(±)-2-Alkyl-1,2,3,4-tetrahydroquinoline-3-carboxylic Esters by a Catalyst and Pressure Dependent Tandem Reduction-Reductive Amination Reaction

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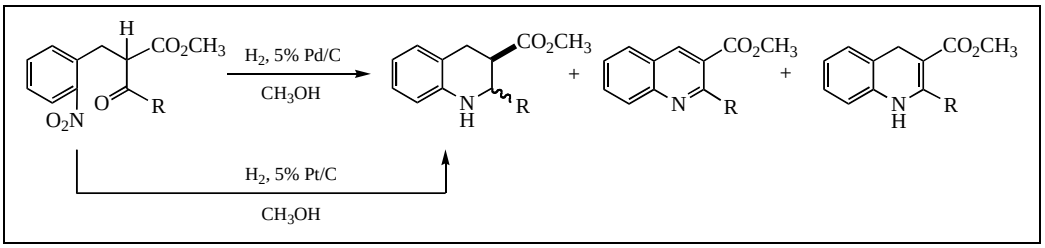

A series of 2-(2-nitrobenzyl)-substituted β-keto ester derivatives has been subjected to reductive cyclization under catalytic hydrogenation conditions. The reactions were found to be highly dependent on the catalyst and hydrogen pressure used. Hydrogenation over 5% palladium-on-carbon at 4 atmospheres pressure produced complex mixtures of products that included predominantly 1,2,3,4-tetrahydroquinoline and quinoline products; at 1 atmosphere pressure, the same reactions gave mixtures containing predominantly tetrahydroquinoline and 1,4-dihydroquinoline derivatives. Hydrogenation using 5% platinum-on-carbon was much cleaner and afforded the desired *cis*- and *trans*-(±)-2-alkyl-1,2,3,4-tetrahydroquinoline-3-carboxylic esters, with the *cis* product predominating by ≥ 13:1.

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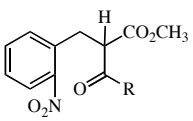
INTRODUCTION

A previous report from this laboratory described the highly diastereoselective synthesis of (±)-2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylic esters by reductive cyclization of 2-(2-nitrophenyl)-substituted γ-keto esters [2,3]. Selectivity in these ring closures was attributed to a steric effect imposed by the ester group on the benzylic carbon (α to the aromatic ring), which directs the hydrogenation to give the product bearing the C2 alkyl and C4 ester substituents *cis*. In the preceding paper [4], we evaluated selectivity in the cyclization of substrates having the ester and a geminal methyl group on the β carbon relative to the aromatic ring. Selectivity for the *cis* product in these systems was somewhat reduced due to the greater conformational flexibility around the β carbon, though the magnitude of this effect may have been partially offset by the geminal methyl. Initially, the current work was undertaken to observe the selectivity of this cyclization in the absence of the geminal methyl substituent. When these reactions were run under our standard conditions at 1 or 4 atmospheres of hydrogen with 5% palladium-on-carbon, however, complex mixtures of products were obtained. These more complicated product mixtures derived from the tendency of the imine intermediates to undergo double bond migration and aromatization. The project goal was, therefore, modified to include optimization of 1,2,3,4-tetrahydroquinoline formation through the use of different catalysts.

The 2-alkyl-3-quinolinecarboxylate and 2-alkyl-1,2,3,4-tetrahydroquinoline-3-carboxylate esters encountered during this study, are known to have a variety of uses. Quinoline-3-carboxylic esters have been evaluated as herbicides [5] and as key intermediates in synthetic approaches to several biologically active alkaloids [6,7]. Tetrahydroquinoline-3-carboxylic esters have been investigated as renin inhibitors [8] and as synthetic precursors to a new class of growth hormone release promoters [9]. New methodology to prepare these ring systems may provide easy access to these targets as well as other useful analogues.

RESULTS AND DISCUSSION

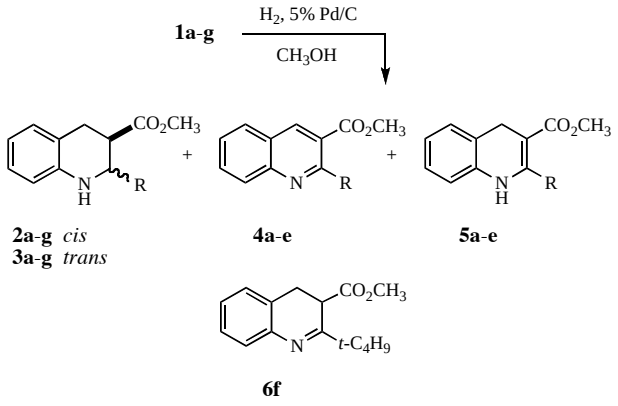
Substrates **1a**-**g** required for the current study were prepared by alkylation of a series of β-keto esters with 2-nitrobenzyl bromide using potassium carbonate in acetone [4]. The use of 3 equivalents of the β-keto ester for each equivalent of the bromide was optimum to minimize dialkylation. Yields were 66-80% following chromatographic purification.



1a (R = CH_3) **1e** (R = *c*-C_6H_{11})
1b (R = *n*-C_5H_{11}) **1f** (R = *t*-C_4H_9)
1c (R = $CH_2CH_2C_6H_5$) **1g** (R = C_6H_5)
1d (R = *i*-C_3H_7)

Cyclizations of **1** were initially run using 5% palladium-on-carbon under 4 atmospheres of hydrogen as per our previous work [2,4]. This resulted in a surprisingly complex mixture of products that included the expected *cis*- and *trans*-1,2,3,4-tetrahydroquinolines, **2** and **3** respectively, along with the corresponding quinoline **4** and a small amount of the 1,4-dihydroquinoline **5** [10]. Repeating the experiments at 1 atmosphere pressure yielded larger proportions of the 1,4- dihydroquinolines, and lesser quantities of the quinolines. In each case, these complex mixtures included combinations of products that were only partially separable (see Scheme 1). Additionally, the dihydroquinolines slowly aromatized to the quinolines upon extended exposure to air.

Scheme 1

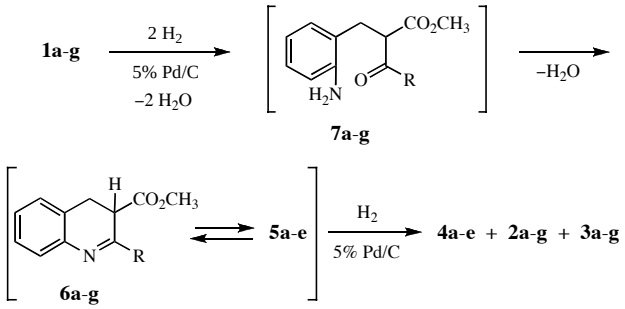


1		% Yield of the Major Product [a] 4 atm H_2 **4**	1 atm H_2 **5**
a	(R = CH_3)	44	74
b	(R = C_5H_{11})	57	57
c	(R = CH_2CH_2Ph)	64	86
d	(R = *i*-C_3H_7)	32	52
e	(R = *c*-C_6H_{11})	33	49
f	(R = *t*-C_4H_9)	[b]	[d]
g	(R = C_6H_5)	[c]	[e]

[a] Reactions using 5% Pd/C gave complex mixtures of products that were only partially separable. Only the yield of the major product is given. [b] **2f** (68%) and **3f** (3%) were isolated. [c] **2g** (72%) and **3g** (3%) were isolated. [d] **6f** (58%) was isolated; **2f** and **3f** (28% total) were also isolated. [e] **2g** (62%) and **3g** (2%) were isolated.

The results obtained using palladium-on-carbon at different hydrogen pressures offer some important insights into the mechanism of the process. Initial reduction of **1** to amino keto ester **7** followed by condensative ring closure gives imine **6**. With a proton geminal to the ester at C3, the imine double bond then migrates away from the aromatic ring and into conjugation with the ester to generate the 1,4-dihydroquinoline **5**. Upon continued hydrogenation, the 1,4-dihydroquinoline **5** undergoes disproportionation to give a mixture of quinoline **4** and the diastereomeric tetrahydroquinolines **2** and **3** (see Scheme 2). Evidence for disproportionation was obtained by hydrogenating **5c** (R = CH_2CH_2Ph) at 4 atmospheres pressure, which led to a 3.5:1 mixture of quinoline and tetrahydroquinoline products [11]. While reduction of dihydroquinoline **5c** would be expected to give exclusively the *cis* tetrahydroquinoline, imine **6c** could provide either the *cis* or the *trans* product isomers. The observation that both the *cis* and *trans* tetrahydroquinolines are produced on reduction of **5c** suggests that some interconversion of **5c** and **6c** occurs under the reduction conditions.

Scheme 2

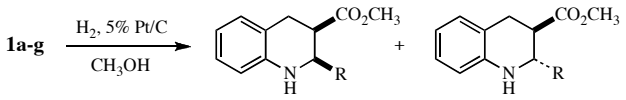


Interestingly, the proportion of dihydroquinoline and quinoline products decreased as the size of the alkyl group R increased. Substrates where R was a primary alkyl group (*i.e.* R = CH_3, *n*-C_5H_{11} or CH_2CH_2Ph) gave the highest yields of dihydroquinolines and quinolines. When R was secondary (*i.e.* R = *i*-C_3H_7 or *c*-C_6H_{11}), the proportion of these products was reduced and larger amounts of the tetrahydroquinolines were isolated. These observations are readily explained in terms of a steric effect. In forming the dihydroquinolines and quinolines, it is necessary for the C2 substituent to become co-planar with the C3 ester, which creates a destabilizing steric interaction for larger R groups. The *tert*-butyl ketone **1f** afforded none of the dihydroquinoline and quinoline products. Instead, low-pressure hydrogenation gave a *ca* 2:1 mixture of the 3,4-dihydroquinoline (*i.e.* the initial cyclized imine **6f**) and the diastereomeric tetrahydroquinolines **2f** and **3f**. Further reduction of **6** resulted in the formation of the *cis* and *trans* tetrahydroquinolines, but gave none of the sterically congested aromatic product. Reaction of phenyl-substituted ketone **1g** yielded only tetrahydroquinolines **2g** and **3g** under all conditions explored.

Disproportionation to give aromatic and alicyclic products has been previously observed in the catalytic reduction of 1,3-cyclohexadiene using a palladium catalyst [11]. This earlier study also noted that platinum catalysts gave only reduction products from these same substrates. Based on this report, the current substrates

were hydrogenated at 4 atmospheres over 5% platinum-on-carbon in an effort to optimize the formation of the desired tetrahydroquinolines. Under these conditions, the reaction cleanly provided mixtures of the *cis* and *trans* tetrahydroquinolines in all cases [12]. Furthermore, the ratios observed were synthetically useful providing the isomer bearing the C2 alkyl group *cis* to the C3 ester as the major product in a ≥ 13:1 ratio; for R = *c*-C_6H_{11} and *t*-C_4H_9, < 2% of the *trans* product was observed. Though none of the dihydroquinoline was observed in reductions catalyzed by platinum-on-carbon even at low hydrogen pressures [12], we cannot rule out this intermediate as a contributor to the *cis* product. The two diastereomers were easily separated by preparative thin layer chromatography (Scheme 3).

Scheme 3

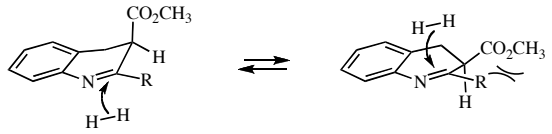


2a-g **3a-g**

1		Isolated Yields (%) 2	3	Ratio
a	(R = CH_3)	64	4	16:1
b	(R = C_5H_{11})	74	5	15:1
c	(R = CH_2CH_2Ph)	77	6	13:1
d	(R = *i*-C_3H_7)	76	3	25:1
e	(R = *c*-C_6H_{11})	83	< 2	> 42:1
f	(R = *t*-C_4H_9)	86	< 2	> 43:1
g	(R = C_6H_5)	82	2	41:1

In the ring closure reactions to give tetrahydroquinolines, all of the reactions showed synthetically useful selectivities. Substrates incorporating primary alkyl R groups adjacent to the side chain ketone gave product ratios in the range of 15:1, while those with more branched alkyl and aromatic R groups gave ratios of ≥ 25:1. Since the more congested molecules do not readily form the dihydroquinolines, the tetrahydroquinoline products most likely arise primarily from reduction of imine **6**. Conformational analysis of this imine (Scheme 4) indicates a significant steric interaction between the C2 alkyl and the C3 ester when the ester occupies a pseudo-equatorial orientation (*e.g.* **6B**). Thus, the ester should preferentially adopt a pseudoaxial orientation as in **6A** where it can sterically control the course of the final hydrogenation. Finally, none of the current reactions gave any products resulting from capture of an intermediate hydroxylamine seen in earlier reductive cyclizations using platinum catalysts [13].

Scheme 4



6A major **6B** minor

CONCLUSION

We have successfully carried out the reductive cyclization of 2-(2-nitrobenzyl)-substituted β-keto esters. The reaction is somewhat tunable based upon the catalyst and the hydrogen pressure used. The use of 5% palladium-on-carbon afforded complex reaction mixtures from which 2-alkylquinoline-3-carboxylate esters (4 atmospheres pressure) and 2-alkyl-1,4-dihydroquinoline-3-carboxylate esters (1 atmosphere pressure) could be isolated. The production of *cis*- and *trans*-(±)-2-alkyl-1,2,3,4-tetrahydroquinoline-3-carboxylic esters was optimized by using 5% platinum-on-carbon, a catalyst known to disfavor the double bond migration and disproportionation reactions observed with palladium catalysts. The current work, thus, extends a previous report and establishes platinum as the catalyst of choice in reductions of heterocyclic substrates prone to aromatization. These tetrahydroquinolines were produced cleanly and were readily separated. The *cis* isomer was favored by ≥ 13:1 making this a useful approach to the synthesis of these compounds and again demonstrating the stereodirecting effect of the ester in the final reduction of the sequence. The current substrates showed improved selectivity relative to substrates bearing a geminal methyl at the ester carbon but still afforded small amounts of the *trans* products.

EXPERIMENTAL

Separations were performed by preparative thin layer chromatography on 20-cm x 20-cm silica gel GF plates (Analtech No. 02015); band elution 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 were referenced to polystyrene. ^1H 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. Unless otherwise indicated, mass spectra (electron impact/direct probe) were obtained at 70 electron volts. The 2-(2-nitrobenzyl)-substituted β-keto esters used in this work were prepared as described in the accompanying paper [4].

Representative Hydrogenation Procedure. Caution! Addition of 5% palladium-on-carbon and 5% platinum-on-carbon to methanol can cause fires. This operation should be performed under a nitrogen atmosphere.

A solution of 300 mg of β-keto ester **1** in 125 mL of methanol containing 100 mg of catalyst 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 pressurized to the appropriate level 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 crude product mixtures.

A. Reductive Cyclization (4 atm H_2, 5% Pd/C). These reactions gave mixtures containing the major quinoline product along with the *cis* and *trans* tetrahydroquinolines and a small amount of the 1,4-dihydroquinoline [10]. The products were partially separated by preparative thin layer chromatography using 15% ether in hexanes. In the *tert*-butyl- and phenyl-substituted cases, only the tetrahydroquinoline products were isolated. The physical and spectral data for the major quinoline products follow. Solid compounds were recrystallized from petroleum ether.

Methyl 2-Methylquinoline-3-carboxylate (4a). This compound (104 mg, 44%) was isolated a white solid, mp 48-49°, lit [13] mp 50°. The spectral data matched those previously reported [14].

Methyl 2-Pentylquinoline-3-carboxylate (4b). This compound (178 mg) was isolated as an oil contaminated with ca 20% of the major tetrahydroquinoline product. ir: 1727 cm^{-1}; ^1H nmr: δ 8.75 (s, 1H), 8.11 (dd, 1H, J = 8.4, 0.8), 7.89 (dd, 1H, J = 7.9, 1.1), 7.83 (ddd, 1H, J = 8.4, 7.0, 1.6), 7.58 (ddd, 1H, J = 7.9, 7.0, 1.1), 4.03 (s, 3H), 3.37 (m, 2H), 1.82 (m, 2H), 1.47 (m, 4H), 0.96 (t, 3H, J = 7.1); ^{13}C nmr: δ 167.1, 162.2, 148.7, 140.0, 131.5, 128.7, 128.4, 126.5, 125.6, 123.5, 52.4, 37.8, 32.1, 29.8, 22.6, 14.1; ms (30 eV): *m/z* 257 (M^+).

Methyl 2-(2-Phenylethyl)quinoline-3-carboxylate (4c). This compound (165 mg, 64%) was isolated as a light yellow solid, mp 58-59°. ir: 1723 cm^{-1}; ^1H nmr: δ 8.72 (s, 1H), 8.09 (d, 1H, J = 8.4), 7.84 (d, 1H, J = 8.1), 7.78 (ddd, 1H, J = 8.1, 7.0, 1.6), 7.33 (ddd, 1H, J = 8.4, 7.0, 0.8), 7.37-7.12 (complex, 5H), 3.95 (s, 3H), 3.64 (m, 2H), 3.12 (m, 2H); ^{13}C nmr: δ 167.0, 161.0, 148.8, 142.0, 140.2, 131.7, 128.7, 128.6, 128.5, 128.3, 126.7, 125.8, 125.7, 123.5, 52.4, 39.6, 35.9; ms (30 eV): *m/z* 291 (M^+). *Anal.* Calcd. for $C_{19}H_{17}NO_2$: C, 78.35; H, 5.84; N, 4.81. Found: C, 78.22; H, 5.76; N, 4.87.

Methyl 2-Isopropylquinoline-3-carboxylate (4d). This compound (80 mg, 32%) was isolated as a light yellow oil. ir: 1722 cm^{-1}; ^1H nmr: δ 8.59 (s, 1H), 8.06 (dd, 1H, J = 8.4, 0.8), 7.81 (dd, 1H, J = 8.2,1.4), 7.75 (ddd, 1H, J = 8.4, 7.0, 1.4), 7.51 (ddd, 1H, J = 8.2, 7.0, 1.4), 3.99 (septet, 1H, J = 6.8), 3.97 (s, 3H), 1.40 (d, 6H, J = 6.8); ^{13}C nmr: δ 167.6, 165.8, 18.7, 139.2, 131.2, 129.0, 128.2, 126.4, 125.4, 123.7, 52.4, 32.9, 22.3 (2C); ms (30 eV): *m/z* 229 (M^+). *Anal.* Calcd. for $C_{14}H_{15}NO_2$: C, 73.36; H, 6.55; N, 6.11. Found: C, 73.55; H, 6.57; N, 6.02.

Methyl 2-Cyclohexylquinoline-3-carboxylate (4e). This compound (82 mg, 33%) was isolated as a light yellow oil. ir: 1723 cm^{-1}; ^1H nmr: δ 8.59 (s, 1H), 8.06 (d, 1H, J = 8.4), 7.81 (d, 1H, J = 8.2), 7.75 (ddd, 1H, J = 8.4, 6.9, 1.4), 7.51 (td, 1H, J = 8.2, 1.1), 3.98 (s, 3H), 3.62 (tt, 1H, J = 11.2, 3.0), 1.97-1.75 (complex, 7H), 1.54-1.34 (complex, 3H); ^{13}C nmr: δ 167.6, 165.2, 148.8, 139.3, 131.2, 129.0, 128.2, 126.3, 125.3, 123.7, 52.4, 43.3, 32.6, 26.7, 26.2; ms: *m/z* 269 (M^+). *Anal.* Calcd. for $C_{17}H_{19}NO_2$: C, 75.84; H, 7.06; N, 5.20. Found: C, 75.95; H, 7.11; N, 5.09.

B. Reductive Cyclization (1 atm H_2, 5% Pd/C). These reactions gave mixtures containing the major 1,4-dihydroquinoline product along with the *cis* and *trans* tetrahydroquinolines and a small amount of the quinoline [10]. In the *tert*-butyl-substituted case, the 3,4-dihydroquinoline was isolated; the phenyl-substituted substrate gave only the tetrahydroquinolines. The physical and spectral data for the major 1,4-dihydroquinoline products follow. Solid compounds were triturated with 5% ether in petroleum ether.

Methyl 2-Methyl-1,4-dihydroquinoline-3-carboxylate (5a). This compound (176 mg, 74%) was isolated as a light yellow solid, mp 120-122°. ir: 3330, 1692, 1674, 1612, 1489 cm^{-1}; ^1H nmr: δ 7.03 (t, 1H, J = 7.6), 7.02 (dd, 1H, J = 7.4, 0.8), 6.89 (td, 1H, J = 7.4, 1.1), 6.55 (dd, 1H, J = 7.6, 0.8), 5.71 (br s, 1H), 3.75 (s, 2H), 3.72 (s, 3H), 2.33 (s, 3H); ^{13}C nmr: δ 168.5, 147.8, 137.1, 128.9, 126.8, 122.8, 121.8, 113.8, 93.9, 50.8, 27.5, 20.3; ms: *m/z* 203 (M^+). *Anal.* Calcd. for $C_{12}H_{13}NO_2$: C, 70.94; H, 6.40; N, 6.90. Found: C, 71.17; H, 6.45; N, 6.82.

Methyl 2-Pentyl-1,4-dihydroquinoline-3-carboxylate (5b). This compound (145 mg, 57%) was isolated as a light yellow solid, mp 87-89°. ir: 3321, 1693, 1671, 1613, 1489 cm^{-1}; ^1H nmr: δ 7.03 (t, 1H, J = 7.9), 7.02 (d, 1H, J = 7.4), 6.88 (td, 1H, J = 7.4, 1.1), 6.56 (d, 1H, J = 7.9), 5.76 (br s, 1H), 3.75 (s, 2H), 3.72 (s, 3H), 2.69 (m, 2H), 1.61 (m, 2H), 1.37 (m, 4H), 0.90 (t, 3H, J = 6.8); ^{13}C nmr: δ 168.0, 152.4, 137.3, 128.9, 126.8, 122.7, 121.8, 113.8, 93.4, 50.8, 33.4, 31.9, 28.3, 27.6, 22.5, 14.0; ms (30 eV): *m/z* 259 (M^+). *Anal.* Calcd. for $C_{16}H_{21}NO_2$: C, 74.13; H, 8.11; N, 5.41. Found: C, 74.25; H, 8.14; N, 5.33.

Methyl 2-(2-Phenylethyl)-1,4-dihydroquinoline-3-carboxylate (5c). This compound (221 mg, 86%) was isolated as a light yellow solid, mp 140-142°. ir: 3313, 1692, 1670, 1612, 1489 cm^{-1}; ^1H nmr: δ 7.31-7.16 (complex, 5H), 7.00 (m, 2H), 6.87 (td, 1H, J = 7.6, 1.4), 6.34 (d, 1H, J = 7.9), 5.51 (br s, 1H), 3.76 (s, 2H), 3.75 (s, 3H), 2.95 (m, 4H); ^{13}C nmr: δ 167.9, 151.6, 141.2, 137.1, 128.7, 128.5 (2C), 126.7, 126.2, 122.8, 121.8, 113.9, 93.5, 50.9, 35.8, 34.9, 27.6; ms (30 eV): *m/z* 293 (M^+). *Anal.* Calcd. for $C_{19}H_{19}NO_2$: C, 77.82; H, 6.48; N, 4.78. Found: C, 77.73; H, 6.45; N, 4.81.

Methyl 2-Isopropyl-1,4-dihydroquinoline-3-carboxylate (5d). This compound (128 mg, 52%) was isolated as a light yellow solid, mp 145-147°. ir: 3365, 1691, 1674, 1612, 1489 cm^{-1}; ^1H nmr: δ 7.13 (m, 2H), 6.89 (td, 1H, J = 7.6, 1.1), 6.59 (dd, 1H, J = 8.1, 1.1), 5.91 (br s, 1H), 4.26 (septet, 1H, J = 6.9), 3.76 (s, 2H), 3.72 (s, 3H), 1.17 (d, 6H, J = 6.9); ^{13}C nmr: δ 168.0, 156.3, 137.2, 128.8, 126.8, 122.7, 121.8, 113.8, 92.5, 50.8, 27.9, 27.6, 20.4 (2C); ms (30 eV): *m/z* 231 (M^+). *Anal.* Calcd. for $C_{14}H_{17}NO_2$: C, 72.73; H, 7.36; N, 6.06. Found: C, 72.61; H, 7.29; N, 6.08.

Methyl 2-Cyclohexyl-1,4-dihydroquinoline-3-carboxylate (5e). This compound (126 mg, 49%) was isolated as a light yellow oil. ir: 3377, 1694, 1672, 1613, 1489 cm^{-1}; ^1H nmr: δ 7.02 (m, 2H), 6.88 (td, 1H, J = 7.4, 1.1), 6.58 (d, 1H, J = 7.6), 6.03 (br s, 1H), 3.91 (tt, 1H, J = 12.0, 2.8), 3.76 (s, 2H), 3.71 (s, 3H), 1.94-1.70 (complex, 5H), 1.57-1.38 (complex, 2H), 1.38-1.10 (complex, 3H); ^{13}C nmr: δ 168.1, 156.2, 137.2, 128.7, 126.7, 122.7, 121.8, 113.9, 92.2, 50.8, 38.4, 30.9, 27.8, 26.3, 26.1; ms: *m/z* 271 (M^+). *Anal.* Calcd. for $C_{17}H_{21}NO_2$: C, 75.28; H, 7.75; N, 5.17. Found: C, 75.21; H, 7.78; N, 5.19.

Methyl (±)-2-*tert*-Butyl-3,4-dihydroquinoline-3-carboxylate (6). This compound (151 mg, 60%), was isolated as a colorless oil that crystallized on standing at 0°, mp 25-26°. ir: 1736, 1622 cm^{-1}; ^1H nmr: δ 7.36 (d, 1H, J = 7.6), 7.25 (m, 1H), 7.10 (m, 2H), 3.65 (dd, 1H, J = 6.8, 1.4), 3.51 (s, 3H), 3.15 (dd, 1H, J = 16.0, 1.4), 2.89 (dd, 1H, J = 16.0, 6.8), 1.27 (s, 9H); ^{13}C nmr: δ

173.8, 170.9, 144.0, 127.7, 127.2, 126.3, 126.2, 124.3, 52.2, 40.1, 37.9, 29.3, 27.5 (3C); ms (30 eV): *m/z* 245 (M^+). *Anal.* Calcd. for $C_{15}H_{19}NO_2$: C, 73.47; H, 7.76; N, 5.71. Found: C, 73.60; H, 7.82; N, 5.59.

C. Reductive Cyclization (4 atm H_2, 5% Pt/C). These reactions gave mixtures containing only the *cis* and *trans* tetrahydroquinolines [10]. The products were separated by preparative thin layer chromatography eluted with 15% ether in hexanes to give two major bands. Band 1 was the minor *trans* isomer **3**; band 2 was the major *cis* isomer **2**. Solid compounds were recrystallized from petroleum ether.

Methyl (±)-(2*R,3*S**)-2-Methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (3a).** This product (10 mg, 4%) was isolated as a light yellow oil. ir: 3392, 1731 cm^{-1}; ^1H nmr: δ 7.00 (t, 1H, J = 7.6), 6.98 (d, 1H, J = 7.4), 6.63 (td, 1H, J = 7.4, 1.1), 6.50 (d, 1H, J = 7.6), 3.74 (s, 3H), 3.70 (br s, 1H), 3.53 (dq, 1H, J = 9.3, 6.3), 3.06 (dd, 1H, J = 16.1, 11.2), 2.92 (dd, 1H, J = 16.1, 4.9), 2.45 (ddd, 1H, J = 11.2, 9.3, 4.9), 1.23 (d, 3H, J = 6.3); ^{13}C nmr: δ 174.9, 143.5, 129.1, 127.1, 119.3, 117.3, 113.8, 51.8, 49.1, 45.5, 30.6, 20.6; ms: *m/z* 205 (M^+). *Anal.* Calcd. for $C_{12}H_{15}NO_2$: C, 70.24; H, 7.32; N, 6.83. Found: C, 70.17; H, 7.28; N, 6.79.

Methyl (±)-(2*R,3*R**)-2-Methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2a).** This product (157 mg, 64%) was isolated as a light yellow oil. ir: 3392, 1731 cm^{-1}; ^1H nmr: δ 7.00 (m, 2H), 6.65 (td, 1H, J = 7.4, 1.1), 6.51 (dd, 1H, J = 7.9, 0.8), 3.91 (br s, 1H), 3.86 (m, 1H), 3.72 (s, 3H), 3.14-2.88 (complex, 3H), 1.13 (d, 3H, J = 6.5); ^{13}C nmr: δ 173.4, 142.8, 129.5, 127.0, 118.9, 117.4, 114.5, 51.7, 47.2, 42.0, 25.4, 17.9; ms: *m/z* 205 (M^+). *Anal.* Calcd. for $C_{12}H_{15}NO_2$: C, 70.24; H, 7.32; N, 6.83. Found: C, 70.14; H, 7.36; N, 6.72.

Methyl (±)-(2*R,3*S**)-2-Pentyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (3b).** This product (13 mg, 5%) was isolated as a light yellow oil. ir: 3401, 1731 cm^{-1}; ^1H nmr: δ 6.98 (t, 1H, J = 7.6), 6.97 (d, 1H, J = 7.4), 6.62 (td, 1H, J = 7.4, 1.1), 6.50 (d, 1H, J = 7.6), 3.83 (br s, 1H), 3.72 (s, 3H), 3.48 (td, 1H, J = 8.0, 3.5), 3.06 (dd, 1H, J = 16.1, 10.4), 2.90 (dd, 1H, J = 16.1, 4.9), 2.62 (ddd, 1H, J = 10.4, 8.0, 4.9), 1.49 (m, 2H), 1.32 (m, 6H), 0.90 (t, 3H, J = 6.8); ^{13}C nmr: δ 174.9, 143.4, 129.0, 127.1, 119.3, 117.2, 114.0, 52.9, 51.8, 43.6, 34.3, 31.8, 29.8, 24.9, 22.6, 14.0; 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, 73.67; H, 8.84; N, 5.24.

Methyl (±)-(2*R,3*R**)-2-Pentyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2b).** This product (190 mg, 74%) was isolated as a light yellow oil that crystallized on standing at 0°, mp 35-36°; ir: 3408, 1731 cm^{-1}; ^1H nmr: δ 7.00 (d, 1H, J = 7.6), 6.99 (t, 1H, J = 7.9), 6.64 (td, 1H, J = 7.4, 1.1), 6.52 (d, 1H, J = 7.9), 4.09 (br s, 1H), 3.71 (s, 3H), 3.61 (dt, 1H, J = 9.3, 3.0), 3.12-2.87 (complex, 3H), 1.46 (m, 2H), 1.28 (m, 6H), 0.87 (t, 3H, J = 6.5); ^{13}C nmr: δ 173.5, 142.8, 129.5, 127.0, 119.2, 117.3, 114.5, 52.0, 51.7, 41.8, 31.6, 31.0, 26.0 (2C), 22.6, 14.0; 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, 73.45; H, 8.80; H, 5.32.

Methyl (±)-(2*R,3*S**)-2-(2-Phenylethyl)-1,2,3,4-tetrahydroquinoline-3-carboxylate (3c).** This product (15 mg, 6%) was isolated as a light yellow oil. ir: 3401, 1731 cm^{-1}; ^1H nmr: δ 7.34-7.16 (complex, 5H), 6.99 (t, 1H, J = 7.6), 6.98 (d, 1H, J = 7.4), 6.63 (td, 1H, J = 7.4, 1.1), 6.45 (d, 1H, J = 7.6), 3.82 (br s, 1H), 3.71 (s, 3H), 3.58 (td, 1H, J = 7.9, 4.1), 3.08 (dd, 1H, J = 16.1, 9.8), 2.92 (dd, 1H, J = 16.1, 4.9), 2.87-2.65 (complex, 3H), 1.96-1.75 (complex, 2H); ^{13}C nmr: δ 174.6, 143.2, 141.4, 129.0, 128.5, 128.3, 127.1, 126.1, 119.2, 117.4, 114.1, 52.7, 51.9, 43.4, 36.0, 31.8, 29.5; ms (30 eV): *m/z* 295 (M^+). *Anal.* Calcd. for $C_{19}H_{21}NO_2$: C, 77.29; H, 7.12; N, 4.75. Found: C, 77.05; H, 7.22; H, 4.78.

Methyl (±)-(2*R,3*R**)-2-(2-Phenylethyl)-1,2,3,4-tetrahydroquinoline-3-carboxylate (2c).** This product (200 mg, 77%) was isolated as a light yellow oil. ir: 3408, 1731 cm^{-1}; ^1H nmr: δ 7.31-7.12 (complex, 5H), 7.00 (d, 1H, J = 7.4), 6.99 (t, 1H, J = 7.9), 6.65 (t, 1H, J = 7.4), 6.44 (d, 1H, J = 7.9), 3.96 (br s, 1H), 3.69 (s, 3H), 3.65 (dt, 1H, J = 9.8, 6.5), 3.11-2.87 (complex, 3H), 2.85-2.62 (complex, 3H), 1.80 (m, 2H), 1.67 (m, 1H); ^{13}C nmr: δ 173.3, 142.5, 141.4, 129.5, 128.4, 128.3, 127.0, 126.0, 119.1, 117.4, 114.7, 51.7, 51.5, 41.8, 32.7, 32.4, 25.9; ms (30 eV): *m/z* 295 (M^+). *Anal.* Calcd. for $C_{19}H_{21}NO_2$: C, 77.29; H, 7.12; N, 4.75. Found: C, 77.12; H, 7.19; H, 4.69.

Methyl (±)-(2*R,3*S**)-2-Isopropyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (3d).** This product (7 mg, 3%) was isolated as a light yellow oil. ir: 3409, 1731 cm^{-1}; ^1H nmr: δ 6.98 (t, 1H, J = 7.6), 6.97 (d, 1H, J = 7.4), 6.61 (td, 1H, J = 7.4, 1.1), 6.50 (d, 1H, J = 7.6), 3.88 (br s, 1H), 3.71 (s, 3H), 3.37 (dd, 1H, J = 7.9, 4.6), 3.08 (dd, 1H, J = 15.8, 9.0), 2.88 (dd, 1H, J = 15.8, 4.9), 2.79 (ddd, 1H, J = 9.0, 7.9, 4.9), 1.83 (m, 1H), 1.03 (d, 3H, J = 6.8), 0.96 (d, 3H, J = 6.5); ^{13}C nmr: δ 174.9, 143.6, 128.9, 127.1, 119.3, 117.0, 113.9, 58.1, 51.9, 41.1, 30.1, 29.5, 19.5, 16.3; ms: *m/z* 233 (M^+). *Anal.* Calcd. for $C_{14}H_{19}NO_2$: C, 72.10; H, 8.15; N, 6.01. Found: C, 72.23; H, 8.19; N, 5.90.

Methyl (±)-(2*R,3*R**)-2-Isopropyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2d).** This product (191 mg, 76%) was isolated as a light yellow solid, mp 57-59°. ir: 3409, 1731 cm^{-1}; ^1H nmr: δ 6.99 (d, 1H, J = 7.4), 6.98 (t, 1H, J = 7.9), 6.65 (td, 1H, J = 7.4, 1.1), 6.53 (d, 1H, J = 7.9), 4.01 (br s, 1H), 3.65 (s, 3H), 3.18-2.92 (complex, 4H), 1.87 (m, 1H), 1.02 (d, 3H, J = 6.5), 0.97 (d, 3H, J = 6.8); ^{13}C nmr: δ 173.3, 143.7, 129.2, 126.8, 119.6, 117.5, 114.5, 59.3, 51.4, 40.0, 30.1, 28.3, 20.2, 19.5; ms: *m/z* 233 (M^+). *Anal.* Calcd. for $C_{14}H_{19}NO_2$: C, 72.10; H, 8.15; N, 6.01. Found: C, 72.16; H, 8.14; N, 5.97.

Methyl (±)-(2*R,3*R**)-2-Cyclohexyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2e).** This product (214 mg, 83%) was isolated as a light yellow solid, mp 95-97°. ir: 3409, 1731 cm^{-1}; ^1H nmr: δ 6.99 (d, 1H, J = 7.4), 6.98 (t, 1H, J = 7.6), 6.65 (td, 1H, J = 7.4, 1.1), 6.52 (d, 1H, J = 7.6), 4.05 (br s, 1H), 3.66 (s, 3H), 3.22 (dd, 1H, J = 8.7, 2.7), 3.13-2.91 (complex, 3H), 2.00-1.50 (complex, 6H), 1.32-1.08 (complex, 3H), 1.08-0.92 (complex, 2H); ^{13}C nmr: δ 173.3, 143.7, 129.3, 126.8, 119.6, 117.4, 114.5, 58.0, 51.5, 39.7, 39.3, 30.0, 29.4, 28.2, 26.2, 26.0, 25.8; ms: *m/z* 273 (M^+). *Anal.* Calcd. for $C_{17}H_{23}NO_2$: C, 74.73; H, 8.42; N, 5.13. Found: C, 74.75; H, 8.43; N, 5.09.

Methyl (±)-(2*R,3*R**)-2-*tert*-Butyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2f).** This product (218 mg, 86%) was isolated as a light yellow solid, mp 73-74°. ir: 3418, 1735 cm^{-1}; ^1H nmr: δ 6.98 (m, 2H), 6.64 (td, 1H, J = 7.4, 1.1), 6.58 (dd, 1H, J = 7.9, 0.8), 3.85 (br s, 1H), 3.60 (s, 3H), 3.18-2.85 (complex, 4H), 1.01 (s, 9H); ^{13}C nmr: δ 173.6, 144.6, 129.0, 126.6, 119.3, 117.5, 114.5, 62.5, 51.3, 37.4, 31.2, 28.0, 26.8 (3C); ms (30 eV): *m/z* 247 (M^+). *Anal.* Calcd. for $C_{15}H_{21}NO_2$: C, 72.87; H, 8.50; N, 5.67. Found: C, 72.89; H, 8.54; N, 5.59.

Methyl (±)-(2*R,3*S**)-2-Phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (3g).** This compound (5 mg, 2%) was isolated as a light yellow oil. ir: 3383, 1731 cm^{-1}; ^1H nmr: δ 7.42 (complex, 5H), 7.03 (m, 2H), 6.68 (td, 1H, J = 7.4, 1.1), 6.54 (dd, 1H, J = 8.2, 0.8), 4.56 (d, 1H, J = 8.5), 4.05 (br s, 1H), 3.47 (s, 3H), 3.20 (dd, 1H, J = 17.2, 12.0), 2.95 (m, 2H); ^{13}C nmr: δ 173.9, 143.6, 141.6, 129.1, 128.6, 128.1, 127.3 (2C), 119.0, 117.5, 113.8, 58.3, 51.7, 46.2, 30.2; ms: *m/z* 267 (M^+). *Anal.* Calcd. for

$C_{17}H_{17}NO_2$: C, 76.40; H, 6.37; N, 5.24. Found: C, 76.36; H, 6.34; N, 5.27.

Methyl (±)-(2*R,3*R**)-2-Phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (2g).** This compound (209 mg, 82%) was isolated as a white solid, mp 88-90°. ir: 3396, 1731 cm^{-1}; ^1H nmr: δ 7.23 (m, 3H), 7.14 (m, 2H), 7.03 (m, 2H), 6.67 (td, 1H, J = 7.4, 1.1), 6.56 (d, 1H, J = 7.9), 4.95 (t, 1H, J = 3.5), 4.40 (br s, 1H), 3.62 (s, 3H), 3.23 (ddd, 1H, J = 10.6, 6.0, 4.4), 2.88 (m, 2H); ^{13}C nmr: δ 172.4, 143.3, 142.0, 129.5, 128.2, 127.6, 127.4, 126.7, 118.7, 117.1, 113.3, 55.8, 51.5, 43.2, 24.8; ms: *m/z* 267 (M^+). *Anal.* Calcd. for $C_{17}H_{17}NO_2$: C, 76.40; H, 6.37; N, 5.24. Found: C, 76.40; H, 6.36; N, 5.22.

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