A Facile Asymmetric Synthesis of 1,2,3-Substituted Indenes

Karen R. Romines,*,† Kristine D. Lovasz, Stephen A. Mizsak, Jeanette K. Morris, Eric P. Seest, Fusen Han, John Tulinsky, Thomas M. Judge, and Ronald B. Gammill‡

Structural, Analytical, and Medicinal Chemistry Research, Pharmacia & Upjohn, Kalamazoo, MI, 49001

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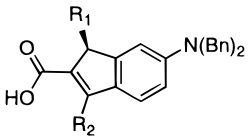
Introduction

The indene nucleus has been known for many years,[1] and highly substituted indenes have recently been prepared by numerous methods. These include manganese-mediated cyclization of aryl ketones and acetylenes,[2] rearrangement of arylcyclopropenes,[3] sigmatropic[4] or free-radical[5] cyclization of phenylvinyl derivatives, and Lewis acid mediated cyclization of α-oxoketenedithioacetal/phenyl Grignard adducts.[6] These methods, however, do not allow for stereocontrol of a C-1 stereogenic center. Asymmetric indenes have previously been prepared using resolution strategies.[7] Recently, we have developed an efficient asymmetric synthesis of 1,2,3-substituted indenes (**1**) from readily available α,β-unsaturated acids. Our strategy involved the use of a chiral imide derivative, which through standard protocols enabled us to selectively form the C-1 stereogenic center of the indene nucleus.



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Results and Discussion

Our indene synthesis begins by establishing the asymmetric center at what will become the C-1 position via an organocuprate addition to an unsaturated imide (Scheme 1). The desired unsaturated imide substrate **3** was prepared by addition of the lithium salt of (*S*)-4-phenyloxazolidinone (**2**) to (*E*)-pentenoyl chloride. Addition of the aryl cuprate derived from 3-[bis(trimethylsilyl)-amino]phenylmagnesium chloride[8] to **3** then gave Michael adduct **4** as a single diastereomer after bisbenzylation and recrystallization.[9] Introduction of an acetyl group to **4** was accomplished via formation of the potassium enolate of **4** with potassium bis(trimethylsilyl)amide, followed by treatment of that enolate with $MgBr_2 \cdot OEt_2$ and subsequent addition of acetyl chloride to yield **5** as a single diastereomer.[10a] Assignment of the absolute stereochemistry of both asymmetric centers was based on literature precedent.[11,12] Synthesis of indene **6** was completed via the facile cyclization of methyl ketone **5** in the presence of titanium tetrachloride and a tertiary amine, and the chiral auxiliary was readily cleaved with lithium peroxide to produce **1**. Both the cyclization and oxazolidinone cleavage steps proceeded without racemization of the C-1 stereogenic center.[13]

We examined this intriguing and quite facile cyclization of the methyl ketone to the indene nucleus in some detail. Our standard cyclization conditions required treatment of **5** with 1.0 M $TiCl_4$ in CH_2Cl_2 (1 equiv), followed by addition of diisopropylethylamine (1.2 equiv) at low temperatures. The reaction mixture was then warmed to ambient temperature to effect complete cyclization. After 1.5 h at −15 °C, conversion was 15%. In the same time period at 0 °C, conversion proceeded to 52%, and at ambient temperatures, 60% conversion was realized. HPLC studies of quenched aliquots from the reaction mixture showed complete consumption of starting material after 3.75 h at ambient temperature. The only product from this reaction was the desired indene, and when conversion was not complete, only starting material was recovered.

The relative stereochemistry of the two centers established by the cuprate addition and the acylation steps was crucial. Cyclization did not occur when the substituents of the methyl ketone at C-2 and C-3 were syn to one another. For example, in the case of methyl ketone **8**,[10a] even after stirring at room temperature for 20 h

† Current address: Glaxo Wellcome, Five Moore Drive, Research Triangle Park, NC 27709. E-mail: krr92858@glaxowellcome.com.

‡ Current address: Central Research Division, Pfizer, Inc., Eastern Point Road, Groton, CT 06340

(1) Heller, H. G. In *Aromatic Compounds with Two Fused Carbocyclic Ring Systems: Benzocyclopropene, Benzocyclobutene, and Indene and their Derivatives*, 2nd ed.; Correy, S., Ansell, M. F., Eds.; Rodd's Chemistry of Carbon Compounds; Elsevier: Amsterdam, The Netherlands, 1978; Vol. 3, Issue G.

(2) (a) Liebeskind, L. S.; Gasdaska, J. R.; McCallum, J. S. *J. Org. Chem.* **1989**, *54*, 669. (b) Robinson, N. P.; Main, L.; Nicholson, B. K. *J. Organomet. Chem.* **1989**, *364*, C37. (c) Cambie, R. C.; Metzler, M. R.; Rutledge, P. S.; Woodgate, P. D. *J. Organomet. Chem.* **1992**, *429*, 41.

(3) (a) Padwa, A.; Blacklock, T. J.; Getman, D.; Hatanaka, N. *J. Am. Chem. Soc.* **1977**, *99*, 2344. (b) Semmelhack, M. F.; Ho, S.; Cohen, D.; Steigerwald, M.; Lee, M. C.; Lee, G.; Gilbert, A. M.; Wulff, W. D.; Ball, R. G. *J. Am. Chem. Soc.* **1994**, *116*, 7108.

(4) Gassman, P. G.; Ray, J. A.; Wenthold, P. G.; Mickelson, J. W. *J. Org. Chem.* **1991**, *56*, 5143.

(5) Yamamura, K.; Miyake, H.; Seta, A. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3699.

(6) Singh, G.; Ila, H.; Junjappa, H. *Synthesis* **1986**, 744.

(7) For example, see: (a) Weidler, A.-M.; Bergson, G *Acta Chem. Scand.* **1964**, *18*, 1483. (b) Hussenius, A.; Matsson, O.; Bergson, G. *J. Chem. Soc., Perkin Trans. 2* **1989**, 851.

(8) Purchased from Aldrich Chemical Co.

(9) For reviews, see: (a) Rossiter, B. E.; Swinge, N. M. *Chem. Rev.* **1992**, *92*, 771. (b) Nicolas, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766.

(10) (a) A full account of this work, which was initially described in ref 10b, is currently under revision and will appear shortly. (b) Judge, T. M.; Phillips, G.; Morris, J. K.; Lovasz, K. D.; Romines, K. R.; Luke, G. P.; Tulinsky, J.; Tustin, J. M.; Chrusciel, R. A.; Dolak, L. A.; Mizsak, S. A.; Watt, W.; Morris, J.; Vander Velde, S. L.; Strohbach, J. W.; Gammill, R. B. *J. Am. Chem. Soc.* **1997**, *119*, 3627.

(11) (a) Nicholas, E.; Dharanipragada, R.; Toth, G.; Hruby, V. J. *Tetrahedron Lett.* **1989**, *30*, 6845. (b) Qian, X.; Russell, K. D.; Boteju, L. W.; Hruby, V. J. *Tetrahedron Lett.* **1995**, *51*, 1033.

(12) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215.

(13) To evaluate the stability of the stereogenic center of **6** and **1** (R_1 = Et, R_2 = Me), the enantiomers of these compounds were prepared from (*R*)-4-phenyloxazolidinone, which is the enantiomer of **2** (Scheme 1). Analytical chiral HPLC indicated that **6**, **1** (R_1 = Et, R_2 = Me), and their enantiomers were of >99% ee. Compounds **6** (t_R 18.51 min) and its enantiomer **22** (t_R 22.20 min) were analyzed using a 0.46 × 25 cm Whelk-O column (elution of 0.5 mL/min with EtOH, detection at 380 nm). Compounds **1** (R_1 = Et, R_2 = Me) (t_R 16.78 min) and its enantiomer **23** (t_R 14.70 min) were analyzed using a 0.46 × 25 cm Chiralcel OD-H column (elution of 0.5 mL/min with 5% 2-propanol/0.5% acetic acid/heptane, detection at 353 nm).

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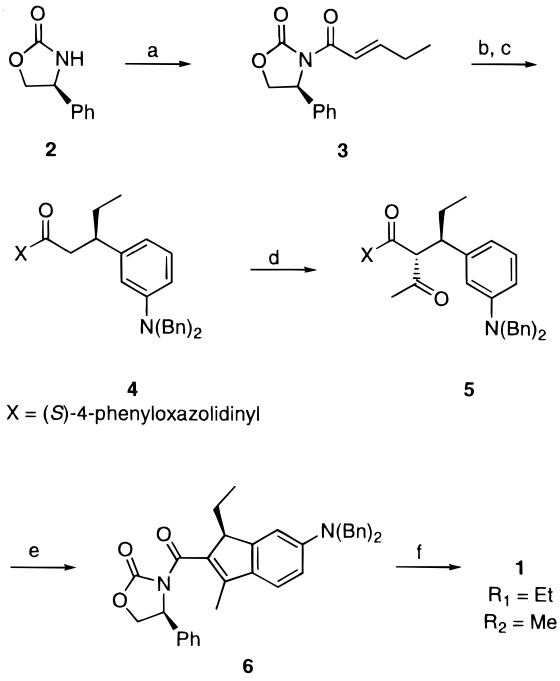
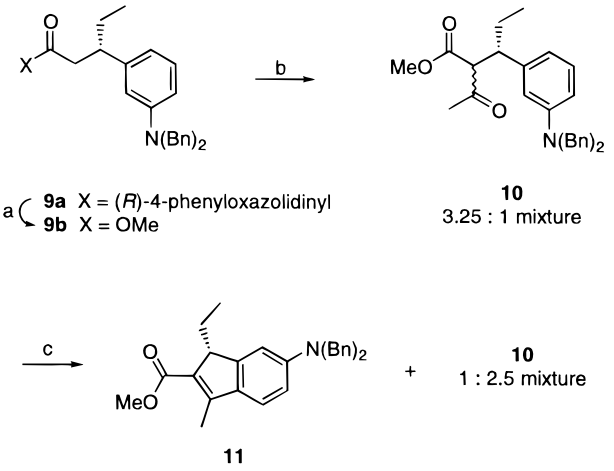
Scheme 1[a]



2 **3** **4** **5** **6** **1**

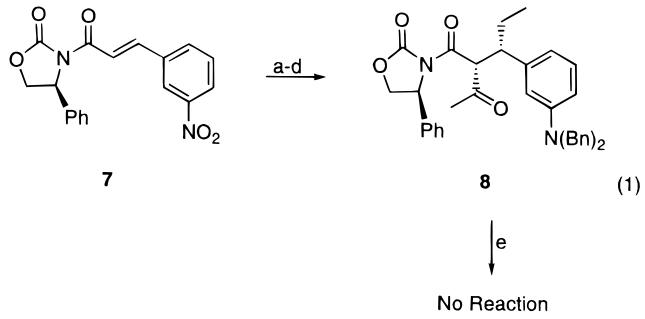
[a] (a) *n*-BuLi, THF, -78 °C; then, ClC(O)CH=CHCH$_2$CH$_3$, 82%; (b) CuBr-Me$_2$S, 3-[N(SiMe$_3$)$_2$]C$_6$H$_4$MgBr, THF, 0 °C, 71%; (c) Na$_2$CO$_3$, BnBr, H$_2$O, CH$_2$Cl$_2$, 81%; (d) KHMDS, MgBr$_2$-OEt$_2$; then, AcCl, 61%; (e) TiCl$_4$, EtN(*i*-Pr)$_2$, CH$_2$Cl$_2$, -78 °C to rt, 63%; (f) H$_2$O$_2$, LiOH, THF, H$_2$O, 53%.

Scheme 2[a]



[a] (a) TiCl$_4$, MeOH, 83%; (b) LDA, THF, -78 °C; then, AcCl, 78%; (c) TiCl$_4$, EtN(*i*-Pr)$_2$, CH$_2$Cl$_2$, -78 °C to rt, 30% of **11**, 43% of **10**.

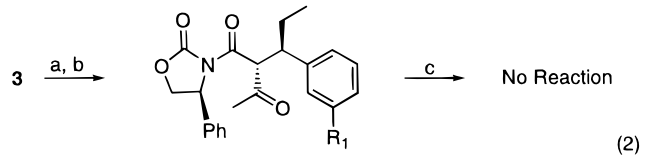
under the standard reaction conditions, there was no evidence of conversion to indene (NMR, HPLC, MS, or TLC) (eq 1). A similar result was also noted with the *β*-keto ester **10**, which was prepared from the imide **9a**[10b] (Scheme 2). First, the chiral auxiliary was converted to the methyl ester **9b**.[14] In the subsequent acylation step, the existing stereogenic center exerted some stereochemical influence and the *β*-keto ester **10** was formed as a 3.25:1 mixture of diastereomers. Treatment of this mixture with TiCl$_4$ and Hunig's base yielded indene **11** and recovered *β*-keto ester **10**; however, the ratio of diastereomers in the recovered *β*-keto ester was reversed to 1:2.5. This result indicated a very substantial rate difference between cyclization of the major diastereomer from the acylation, in which the substituents at C-2 and C-3 are anti, and cyclization of the minor diastereomer, in which the C-2 and C-3 substituents are syn.



7 **8** (1)

(a) Fe, NH$_4$Cl, H$_2$O, MeOH, MeCN; (b) BnBr, K$_2$CO$_3$, MeCN, reflux, 73% for 2 steps; (c) CuBr-Me$_2$S, EtMgBr, THF, -10°C, 74%; (d) KHMDS, MgBr$_2$-OEt$_2$; then, AcCl, -78 °C, 58%; (e) TiCl$_4$, EtN(*i*-Pr)$_2$, CH$_2$Cl$_2$, -78 °C to rt.

We also investigated the electronic influence of the substituent on the aryl ring. Initially, we used a methyl ketone with a *p*-*N*,*N*-bisbenzyl group which introduces a convenient site for further chemistry. To explore the role of the para substituent, we synthesized substrates with an electronically neutral group (H, **12a**), an electron-withdrawing group (F, **12b**), or a mildly electron donating group (OMe, **12c**) at the para position (eq 2). When submitted to our standard protocol, all of these substrates failed to produce the cyclization products, and only starting materials were recovered. These results illustrate the significant electronic contributions of the para-substituted amino group.



(2)

12a X = H
12b X = F
12c X = OMe

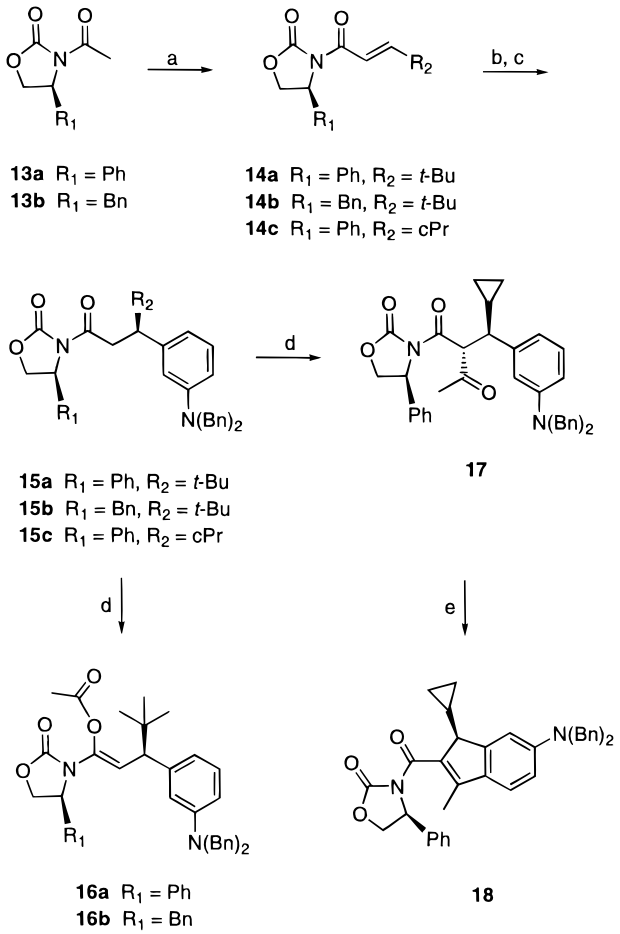
(a) CuBr-Me$_2$S, ArMgBr, THF; (b) KHMDS, MgBr$_2$-OEt$_2$; then, AcCl; (c) TiCl$_4$, EtN(*i*-Pr)$_2$, CH$_2$Cl$_2$, -78 °C to rt.

One feature of this new synthetic route is the ability to modify the C-1 substituent of the indene. We chose to acylate the chiral oxazolidinones to give **13a**,**b** so that the C-1 substituent could be installed via condensation of **13a**,**b** with the appropriate aldehyde (Scheme 3). In all cases, Michael addition and bis-benzylation proceeded smoothly. For the cyclopropyl derivative **15c**, the acylation and cyclization steps then produced indene **18**. It was interesting to note that use of a *tert*-butyl substituent precluded C-acylation. The only product observed with **15a** was the O-acylated derivative **16a**. Use of a benzyl oxazolidinone as the chiral source did not sufficiently relieve the steric strain to alter the course of the acylation step, and **16b** was the only product observed.

A potentially important feature of this methodology was the ability to modify the C-3 substituent of the

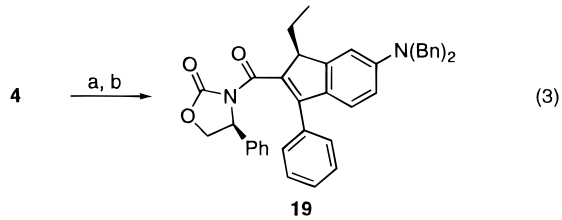
(14) Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982**, 138.

Scheme 3[a]



[a] (a) $TiCl_4$, EtN(*i*-Pr)$_2$, CH_2Cl_2, -78 °C; then, R_2CHO, EtN(*i*-Pr)$_2$, -78 °C to rt; (b) CuBr-Me_2S, 3-[N(SiMe$_3$)$_2$]C_6H_4MgBr, THF, 0 °C (c) Na_2CO_3, BnBr, H_2O, CH_2Cl_2; (d) KHMDS, $MgBr_2$-OEt_2; then, AcCl; (e) $TiCl_4$, EtN(*i*-Pr)$_2$, CH_2Cl_2, -78 °C to rt.

indene. By simply choosing different acid chlorides, indenes with different C-3 substituents can be synthesized. For example, treatment of the enolate of *β*-ketoimide **4** with benzoyl chloride afforded the phenyl ketone intermediate in good yield (eq 3). Cyclization under standard conditions then readily gave the 3-phenyl indene derivative **19**.

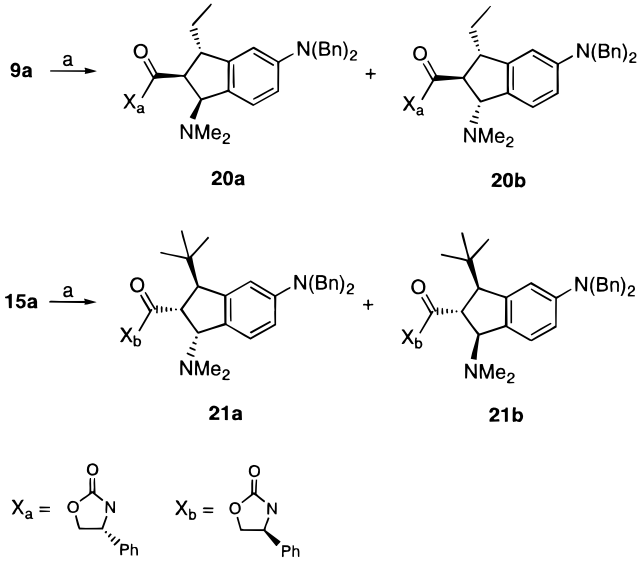


(3)

(a) KHMDS, $MgBr_2$-OEt_2; then, PhC(O)Cl, 62%; (b) $TiCl_4$, EtN(*i*-Pr)$_2$, CH_2Cl_2, -78 °C to rt, 62%

A variation of the C-3 substitution step allowed us to extend our strategy to the preparation of 3-aminoindanes. Treatment of ketoimide **9a** at −78 °C with $TiCl_4$, Hunig's base, and the Vilsmeier reagent provided the novel aminoindans **20a** and **20b** in a 2:1 ratio (Scheme 4).[15] Interestingly, use of Vilsmeier reagent to form indans was not sterically limited. Using the *tert*-butyl intermediate **15a**, we readily obtained **21a** and **21b**.

Scheme 4[a]



[a] (a) $TiCl_4$, EtN(*i*-Pr)$_2$, CH_2Cl_2, -78 to 0 °C, 30 min; then, Me_2N^+=CHCl Cl^-, -78 to 0 °C, 1 h.

Conclusions

We have developed a simple and efficient asymmetric route to prepare highly substituted indenes. Our chiral sources are the readily available phenyloxazolidinones, and the stereogenic center is efficiently prepared via a Michael addition to a chiral imide. Ambient temperatures and Lewis acid conditions provide an attractive, mild procedure for the cyclization to indene. Both the cyclization and subsequent removal of the chiral auxiliary take place without corruption of the stereogenic center. This procedure also provides flexibility for indene substitution, particularly at the C-3 position. Furthermore, this route can be readily modified to yield 1-aminoindans.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded using tetramethylsilane as an internal standard. Flash chromatography was performed on 230−400 mesh silica gel 60.

(4*S*)-3-[[(1*S*)-6-[Bis(phenylmethyl)amino]-1-ethyl-3-methyl-1*H*-inden-2-yl]carbonyl]-4-phenyl-2-oxazolidinone (**6**). A solution of **5**[10a,16] (0.200 g, 0.357 mmol) in CH_2Cl_2 (3 mL) was cooled to −78 °C, and titanium tetrachloride (0.36 mL of a 1.0 M solution in CH_2Cl_2, 0.357 mmol) was added dropwise. Diisopropylethylamine (0.075 mL, 0.428 mmol) was added, and the resulting mixture was stirred at −78 °C for 80 min and then allowed to warm to room temperature over 3.5 h. The mixture was quenched with half-saturated NH_4Cl (aq, 3 mL) and partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with three portions of CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ (aq), water, and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give 0.182 g of crude material. Column chromatography on silica gel (elution with 50−80% CH_2Cl_2/hexanes) afforded 0.123 g (63%) of the title compound as a yellow solid: mp 159−162 °C; $[\alpha]^{25}_D$ (*c* 1.0, $CHCl_3$) −148; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.45−7.20 (m, 16 H), 6.75 (br s, 1 H), 6.69 (dd, *J* = 2.2, 8.4 Hz, 1 H), 5.64 (t, *J* = 8.9 Hz, 1 H), 4.73−4.67 (m, 5 H), 4.31 (t, *J* = 8.9 Hz, 1 H), 4.07 (br s, 1 H), 2.31 (s, 3 H), 1.79−1.70 (m, 2 H), 0.38 (br

(15) NMR spectra indicated the diastereomers were epimeric at the C-1 position (NMe_2 substituent). An X-ray crystal structure was obtained of **20a** to assign the absolute stereochemistry based on the known configuration of the C-3 ethyl substituent.

(16) Synthesis and characterization of the enantiomers of compounds **3**−**5** have been previously described in ref 10b.

s, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 153.5, 150.3, 149.9, 138.2, 137.6, 134.1, 132.7, 129.1, 128.8, 128.7, 127.4, 127.1, 126.7, 122.3, 111.4, 107.5, 69.4, 58.9, 54.6, 50.5, 23.4, 13.0, 8.8 ppm; IR (mull) 1778, 1655 cm^{-1}; MS (EI) *m*/z 542 ($M^{+\bullet}$). Anal. Calcd for $C_{36}H_{34}N_2O_3$: C, 79.68; H, 6.32; N, 5.16. Found: C, 79.67; H, 6.47; N, 5.20.

(1*S*)-6-[Bis(phenylmethyl)amino]-1-ethyl-3-methyl-1*H*-indene-2-carboxylic Acid (1, R_1 = Et, R_2 = Me). A solution of **6** (0.486 g, 0.90 mmol) in THF (10 mL) was diluted with water (5 mL) and cooled to 0 °C in an ice bath. Hydrogen peroxide (1.5 mL of a 30% aqueous solution, 13.4 mmol) and lithium hydroxide (5.6 mL of a 0.8 M aqueous solution, 4.5 mmol) were added dropwise, and the resulting mixture was stirred at ambient temperature for 19 h. The reaction mixture was then cooled to 0 °C, quenched with Na_2SO_3 (10.3 mL of a 1.3 M solution, 13.4 mmol), and extracted with two 50-mL portions of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give 0.605 g of yellow oil. Column chromatography on 35 g silica gel (elution with 10−30% EtOAc/hexanes) yielded 0.186 g (53%) of the title compound as a yellow foam: $[\alpha]^{25}_D$ (*c* 0.9, $CHCl_3$) +86; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.29 (m, 11 H), 6.85 (s, 1 H), 6.76 (d, *J* = 10.1 Hz, 1 H), 4.74 (br s, 4 H), 3.73 (br s, 1 H), 2.53 (s, 3 H), 2.16−2.06 (m, 1 H), 2.01−1.92 (m, 1 H), 0.47 (t, *J* = 7.3 Hz, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 155.4, 151.1, 150.1, 138.2, 134.2, 128.8, 128.2, 127.1, 126.7, 122.4, 111.3, 107.7, 54.6, 49.9, 23.7, 12.9, 8.5 ppm; IR (drift) 2961, 1652 cm^{-1}; MS (EI) *m*/z 397 ($M^{+\bullet}$); HRMS (EI) calcd 397.2042, found 397.2044. Anal. Calcd for $C_{27}H_{27}NO_2$: C, 81.58; H, 6.85; N, 3.52. Found: C, 81.21; H, 6.87; N, 3.56.

(*S*)-3-[Bis(phenylmethyl)amino]-β-ethylbenzenpropanoic Acid Methyl Ester (9b). Titanium tetrachloride (6.64 mL, 60.4 mmol) was added dropwise to methanol (150 mL) in an ice bath. The resulting mixture was stirred at ambient temperature for 2 h, and then **9a**[10b] (9.5 g, 18.3 mmol) was added. The mixture was warmed to reflux overnight and then quenched with saturated NH_4Cl (aq) and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ (aq) and concentrated. Column chromatography on 200 g of silica gel (elution with 5−20% EtOAc/hexanes) gave 5.91 g (83%) of the title compound as an oil: $[\alpha]^{25}_D$ (*c* 0.5, MeOH) +16; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.30 (m, 4 H), 7.25−7.22 (m, 6 H), 7.09 (app t, *J* = 7.8 Hz, 1 H), 6.58 (d, *J* = 8.4 Hz, 1 H), 6.53−6.51 (m, 2 H), 4.62 (s, 4 H), 3.57 (s, 3 H), 2.92−2.81 (m, 1 H), 2.51 (d, *J* = 7.3 Hz, 2 H), 1.58−1.45 (m, 2 H), 0.69 (t, *J* = 7.3 Hz, 3 H) ppm; IR (liquid) 1738 cm^{-1}; MS (EI) *m*/z 387 ($M^{+\bullet}$); HRMS (EI) calcd for $C_{26}H_{29}NO_2$ 387.2198, found 387.2196. Anal. Calcd for $C_{26}H_{29}NO_2$: C, 80.59; H, 7.54; N, 3.61. Found: C, 80.71; H, 7.69; N, 3.77.

(β*S*)-Methyl α-Acetyl-3-[bis(phenylmethyl)amino]-β-ethylbenzenepropanoate (10). A solution of **9b** (0.775 g, 2.0 mmol) in THF (5 mL) was cooled to −78 °C, and LDA (1.1 mL of a 2.0 M solution, 2.2 mmol) was added dropwise over 2 min. The reaction mixture was stirred at −78 °C for 5 min and then transferred via cannula over 10 min to a solution of acetyl chloride (1.4 mL, 19.7 mmol) in 5 mL of THF at −78 °C. After an additional 10 min of stirring, the reaction mixture was allowed to warm to room temperature over 10 min, diluted with EtOAc, and washed with saturated $NaHCO_3$ (aq) until the aqueous layer was neutral. The organic layer was then washed with water and concentrated to give 1.05 g of a greenish oil. Column chromatography on 100 g of silica gel (elution with 5−30% EtOAc/hexanes) gave 0.67 g (78%) of the title compound: mp 86−103 °C; $[\alpha]^{25}_D$ (*c* 1.1, MeOH) +30; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.21 (m, 10 H), 7.08 (t, *J* = 7.8 Hz, 1 H), 6.80−6.57 (m, 3 H), 4.62 (br s, 4 H), 3.72 (t, *J* = 4.1 Hz, 3 H), 3.38 (s, 1 H), 3.28−3.09 (m, 1 H), 2.25 (s, 1 H), 1.78 (s, 1 H), 1.58−1.56 (m, 2 H), 1.55−1.37 (m, 1 H), 0.60−0.55 (m, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 202.5, 169.3, 168.5, 141.6, 138.6, 129.4, 129.1, 128.6, 128.5, 128.3, 128.2, 127.0, 125.4, 116.5, 113.0, 111.3, 66.6, 66.0, 54.4, 52.4, 52.1, 47.7, 47.3, 29.8, 29.7, 27.4, 26.8, 11.7, 11.5 ppm; IR (mull) 1740, 1714 cm^{-1}; MS (EI) *m*/z 429 ($M^{+\bullet}$). Anal. Calcd for $C_{28}H_{31}NO_3$: C, 78.29; H, 7.27; N, 3.26. Found: C, 78.29; H, 7.33; N, 3.33.

(*R*)-Methyl 6-[Bis(phenylmethyl)amino]-1-ethyl-3-methyl-1*H*-indene-2-carboxylate (11). Using the procedure described above for **6**, 0.141 g (30%) of the title compound was prepared from **10** and 0.185 g (43%) of starting material was recovered. Physical characteristics for **11**: mp 104−106 °C; $[\alpha]^{25}_D$ (*c* 0.9, $CHCl_3$) −40; ^{1}H NMR ($CDCl_3$) δ 7.35−7.24 (m, 11 H), 6.84−6.75 (m, 2 H), 4.71 (s, 4 H), 3.79 (s, 3 H), 3.67 (br s, 1 H), 2.45 (s, 3 H), 1.99−1.89 (m, 2 H), 0.41 (t, *J* = 7 Hz, 3 H) ppm; ^{13}C NMR ($CDCl_3$) δ 166.5, 152.3, 150.5, 149.9, 138.4, 134.5, 129.2, 128.7, 127.1, 126.8, 121.9, 111.6, 108.1, 54.9, 50.6, 50.2, 24.0, 12.6, 8.6 ppm; IR (mull) 1689 cm^{-1}; UV λ_{max} 359 (ϵ 26100, MeOH); MS (EI) *m*/z 411 ($M^{+\bullet}$). Anal. Calcd for $C_{28}H_{29}NO_2$: C, 81.72; H, 7.10; N, 3.40. Found: C, 81.49; H, 7.12; N, 3.52.

(4*S*)-4-Phenyl-3-[(3*R*)-3-phenylpentanoyl]-1,3-oxazolidin-2-one (24a). A solution of CuBr·Me_2S (2.01 g, 9.78 mmol) in 18 mL of THF was cooled to −50 °C, and phenylmagnesium bromide (9.8 mL of a 1.0 M solution, 9.78 mmol) was added dropwise over 15 min. The reaction mixture was stirred an additional 30 min at ca. −20 °C. The reaction mixture was then placed in an ice bath, and a solution of **3**[10a,16] (1.999 g, 8.15 mmol) in 6 mL of THF was added dropwise over 9 min. The resulting mixture was stirred at 0 °C for 35 min and then quenched with 50 mL of saturated NH_4Cl (aq, pH = 8). Extraction with 100 mL of ether gave an organic layer which was washed with three 50-mL portions of NH_4Cl (saturated aq, pH = 8), washed with water, dried over $MgSO_4$, filtered, and concentrated to give 2.662 g of yellow solid. Crystallization from Et_2O afforded 1.845 g (70%) of the title compound as white crystals: mp 68−70 °C; $[\alpha]^{25}_D$ (*c* 0.9, $CHCl_3$) +60; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 8 H), 6.98−6.95 (m, 2 H), 5.36 (dd, *J* = 4.0, 8.8 Hz, 1 H), 4.62 (t, *J* = 8.8 Hz, 1 H), 4.15 (dd, *J* = 4.0, 8.8 Hz, 1 H), 3.57−3.48 (m, 1 H), 3.13−3.06 (m, 2 H), 1.70−1.55 (m, 2 H), 0.76 (t, *J* = 7.3 Hz, 3 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.6, 153.5, 143.5, 138.5, 128.9, 128.2, 127.6, 126.2, 125.3, 69.7, 57.4, 43.5, 41.3, 29.1, 11.7 ppm; IR (mull) 1788, 1697 cm^{-1}; MS (EI) *m*/z 323 ($M^{+\bullet}$). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.24; H, 6.69; N, 4.36.

(2*R*)-1-[(4*S*)-2-Oxo-4-phenyl-1,3-oxazolidin-3-yl]-2-[(1*R*)-1-phenylpropyl]-1,3-butanedione (12a). A solution of $MgBr_2$·Et_2O (0.661 g, 2.56 mmol) and **24a** (0.754 g, 2.33 mmol) in THF (5 mL) was cooled to −78 °C, and potassium bis(trimethylsilyl)-amide (7 mL of a 0.5 M solution in toluene, 3.5 mmol) was added dropwise over 7 min. The resulting mixture was stirred at −78 °C for 30 min, and then a solution of acetyl chloride (0.25 mL, 3.5 mmol) in THF (5 mL) was added dropwise over 3 min. The reaction mixture was stirred at −78 °C for 20 min and then allowed to slowly warm to ambient temperature overnight. The reaction mixture was then quenched with half-saturated NH_4Cl (aq, 5 mL) and extracted with EtOAc (100 mL). The organic layer was washed with saturated $NaHCO_3$ (aq, 25 mL), water (25 mL), and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated to give 1.105 g of yellow solid. Recrystallization from EtOAc/hexanes gave 0.319 g (37%) of the title compound as yellow crystals: mp 128−131 °C; $[\alpha]^{25}_D$ (*c* 1.0, $CHCl_3$) +3; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.21 (m, 10 H), 5.48 (dd, *J* = 3.9, 8.7 Hz, 1 H), 5.14 (d, *J* = 10.5 Hz, 1 H), 4.71 (app t, *J* = 8.8 Hz, 1 H), 4.25 (dd, *J* = 3.9, 8.9 Hz, 1 H), 3.28 (dt, *J* = 4.1, 10.5 Hz, 1 H), 1.75−1.68 (m, 2 H), 1.65 (s, 3 H), 0.69 (t, *J* = 7.3 Hz, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 153.7, 140.1, 138.1, 129.1, 128.7, 128.6, 127.0, 125.5, 70.0, 64.4, 57.8, 47.4, 31.0, 26.8, 11.7 ppm; IR (mull) 1789, 1723, 1687 cm^{-1}; MS (EI) *m*/z 365 ($M^{+\bullet}$); HRMS (EI) calcd 365.1627, found 365.1604. Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 71.93; H, 6.43; N, 3.99.

(*S*)-3-Acetyl-4-phenyl-2-oxazolidinone (13a). A solution of (*S*)-4-phenyl-2-oxazolidinone (10.16 g, 62.2 mmol) in THF (350 mL) was cooled to −78 °C, and *n*-butyllithium (39 mL of a 1.6 M solution, 62.2 mmol) was added dropwise over 15 min. The reaction mixture was stirred at −78 °C for an additional 15 min; then a solution of acetyl chloride (4.9 mL, 68.4 mmol) in THF (25 mL) was added dropwise over 5 min. The reaction mixture was then allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched by pouring into saturated NH_4Cl (aq, 250 mL) and extracted with EtOAc (250 mL). The aqueous layer was extracted with additional EtOAc (100 mL); then the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to give 12.88 g of a white solid. Recrystallization from EtOAc/hexanes gave 9.436 g (74%) of the title compound as white crystals: mp 90−91 °C; $[\alpha]^{25}_D$ (*c* 1.0, $CHCl_3$) +56; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.28 (m, 5 H),

5.42 (dd, J = 3.5, 8.7 Hz, 1 H), 4.68 (app t, J = 8.8 Hz, 1 H), 4.28 (dd, J = 3.5, 8.9 Hz, 1 H), 2.53 (s, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 153.7, 138.8, 129.0, 128.6, 125.8, 69.8, 57.2, 23.6 ppm; IR (mull) 1772, 1701 cm^{-1}; MS (EI) m/z 205 ($M^{+\bullet}$), 162, 161, 145, 132, 119, 105, 104, 91, 77, 51. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.82. Found: C, 64.22; H, 5.50; N, 6.77.

(*S*)-3-(1-Oxo-4,4-dimethyl-2-pentenyl)-4-phenyl-2-oxazolidinone (14a). A solution of **13a** (5.093 g, 24.8 mmol) in CH_2Cl_2 (125 mL) was cooled to −78 °C, and $TiCl_4$ (2.9 mL, 26.0 mmol) was added dropwise over 2 min. *N*,*N*-Diisopropylethylamine (4.8 mL, 27.3 mmol) was added dropwise over 5 min, and the resulting mixture was stirred for 40 min at −78 °C. *tert*-Butylcarboxaldehyde (2.7 mL, 25.1 mmol) was then added dropwise over 3 min, and diisopropylethylamine (4.8 mL, 27.3 mmol) was added dropwise over 2 min. The resulting mixture was allowed to warm to room temperature over 1 h and then poured into water (100 mL) and stirred for 15 min. The organic layer was then separated, washed with 1:1 saturated $NaHCO_3$ (aq)/brine (100 mL), dried over $MgSO_4$, filtered, and concentrated to give 6.922 g of a yellow solid. Recrystallization from EtOH yielded 4.707 g (69%) of the title compound: mp 138−142 °C; $[\alpha]^{25}_D$ (c 1.1, $CHCl_3$) +103; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.30 (m, 5 H), 7.19 (d, J = 15.6 Hz, 1 H), 7.13 (d, J = 15.6 Hz, 1 H), 5.49 (dd, J = 3.9, 8.8 Hz, 1 H), 4.69 (t, J = 8.8 Hz, 1 H), 4.28 (dd, J = 3.9, 8.8 Hz, 1 H), 1.09 (s, 9 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 162.1, 154.2, 139.6, 129.6, 129.1, 126.4, 116.1, 70.3, 58.2, 34.8, 29.0 ppm; IR (mull) 1777, 1686, 1633 cm^{-1}; MS (EI) m/z 273 ($M^{+\bullet}$); HRMS (EI) calcd 273.1365, found 273.1362.

(4*S*)-3-[(3*S*)-3-[3-(Dibenzylamino)phenyl]-4,4-dimethylpentanoyl]-4-phenyl-1,3-oxazolidin-2-one] (15a). Using the procedure described above for **24a**, 4.804 g of (4*S*)-3-[(3*S*)-3-(3-aminophenyl)-4,4-dimethylpentanoyl]-4-phenyl-1,3-oxazolidin-2-one (**25a**) was prepared from **14a**. This material was used immediately without further purification. A solution of **25a** (4.8 g), potassium carbonate (3.8 g, 27.8 mmol), and benzyl bromide (3.3 mL, 27.8 mmol) in acetonitrile (20 mL) was heated to reflux for 1.25 h. The reaction mixture was then diluted with EtOAc (100 mL) and washed with two 30-mL portions of water. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give 7.295 g of a black oil. Column chromatography on 100 g of silica gel (elution with 3−20% EtOAc/hexanes) gave 1.068 g (18% for two steps) of the title compound as an off-white solid: mp 156−158 °C; $[\alpha]^{25}_D$ (c 1.0, DMSO) +42; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.25−7.19 (m, 10 H), 7.11 (d, J = 7.2 Hz, 1 H), 7.04−6.94 (m, 3 H), 6.64−6.58 (m, 3 H), 6.50 (s, 1 H), 6.34 (d, J = 7.3 Hz, 1 H), 5.36 (dd, J = 3.5, 8.4 Hz, 1 H), 4.76−4.59 (m, 5 H), 4.07−3.95 (m, 2 H), 2.78−2.65 (m, 2 H), 0.63 (s, 9 H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.6, 153.7, 147.4, 141.3, 139.2, 128.4, 128.3, 127.8, 127.0, 126.5, 124.5, 110.4, 69.8, 56.7, 54.4, 52.2, 33.5, 33.0, 27.6 ppm; IR (mull) 1775, 1714 cm^{-1}; MS (EI) m/z 546 ($M^{+\bullet}$). Anal. Calcd for $C_{36}H_{38}N_2O_3$: C, 79.09; H, 7.01; N, 5.12. Found: C, 79.11; H, 7.02; N, 5.08.

(*Z*,3*S*)-3-[3-(Dibenzylamino)phenyl]-4,4-dimethyl-1-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]-1-pentenyl Acetate (16a). Using the procedure described above for **12a**, 0.443 g (48%) of the title compound was prepared from **15a**: $[\alpha]^{25}_D$ (c 1.0, MeOH) +6; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.37−7.22 (m, 15 H), 6.88 (app t, J = 7.8 Hz, 1 H), 6.44 (d, J = 7.8 Hz, 1 H), 6.30 (s, 1 H), 6.24 (d, J = 7.8 Hz, 1 H), 5.19−5.12 (m, 1 H), 5.08 (d, J = 10.7 Hz, 1 H), 4.73−4.65 (m, 5 H), 4.07−4.01 (m, 1 H), 2.84 (d, J = 10.7 Hz, 1 H), 2.00 (s, 3 H), 0.40 (s, 9 H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.3, 153.8, 147.3, 141.5, 139.2, 138.1, 135.5, 128.7, 128.3, 127.7, 126.8, 126.5, 117.3, 113.4, 110.5, 110.1, 69.4, 58.9, 54.4, 51.4, 33.6, 27.1, 19.9 ppm; IR (mull) 1770 cm^{-1}; MS (EI) m/z 588 ($M^{+\bullet}$). Anal. Calcd for $C_{38}H_{40}N_2O_4$: C, 77.52; H, 6.85; N, 4.76. Found: C, 77.55; H, 6.81; N, 4.71.

(4*R*)-3-{[(1*S*,2*S*,3*S*)-5-(Dibenzylamino)-1-(dimethylamino)-3-ethyl-2,3-dihydro-1*H*-inden-2-yl]carbonyl}-4-phenyl-1,3-oxazolidin-2-one (20a) and (4*R*)-3-{[(1*R*,2*S*,3*S*)-5-(Dibenzylamino)-1-(dimethylamino)-3-ethyl-2,3-dihydro-1*H*-inden-2-yl]carbonyl}-4-phenyl-1,3-oxazolidin-2-one (20b). A solution of **9a**[10b] (2.033 g, 3.92 mmol) in CH_2Cl_2 (25 mL) was cooled to −78 °C, and titanium tetrachloride (0.42 mL, 3.92 mmol) was added dropwise. Diisopropylethylamine (0.68 mL, 3.92 mmol) was then added dropwise, and the resulting solution was stirred at 0 °C for 30 min. The reaction mixture was then cooled to −78 °C, and (chloromethylene)dimethylammonium chloride (0.602 g, 4.70 mmol) was added over 4 min. The reaction mixture was stirred at 0 °C for 3 h, quenched with saturated $NaHCO_3$ (aq, 150 mL), and extracted with two 150-mL portions of EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give 2.663 g of a green-yellow oil. Column chromatography on 225 g of silica gel (elution with 10−30% EtOAc/hexanes) gave 1.137 g (51%) of **20a** as a white foam and 0.580 g (26%) **20b** as a pale green foam. **Physical characteristics for 20a:** $[\alpha]^{25}_D$ (c 0.9, $CHCl_3$) −145; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, J = 1.5, 6.6 Hz, 2 H), 7.35−7.21 (m, 13 H), 7.01 (d, J = 9.1 Hz, 1 H), 6.59−6.57 (m, 2 H), 5.52 (dd, J = 4.0, 8.8 Hz, 1 H), 4.90 (d, J = 9.2 Hz, 1 H), 4.72 (t, J = 8.8 Hz, 1 H), 4.61 (s, 4 H), 4.28 (dd, J = 4.0, 8.8 Hz, 1 H), 4.08 (dd, J = 4.0, 8.8 Hz, 1 H), 3.81 (ddd, J = 4.2, 9.2, 9.2 Hz, 1 H), 1.89 (s, 6 H), 1.78−1.71 (m, 1 H), 1.33−1.26 (m, 1 H), 0.76 (t, J = 7.4 Hz, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 153.4, 149.6, 147.0, 139.0, 138.6, 128.5, 128.3, 127.9, 127.7, 126.7, 126.3, 125.8, 111.2, 107.7, 69.9, 69.6, 58.0, 55.1, 54.4, 45.4, 42.0, 27.0, 11.2 ppm; IR (mull) 1778, 1702 cm^{-1}; UV λ_{max} 258 (ϵ 18900, 95% EtOH); MS (EI) m/z 573 ($M^{+\bullet}$); HRMS (EI) calcd 573.2991, found 573.2986. Anal. Calcd for $C_{37}H_{39}N_3O_3$: C, 77.46; H, 6.85; N, 7.32. Found: C, 77.33; H, 6.92; N, 7.09. **Physical characteristics for 20b:** $[\alpha]^{25}_D$ (c 1.0, $CHCl_3$) −79; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.22 (m, 15 H), 7.02−6.98 (m, 1 H), 6.62 (dd, J = 2.4, 8.5 Hz, 1 H), 6.45 (d, J = 2.4 Hz, 1 H), 5.52 (dd, J = 3.6, 8.8 Hz, 1 H), 4.69 (dd, J = 8.8, 8.8 Hz, 1 H), 4.63−4.58 (m, 1 H), 4.61 (s, 4 H), 4.40−4.38 (m, 1 H), 4.34 (dd, J = 3.6, 8.8 Hz, 1 H), 3.29−3.21 (m, 1 H), 2.14 (s, 6 H), 1.79−1.58 (m, 2 H), 0.85 (t, J = 7.4 Hz, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 153.3, 149.6, 144.9, 138.6, 128.9, 128.7, 128.5, 126.7, 126.3, 125.2, 112.0, 107.0, 75.9, 69.2, 58.0, 54.3, 50.4, 46.0, 40.6, 25.9, 10.6 ppm; IR (mull) 1776, 1693 cm^{-1}; UV λ_{max} 258 (ϵ 18900, 95% EtOH); MS (EI) m/z 573 ($M^{+\bullet}$); HRMS (EI) calcd 573.2991, found 573.2985. Anal. Calcd for $C_{37}H_{39}N_3O_3$: C, 77.46; H, 6.85; N, 7.32. Found: C, 77.12; H, 6.73; N, 7.06.

Supporting Information Available: Experimental information for compounds **22** (enantiomer of **6**), **23** (enantiomer of **1**, R_1 = Et, R_2 = Me), **12b**,**c**, **14b**,**c**, **15b**,**c**, **16b**, **17**, **18**, **19**, and **21a**,**b** and X-ray crystal structure of **20a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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