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Oxidation of chiral α-phenylacetate derivatives: formation of dimers with contiguous quaternary stereocenters versus tertiary alcohols

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Abstract—The menthol esters of α-phenylacetate derivatives undergo diastereoselective oxidative dimerizations (α-cyano) in the presence of oxidants, and nitrosylation (α-amido) in the presence of CAN to form products containing adjacent functionalized quaternary stereocenters and tertiary alcohols, respectively.

1. Introduction

The formation of carbon–carbon bonds by the oxidative coupling of carbonyl compounds at the α-position is useful and complementary to its ionic counterparts. There are numerous reports on the syntheses of 1,4-dicarbonyl compounds,[1,2] radical cyclizations,[3] and synthesis of functionalized pyrrolidines[4] using metallic oxidants. Furthermore, the diastereoselective oxidative intermolecular coupling of monosubstituted enolates employing chiral auxiliaries has been reported by several groups.[5] For example, Kise et al.[6] have used chiral oxazolidinones in the homocoupling of 3-arylpropanoic acid derivatives to obtain the dimer with up to 98% de.[7,8] Using chiral BINOL as an auxiliary, Csákÿ et al.[9] performed intramolecular diastereoselective homo- and heterocouplings of monosubstituted enolates. The asymmetric coupling of disubstituted enolates, however, remains a challenge.

Diastereoselective copper(II) amine catalyzed oxidative dimerization of phenylcyanoacetate derivatives as reported by De Jongh et al.[10] resulted in the formation of a carbon–carbon bond between two highly functionalized quaternary carbons (Fig. 1). In forming this bond through an achiral radical intermediate, the relative stereochemistry of these quaternary carbons is established. Under the reaction conditions reported by De Jongh, the *meso* diastereomer was formed in excess with respect to the racemic C_2 diastereomer. However, upon heating the *meso* diastereomer equilibrates to provide predominately the C_2 compound. Due to the steric hindrance present, these compounds are difficult to synthesize utilizing ionic bond disconnections. To date, there has been no report on the asymmetric dimerization of this substrate. Herein, we report the diastereoselective oxidative reactions of chiral phenylcyanoacetate derivatives.

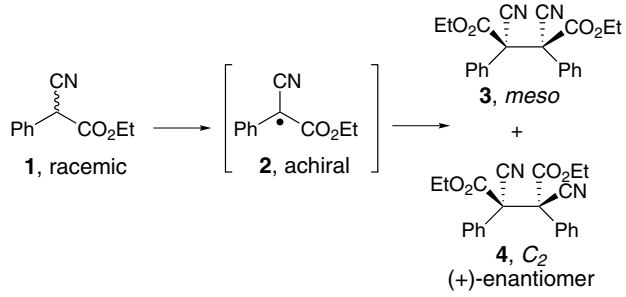

Figure 1.

2. Diastereoselective dimerization

The first chiral phenylacetate, which we examined, was the menthol phenylcyanoacetate derivative. We

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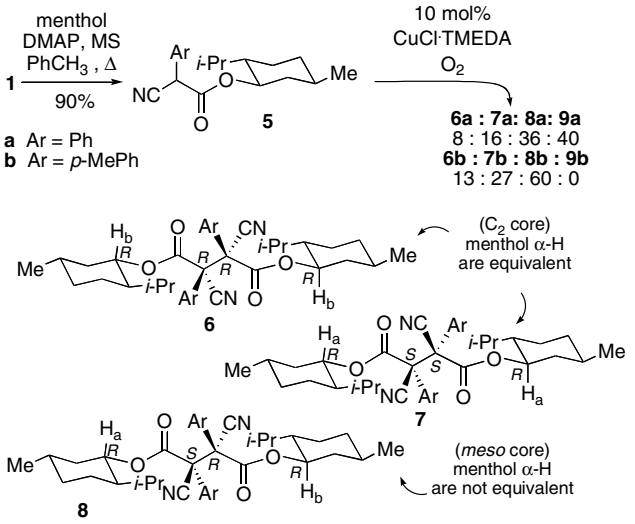
proposed that the chiral menthol ester would direct the approach in the dimerization of the radical intermediate (Scheme 1). Menthol ester **5a** was made efficiently via the ketene by heating a mixture of **1**, menthol, DMAP, and molecular sieves in toluene at reflux, overnight. Dimerization of ester **5a** using CuCl·(TMEDA) in the presence of air afforded three dimeric products **6a–8a** in 60% yield as well as an oligomeric material **9a** in 40% yield. Two overlapping doublets of triplets for the C–H adjacent to the menthol oxygen[11] of **8a** indicated that this isomer was not symmetric, which is only consistent with the *meso* configuration for the two central quaternary centers (*meso* core). The ^{1}H NMR spectra of dimeric products **6a** and **7a** showed two well-resolved doublets of triplets around 5 ppm for the C–H adjacent to menthol oxygen. The integrals of these two signals were different, indicating the presence of two different compounds. Each of these compounds is symmetrical, as would be expected, for **6a** and **7a** (i.e., C_2 with respect to the two quaternary centers; C_2 core).



Scheme 1.

Due to the formation of oligomeric material **9a** via reaction at the *para*-phenyl position[10], the chiral *para*-methylphenylcyanoacetate was also investigated. Starting from benzyl cyanide, acylation was accomplished with NaH and dimethyl carbonate to yield **1b**. The menthol ester was then formed following the procedure for **5a**. Dimerization was undertaken using CuCl·(TMEDA) in the presence of air. A quantitative yield of diastereomers **6b–8b** was obtained indicating that oligomerization was effectively suppressed (Scheme 1). Unfortunately, a mixture of a 13:27:60 of **6b**:**7b**:**8b** was still obtained. Similar ratios were observed for **6a–8a** compared to **6b–8b** indicating a similar stereochemical course for **5a** and **5b**. Based upon the success of De Jongh in equilibrating a mixture of **3** and **4** to predominantly one isomer under thermal conditions,[10] we were surprised to find no change in the composition of the **6b**:**7b**:**8b** mixture upon prolonging heating.

However, the major compound **8b** with the *meso* core could be separated chromatographically from the two compounds **6b** and **7b** with the C_2-core. Upon further recrystallization, the major C_2 isomer, highly functionalized **7b**, was obtained in its pure form and the configuration illustrated in Scheme 1 was established definitively from the X-ray crystal structure (Fig. 2). Since the separation of these compounds is straightforward and the preparative (10–100 g) generation of precursors is uncomplicated, this method offers a simple means of preparing a highly functionalized array containing contiguous quaternary centers in stereochemically pure form (either *meso* or C_2).

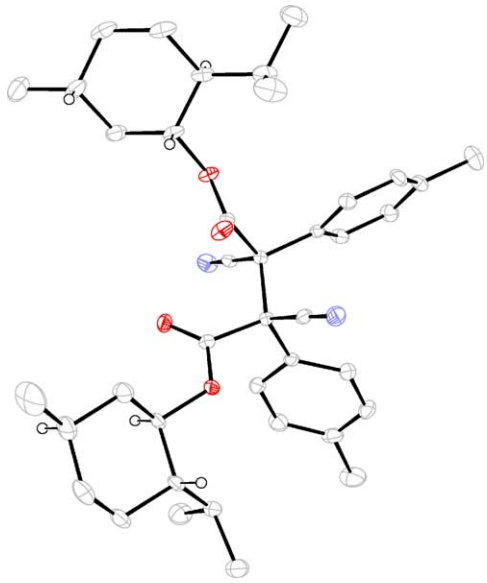
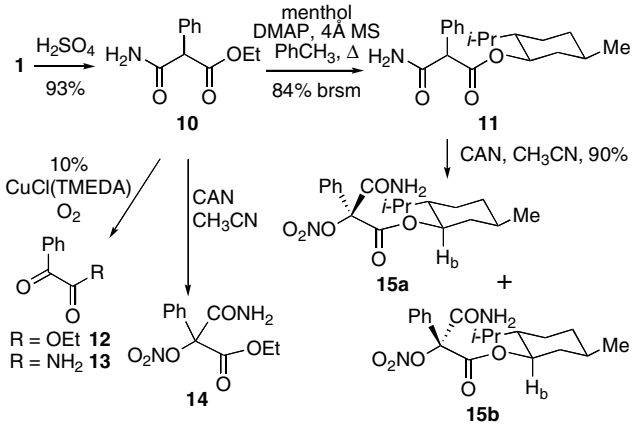


Figure 2. X-ray structure of **7b**. For clarity, only the hydrogens on stereogenic centers are illustrated.

3. β-Dicarbonyl reactions: oxidative coupling versus nitrosylation

Although, the above results using **5** were encouraging, the low *meso*:C_2 selectivity prompted further exploration. From the structure of menthol ester **5**, selectivity was induced by an isopropyl group blocking one face of the radical formed during the reaction. However, there were two orientations possible in the carbon radical (nitrile *syn* or *anti* to the ester). In order to ensure that a single isomer of the radical intermediate was formed, the cyano group was replaced with an amide. The resultant substrate **11** should thus form a single isomeric radical species in the presence of a chelating metal (Scheme 2).

The treatment of **1** with concentrated H_2SO_4 afforded **10**, which was converted into compound **11** following the same procedure for **5** (Scheme 2). Since the treatment of **10** with CuCl·(TMEDA) catalyst in the presence of oxygen caused the formation of the α-keto products **12** and **13** (~1:1) exclusively, several other oxidants were screened. Potassium ferricyanide and manganese(III) acetate provided no new compounds even after several hours, although ceric ammonium nitrate (CAN) proved to be an effective oxidant. However, the nitrosylation[12]



Scheme 2.

product **14** was obtained in high yield (70%). The identity of **14** was confirmed by crystallographic analysis (Fig. 3).

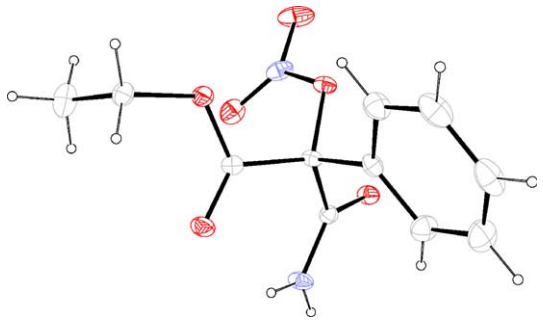
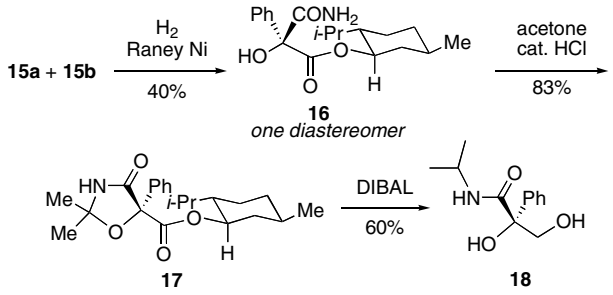


Figure 3. X-ray Structure of **14**.

In order to determine if this nitrosylation was general, nitrile **1** was also subjected to CAN oxidation. Dimeric products **3** and **4** were obtained in 65% yield and the oligomeric material in 35% yield. However, the reaction required one day at 40 °C versus 10 min at room temperature for the CuCl·(TMEDA) catalyst. No nitrosylated product was evident indicating that the nitrile (favors dimerization) versus amide (favors nitrosylation) substituent is key to controlling the chemoselectivity of these oxidations. Overall, it appeared that the less electron-withdrawing amide (vs nitrile) permits pathways with a more positive charge character. For example, the presence of a radical cation from amides **10** and **11** accounts for the observed decarboxylation (**12** and **13**) and trapping with nitrate (**14** and **15**). In contrast, the dimerization behavior exhibited by nitriles **1** and **5** is consistent with reaction via a neutral radical species.

Since this reaction is an efficient entry into highly functionalized tertiary alcohols, the corresponding chiral menthol ester amide **11** was also examined. Under the same conditions used with **10**, the nitrosylated product was obtained as a mixture of diastereomers **15a** and **15b** in 90% yield. Although **15a** and **15b** were inseparable by chromatography, the ratio could be readily ascertained by ^{1}H NMR spectroscopy. With CAN, a 1.3:1 ratio of the two diastereomers was observed. The relatively low selectivity shown for **15a** and **15b** with CAN may be a consequence of poor chelation within **11** such that a single conformationally defined reactive species is not formed. To determine if this was the case, stoichiometric amounts of Lewis acids were screened in the CAN/CH_3CN reactions. Little or no improvement was seen with $TiCl_4$ (1.3:1), Ti(O*i*-Pr)$_4$ (1.3:1), LiCl (1.3:1), $ZnCl_2$ (1.4:1), or $MgSO_4$ (1.5:1)[13] indicating that the generation of a chelated adduct with an external Lewis acid does not provide superior facial control. With other chiral auxiliaries, including the 8-phenyl menthol and borneol chiral esters, a 1:1 ratio of diastereomers was realized when subjected to CAN/$MgSO_4$.



Scheme 3.

To transform **15** to further derivatives, it was found that steric congestion at the quaternary center needed to be alleviated first by the removal of the nitro group; reductive removal was accomplished in quantitative yield using Raney nickel (Scheme 3). Recrystallization at this stage gave **16** in 40% yield as one diastereomer, which was determined by crystallographic analysis to have an (*S*)-configuration at the quaternary center (Fig. 4). Reaction of **16** with acetone gave acetonide **17** in 83% yield. DIBAL reduction of **17** gave α-hydroxy amide **18** in 60% yield as a result of menthol ester reduction accompanied by reductive cleavage of the hemiaminal.

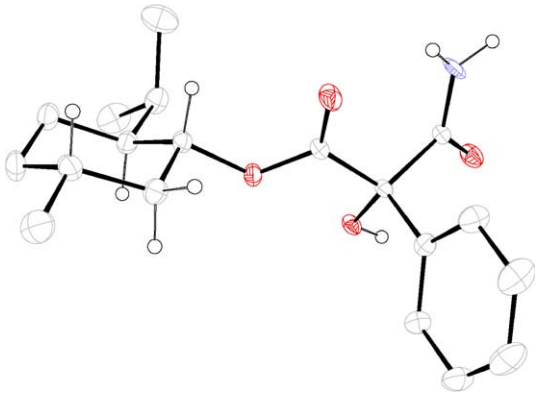


Figure 4. X-ray structure of **16**. For clarity, only selected hydrogens are illustrated.

4. Conclusion

In conclusion, we have found that the menthol esters of α-phenyl-α-cyanoacetates undergo oxidative dimerizations

in the presence of either copper(II) catalysts or CAN. Although the product with the *meso* core predominates, an approximate 2:1 diastereoselection was seen in the formation of the products with the C_2 core. Both the *meso* core diastereomer and the major C_2 core diastereomer were obtained in pure form to supply the compounds containing two new adjacent functionalized quaternary stereocenters. In contrast, the menthol esters of α-phenyl-α-amidoacetates undergo decarboxylation with copper(II) catalysts and oxidative nitrosylation in the presence of CAN. In the CAN reaction, two highly functionalized tertiary alcohol products are formed cleanly, one of which was isolated in >99% de and 40% yield upon recrystallization.

5. Experimental

5.1. General considerations

Unless otherwise noted, all non-aqueous reactions were carried out under an atmosphere of dry N_2 in dried glassware. When necessary, solvents and reagents were dried prior to use. Toluene was de-oxygenated by purging with N_2 and then dried by passing through activated alumina. CH_3CN, MeOH, TMEDA, dimethoxyethane, and hexanes were distilled from CaH_2. Cu(TMEDA)Cl(OH) was prepared by sonicating CuCl with TMEDA in CH_3CN under aerobic conditions. Removal of the solvent yielded Cu(TMEDA)Cl(OH) as a blue-purple crystalline powder.

Analytical thin layer chromatography (TLC) was performed on EM reagents 0.25 mm Silica Gel 60-F plates. Preparative thin layer chromatography was performed on EM reagents 1.00 mm Silica Gel plates. Visualization was accomplished with UV light. Chromatography on Silica Gel was performed using a forced flow of the indicated solvent system on EM reagents Silica Gel 60 (230–400 mesh).[14] ^{1}H NMR spectra were recorded on Bruker AM-500 (500 MHz), AM-250 (250 MHz), or AM-200 (200 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane (0 ppm) or from the solvent resonance ($CDCl_3$ 7.26 ppm, DMSO-d_6 2.49 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and number of protons. Mass spectra were obtained on a low resonance Micromass Platform LC in electron spray mode and high resonance VG autospec with an ionization mode of either CI or ES. IR spectra were taken on a Perkin–Elmer FT-IR spectrometer using a thin film on NaCl plates. Melting points were obtained on Thomas Scientific Unimelt apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer Polarimeter 341 with a sodium lamp and are reported as follows $[\alpha]_\lambda^T$ (c = g/100 mL, solvent).

5.2. Cyano-phenyl-acetic acid menthyl ester 5a

To a solution of ethyl phenylcyanoacetate (584 mg, 3.09 mmol) in $PhCH_3$ were added (1*R*,2*S*,5*R*)-(−)-menthol (1.27 g, 8.11 mmol), DMAP (990 mg, 8.11 mmol), and 4 Å MS (1 g). The mixture was heated at reflux in $PhCH_3$ overnight and then diluted with EtOAc. After washing three times with 1 M HCl, the organic layer was dried over anhydrous Na_2SO_4 and concentrated to a solid. Chromatography (50% CH_2Cl_2/hexanes) afforded the two diastereomers of **5a** (875 mg) in 90% yield as a white solid: mp 80–82 °C; $[\alpha]_D^{23} = -83.3$ (c 1.71, $CHCl_3$); IR (film) 2364, 1742 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.47–7.38 (m, 5H), 4.74–4.62 (m, 2H), 2.00–1.85 (m, 1H), 1.67–1.20 (m, 5H), 1.10–0.90 (m, 2H), 0.87 (d, $J = 6.5$ Hz, 3H), 0.86–0.83 (m, 1H), 0.77 (d, $J = 7$ Hz, 3H), 0.58 (d, $J = 7$ Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.5, 130.3, 129.1, 129.0, 127.8, 115.6, 77.6, 46.8, 44.0, 40.1, 33.9, 31.2, 25.8, 23.1, 21.8, 20.5, 15.8; HRMS (ES) calcd for $C_{19}H_{25}NO_2$ (MNa^+) 322.1787, found 322.1861.

5.3. Dimerization of 5a

To a solution of **5a** (300 mg, 0.9509 mmol) in MeOH was added Cu(TMEDA)Cl(OH) (43 mg, 10 mol %). After stirring for 5 min, the reaction mixture was quenched with 1 M HCl and extracted with EtOAc. Chromatography (50% CH_2Cl_2/hexanes) afforded **6a** and **7a** (110 mg), **8a** (180 mg), and **9a** (120 mg) in 22%, 36%, and 40% yields, respectively as white solids.

Compounds **6a** and **7a** (1:2 mixture): mp 191–193 °C; $[\alpha]_D^{23} = -129.6$ (c 0.47, $CHCl_3$); IR (film) 2362, 1736 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (t, $J = 7.2$ Hz, 1H), 7.29 (t, $J = 7.2$ Hz, 2H), 7.12 (d, $J = 7.6$ Hz, 2H), 4.88 (dt, $J = 4.2$, 10.6 Hz, 1H), 2.22–2.14 (m, 1H), 1.75–0.75 (m, 11H), 0.65 (d, $J = 6.8$ Hz, 3H), 0.62 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 165.7, 165.5, 130.0, 128.9, 128.7, 128.4, 128.3, 115.6, 79.1, 78.9, 60.6, 46.6, 46.5, 39.8, 39.5, 34.0, 31.5, 31.4, 25.7, 25.6, 23.2, 23.0, 21.9, 21.8, 20.7, 20.3, 15.9; HRMS (ES) calcd for $C_{38}H_{24}N_2O_4$ (MNa^+) 619.3510, found (MNa^+) 619.3513.

Compound **8a**: mp 184–186 °C; $[\alpha]_D^{23} = -45.1$ (c 0.61, $CHCl_3$); IR (film) 1743, 1582 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40–7.30 (m, 5H), 4.80 (m, 1H), 2.00–1.80 (m, 1H), 1.79–0.70 (m, 11H), 0.60 (d, $J = 6.8$ Hz, 3H), 0.49 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 163.7, 129.9, 129.3, 128.7, 128.2, 116.1, 116.0, 78.9, 78.8, 46.5, 44.8, 39.8, 39.5, 33.9, 31.4, 31.3, 29.7, 25.7, 23.2, 22.9, 21.8, 20.6, 20.3, 15.9, 15.7; HRMS (ES) calcd for $C_{38}H_{24}N_2O_4$ (MNa^+) 619.3510, found (MNa^+) 619.3513.

5.4. Cyano-*p*-tolyl-acetic acid menthyl ester 5b

4-Methylbenzylcyanide (0.990 g, 7.55 mmol) was added to a suspension of NaH (60% in mineral oil, 0.4526 g, 11.32 mmol) in 1,2-dimethoxyethane (5 mL). After stirring for 30 min at 60 °C, dimethyl carbonate (1.36 g, 15.1 mmol) was added. After completion, the reaction mixture was neutralized with 1 M HCl and extracted with ether. The extracts were concentrated and the resultant material used in the next step without purification.

Toluene (5 mL), menthol (1.18 g, 7.55 mmol), and catalytic DMAP (0.75 mmol) were combined and the mixture heated at reflux for 48 h. After cooling and concentrating, chromatography (7.5% EtOAc/hexanes) yielded **5b** (950 mg) in 40% yield from 4-methyl benzyl cyanide as a white solid: mp 78–79 °C; $[\alpha]_D^{23} = -50.4$ (*c* 1.21, $CHCl_3$); IR (film) 2358.9, 1741.5 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, $J = 8$ Hz, 2H), 7.24 (d, $J = 8$ Hz, 2H), 4.70 (dt, $J = 11$ Hz, 1H), 4.67 (s, 1H), 2.38 (s, 3H), 1.97 (d, $J = 12$ Hz, 1H), 1.71–1.67 (m, 2H), 1.63–1.57 (m, 1H), 1.51–1.40 (m, 2H), 1.07–0.99 (m, 2H), 0.92 (d, $J = 6.5$ Hz, 3H), 0.89–0.85 (m, 1H), 0.81 (d, $J = 7$ Hz, 3H), 0.64 (d, $J = 7$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.5, 139.5, 130.2, 128.1, 127.7, 116.2, 77.9, 47.2, 44.1, 40.6, 34.4, 31.7, 26.2, 23.5, 22.2, 21.4, 20.9, 16.3; HRMS (ES) calcd for $C_{20}H_{27}NO_2$ (MNa^+) 336.1940, found 336.1934.

5.5. Dimerization of 5b

Oxygen was bubbled into a round bottom flask containing MeOH (11 mL). To this solution was added **5b** (500 mg, 1.60 mmol) and, upon dissolution, Cu(TMEDA)Cl(OH) (72.8 mg, 0.16 mmol) was added. After stirring for 15 min, the reaction mixture was quenched with 1 M HCl. Cold water was added and the resulting precipitate was filtered. The crude reaction mixture was chromatographed twice (30% CH_2Cl_2/hexanes) to give **6b** and **7b** (158.6 mg, 32%), **8b** (234.7 mg, 47%), and unseparated **6b**, **7b**, and **8b** (94.6 mg, 19%). Compounds **6b** and **7b** mixture was further recrystallized from EtOAc/hexanes to provide X-ray quality crystals of **7b** (70.0 mg, 14% from **5b**).[15]

Compounds **6b** and **7b**: mp 167–170 °C; IR (film) 1740, 1613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.1 (m, 2H), 7.0 (m, 2H), 4.9 (m, 1H), 2.36 (s, 3H), 2.16 (d, $J = 12.5$ Hz, 1H), 1.72–1.25 (m, 5H), 1.09–1.01 (m, 1H), 0.98–0.92 (m, 3H), 0.90–0.84 (m, 2H), 0.67–0.64 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.4, 166.1, 140.5, 129.4, 129.3, 129.0, 126.5, 126.4, 116.2, 116.1, 79.3, 79.0, 60.9, 47.0, 46.8, 40.2, 39.9, 34.4, 31.9, 31.8, 31.7, 26.1, 26.0, 23.5, 23.4, 22.3, 22.2, 21.5, 21.1, 20.7, 16.3, 16.2; HRMS (ES) calcd for $C_{40}H_{52}N_2O_4Na$ (MNa^+) 647.3825, found (MNa^+) 647.3835.

Compound **7b**: mp 171–173 °C; $[\alpha]_D^{23} = -148.5$ (*c* 0.90, $CHCl_3$); IR (film) 1740, 1613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.1 (d, $J = 8.2$ Hz, 2H), 7.0 (d, $J = 8.2$ Hz, 2H), 4.9 (m, 1H) 2.36 (s, 3H), 2.16 (d, $J = 12.5$ Hz, 1H), 1.72–1.25 (m, 5H), 1.09–1.01 (m, 2H), 0.98–0.92 (m, 3H), 0.90–0.84 (m, 1H), 0.67–0.64 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.0, 140.1, 128.9, 126.1, 126.5, 115.8, 78.9, 60.5, 46.5, 39.8, 34.0, 31.5, 25.6, 23.2, 21.9, 21.1, 20.3, 15.9.

Compound **8b**: mp 169–171 °C; $[\alpha]_D^{23} = -50.2$ (*c* 0.96, $CHCl_3$); IR (film) 1745, 1613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.40 (s, 2H), 7.13 (m, 2H), 4.71 (m, 1H), 2.37 (d, $J = 5.5$ Hz, 3H), 1.88 (s, 1H), 1.63 (m, 2H), 1.36 (m, 2H), 0.94–0.78 (m, 7H), 0.63 (d, $J = 6.5$ Hz, 3H), 0.51 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.2, 140.4, 129.2, 126.9, 116.6, 79.1, 46.9, 46.8, 40.2, 39.9, 34.3, 31.8, 31.7, 26.1, 26.0, 23.6, 23.3, 22.2, 21.5, 21.4, 21.1, 20.7, 16.3, 16.0; HRMS (ES) calcd for $C_{40}H_{52}N_2O_4Na$ (MNa^+) 647.3825, found (MNa^+) 647.3821.

5.6. 2-Phenyl-malonamic acid ethyl ester 10

Ethyl phenylcyanoacetate **1** (5.3 g, 28 mmol) was stirred with 96% H_2SO_4 (15 mL) for 3 h. The mixture was neutralized with aqueous $NaHCO_3$ and the product extracted with EtOAc (3 × 50 mL). The organic extracts were dried over anhydrous Na_2SO_4 and concentrated to give **10** (5.2 g) in 93% yield as a white powder: mp 132–135 °C; IR (film) 3394, 1737, 1655 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.51–7.28 (m, 5H), 6.87 (br s, 1NH), 6.02 (br s, 1NH), 4.50 (s, 1H), 4.20 (q, $J = 7.2$ Hz, 2H), 1.25 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 170.8, 170.3, 134.0, 124.4, 128.6, 128.4, 62.2, 58.4, 14.1; HRMS (ES) calcd for $C_{11}H_{14}NO_3$ (MH^+) 208.0973, found 208.0976.

5.7. 2-Phenyl-malonamic acid menthyl ester 11

To a solution of **10** (1.00 g, 4.8 mmol) in $PhCH_3$ was added (1*R*,2*S*,5*R*)-(−)-menthol (800 mg, 5.1 mmol), DMAP (1.20 g, 1 mmol), and 4 Å MS (1 g). After heating at reflux in $PhCH_3$ overnight, the mixture was cooled, diluted with EtOAc, and washed with 1 M HCl. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to a solid. Chromatography (98% CH_2Cl_2/EtOAc) afforded **11** (900 mg) in 43% yield (84% brsm) as a 1:1 ratio of diastereomers in the form of a white solid: mp 162–168 °C; $[\alpha]_D^{23} = -53.7$ (*c* 0.57, $CHCl_3$); IR (film) 3413, 1735, 1656 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.39–7.31 (m, 10H), 7.13 (br s, 1NH), 6.99 (br s, 1NH), 6.09 (br s, 2NH), 4.74 (dt, $J = 4.2$, 11 Hz, 1H), 4.66 (dt, $J = 4.5$ 10 Hz, 1H), 4.47 (s, 1H), 4.45 (s, 1H), 2.03 (br s, 2H), 1.85–1.95 (m, 2H), 1.79–1.61 (m, 4H), 1.60–1.20 (m, 5H), 1.20–0.80 (m, 5H), 1.10–0.90 (m, 6H), 0.90 (d, $J = 7$ Hz, 3H), 0.87 (d, $J = 8$ Hz, 3H), 0.84 (d, $J = 6.8$ Hz, 3H), 0.49 (d, $J = 7$ Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 170.6 170.1, 134.4, 129.2, 129.1, 128.4, 128.4, 128.3, 76.3, 58.7, 58.6, 47.2, 47.0, 40.3, 34.3, 31.62, 31.55, 26.3, 25.9, 23.49, 23.4, 22.1, 20.9, 20.7, 16.4, 16.0; HRMS (ES) calcd for $C_{19}H_{27}NO_3$ (MH^+) 340.2252, found 340.2234.

5.8. 2-Nitrooxy-2-phenyl-malonamic acid ethyl ester 14

A solution of **10** (55.2 mg, 0.2663 mmol) in CH_3CN (10 mL) was stirred with CAN (292 mg, 0.5326 mmol) for 4 h. Water was added, and the resultant mixture extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to a solid. Chromatography (10% hexanes/CH_2Cl_2) afforded **14** (51.3 mg) in 70% yield as a white solid: mp 116–117 °C; IR (film) 3409, 1735, 1710, 1598 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.01 (br s, 1H), 7.58–7.53 (m, 2H), 7.46–7.41 (m, 3H), 6.80 (br s, 1H), 4.43–4.33 (m, 2H), 1.32 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6, 166.6 130.8, 129.5, 126.5, 87.5, 64.1, 14.1; HRMS (ES) calcd for $C_{11}H_{12}N_2O_6$

(MNa^+) 291.0593, found 291.0590. Compound **14** was further recrystallized from EtOAc/hexanes to provide X-ray quality crystals.[15]

5.9. 2-Nitrooxy-2-phenyl-malonamic acid menthyl ester 15

A solution of **11** (140 mg, 0.419 mmol) in CH_3CN was stirred with $MgSO_4$ (101 mg, 0.837 mmol) at room temperature. After 20 min, CAN (459 mg, 0.837 mmol) was added. After 6 h, water was added and the resultant mixture extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to a solid. Chromatography (98% CH_2Cl_2/EtOAc) afforded a 1.5:1 mixture of **15a**:**15b** (149 mg) in 90% yield as a white solid: mp 101–118 °C; $[\alpha]_D^{23} = -38.5$ (*c* 2.70, $CHCl_3$); IR (film) 3471, 1713, 1694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.13 (d, $J = 23$ Hz, 2H), 7.57–7.55 (m, 4H), 7.43–7.38 (m, 6H), 6.56 (d, $J = 26$ Hz, 2H), 4.88–4.81 (m, 2H), 2.02–1.98 (m, 2H), 1.73–1.68 (m, 6H), 1.57–1.44 (m, 6H), 1.07–0.96 (m, 8H), 0.94–0.86 (m, 9H), 0.77–0.72 (m, 6H), 0.64–0.62 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.35, 168.22, 166.82, 166.78, 131.01, 130.87, 130.68, 130.64, 129.47, 129.34, 126.50, 126.25, 87.61, 87.41, 79.36, 78.90, 47.04, 46.89, 40.16, 40.09, 34.23, 31.80, 26.09, 25.87, 23.35, 23.01, 22.24, 22.21, 21.14, 20.84, 16.03, 15.66; HRMS (ES) calcd for $C_{19}H_{26}N_2O_6$ (MNa^+) 401.1698, found 401.1701.

5.10. (−)-2-Hydroxy-2-phenyl-malonamic acid menthyl ester (16)

To a solution of **15a** and **15b** (1.0 g, 2.6 mmol) in MeOH (25 mL) was added activated Raney nickel catalyst (50% slurry in H_2O, 1.0 g). After stirring at room temperature overnight under an atmosphere of H_2, the mixture was diluted with H_2O and EtOAc. The Raney Ni was carefully filtered away through a column of Celite. The organic layer was separated and concentrated to a white solid. Recrystallization from CH_2Cl_2/hexanes afforded **16** in 40% yield as white crystals suitable for X-ray diffraction:[15] $[\alpha]_D^{23} = -88.7$ (*c* 0.62, $CHCl_3$); IR (film) 1710, 1588 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.70–7.67 (m, 2H), 7.40–7.30 (m, 3H), 6.94 (s, 1H), 5.48 (s, 1H), 4.82 (s, 1H), 4.81–4.76 (m, 1H), 2.05–2.02 (m, 1H), 1.69–1.65 (m, 2H), 1.49–1.44 (m, 3H), 1.18–1.11 (m, 1H), 1.03–1.00 (m, 1H), 0.92–0.89 (m, 1H), 0.87 (d, $J = 7$ Hz, 3H), 0.74 (d, $J = 7$ Hz, 3H), 0.59 (d, $J = 7$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.6, 171.1, 138.0, 128.9, 128.6, 126.5, 80.2, 78.6, 47.l, 40.5, 34.4, 31.8, 26.1, 23.5, 22.3, 21.0, 16.2; HRMS (ES) calcd for $C_{19}H_{27}NO_4$ (MNa^+) 356.1838, found 356.1847.

5.11. 2,2-Dimethyl-4-oxo-5-phenyl-oxazolidine-5-carboxylic acid menthyl ester 17

A solution of **16** (0.33 g, 0.101 mmol) and PTSA (1.9 mg, 0.010 mmol) in acetone (5 mL) was heated to 50 °C overnight. Concentration and purification by chromatography (90% hexanes/EtOAc) provided **17** in 83% yield as a white solid: $[\alpha]_D^{23} = -53.42$ (*c* 0.72, $CHCl_3$); IR (film) 2955, 2869, 1743, 1643 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.70–7.68 (m, 2H), 7.37–7.30 (m, 3H), 4.78–4.73 (m, 1H), 1.99–1.97 (m, 1H), 1.69–1.63 (s, 6H), 1.48–1.38 (m, 5H), 1.05–0.98 (m, 2H), 0.89 (d, $J = 7$ Hz, 3H), 0.86–0.84 (m, 1H), 0.79 (d, $J = 7$ Hz, 3H), 0.67 (d, $J = 7$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.8, 168.0, 136.4, 128.3, 127.9, 125.7, 91.5, 84.9, 46.8, 40.1, 34.1, 31.3, 29.6, 29.0, 25.7, 23.1, 21.9, 20.6, 15.9; HRMS (ES) calcd for $C_{22}H_{31}NO_4$ (MNa^+) 396.2151, found 396.2153.

5.12. 2,3-Dihydroxy-*N*-isopropyl-2-phenyl-propionamide 18

DIBAL (1.0 M in hexanes, 0.75 mL, 0.75 mmol) was added to **17** (55 mg, 0.15 mmol) in THF (5 mL) and the resultant clear solution stirred at −78 °C overnight. The mixture was then treated with a saturated solution of Rochelle's salt in water (5 mL) and stirred for 3 h. The resultant mixture was concentrated and diluted with water (2 mL). After extraction with EtOAc (3 × 5 mL), the combined organic layers were dried over Na_2SO_4 and concentrated. Chromatography (50% hexanes/EtOAc) afforded the product diol in 60% yield as a white powder: mp 87–89 °C; $[\alpha]_D^{23} = +3.5$ (*c* 0.38, $CHCl_3$); IR (film) 2974, 1644, 1530 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, $J = 7.6$ Hz, 2H), 7.38–7.30 (m, 3H), 4.44–4.41 (m, 1H), 4.1 (s, 1H), 4.05–4.00 (m, 1H), 3.59–3.56 (m, 1H), 3.31–3.28 (m, 1H), 1.17, (d, $J = 7$ Hz, 3H), 1.07 (d, $J = 7$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6, 138.8, 128.4, 128.0, 125.2, 79.4, 67.9, 41.5, 22.6, 22.3; MS (ES) *m*/*z* HRMS (ES) calcd for $C_{12}H_{17}NO_3$ (MH^+) 224.1286, found 224.1281.

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