Table V. Crystal and Experimental Data for 11

formula	$C_{22}H_{30}N_2O_4$
formula weight	386.6
$F(000)$	416
crystal size, mm	0.05 × 0.15 × 0.60
Space group	$P2_1$
a, Å	12.204 (5)
b, Å	6.320 (3)
c, Å	13.895 (8)
β, deg	93.26 (4)
V, Å^3	1070.0 (9)
Z	2
d_{calcd}, g cm^{-3}	1.20
μ, cm^{-1}	0.77
sin θ/λ	0.55
total data	1658
obsd data	901
unobsd data	757
R_m	0.02
R	0.078
no. of parameters refined	124
goodness of fit	1.29

effect on the $\Delta\Delta G_c^*$ and was therefore ignored.

X-ray Structural Determination of 11. Crystals of compound 11 were often twinned and those that were not grew as very thin needles so a crystal suitable for an X-ray structural study was difficult to find. After several attempts, a crystal with dimension of 0.05 mm × 0.15 mm × 0.60 mm was chosen for the study. Even this crystal was not totally suitable as very few reflections above a 2θ limit of 40° were observed. Data were collected to a sin θ/λ limit of 0.55 (2θ = 46°). Some data between 2θ values of 46 and 50 were measured but none were greater than $3\sigma(I)$.

Lattice parameters and the orientation matrix were obtained by using a least-squares procedure involving 22 centered reflections 7° < 2θ < 22°. These data as well as single-crystal data were obtained on a Nicolet R3 automated diffractometer which used monochromated Mo Kα radiation (λ = 0.71073 Å). Crystal data and experimental conditions are summarized in Table V. Single-crystal data were measured by using θ-2θ scans with a variable scan rate (2.93 to 29.3°/min) and backgrounds on each side of the peak were measured so that the total time used to measure the background was equal to the scan time. A total of 901 observed unique data were obtained ($F > 4\sigma(F)$).

The structure was solved by using direct methods. All nonhydrogen atoms were located in the E map. Positions for all hydrogens were calculated on the basis of known stereochemical conditions. All hydrogens were allowed to ride on neighboring atoms and the thermal parameters of the hydrogen atoms were not refined. Because of the relatively few observed data and the large number of possible parameters only an isotropic refinement was used. The structure was refined to an R value of 0.078. With these conditions the observation/parameter ratio was about 7.2. Unit weights were used in the refinement. All programs used in the structure solution, refinement, and display are included in the SHELXTL program package.[36] Atomic scattering factors were obtained from ref 37.

Acknowledgment. This work was supported by the Office of Naval Research. We are grateful to Dr. C. E. Felder for his assistance in the force field calculations.

Supplementary Material Available: Tables containing hydrogen atom atomic parameters and bond lengths and angles for 11 and ^{1}H NMR spectra for compounds **15** (R = benzyl), **16** (R = benzyl), **17** (R = benzyl), **13** (R = benzyl, R = isopropyl, R = isobutyl, R = *sec*-butyl), **21-25**, and **28** (17 pages); table of observed and calculated structure factors for 11 (6 pages). Ordering information is given on any current masthead page.

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The Asymmetric Synthesis of 2,2-Dialkyl Carboxylic Esters and 2,2-Disubstituted Dihydronaphthalenes

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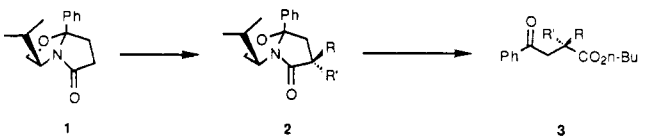
The bicyclic lactams derived from (*S*)-valinol and 3-benzoylpropionic acid or levulinic acid are useful chiral precursors to the title compounds. Metalation of bicyclic lactams **1** or **4** and alkylation followed by acidic hydrolysis leads to racemic 2-alkyl carboxylic acids. However, sequential metalation-alkylation to 2,2-dialkyl bicyclic lactams **2** and **5** furnishes these systems with good diastereoselectivity. Treatment of **5** with triflic acid causes a facile rearrangement to the oxazolines **7** and hydrolysis leads to the carboxylic esters. Under certain conditions, hydrolysis leads directly to naphthalenes **11**.

Several years ago we reported that the bicyclic lactams **1** were very useful precursors to chiral, nonracemic 2,2-dialkyl carboxylic esters **3** prepared in very high enantiomeric excess.[1] These initial studies on this versatile template required that the two α-protons in **1** were sequentially removed and alkylated with two different electrophiles to furnish **2** followed by hydrolysis in acidic 1-butanol. The method was found to be quite suitable for a number of 2,2-dialkyl carboxylic esters. Subsequent to that preliminary report we have shown in a number of other instances that the bicyclic lactams are indeed highly useful for the efficient asymmetric synthesis of geminally substituted chiral cyclopentenones,[2] cyclohexenones,[3] and a number of naturally occurring substances.[4]



1 2 3

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0022-3263/90/1955-3137$02.50/0

Table I. Chiral Lactams 2 and 2,2-Dialkyl Carboxylic Esters 3

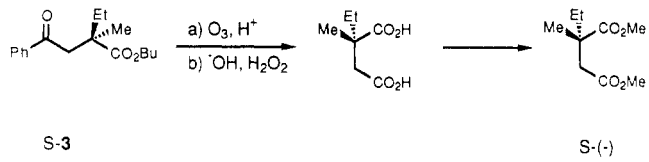
lactam 2[a]				*n*-butyl esters 3			
R[b]	R[c]	endo/exo[e]	yield,[d] %	R	R^1	yield, %	confn
Me	$PhCH_2$	42:1	75	Me	$PhCH_2$	79	*S*
$PhCH_2$	Me	12:1	74	$PhCH_2$	Me	78	*R*
Me	Et	7.5:1	80	Me	Et	71	*S*
Et	Me	10:1	75	Et	Me	87	*R*
p-MeOPhCH_2	Me	13:1	90	*p*-MeOPhCH_2	Me	92	*R*
Me	*p*-MeOPhCH_2	30:1	85	Me	*p*-MeOPhCH_2	88	*S*
Me	*i*-Pr	3:1	59				
i-Pr	Me	1:10	49				

[a] All were derived from alkyl iodides, except for benzyl and *p*-methoxybenzyl, which were derived from bromides. [b] First alkylation. [c] Second alkylation. [d] Yields of pure diastereomers from silica gel chromatography (10% ethyl acetate in hexane). [e] Endo/exo ratios determined by HPLC on a μ-Porosil column using 5–20% ethyl acetate–hexane.

We now further describe the asymmetric route to 2,2-dialkyl carboxylic esters **3** and **8** and chiral 2,2-disubstituted dihydronaphthalenes **12** by furnishing more complete details on this process as well as some major improvements and broader scope. We feel that the current level of efficiency is superior to the earlier preliminary report, and further studies also revealed some interesting molecular rearrangements.

The bicyclic lactam **1** was prepared in 85% yield by condensing (*S*)-valinol with 3-benzoylpropionic acid in toluene and heating to azeotropically remove water. Metalation of **1** with LDA at −78 °C and addition of various alkyl halides (RX) gave good yields of the 2-alkyl derivatives **2** (R = H), which proved to be mainly endo alkyl product from X-ray analysis. Pure endo lactams were readily obtained by column chromatography. Treatment of the pure or mixture of diastereomers with LDA and another alkyl halide (RX) gave the α,α-dialkyl lactam **2** in good yields and with excellent to good diastereomeric ratios (Table I). The major product, also confirmed by X-ray analysis, was shown to be that derived from endo entry of the second alkyl halide. The reasons for endo alkylation as the major mode of entry is probably due to steric effects presented by the angular phenyl group in **1** and some torsional strain effects created by the methylene group adjacent to the site of alkylation.[5] Additionally, there may be, in some cases, a stereoelectronic effect favoring endo addition due to hyperconjugation of adjacent C–H bonds and the σ* orbitals in the developing transition states (Cieplak Effect).[6] That there is a significant steric component to these alkylations can be seen when **1** is alkylated with isopropyl iodide and methyl iodide. In both sequential alkylations the isopropyl group is endo situated. Thus, when the methyl iodide group approaches the enolate from the endo face, the isopropyl group in the product is probably too large to move up into the exo plane. This causes the methyl iodide to enter the exo face, which forces the isopropyl down into the endo plane. From Table I it can be seen that except for the bulky isopropyl group, the other electrophiles utilized gave very good yields of the dialkylated lactams, and reversing the order of introduction led to good to excellent ratios of the respective diastereomers. Transformation of the chiral α,α-dialkyl lactams **2** to the corresponding 2,2-dialkyl carboxylates **3** was not a trivial matter. Hydrolysis using concentrated hydrochloric acid at reflux resulted in virtually no reaction, attesting to the extreme stability of this bicyclic system. Perhaps the α-quaternary center serves to block any nucleophilic attack on the carbonyl group. Eventually, higher temperatures proved to be the key parameter to hydrolysis. Heating **2** in 1-butanol containing 10% concentrated sulfuric acid for 90–100 h gave clean conversion to the *n*-butyl esters **3**. The products were obtained in good yields (Table I) with little or no decomposition accompanying the solvolysis process. It should also be mentioned that hydrolysis attempts of the monoalkylated lactams **2** (R = H) led to mainly *racemic* keto esters **3** (R = H).

Scheme I



S-3 S-(-)

An effort was made to confirm the absolute configuration of the keto esters **3** using chemical correlation to known compounds. This was successfully implemented via the reaction sequence shown in Scheme I. The butyl ester **3** was ozonized smoothly to the dicarboxylic acid, which was esterified with diazomethane to the known[7] dimethyl (*S*)-2-methyl-2-ethylsuccinate. Comparison of the data showed that the negative rotation is that of the *S* enantiomer, which confirmed the absolute configuration of **3** in Scheme I.

To further explore the scope of this asymmetric process we examined the bicyclic lactam **4** derived from valinol and levulinic acid.[8] Successive metalation–alkylation with various alkyl halides again provided geminally alkylated derivatives **5** or **9**. These adducts have already been shown to lead to a number of chiral cyclopentenone systems[2] via a reduction–hydrolysis sequence, but direct acidic hydrolysis to the keto esters **8** required stringent conditions. After the mixture of endo–exo diastereomers in **5** and **9** were readily separated via silica gel chromatography, they were examined regarding their ease of hydrolysis to the carboxylic esters **8**. It was found that heating a solution of **5a** or **5b** in 1,2-dichloroethane containing 5 equiv of trifluoromethanesulfonic acid (Triflic acid) resulted in 70–90% yields of the 4-ketooxazolines **7a**, **7b**. This facile rearrangement of the bicyclic lactam to the oxazoline is, to the best of our knowledge, unprecedented.

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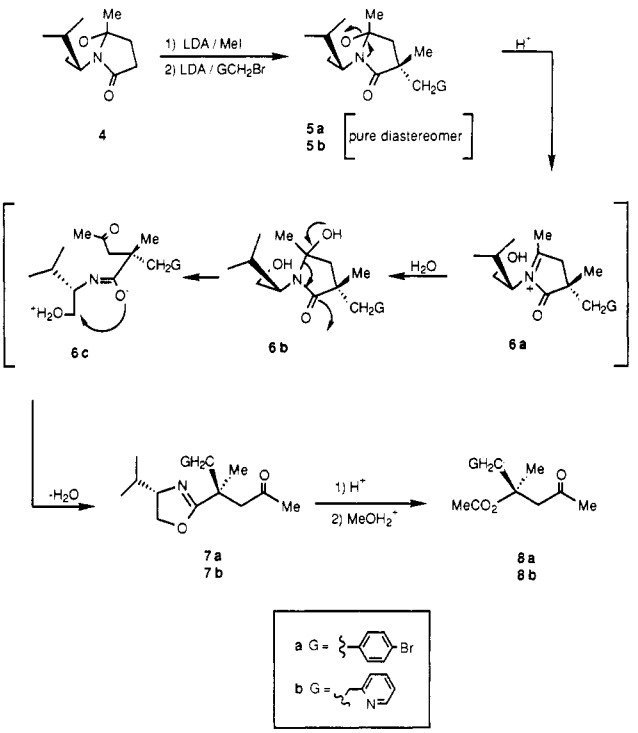
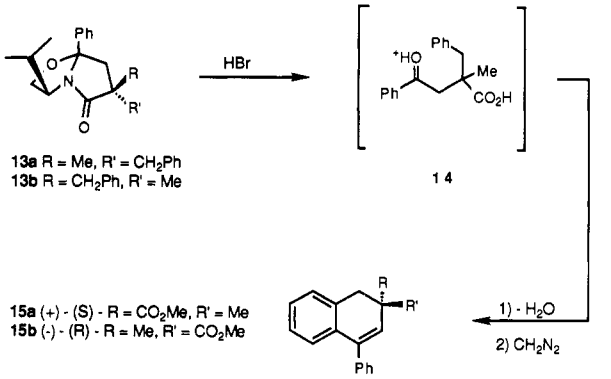


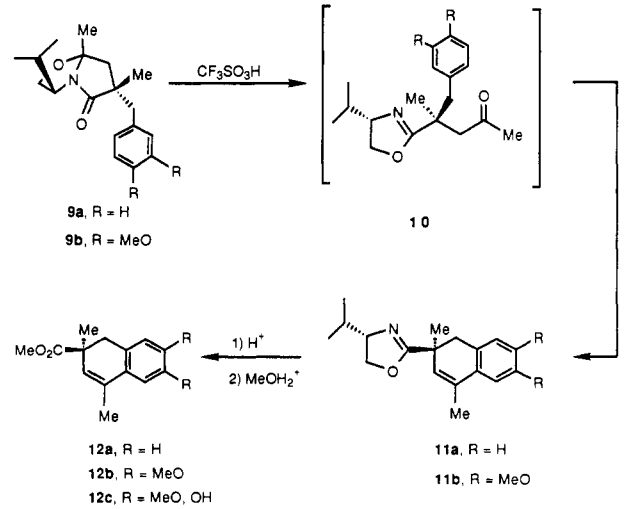
We envision this rearrangement to occur via the now known reversible fragmentation of **5** to the acyl imminium ion **6a**.[9] Attack by water, present in the triflic acid, leads to the carbinol amine **6b**, which cleaves to the keto imidate **6c**, which in turn cyclizes to the oxazoline **7**. This facile approach to enantiomerically pure 2,2-oxazolines now provides an opportunity to directly hydrolyze them to the carboxylic acids under milder acidic conditions. The hydrolysis was performed using aqueous sulfuric acid and heating for 4 h. This is a considerable improvement over direct hydrolysis of the corresponding lactams **5**, which require refluxing in 1-butanol containing concentrated sulfuric acid for 4 days (vide supra).

When the bicyclic lactams **9a, 9b** were prepared using benzyl bromide and 3,4-dimethoxybenzyl bromide, respectively, in the second alkylation step, they were likewise subjected to the aforementioned acidic conditions. However, rather than producing the ketooxazolines **10**, in analogy to the previous results, they gave the dihydronaphthalenes **11** in 70–85% yield. The naphthalene derivatives were undoubtedly the result of an acid-catalyzed intramolecular alkylation of the ketone **10** when an electron-rich aromatic ring was present. For the bicyclic lactams **5a**, **5b** the *p*-bromo substituent or the 2-pyridyl substituent are too electron poor to allow the intramolecular cyclization to occur. It is interesting to compare the direct formation of these dihydronaphthalenes from the bicyclic lactams without the intermediacy of the ketooxazoline. For example, when the 2-methyl-2-benzyl lactam **13a** was heated in 48% hydrobromic acid for 24 h it gave the dihydronaphthalene (*S*)-(+)-**15** in 85% yield after esterification with diazomethane. Similarly, the diastereomeric lactam **13b** under the same conditions gave (*R*)-(−)-**15** in 79% yield. Any acid conditions weaker than



these gave poor yields or mixtures of products. On the other hand, after the lactams **9a, 9b** were transformed with triflic acid into the naphthalene oxazolines **11a, 11b**, heating them in a 4–5 M solution of sulfuric acid for 4 h furnished the naphthalenecarboxylic acids. Fischer esterification with methanol–sulfuric acid gave the methyl esters **12a, 12b** in 75–85% yield. Thus the hydrolytic method to the chiral methyl esters was performed under much milder conditions by first allowing the lactams to pass through the oxazolines. This synthesis of dihydronaphthalenes represents an improvement over earlier methods of which there are relatively few.[10] Furthermore, there are no known routes to these systems in enantiomerically pure form, and thus this route takes on somewhat more improtance.

An interesting aspect of this study was revealed when the lactam enolate **16** was alkylated with 2-(chloromethyl)pyridine. The process led to two products **5b** and **17** in a 1.4:1 ratio, respectively. The unusual monocyclic product **17** is probably derived from the exo alkylation product, **18**. It may be assumed that the exo pyridylmethyl derivative **18** initially formed on alkylation of the enolate **16** tautomerizes via a proton shift to the pyridine nitrogen to afford the observed product **17**. The endo-alkylated product **5b** (G = 2-pyridylmethyl) cannot reach for the adjacent proton, or even more significant, the adjacent proton is not properly aligned with the departing oxygen to effect ring fracture. This behavior once again points to the facile ring–chain tautomerism of these bicyclic lactams. When the pyrrolidinone **17** was treated with TFA, it readily cyclized to the bicyclic lactam **18**.



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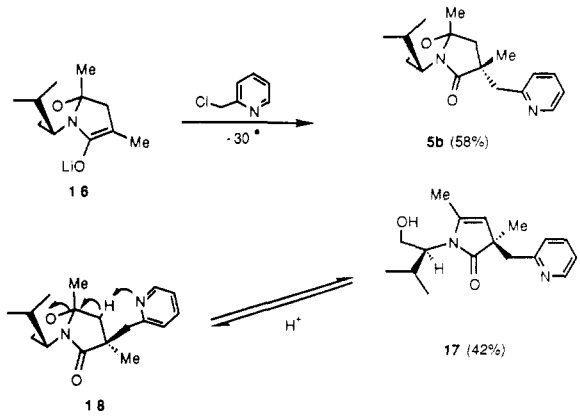

In summary, the sequential alkylation of bicyclic lactams by various alkyl halides leads to 2,2-dialkyl-3-benzoyl carboxylic esters in high ee's and to optically active 2-(α,α-quaternary substituted) oxazolines which are also precursors to carboxylic acids or their methyl esters. Under certain hydrolysis conditions, the products are optically active 2,2-dialkyl-1,2-dihydronaphthalenes.

Experimental Section

General. All ratios of diastereomers were determined on the crude alkylated materials using HPLC with a μ-Porosil column and eluding with 5–20% ethyl acetate in hexane. Microanalyses were performed by Desert Analytics, Tucson, AZ. Further analyses were performed by GC or ^{1}H NMR. NMR spectra were determined using a Bruker 270 MHz instrument.

(3*S*,7a*S*)-3-Isopropyl-7a-phenyl-5-oxo-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole 1. A solution containing 4.33 g (0.042 mol) of (*S*)-(+)-valinol, 7.6 g (0.42 mol) of 3-benzoylpropionic acid, and 100 mg of *p*-toluenesulfonic acid in 150 mL of toluene was heated with azeotropic removal of water. After 8 h, the mixture was cooled to room temperature and the solvent was removed in vacuo. The resulting oil was filtered through a short silica column (hexane–ethyl acetate, 9:1) and then recrystallized from hexane to give 8.3 g (83.6%) of a colorless solid: mp 52–54 °C; $[\alpha]^{20}_D$ 80.1° (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.4 (m, 5 H), 4.2 (t, J = 7 Hz, 1 H), 3.6 (m, 1 H), 3.4 (t, J = 7 Hz, 1 H), 2.0–3.0 (m, 4 H), 1.1 (m, 1 H), 1.05 (d, J = 1 Hz, 3 H), 0.65 (d, J = 6 Hz, 3 H); IR ($CHCl_3$), 1700, 1450 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.80. Found: C, 73.80; H, 7.53.

Endo α-Alkyl Lactams 2 (R = H, R′ = Alkyl). General Procedure. A solution of 1 mmol of lactam 1 in 1 mL of THF was added to 10 mL of a THF solution of lithium diisopropylamide (1.1 equiv) at −78 °C. The mixture was stirred for 2 h, and a solution of the alkyl halide (1.0 equiv) in 2 mL of THF was added via syringe. The mixture was stirred at −78 °C until TLC analysis showed reaction to be complete, usually 1–2 h. In the case of isopropyl iodide, warming to room temperature was necessary causing a severe drop in stereoselectivity (Table I). The cold reaction mixture was poured into saturated ammonium chloride solution, extracted with dichloromethane, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (silica gel, ethyl acetate–hexane, 1:9) gave pure material. Analytical samples were prepared by Kugelrohr distillation and/or crystallization.

2 (R = H, R′ = Me): yield 85%; mp 84–85 °C (hexane); bp 130 °C (0.05 Torr); IR ($CHCl_3$) 3030, 2965, 1710, 1470, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.2 (s, 5 H), 4.20 (t, J = 7 Hz, 1 H), 3.50 (m, 1 H), 3.40 (t, J = 7 Hz, 1 H), 3.0 (m, 1 H), 2.38 (dd, J = 8.5, 12.6 Hz, 1 H), 2.05 (dd, J = 10, 12.6 Hz, 1 H), 1.21 (d, J = 7 Hz, 3 H), 1.10 (m, 1 H), 1.08 (s, 3 H), 0.68 (d, J = 5.5 Hz, 3 H). Anal. Calcd for $C_{16}H_{21}O_2N$: C, 74.10; H, 8.16. Found: C, 73.82; H, 8.33.

2 (R = H, R′ = $PhCH_2$): yield 88%; mp 175–177 °C (hexane); IR (KBr) 3040, 3000, 1720, 1500, 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 10 H), 4.26 (dd, J = 7.6, 8.5 Hz, 1 H), 3.70 (m, 1 H), 3.46 (dd, J = 7.6, 8.5 Hz, 1 H), 3.37 (dd, J = 4.2, 13.8 Hz, 1 H), 3.20 (m, 1 H), 2.60 (dd, J = 10.4, 13.8 Hz, 1 H), 2.24 (m, 2 H), 1.16 (m, 1 H), 1.08 (d, J = 6.1 Hz, 3 H), 0.69 (d, J = 6.3 Hz, 3 H). Anal. Calcd for $C_{22}H_{25}O_2N$: C, 78.77; H, 7.51; N, 4.17. Found: C, 78.55; H, 7.46; N, 4.10.

2 (R = H, R′ = Et): yield 80%; bp 130 °C (0.05 Torr); IR (film) 3060, 3028, 2960, 2878, 1720, 1490, 1466, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5), 4.20 (dd, J = 6.8, 7.8 Hz, 1 H), 3.60 (m, 1 H), 3.46 (m, 1 H), 2.82 (t of dd, J = 10.3, 8.8, 4.64 Hz, 1 H), 2.34 (dd, J = 8.8, 12.8 Hz, 1 H), 2.13 (dd, J = 10.3, 12.8 Hz, 1 H), 1.8 (m, 2 H), 1.4 (m, 1 H), 1.07 (d, J = 2.4 Hz, 3 H), 0.91 (t, J = 7.3 Hz, 3 H), 0.68 (d, J = 5.8 Hz, 3 H). Anal. Calcd for $C_{17}H_{23}O_2N$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.39; H, 8.48; N, 5.07.

2 (R = H, R′ = *p*-MeOPhCH_2): yield 82%; mp 117 °C (heptane); IR (KBr) 3058, 3023, 2960, 1705, 1610, 1510, 1465 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 5 H), 7.1 (d, J = 8.5 Hz, 2 H), 6.8 (d, J = 8.5 Hz, 2 H), 4.2 (t, 1 H), 3.76 (s, 3 H), 3.7 (m, 1 H), 3.45 (m, 1 H), 3.3 (m, 1 H), 3.18 (m, 1 H), 2.57 (dd, J = 11, 15 Hz, 1 H), 2.20 (m, 2 H), 1.15 (m, 1 H), 1.10 (br s, 3 H), 0.69 (d, J = 5.6 Hz, 3 H). Anal. Calcd for $C_{23}H_{27}O_3N$: C, 75.56; H, 7.45; N, 3.83. Found: C, 75.54; H, 7.46; N, 3.82.

2 (R = H, R′ = *i*-Pr): yield 86%; bp 140 °C (0.2 Torr); IR (film) 3060, 3022, 2960, 2870, 1715, 1490, 1463, 1446 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.60–7.20 (m, 5 H), 4.25 (t, J = 8.5 Hz, 1 H), 3.65 (m, 1 H), 3.46 (t, J = 8.5 Hz, 1 H), 2.91 (ddd, J = 5, 10, 9 Hz, 1 H), 2.28 (dd, J = 9.3, 13.3 Hz, 1 H), 2.21 (dd, J = 10, 13.3 Hz, 1 H), 2.20 (m, 1 H), 1.10 (m, 1 H), 1.05 (d, J = 6.6 Hz, 3 H), 0.96 (d, J = 6.6 Hz, 3 H), 0.85 (d, J = 6.6 Hz, 3 H), 0.67 (d, J = 6 Hz, 3 H). Anal. Calcd for $C_{18}H_{25}O_2N$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.41; H, 9.07; N, 4.73.

α,α-Dialkyl Lactams 2 (R = R′ = Alkyl). General Procedure. A solution of 1 mmol of monoalkylated lactam (pure or mixture of endo–exo product) in 2 mL of dry THF was added to a solution of 1.1 equiv of lithium diisopropylamide in THF at −78 °C. The mixture was stirred for 2 h, and a solution containing 2–3 equiv of the alkyl halide in 2 mL of THF was added via syringe at −78 °C. The solution was stirred at this temperature until TLC analysis indicated absence of starting material, usually 2 h. The reaction mixture was poured into saturated ammonium chloride solution, extracted with dichloromethane, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (silica gel, ethyl acetate–hexane, 1:9) gave pure material. Analytical samples were prepared by Kugelrohr distillation and/or recrystallization.

2 (R = Me, R′ = Et): yield 85%; bp 130 °C (0.05 Torr); IR (film) 3030, 2963, 2875, 1720, 1490, 1460, 1450, 1332 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 4.18 (t, J = 7.5 Hz, 1 H), 3.60 (m, 1 H), 3.30 (t, J = 7.5 Hz, 1 H), 2.55 (d, J = 14 Hz, 1 H), 1.96 (d, J = 14 Hz, 1 H), 1.80–1.20 (m, 3 H), 1.28 (s, 3 H), 1.09 (d, J = 1.7 Hz, 3 H), 0.86 (t, J = 7.3 Hz, 3 H), 0.67 (d, J = 6.5 Hz, 3 H). Anal. Calcd for $C_{18}H_{25}O_2N$: C, 75.22; H, 8.77; N, 4.87. Found: C, 74.96; H, 8.72; N, 4.75.

2 (R = Et, R′ = Me): yield 75%; bp 130 °C (0.05 Torr); mp 100 °C (heptane); IR (KBr) 3060, 3040, 2965, 2880, 1705, 1590, 1450, 1350 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 4.10 (t, J = 7.6 Hz, 1 H), 3.60 (m, 1 H), 3.3 (t, J = 7.6 Hz, 1 H), 2.34 (d, J = 14 Hz, 1 H), 2.10 (d, J = 14 Hz, 1 H), 1.58 (m, 2 H), 1.21 (s, 3 H), 1.0–1.21 (m, 1 H), 1.10 (s, 3 H), 0.90 (t, J = 7 Hz, 3 H), 0.66 (d, J = 5.6 Hz, 3 H). Anal. Calcd for $C_{18}H_{25}O_2N$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.30; H, 8.92; N, 4.86.

2 (R = Me, R′ = *p*-MeO$C_6H_4CH_2$): yield 85%; bp 160 °C (0.05 Torr); mp 85 °C (heptane); IR (KBr) 3050, 3000, 2970, 1710, 1612, 1513, 1460, 1442, 1380 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30–6.50 (m, 9 H), 3.98 (t, 1 H), 3.77 (s, 3 H), 3.50 (m, 1 H), 3.25 (t, J = 7.5 Hz, 1 H), 2.95 (d, J = 13.7 Hz, 1 H), 2.65 (d, J = 13.7 Hz, 1 H), 2.68 (d, J = 14.2 Hz, 1 H), 1.89 (d, J = 14.2 Hz, 1 H), 1.29 (s, 3 H), 1.20 (m, 1 H), 1.10 (s, 3 H), 0.70 (s, 3 H). Anal. Calcd for $C_{24}H_{29}O_3N$: C, 75.96; H, 7.70; N, 3.69. Found: C, 75.80; H, 7.56; N, 3.69.

2 (R = *p*-MeO$C_6H_4CH_2$, R′ = Me): yield 90%; mp 134–135 °C (heptane); IR (KBr) 3050, 2960, 2922, 1701, 1612, 1510, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30–6.40 (m, 9 H), 4.18 (t, J = 7.8 Hz, 1 H), 3.80 (s, 3 H), 3.60 (m, 1 H), 3.20 (t, J = 7.8 Hz, 1 H), 3.13 (d, J = 14 Hz, 1 H), 2.70 (d, J = 14 Hz, 1 H), 2.30 (d, J = 18 Hz, 1 H), 2.10 (d, J = 18 Hz, 1 H), 1.32 (s, 3 H), 0.94 (s, 3 H), 0.87 (m, 1 H), 0.68 (s, br, 3 H). Anal. Calcd for $C_{24}H_{29}O_3N$: C, 75.96; H, 7.70; N, 3.69. Found: C, 75.69; H, 7.80; N, 3.96.

2 (R = Me, R′ = *i*-Pr): yield 59%; bp 145 °C (0.2 Torr); IR (film) 3050, 2960, 2870, 1715, 1488, 1465, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.2 (m, 5 H), 4.20 (t, J = 8 Hz, 1 H), 3.70 (m, 1 H), 3.30 (t, J = 8 Hz, 1 H), 2.70 (d, J = 14.5 Hz, 1 H), 2.03 (d, J = 14.5 Hz, 1 H), 2.00–1.80 (m, 1 H), 1.23 (s, 3 H), 1.10 (s, br, 3 H), 1.00

(m, 1 H), 0.92 (d, J = 6.5 Hz, 3 H), 0.85 (d, J = 6.5 Hz, 3 H), 0.66 (d, J = 5 Hz, 3 H). Anal. Calcd for $C_{19}H_{27}O_2N$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.83; H, 9.19; N, 4.55.

Solvolysis to Butyl Esters 3. General Procedure. A solution of 1.0 mmol of the dialkyl bicyclic lactam **2** in 20 mL of 1-butanol was treated with 2 mL of concentrated sulfuric acid, heated to reflux for 90–96 h, cooled, and poured into ice water. The mixture was extracted several times with dichloromethane, and the organic phase was washed with brine and then dried (Na_2SO_4). Evaporation, in vacuo, of the dichloromethane, excess 1-butanol, and di-*n*-butyl ether gave a residue which was purified by column chromatography (silica gel, ethyl acetate–hexane, 9:1) and then by Kugelrohr distillation.

(*S*)-*n*-Butyl 2-methyl-2-benzyl-3-benzoylpropionate, 3 (R = Me, R′ = PhCH$_2$): yield 79%; $[\alpha]^{23}_D$ +23.90° (*c* 1.25, $CHCl_3$); bp 150 °C (0.3 Torr); IR (film) 3065, 3030, 2960, 2940, 1730, 1690, 1600, 1585, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.00 (m, 2 H), 7.80–7.00 (m, 8 H), 3.36 (d, J = 18 Hz, 1 H), 3.08 (d, J = 18 Hz, 1 H), 3.06 (s, 2 H), 1.80–1.00 (m, 4 H), 1.29 (s, 3 H), 0.86 (t, J = 6.5 Hz). Anal. Calcd for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 78.04; H, 7.92.

The *R* enantiomer (3, R = PhCH$_2$, R′ = Me) was obtained in 78% yield and gave $[\alpha]^{23}_D$ −24.80° (*c* 1.56, $CHCl_3$). All spectral data was identical with the *S* enantiomer given above.

(*S*)-*n*-Butyl 2-methyl-2-ethyl-3-benzoylpropionate, 3 (R = Me, R′ = Et): yield 71%; $[\alpha]^{23}_D$ 29.96° (*c* 4.15, $CHCl_3$); bp 115 °C (0.05 Torr); IR (film) 3035, 2975, 2942, 1735, 1695, 1605, 1590, 1458 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.9 (m, 2 H), 7.4 (m, 3 H), 4.07 (t, J = 6.4 Hz, 2 H), 3.45 (d, J = 17.6 Hz, 1 H), 3.08 (d, J = 17.6 Hz, 1 H), 1.29 (s, 3 H), 1.80–0.90 (m, 9 H), 0.88 (t, J = 7 Hz, 3 H). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.96; H, 8.55.

The *R* enantiomer of 3 (R = Et, R′ = Me) was obtained in 87% yield and gave $[\alpha]^{23}_D$ +31.50° (*c* 4.2, $CHCl_3$). All spectral data were identical with the *S* enantiomer given above.

(*S*)-*n*-Butyl 2-methyl-2-(*p*-methoxybenzyl)-3-benzoylpropionate, 3 (R = Me, R′ = *p*-MeOPhCH$_2$): yield 88%; $[\alpha]^{23}_D$ +22.23° (*c* 2.38, $CHCl_3$); bp 145 °C (0.1 Torr); IR (film) 3055, 2950, 2930, 1725, 1685, 1612, 1598, 1513, 1460, 1445; ^{1}H NMR ($CDCl_3$) δ 7.80–7.00 (m, 9 H), 4.07 (t, J = 6.5 Hz, 2 H), 3.77 (s, 3 H), 3.36 (d, J = 18 Hz, 1 H), 3.08 (d, J = 18 Hz, 1 H), 3.00 (s, 2 H), 1.28 (s, 3 H), 1.60–1.00 (m, 4 H), 0.86 (t, J = 7 Hz, 3 H). Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.84; H, 7.58.

The *R* enantiomer of 3 (R = *p*-MeOPhCH$_2$, R′ = Me) was obtained in 92% yield and gave $[\alpha]^{23}_D$ −23.08° (*c* 1.98, $CHCl_3$). All spectral data were identical with the *S* enantiomer given above.

(*S*)-Dimethyl 2-Methyl-2-ethylsuccinate. A solution of 350 mg of keto ester **3** (R = Me, R′ = Et) in 20 mL of acetic acid was treated with a stream of ozone for 24 h. TLC indicated disappearance of starting material after that length of time. Hydrogen peroxide (3 mL, 30%) was added to the solution, and the mixture was stirred overnight. Concentrated sodium hydroxide (40%) was added to neutralize the acid, and then 5 mL of hydrogen peroxide (30%). The mixture was again stirred for 48 h at room temperature and then subjected to acid–base separation. The acidic layer was treated with diazomethane and purified by preparative-layer chromatography and finally Kugelrohr distillation, to give 100 mg of the succinate ester: 42%; bp 50–60 °C (0.2 Torr); IR (film) 1740 cm^{-1}; $[\alpha]^{23}_D$ −3.79° (*c* 4.56, hexane) [lit.[7] $[\alpha]_D$ −8.87° (neat)]. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.51; H, 8.66.

(3*S*,6*S*,7a*R*)-3-Isopropyl-7a-methyl-5-oxo-6-methyl-6-(*p*-bromobenzyl)-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole (5a). Lactam **4** (3.00 g, 0.0164 mol) was dissolved in THF (25 mL) and added to freshly prepared LDA (0.018 mol) in THF (80 mL) at −78 °C. The resulting solution was stirred at −78 °C for 1 h, at which time neat MeI (2.0 mL, 0.033 mol) was added dropwise. The mixture was stirred at −78 °C for 2 h and was quenched with NH_4Cl (2 mL). The reaction mixture was warmed to ambient temperature, and the volatiles were removed on a rotary evaporator. The residue was taken up in ether (75 mL). The ether was washed with water (10 mL) and brine (25 mL) and dried (K_2CO_3). The ether was evaporated to yield the crude monomethyl lactam (3.15 g). The crude material was used without purification in the following reaction. Monomethyl lactam (1.00 g, 5.07 mmol) was dissolved in THF (25 mL) and added to freshly prepared LDA (5.6 mmol) in THF (50 mL) at −78 °C. The resulting solution was stirred at −78 °C for 15 min and was then warmed to 0 °C. The reaction was stirred at 0 °C for 40 min and cooled back to −78 °C. At this time *p*-bromobenzyl bromide (2.50 g, 0.010 mol) was dissolved in THF (15 mL) and added dropwise, and the resulting mixture stirred at −78 °C for 4 h, at which time the reaction and cold bath were transferred to a freezer at −30 °C. The reaction was allowed to warm to −30 °C overnight. The reaction was then quenched with NH_4Cl (1 mL) and warmed to room temperature. The volatiles were removed on a rotary evaporator, and the residue was taken up in ether (50 mL). The ether was washed with water (10 mL) and brine (20 mL) and dried (K_2CO_3). The ether was evaporated to yield the crude material (3.25 g) which was purified by chromatography (silica gel, hexane–EtOAc, 85:15) affording 680 mg, (37%) of **5a**. This material was recrystallized from pentane–ether, 3:1, and the product was obtained as a white solid: mp 103.5–105 °C; $[\alpha]^{23}_D$ +101.17° (*c* 0.9, abs EtOH); ^{1}H NMR ($CDCl_3$) δ 7.36 (d, J = 8.31 Hz, 2 H), 7.02 (d, J = 8.23 Hz, 2 H), 3.92 (dd, J = 7.84, 8.39 Hz, 1 H), 3.67 (dd, J = 6.67, 8.24 Hz, 1 H), 3.56–3.46 (m, 1 H), 2.90 (d, J = 13.48 Hz, 1 H), 2.63 (d, J = 13.50 Hz, 1 H), 2.28 (d, J = 13.58 Hz, 1 H), 1.80 (d, J = 13.58 Hz, 1 H), 1.65–1.57 (m, 1 H), 1.43 (s, 3 H), 1.29 (s, 3 H), 1.03 (d, J = 6.65 Hz, 3 H), 0.86 (d, J = 6.62 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 183.03, 136.63, 131.94, 130.98, 122.32, 96.44, 70.14, 61.81, 48.57, 45.15, 43.14, 33.64, 25.91, 25.81, 20.43, 18.79; IR 2964, 2877, 1714, 1376, 1349 cm^{-1} (*m/e*) 367 (7.7), 365 (8.6), 352 (12.0), 350 (12.5), 324 (8.2), 322 (9.0), 196 (12.9), 169 (8.4), 128 (15.2), 84 (58.0). Anal. Calcd for $C_{18}H_{24}O_2NBr$: C, 59.02; H, 6.60. Found: C, 59.12; H, 6.56.

(3*S*,6*S*,7a*R*)-3-Isopropyl-6,7a-dimethyl-5-oxo-6-(2-pyridylmethyl)-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole, 5b. Lactam **4** (3.00 g, 6.4 mmol) was dissolved in THF (25 mL) and added to freshly prepared LDA (18 mmol) in THF (80 mL) at −78 °C. The resulting solution was stirred at −78 °C for 1 h at which time neat MeI (2.0 mL, 33 mmol) was added dropwise. The mixture was stirred at −78 °C for 2 h and was quenched with NH_4Cl (2 mL). The reaction was warmed to ambient temperature, and the volatiles were removed on a rotary evaporator. The residue was taken up in ether (75 mL). The ether was washed with water (10 mL) and brine (25 mL) and dried (K_2CO_3). The ether was evaporated to yield the crude monomethyl lactam (3.15 g). The crude material was used without purification in the following reaction. Monomethyl lactam (1.029 g, 5.2 mmol) was dissolved in THF (25 mL) and added to freshly prepared LDA (5.9 mmol) in THF (50 mL) at −78 °C. The resulting solution was stirred at −78 °C for 15 min and was then warmed to 0 °C. The reaction was stirred at 0 °C for 40 min and cooled back to −78 °C. At this time 2-(chloromethyl)pyridine (0.73 g, 5.7 mmol) was dissolved in THF (15 mL) and added dropwise, and the resulting mixture stirred at −78 °C for 4 h, at which time the reaction and cold bath were transferred to a freezer at −30 °C. The reaction was allowed to warm to −30 °C overnight. The reaction was then quenched with NH_4Cl (1 mL) and warmed to room temperature. The volatiles were removed on a rotary evaporator, and the residue was taken up in ether (50 mL). The ether was washed with water (10 mL) and brine (20 mL) and dried (K_2CO_3). The ether was evaporated to yield the crude material (1.57 g), which was purified by chromatography (silica gel, hexane–EtOAc–Et_3N, 75:20:5), affording 359 mg (25%) of **5b**: $[\alpha]^{23}_D$ +91.85° (*c* 0.65, abs EtOH); ^{1}H NMR ($CDCl_3$) δ 8.51–8.48 (m, 1 H), 7.57–7.51 (m, 1 H), 7.17–7.08 (m, 2 H), 3.88 (dd, J = 7.87, 8.27 Hz, 1 H), 3.65 (dd, J = 6.47, 8.45 Hz, 1 H), 3.57–3.5 (m, 1 H), 3.16 (d, J = 13.42 Hz, 1 H), 2.86 (d, J = 13.37 Hz, 1 H), 2.58 (d, J = 13.87 Hz, 1 H), 1.87 (d, J = 13.91 Hz, 1 H), 1.68–1.55 (m, 1 H), 1.43 (s, 3 H), 1.37 (s, 3 H), 1.04 (d, J = 6.67 Hz, 3 H), 0.85 (d, J = 6.61 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 183.74, 158.55, 149.05, 135.99, 124.77, 121.45, 96.94, 70.29, 62.10, 48.70, 45.81, 45.10, 33.92, 26.55, 26.23, 20.72, 19.06; IR (cm^{-1}) 2964, 2868, 1704, 1375, 1351; (*m/e*) 288 (3.7), 273 (4.0), 245 (4.1), 196 (7.3), 146 (47.4), 118 (11.0), 93 (91.2). Anal. Calcd for $C_{17}H_{24}O_2N_2$: C, 70.80; H, 8.39. Found: C, 70.42; H, 8.49.

2-[(2*S*)-2-(*p*-Bromophenyl)-4-oxopentyl]-4(*S*)-isopropyl-1,3-oxazoline, 7a. Lactam **5a** (200 mg, 0.550 mmol) was dissolved in 1,2-dichloroethane (5 mL) and added to a solution of triflic acid (0.24 mL, 2.7 mmol) in 1,2-dichloroethane (30 mL) at 0 °C. The resulting solution was warmed to room temperature, and

heated at reflux for 24 h. The reaction was cooled to room temperature and poured into $NaHCO_3$ (15 mL) and extracted with CH_2Cl (2 × 30 mL). The CH_2Cl_2 was washed with brine (15 mL), dried (K_2CO_3), and evaporated to yield the crude ketooxazoline. The crude compound was purified by chromatography (silica gel, hexane–EtOAc, 7:3), affording 182 mg, 0.497 mmol (90%), of **7a**: ^1H NMR ($CDCl_3$) δ 7.36 (d, J = 7.99 Hz, 2 H), 6.97 (d, J = 7.98 Hz, 2 H), 4.18 (dd, J = 8.15, 8.15 Hz, 1 H), 3.95–3.89 (m, 2 H), 3.05 (d, J = 13.27 Hz, 1 H), 2.94 (9 d, J = 13.27 Hz, 1 H), 2.66 (d, J = 17.16 Hz, 1 H), 2.53 (d, J = 17.16 Hz, 1 H), 2.10 (s, 3 H), 1.79–1.58 (m, 1 H), 1.26 (s, 3 H), 0.92 (d, J = 6.76 Hz, 3 H), 0.85 (d, J = 6.69 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 206.43, 170.24, 136.43, 132.01, 130.97, 120.46, 72.08, 69.81, 49.16, 43.14, 39.57, 32.46, 31.28, 23.53, 18.84, 17.99.

2-[(2*S*)-4-Oxo-2-(2-pyridylmethyl)pentyl]-4(*S*)-isopropyl-1,3-oxazoline, 7b. Lactam **5b** (200 mg, 0.694 mmol) was dissolved in 1,2-dichloroethane (5 mL) and added to a solution of triflic acid (0.31 mL, 3.4 mmol) in 1,2-dichloroethane (30 mL) at 0 °C. The resulting solution was warmed to room temperature and heated at reflux for 8 h. The reaction was cooled to room temperature, poured into $NaHCO_3$ (15 mL), and extracted with CH_2Cl_2 (2 × 30 mL). The CH_2Cl_2 was washed with brine (15 mL), dried (K_2CO_3), and evaporated to yield the crude ketooxazoline. The crude compound was passed through a plug of silica (hexane–EtOAc–Et_3N, 75:20:5), affording 166 mg, 0.583 mmol (84%), of pure **7b**: ^1H NMR ($CDCl_3$) δ 8.42–8.41 (m, 1 H), 7.49–7.43 (m, 1 H), 7.02–6.99 (m, 2 H), 4.05 (dd, J = 7.94, 8.59 Hz, 1 H), 3.85–3.74 (m, 2 H), 3.13 (d, J = 13.03 Hz, 1 H), 3.05 (d, J = 12.98 Hz, 1 H), 2.78 (d, J = 17.24 Hz, 1 H), 2.59 (d, J = 17.29 Hz, 1 H), 2.02 (s, 3 H), 1.68–1.60 (m, 1 H), 1.25 (s, 3 H), 0.81 (d, J = 6.77 Hz, 3 H), 0.74 (d, J = 6.73 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 206.40, 170.48, 158.25, 148.76, 135.57, 124.66, 121.19, 71.89, 69.61, 49.23, 45.70, 39.29, 32.27, 31.03, 23.86, 18.76, 17.79.

(*S*)-Methyl 2-Methyl-2-(*p*-bromobenzyl)-4-oxopentanoate, 8a. Ketooxazoline **7a** (170 mg, 0.460 mmol) was dissolved in 5 N H_2SO_4 (10 mL), and the resulting mixture was heated for 4 h at reflux. The reaction was cooled to room temperature and extracted with ether (3 × 30 mL); the ether was washed with brine (10 mL), dried with Na_2SO_4, and evaporated to yield the crude carboxylic acid. The crude acid was taken up in anhydrous methanol (5 mL), 5 drops of concentrated H_2SO_4 were added, and the reaction mixture was heated at reflux overnight. The excess methanol was distilled out of the reaction mixture at atmospheric pressure. The residue was cooled to room temperature, and extracted with ether (3 × 35 mL). The ether was dried (K_2CO_3) and evaporated to yield the crude ester, which was purified by chromatography (silica gel, hexane–EtOAc, 75:25), affording 84 mg, 0.268 mmol (58% over the 2 steps, 52% from lactam **5a**), of **8a**: $[\alpha]^{23}_D$ −6.10° (*c* 0.59, abs EtOH); ^1H NMR ($CDCl_3$) δ 7.36 (d, J = 8.37 Hz, 2 H), 6.89 (d, J = 8.35 Hz, 2 H), 3.61 (s, 3 H), 2.85 (d, J = 1.45 Hz, 2 H), 2.75 (d, J = 17.99 Hz, 1 H), 2.51 (d, J = 17.98 Hz, 1 H), 2.06 (s, 3 H), 1.16 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 206.10, 176.42, 135.862, 131.84, 131.18, 120.73, 51.85, 50.31, 44.49, 43.54, 30.47, 22.06; IR (cm^{-1}) 2939, 2974, 2949, 1738, 1722, 1489, 1361, 1115; (*m/e*) 313 (3.3), 311 (3.3), 255 (43.5), 253 (41.0), 224 (11.1), 222 (10.9), 195 (16.5), 193 (17.2) Anal. Calcd for $C_{14}H_{17}O_3Br$: C, 53.69; H, 5.47. Found: C, 53.65; H, 5.45.

(*S*)-Methyl 2-Methyl-2-(2-pyridylmethyl)-4-oxopentanoate, 8b. Ketooxazoline **7b** (153 mg, 0.530 mmol) was dissolved in 5 N H_2SO_4 (10 mL), and the resulting mixture was heated at reflux for 5 h. The crude acid was isolated by distillation of the water from the hydrolysis mixture and repeated azeotroping of the mixture with benzene (3 × 30 mL). The crude acid was taken up in anhydrous methanol (5 mL), 5 drops concentrated H_2SO_4 were added, and the reaction mixture was heated at reflux overnight. The excess methanol was distilled out of the reaction mixture at atmospheric pressure. The residue was cooled to room temperature and extracted with ether (3 × 35 mL). The ether was dried (K_2CO_3) and evaporated to yield the crude ester, which was purified by passing through a plug of silica (hexane–EtOAc–Et_3N, 75:20:5), affording 116 mg, 0.494 mmol (93% over the 2 steps, 78% from lactam **5b**) of **8b**: $[\alpha]^{23}_D$ −7.93° (*c* 0.58, abs EtOH); ^1H NMR ($CDCl_3$) δ 8.47–8.45 (m, 1 H), 7.54–7.48 (m, 1 H), 7.09–6.99 (m, 2 H), 3.59 (s, 3 H), 3.07 (d, J = 13.15 Hz, 1 H), 2.99 (d, J = 13.16 Hz, 1 H), 2.89 (d, J = 18.07 Hz, 1 H), 2.62 (d, J = 18.00 Hz, 1 H), 2.04 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 206.28, 176.56, 157.79, 148.95, 135.90, 124.59, 121.48, 51.75, 50.19, 45.68, 44.21, 30.34, 22.63; IR (cm^{-1}) 3070, 3006, 2953, 1734, 1722, 1589, 1434; CI (*m/e*) 235 (52.5), 203 (38.0). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.31; H, 7.28. Found: C, 66.18; H, 7.48.

(2*S*,4*S*)-Dihydronaphthalyloxazoline 11a. Lactam **9a** (200 mg, 0.697 mmol) was dissolved in 1,2-dichloroethane (5 mL) and added to a solution containing triflic acid (0.30 mL, 3.5 mmol) in 1,2-dichloroethane (30 mL) at 0 °C. The resulting solution was warmed to room temperature and heated at reflux for 12 h. The reaction was cooled to room temperature, poured into $NaHCO_3$ (15 mL), and extracted with CH_2Cl_2 (2 × 30 mL). The CH_2Cl_2 was washed with brine (15 mL), dried (K_2CO_3), and evaporated to yield the crude dihydronaphthalene. The crude compound was purified by chromatography (silica gel, hexane–EtOAc, 8:2), affording 157 mg, 0.584 mmol (84%), of **11a**: $[\alpha]^{23}_D$ −100.2° (*c* 0.55, abs EtOH); ^1H NMR ($CDCl_3$) δ 7.25–7.12 (m, 4 H), 5.91 (s, 1 H), 4.17–4.14 (m, 1 H), 4.01–3.91 (m, 2 H), 3.26 (d, J = 15.34 Hz, 1 H), 2.81 (d, J = 15.36 Hz, 1 H), 2.08 (d, J = 1.22, 3 H), 1.84–1.71 (m, 1 H), 1.23 (s, 3 H), 0.86 (d, J = 6.8 Hz, 3 H), 0.77 (d, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.46, 134.40, 134.08, 131.44, 129.75, 128.06, 127.11, 126.53, 122.93, 71.70, 69.54, 39.36, 37.83, 32.17, 23.56, 19.12, 18.44, 17.27; IR (cm^{-1}) 3062, 3030, 2964, 2932, 1659, 1256, 1212, 1082; (*m/e*) 269 (9.0), 254 (77.9), 169 (44.7), 156 (56.6), 141 (61.7), 115 (21.5).

(2*S*,4*S*)-Dihydronaphthyloxazoline 11b. Lactam **9b** (170 mg, 0.490 mmol) was dissolved in 1,2-dichloroethane (5 mL) and added to a solution of triflic acid (0.22 mL, 2.4 mmol) in 1,2-dichloroethane (30 mL) at 0 °C. The resulting solution was warmed to room temperature and heated at reflux for 5 h. The reaction was cooled to room temperature, poured into $NaHCO_3$ (15 mL), extracted with CH_2Cl_2 (2 × 30 mL). The CH_2Cl_2 was washed with brine (15 mL), dried (K_2CO_3), and evaporated to yield the crude dihydronaphthalene, which was purified by chromatography (silica gel, hexane–EtOAc, 7:3), affording 110 mg, 0.334 mmol (68%), of pure **11b**: ^1H NMR ($CDCl_3$) δ 6.78 (s 1 H), 6.67 (s, 1 H), 5.78 (s, 1 H), 4.16–4.12 (m, 1 H), 4.00–3.85 (m, 2 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.20 (d, J = 15.34 Hz, 1 H), 2.72 (d, J = 15.34 Hz, 1 H), 2.04 (d, J = 1.06 Hz, 3 H), 1.82–1.68 (m, 1 H), 1.22 (s, 3 H), 0.86 (d, J = 6.84 Hz, 3 H), 0.77 (d, J = 6.78 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.57, 148.30, 147.59, 130.98, 128.25, 127.38, 127.02, 112.32, 108.04, 71,59, 69.48, 56.29, 56.04, 38.97, 37.88, 32.10, 23.53, 19.27, 18.43, 17.21.

(*S*)-2,4-Dimethyl-2-carbomethoxy-1,2-dihydronaphthalene, 12a. Dihydronaphthyloxazoline **11a** (147 mg, 0.546 mmol) was dissolved in 5 N H_2SO_4 (10 mL), and the resulting mixture was heated at reflux for 4 h. The reaction was cooled to room temperature and extracted with ether (3 × 30 mL); the ether was washed with brine (10 mL), dried (Na_2SO_4), and evaporated to yield the crude carboxylic acid. The crude acid was taken up in anhydrous methanol (5 mL), 5 drops of concentrated H_2SO_4 were added, and the reaction was heated at reflux overnight. The excess methanol was distilled out of the reaction mixture at atmospheric pressure. The residue was cooled to room temperature and extracted with ether (3 × 35 mL). The ether was dried (K_2CO_3) and evaporated to yield the crude ester, which was purified by chromatography (silica gel, hexane–EtOAc, 95:5), affording 103 mg, 0.481 mmol, of **12a** (88% over the 2 steps, 74% from the lactam **9a**): $[\alpha]^{23}_D$ −72.75° (*c* 1.2, abs EtOH); ^1H NMR ($CDCl_3$) δ 7.26–7.18 (m, 4 H), 5.90 (s, 1 H), 3.71 (s, 3 H), 3.32 (d, J = 15.47 Hz, 1 H), 2.83 (d, J = 15.48 Hz, 1 H), 2.11 (d, J = 1.42 Hz, 3 H), 1.30 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.83, 133.97, 133.81, 131.94, 128.53, 127.97, 127.27, 126.56, 123.00, 52.00, 43.21, 38.33, 23.67, 19.18; IR (Cm^{-1}) 3062, 3019, 2964, 2953, 2877, 1730, 1452, 1229, 1098; (*m/e*) 216 (6.9), 157 (87.5), 142 (42.2), 115 (15.3), 77 (4.7). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.78; H, 7.50.

(*S*)-2,4-Dimethyl-4-carbomethoxy-6(or 7)-hydroxy-6(or 7)-methoxy-1,2-dihydronaphthalene, 12c, and the Dimethoxynaphthalene, 12b. Dihydronaphthyloxazoline **11b** (100 mg, 0.304 mmol) was dissolved in 5 N H_2SO_4 (10 mL), and the resulting mixture was heated at reflux for 4 h. The reaction was cooled to room temperature and extracted with ether (3 × 30 mL); the ether was washed with brine (10 mL), dried (Na_2SO_4), and evaporated to yield the crude carboxylic acid. The crude acid was taken up in anhydrous methanol (5 mL), 5 drops of concentrated H_2SO_4 were added, and the reaction was heated at reflux

overnight. The excess methanol was distilled out of the reaction mixture at atmospheric pressure. The residue was cooled to room temperature and extracted with ether (3 × 35 mL). The ether was dried (K_2CO_3) and evaporated to yield the crude ester, which were found to be a mixture of the desired product and the phenol **12c**. Separation of the two compounds on preparative TLC (silica gel, hexane–EtOAc, 9:1) afforded **12b**, 18 mg, 0.065 mmol (21%), and phenol **12c**, 18 mg, 0.069 mmol (23%). The dimethoxy ester was recrystallized from pentane to yield **12b** a white solid: mp 65.5–67 °C; $[\alpha]^{23}_D$ −37.7° (*c* 1.0, abs EtOH); ^{1}H NMR ($CDCl_3$) δ 6.77 (s, 1 H), 6.68 (s, 1 H), 5.72 (d, *J* = 1.31 Hz, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.66 (s, 3 H), 3.19 (d, *J* = 15.42 Hz, 1 H), 2.68 (d, *J* = 15.44 Hz, 1 H), 2.04 (d, *J* = 1.45 Hz, 3 H), 1.24 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.19, 148.33, 147.55, 131.73, 127.05, 126.89, 126.72, 111.92, 107.76, 56.28, 56.07, 52.16, 43.45, 38.20, 23.93, 19.51; IR (cm^{-1}) 2953, 2932, 2866, 1730, 1605, 1512; MS (*m/z*) 276 (9.1), 217 (86.3), 202 (36.4), 186 (14.7); HRMS found 276.1371.

The phenolic product, **12c**, isolated above gave the following spectral properties: ^{1}H NMR ($CDCl_3$) δ 6.74 (s, 1 H), 6.73 (s, 1 H), 5.72 (s, 1 H), 5.55 (s, 1 H (OH)), 3.87 (s, 3 H), 3.66 (s, 3 H), 3.16 (d, *J* = 15.40 Hz, 1 H), 2.66 (d, *J* = 15.41 Hz, 1 H), 2.03 (d, *J* = 1.42 Hz, 3 H), 1.22 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.20, 145.08, 144.93, 131.65, 127.60, 126.69, 114.79, 106.72, 56.26, 52.13, 43.40, 37.98, 23.75, 19.56; IR (cm^{-1}) 3444, 2954, 2932, 1730, 1583, 1512; (*m/e*) 262 (10.0), 203 (73.4).

This material was converted into dihydronaphthalene **12b** by the following reaction conditions:

Ester **11c** (10 mg, 0.038 mmol) was dissolved in THF (3 mL) and added to NaH (0.0017 g, 0.071 mmol, washed free of oil with pentane) in THF (2 mL). The reaction was stirred at room temperature for 1 h, at this time methyl iodide (0.057 mL, 0.090 mmol) was added. The reaction was stirred for 2 h at room temperature and was worked up by pouring into NH_4Cl and extracting with ether (2 × 25 mL). The ether was dried (K_2CO_3) and evaporated to yield 7 mg (0.025 mmol, 67%) of pure **12b**.

(*S*)-2-Methyl-2-carbomethoxy-4-phenyl-1,2-dihydronaphthalene, 15a. A solution of 300 mg of lactam **13a** in 10 mL of 48% hydrobromic acid was heated to reflux for 24 h. After cooling to room temperature, the solution was diluted with water and extracted three times with ethyl acetate. The extracts were dried (Na_2SO_4) and concentrated in vacuo, and the residue was dissolved in ether. The ethereal solution was treated with excess diazomethane, and the solution was filtered and then concentrated. The residue was purified by preparative TLC and then distilled via Kugelrohr, to give 200 mg (85%): bp 120 °C (0.07 Torr); $[\alpha]^{23}_D$ +12.79° (*c* 1.15, $CHCl_3$); IR (film) 3050, 3020, 2942, 1736, 1598, 1492, 1483, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40–7.00 (m, 9 H), 6.05 (s, 1 H), 3.7 (s, 3 H), 3.38 (d, *J* = 15.5 Hz, 1 H), 2.85 (d, *J* = 15.5 Hz, 1 H), 1.35 (s, 3 H). Anal. Calcd for $C_{19}H_{18}O_2$: C, 82.00; H, 6.52. Found: C, 82.80; H, 6.76. The *R* enantiomer of the above, **15b** was prepared in the same manner, affording 190 mg (79%) of a clear oil whose boiling point and spectral properties were identical with those of **15a**: $[\alpha]^{23}_D$ −12.56° (*c* 1.15, $CHCl_3$). Anal. Found: C, 81.73; H, 6.69.

Dehydropyrrolidone, 17. This material was isolated from the chromatographic separation of **5b** (vide supra), affording 260 mg (17%): ^{1}H NMR ($CDCl_3$) δ 8.37–8.35 (m, 1 H), 7.55–7.49 (m, 1 H), 7.07–7.03 (m, 2 H), 4.91 (d, *J* = 1.37 Hz, 1 H), 4.58 (s, 1 H, (OH)), 4.27–4.21 (m, 1 H), 3.76–3.61 (m, 1 H), 3.29 (d, *J* = 13.99 Hz, 1 H), 3.05–2.98 (m, 1 H), 2.83 (d, *J* = 13.99 Hz, 1 H), 2.63–2.53 (m, 1 H), 1.72 (d, *J* = 1.34 Hz, 3 H), 1.23 (s, 3 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 0.79 (d, *J* = 6.59 Hz, 3 H); ^{13}C NMR (ppm) 183.67, 158.18, 148.96, 140.39, 136.34, 123.91, 121.59, 110.50, 63.00, 61.94, 49.03, 45.19, 26.69, 24.03, 20.45, 20.01, 14.33; IR 3383, 2964, 2928, 2868, 1704, 1548 cm^{-1}; *m/e* 288 (3.2), 272 (9.2), 147 (20.6), 118 (6.8), 93 (57.4), 69 (5.3).

(3*S*,6*R*,7a*R*)-3-Isopropyl-6,7a-dimethyl-5-oxo-6-(2-pyridylmethyl)-2,3,5,6,7,7a-hexahydro[2,1-*b*]oxazole, 18. Trifluoroacetic acid (0.13 mL, 1.5 mmol) was dissolved in 20 mL of dichloromethane at 0 °C, and 100 mg of **17** in 5 mL of dichloromethane was added. The solution was warmed to room temperature and stirred for 3 h. The mixture was poured in 10 mL of $NaHCO_3$ solution and extracted with dichloromethane (2 × 25 mL), and the extracts were dried (K_2CO_3) and concentrated, leaving the bicyclic lactam in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 8.52–8.49 (m, 1 H), 7.57–7.51 (m, 1 H), 7.15–7.09 (m, 2 H), 4.10 (dd, *J* = 7.20, 7.80 Hz, 1 H), 3.63–3.51 (m, 2 H), 3.13 (d, *J* = 12.88 Hz, 1 H), 2.81 (d, *J* = 12.83 Hz, 1 H), 2.51 (d, *J* = 14.29 Hz, 1 H), 1.97 (d, *J* = 14.30 Hz, 1 H), 1.47–1.39 (m, 1 H), 1.24 (s, 3 H), 0.96 (d, *J* = 6.56 Hz, 3 H), 0.84 (s, 3 H), 0.80 (d, *J* = 6.53 Hz, 3 H); ^{13}C NMR 184.00, 158.12, 148.92, 136.02, 124.75, 121.76, 96.77, 69.98, 62.58, 48.63, 46.88, 42.99, 34.19, 26.84, 24.08, 20.69, 18.89; IR 2967, 2933, 2877, 1705, 1377, 1355 cm^{-1}; (*m/e*) 288 (7.4), 273 (16.2), 245 (3.9), 146 (45.5), 134 (8.3), 118 (8.7), 93 (79.6).

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Registry No. 1, 88670-16-0; **2** (R = H, R′ = Me), 88670-17-1; **2** (R = H, R′ = $PhCH_2$), 88670-18-2; **2** (R = H, R′ = Et), 88670-19-3; **2** (R = H, R′ = 4-$MeOC_6H_4CH_2$), 88670-20-6; **2** (R = H, R′ = *i*-Pr), 88670-21-7; **2** (R = Me, R′ = $PhCH_2$), 88670-22-8; **2** (R = $PhCH_2$, R′ = Me), 88728-90-9; **2** (R = Me, R′ = Et), 88670-23-9; **2** (R = Et, R′ = Me), 88728-91-0; **2** (R = 4-$MeOC_6H_4CH_2$, R′ = Me), 88728-92-1; **2** (R = Me, R′ = 4-$MeOC_6H_4CH_2$), 88670-24-0; **2** (R = Me, R′ = *i*-Pr), 88670-25-1; **3** (R = Me, R′ = $PhCH_2$), 88685-64-7; **3** (R = $PhCH_2$, R′ = Me), 88670-26-2; **3** (R = Me, R′ = Et), 88670-27-3; **3** (R = Et, R′ = Me), 88670-28-4; **3** (R = 4-$MeOC_6H_4CH_2$, R′ = Me), 88670-30-8; **3** (R = Me, R′ = 4-$MeOC_6H_4CH_2$), 88670-29-5; **4**, 98203-44-2; **5a**, 126062-89-3; **5b**, 126062-90-6; **7a**, 126062-91-7; **7b**, 126062-92-8; **8a**, 126062-93-9; **8b**, 126062-94-0; **9a**, 112522-04-0; **9b**, 126062-95-1; **11a**, 126062-96-2; **11b**, 126062-97-3; **12a**, 126062-98-4; **12b**, 126062-99-5; **12c**, 126063-02-3; **15a**, 88670-33-1; **15b**, 88670-34-2; **16**, 126082-45-9; **17**, 126063-00-1; **18**, 126109-26-0; (*S*)-(+)-$Me_2CHCH(NH_2)CH_2OH$, 2026-48-4; $PhC(O)CH_2CH_2CO_2H$, 2051-95-8; (*S*)-$MeOC(O)CH_2C(Me)(Et)C(O)OMe$, 4727-78-0.

One-Pot Synthesis of *N*-(2-Heteroaryl)-α-amino Esters by the Regiospecific 2-*N*-(α-Alcoxycarbonyl)alkylation of 2-Aminoazines and -azoles with Glyoxals and Alcohols Promoted by Perchloric Acid

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2-Amino heterocycles, including pyridine, diazine, andd azole derivatives, are readily converted into *N*-(2-heteroaryl)-α-amino esters **4** in a one-pot sequence by reaction with glyoxals and alcohols in the presence of perchloric acid. In addition, the corresponding α-amino acids **5** are quantitatively obtained by acidic hydrolysis of compounds **4**.

Naturally occurring *N*-alkyl-α-amino acids are widely distributed, being metabolically important in some cases.[1,2] Furthermore, *N*-alkyl- and *N*-aryl-α-amino acids have been used as starting materials both in drug[3] and heterocyclic

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