New Chiral Auxiliaries: Their Use in the Asymmetric Hydrogenation of β-Acetamidocrotonates

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Abstract: Synthesis of chiral β-amido esters 7 with high diastereoisomeric excess was achieved by asymmetric hydrogenation (H_2/PtO_2) of stereogenic β-acetamidocrotonates **6** in which the chirality is present in the alkyl of the ester part. For such a purpose, new efficient chiral auxiliaries such as 2,2-diphenylcyclopentanol (**12**) and 1,1-diphenyl-3-methyl-2-butanol (**13**) were developed.

β-Amino esters **1** are important intermediates in organic synthesis because, for example, by ring closure they lead to β-lactam derivatives. Although several efficient routes have been proposed for the preparation of such compounds,[1] only a few of them are enantioselective. One of the most effective is the addition of primary amines to chiral crotonates **2** (Scheme I), recently developed in our laboratory;[2] we were thus able to achieve the preparation of amino esters **1** with a diastereoisomeric excess (de) as high as 99%, on a medium scale (up to 1-2 g/batch). However, the extension of such a methodology on a larger scale suffers undeniably from a major drawback: the limited availability of 8-arylmenthols as chiral auxiliaries.

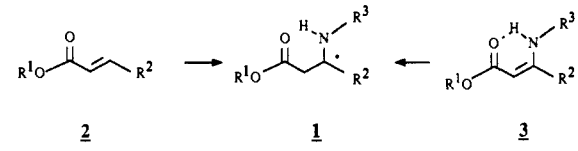
Other simple, attractive routes for the asymmetric synthesis of compounds **1** have been reported: the hydrogenation of stereogenic enamino esters **3**, in which the chirality is present in the amine moiety (5.9-46% de)[3,4] and the homogeneous catalytic hydrogenation of the nonstereogenic forms of these enamino esters, in the presence of optically active catalysts (2.6-78% ee).[5,6]

In this article, we report on the asymmetric hydrogenation of such stereogenic enamino esters **3** in which the chirality is present in the alkyl of the ester part and on the development, for such a purpose, of several new efficient chiral auxiliaries.

Chiral alcohols **4** were thus transformed into acetoacetates **5** (diketene)[7] and the latter into (*Z*)-β-acetamidocrotonates **6** (NH_3 then Ac_2O-pyridine)[8] which were finally hydrogenated (PtO_2, 3-5 bar of hydrogen) into β-acetamidobutyrates **7** (Scheme II). These were obtained as mixtures of diastereoisomers which were analyzed by using both capillary GC and (^1H and ^{13}C) NMR measurement techniques.

Six chiral alcohols (**8-13**, Table I) were examined. Although an excellent selectivity was achieved with (-)-8-phenylmenthol (8-PhM) (**8**), a "standard" auxiliary containing three asymmetric centers developed by Corey,[9,12] a substantial decrease of the de was observed by comparison with *trans*-2-phenylcyclohexanol (**9**), a "simplified" substitute for 8-PhM containing only two asymmetric centers, introduced by Whitesell.[10] In order to improve the selectivity, we have modified the latter auxiliary by replacing the phenyl ring with more bulky aromatic nuclei (alcohols **10** and **11**),[11] because we have demonstrated that such a modification in the 8-arylmenthol series provides much more efficient auxiliaries than 8-PhM itself.[2] *trans*-2-(*p*-*tert*-Butylphenyl)cyclohexanol (**10**) leads to a mixture of *Z* and *E* acetamidocrotonates **6**[8] which were hydrogenated separately. While no significant change of the selectivity was observed with the (*Z*)-acetamidocrotonate, a dramatic decrease of the de was obtained with the corresponding *E* isomer. By contrast, a notable enhancement of the de resulted from the use of *trans*-2-(4-biphenylyl)cyclohexanol (**11**). However in the latter case, substantial amounts of byproducts, resulting from the further hydrogenation of the biphenylyl moiety, were isolated.

Scheme I



Scheme II

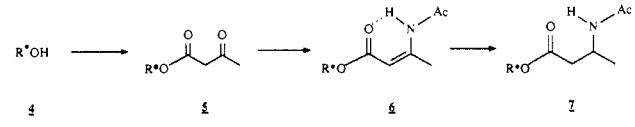
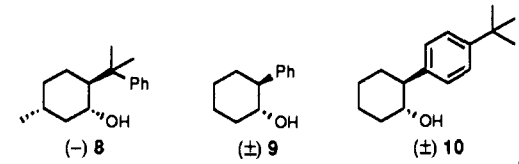
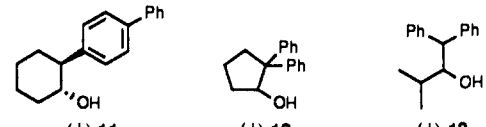


Table I. Chiral Alcohols Used in the Asymmetric Hydrogenation of Enamido Esters **6** (Diastereoisomeric Excess in Brackets)



(-) **8** (95)	(±) **9** (77)	(±) **10** (80) from *Z* isomer[a] (6) from *E* isomer[a]



(±) **11** (95)[b]	(±) **12** (96)	(±) **13** (86)

[a] In that case, the corresponding enamido ester 6 was obtained as a 1.5:1 mixture of *Z*/*E* isomers which were hydrogenated separately. [b] In that case, substantial amounts of byproducts, resulting from the further hydrogenation of the biphenyl moiety, were isolated.

(1) Estermann, H.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1824-1839 and references cited therein.
(2) d'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112-8114.
(3) Furukawa, M.; Okawara, T.; Noguchi, Y.; Terawaki, Y. *Chem. Pharm. Bull. (Tokyo)* **1979**, *27*, 2223-2226.
(4) Jolidon, S.; Meul, T. Eur. Pat. Appl. EP 144,980 (19 Jun 1985); *Chem. Abstr.* **1986**, *105*, 43325 p.
(5) Achiwa, K.; Soga, T. *Tetrahedron Lett.* **1978**, 1119-1120.
(6) Achinami, K. Jpn. Kokai Tokkyo Koho 79,119,414 (17 Sep 1979); *Chem. Abstr.* **1980**, *92*, 76282 p.
(7) Clemens, R. J. *Chem. Rev.* **1986**, *86*, 241-318.
(8) Anderson, P. C.; Staskun, B. *J. Org. Chem.* **1965**, *30*, 3033-3037. While enamidoesters **6** derived from auxiliaries **8**, **9**, **11**, **12**, and **13** were obtained as single *Z* isomers, alcohol **10** led inexplicably to a nearly equivalent mixture of *Z* and *E* stereoisomers (Table I).
(9) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908-6909.
(10) Whitesell, J. K.; Chen, H. H.; Lawrence, R. M. *J. Org. Chem.* **1985**, *50*, 4663-4664. Whitesell, J. K.; Lawrence, R. M.; Chen, H. H. *Ibid.* **1986**, *51*, 4779-4784.
(11) Prepared according to Huynh, C.; Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, *17*, 1503-1506.

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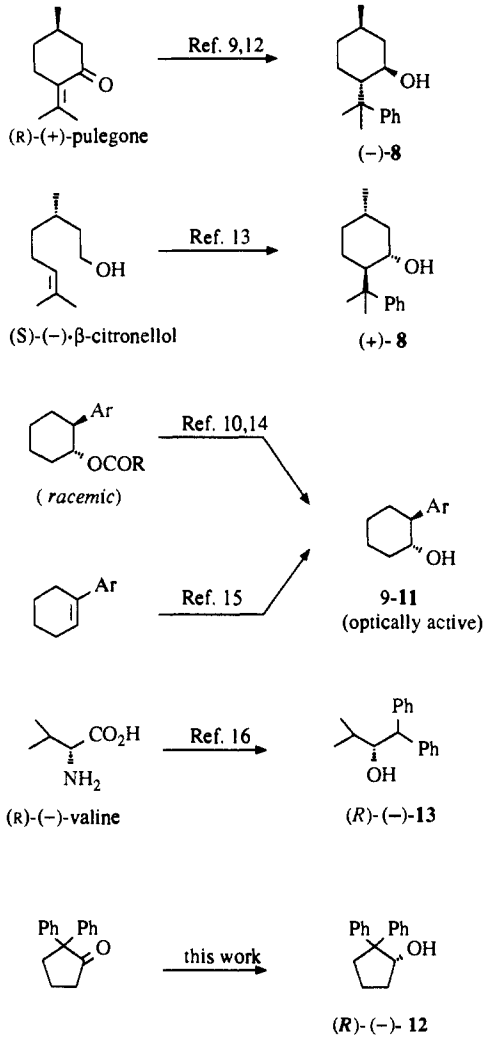
Scheme III. Preparation of the Optically Active Forms of the Chiral Auxiliary Alcohols



Next, we decided to design simpler chiral auxiliary alcohols than the foregoing *trans*-2-arylcyclohexanols, bearing in mind the remarkable "masking properties" of an aryl moiety in the vicinal position to the hydroxyl function. We reasoned that, if two *identical* aryl groups are introduced on the same carbon atom, the stereogenecity of this center is de facto suppressed, and therefore, the construction of chiral alcohols containing *a single asymmetric center* (the one bearing the hydroxyl group) can be achieved. Another major advantage, due to the presence of these two geminal aromatic nuclei, is that one of them is *necessarily gauche* (*synclinal*) to the adjacent hydroxyl group, an appropriate spacial relationship for masking one of the π-faces in the corresponding acetamidocrotonate derivatives. 2,2-Diphenylcyclopentanol (**12**) and 1,1-diphenyl-3-methyl-2-butanol (**13**), which fulfill these requirements, were thus prepared and tested. Good to excellent stereochemical results were obtained with these compounds: *thus cyclopentanol derivative* **12** *proved to be a highly potent auxiliary, as efficient as 8-PhM* **8**, while the related "open-chain" alcohol **13** gave, by comparison, a lower, but still satisfactory de (Table I).

It is worthy of note that all the aforementioned auxiliaries can be obtained in pure enantiomeric forms (Scheme III): (−)-8-PhM **8** was prepared in three steps from the terpene (*R*)-(+)-pulegone,[9,12] and its enantiomer (+)-**8**, from (*S*)-(−)-β-citronellol.[13] *trans*-2-Phenylcyclohexanol (**9**) and related compounds were obtained either by enzymatic resolution of the corresponding

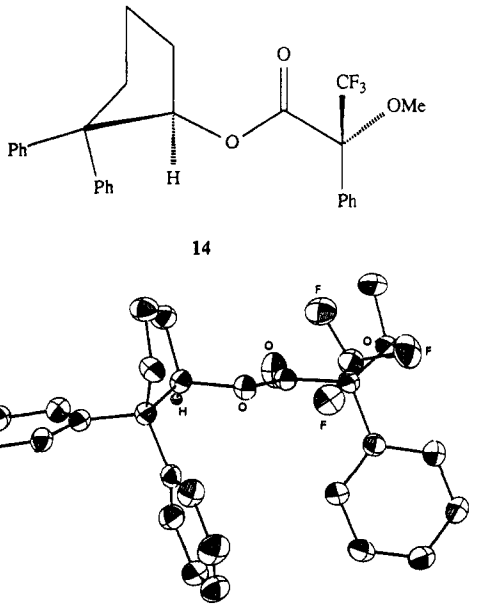


Figure 1. Top: (*R*)-MTPA derivative of (*R*)-alcohol **12**. Bottom: Perspective view of the crystal structure of ester **14**.

racemic esters[10,14] or by Brown's asymmetric hydroboration of 1-arylcyclohexenes,[15] and the auxiliary **13** has been prepared by Horeau in four steps, starting from the amino acid valine.[16] We have prepared cyclopentanol **12** with an ee of 96%, determined by its (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(*R*)-MTPA] derivative[17] **14**, through the asymmetric reduction of the corresponding ketone,[18] by means of (+)-*B*-chlorodiisopinocampheylborane.[19] Applying the stereocorrelation model proposed by Brown,[19] we first attributed the *R* configuration to this alcohol. However, the application of the Mosher's rules (Yamaguchi's method)[20] in ^{1}H NMR on the foregoing MTPA ester **14** led to the reverse stereochemical assignment (*S*). This ambiguity was removed by making an X-ray analysis of this MTPA derivative which definitively established that the absolute configuration of this alcohol is *R* (Figure 1).

While the π-facial discrimination obtained in the hydrogenation of the enamido ester derived from (−)-8-PhM **8** may reasonably be rationalized in terms of a "π-stacking interaction",[2,21] the origin of the diastereofacial differentiation observed with the other auxiliaries, **9**–**13**, still remains to be elucidated. Nevertheless, it is manifest that the aromatic part of these auxiliaries plays a crucial role, probably in masking one of the π-faces in the corresponding enamido esters **6**. One should also noted that the presence of a pseudoring, due to the intramolecular hydrogen bonding, in (*Z*)-enamido esters **6** appears crucial to ensure a good diastereofacial differentiation in this hydrogenation reaction; indeed the (*E*)-enamido ester derived from alcohol **10** gave insig-

(12) Herzog, H.; Scharf, H. D. *Synthesis* **1986**, 420–421. Ort, O. *Org. Synth.* **1987**, *65*, 203–214.
(13) Buschmann, H.; Scharf, H. D. *Synthesis* **1988**, 827–829.
(14) Laumen, K.; Breitgoff, D.; Seemayer, R.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1989**, 148–150.
(15) Brown, H. C.; Vara Prasad, J. V. N.; Gupta, A. K.; Bakshi, R. K. *J. Org. Chem.* **1987**, *52*, 310–311.
(16) Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1977**, *33*, 507–510.
(17) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.
(18) Sneen, R. A.; Jenkins, R. W.; Riddle, F. L. *J. Am. Chem. Soc.* **1962**, *84*, 1598–1601.
(19) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539–1546. Commercially available from Aldrich-Chimie.
(20) Yamaguchi, S. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: 1983; Vol. 1, pp 125–152. See also: Kusumi, T.; Ohtani, I.; Inouye, Y.; Kakisawa, H. *Tetrahedron Lett.* **1988**, *29*, 4731–4734. Ohtani, I.; Kusumi, T.; Ishitsuka, M. O.; Kakisawa, H. *Ibid.* **1989**, *30*, 3147–3150.
(21) The sense of the induction of this reaction, determined as follows, supports this proposal. Ester **7**, derived from (−)-8-PhM, was transformed in two steps (saponification with LiOH, then CH_2N_2) into (*R*)-(+)-methyl 3-acetamidobutyrate of known configuration.[5]

nificant de. In this respect, the X-ray structure determinations of enamido esters **6**, which are currently under way, should provide essential geometrical data.

Experimental Section

Preparation of the Chiral Auxiliaries. (±)-*trans*-2-Arylcyclohexanols 10 and 11. Compounds **10** and **11** have been prepared by the procedure reported by Linstrumelle:[11] arylmagnesium bromide (23 mmol) in Et_2O (12 mL) was added dropwise at −40 °C into a solution of copper iodide (430 mg, 2.3 mmol, solubilized in the minimum of Me_2S) in THF (10 mL). After 5 min, cyclohexene oxide (1.47 g, 15 mmol) was added. The mixture was allowed to warm to 0 °C and maintained at this temperature for 2 h. Workup (aqueous NH_4Cl, extraction with Et_2O, drying over $MgSO_4$) and chromatography over silica gel (cyclohexane/AcOEt, 95:5) gave the pure cyclohexanols.

(±)-*trans*-2-(4-*tert*-Butylphenyl)cyclohexanol (10): yield 77%; white solid; mp 68 °C (pentane); ^1H NMR (CCl_4, 90 MHz) δ 7.25 (d, 2 H, J = 8.6 Hz), 7.05 (d, 2 H, J = 8.6 Hz), 3.5 (dt, 1 H, J_1 = 4.5 Hz, J_2 = 10.5 Hz), 2.3 (dt, 1 H, J_1 = 3.8 Hz, J_2 = 11 Hz), 1.3 (s, 9 H), 1.1–2.15 (m, 9 H); IR (CCl_4) 3550, 3410, 2960, 2930, 2850, 1510, 1475, 1460, 1450, 1365, 1350, 1270, 1110, 1060 cm^{-1}. Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.96; H, 10.16.

(±)-*trans*-2-(4-Biphenylyl)cyclohexanol (11): yield 70%; white solid; mp > 260 °C; ^1H NMR (CD_3OD, 90 MHz) δ 7.15–7.65 (m, 9 H), 3.65 (dt, 1 H, J_1 = 4.5 Hz, J_2 = 10.5 Hz), 2.45 (dt, 1 H, J_1 = 4 Hz, J_2 = 10.5 Hz), 1.25–2.25 (m, 8 H); IR (KBr) 3530, 3410, 3050, 3030, 2915, 2840, 1480, 1445 cm^{-1}.

(±)-2,2-Diphenylcyclopentanol (12). Sodium borohydride (1.6 g, 42.3 mmol) was added to a solution of 2,2-diphenylcyclopentanone[18] (6.73 g, 28.5 mmol) in 30 mL of EtOH at 0 °C. This mixture was allowed to stand 12 h at 20 °C. Workup (0.1 N HCl, evaporation of EtOH, extraction with CH_2Cl_2, washing with saturated aqueous NaCl, drying over $MgSO_4$) and chromatography over silica gel (cyclohexane/AcOEt, 9:1) gave 6.54 g of 2,2-diphenylcyclopentanol (**96%**) as a white solid: mp 50 °C (pentane); IR (CCl_4) 3580, 3440, 3080, 3060, 2960, 2870, 1490, 1445 cm^{-1}; ^1H NMR (CCl_4, 90 MHz) δ 6.9–7.35 (m, 10 H), 4.65 (m, 1 H), 1.4–2.8 (m, 6 H), 1.25 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 147.0 (s), 144.4 (s), 128.5 (d), 128.4 (d), 128.2 (d), 127.0 (d), 126.3 (d), 77.4 (d), 59.7 (s), 34.7 (t), 31.7 (t), 19.9 (t).

(*R*)-(−)-2,2-Diphenylcyclopentanol (12). 2,2-Diphenylcyclopentanone[18] (0.92 g, 3.9 mmol) dissolved in the minimum of dry THF was added to (+)-*B*-chlorodiisopinocampheylborane[19] (3.3 g, 10.3 mmol) and allowed to stand at room temperature for 5 days. The solvent and the α-pinene released during the reaction were evaporated under vacuum. The crude product was dissolved in Et_2O (5 mL) and treated with diethanolamine (3 mL) for 2 h. The separated solid was filtered off and washed with hexane. The organic filtrate was concentrated and chromatographed over silica gel (cyclohexane/AcOEt, 9:1) to yield 0.65 g of alcohol (70%): mp 76 °C (pentane); $[\alpha]^{20}_D$ −116° (c = 0.97, EtOH). The 96% ee was determined by examination of the ^1H NMR spectrum of its MTPA ester.

(*R*)-MTPA Ester of (*R*)-(−)-2,2-Diphenylcyclopentanol (14). (*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (505 mg, 2.16 mmol) and sodium hydrogen carbonate (284 mg, 3.4 mmol) were stirred with water (2 mL), and the solution was evaporated to dryness. Benzene (5 mL) and then oxalyl chloride (0.6 mL, 6.9 mmol) were added, and the resulting mixture was stirred overnight. NaCl was removed by filtration, the solvent was evaporated, and CCl_4 (3 mL) was added. This solution was added to (*R*)-(−)-2,2-diphenylcyclopentanol (**12**) (75 mg, 0.315 mmol) followed by 4-pyrrolidinopyridine (500 μL of a 1 M solution in CCl_4). Usual workup and chromatography over silica gel (cyclohexane/AcOEt, 9:1) gave 135 mg of pure MTPA ester **14** (94% yield): white solid; mp 118 °C; IR (CCl_4) 3060, 2950, 1740, 1490, 1445 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.0–7.4 (m, 15 H), 6.40 (d, 1 H, J = 4.5 Hz) 3.18 (q, 3 H, J = 1 Hz) 2.58 (m, 2 H), 0.8–2.4 (m, 4 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 165.83 (Cq), 144.78 (Cq), 144.47 (Cq), 132.13 (Cq), 128.50 (CH), 128.27 (CH), 128.15 (CH), 127.78 (CH), 127.15 (CH), 127.14 (CH), 126.27 (CH), 126.24 (CH), 126.08 (CH), 123.30 (Cq, q, J_{CF} = 289 Hz), 84.53 (Cq, q, J_{CF} = 28 Hz), 83.32 (CH), 59.21 (Cq), 54.89 (CH_3), 34.46 (CH_2), 30.71 (CH_2), 20.00 (CH_2).

(±)-1,1-Diphenyl-3-methyl-2-butanol (13). BuLi (2.5 M in hexane, 22 mL, 55 mmol) was slowly added to diphenylmethane (8.45 g, 50.3 mmol) in 25 mL of THF at 0 °C. The deep orange solution was then cooled to −78 °C and isobutyraldehyde (5 mL, 55 mmol) in THF (25 mL) was added over 1 h. After 2 h, the solution was treated with a saturated solution of NH_4Cl, extracted with Et_2O, and dried over $MgSO_4$. The crude product was chromatographed on silica gel (cyclohexane/AcOEt, 95:5) to yield 10.29 g (85%) of pure alcohol as a colorless oil: IR (CCl_4) 3570, 3460, 3020, 2960, 1490, 1445 cm^{-1}; ^1H NMR (CCl_4, 90 MHz) δ 6.95–7.4 (m, 10 H), 3.9 (m, 2 H), 1.65 (m, 1 H), 2.0 (br s, 1 H), 0.95 (d, 6 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 142.6 (s), 141.7 (s), 128.9 (d), 128.6 (d), 128.5 (d), 128.2 (d), 126.6 (d), 126.4 (d), 78.1 (d), 55.9 (d), 29.8 (d), 20.5 (q), 15.2 (q).

Preparation of the Acetoacetates 5. Triethylamine (70 μL, 0.5 mmol) followed by diketene (650 μL, 8.4 mmol) was added to the alcohol (5 mmol) in 5 mL of acetone in a round-bottom flask. The mixture was refluxed 3 h. After evaporation of the solvent the crude product was chromatographed over silica gel (cyclohexane/AcOEt, 9:1) to give the acetoacetate.

(+)-(1*R*,2*S*,5*R*)-8-Phenylmenthyl 3-oxobutanoate: yield 95%; colorless oil; IR (neat) 2950, 2920, 2870, 1735, 1715, 1640, 1595, 1440, 1410, 1355, 1315, 1240 cm^{-1}; ^1H NMR (CCl_4, 90 MHz) δ 6.8–7.35 (m, 5 H), 4.75 (dt, 1 H, J_1 = 4.5 Hz, J_2 = 10.8 Hz), 2.6 (s, 2 H), 2.0 (s, 3 H), 1.3 (s, 3 H), 1.15 (s, 3 H), 0.9 (d, 3 H, J = 6 Hz), 0.7–2.2 (m, 8 H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 200.6 (s), 166.4 (s), 151.8 (s), 127.9 (d), 125.5 (d), 125.0 (d), 75.0 (d), 50.1 (d), 49.7 (t), 41.4 (t), 39.5 (s), 34.5 (t), 31.2 (d), 30.0 (q), 29.1 (q), 26.3 (t), 23.4 (q), 21.8 (q);$[\alpha]^{20}_D$ +14.2° (c = 3, EtOH). Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91, H, 8.92. Found: C, 75.88; H, 9.07.

(±)-*trans*-2-Phenylcyclohexyl 3-oxobutanoate: yield 95%; colorless oil; IR (neat) 3030, 2940, 2860, 1740, 1720, 1650, 1605, 1495, 1450 cm^{-1}; ^1H NMR (CCl_4, 90 MHz) δ 6.95–7.35 (m, 5 H), 4.95 (dt, 1 H, J_1 = 5 Hz, J_2 = 10.5 Hz), 2.95 (s, 2 H), 2.6 (dt, 1 H, J_1 = 4 Hz, J_2 = 11 Hz), 1.65 (s, 3 H), 1.1–2.2 (m, 8 H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 200.3 (s), 166.3 (s), 142.9 (s), 128.4 (d), 127.5 (d), 126.6 (d), 77.2 (d), 50.4 (t), 49.7 (d), 33.9 (t), 32.1 (t), 29.0 (q), 25.7 (t), 24.7 (t). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.68; H, 7.51.

(±)-*trans*-2-(4-*tert*-Butylphenyl)cyclohexyl 3-oxobutanoate: yield 92%; colorless oil; IR (neat) 2950, 2930, 2850, 1735, 1715, 1640, 1510, 1450, 1410, 1360, 1320, 1270, 1240, 1190, 1150, 1030 cm^{-1}; ^1H NMR (CCl_4, 90 MHz) δ 7.25 (d, 2 H, J = 8.3 Hz), 7.0 (d, 2 H, J = 8.3 Hz), 4.95 (dt, 1 H, J_1 = 4.5 Hz, J_2 = 10.5 Hz), 2.95 (s, 2 H), 2.6 (dt, 1 H, J_1 = 4 Hz, J_2 = 10.5 Hz), 1.55 (s, 3 H), 1.3 (s, 9 H), 1.25–2.25 (m, 8 H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 200.5 (s), 166.4 (s), 149.4 (s), 139.8 (s), 127.2 (d), 125.3 (d), 77.4 (d), 50.7 (t), 49.2 (d), 34.4 (s), 33.9 (t), 32.2 (t), 31.4 (q), 28.8 (q), 25.8 (t), 24.7 (t). Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.80; H, 9.08.

(±)-*trans*-2-(4-Biphenylyl)cyclohexyl 3-oxobutanoate: yield 76%; white solid; mp 84 °C (from Et_2O); IR (KBr) 2910, 2840, 1730, 1720, 1480, 1440, 1410, 1360, 1320, 1310, 1270, 1150 cm^{-1}; ^1H NMR (CCl_4, 90 MHz) δ 7.15–7.6 (m, 9 H), 5.0 (dt, 1 H, J_1 = 4.5 Hz, J_2 = 10.2 Hz), 3.0 (s, 2 H), 2.65 (dt, 1 H, J_1 = 3.6 Hz, J_2 = 10.5 Hz), 1.65 (s, 3 H), 1.1–2.2 (m, 8 H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 200.3 (s), 166.4 (s), 142.0 (s), 140.8 (s), 139.5 (s), 128.7 (d), 128.0 (d), 127.1 (d), 126.9 (d), 77.2 (d), 50.5 (t), 49.3 (d), 33.9 (t), 32.2 (t), 29.0 (q), 25.7 (t), 24.7 (t). Anal. Calcd for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.70; H, 7.15.

(±)-2,2-Diphenylcyclopentyl 3-oxobutanoate: yield 98%; white solid; mp 50 °C (from pentane); IR (CCl_4) 3060, 3020, 2980, 1950, 1870, 1745, 1720, 1645, 1600, 1495, 1450, 1410 cm^{-1}; ^1H NMR (CCl_4, 90 MHz) δ 6.8–7.35 (m, 10 H), 6.05 (d, 1 H, J = 4.5 Hz), 2.95 (s, 2 H), 1.75 (s, 3 H), 1.4–2.6 (m, 6 H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 200.3 (s), 166.4 (s), 145.0 (s), 144.8 (s), 128.5 (d), 128.1 (d), 127.8 (d), 126.5 (d), 126.3 (d), 126.0 (d), 81.0 (d), 59.4 (s), 50.2 (t), 35.0 (t), 30.7 (t), 29.7 (q), 20.4 (t). Anal. Calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.28; H, 6.71.

(±)-1,1-Diphenyl-3-methyl-2-butyl 3-oxobutanoate: yield 84%; white solid; mp 86–87 °C (from Et_2O); IR (CCl_4) 3060, 3030, 2960, 2930, 2870, 1945, 1740, 1720, 1595, 1545, 1490, 1465, 1450, 1410, 1390 cm^{-1}; ^1H NMR (CCl_4, 90 MHz) δ 6.9–7.4 (m, 10 H), 5.7 (dd, 1 H, J_1 = 3 Hz, J_2 = 10.5 Hz), 4.1 (d, 1 H, J = 10.5 Hz), 3.0 (s, 2 H), 1.75 (s, 3 H), 1.55–2.2 (m, 1 H), 0.9 (d, 6 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 200.3 (s), 166.6 (s), 141.3 (s), 141.2 (s), 128.8 (d), 128.5 (d), 128.1 (d), 126.9 (d), 126.7 (d), 80.2 (d), 54.3 (d), 50.0 (t), 29.5 (q), 29.4 (d), 20.1 (q), 15.3 (q). Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.89; H, 7.46.

Preparation of the Enamido Esters 6. A 10-mL methanolic solution of the acetoacetate (10 mmol) was cooled to 0 °C and saturated with gaseous NH_3. The solution was then maintained at room temperature for 48 h. After concentration under vacuum, the crude product was dissolved in THF (10 mL). To this mixture was added pyridine (1.3 mL, 16 mmol) and acetic anhydride (5.2 mL, 55 mmol). The solution was refluxed for 6 h. After concentration under vacuum, the product was chromatographed over silica gel (cyclohexane/AcOEt/Et_3N, 85:10:5) to yield pure enamido ester.

(+)-(1*R*,2*S*,5*R*)-8-Phenylmenthyl (*Z*)-3-acetamido-2-butenoate: yield 93%; colorless oil; IR (CCl_4) 3230, 2970, 2920, 2870, 1720, 1660, 1625, 1485, 1435, 1385, 1365, 1260, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 11.05 (br s, 1 H), 7.05–7.35 (m, 5 H), 4.76 (dt, 1 H, J_1 = 4.3 Hz, J_2 = 10.7 Hz), 4.23 (d, 1 H, J = 1 Hz), 2.28 (d, 3 H, J = 1 Hz), 2.13 (s, 3 H), 1.3 (s, 3 H), 1.23 (s, 3 H), 0.87 (d, 3 H, J = 6.4 Hz),

0.7–2.2 (m, 8 H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 168.9 (s), 168.3 (s), 154.3 (s), 151.4 (s), 127.9 (d), 125.5 (d), 124.9 (d), 97.3 (d), 74.0 (d), 50.7 (q), 41.8 (t), 39.8 (s), 34.6 (t), 31.4 (d), 27.0 (q), 26.7 (t), 25.9 (q), 25.2 (d), 21.8 (q), 21.7 (q); $[\alpha]^{20}_D$ +37.3° (c = 4.19, EtOH).

(±)-*trans*-2-Phenylcyclohexyl (*Z*)-3-acetamido-2-butenoate: yield 74%; white solid; mp 90–91 °C (from diisopropyl ether); IR (CCl_4) 3240, 3030, 2940, 2860, 1725, 1660, 1630, 1490, 1450, 1440, 1370 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 10.95 (broad s, 1 H), 7.15–7.35 (m, 5 H), 4.97 (dt, 1 H, J_1 = 4.5 Hz, J_2 = 10.5 Hz), 4.64 (d, 1 H, J = 1 Hz), 2.65 (dt, 1 H, J_1 = 3.8 Hz, J_2 = 11.4 Hz), 2.26 (d, 3 H, J = 1 Hz), 2.08 (s, 3 H), 1.3–2.2 (m, 8 H); ^{13}C NMR ($CDCl_3$, 20 MHz) 168.7 (s), 168.4 (s), 154.6 (s), 143.1 (s), 128.3 (d), 127.4 (d), 126.3 (d), 96.6 (d), 75.4 (d), 49.5 (d), 34.0 (t), 32.5 (t), 25.8 (t), 25.1 (q), 24.8 (t), 21.7 (q). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.71; H, 7.71; N, 4.59.

(±)-*trans*-2-(4-*tert*-Butylphenyl)cyclohexyl 3-acetamido-2-butenoates was obtained as a 1.5:1 mixture of Z/E isomers which were separated by fractional recrystallization in CH_3CN. Purification of the Z isomer was achieved by distillation, bp 110 °C (0.01 mmHg).

***Z* isomer**: yield 44%; white solid; mp 92 °C (from pentane); IR (KBr) 3220, 2920, 2850, 1720, 1660, 1625, 1490, 1365, 1260, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 11.0 (br s, 1 H), 7.28 (d, 2 H, J = 8.4 Hz), 7.10 (d, 2 H, J = 8.4 Hz), 4.94 (dt, 1 H, J_1 = 4.5 Hz, J_2 = 10.5 Hz), 4.69 (d, 1 H, J = 1 Hz), 2.67 (dt, 1 H, J_1 = 3.7 Hz, J_2 = 11.3 Hz), 2.27 (d, 3 H, J = 1 Hz), 2.08 (s, 3 H), 1.28 (s, 9 H), 1.35–2.2 (m, 8 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 168.9 (s), 168.6 (s), 154.5 (s), 149.0 (s), 140.0 (s), 127.0 (d), 125.1 (d), 96.9 (d), 75.6 (d), 48.8 (d), 34.4 (s), 34.1 (t), 32.5 (t), 31.4 (q), 25.9 (t), 25.2 (q), 24.8 (t), 21.8 (q).

***E* isomer**: yield 29%; white solid; mp 209 °C (from acetonitrile); IR (KBr) 3240, 2950, 2920, 1850, 1710, 1700, 1680, 1660, 1520, 1330, 1270, 1230 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.25 (d, 2 H, J = 8.4 Hz), 7.10 (d, 2 H, J = 8.4 Hz), 6.60 (br s, 1 H), 6.46 (d, 1 H, J = 0.8 Hz), 4.98 (dt, 1 H, J_1 = 4.4 Hz, J_2 = 10.4 Hz), 2.66 (dt, 1 H, J_1 = 3.4 Hz, J_2 = 11.3 Hz), 2.12 (d, 3 H, J = 0.8 Hz), 2.04 (s, 3 H), 1.27 (s, 9 H), 1.32–2.19 (m, 8 H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 168.8 (s), 167.5 (s), 148.7 (s), 147.7 (s), 140.3 (s), 127.1 (d), 125.0 (d), 103.3 (d), 75.1 (d), 48.9 (d), 34.3 (s), 34.2 (t), 32.5 (t), 31.4 (q), 25.9 (t), 25.0 (q), 24.8 (t), 18.4 (q).

(±)-*trans*-2-(4-Biphenylyl)cyclohexyl (*Z*)-3-acetamido-2-butenoate: yield 70%; white solid; mp 112 °C (from diisopropyl ether); IR (CCl_4) 3230, 3030, 2930, 2850, 1720, 1665, 1630, 1485, 1435, 1365, 1260, 1165, 1015 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 11.0 (br s, 1 H), 7.61–7.47 (m, 4 H), 7.36–7.45 (m, 2 H), 7.22–7.37(m, 3 H), 5.0 (dt, 1 H, J_1 = 4.5 Hz, J_2 = 10.4 Hz), 4.69 (d, 1 H, J = 0.8 Hz), 2.74 (dt, 1 H, J_1 = 3.7 Hz, J_2 = 11.4 Hz), 2.26 (d, 3 H, J = 0.8 Hz), 2.06 (s, 3 H), 1.4–2.2 (m, 8 H); ^{13}C NMR ($CDCl_3$, 20 MHz) 168.8 (s), 168.5 (s), 154.7 (s), 142.3 (s), 140.9 (s), 139.1 (s), 128.7 (d), 127.9 (d), 127.8 (d), 127.1 (d), 127.0 (d), 126.9 (d), 96.7 (d), 75.5 (d), 49.1 (d), 34.0 (t), 32.5 (t), 25.8 (t), 25.2 (q), 24.8 (t), 21.8 (q). Anal. Calcd for $C_{24}H_{27}NO_3$: C, 76.36; H, 7.21; N, 3.71. Found: C, 76.06; H, 7.22; N, 3.53.

(±)-2,2-Diphenylcyclopentyl (*Z*)-3-acetamido-2-butenoate: yield 75%; white solid; mp 133 °C (from Et_2O); IR (CCl_4) 3230, 3060, 3020, 2970, 2870, 1720, 1665, 1625, 1490, 1435, 1365, 1260, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 11.1 (broad s, 1 H), 7.05–7.35 (m, 10 H), 6.0 (dd, 1 H, J_1 = 2.4 Hz, J_2 = 5.3 Hz); 4.65 (d, 1 H, J = 1 Hz), 2.5–2.6 (m, 2 H), 2.3 (d, 3 H, J = 1 Hz), 2.1 (s, 3 H), 1.55–2.2 (m, 4 H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 168.7 (s), 168.5 (s), 155.0 (s), 145.5 (s), 144.8 (s), 128.4 (d), 127.92 (d), 127.87 (d), 126.5 (d), 126.1 (d), 125.8 (d), 96.5 (d), 79.3 (d), 59.0 (s), 35.0 (t), 30.5 (t), 25.1 (q), 21.7 (q), 20.3 (t).

(±)-1,1-Diphenyl-3-methyl-2-butyl (*Z*)-3-acetamido-2-butenoate: yield 57%; white solid; mp 108 °C (from diisopropyl ether); IR (CCl_4) 3280, 3240, 3060, 3030, 2970, 2940, 2875, 1725, 1670, 1630, 1490, 1450, 1440, 1390, 1370, 1260, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 10.9 (br s, 1 H), 7.1–7.4 (m, 10 H), 5.67 (dd, 1 H, J_1 = 3.8 Hz, J_2 = 9.6 Hz), 4.74 (d, 1 H, J = 1 Hz), 4.18 (d, 1 H, J = 9.6 Hz), 2.29 (d, 3 H, J = 1 Hz), 2.09 (s, 3 H), 1.83 (m, 1 H), 0.91 (d, 3 H, J = 6.8 Hz), 0.90 (d, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 168.7 (s), 168.5 (s), 154.7 (s), 141.6 (s), 141.3 (s), 128.7 (d), 128.5 (d), 128.3 (d), 126.6 (d), 126.5 (d), 96.2 (d), 78.3 (d), 54.2 (d), 29.7 (d), 25.1 (q), 21.8 (q), 20.2 (q), 15.7 (q).

Preparation of the β-Acetamidobutyrates 7. A solution of the enamido ester (5.2 mmol) in AcOEt (2 mL), AcOH (0.6 mL) and Ac_2O (0.2 mL) was stirred in the presence of PtO_2 (0.9 mmol) for 3 h under 3–5 bar of hydrogen. The catalyst was filtered off, and the product was chromatographed over silica gel (cyclohexane/AcOEt/Et_3N, 85:10:5) to yield the β-acetamidobutyrate as a mixture of diastereoisomers. Spectroscopic data are given only for the major diastereoisomer.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl 3-acetamidobutanoate: yield 98%; pale yellow oil; IR (neat) 3270, 2950, 2915, 2860, 1725, 1650, 1550, 1455, 1440, 1370, 1300, 1185 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) 7.05–7.35 (m, 5 H), 5.99 (br d, J = 8.5 Hz), 4.79 (dt, 1 H, J_1 = 4.5 Hz, J_2 = 10.8 Hz), 4.1 (m, 1 H), 1.92 (s, 3 H), 1.30 (s, 3 H), 1.2 (s, 3 H), 1.11 (d, 3 H, J = 6.8 Hz), 0.87 (d, 3 H, J = 6.4 Hz), 0.8–2.15 (m, 10 H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 170.7 (s), 169.0 (s), 151.5 (s), 127.9 (d), 125.3 (d), 125.0 (d), 74.3 (d), 50.1 (d), 41.9 (d), 41.5 (d), 40.2 (t), 39.5 (s), 34.5 (t), 31.2 (t), 28.3 (q), 26.4 (t), 24.5 (q), 23.2 (q), 21.7 (q), 20.1 (q).

(±)-*trans*-2-Phenylcyclohexyl 3-acetamidobutanoate: yield 94%; pale yellow oil; IR (neat) 3280, 3060, 2925, 2850, 1725, 1640, 1545, 1450, 1370, 1255, 1190 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.35–7.1 (m, 5 H), 5.91 (br d, 1 H, J = 8 Hz), 5.03 (dt, 1 H, J_1 = 4.4 Hz, J_2 = 10.6 Hz), 4.09 (m, 1 H), 2.66 (dt, 1 H, J_1 = 3.7 Hz, J_2 = 11.4 Hz), 2.30 (dd, 1 H), J_1 = 5.6 Hz, J_2 = 15.3 Hz), 2.19 (dd, 1 H, J_1 = 4.7 Hz, J_2 = 15.3 Hz), 1.85 (s, 3 H), 0.68 (d, 3 H, J = 6.8 Hz), 0.8–2.15 (m, 8 H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 170.7 (s), 169.1 (s), 143.1 (s), 128.3 (d), 127.6 (d), 126.5 (d), 76.3 (d), 49.8 (d), 41.9 (d), 40.3 (t), 33.9 (t), 32.3 (t), 25.7 (t), 24.7 (t), 23.2 (q), 19.2 (q).

(±)-*trans*-2-(4-*tert*-Butylphenyl)cyclohexyl 3-acetamidobutanoate: yield 98%; white solid; IR (CCl_4) 3280, 3060, 2960, 2930, 1730, 1650, 1550, 1450, 1370, 1260, 1185 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.20 (d, 2 H, J = 8.4 Hz), 7.04 (d, 2 H, J = 8.4 Hz), 6.05 (br d, J = 8.5 Hz), 4.92 (dt, 1 H, J_1 = 4.4 Hz, J_2 = 10.5 Hz), 3.99 (m, 1 H), 2.55 (dt, 1 H, J_1 = 3.5 Hz, J_2 = 11.5 Hz), 2.21 (dd, 1 H, J_1 = 6 Hz, J_2 = 16 Hz), 2.12 (dd, 1 H, J_1 = 5 Hz, J_2 = 16 Hz), 1.78 (s, 3 H), 1.18 (s, 9 H), 0.48 (d, 3 H, J = 6.8 Hz), 1.2–2.5 (m, 8 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 171.2 (s), 169.0 (s), 149.4 (s), 140.0 (s), 127.2 (d), 125.3 (d), 76.6 (d), 49.4 (d), 41.6 (d), 39.8 (t), 34.4 (s), 33.8 (t), 32.3 (t), 31.4 (q), 25.8 (t), 24.8 (t), 23.5 (q), 19.0 (q). Anal. Calcd for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.45; H, 9.26; N, 3.83.

(±)-*trans*-2-(4-Biphenylyl)cyclohexyl 3-acetamidobutanoate: yield 50%; pale yellow solid; IR (KBr) 3310, 2910, 2845, 1720, 1640, 1525, 1480, 1375, 1255, 1200, 1015 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.45–7.6 (m, 4 H), 7.35–7.45 (m, 2 H), 7.2–7.35 (m, 3 H), 6.13 (br d, J = 8.7 Hz), 5.03 (dt, 1 H, J_1 = 4.4 Hz, J_2 =10.4 Hz), 4.07 (m, 1 H), 2.70 (dt, 1 H, J_1 = 3.5 Hz, J_2 = 11.5 Hz), 1.80 (s, 3 H), 0.65 (d, 3 H, J = 6.8 Hz), 2.24 (d, 2 H, J = 5.4 Hz), 1.2–2.1 (m, 8 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 170.7 (Cq), 168.9 (Cq), 142.0 (Cq), 140.7 (Cq), 139.3 (Cq), 128.5 (CH), 127.8 (CH), 126.9 (CH), 126.8 (CH), 126.7 (CH), 76.2 (CH), 49.3 (CH), 41.7 (CH), 40.0 (CH_2), 33.6 (CH_2), 32.1 (CH_2), 25.5 (CH_2), 24.6 (CH_2), 23.0 (CH_3), 18.9 (CH_3).

(±)-2,2-Diphenylcyclopentyl 3-acetamidobutanoate: yield 89%; yellow oil; IR (neat) 3280, 3050, 2970, 2870, 1730, 1650, 1550, 1450, 1375, 1255, 1185, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.05–7.35 (m, 10 H), 6.15 (br d, 1 H, J = 4.5 Hz), 5.85 (br d, 1 H, J = 7.4 Hz), 4.12 (m, 1 H), 1.87 (s, 3 H), 1.45–2.65 (m, 8 H), 0.89 (d, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 20 MHz) 170.8 (s), 169.1 (s), 145.1 (s), 144.9 (s), 128.4 (d), 128.0 (d), 127.9 (d), 126.5 (d), 126.2 (d), 125.9 (d), 80.0 (d), 59.4 (s), 41.7 (d), 40.3 (t), 35.0 (t), 30.8 (t), 23.2 (q), 20.4 (t), 19.6 (q).

(±)-1-Diphenyl-3-methyl-2-butyl 3-acetamidobutanoate: yield 96%; pale yellow solid; IR (KBr) 3275, 3060, 3020, 2960, 2925, 1730, 1650, 1550, 1495, 1450, 1370, 1295, 1275, 1260, 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.1–7.4 (m, 10 H), 5.96 (br d, 1 H, J = 8.4 Hz), 5.77 (dd, 1 H, J_1 = 3.4 Hz, J_2 = 10.2 Hz), 4.16 (d, 1 H, J = 10.2 Hz), 4.13 (m, 1 H), 2.39 (dd, 1 H, J_1 = 5.3 Hz, J_2 = 15.8 Hz), 2.19 (dd, 1 H, J_1 = 4.4 Hz, J_2 = 15.8 Hz), 1.90 (s, 3 H), 1.83 (m, 1 H), 0.91 (d, 3 H, J = 7.1 Hz), 0.88 (d, 3 H, J = 7.5 Hz), 0.75 (d, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 171.2 (s), 169.1 (s), 141.4 (s), 141.3 (s), 128.8 (d), 128.5 (d), 128.4 (d), 128.1 (d), 126.8 (d), 126.6 (d), 79.2 (d), 54.3 (d), 41.7 (d), 39.6 (t), 29.4 (d), 23.4 (q), 20.1 (q), 19.4 (q), 15.4 (q). Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.42; H, 7.89; N, 3.85.

Acknowledgment. D.P. thanks Rhône-Poulenc Santé for a Fellowship.

Supplementary Material Available: General experimental procedures and tables giving the crystallographic data, the final coordinates and equivalent thermal parameters, bond lengths and angles, and dihedral angles (7 pages). Ordering information is given on any current masthead page.