z* 341 (M^+). *Anal.* Calcd. for $C_{19}H_{19}NO_5$: C, 66.86; H, 5.57; N, 4.11. Found: C, 66.76; H, 5.68; N, 4.08.

Methyl (±)-4-Methyl-2-(2-nitrobenzyl)-3-oxopentanoate (2d). This compound (1.38 g, 69%) was isolated as a light yellow oil. ir: 1745, 1715, 1528, 1348 cm^{-1}; ^{1}H nmr: δ 8.03 (d, 1H, J = 7.4), 7.55 (ddd, 1H, J = 7.6, 7.1, 1.4), 7.44 (dd, 1H, J = 7.4, 1.6), 7.42 (d, 1H, J = 7.6), 4.30 (t, 1H, J = 7.1), 3.72 (s, 3H), 3.46 (d, 2H, J = 7.1), 2.81 (septet, 1H, J = 6.8), 1.12 (d, 3H, J = 6.8), 0.97 (d, 3H, J = 6.8); ^{13}C nmr: δ 208.0, 169.0, 149.1, 133.7, 133.5, 133.3, 128.1, 125.1, 56.7, 52.5, 41.2, 31.9, 17.7 (2C); ms: *m/z* 279 (M^+). *Anal.* Calcd. for $C_{14}H_{17}NO_5$: C, 60.22; H, 6.09; N, 5.02. Found: C, 60.45; H, 6.16; N, 4.97.

Methyl (±)-3-Cyclohexyl-2-(2-nitrobenzyl)-3-oxopropanoate (2e). This compound (1.63 g, 71%) was isolated as a light

yellow oil. ir: 1745, 1711, 1528, 1348 cm^{-1}; ^1H nmr: δ 7.99 (dd, 1H, J = 7.6, 1.1), 7.51 (td, 1H, J = 7.4, 1.4), 7.40 (td, 1H, J = 7.4, 1.4), 7.38 (d, 1H, J = 7.9), 4.24 (t, 1H, J = 7.4), 3.68 (s, 3H), 3.41 (d, 2H, J = 7.6), 2.50 (tt, 1H, J = 11.2, 3.3), 1.82-1.58 (complex, 5H), 1.44-0.99 (complex, 5H); ^{13}C nmr: δ 207.2, 169.1, 149.3, 133.7, 133.6, 133.3, 128.1, 125.1, 56.7, 52.5, 50.9, 31.8, 28.0, 27.8, 25.6, 25.5, 25.2; ms: *m/z* 319 (M^+). *Anal.* Calcd. for $C_{17}H_{21}NO_5$: C, 63.95; H, 6.58; N, 4.39. Found: C, 64.01; H, 6.61; N, 4.34.

Methyl (±)-4,4-Dimethyl-2-(2-nitrobenzyl)-3-oxopentanoate (2f). This compound (1.39 g, 66%) was isolated as a light yellow oil. ir: 1744, 1708, 1528, 1348 cm^{-1}; ^1H nmr: δ 7.98 (dd, 1H, J = 8.2, 1.4), 7.51 (td, 1H, J = 7.4, 1.4), 7.40 (td, 1H, J = 7.4, 1.6), 7.32 (dd, 1H, J = 7.6, 1.6), 4.52 (t, 1H, J = 7.5), 3.66 (s, 3H), 3.47 (dd, 1H, J = 13.4, 7.1), 3.38 (dd, 1H, J = 13.4, 7.9), 1.02 (s, 9H); ^{13}C nmr: δ 209.2, 169.2, 149.4, 133.7, 133.3, 133.2, 128.2, 125.1, 52.5, 52.4, 45.5, 33.6, 25.7 (3C); ms: *m/z* 293 (M^+). *Anal.* Calcd. for $C_{15}H_{19}NO_5$: C, 61.43; H, 6.48; N, 4.78. Found: C, 61.56; H, 6.54; N, 4.73.

Methyl (±)-2-(2-Nitrobenzyl)-3-phenyl-3-oxopropanoate (2g). This compound (1.67 g, 80%) was isolated as a light yellow solid, mp 76-78° (ether-petroleum ether). ir: 1740, 1687, 1525, 1346 cm^{-1}; ^1H nmr: δ 7.97 (m, 3H), 7.60-7.33 (complex, 6H), 4.96 (t, 1H, J = 7.1), 3.63 (s, 3H), 3.60 (d, 2H, J = 7.1); ^{13}C nmr: δ 194.2, 169.3, 149.2, 135.9, 133.8, 133.6, 133.4, 133.3, 128.7 (2C), 128.1, 125.1, 53.9, 52.6, 32.5; ms (30 eV): *m/z* 313 (M^+). *Anal.* Calcd. for $C_{17}H_{15}NO_5$: C, 65.18; H, 4.79; N, 4.47. Found: C, 65.26; H, 4.85; N, 4.43.

Representative Procedure for Methylation of β-Keto Esters 2a-e: Methyl (±)-2-Methyl-2-(2-nitrobenzyl)-3-oxobutanoate (3a). A solution of 1.15 g (4.58 mmoles) of **2a** was added dropwise to a stirred suspension of 3.52 g (25.5 mmoles) of potassium carbonate in 50 mL of dry acetone. A solution of 1.95 g (13.8 mmoles) of iodomethane in 10 mL of acetone was added dropwise to this solution at room temperature and the reaction was stirred for 24 hours. The crude reaction mixture was vacuum filtered through a pad of Celite® and concentrated under reduced pressure. The resulting residue was diluted with ether, washed with aqueous solutions of ammonium chloride (three times), sodium thiosulfate (one time) and sodium chloride (one time), and then dried (magnesium sulfate). The crude product was concentrated under vacuum and purified by flash chromatography on a 30-cm x 2-cm silica gel column using 5% ether in hexanes to give 1.05 g (85%) of **3a** as a light yellow oil. ir: 1745, 1714, 1529, 1353 cm^{-1}; ^1H nmr: δ 7.85 (dd, 1H, J = 7.9, 1.4), 7.49 (td, 1H, J = 7.6, 1.4), 7.38 (td, 1H, J = 7.9, 1.4), 7.28 (dd, 1H, J = 7.6, 1.4), 3.71 (s, 3H), 3.67 (d, 1H, J = 14.2), 3.56 (d, 1H, J = 14.2), 2.18 (s, 3H), 1.28 (s, 3H); ^{13}C nmr: δ 204.3, 172.4, 150.5, 133.1, 132.4, 131.4, 128.0, 124.8, 60.5, 52.5, 35.2, 26.3, 19.0. *Anal.* Calcd. for $C_{13}H_{15}NO_5$: C, 58.87; H, 5.66; N, 5.28. Found: C, 59.03; H, 5.71; N, 5.20.

Methyl (±)-2-Methyl-2-(2-nitrobenzyl)-3-oxooctanoate (3b). This compound (1.48 g, 84%) was isolated as a light yellow oil. ir: 1744, 1715, 1528, 1351 cm^{-1}; ^1H nmr: δ 7.85 (dd, 1H, J = 8.2, 1.4), 7.48 (td, 1H, J = 7.6, 1.4), 7.38 (ddd, 1H, J = 8.2, 7.6, 1.6), 7.28 (ddd, 1H, J = 7.6, 1.6), 3.69 (s, 3H), 3.67 (d, 1H, J = 14.2), 3.57 (d, 1H, J = 14.2), 2.43 (t, 2H, J = 7.4), 1.58 (quintet, 2H, J = 7.6), 1.26 (m, 4H), 1.26 (s, 3H), 0.88 (t, 3H, J = 6.8); ^{13}C nmr: δ 206.7, 172.5, 150.7, 133.1, 132.3, 131.6, 127.9, 124.8, 60.5, 52.5, 38.4, 35.2, 31.1, 23.5, 22.4, 19.0, 13.9. *Anal.* Calcd. for $C_{17}H_{23}NO_5$: C, 63.55; H, 7.17; N, 4.36. Found: C, 63.66; H, 7.19; N, 4.33.

Methyl (±)-2-Methyl-2-(2-nitrobenzyl)-5-phenyl-3-oxopentanoate (3c). This compound (1.63 g, 83%) was isolated as a light yellow oil. ir: 1744, 1715, 1528, 1351 cm^{-1}; ^1H nmr: δ 7.84 (dd, 1H, J = 7.9, 1.6), 7.45 (td, 1H, J = 7.6, 1.6), 7.36 (td, 1H, J = 7.9, 1.6), 7.31-7.12 (complex, 6H), 3.65 (d, 1H, J = 14.2), 3.61 (s, 3H), 3.54 (d, 1H, J = 14.2), 2.91 (t, 2H, J = 7.1), 2.75 (t, 2H, J = 7.1), 1.20 (s, 3H); ^{13}C nmr: δ 205.6, 172.4, 150.3, 140.7, 133.2, 132.4, 131.4, 128.5, 128.4, 127.9, 126.2, 124.8, 60.4, 52.6, 40.5, 35.2, 30.0, 18.8. *Anal.* Calcd. for $C_{20}H_{21}NO_5$: C, 67.61; H, 5.92; N, 3.94. Found: C, 67.50; H, 5.95; N, 3.92.

Methyl (±)-2,4-Dimethyl-2-(2-nitrobenzyl)-3-oxopentanoate (3d). This compound (1.16 g, 80%) was isolated as a light yellow oil. ir: 1745, 1714, 1528, 1351 cm^{-1}; ^1H nmr: δ 7.84 (dd, 1H, J = 7.9, 1.6), 7.48 (td, 1H, J = 7.6, 1.4), 7.38 (td, 1H, J = 7.6, 1.6), 7.27 (dd, 1H, J = 7.9, 1.6), 3.69 (s, 3H), 3.68 (d, 1H, J = 14.2), 3.54 (d, 1H, J = 14.2), 2.83 (septet, 1H, J = 6.5), 1.28 (s, 3H), 1.09 (d, 6H, J = 6.5); ^{13}C nmr: δ 211.1, 172.3, 150.1, 133.2, 132.3, 131.7, 127.9, 124.8, 61.0, 52.4, 37.2, 35.0, 20.7, 20.2, 18.6. *Anal.* Calcd. for $C_{15}H_{19}NO_5$: C, 61.43; H, 6.48; N, 4.78, Found: C, 61.47; H, 6.51; N, 4.74.

Methyl (±)-3-Cyclohexyl-2-methyl-2-(2-nitrobenzyl)-3-oxopropanoate (3e). This compound (1.38 g, 81%) was isolated as a light yellow oil. ir: 1745, 1710, 1528, 1351 cm^{-1}; ^1H nmr: δ 7.84 (dd, 1H, 8.2, 1.4), 7.48 (td, 1H, J = 7.4, 1.4), 7.37 (ddd, 1H, J = 8.2, 7.4, 1.4), 7.26 (dd, 1H, J = 7.6, 1.4), 3.70 (s, 3H), 3.66 (d, 1H, J = 14.2), 3.54 (d, 1H, J = 14.2), 2.54 (tt, 1H, J = 11.5, 3.3), 1.75 (m, 2H), 1.66 (m, 4H), 1.44 (m, 2H), 1.27 (s, 3H), 1.24 (m, 2H); ^{13}C nmr: δ 209.7, 172.3, 150.7, 133.1, 132.3, 131.7, 127.9, 124.8, 60.9, 52.4, 47.8, 34.9, 30.6, 30.0, 25.6, 25.5 (2C), 18.5. *Anal.* Calcd. for $C_{18}H_{23}NO_5$: C, 64.91; H, 6.92; N, 4.20. Found: C, 65.01; H, 6.94; N, 4.11.

Representative Procedure for Alkylation of β-Keto Esters 2f-g with Iodomethane: Methyl (±)-2,4,4-Trimethyl-2-(2-nitrobenzyl)-3-oxopentanoate (3f). To a suspension of 0.17 g (7.11 mmoles) of oil-free sodium iodide in 12 mL of anhydrous *N*,*N*-dimethylformamide was added 1.39 g (4.74 mmoles) of **2f** in 5 mL of *N*,*N*-dimethylformamide. The reaction was stirred for 30 minutes and a solution of 2.02 g (14.2 mmoles) of iodomethane in 5 mL of *N*,*N*-dimethylformamide was added. The reaction mixture was stirred at room temperature for 24 hours, then added to 40 mL of saturated aqueous ammonium chloride and extracted with ether (three times). The combined ether layers were washed with aqueous solutions of sodium thiosulfate (one time) and sodium chloride (one time), and then dried (magnesium sulfate). The crude product was concentrated under vacuum and purified by flash chromatography on a 30-cm x 2-cm silica gel column using 5% ether in hexanes to give 1.34 g (92%) of **3f** as a light yellow oil. ir: 1745, 1698, 1528, 1351 cm^{-1}; ^1H nmr: δ 7.83 (dd, 1H, J = 7.9, 1.4), 7.48 (td, 1H, J = 7.4, 1.4), 7.37 (td, 1H, J = 7.9, 1.4), 7.22 (dd, 1H, J = 7.6, 1.4), 3.66 (s, 3H), 3.62 (d, 2H, J = 1.6), 1.30 (s, 3H), 1.20 (s, 9H); ^{13}C nmr: δ 210.8, 172.4, 150.8, 133.4, 132.1, 131.4, 127.9, 124.8, 59.4, 52.2, 45.9, 37.1, 28.5 (3C), 19.1. *Anal.* Calcd. for $C_{16}H_{21}NO_5$: C, 62.54; H, 6.84; N, 4.56. Found: C, 62.71; H, 6.86; N, 4.51.

Methyl (±)-2-Methyl-2-(2-nitrobenzyl)-3-phenyl-3-oxopropanoate (3g). This compound (1.07 g, 85%) was isolated as a light yellow solid, mp 97-98° (ether-petroleum ether). ir: 1736, 1683, 1527, 1353 cm^{-1}; ^1H nmr: δ 7.85 (dd, 1H, J = 8.2, 1.6), 7.80 (m, 2H), 7.52 (m, 1H), 7.48-7.34 (complex, 4H), 7.22 (dd, 1H, J = 7.6, 1.6), 3.94 (ABd, 1H, J = 14.4), 3.75 (d, 1H, J = 14.4), 3.60 (s, 3H), 1.43 (s, 3H); ^{13}C nmr: δ 196.3, 173.7, 150.8, 135.2, 133.4, 132.9, 132.2, 131.1, 128.6, 128.5, 128.0, 124.9,

58.0, 52.6, 36.9, 20.9. *Anal.* Calcd. for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.20; N, 4.28. Found: C, 66.12; H. 5.27; N, 4.24.

Representative Procedure for the Reductive Cyclization. Caution! Addition of 5% palladium-on-carbon to methanol can cause fires. This operation should be performed under a nitrogen atmosphere.

A solution of 300 mg the β-keto ester in 125 mL of methanol containing 75 mg of 5% palladium-on-carbon was placed in a sealed stainless steel pressure vessel in a Paar apparatus. The vessel was evacuated once, shaking was initiated and the apparatus was rapidly pressurized to 4 atmospheres with hydrogen gas. The reaction was continued for 3 hours at 30°. At the end of this time, hydrogen was purged from the reactor and the crude reaction mixture was concentrated. The residue was diluted with ether, and filtered through a pad of Celite® topped with a layer of anhydrous magnesium sulfate to remove the catalyst. Removal of the ether gave the cyclized product as a mixture of *cis* and *trans* isomers. The major isomer **4a** was purified by preparative thin layer chromatography; the minor isomer **5a** was isolated with **4a** as a minor contaminant. Solids were triturated with 2% ether in petroleum ether.

Methyl (±)-(2*R,3*R**)-2,3-Dimethyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (4a).** This compound (178 mg, 72%) was isolated as a light yellow solid, mp 58-59°. ir: 3401, 1727 cm^{-1}; ^1H nmr: δ 7.01 (d, 1H, J = 7.4), 6.99 (t, 1H, J = 7.9), 6.65 (td, 1H, J = 7.4, 1.1), 6.49 (d, 1H, J = 7.9), 3.91 (br s, 1H), 3.69 (s, 3H), 3.45 (qd, 1H, J = 6.5, 0.8). 3.19 (d, 1H, J = 16.6), 2.62 (d, 1H, J = 16.6), 1.24 (s, 3H), 1.09 (d, 3H, J = 6.5); ^{13}C nmr: δ 176.3, 141.8, 129.9, 126.8, 118.6, 117.3, 114.2, 52.5, 51.8, 43.3, 32.4, 23.2, 18.8; ms: *m/z* 219 (M^+). *Anal.* Calcd. for $C_{13}H_{17}NO_2$: C, 71.23; H, 7.76; N, 6.39. Found: C, 71.32; H, 7.79; N, 6.33.

Methyl (±)-(2*R,3*R**)-3-Methyl-2-pentyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (4b).** This compound (185 mg, 72%) was isolated as a light yellow oil that crystallized on standing, mp 48-50°. ir: 3413, 1728 cm^{-1}; ^1H nmr: δ 7.01 (d, 1H, J = 7.4), 7.00 (t, 1H, J = 7.4), 6.64 (td, 1H, J = 7.4, 1.1), 6.52 (d, 1H, J = 7.6), 4.17 (br s, 1H), 3.72 (s, 3H), 3.23 (m, 1H), 3.18 (d, 1H, J = 16.6), 2.60 (d, 1H, J = 16.6), 1.57-1.10 (complex, 8H), 1.23 (s, 3H), 0.87 (t, 3H, J = 6.7); ^{13}C nmr: δ 176.8, 141.4, 130.2, 126.8, 118.5, 117.1, 114.2, 56.8, 51.8, 43.4, 32.1, 32.0. 31.5, 26.4, 23.5, 22.6, 14.0; ms: *m/z* 275 (M^+). *Anal.* Calcd. for $C_{17}H_{25}NO_2$: C, 74.18; H, 9.09; N, 5.09. Found: C, 74.27; H, 9.14; N, 5.07.

Methyl (±)-(2*S,3*R**)-3-Methyl-2-pentyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (5b).** This compound (23 mg, 9%) was isolated as a light yellow oil that contained a small amount of **4b**. ir: 3410, 1728 cm^{-1}: ^1H nmr: δ 7.00 (t, 1H, J = 7.6), 6.96 (d, 1H, J = 7.4), 6.63 (td, 1H, J = 7.4, 1.1), 6.50 (d, 1H, J = 7.6), 3.88 (br s, 1H), 3.70 (s, 3H), 3.50 (dd, 1H, J = 8.7, 3.0), 3.25 (d, 1H, J = 16.1), 2.57 (d, 1H, J = 16.1), 1.58-1.10 (complex, 8H), 1.11 (s, 3H), 0.90 (t, 3H, J = 6.8); ^{13}C nmr: δ 177.1, 142.6, 130.2, 129.4, 126.8, 117.2, 113.9, 56.0, 52.0, 43.9, 37.9, 31.7, 30.7, 26.2, 22.6, 16.4, 14.0; ms: *m/z* 275 (M^+). *Anal.* Calcd. for $C_{17}H_{25}NO_2$: C, 74.18; H, 9.09; N, 5.09. Found: C, 74.31; H, 9.12; N, 5.01.

Methyl (±)-(2*R,3*R**)-3-Methyl-2-(2-phenylethyl)-1,2,3,4-tetrahydroquinoline-3-carboxylate (4c).** This compound (191 mg, 73%) was isolated as a light yellow oil. ir: 3413, 1728 cm^{-1}; ^1H nmr: δ 7.31-7.11 (complex, 5H), 7.01 (t, 1H, J = 7.4), 7.00 (t, 1H, J = 7.6), 6.65 (td, 1H, J = 7.4, 1.1), 6.43 (d, 1H, J = 7.9), 4.03 (br s, 1H), 3.68 (s, 3H), 3.22 (d, 1H, J = 10.1), 3.16 (d, 1H, J = 16.6), 2.80 (ddd, 1H, J = 13.9, 8.7, 6.0), 2.62 (m, 1H), 2.61 (d, 1H, J = 16.6), 1.67 (m, 1H), 1.52 (m, 1H), 1.20 (s, 3H); ^{13}C nmr: δ 176.6, 141.5, 141.1, 130.2, 128.4, 128.3, 126.9, 126.0, 118.5, 117.3, 114.4, 56.3, 51.9, 43.4, 33.6, 33.2, 31.9, 23.4; ms: *m/z* 309 (M^+). *Anal.* Calcd. for $C_{20}H_{23}NO_2$: C, 77.67; H, 7.44; N, 4.53. Found: C, 77.56; H, 7.47; N, 4.49.

Methyl (±)-(2*S,3*R**)-3-Methyl-2-(2-phenylethyl)-1,2,3,4-tetrahydroquinoline-3-carboxylate (5c).** This compound (26 mg, 10%) was isolated as a light yellow oil that contained a small amount of **4c**. ir: 3406, 1728 cm^{-1}; ^1H nmr: δ 7.33-7.12 (complex, 5H), 6.97 (m, 2H), 6.63 (td, 1H, J = 7.4, 1.1), 6.42 (dd, 1H, J = 7.9, 0.8), 3.80 (br s, 1H), 3.65 (s, 3H), 3.56 (dd, 1H, J = 10.1, 2.5), 3.22 (d, 1H, J = 16.1), 2.82 (ddd, 1H, J = 13.6, 9.5, 6.3), 2.68 (m, 1H), 2.54 (d, 1H, J = 16.1), 1.76 (m, 1H), 1.66 (m, 1H), 1.12 (s, 3H); ^{13}C nmr: δ 176.7, 142.4, 141.4, 129.4, 128.5, 128.4, 126.9, 126.1, 119.1, 117.4, 114.1, 55.9, 52.0, 44.0, 37.5, 33.2, 32.6, 16.9; ms: *m/z* 309 (M^+). *Anal.* Calcd. for $C_{20}H_{23}NO_2$: C, 77.67; H, 7.44; N, 4.53. Found: C, 77.73; H, 7.48; N, 4.44.

Methyl (±)-(2*R,3*R**)-2-Isopropyl-3-methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (4d).** This product was formed along with < 5% (by ^1H nmr) of the minor (2*S**,3*R**) isomer. Compound **4d** (198 mg, 78%) was isolated as a light yellow oil that crystallized on standing, mp 75-77°. ir: 3411, 1728 cm^{-1}; ^1H nmr: δ 7.00 (d, 1H, J = 7.4), 7.00 (t, 1H, J = 7.4), 6.62 (td, 1H, J = 7.4, 1.1), 6.51 (dd, 1H, J = 8.2, 1.1), 4.24 (br s, 1H), 3.72 (s, 3H), 3.21 (d, 1H, J = 16.2), 3.08 (dd, 1H, J = 5.5, 1.6), 2.61 (d, 1H, J = 16.2), 1.63 (septet, 1H, J = 6.8), 1.23 (s, 3H), 0.87 (d, 3H, J = 6.8), 0.84 (d, 3H, J = 6.8); ^{13}C nmr: δ 177.1, 142.1, 130.2, 126.9, 118.4, 116.8, 113.5, 61.9, 51.7, 43.0, 31.9, 31.7, 25.1, 21.2, 19.4; ms: *m/z* 247 (M^+). *Anal.* Calcd. for $C_{15}H_{21}NO_2$: C, 72.87; H, 8.50; N, 5.67. Found: C, 72.95; H, 8.48; N, 5.61.

Methyl (±)-(2*R,3*R**)-2-Cyclohexyl-3-methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (4e).** This product was formed along with < 5% (by ^1H nmr) of the minor (2*S**,3*R**) isomer. Compound **4e** (206 mg, 80%) was isolated as a light yellow oil that crystallized on standing, mp 104-105°. ir: 3419, 1728 cm^{-1}; ^1H nmr: δ 7.00 (d, 1H, J = 7.4), 6.99 (t, 1H, J = 7.4), 6.62 (td, 1H, J = 7.4, 1.1), 6.49 (dd, 1H, J = 7.4, 1.1), 4.26 (br s, 1H), 3.72 (s, 3H), 3.19 (d, 1H, J = 16.8), 3.07 (dd, 1H, J = 5.5, 1.6), 2.63 (dd, 1H, J = 16.8, 1.4), 1.75-1.45 (complex, 5H), 1.38-0.90 (complex, 6H), 1.21 (s, 3H); ^{13}C nmr: δ 177.2, 142.2, 130.2, 126.9, 118.4, 116.6, 113.4, 61.3, 51.7, 42.9, 42.0, 31.9, 31.4, 29.6, 26.6, 26.1 (2C), 25.0; ms: *m/z* 287 (M^+). *Anal.* Calcd. for $C_{18}H_{25}NO_2$: C, 75.26; H, 8.71; N, 4.88. Found: C, 75.08; H, 8.76; N, 4.81.

Methyl (±)-(2*S,3*R**)-2-*tert*-Butyl-3-methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (5f).** The *tert*-butyl-substituted products showed the reverse order of elution. This compound (29 mg, 11%) was isolated as a light yellow oil that contained a small amount of **4f**. ir: 3427, 1726 cm^{-1}; ^1H nmr: δ 7.00 (t, 1H, J = 7.9), 6.90 (d, 1H, J = 7.4), 6.57 (td, 1H, J = 7.4, 0.8), 6.51 (d, 1H, J = 7.9), 3.84 (br s, 1H), 3.71 (s, 3H), 3.57 (s, 1H), 3.28 (d, 1H, J = 15.5), 2.44 (d, 1H, J = 15.5), 1.14 (s, 3H), 1.02 (s, 9H); ^{13}C nmr: δ 178.3, 143.1, 128.9, 127.0, 118.1, 116.4, 112.7, 64.0, 51.9, 43.0, 42.7, 35.3, 27.9 (3C), 16.8; ms: *m/z* 261 (M^+). *Anal.* Calcd. for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.81; N, 5.36. Found: C, 73.80; H, 8.92; N, 5.23.

Methyl (±)-(2*R,3*R**)-2-*tert*-Butyl-3-methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (4f).** This compound (171 mg, 67%) was isolated as a light yellow oil. ir: 3420, 1728 cm^{-1}; ^1H nmr: δ 6.98 (t, 1H, J = 7.9), 6.97 (d, 1H, J = 7.4), 6.59 (td, 1H, J = 7.4, 1.1), 6.49 (dd, 1H, J = 7.9, 1.1), 4.32 (br s, 1H), 3.71 (s, 3H), 3.37 (d, 1H, J = 16.9), 3.12 (d, 1H, J = 1.6), 2.56 (dd, 1H, J =

16.9, 1.6), 1.25 (s, 3H), 0.89 (s, 9H); ^{13}C nmr: δ 177.4, 142.7, 130.1, 126.9, 118.1, 116.3, 112.7, 64.8, 51.6, 42.7, 38.5, 32.4, 27.9 (3C), 27.5; ms: *m/z* 261 (M^+). *Anal.* Calcd. for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.81; N, 5.36. Found: C, 73.59; H, 8.82; N, 5.33.

Methyl (±)-(2*S,3*R**)-3-Methyl-2-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (5g).** The phenyl-substituted products showed the reverse order of elution. This compound (27 mg, 10%) was isolated as a light yellow oil. ir: 3383, 1727 cm^{-1}; ^{1}H nmr: δ 7.35-7.27 (complex, 5H), 7.03 (td, 1H, J = 7.6, 1.4), 7.02 (d, 1H, J = 7.4), 6.68 (td, 1H, J = 7.4, 1.1), 6.55 (d, 1H, J = 7.6), 4.78 (s, 1H), 4.16 (br s, 1H), 3.60 (s, 3H), 3.41 (d, 1H, J = 16.1), 2.63 (d, 1H, J = 16.1), 1.09 (s, 3H); ^{13}C nmr: δ 176.2, 143.0, 140.5, 129.4, 128.2, 128.0, 127.9, 127.0, 118.9, 117.4, 113.6, 60.7, 52.0, 45.0, 36.8, 17.7; ms: *m/z* 281 (M^+). *Anal.* Calcd. for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.76; N, 4.98. Found: C, 76.69; H, 6.78; N, 4.93.

Methyl (±)-(2*R,3*R**)-3-Methyl-2-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (4g).** This compound (198 mg, 77%) was isolated as a light yellow oil. ir: 3402, 1727 cm^{-1}; ^{1}H nmr: δ 7.24-7.18 (complex, 3H), 7.17-7.10 (complex, 2H), 7.06 (t, 1H, J = 7.4), 7.05 (d, 1H, J = 7.4), 6.69 (td, 1H, J = 7.4, 1.1), 6.55 (dd, 1H, J = 7.4, 1.1), 4.46 (s, 1H), 4.42 (br s, 1H), 3.56 (s, 3H), 3.18 (d, 1H, J = 16.6), 2.60 (d, 1H, J = 16.6), 1.37 (s, 3H); ^{13}C nmr: δ 175.2, 143.0, 142.3, 130.0, 128.1, 127.6, 127.2, 127.0, 118.4, 117.1, 113.0, 61.4, 51.6, 44.6, 31.4, 23.7; ms: *m/z* 281 (M^+). *Anal.* Calcd. for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.76; N, 4.98. Found: C, 76.85; H, 6.74; N, 4.99.

(±)-(2*R,3*R**)-3-Hydroxymethyl-2,3-dimethyl-1,2,3,4-tetrahydroquinoline (6).** To a stirred suspension of 87 mg (2.28 mmoles) of lithium aluminum hydride in 20 mL of dry ether at 0° was slowly added a solution of 500 mg (2.28 mmoles) of **4a** in 5 mL of ether. Following the addition, the reaction mixture was stirred for 3 hours with slow warming to room temperature. The reaction was cautiously quenched with three drops of water followed by three drops of 1 *M* sodium hydroxide. The crude reaction mixture was filtered through Celite and the precipitate was washed with ether (three times). Concentration yielded the product as an oily solid. This solid was triturated with 5% petroleum ether in ether and filtered to give 406 mg (93%) of **6** as an off-white powder, mp 149-151°. ir: 3544, 3351 cm^{-1}; ^{1}H nmr: δ 6.97 (m, 2H), 6.65 (td, 1H, J = 7.4, 1.1), 6.48 (dd, 1H, J = 8.2, 1.1), 3.69 (br s, 1H), 3.66 (ABd, 1H, J = 10.9), 3.49 (ABd, 1H, J = 10.9), 3.26 (q, 1H, J = 6.5), 2.76 (ABd, 1H, J = 16.6), 2.52 (ABd, 1H, J = 16.6), 2.14 (br s, 1H), 1.19 (d, 3H, J = 6.5), 1.00 (s, 3H); ^{13}C nmr: δ 143.9, 129.5, 126.5, 120.9, 117.7, 113.8, 67.2, 54.6, 36.5, 35.5, 22.4, 16.7. *Anal.* Calcd. for $C_{12}H_{17}NO$: C, 75.39; H, 8.90; N, 7.33. Found: C, 75.44; H, 8.94; N, 7.28.

X-ray Structure of 6. Crystals of **6** were obtained as colorless plates by vapor diffusion of pentane into a solution of **6** in ether. A specimen measuring 0.4 x 0.4 x 0.1 mm was immersed in polyisobutylene and placed in a nylon loop, and the sample was mounted in 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-second exposure times. Data integration employed the Bruker SAINT software package [14]. Data were corrected for absorption effects using the SADABS multi-scan technique. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 using the Bruker SHELXTL software suite [14]. Non-hydrogen atoms were assigned anisotropic temperature factors. All hydrogens except for the NH group were placed in calculated positions (riding model). The NH hydrogen (H1) was located in the difference Fourier map and allowed to refine without constraints. The refined H1 position was consistent with a hydrogen bond to O1 in an adjacent molecule with d(H1···O1) = 2.108(17) Å. Refined formula: $C_{12}H_{17}NO$, M = 194.27, triclinic, space group P-1, a = 6.7282(8) Å, b = 9.1730(11) Å, c = 9.2223(12) Å, α = 88.759(7)°, β = 69.472(6)°, γ = 74.386(7)°, U = 511.70(11) Å^3, Z = 2, D_c = 1.241 g cm^{-1}, μ = 0.078 mm^{-1}, T = 115(2) K, $2\theta_{max}$ = 50.0°, completeness to $2\theta_{max}$ = 99.7%, 6299 total reflections, 1787 independent (R_{int} = 0.0408), 1648 observed [$I > 2\sigma(I)$]. Final $R1$ [$I > 2\sigma(I)$] = 0.0374, $wR2$ (all data) = 0.1089, largest difference peak and hole 0.298 and –0.201 eÅ^{-3}. CCDC 644646 contains the supplementary crystallographic data for compound **6**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Acknowledgement. The authors wish to acknowledge the Oklahoma Center for the Advancement of Science and Technology (OCAST HR01-015) for support of this research. J. E. S. also thanks the Oklahoma State University College of Arts and Sciences for a Niblack Research Scholarship and the Department of Chemistry for a Moore Scholarship. Finally, we wish to thank the NSF (BIR-9512269), the Oklahoma State Regents for Higher Education (OSRHE), the W. M. Keck Foundation, and Conoco Inc. for funding our Oklahoma Statewide Shared NMR Facility and the OSRHE for funding our crystallographic facility.

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