A solution of hemiketals **29a** and **29b** (60.0 mg, 0.34 mmol), hydrazine (14.0 mg, 0.44 mmol), and acetic acid (14.0 mg, 0.22 mmol) in 10 mL of MeOH was stirred at room temperature for 48 h. The mixture was treated with water (10 mL) and extracted with ether (3 × 20 mL). The ether solution was dried (Na_2SO_4). Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (8:1 hexane–EtOAc) gave 20.9 mg (72%) of 3-methylpyrazole (**54**) and 10.3 mg (19%) of **52**.

Data for **52**: ^{1}H NMR 7.23 (d, 1, J = 8.6), 7.20 (d, 1, J = 8.6), 2.94 (t, 2, J = 7.8), 2.67 (s, 3), 1.68–1.79 (m, 2), 1.40 (tq, 2, J = 7.4, 7.3), 0.95 (t, 3, J = 7.3); ^{13}C NMR 161.5, 157.7, 126.8, 126.2, 35.6, 31.8, 22.3, 22.0, 13.8; IR (neat) 2960, 1590, 1505, 1440, 1380 cm^{-1}; MS m/z 150 (M^+, 6.3), 108 (100). The data are similar to those of other 3,6-dialkylpyridazines.[42]

Data for **54**: ^{1}H NMR 7.49 (d, 1, J = 1.2), 6.09 (d, 1, J = 1.2), 2.34 (s, 3); IR (neat) 3250, 1580, 1450, 1100, 1045, 930 cm^{-1}. The ^{1}H NMR data are identical to those previously described.[50]

3- and/or 4-Methoxy-2,5-nonanedione (55), 4-Hydroxy-4-methyl-5-*n*-propyl-2-cyclopentenone (56), and 4-Hydroxy-4-*n*-butyl-2-cyclopentenone (57). A solution of hemiketals **29a** and **30a** (80.0 mg, 0.45 mmol) and Et_3N (300 mg, 3.0 mmol) in 15 mL of MeOH was stirred at room temperature for 48 h. The mixture was treated with water (20 mL) and extracted with ether (3 × 20 mL). The combined ether layers were dried with Na_2SO_4. Removal of the solvent at reduced pressure followed by flash chromatography on silica gel (8:1 hexane–EtOAc) gave 40.8 mg (47%) of **55** as a colorless oil followed by 18.4 mg (23%) of a 5:1 mixture of **56** and **57**.

Data for **55**: ^{1}H NMR 4.32 (dd, 1, J = 5.7, 1.1), 3.39 (s, 3), 2.62 (dd, 1, J = 18.2, 5.7), 2.29 (dd, 1, J = 18.2, 1.1), 2.17 (t, 2, J = 7.5), 2.06 (s, 3), 1.30–1.50 (m, 4), 0.89 (t, 3, J = 7.4).

(50) Pouchert, C. J. *The Aldrich Library of NMR Spectra Edition II*; Aldrich: Milwaukee, WI, 1983; Vol. 2, p 480-D.

Data for **56** were determined from the mixture: ^{1}H NMR 7.40 (d, 1, J = 5.8), 6.09 (d, 1, J = 5.8), 2.37 (dd, 1, J = 8.6, 5.4), 1.30–1.82 (m, 4), 1.37 (s, 3), 0.99 (t, 3, J = 7.2); ^{13}C NMR 200.6, 165.5, 131.4, 79.5, 58.8, 27.4, 24.1, 21.5, 14.2.

Data for **57** were determined from the mixture: ^{1}H NMR 7.42 (d, 1, J = 5.8), 6.13 (d, 1, J = 5.8), 2.57 (d, 1, J = 17.9), 2.45 (d, 1, J = 17.9), 1.30–1.83 (m, 6), 0.92 (t, 3, J = 7.2).

Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No. (±)-**1a**, 130296-76-3; (±)-**1b**, 138380-85-5; (±)-**2a**, 130296-77-4; (±)-**2b**, 138380-86-6; (3*E*,5*E*)-**3a**, 138286-30-3; (3*E*,5*Z*)-**3a**, 138286-31-4; (3*Z*,5*E*)-**3a**, 138286-57-4; (3*Z*,5*Z*)-**3a**, 138286-58-5; **4a**, 130296-70-7; **4b**, 138286-29-0; **5a**, 130296-69-4; **5b**, 138286-28-9; (±)-**6a**, 138286-26-7; (±)-**6b**, 138286-27-8; **7a**, 5284-29-7; **7b**, 25401-86-9; **8**, 824-91-9; **9a**, 130296-78-5; **9b**, 138286-25-6; (±)-**12a**, 130296-80-9; (±)-**13a**, 130296-72-9; **14a**, 138286-32-5; (±)-**15a**, 130296-74-1; (±)-**15b**, 138286-33-6; (±)-**16a**, 130296-75-2; (±)-**16b**, 138286-34-7; **19a**, 138286-35-8; **19b**, 138286-37-0; (±)-**20**, 138286-38-1; (±)-**21a**, 138286-39-2; (±)-**21b**, 138286-40-5; **22**, 18402-83-0; (*E*)-**25**, 59637-34-2; (*Z*)-**25**, 138286-47-2; (±)-**26**, 138286-46-1; (±)-**27**, 138286-42-7; (±)-**29a**, 138286-41-6; (±)-**29b**, 138286-44-9; (±)-**30a**, 138286-43-8; (±)-**30b**, 138286-45-0; **31a**, 138380-87-7; **31b**, 138286-50-7; (+)-**32**, 89-82-7; **33a**, 138286-48-3; **33b**, 138286-49-4; **40**, 141-79-7; **41**, 60026-75-7; **42**, 60026-74-6; **43**, 138286-51-8; **45**, 138286-52-9; (±)-**46a**, 138286-53-0; (±)-**46b**, 138286-54-1; (±)-**48b**, 138286-55-2; **49**, 14698-76-1; **50**, 17957-94-7; **52**, 23990-19-4; **54**, 88054-14-2; **55**, 138286-56-3; **56**, 79547-21-0; **57**, 104248-54-6; 1-bromododecane, 143-15-7; *n*-hexadecyl bromide, 1127-15-7; 6-oxo-4-hydroxyoctadecanoic acid, 138286-36-9; 3-penten-2-one, 625-33-2; 5-methyl-3-hexen-2-one, 5166-53-0; *trans*-2-hexenal, 6728-26-3; *trans*-1-chloro-1-tetradecen-3-one, 80037-06-5.

Enantiomerically Pure Dihydropyrimidinones as Reagents and Auxiliaries for Asymmetric Synthesis

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Abstract: We report herein full experimental details of the synthesis, structure, and reactivity of (*R*)- and (*S*)-2-*tert*-butyl-1-carbomethoxy-2,3-dihydropyrimidin-4(1*H*)-one (**1**). The synthesis employs asparagine as the starting material and provides **1** in 55% yield without the need for chromatographic purification. The structure of **1**, as determined by X-ray crystallographic analysis, demonstrates significant pyramidalization at the C4 (carbonyl) and N1 centers, with little evidence of conjugation of N1 with the α,β-unsaturated (vinylogous urea) system. In contrast, compound **11** [2-*tert*-butyl-3-((*S*)-*O*-methylmandeloyl)-2,3-dihydropyrimidin-4(1*H*)-one] shows strong coupling of N1 to the α,β-unsaturated system, as evidenced by changes in bond lengths and torsional angles. Compound **1** has proven useful as a *reagent* for the synthesis of enantiomerically pure β-aryl-β-amino acids. The key step in this protocol is the palladium-catalyzed conjugate addition of aryl iodides to **1**. Evidence is presented to support a mechanism for this reaction that involves an unprecedented transannular hydride transfer into the palladium coordination sphere. In additional experiments, **1** has been employed as an *auxiliary* for the synthesis of enantiomerically pure α-substituted carboxylic acids. The crystalline properties of **1** and many of its derivatives allow for simplified purification procedures to be utilized.

In two recent papers,[4,5] we disclosed preliminary results concerning the synthesis and reactivity of (*R*)- and (*S*)-2-*tert*-butyl-1-carbomethoxy-2,3-dihydropyrimidin-4(1*H*)-one (**1**). Herein we report, in full detail, our work on this compound and its derivatives.

Synthesis

As part of our total synthesis of the marine depsipeptide (+)-jasplakinolide (**2**),[6] we sought a new route to the requisite

(1) (a) University of California at Santa Cruz. (b) University of California at Davis.

(2) American Cancer Society Junior Faculty Research Awardee, 1987–1990.

(3) Author to whom correspondence concerning X-ray crystallography should be addressed.

(4) Konopelski, J. P.; Chu, K. S.; Negrete, G. R. *J. Org. Chem.* **1991**, *56*, 1355–7.

(5) Negrete, G. R.; Konopelski, J. P. *Tetrahedron: Asymmetry* **1991**, *2*, 105–8.

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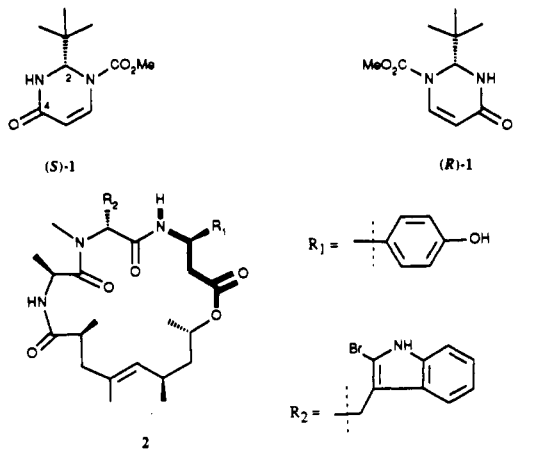
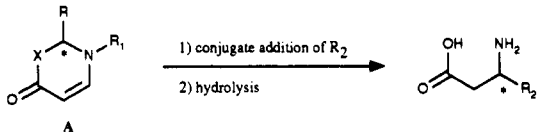
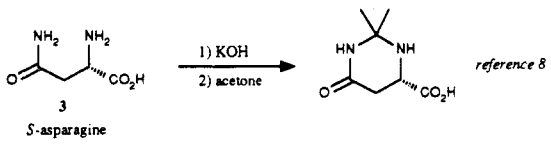


β-tyrosine fragment (highlighted) in enantiomerically pure form. Mindful of the seminal work of Seebach on the "self-reproduction of chirality",[7] we envisioned the use of an enantiomerically pure heterocycle of type A as a substrate for conjugate addition reactions with transfer of chirality from the existing to the nascent chiral center. Hydrolytic cleavage of the product would then afford the desired β-amino acid.



Initially, we explored the chemistry of oxazenones of type A (X = O, R = *tert*-butyl, R_1 = benzoyl). However, in our hands the synthetic yield of this compound, and other members of this class of compounds, proved to be very low (≤20%). In addition, key derivatives in our synthetic scheme appeared to be hydrolytically unstable. However, we did experience some success in conjugate addition reactions which prompted our continued exploration of this general approach.

Some years ago, Hardy and Samworth[8] demonstrated that the acid salt of asparagine **3** condensed with acetone to form the



corresponding pyrimidone. If the same reaction would occur with aldehydes instead of acetone, and the requisite protection and oxidative decarboxylation steps could be controlled, this sequence would lead to type A molecules (X = N, R = aldehyde alkyl group).

In the event (Scheme I), treatment of the potassium salt of (*S*)-asparagine (**3**) with pivaldehyde (**4**) in methanol for 6–8 h at reflux produces a white powder with spectral characteristics consistent with desired cyclized product **5** as a single isomer. In particular, the ^{1}H NMR (DMSO-d_6) of **5** displays an ABX pattern for the three protons in the C5–C6 spin system with one axial–axial coupling (10.2 Hz) and one equatorial–axial coupling (4.8 Hz). Molecular mechanics calculations[9] of the minimum energy conformation of **5** (which places both the acid and *tert*-butyl groups as equatorial substituents) accurately reproduce the observed coupling constants, whereas the minimum energy conformation of the corresponding trans isomer does not. Protection of the amine nitrogen of **5** with benzyl chloroformate ($NaHCO_3$, H_2O) yields **6** as a crystalline solid in 80% yield from asparagine. Similar treatment of **5** with methyl chloroformate affords **7** as an amorphous solid that has resisted attempts at crystallization. The physical characteristics are reversed upon treatment of **6** and **7** under oxidative decarboxylation conditions ($Pb(OAc)_4$, catalytic $Cu(OAc)_2$[10]). Thus, **1** is a crystalline solid isolable from the crude reaction mixture by crystallization from EtOAc in 55% yield from asparagine. An additional 12% could be recovered from the concentrated mother liquors via chromatography and subsequent crystallization, bringing the total yield of **1** to 67%. By contrast, **8** could only be obtained in 60% yield from **6** by chromatography. Furthermore, the oxidative decarboxylation of **6** gave a number of compounds, including bicyclic carbamate **9**. Indeed, **9** was a principal product when the decarboxylation was performed in THF (55%). Given its higher synthetic yield and crystalline nature, all subsequent experimentation was performed on **1**.

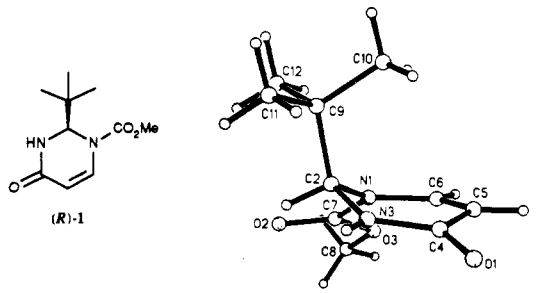
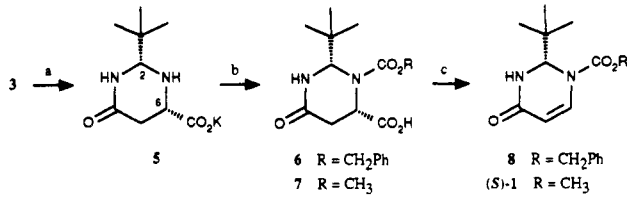
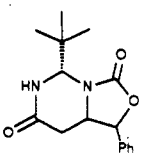


Figure 1. Computer-generated perspective drawing of the final X-ray model of (*R*)-**1**.

Scheme I

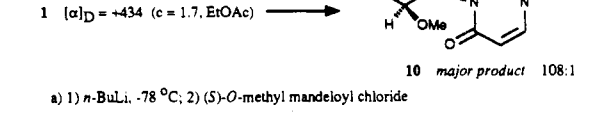


a) KOH, C_4H_9CHO (**4**); b) ROCOCl, $NaHCO_3$, H_2O; **6**, 80% from **3**; **7**, 100% mass recovery from **3**; c) **8**, $Pb(OAc)_4$, cat. $Cu(OAc)_2$, C_6H_6, pyridine, 60%; **1**, $Pb(OAc)_4$, cat. $Cu(OAc)_2$, $CH_3C_6H_5$, THF, pyridine, 55% from **3**.



Stereochemical and Structural Studies

Compound (*S*)-**1** displayed a large specific rotation {$[\alpha]_D$ = +434 (*c* 1.7, EtOAc)} which remained constant upon repeated recrystallizations. Deprotonation of (*S*)-**1** (1.05 equiv of *n*-BuLi, −78 °C) and treatment with the acid chloride of (*S*)-*O*-methyl mandelic acid[11] resulted in the production of imide **10**. Analysis



a) 1) *n*-BuLi, -78 °C; 2) (*S*)-*O*-methyl mandeloyl chloride

of the crude reaction mixture by gas chromatography showed the

(6) Chu, K. S.; Negrete, G. R.; Konopelski, J. P. *J. Org. Chem.* **1991**, *56*, 5196–202.

(7) (a) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390–8. (b) For a broad discussion of the synthesis of enantiomerically pure compounds, see: Seebach, D.; Imwinkelried, R.; Weber, T. *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer: Berlin, 1986; Vol. 4, pp 125–260.

(8) Hardy, P. M.; Samworth, D. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1954–60.

(9) PCMODEL, Serena Software, Bloomington, IN.

(10) McMurry, J. E.; Blaszczak, L. C. *J. Org. Chem.* **1974**, *39*, 2217–22.

(11) For a recent example of mandelic acid use in synthesis, see: Smith, A. B., III; Konopelski, J. P. *J. Org. Chem.* **1984**, *49*, 4094–5.

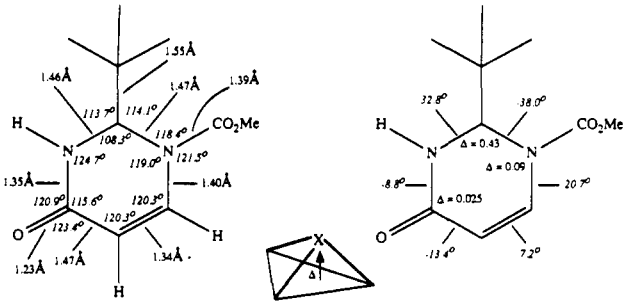


Figure 2. Bond lengths and angles (left structure) and torsion angles and pyramidalization (angstroms) of 1.

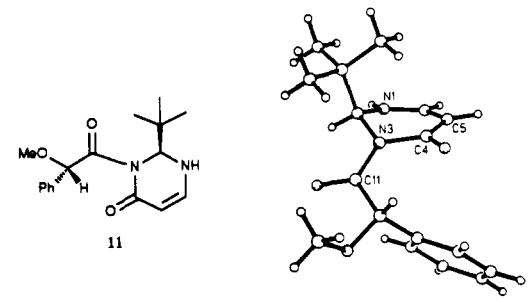


Figure 3. Computer-generated perspective drawing of the final X-ray model of 11.

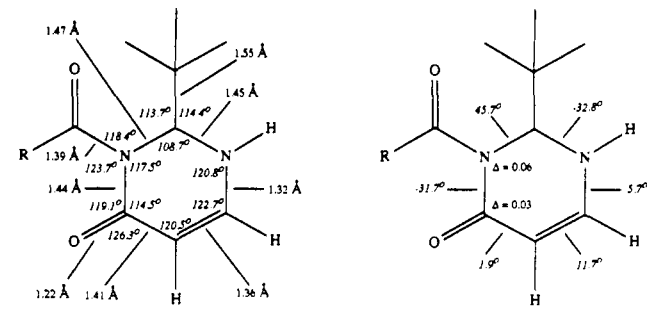


Figure 4. Bond lengths and angles (left structure) and torsion angles and pyramidalization (angstroms) of 11.

ratio of diastereomeric products to be 108:1, which is at the enantiomeric purity level of commercially available mandelic acid (99+%).[12] Reversal of the peak intensities was observed when (*R*)-1 was employed in this sequence.

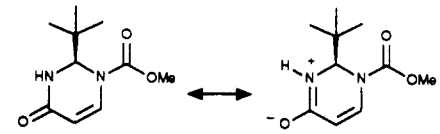
The basis of our route to β-amino acids from type A compounds was the efficient chirality transfer from C2 to C6. Literature precedent suggested that in compounds such as 1 the *tert*-butyl group would be axial, inasmuch as the dominant steric force is $A^{(1,2)}$ strain between the N1 and C2 substituents.[13] Such a conformation would effectively block the face syn to the *tert*-butyl group from attack, while the anti face would be sterically unencumbered.

Few compounds of structural type 1 have been described in the literature, and the only crystallographic studies have been on the related quinazoline system.[14] An X-ray crystal structure determination[15] of (*R*)-1 is shown in Figure 1. Five of the six atoms of the ring are approximately planar, with the only tetrahedral atom (C2) at the apex of a sofa-type conformation. The *tert*-butyl group occupies an axial position to the ring. This conformation is similar to that of the corresponding saturated racemic compounds synthesized by Juaristi and co-workers.[16]

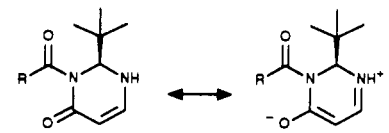
Figure 2 presents the bond lengths and angles and torsion angles and pyramidalization of (*R*)-1. The definition of pyramidalization is also given in Figure 2. These values are in general accord with related structures.[14,17] While the equivalent bond lengths between C2 and the nitrogen atoms in 1 are consistent with a vinylogous urea arrangement with significant conjugation to the carbonyl group, the structure and UV spectrum would suggest limited interaction of N1 with the conjugated system. The C6–N1 bond is at an average enamine bond length,[18] although the pyramidalization at N1 (see below) is below the norm for the same set of enamine structures. A bond length/pyramidalization correlation was evident in the work of Dunitz and co-workers, but the carbomethoxy group in 1 is likely to have a significant impact on such a correlation. Bond angle distortion is evident at N3, C2, and C4.

Of particular interest is the pyramidalization at C4 and N1.[19] The value for a tetrahedral center (C2) is given for comparison. While not as profound at that observed in β-lactam structures[20] or the five-membered ring systems recently studied by Seebach,[21] the deviation from planarity in 1 is congruent with the corresponding 1,3-dioxin-4-one system.[17] The pyramidalization at both C4 and N1 in 1 is in the same direction, placing the carbomethoxy group and the carbonyl oxygen below the mean plane of the ring and opposite the axial *tert*-butyl group (torsion angles C6–C5–C4–O1 = 162.9°; C5–C6–N1–C7 = −146.6° in 1).

Figure 3 depicts the ORTEP drawing and Figure 4 gives the bond lengths and angles plus the torsion angles and pyramidalization from the X-ray structure determination[22] of 11.[23] The distinctions between 1 and 11 are conspicuous. Beyond the obvious verification of the stereochemical course of the initial cyclization between asparagine and pivaldehyde, the structure of 11 signals significant changes in the electronic nature of the heterocycle. While the C4–O1 double bond remains essentially unchanged,



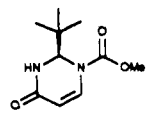
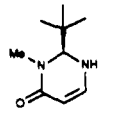
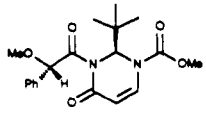
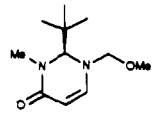
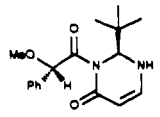
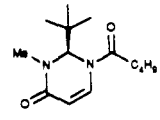
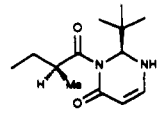
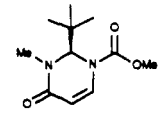
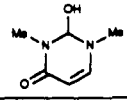
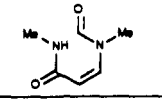
1



11

(12) Mandelic acid obtained from Aldrich Chemical Co., Milwaukee, WI.
(13) Johnson, F. *Chem. Rev.* **1968**, *68*, 375–413.
(14) Mangia, A.; Nardelli, M.; Pelizzi, C.; Pelizzi, G. *Acta Crystallogr.* **1974**, *B30*, 1722. Mangia, A.; Nardelli, M.; Pelizzi, G. *Acta Crystallogr.* **1974**, *B30*, 487–91. Pelizzi, C.; Pelizzi, G. *Acta Crystallogr.* **1974**, *B30*, 2421–5. Nardelli, M.; Pelizzi, C.; Pelizzi, G. *Transition Met. Chem.* **1977**, *2*, 174–80. Pelizzi, C.; Pelizzi, G.; Predieri, G. *Gazz. Chim. Ital.* **1982**, *112*, 343–4.
(15) Crystals of 1 are orthorhombic, a = 6.289 (2), b = 12.662 (4), c = 13.902 (3) Å, space group $P2_12_12_1$, Z = 4, ρ = 1.275 g/cm³ for $C_{10}H_{16}N_2O_3$. A total of 1498 independent reflections were measured with graphite-monochromated Mo Kα radiation at 130 K on a Syntex $P2_1$ diffractometer to a maximum 2θ of 55°. The structure was solved by using direct methods and refined to a final R value of 3.85%. The primary program used was SHELXTL PLUS, Version 4.0, 1989, by G. M. Sheldrick.
(16) Juaristi, E.; Quintana, D.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 2553–7.
(17) Seebach, D.; Zimmermann, J.; Gysel, U.; Ziegler, R.; Ha, T.-K. *J. Am. Chem. Soc.* **1988**, *110*, 4763–72.
(18) Brown, K. L.; Damm, L.; Dunitz, J. D.; Eschenmoser, A.; Hobi, R.; Kratky, C. *Helv. Chim. Acta* **1978**, *61*, 3108–35.
(19) The precision of the data concerning the position of the hydrogen atoms at C5 and C6 precludes any detailed analysis of the pyramidalization at these trigonal centers.
(20) Williams, R. M.; Lee, B. H.; Miller, M. M.; Anderson, O. P. *J. Am. Chem. Soc.* **1989**, *111*, 1073–81.
(21) Seebach, D.; Maetzke, T.; Petter, W.; Klötzer, B.; Plattner, D. A. *J. Am. Chem. Soc.* **1991**, *113*, 1781–6.
(22) Crystals of 11 are orthorhombic, a = 13.962 (4), b = 18.752 (4), c = 6.573 (2) Å, space group $P2_12_12$, Z = 4, ρ = 1.167 g/cm³ for $C_{17}H_{22}N_2O_3$. A total of 1771 independent reflections were measured with graphite-monochromated Mo Kα radiation at 130 K on a Siemens R3m/V diffractometer to a maximum 2θ of 50°. The structure was solved by using direct methods and refined to a R value of 4.10%. The primary program used was SHELXTL PLUS, Version 4.0, 1989, by G. M. Sheldrick.
(23) Compound 11 is prepared from the diastereomer of 10 derived from (*R*)-1 by the action of LiI in DMF at 100 °C for 6.5 h (62%).

Table I. UV Spectral Data for **1**, **11**, and Selected Derivatives and Model Compounds

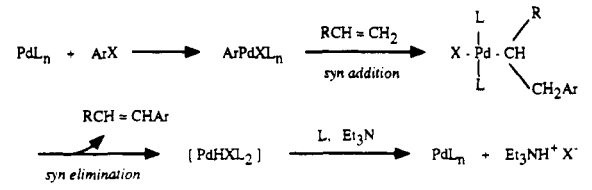
compound	λ_{max}, nm (log ε)	compound	λ_{max}, nm (log ε)
 **1**	230 (4.10) 271 (3.92)	 **13**	237 (3.67) 282 (3.83)
 **10**	270 (3.99)	 **14**	230 (3.58) 290 (3.56)
 **11**	232 (3.59) 323 (3.86)	 **15**	245 (3.45) 277 (3.30)
 **12**	230 (3.85) 320 (4.01)	 **16**	239 (3.75) 272 (shoulder)
	289 (3.96)[24]		257-263[24]

the N3–C4 and the C5–C6 bonds have lengthened (0.09 and 0.02 Å, respectively). Likewise, the C6–N1 and the C4–C5 bonds have shortened (0.08 and 0.06 Å, respectively). These structural changes can be explained by a change in the predominant resonance contribution, as shown below. In **1**, amide resonance dictates a comparatively short N3–C4 bond length, with little in the way of N1 interaction with the conjugated system. In **11**, on the other hand, cancellation of the N1-carbamate resonance provides access to the alternative diene-type resonance structure with little apparent interaction between N3 and C4 (torsion angle C6–C5–C4–O1 = 177.7°; C5–C4–N3–C11 = 140.0° in **11**).

The ultraviolet spectral data of **1**, **11**, and selected derivatives and model compounds are given in Table I and fully support this analysis. Model compounds[24] indicate a 25–30-nm shift to lower wavelength with the addition of a carbonyl to the β-amino group of the enone system. The absorption maxima of **1**, **10**, **15**, and **16** (270–277 nm) would indicate that this large difference in the spectral data of the model systems is based partly on their acyclic/cyclic nature. Nonetheless, there is a consistent shift to higher wavelength absorptions with the removal of the acyl group at N1 (**1** and **15** vs **13**). Alkyl substituents on either nitrogen have little effect on the absorption spectrum (**1** vs **16**, **13** vs **14**). Introduction of an N3 acyl group in conjunction with deacylation at N1, however, is accompanied by a significant shift to higher wavelength, indicative of a longer continuous π-system (**11** and **12**). Thus, although the X-ray structure of **11** indicates a significant deviation from planarity for the two acyl systems bound to N3, the absorption spectrum of this compound would indicate pronounced interaction of the imide carbonyl with the enone system, including N1. *Moreover, these results indicate that the electronic structure of the heterocyclic system can be modulated by the substituents on the nitrogen atoms. Since electronic structure dictates reactivity, this sense of modulation should carry over to the reactions of these compounds.* Experiments are underway to explore this idea.

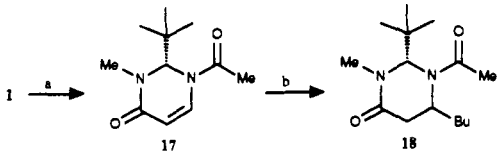
(24) (a) Niederhauser, A.; Neuenschwander, M. *Helv. Chim. Acta* **1973**, *56*, 1318–30. (b) Moore, R. E.; Woolard, F. X.; Sheikh, M. Y.; Scheuer, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 7758–9. (c) Tee, O. S.; Banerjee, S. *J. Org. Chem.* **1979**, *44*, 3256–61. (d) Tee, O. S.; Paventi, M. *J. Org. Chem.* **1981**, *46*, 4172–8.

Scheme II



Palladium-Catalyzed Additions to 1

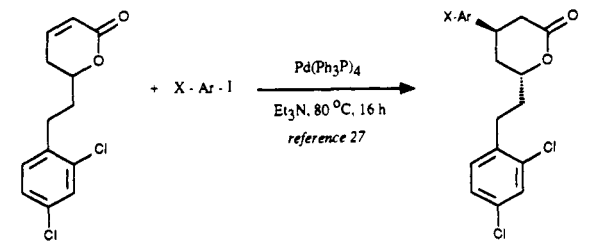
Our synthetic goal of a β-aryl-β-amino acid synthesis required the formation of a C–C bond between C6 of the heterocyclic system and a suitably substituted aryl group. We initially undertook a study of the copper-mediated conjugate addition of alkyls and aryls to derivatives of **1**. Our substantial efforts in this area bore little in the way of positive results. A one-pot method for the derivatization of **1** was developed that involved (1) 1 equiv of *n*-BuLi followed by reaction with an appropriate electrophile and (2) subsequent treatment with 2 equiv of *n*-BuLi (to cleave the carbomethoxy group) followed by a second electrophile. In this way, a number of base-stable derivatives of **1** could be prepared with ease, as shown. However, with the exception of the formation of **18**, we were unsuccessful in these conjugate addition endeavors.



a) 1) *n*-BuLi, 2) MeI, 3) 2 *n*-BuLi, 4) MeC(O)Cl, 77%; b) $Bu_2Cu(CN)Li$, 44%

We next turned our attention to other organometallic-mediated C–C coupling protocols. Perhaps most notable in this regard are organopalladium methods. We entertained this notion with some misgivings, however. While the Heck[25] reaction is firmly established as a premier method for aryl–vinyl coupling in acyclic systems, the accepted mechanism of this reaction would appear to make it unsuitable for use in a cyclic system such as ours. As depicted in Scheme II, this mechanism involves an arylpalladium complex, formed by the oxidative addition of an aryl iodide to a palladium(0) complex. Syn addition to the substrate alkene, followed by rotation around the new single bond, allows for the syn elimination of an hydridopalladium species, producing the vinyl substitution product. The hydridopalladium compound subsequently reacts with the amine base to afford palladium(0) and trialkylammonium halide. In the present case, however, there would be no hydrogen in a syn orientation to the palladium, since rotation is precluded by the cyclic nature of the substrate.

Cyclic systems had been employed as substrates for the Heck reaction on a limited basis; however, in most of these cases the conventional mechanism can be accommodated.[26] Most intriguing for our present purpose were the results of Stokker[27] on the palladium-catalyzed conjugate arylation of 5,6-dihydro-2*H*-pyran-2-ones.



In this instance, the author presents evidence to support reduction

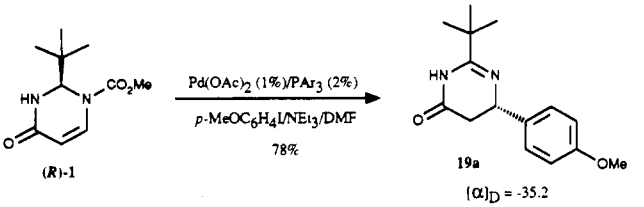
(25) (a) Ziegler, C. B., Jr.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2941–6. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985.

(26) Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 2464–70.

(27) Stokker, G. E. *Tetrahedron Lett.* **1987**, *28*, 3179–82.

of the C–Pd bond by triethylamine to yield the formal conjugate addition reaction rather than the substitution reaction shown in Scheme II.

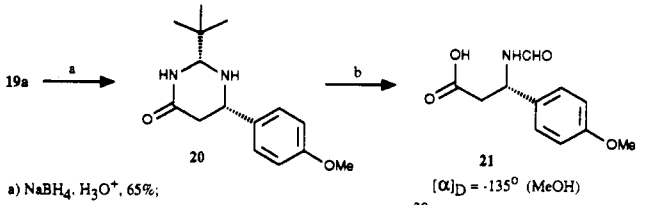
In the event, **1** is treated with 4-iodoanisole (1.1 equiv) and triethylamine (1.5 equiv) in dimethylformamide (DMF) containing a catalytic amount of palladium acetate and tri-*o*-tolylphosphine at 100 °C for 24 h to give **19a** as a crystalline product in 78%



isolated yield. Use of 4-iodophenol, 4-((*tert*-butyldimethylsilyl)oxy)iodobenzene, and iodobenzene results in analogous products being formed in 50, 76, and 60% yield, respectively. Biaryls, presumably formed by the oxidative coupling of the aryl iodide substrate, are also obtained. The use of acetonitrile as solvent affords lower yields, as does the use of lower temperature. Increases in the amount of amine base relative to substrate and attempts to perform the reaction without DMF (triethylamine as solvent) result in a multitude of uncharacterized products with little or no formation of **19**. Tributylamine can be substituted for triethylamine with no apparent change in the reaction performance. Similarly, tetrakis(triphenylphosphine)palladium(0), palladium acetate/tri-*o*-tolylphosphine, and palladium acetate/triphenylphosphine are approximately equivalent in efficacy.

The basic nature of the heterocyclic product makes isolation facile.[28] The crude reaction mixture is partitioned between an aqueous HCl solution at pH 2 and an organic solvent. Multiple extractions remove the biaryl product. Adjustment of the pH of the aqueous layer to 12 and extraction with organic solvent affords **19** sufficiently pure for subsequent transformations. Treatment of **19** with $NaBH_4/H_3O^+$ followed by hydrolysis with 3 N HCl affords the corresponding derivatives of β-tyrosine hydrochloride in 85% yield.

Heterocycle **19a** was subjected to the protocol described above followed by reaction with acetic formic anhydride[29] to yield the known formamide of (*S*)-β-tyrosine *O*-methyl ether.[30] Comparison of the reported rotation for 91% ee material with our compound indicates that the chirality transfer in the palladium-catalyzed reaction is complete. Additional evidence for the enantiomeric purity of this β-tyrosine derivative comes from its successful use in the total synthesis of jasplakinolide.[6]



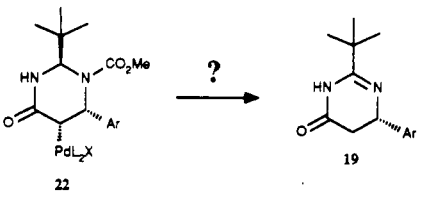
a) $NaBH_4$, H_3O^+, 65%;
b) 1) 3 *N* HCl, 90%; 2) Ac_2O, HCOOH, 100%

[α]D = -135° (MeOH)
Lit[30] [α]D = -125° (MeOH, 91% ee)

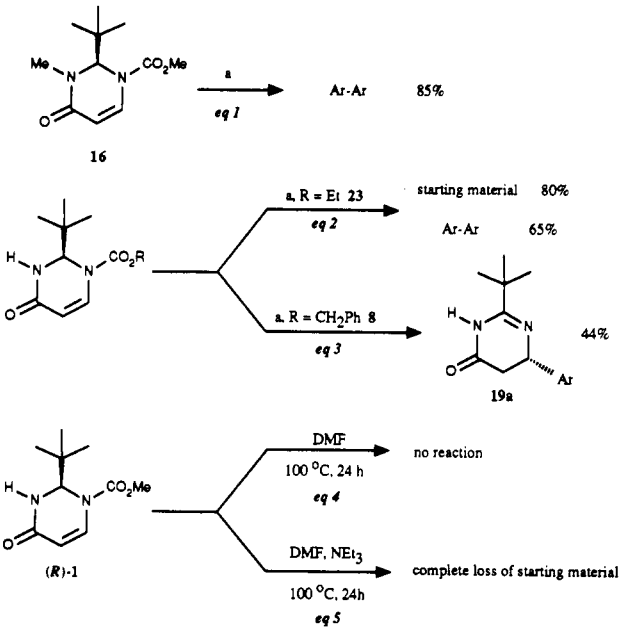
Mechanism

In the reaction of **1** under Heck conditions, we see formal conjugate addition of the aryl group to the C5–C6 bond with concomitant oxidation at N1–C2. Given the high fidelity of chirality transfer, we take as our initial assumption that the formation and addition of the arylpalladium(II) complex follows the course of the normal Heck reaction, affording intermediate **22** (Scheme III). Since there is no syn C–H bond adjacent to the C5–Pd bond, the normal syn elimination/addition mechanism

Scheme III



Scheme IV



a) 0.01 equiv $Pd(OAc)_2$, 0.02 equiv $P(o\text{-}CH_3C_6H_5)_3$, NEt_3, $p\text{-}IC_6H_4OCH_3$, DMF, 100 °C, 24 h

cannot be in force.[26] This raises a number of questions, such as the origin of the agent responsible for the reduction of the C5–Pd bond, the mechanism of N1–C2 oxidation, and the coordination of the two events.

A number of reactions were performed to probe the mechanism for the transformation of **1** to **19** (Scheme IV).[31] Reaction of **16**, in which a methyl group has been added to N3, resulted in the isolation of biaryl coupled product in 85% isolated yield (eq 1). Neither starting material nor any heterocyclic product could be isolated following normal workup conditions. Additional substitution on the carbamate group was also deleterious to the reaction. Thus, compound **23**, bearing the carbethoxy group, affords no desired product; starting material (80%) and biaryl product (65%) are isolated (eq 2). With the carbobenzoxy (CBZ) group, compound **8** does yield **19a** but in a reduced yield (44%, eq 3).

Heterocycle **1** is not stable under the reaction conditions. In separate experiments in which one or more of the reagents of the normal Heck reaction are removed ($Pd(OAc)_2$/phosphine, ArI, and $Pd(OAc)_2$/phosphine/ArI), **1** decomposes to an intractable mixture of compounds (eqs 4 and 5). This is attributed to the known[32] S_N2 reaction of tertiary amines on the methyl group of methyl esters. In the present case, we believe the methyl carbamate functionality is susceptible to nucleophilic attack, leading to decarbomethoxylation. The decomposition of this material is likely to follow a number of pathways, leading to numerous compounds.

A series of experiments employing deuterium proved most interesting (Scheme V). As shown, when either the substrate

(28) Isolation of **19** and subsequent transformation to β-tyrosine derivatives follows the procedure of: Politzer, I. R.; Meyers, A. I. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, pp 905–9.

(29) Krimen, L. I. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, pp 8–9.

(30) Keller-Schierlein, W.; Klaus, A.; Naegeli, H. U.; Wolf, G.; Zähner, H. *Experientia* **1975**, *31*, 1001–2.

(31) All reactions aimed at elucidation of the mechanism were performed with 1.4–1.5 equiv of NEt_3, 1.1 equiv of *p*-iodoanisole, 0.01 equiv of $Pd(OAc)_2$, and 0.02 equiv of tri-*o*-tolylphosphine in DMF.

(32) (a) Hammett, L. P.; Pfluger, H. L. *J. Am. Chem. Soc.* **1933**, *55*, 4079–89. (b) Miles, D. H.; Parish, E. J. *Tetrahedron Lett.* **1972**, 3987–90. (c) Parish, E. J.; Miles, D. H. *J. Org. Chem.* **1973**, *38*, 1223–5. (d) McMurry, J. *Org. React.* **1976**, *24*, 187–224.

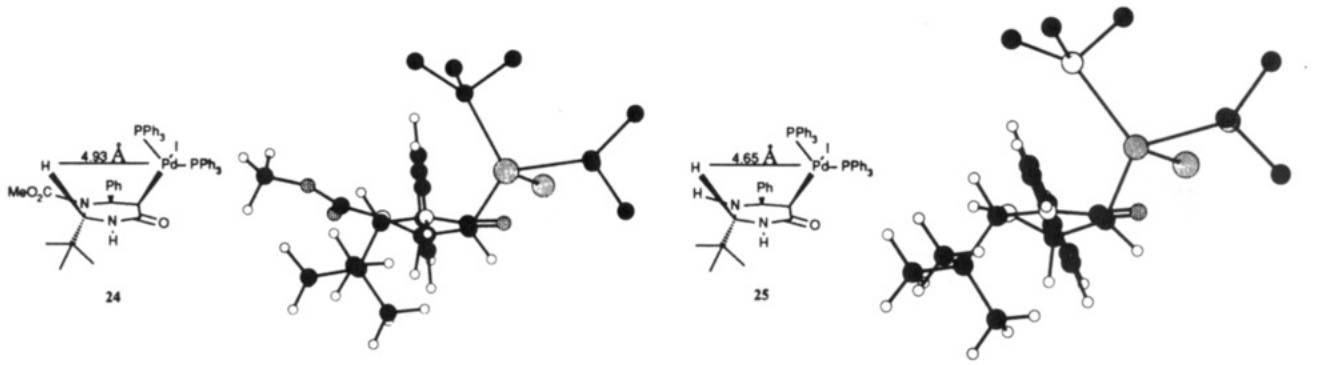
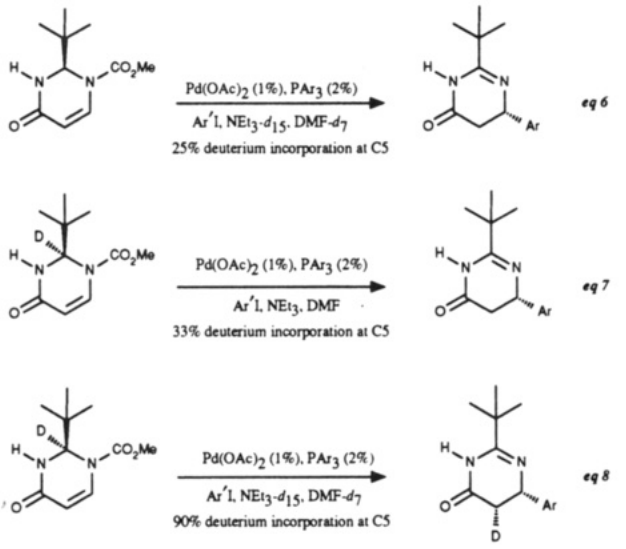


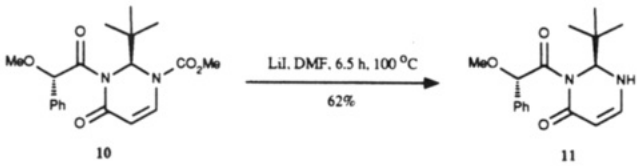
Figure 5. Computer-generated drawing of the structures from molecular mechanics calculations on **24** and **25**. View is edge on to the planes of both the heterocycle and the phenyl substituent. Only the carbon atoms directly bonded to the phosphorus of the triphenylphosphine ligands are shown.

Scheme V



or the solvent/amine mixture contains only hydrogen, modest amounts of deuterium are present in the product at C5 (eqs 6 and 7). Additional experiments indicate that the solvent does not transfer deuterium to the product in any detectable amount. However, when the solvent, tertiary amine, and substrate C2 position are deuterated, the product shows significant amounts of deuterium at C5, in certain cases quite predominantly syn to the aryl group (eq 8).

The experiments depicted in eqs 1–8, taken together with established chemistry, suggest the following mechanism (Scheme VI): (1) Triethylamine enters the coordination sphere of palladium to afford B and E from **22**. The presence of deuterium in the reaction mixture has no effect on this event. (2) Insertion into the C_α–H bond of triethylamine by palladium produces hydridopalladium/imminium species F.[33] This reaction is less competitive when NEt_3-d_{15} is employed, leaving B as the predominant reactive intermediate when deuterated base is employed. (3) Either iodide or tertiary amine[32] acts as nucleophile toward the methyl group of the carbamate, precipitating an electron reorganization with oxidation of the N1–C2 bond and formation of hydride or deuteride ion. We have independently verified the iodide route as shown. The results of eqs 2 and 3 are explained by the reluctance of **8** and **23** to undergo this key reaction.



The palladium present on the molecule in B and F offers a ready acceptor for the hydride from C2. Without such an acceptor, decomposition is competitive (eq 5). As the rehybridization of C2 proceeds, the hydrogen (or deuterium) at C2 moves from an equatorial position (see X-ray of **1**) to an axial position cis to the palladium atom. Thus, transfer can be efficiently made only as a result of the release of the $A^{(1,2)}$ strain between the *tert*-butyl and the carbomethoxy groups. In eq 1, the $A^{(1,2)}$ strain between N3–CH_3 and the *tert*-butyl groups is in opposition to this transfer.

We have no knowledge of the exact coordination sphere of palladium. For example, it is possible that the hydride acceptor in B is a coordinatively unsaturated palladium species that arises from ligand dissociation rather than the direct displacement reaction depicted in Scheme VI. Alternatively, the intermediacy of an oxa-π-allyl palladium species cannot be dismissed.

In the case of B, hydridopalladium species C is formed directly, followed by reductive elimination to D. The R group originally at C2 is efficiently and stereospecifically transferred to C5. In the case of F, an hydridopalladium species is already in place and the best acceptor is the imminium carbon.[34] Hydride transfer from C2 to this electron-deficient carbon regenerates the requisite hydridopalladium species (G) capable of reductive elimination to H. The two pathways appear to be balanced on the strength of the C–H vs C–D bond with regard to the formation of F. *To our knowledge, this is the first example of a transannular hydride transfer in a palladium-catalyzed reaction.*

To further probe this mechanism, a molecular mechanics study was undertaken[35] on **24** and **25** (Figure 5). Structure **24**, as expected, displays the *tert*-butyl group and the palladium system as pseudoaxial substituents. Structure **25**, without the carbomethoxy, shows the *tert*-butyl closer to the equatorial plane as compared to **24**, with the distance between the palladium and the hydrogen on C2 decreasing from 4.93 to 4.65 Å. More interestingly, a graph of the trajectory of this hydrogen as it approaches the palladium atom indicates a 15-kcal barrier for **24** and only a 7.4-kcal barrier for **25**.

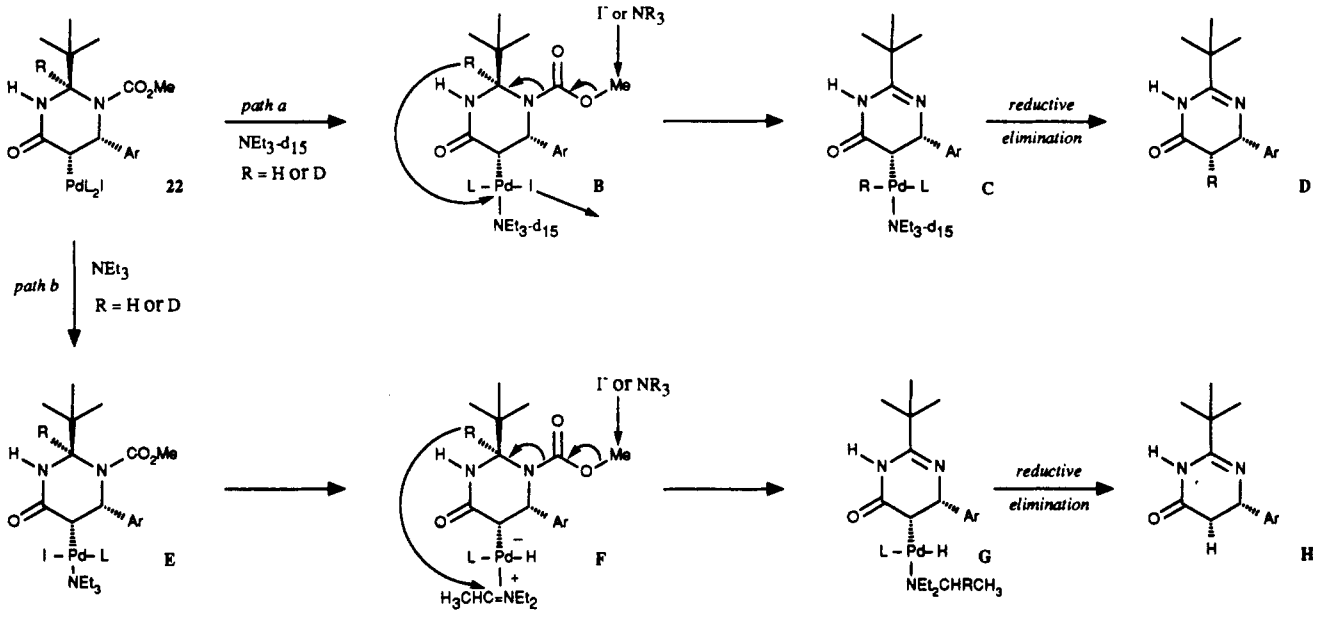
The final reductive elimination is expected to proceed with retention of configuration. In our experiments, however, we observe varying and nonreproducible amounts of deuterium in both C5 positions. However, we have experimentally verified that under the reaction conditions equilibration can take place at C5. We have not investigated the origin of this phenomenon but speculate that the nonreproducibility of this equilibration is due to small amounts of water in the reaction mixture, which can react with the imminium functionality in F to form secondary amine. It is reasonable to suppose that a secondary amine would be sterically more reactive than the tertiary amine.[36]

(33) Murahashi, S.-I.; Watanabe, T. *J. Am. Chem. Soc.* **1979**, *101*, 7429–30.

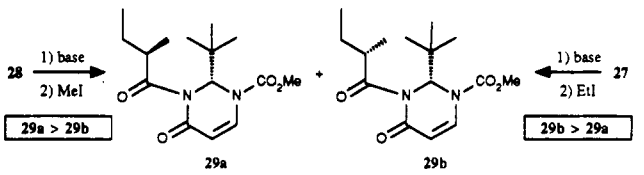
(34) (a) Murahashi, S.-I.; Hirano, T.; Yano, T. *J. Am. Chem. Soc.* **1978**, *100*, 350–2. (b) Murahashi, S.-I.; Yano, T. *J. Am. Chem. Soc.* **1980**, *102*, 2456–8.

(35) Molecular mechanics calculations were performed with an augmented parameter set, a product of the CAChe Group, Tektronix Inc., Beaverton, OR. Trajectory analysis was performed on **24** from 5.0 to 3.5 Å and on **25** from 4.8 to 3.5 Å distance between the C2 hydrogen and the palladium atom. Full minimization was performed on the structures at each interval.

Scheme VI



Scheme VII



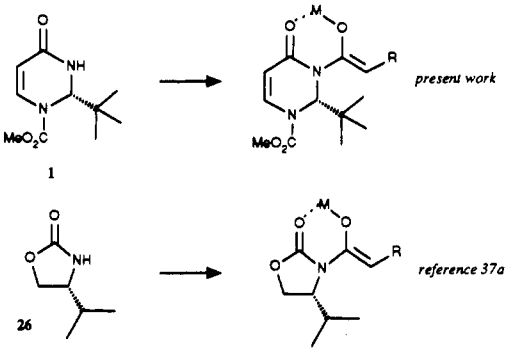
Chiral Auxiliary Capabilities of 1

Auxiliary mediated asymmetric enolate alkylation is an important strategy for the elaboration of stereogenic centers in acyclic hydrocarbons.[37] The auxiliary approach to acyclic stereoselection relies on the covalent attachment of a chiral appendage to the carbonyl substrate requiring alkylation. Under the influence of the auxiliary's chiral center(s), diastereotopic π-faces are generated upon enolate formation which can be differentiated by approaching electrophiles. The stereoselective additions are followed by removal of the auxiliary to unveil the nonracemic alkylated product. This mode of influence of the otherwise stereorandom alkylation process has been invaluable in the synthesis of complex acyclic natural products and acyclic synthetic intermediates en route to macrocyclic products.[38] Intensive efforts have led to the development of effective auxiliaries, including those introduced by Evans,[39] Meyers,[40] Oppolzer,[41] and Helmchen[42] for the asymmetric alkylation of acyclic substrates.

Concurrent with our development of **1** as a route to β-aryl-β-amino acids, we had occasion to employ Evans auxiliary **26** for the synthesis of the polypropionate-derived chain of jasplakinolide.[6] Having recognized the structural similarity of **1** and **26**, we determined to investigate any corresponding similarity in reactivity.

Herein we describe the use of **1** as a chiral auxiliary for the asymmetric alkylation of acyl derivatives.

With regard to the distribution and orientation of functionality required for communication of stereochemistry, **1** is almost identical to **26** (see below for comparable N-acylated analogues).



Both heterocycles contain secondary amide moieties that are part of structurally constricted ring systems. In each case, the amide is flanked by a chiral methine center bearing a bulky aliphatic group. Furthermore, we expected the *tert*-butyl group of **1** to enforce π-facial selectivity analogously to the isopropyl group of **26**.

For **1** to be successful as an auxiliary by contemporary standards, several criteria must be addressed. First, the auxiliary must be both available as a relatively inexpensive compound and easily appended to the acyl group. Second, the auxiliary must provide high efficiency in the alkylation process in both yield and π-facial selection. If complete alkylation diastereoselectivity is not obtained, then isolation of the predominant diastereomer in at least 99:1 de must be possible. Third, facile removal of the auxiliary without epimerization at the alkylated center and with attendant recovery of the auxiliary is essential. In the remaining portion of this paper, the assessment of **1**, in view of these outlined requirements, will be discussed and the results presented.

The synthesis of **1** has already been presented. The material is easily obtained in enantiomerically pure form in good overall yield from asparagine. Both enantiomeric forms of asparagine are available, and they rank as some of the least expensive amino acids.[43]

(36) Saá, J. M.; Dopico, M.; Martorell, G.; García-Raso, A. *J. Org. Chem.* **1990**, *55*, 991–5.

(37) (a) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3; pp 1–110, and references cited therein. (b) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969–2004. (c) Meyers, A. I. *Acc. Chem. Res.* **1978**, *11*, 375–81.

(38) For examples see: (a) Grieco, P. A.; Hon, Y. S.; Perez-Medrano, A. *J. Am. Chem. Soc.* **1988**, *110*, 1630–1. (b) Taber, D. F.; Petty, E. H.; Krishna, R. *J. Am. Chem. Soc.* **1985**, *107*, 196–9.

(39) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–9. For a new synthesis of **27** see: Wuts, P. G. M.; Pruitt, L. E. *Synthesis* **1989**, 622–3.

(40) Meyers, A. I. *Pure Appl. Chem.* **1979**, *51*, 1255–64.

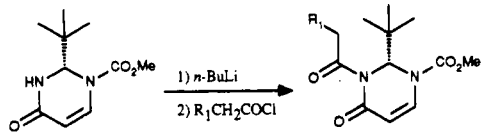
(41) Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. *Helv. Chim. Acta* **1985**, *68*, 212–5.

(42) (a) Abe, E.; Helmchen, G.; Heiligenmann, G. *Tetrahedron Lett.* **1980**, *21*, 1137–40. (b) Helmchen, G.; Selim, A.; Dorsch, D.; Taufer, I. *Tetrahedron Lett.* **1983**, *24*, 3213–6.

(43) For a graph of the costs of amino acids, see: Williams, R. M. *The Synthesis of Optically Active α-Amino Acids*; Baldwin, J. E., Ed.; Organic Chemistry Series; Pergamon Press: Oxford, U.K., 1989.

Several physical qualities of **1** and its derivatives are notable. First, **1** is highly crystalline and can be isolated without chromatography in 55% yield (12% additional product is recovered after chromatography). Second, because of strong UV absorbance, the transformations and isolation of **1** and its derivatives are easily monitored by TLC. In addition, ^{1}H NMR signals for **1** are well separated and, with the exception of the *tert*-butyl singlet, are downfield of the aliphatic region. This was particularly advantageous in the interpretation of the selectivity of methylation product mixtures, wherein the methyl doublets are clearly distinguished.

As discussed previously, acylation of **1** occurs via amide deprotonation in THF (*n*-BuLi; −78 °C; 2 h) followed by addition of carboxylic acid halide or anhydride (1.1 equiv) and stirring at room temperature. Following this protocol, highly crystalline propionyl derivative **27** was isolated without chromatography as



1

27 R_1 = Me 94%
28 R_1 = Et 89%

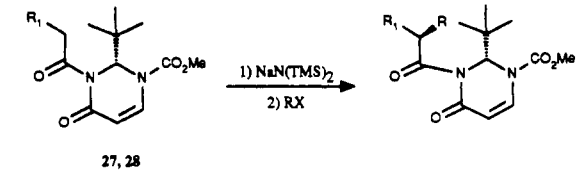
large colorless crystals in 80% yield (this yield can be increased to 94% by chromatographic isolation of **27** from the mother liquors and subsequent recrystallization). Butyryl derivative **28** was isolated as an oil in 89% yield after silica gel chromatography.

We began our alkylation studies with an investigation of the methylation of the enolate of **28** with iodomethane to yield **29a**. Methylations constitute a particularly sensitive probe for the assessment of reaction parameters on stereoselectivity, inasmuch as iodomethane has a low intrinsic steric demand. Multiple experiments were run to determine the effect of counterion (Li vs Na), the quantity of base, the time required for deprotonation, and the amount, time, and temperature for methylation.[44] To assure the identification of the minor component, **29b** was prepared by the addition of ethyl iodide to the sodium enolate of **27** (Scheme VII). We did not ascertain the absolute sense of asymmetric induction in these studies; however, this information was assigned via specific rotation measurements of the product carboxylic acid after removal of the auxiliary.

In our studies, the observed kinetic diastereoselection (kinetic de) ranged from 82 to 90% for the methylation of **28**, with a mean value of 86% de. Maximization of diastereoselectivity resulted when the iodomethane was added slowly (20 min/mmol of substrate) to a cooled portion of the reaction vessel containing the solution of the substrate anion.[45] Enolate formation with NaHMDS was complete in 2 h. The use of LDA resulted in severely reduced yields and poor selectivity. Extended exposure to enolate forming conditions resulted in no significant loss of alkylation diastereoselectivity, demonstrating the stability of the enolate. The transformation favored 6–10 equiv of methyl iodide for conversion in a reasonable reaction time (4 h) under kinetic conditions. Warming of the reaction mixture to 0 °C prior to addition of a saturated ammonium chloride solution caused significant decomposition of the alkylated products.

With a set of optimum conditions for the methylation of **28**, we next investigated the alkylation of **27** and **28** with various electrophiles (Table II). In addition to the reactions given above, both **27** and **28** were treated with alkyl iodide, propargyl bromide, and benzyl bromide.[46,47] Allylation (entries 2 and 6), propargylation (entries 3 and 7), and benzylation (entries 4 and 8) proceeded uneventfully in at least 96% kinetic de. As presented above, the sterically undemanding methylation (entry 5) proceeded with good diastereoselection (86% de) and in excellent yield (91%). Ethylation (entry 1), although exhibiting 94% kinetic de, gave poor results, requiring extended reaction time and yielding significant amounts of an unidentified byproduct.[48] These results are comparable to those obtained by alternate auxiliary methods in both yields and selectivities and amply demonstrate the viability of **1** as a stereo-directing element.

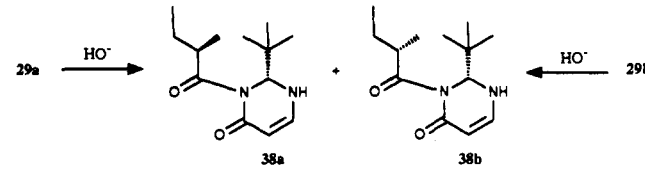
Table II



27, 28

product	R_1	RX (equivalents, temperature, time)	diastereomic ratio of product kinetic	diastereomic ratio of product isolated	isolated yield
29b	Me (**27**)	ethyl iodide (4, -78 °C, 6 h)	97:3	98:2	44%
30	Me (**27**)	allyl iodide (2, -78 °C, 4 h)	99:1	98:2	95%
31	Me (**27**)	propargyl bromide (2, -78 °C, 4 h)	99:1	100:0	86%
32	Me (**27**)	benzyl bromide (1.2, -23 °C, 2 h)	99:1	150:1	93%
29a	Et (**28**)	methyl iodide (5, -78 °C, 5 h)	93:7	98:2	91%
33	Et (**28**)	allyl iodide (2, -78 °C, 4 h)	98:2	98:2	87%
34	Et (**28**)	propargyl bromide (2, -78 °C, 4 h)	99:1	255:1	80%
35	Et (**28**)	benzyl bromide (1.2, -23 °C, 2 h)	99:1	100:0	83%

Scheme VIII



38a **38b**

Having established excellent selectivity and yield upon alkylation, we turned our attention to auxiliary removal. Amide-linked auxiliaries have been removed by benzyloxylithium or methoxylithium transesterification, potassium hydroxide hydrolysis, and reduction via boron and aluminum hydrides reagents to the alcohol or aldehyde.[37] More recently, Evans and co-workers introduced the use of lithium hydroperoxide for mild and direct deacylation to the acid.[49] This latter reagent has proven particularly useful for sterically encumbered acyl derivatives that have kinetically competitive hydrolysis and epimerization pathways. Our concern for the possible cleavage of the carbomethoxy group directed our

(44) Reaction progress was monitored by TLC and assayed for kinetic diastereomeric excess (de) by gas chromatography (GC).

(45) Our 25-mL reaction vessels have 3 cm long necks that are partially submerged in the cooling bath. Reagents are carefully added to the side walls of the flask neck below the cooling bath level. After alkyl halide addition, the flasks are tilted to allow dissolution of frozen electrophile. For a similar example see: Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718–26.

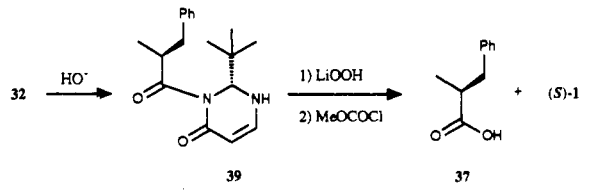
(46) A 50% solution of benzyl bromide in THF was used to prevent the sample from freezing in the syringe needle.

(47) Alkylating agents were added dropwise to uniformly formed enolates (0.25 mmol, 1.1 equiv base, 2.5 h). For each combination, electrophiles were added at −78 °C and assayed by GC for reaction progress and stereoselectivity after 2 h. Reactions showing no progress were warmed to −46 °C and assayed after 2 h, and this sequence was repeated at −23 °C. Additional warming to 0 °C, in the case of entry 1, caused significant decomposition of the substrate without additional reaction progress. When appropriate temperatures were determined for each combination, the reactions were repeated at a 1.0-mmol scale to obtain the reported yields and kinetic de. The major diastereomer in all cases was enriched by silica gel chromatography. The enriched major alkylation products were assessed for de by GC. Each compound gave spectroscopic results consistent with the anticipated product. The slightly enriched minor products showed ^{1}H NMR spectra consistent with the presence of the minor diastereomer in proportion to the amount indicated by GC for these samples.

(48) An elimination pathway for imide enolates leading to ketene byproducts was observed in the work of Evans and co-workers. See: Ennis, M. D. Thesis Dissertation, California Institute of Technology, 1983.

(49) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–4.

Scheme IX



efforts toward the use of this latter deacylation method.

Representative LiOOH deacylation reactions were performed on **29a** and the sterically more encumbered **32**. Fortunately, our apprehension that the auxiliary might suffer significant methoxycarbonyl hydrolysis under these conditions was unwarranted. Chromatographic isolation of the hydrolysis mixture of **29a** yielded (*R*)-2-methylbutyric acid (**36**) in 74% yield (46% after distillation) and concomitant recovery of enantiomerically pure **1** in 85% yield. Under similar conditions, (*S*)-2-methyl-3-phenylpropionic acid (**37**) was obtained in 94% yield from hydrolysis of **32** with similar heterocycle recovery (87%). The acids, obtained after distillation, exhibited the expected specific rotations,[50] supporting both our analysis of the mode of π-facial selectivity and the isomeric ratios obtained in the alkylation event.

Hydrolysis of **29a** (92:8 isomeric mixture with **29b**) with 1 equiv of methanolic hydroxide reagent[51] at 0 °C showed several interesting trends. The hydroxide reagent selectively removed the carbomethoxy group to give **38a,b** without interfering with the integrity of the heterocycle or the acyl–amide bond.[52] To ensure the assignment of these compounds, **29b** was likewise hydrolyzed to give a mixture in which the major and minor products were present in reversed proportions (Scheme VIII). In recognition of the catalytic nature of this transformation, **29a** was treated with 0.1 equiv of KOH. As expected, the transformation was slowed considerably; however, GC analysis indicated a similar reaction profile. Acidic hydrolysis methods applied to **29a** (5% HCl and 30% HBr in AcOH) showed no evidence of reaction (room temperature, 3 days).

Compound **38a** was enriched in the major diastereomer upon crystallization from hexanes. Thus, we considered the possibility of an alternate, largely nonchromatographic approach to the isolation of the alkylated products. In this scenario, the alkylation product (e.g., **29–35**) is decarbomethoxylated, recrystallized to purity, and subsequently deacylated to give the enantiomerically pure acid. Finally, recovery of the auxiliary would be accomplished via reintroduction of the carbomethoxy group. In the event, **32** was subjected to decarbomethoxylation to afford **39** as a 5:1 diastereomeric mixture[53] (Scheme IX). Recrystallization afforded diastereomerically pure material as measured by ^{1}H and ^{13}C NMR. Deacylation of **39** and refunctionalization to **1** occurred cleanly in one pot with LiOOH followed by methyl chloroformate to give acid **37** and (*S*)-**1** after column chromatography. Thus, the formation of **37** occurs from asparagine through (*S*)-**1** to **37** to **39** *with a* ***single*** *column chromatography after the final step to separate auxiliary from described product, making the protocol extremely economical.*

Conclusions

While our studies have been of limited scope, our results show immense possibilities for **1** and its derivatives. The work presented herein describes **1** as a readily available substance that can be employed as both a *reagent* and an *auxiliary* for the production of enantiomerically pure compounds.

As a reagent, **1** undergoes an unprecedented palladium-catalyzed reaction leading to β-aryl-β-amino acids, valuable compounds for the synthesis of biologically active molecules. As an auxiliary, **1** offers excellent kinetic stereoselection coupled with attractive isolation capabilities. In addition, a wide array of auxiliary mediated asymmetric reactions can be envisioned with **1**, including aldol,[54] Diels–Alder,[55] and ene[56] reactions, to name a few.

Further studies on **1**, including further optimization of the synthesis as well as additional structural variations and reactivity, are underway in our laboratory and will be reported in due course.

Experimental Section

General. Melting point determinations are reported uncorrected. Proton (^{1}H NMR) and carbon (^{13}C NMR) magnetic resonance spectra were recorded (in $CDCl_3$ unless otherwise noted) at 300 and 75.5 MHz, respectively. Ultraviolet (UV) spectra were recorded in methanol. Analytical gas chromatographic (GC) analyses were carried out with a 5-m methyl silicone, 530 μm wide bore column and flame ionization detector. Two sets of temperature parameters (injection temperature, oven initial temperature, initial time, oven temperature ramp, oven final temperature, final time) found extensive use: conditions A, 150 °C, 50 °C, 5 min, 15 °C/min, 75 °C, 1 min; conditions B, 250 °C, 100 °C, 1 min, 15 °C/min, 200 °C, 10 min. Combustion analysis for carbon and hydrogen were performed by the staff at Atlantic MicroLabs, Norcross, GA.

Tetrahydrofuran (THF) and diethyl ether were distilled from sodium metal benzophenone immediately prior to use. For anhydrous reactions, CH_2Cl_2 and hexanes were distilled from CaH_2 immediately prior to use. Toluene, benzene, and xylenes were refluxed for 24 h over Na and distilled into oven-dried receptacles containing Na. Triethylamine and diisopropylamine were distilled from calcium hydride and stored over KOH. Hexamethyldisilazane (HMDS) and *N,N*-dimethylformamide (DMF) were distilled from calcium hydride and stored over activated 3-Å molecular sieve.

Alkyl and aryllithium reagents were titrated with 1,10-phenanthroline according to the method of Watson and Eastham.[57] *n*-Butyllithium was purchased as a solution in hexane. Sodium hexamethyldisilylamide (NaHMDS) was prepared in THF under nitrogen with sodium amide and 1.05 equiv of $HN(TMS)_2$ in an ice-water bath. The reagent was typically prepared as a 0.7 M solution and was stored under nitrogen for use until the titer had diminished 10% (approximately 7 days). Prior to daily use, the amide base was titrated with 1,3-diphenylacetone-*p*-tosylhydrazone.[58] Unless otherwise indicated, all other reagents were used as received.

The syntheses of **19a**, **20**, and **21** have been reported.[6]

(2*R*,6*S*)-2-*tert*-Butyl-6-potassiumcarboxylate-4-pyrimidone (5) and (2*S*,6*S*)-2-*tert*-Butyl-1-carbomethoxy-6-carboxy-4-pyrimidone (7). A slurry of commercially available L-asparagine monohydrate (15.01 g, 100 mmol) in 10 mL of water was treated with KOH (85.5% assay, 6.56 g, 100 mmol, 1.0 equiv) dissolved in 15 mL of H_2O. The slightly yellow solution was heated to 60 °C and evaporated overnight under high vacuum (0.1 Torr), producing a slightly yellow glassy solid. The solid was redissolved with absolute methanol (150 mL), treated at room temperature with pivaldehyde (10.9 mL, 110 mmol, 1.1 equiv), and heated at reflux with vigorous stirring for 6–8 h. Evaporation of solvent under reduced pressure (50 Torr) and heat (60 °C) left behind **5** as an off-white lumpy solid. The coupling constants of a sample of this crude adduct supported the assignment of an axial orientation for the C6 proton: ^{1}H NMR (DMSO-d_6) δ 0.84 (s, 9 H, CC_4H_9), 1.95 (dd, J = 10.2, 16.8 Hz, 2 H, $COCH_\alpha H_\beta CH$), 2.21 (dd, J = 4.8, 16.8 Hz, $COCH_\alpha H_\beta CH$), 2.96 (dd, J = 4.8, 10.2 Hz, 1 H, $COCH_2CH$), 3.42 (br s, 2 H, CON*H* and COO*H*), 7.24 (br s, C*H*C_4H_9), 12.8 (br s, 1 H, COO*H*). The solid was redissolved in a 200-mL aqueous solution of sodium bicarbonate (7.66 g, 100 mmol, 1.0 equiv), and methyl chloroformate (10.4 g, 8.50 mL, 110 mmol, 1.1 equiv) was added dropwise to the cooled solution (0 °C) from

(50) Literature rotation of **36**: $[\alpha]_D$ = −18 (*c* 0.77, EtOH) (Asahira, Y.; Shimizu, T. *Nippon Yakugaku Kaishi* **1922**, *1*, 479). Observed: $[\alpha]_D$ = −20.7 (*c* 5.30, EtOH). Literature rotation of **37**: $[\alpha]_D$ = +17.87 (*c* 5.30, EtOH) (Kenyon, J.; Phillips, H.; Pittman, V. P. *J. Chem. Soc.* **1935**, 1072). Observed: $[\alpha]_D$ = +17.7 (*c* 2.37, EtOH).

(51) We have employed aqueous solutions of LiOH, NaOH, KOH, and K_2CO_3 with equal success.

(52) Epimerization (3–5%) at the new chiral center was noted in some of the reactions involving **29**.

(53) The sample of **32** employed in this study was purposely prepared in lower diastereomeric purity than is reported in Table II so that the effect of the recrystallization protocol could be thoroughly examined.

(54) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3; pp 111–212, and references cited therein.

(55) Paquette, L. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3; pp 455–502, and references cited therein.

(56) Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3; pp 503–72, and references cited therein.

(57) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165–8.

(58) Lipton, M. F.; Sorenson, C. M.; Sadler, A. C.; Shapiro, R. H. *J. Organomet. Chem.* **1980**, *186*, 155–8. For recent work on the titration of amide bases, see: Ireland, R. E.; Meissner, R. S. *J. Org. Chem.* **1991**, *56*, 4566–8.

a pressure equalizing dropping funnel. (*Caution: vigorous evolution of carbon dioxide.*) After stirring for 8 h at room temperature, the mixture was quenched with 5% HCl (75.8 mL, 110 mmol, 1.1 equiv) and evaporated to one-third volume, whereupon a white precipitate was produced. The slurry was extracted with ethyl acetate (100 mL), and the aqueous layer was back-extracted with 20% methanolic ethyl acetate (3 × 200 mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Filtration, evaporation of solvent, and prolonged evacuation (1 Torr; 48 h) gave a quantitative yield of **7** as a white amorphous solid that resisted crystallization. Chromatographic isolation gave no additional purification; however, repeated precipitation of a sample in ethanol provided limited purification for spectroscopic purposes. ^{1}H NMR (DMSO-d_6) δ 0.89 (s, 9 H, CC_4H_9), 2.42–2.60 (m, 2 H, $COCH_2CH$), 3.40–3.65 (m, 1 H, $COCH_2CH$), 3.56 (s, 3 H, $COOCH_3$), 8.61 (d, 1 H, CHC_4H_9), 12.81 (br s, 1 H, COOH).

(*S*)-2-*tert*-Butyl-1-carbomethoxy-2,3-dihydro-4(1*H*)-pyrimidinone (1). A slurry of crude heterocycle **7** (10.13 g, 41.0 mmol) in pyridine (5 mL), toluene (200 mL), and THF (20 mL) was stirred while copper(II) acetate monohydrate (1.64 g, 8.20 mmol, 0.20 equiv) was added. The blue emulsion was stirred for 2 h at room temperature and cooled (0 °C), and lead(IV) acetate (27.2 g, 61.5 mmol, 1.50 equiv) was added. The mixture was warmed to 70 °C for 12 h and evaporated to half volume under reduced pressure, and the residue was filtered through a 5-cm × 10-cm plug of silica gel with 500 mL of 1:1 hexanes/EtOAc. After solvent evaporation, a brown oily solid was obtained. The product was dissolved in a minimum amount of warm ethyl acetate and allowed to stand at room temperature until nearly all of the solvent was evaporated. Removal of the residual oily yellow liquid left behind **1** as large colorless crystals (11.66 g, 55 mmol, 55% from asparagine). The mother liquor was subjected to an additional chromatographic purification and crystallization from which was collected an additional 1.51 g (67% total yield from asparagine): mp 142.0–142.5 °C; $[\alpha]_D$ = +434 (*c* 1.7, EtOAc); ^{1}H NMR δ 0.95 (s, 9 H, CC_4H_9), 3.83 (s, 3 H, $COOCH_3$), 5.15–5.45 (m, 2 H, $COCH$=CH and CHC_4H_9), 7.20–7.50 (m, 1 H, COCH=C*H*), 8.0–8.5 (m, 1 H, *H*NCO); ^{13}C NMR δ 25.5, 40.7, 54.0, 72.0, 104.8, 137.5, 153.3, 164.6; MS (CI isobutane) *m/z* = 213 $(M + 1)^+$; IR (thin film) 1734 cm^{-1}; UV λ_{max} = 230, 271 nm. Anal. Calcd for $C_{10}H_{16}O_3N_2$: C, 56.58; H, 7.60; N, 13.20. Found: C, 56.62; H, 7.59; N, 13.17.

(2*S*,6*S*)-2-*tert*-Butyl-1-carbobenzoxy-6-carboxy-4-pyrimidone (6). According to the procedure given above for the formation of **7**, compound **5** (prepared from 41.1 mmol of L-asparagine) was treated with benzyl chloroformate (7.28 mL, 49.3 mmol). Product **6** was obtained as a white solid (11.0 g, 80%): mp 192–195 °C; $[\alpha]_D$ = +32.0 (*c* 4.0, MeOH); ^{1}H NMR (acetone-d_6) δ 1.03 (s, 9 H, CC_4H_9), 2.75 (m, 2 H, $COCH_2CH$), 4.79 (m, 1 H, $COCH_2CH$), 5.15 (m, 3 H, CHC_4H_9 and CH_2Ph), 7.34–7.80 (m, 6 H, N*H*, aromatics); ^{13}C NMR δ 26.7, 32.4, 38.2, 52.3, 68.3, 73.2, 127.8, 128.2, 128.9, 129.5, 137.9, 158.2, 170.6, 175.1; IR (KBr) 3413, 3336, 3201, 1892, 1719, 1685, 1619, 1401, 1320, 1264, 1227, 1187, 1087, 994 cm^{-1}; UV λ_{max} = 210, 260 nm. HRMS calcd for $C_{17}H_{22}O_5N_2$ + 1: 335.16079. Found: 335.16069.

(*S*)-2-*tert*-Butyl-1-carbobenzoxy-2,3-dihydro-4(1*H*)-pyrimidinone (8). Following the procedure given above for the synthesis of **1**, compound **6** afforded **8** after chromatography with silica gel and ethyl acetate/hexane (1:1), giving the product as a colorless oil in 60% yield: $[\alpha]_D$ = +139 (*c* 9.1, EtOAc); ^{1}H NMR δ 0.93 (s, 9 H, CC_4H_9), 5.22 (m, 4 H, CHC_4H_9, CH_2Ph, $COCH$=CH), 7.35–7.55 (m, 6 H, COCH=C*H*, aromatics), 7.97 (br s, 1 H, N*H*); ^{13}C NMR δ 25.5, 40.7, 69.0, 71.9, 104.9, 128.5, 128.8, 138.2, 137.2, 152.8, 164.6; IR (neat) 2966, 1725, 1654, 1396, 1320, 1243 cm^{-1}; UV (MeOH) λ_{max} = 240, 260 nm. HRMS (EI) calcd for $C_{16}H_{20}O_3N_2$: 288.14747. Found: 288.14736.

Compound **9** was assigned to a side-product of the above reaction; however, when the reaction was carried out in THF, **9** appeared as one of the major products: $[\alpha]_D$ = +244 (*c* 4.5, EtOAc); ^{1}H NMR δ 0.94 (s, 9 H, CC_4H_9), 2.52–2.98 (AB part of ABX system, 2 H, $COCH_2CH$), 5.00–5.35 (m, 2 H, $CHPh$, CHC_4H_9), 6.76 (m, 1 H, $COCH_2CH$), 7.35 (m, 5 H, aromatics), 7.92 (br s, 1 H, N*H*); ^{13}C NMR δ 26.4, 36.1, 40.9, 68.3, 72.0, 78.3, 128.3, 128.7, 135.6, 135.5, 155.6, 168.7; IR (neat) 3366, 2963, 1721, 1686, 1560, 1508, 1323, 1243, 1076 cm^{-1}. HRMS (EI) calcd for $C_{16}H_{20}O_3N_2$ + 1: 289.15533. Found: 289.15478.

General Procedure for Amide Nitrogen Functionalization of 1. Under nitrogen, a stirred solution of unsaturated heterocycle **1** (0.2 M in THF) was cooled (−78 °C) and *n*-BuLi (1.05 equiv) was added by syringe (10 min/mmol). Continuous agitation for 2 h was followed by the addition of the electrophile (1.20 equiv), and the mixture was allowed to warm to room temperature. After overnight stirring, the mixture was washed with saturated ammonium chloride, saturated bicarbonate, and brine (3 mL each/mmol of heterocycle). The aqueous layer was back-extracted with EtOAc (10 mL/mmol), and the combined organic layers were dried (Na_2SO_4).

(*O*)-Methylmandelic Acid Derivative of 1 (10). Following the general procedure, lithiated heterocycle **1** (134 mg, 0.63 mmol) was treated with the acid chloride of (*S*)-*O*-methylmandelic acid (186 mg, 1.0 mmol). Extractive workup, filtration, and concentration under reduced pressure gave a yellow viscous oil. Isolation by column chromatography on silica gel (EtOAc/hexanes 1:4) afforded **10** as a colorless oil (120 mg, 51%): $[\alpha]_D$ = −165 (*c* 6.6, EtOAc); ^{1}H NMR δ 0.95 (s, 9 H, CC_4H_9), 3.40 (s, 3 H, OCH_3), 3.82 (s, 3 H, $COOCH_3$), 5.10 (s, 1 H, $COCH$=CH), 6.03 (s, 1 H, C*H*), 6.67 (s, 1 H, CHC_4H_9), 7.45 (m, 1 H, COCH=C*H*), 7.27 (s, 5 H, aromatic); ^{13}C NMR δ 26.9, 40.3, 54.3, 57.4, 70.2, 82.8, 104.0, 128.5, 128.7, 135.8, 139.6, 164.0; IR (neat) 3213, 2954, 1731, 1663, 1437, 1325, 1249 cm^{-1}; UV λ_{max} = 270 nm. HRMS (EI) calcd for $C_{19}H_{24}O_5N_2$: 360.16852. Found: 360.16762.

Imide 11. Carbamate **10** (144 mg, 0.40 mmol) and lithium iodide (268 mg, 2.0 mmol) were dissolved in DMF (2.8 mL) under a nitrogen atmosphere, and the solution was stirred at 100 °C for 6.5 h. The reaction mixture was cooled, poured into water, acidified with 2 N HCl to pH 5, and extracted with $CHCl_3$. The organic extracts were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a solid. Recrystallization from $CHCl_3$/hexanes gave colorless needles (75 mg, 62%): mp >120 °C (decomposition); $[\alpha]_D$ = +86 (*c* 0.6, MeOH); ^{1}H NMR δ 0.93 (s, 9 H, CC_4H_9), 3.42 (s, 3 H, OCH_3), 4.62 (d, 1 H, *J* = 7.5 Hz, $COCH$=CH), 5.41 (m, 1 H, N*H*), 5.73 (d, 1 H, *J* = 5.0 Hz, CHC_4H_9), 6.19 (s, 1 H, C*H*), 6.84 (m, 1 H, COCH=C*H*), 7.26–7.38 (m, 5 H, aromatic); ^{13}C NMR δ 25.6, 40.1, 57.4, 70.0, 82.2, 92.5, 128.2, 128.5, 136.5, 146.3, 165.3, 172.6; IR (KBr) 3284, 2966, 1678, 1661, 1596, 1508, 1101 cm^{-1}; UV λ_{max} = 232, 323 nm. HRMS (EI) calcd for $C_{17}H_{22}N_2O_3$: 302.1630. Found: 302.1631.

(*S*)-2-*tert*-Butyl-3-methyl-2,3-dihydro-4(1*H*)-pyrimidinone (13). Pyrimidinone **16** (1.37 g, 6.08 mmol) was treated with KOH (1.37 M, 0.48 mL, 1.5 equiv) in absolute methanol (50 mL) at room temperature. Reaction completion, as monitored by TLC, was observed at 1.5 h. The reaction product was isolated by extractive workup (2 × 20 mL of EtOAc, then 2 × 20 mL of CH_2Cl_2) and washed with 5 mL of aqueous bicarbonate. From this regimen was obtained 868 mg of colorless oil, which in turn gave 480 mg (47%) of white needles after chromatography (silica gel; 10% EtOAc/hexanes). Proton and carbon NMR displayed two sets of signals in approximately 1:1 ratio: mp 139–141 °C; $[\alpha]_D$ = −185.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.93 and 0.96 (s, 9 H, CC_4H_9), 3.02 and 3.03 (s, 3 H, NCH_3), 4.30 and 4.85 (d, *J* = 4 Hz, 1 H, CHC_4H_9), 4.66 (m, 1 H, $COCH$=CH), 5.31 and 7.86 (br s, 1 H, N*H*), 6.73 (m, 1 H, COCH=C*H*); ^{13}C NMR 25.7, 26.2, 36.2, 36.4, 37.9, 40.9, 42.1, 79.8, 88.1, 92.8, 142.7, 158.1; IR (KBr) 3251, 3044, 2936, 1611, 1584, 1542, 1479, 1462, 1393, 1364, 1335, 1220, 1024, 776, 725 cm^{-1}; UV λ_{max} = 237, 282 nm. HRMS calcd for $C_9H_{16}N_2O$ − 1: 167.11855. Found: 167.11843.

(*S*)-2-*tert*-Butyl-1-(methoxymethyl)-3-methyl-2,3-dihydro-4(1*H*)-pyrimidinone (14). Compound **13** (0.59 g, 3.5 mmol) was dissolved in THF (45 mL) and cooled to −78 °C. *n*-BuLi (2.5 M, 1.53 mL, 3.7 mmol) was added dropwise, and the reaction was stirred at that temperature for 3 h. Chloromethyl methyl ether (0.29 mL, 3.7 mmol) was added, and the reaction was continued for another 3 h at low temperature before warming to room temperature overnight. The product was purified with silica gel chromatography, yielding **14** as a slightly yellow crystalline solid. (0.72 g, 95%): mp 84–85 °C; $[\alpha]_D$ = +441 (*c* 0.78, EtOAc); ^{1}H NMR δ 0.96 (s, 9 H, CC_4H_9), 3.10 (s, 3 H, NCH_3), 3.26 (s, 3 H, OCH_3), 4.33 (d, *J* = 1.5 Hz, 1 H, CHC_4H_9), 4.45 (AB system, 2 H, CH_2OCH_3), 5.00 (d, *J* = 7.3 Hz, 1 H, $COCH$=CH), 6.68 (dd, *J* = 1.5, 7.3 Hz, 1 H, COCH=C*H*); ^{13}C NMR δ 26.4, 37.7, 42.5, 55.8, 82.9, 86.3, 99.2, 136.6, 144.6; IR (KBr) 2950, 1700, 1378 cm^{-1}; MS (EI) *m/z* = 212 (M^+); UV λ_{max} = 230, 290 nm. Anal. Calcd for $C_{11}H_{20}N_2O_2$: C, 62.24; H, 9.50. Found: C, 62.33; H, 9.53.

(*R*)-2-*tert*-Butyl-3-methyl-1-(trimethylacetyl)-2,3-dihydro-4(1*H*)-pyrimidinone (15). Compound **13** (1.10 g, 6.9 mmol) was dissolved in THF and cooled to −78 °C. *n*-BuLi (2.5 M, 2.77 mL, 6.9 mmol) was added dropwise, and the reaction mixture was left to stir for 2 h at that temperature. Trimethylacetyl chloride (0.49 mL, 6.9 mmol) was added, and the reaction mixture was allowed to warm to room temperature and stirred over 12 h. The product was purified by silica gel chromatography, giving a white crystalline solid (1.30 g, 75%): mp 160–162 °C; $[\alpha]_D$ = +303 (*c* 0.66, EtOAc); ^{1}H NMR δ 0.93 (s, 9 H, CC_4H_9), 1.34 (s, 9 H, COC_4H_9), 3.10 (s, 3 H, CH_3), 5.40 (m, 1 H, $COCH$=CH), 5.75 (d, *J* = 1.5 Hz, 1 H, CHC_4H_9), 7.49 (m, 1 H, COCH=C*H*); ^{13}C NMR δ 27.4, 28.2, 37.5, 39.9, 41.2, 106.3, 136.1, 162.8, 175.9; IR (KBr) 2966, 1654, 1407, 1302, 1178, 1108, 890, 797 cm^{-1}; UV λ_{max} = 245, 277 nm; MS (EI) *m/z* = 252 (M^+). Anal. Calcd for $C_{14}H_{24}N_2O_2$: C, 66.63; H, 9.59. Found: C, 66.52; H, 9.53.

(*R*)-2-*tert*-Butyl-1-carbomethoxy-3-methyl-2,3-dihydro-4(1*H*)-pyrimidinone (16). Following the general procedure, lithiated heterocycle **1** (276 mg, 1.30 mmol) was treated with neat iodomethane (0.12 mL, 2.0

mmol, 2.0 equiv). Extractive workup, filtration, and solvent evaporation followed by chromatographic purification (silica gel; 2:1 benzene/EtOAc) gave **16** (293 mg, 1.03 mmol, 79% yield) as an oil which slowly crystallized to a white solid: mp 54–56 °C; $[\alpha]_D$ = +235 (*c* 1.7, EtOAc); ^{1}H NMR δ 0.94 (s, 9 H, CC_4H_9), 3.08 (s, 3 H, $CONCH_3$), 3.81 (s, 3 H, $COOCH_3$), 5.31 (m, 2 H, CHC_4H_9 and COC*H*=CH), 7.21 (d, *J* = 6.9 Hz, 1 H, COCH=C*H*); ^{13}C NMR δ 27.0, 37.7, 41.7, 54.1, 78.2, 106.8, 135.4, 153.2, 163.1; IR (thin film) 2966, 1731, 1660, 1443, 1331, 1243 cm^{-1}; UV λ_{max} = 239, 272 nm. HRMS (EI) calcd for $C_{11}H_{18}O_3N_2$: 226.13181. Found: 226.13245.

(*S*)-1-Acetyl-2-*tert*-butyl-3-methyl-2,3-dihydro-4(1*H*)-pyrimidinone (17). Compound (+)-**13** (1.10 g, 6.9 mmol) was dissolved in THF and cooled to −78 °C. *n*-BuLi (2.5 M, 2.77 mL, 6.9 mmol) was added dropwise, and the reaction mixture was stirred for 2 h at that temperature. Acetyl chloride (0.49 mL, 6.9 mmol) was added, and the reaction was warmed to room temperature and stirred for 12 h. Extractive workup preceded purification by silica gel chromatography, giving a crystalline solid (1.10 g, 70%): mp 94–96 °C; $[\alpha]_D$ = +259 (*c* 0.42, EtOAc); ^{1}H NMR δ 0.97 (s, 9 H, CHC_4H_9), 2.20 (s, 3 H, $COCH_3$), 3.10 (s, 3 H, NCH_3), 5.50 (m, 1 H, COC*H*=CH), 5.60 (s, 1 H, CHC_4H_9), 7.10 (m, 1 H, COCH=C*H*); ^{13}C NMR 21.3, 27.2, 37.7, 41.3, 75.6, 107.9, 135.4, 162.8, 168.6; IR (KBr) 2952, 1646, 1312, 1243 cm^{-1}; MS (EI) *m*/*z* = 211 (M + 1)$^+$. Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.63; H, 8.63. Found: C, 62.24; H, 8.59.

(2*S*,6*S*)-1-Acetyl-2-*tert*-butyl-6-*n*-butyl-3-methyl-4-pyrimidone (18). To a 50-mL two-neck flask charged with ether (5 mL) was added CuI (0.35 g, 1.8 mmol), and the resulting slurry was cooled to −78 °C. *n*-BuLi (2.5 M, 1.45 mL, 3.6 mmol) was added. The cooling was removed for 3 min, during which time a green mass precipitated and then dissolved. The reaction was recooled to −78 °C. Addition of chlorotrimethylsilane (0.23 mL, 1.8 mmol) was followed by the addition of **17** (94.5 mg, 0.45 mmol) in ether. The mixture was left overnight and allowed to warm to room temperature. Ammonium chloride/ammonium hydroxide solution was added and stirred for 1 h until the mixture turned blue. Extraction with ether and chromatography (silica gel, EtOAc) afforded **18** as a colorless oil (42 mg, 35%): $[\alpha]_D$ = −78 (*c* 1.1, EtOAc); ^{1}H NMR δ 0.88 (t, *J* = 6.9 Hz, 3 H, $(CH_2)_3CH_3$), 1.00 (s, 9 H, CHC_4H_9), 1.22–1.54 (m, 6 H, $(CH_2)_3CH_3$), 2.17 (s, 3 H, $COCH_3$), 2.49–2.85 (m, 2 H, $COCH_2$), 3.05 (s, 3 H, NCH_3), 3.89 (m, 1 H, $COCH_2CH$), 5.57 (s, 1 H, CHC_4H_9); ^{13}C NMR δ 14.0, 22.4, 28.7, 28.9, 35.7, 36.8, 37.1, 53.6, 76.7; IR (neat) 2954, 1648, 1460, 1396 cm^{-1}. HRMS (EI) calcd for $C_{15}H_{28}O_2N_2$ + 1: 269.22307. Found: 269.22301.

(*S*)-2-*tert*-Butyl-1-carbethoxy-2,3-dihydro-4(1*H*)-pyrimidinone (23). This synthesis was identical to that of **1** with the substitution of ethyl chloroformate for methyl chloroformate: $[\alpha]_D$ = +316 (*c* 1.7, EtOAc); ^{1}H NMR δ 0.84 (s, 9 H, CC_4H_9), 1.20 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 4.15 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 5.05–5.30 (m, 2 H, COC*H*=CH and CHC_4H_9), 7.30 (m, 1 H, COCH=C*H*), 8.25–8.70 (m, 1 H, *H*NCO); ^{13}C NMR δ 25.0, 40.2, 51.9, 62.7, 71.1, 104.5, 136.9, 152.2, 164.4; IR (thin film) 3201, 3060, 2966, 1731, 1666 cm^{-1}. HRMS calcd for $C_{11}H_{18}N_2O_3$: 226.13181. Found: 226.13266.

Neopentyl Alcohol-*d*$_2$. To a stirred solution of $LiAlD_4$ (98% D, 1.00 g, 23.8 mmol) in ether (150 mL) under nitrogen was added methyl pivalate (5.7 mL, 21.6 mmol) at such a rate as to assure gentle reflux. Stirring was continued at room temperature for 12 h, at which point the mixture was carefully quenched with water (5 mL). The precipitate was filtered and the filtrate washed sequentially with water, brine, $NaHCO_3$ solution, and brine. The solution was dried ($MgSO_4$), filtered, and distilled to yield the desired product (3.06 g, 90%): mp 52–54 °C; ^{1}H NMR δ 0.83 (s); ^{13}C NMR δ 26.0, 32.4, 72.3 (quintet, *J* = 21.0 Hz); IR (thin film) 3354, 2954, 2191, 2085, 1108 cm^{-1}.

Pivaldehyde-*d*. To a stirred solution of PCC (32.0 g, 148.4 mmol) in CH_2Cl_2 (200 mL) at room temperature was added the product of the above reaction (8.7 g, 97.6 mmol) in CH_2Cl_2 (16 mL) all at once. The solution was allowed to stir for 10 h before dilution to twice the volume with pentane. This solution was decanted, the residue washed with ether, and the combined organic solution filtered through silica gel. The filtrate was distilled to yield the desired aldehyde (2.9 g, 35%): ^{1}H NMR δ 0.98 (s); ^{13}C NMR δ 23.3, 25.9, 205.5 (t, *J* = 25.2 Hz).

(*S*)-1-*d*. This synthesis was identical to that of **1** with the substitution of pivaldehyde-*d* for unlabeled pivaldehyde: ^{13}C NMR δ 25.0, 40.1, 53.4, 71.0 (t, *J* = 20.6 Hz), 104.4, 136.9, 152.8, 164.4. HRMS (EI) calcd for $C_{10}H_{15}N_2O_3D$: 213.12242. Found: 213.12199.

(*S*)-2-*tert*-Butyl-1-carbomethoxy-3-propionyl-2,3-dihydro-4(1*H*)-pyrimidinone (27). Following the general procedure, lithiated heterocycle **1** (4.13 g, 19.5 mmol) was treated with neat propionyl chloride (3.0 mL, 1.2 mmol, 1.20 equiv). Extractive workup, filtration, and concentration under reduced pressure gave a slightly yellow oily solid. Recrystallization (1:1 hexanes/ethyl acetate) gave 4.20 g (80%) of large colorless crystals. Additional product (0.75 g, 14%) was recovered from the mother liquor after silica gel chromatography and recrystallization: mp 117–118 °C; $[\alpha]_D$ = +158 (*c* 3.55, EtOH); ^{1}H NMR δ 0.89 (s, 9 H, C_4H_9), 1.10 (t, *J* = 7.4 Hz, 3 H, $COCH_2CH_3$), 2.65 (dq, *J* = 7.2, 17.7 Hz, 1 H, COC*H*HCH$_3$), 2.99 (dq, *J* = 7.5, 17.7 Hz, COCH*H*CH$_3$), 3.83 (s, 3 H, $COOCH_3$), 5.29 (d, *J* = 7.5 Hz, COC*H*=CH), 6.79 (s, 1 H, CHC_4H_9), 7.60 (br s, 1 H, COCH=C*H*); ^{13}C NMR δ 9.2, 26.8, 31.5, 40.4, 54.3, 69.1, 105.1, 139.4, 152.7, 164.1, 175.1; MS (CI-NH$_3$) *m*/*z* = 269 (M + 1)$^+$; IR ($CHCl_3$ solution) 2255, 1742, 1696, 1628 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_4N_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.64; H, 7.88; N, 9.89.

(*S*)-2-*tert*-Butyl-3-butyryl-1-carbomethoxy-2,3-dihydro-4(1*H*)-pyrimidinone (28). Following the general procedure, lithiated heterocycle **1** (4.54 g, 21.4 mmol) was treated with neat butyryl chloride (2.67 mL, 25.7 mmol, 1.2 equiv). Extractive workup, filtration, and concentration under reduced pressure gave a slightly yellow thick oil. Silica gel chromatography yielded 5.16 g (86%) of opaque colorless oil: $[\alpha]_D$ = +129 (*c* 3.25, EtOAc); ^{1}H NMR δ = 0.93 (s, 9 H, C_4H_9), 0.95 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.55–1.82 (m, 2 H, $CH_2CH_2CH_3$), 2.63 (m, 1 H, C*H*HCH$_2$CH$_3$), 2.97 (m, 1 H, CH*H*CH$_2$CH$_3$), 3.86 (s, 3 H, $COOCH_3$), 5.33 (d, *J* = 7.5 Hz, COC*H*=CH), 6.83 (s, 1 H, CHC_4H_9), 7.63 (br s, 1 H, COCH=C*H*); ^{13}C NMR δ 13.8, 18.7, 26.8, 39.9, 40.4, 54.3, 69.0, 105.1, 139.3, 152.8, 164.1, 174.2; MS (CI-NH$_3$) *m*/*z* = 283 (M + 1)$^+$; IR (thin film) 3098, 1740, 1694, 1628 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_4N_2$: C, 59.56; H, 7.51; N, 10.44. Found: C, 56.21; H, 7.46; N, 10.45.

(2*S*)-2-*tert*-Butyl-1-carbomethoxy-3-[(*R*)-2-methylbutyryl]-2,3-dihydro-4(1*H*)-pyrimidinone (29a). Compound **28** (282 mg, 1.0 mmol) was weighted into a two-neck 25 mL flask and dried overnight under high vacuum. The oil was dissolved in THF (5 mL), cooled to −78 °C, and treated slowly with sodium hexamethyldisilylamide (0.61 M in THF; 1.80 mL; 1.10 equiv) to a cooled portion of the reactor. The resulting yellow enolate was allowed to stir for 2.5 h, and freshly distilled iodomethane (0.71 g, 0.29 mL, 5.0 mmol, 5.0 equiv) was added by dropwise addition. The reaction progress was monitored by TLC or GC, and when completed (4 h), saturated ammonium chloride (3 mL) was added. The mixture was allowed to warm to room temperature and extracted with ethyl acetate (2 × 5 mL). The combined organic phase was washed sequentially with bicarbonate (5 mL) and brine (5 mL) and dried ($MgSO_4$). Filtration and evaporation of solvent gave a quantitative yield of a yellow oil. GC and ^{1}H NMR gave evidence of a 93:7 ratio of new compounds. Silica gel isolation (9:1 hexanes/ethyl acetate) gave the initially eluted major product **29a** (266 mg, 0.90 mmol, 90%) as a slightly yellow oil in 99:1 isomeric ratio: $[\alpha]_D$ = +86.4 (*c* 2.36, CH_2Cl_2); ^{1}H NMR δ 0.81 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3), 0.93 (s, 9 H, C_4H_9), 1.24 (d, *J* = 6.9 Hz, 3 H, $COCHCH_3$), 1.32–1.44 (m, 1 H, CHC*H*HCH$_3$), 1.59–1.75 (m, 2 H, CH_2CH_3), 3.30–3.43 (m, 1 H, $CHCH_2CH_3$), 3.87 (s, 3 H, $COOCH_3$), 5.34 (d, *J* = 10.8 Hz, 1 H, COC*H*=CH), 6.82 (s, 1 H, CHC_4H_9), 7.65 (br s, 1 H, COCH=C*H*); ^{13}C NMR δ 11.8, 18.0, 26.9, 40.4, 41.8, 54.3, 69.1, 105.2, 139.4, 152.8, 164.2, 178.3; MS (CI-NH$_3$) *m*/*z* = 297 (M + 1)$^+$; IR ($CHCl_3$ solution) 1742, 1690, 1684, 1626 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_4N_2$: C, 60.79; H, 8.16; N, 9.45. Found: C, 60.72; H, 8.20; N, 9.41. The less mobile minor product was obtained in 5% yield as an enriched mixture (15 mg, 1:3 major/minor product). The spectral characteristics of the minor product were identical to those listed for the major compound **29b** below.

(2*S*)-2-*tert*-Butyl-1-carbomethoxy-3-[(*S*)-2-methylbutyryl]-2,3-dihydro-4(1*H*)-pyrimidinone (29b). Following the experimental for **29a**, the sodium enolate of **27** (268 mg, 1.0 mmol) was prepared and treated with iodoethane (0.62 g, 0.59 mL, 4.0 mmol, 4.0 equiv) at −78 °C. The mixture was warmed to −23 °C and stirred for 4 h after which time GC indicated no additional reaction progress. A 97:3 ratio of diastereomers was detected in addition to significant amounts of **27** and unidentified byproducts. Standard extractive workup and silica gel chromatography yielded **29b** (145 mg, 0.49 mmol, 49%) as a slightly yellow oil (98:2 ratio of stereoisomers, contaminated by 10% of **27**; 44% corrected yield): $[\alpha]_D$ = +138 (*c* 5.63, CH_2Cl_2); ^{1}H NMR δ 0.90 (s, 9 H, C_4H_9), 0.94 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 1.03 (d, *J* = 6.6 Hz, 3 H, $COCHCH_3$), 1.30–1.48 (m, 1 H, CHC*H*HCH_3), 1.80–1.85 (m, 1 H, CHCH*H*CH$_3$), 3.39 (dq, *J* = 6.0, 6.0 Hz, 1 H, $CHCH_2CH_3$), 3.84 (s, 3 H, $COOCH_3$), 5.30 (d, *J* = 6.9 Hz, 1 H, COC*H*=CH), 6.84 (s, 1 H, CHC_4H_9), 7.62 (br s, 1 H, COCH=C*H*); ^{13}C NMR δ 9.2, 11.7, 16.3, 26.9, 27.5, 31.5, 40.3, 41.2, 54.3, 68.8, 105.1, 139.3, 152.8, 164.0, 175.1, 177.9; MS (CI-NH$_3$) *m*/*z* = 297 (M + 1)$^+$; IR ($CHCl_3$ solution) 1726, 1690, 1680, 1628 cm^{-1}.

(2*S*)-2-*tert*-Butyl-1-carbomethoxy-3-[(*S*)-2-methyl-4-pentenoyl]-2,3-dihydro-4(1*H*)-pyrimidinone (30). Following the experimental procedure for **29a**, the sodium enolate of **27** (268 mg, 1.0 mmol) was prepared and treated with allyl iodide (0.34 g, 0.18 mL, 2.0 mmol, 2.0 equiv) at −78 °C and stirred for 4 h. Analysis by GC showed a 99:1 ratio of diastereomers. Standard extractive workup and silica gel chromatography (9:1

hexanes/EtOAc) yielded **30** (292 mg, 0.95 mmol, 95%) as a slightly yellow oil in a 99:1 ratio of stereoisomers: $[\alpha]_D$ = +257 (*c* 1.05, CH_2Cl_2); ^1H NMR δ 0.90 (s, 9 H, C_4H_9), 1.04 (d, *J* = 6.9 Hz, 3 H, $CHCH_3$), 2.09 (dt, *J* = 6.0, 13.8 Hz, 1 H, CH_2=CHCH*H*), 2.63 (dt, *J* = 6.0, 12.0 Hz, 1 H, CH_2=CHC*H*H), 3.57 (ddq, 6.0, 6.6, 6.9 Hz, 1 H, COC*H*CH_3), 3.84 (s, 3 H, COOCH_3), 5.02 (dd, *J* = 1.2, 14.1 Hz, 1 H, CH=CHC*H*), 5.07 (dd, *J* = 1.2, 17.1 Hz, 1 H, CH=C*H*CH), 5.31 (d, *J* = 7.2 Hz, 1 H, COC*H*=CH), 5.72–5.88 (m, 1 H, CH_2=C*H*CH_2), 6.83 (s, 1 H, C*H*C_4H_9), 7.63 (br s, 1 H, COCH=C*H*); ^{13}C NMR δ 16.5, 26.9, 38.6, 39.5, 40.3, 54.4, 68.9, 105.0, 116.9, 135.9, 139.4, 139.5, 164.1, 177.3; MS (CI-NH_3) *m/z* = 309 (M + 1)$^+$; IR (neat) 1748, 1698, 1684, 1624 cm^{-1}. HRMS calcd for $C_{16}H_{24}O_4N_2$ + 1: 309.1816. Found: 309.1804.

(2*S*)-2-*tert*-Butyl-1-carbomethoxy-3-[(*S*)-2-methyl-4-pentynoyl]-2,3-dihydro-4(1*H*)-pyrimidinone (31). Following the experimental procedure for **29a**, the sodium enolate of **27** (268 mg, 1.0 mmol) was prepared and treated with propargyl bromide (0.24 g, 0.18 mL, 2.0 mmol, 2.0 equiv). The mixture was stirred for 4 h, whereupon GC showed reaction completion as a 99:1 ratio of diastereomers. Standard extractive workup and silica gel chromatography (9:1 hexanes/EtOAc) yielded a slightly yellow oil (**31**, 264 mg, 86%) as a single stereoisomer: $[\alpha]_D$ = +152 (*c* 1.55, CH_2Cl_2); ^1H NMR δ 0.90 (s, 9 H, C_4H_9), 1.15 (d, *J* = 7.2 Hz, 3 H, $CHCH_3$), 1.95 (dd, *J* = 2.4, 3.6 Hz, 1 H, *H*C≡CCH_2), 2.35–2.46 (ddd, *J* = 3.0, 8.7, 16.2 Hz, 1 H, HC≡CC*H*H), 2.60–2.70 (ddd, *J* = 3.0, 5.4, 16.2 Hz, 1 H, HC≡CCH*H*), 3.78 (ddq, *J* = 6.6, 6.6, 6.6 Hz, 1 H, C*H*CH_3), 3.84 (s, 3 H, COOCH_3), 5.31 (d, 1 H, COC*H*=CH), 6.81 (s, 1 H, C*H*C_4H_9), 7.63 (br s, 1 H, COCH=C*H*); ^{13}C NMR δ 9.2, 16.6, 23.3, 26.9, 31.5, 39.4, 40.2, 54.4, 69.1, 69.9, 81.9, 104.8, 139.5, 152.7, 163.9, 175.9; IR ($CHCl_3$ solution) 3310, 3100, 2257, 1742, 1695, 1680, 1626 cm^{-1}. HRMS calcd for $C_{16}H_{22}O_4N_2$ + 1: 307.16589. Found: 307.16970.

(2*S*)-2-*tert*-Butyl-1-carbomethoxy-3-[(*S*)-2-methyl-3-phenylpropionyl]-2,3-dihydro-4(1*H*)-pyrimidinone (32). Following the experimental procedure for **29a**, the sodium enolate of **27** (268 mg, 1.0 mmol) was prepared and treated with benzyl bromide (0.21 g, 0.14 mL, 1.2 mmol, 1.2 equiv) dissolved in an equal volume of THF (−78 °C). The mixture was allowed to warm to −23 °C and was stirred for 4 h, at which time GC analysis showed a 99:1 ratio of diastereomers. Standard extractive workup and silica gel chromatography (9:1 hexanes/EtOAc) yielded **32** (320 mg, 93%) as a slightly yellow oil in a 150:1 ratio of stereoisomers: $[\alpha]_D$ = +210 (*c* 1.81, CH_2Cl_2); ^1H NMR δ 0.88 (s, 9 H, C_4H_9), 1.03 (d, *J* = 6.6 Hz, 3 H, COCHCH_3), 2.50 (dd, *J* = 9.3, 14.2 Hz, 1 H, C*H*C_6H_5), 3.37 (dd, *J* = 5.1, 14.2 Hz, 1 H, C*H*C_6H_5), 3.8–3.9 (m, 1 H, COC*H*CH_3), 3.88 (s, 3 H, COOCH_3), 5.36 (d, *J* = 7.2 Hz, 1 H, COC*H*=CH), 6.87 (s, 1 H, C*H*C_4H_9), 7.12–7.35 (m, 5 H, aromatic), 7.65 (br s, 1 H, COCH=C*H*); ^{13}C NMR δ 16.3, 38.4, 40.3, 42.0, 54.4, 69.0, 105.1, 126.2, 128.3, 129.3, 139.5, 139.8; IR (thin film) 3083, 3061, 3027, 1744, 1696, 1624 cm^{-1}. HRMS calcd for $C_{20}H_{26}O_4N_2$ + 1: 359.19720. Found: 359.19707.

(2*S*)-2-*tert*-Butyl-1-carbomethoxy-3-[(*S*)-2-ethyl-4-pentenoyl]-2,3-dihydro-4(1*H*)-pyrimidinone (33). Following the experimental procedure for **29a**, the sodium enolate of **28** (282 mg, 1.0 mmol) was prepared and treated with allyl iodide (0.34 g, 0.18 mL, 2.0 mmol, 2.0 equiv). The mixture was stirred for 4 h, at which time GC showed a 98:2 ratio of diastereomers. Standard extractive workup and silica gel chromatography (9:1 hexanes/EtOAc) yielded **33** (283 mg, 87%) as a slightly yellow oil in a 98:2 ratio of stereoisomers: $[\alpha]_D$ = +81.9 (*c* 0.89, CH_2Cl_2); ^1H NMR δ 0.76 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 0.91 (s, 9 H, C_4H_9), 1.39–1.52 (m, 1 H, CHC*H*HCH_3), 1.54–1.63 (m, 1 H, CHCH*H*CH_3), 2.16–2.28 (m, 1 H, CH_2=CHCH*H*), 2.50–2.62 (m, 1 H, CH_2=CHC*H*H), 3.46–3.58 (m, 1 H, COC*H*CH_2), 3.85 (s, 3 H, COOCH_3), 4.96–5.12 (m, 2 H, CH_2=CHCH), 5.32 (d, *J* = 7.8 Hz, 1 H, COC*H*=CH), 5.76–5.90 (m, 1 H, CH_2=C*H*CH), 6.81 (s, 1 H, C*H*C_4H_9), 7.64 (br s, 1 H, COCH=C*H*); ^{13}C NMR δ 11.7, 25.0, 26.9, 36.7, 40.2, 46.2, 54.3, 69.1, 105.1, 116.6, 136.0, 139.4, 164.3, 176.7; IR ($CHCl_3$ solution) 3056, 1740, 1690, 1624 cm^{-1}. HRMS calcd for $C_{17}H_{27}O_4N_2$ + 1: 323.19721. Found: 323.19861.

(2*S*)-2-*tert*-Butyl-1-carbomethoxy-3-[(*S*)-2-ethyl-4-pentynoyl]-2,3-dihydro-4(1*H*)-pyrimidinone (34). Following the experimental procedure for **29a**, the sodium enolate of **28** (282 mg, 1.0 mmol) was prepared as described above and treated with propargyl bromide (0.24 g, 0.18 mL, 2.0 mmol, 2.0 equiv) and allowed to stir 4 h. A sample of the dark brown solution showed a 99:1 ratio of diastereomers by GC analysis. Standard extractive workup and silica gel chromatography (9:1 hexanes/EtOAc) yielded **34** (255 mg, 80%) as a slightly yellow oil in 255:1 ratio of stereoisomers: $[\alpha]_D$ = +99.9 (*c*, 1.95, CH_2Cl_2); ^1H NMR δ 0.72 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 0.90 (s, 9 H, C_4H_9), 1.44–1.77 (m, 2 H, C$H_2$$CH_3$), 1.89 (dd, *J* = 2.4, 2.7, 1 H, *H*C≡CCH_2), 2.38 (ddd, *J* = 2.7, 6.6, 19.8 Hz, 1 H, HC≡CC*H*H), 2.55 (ddd, *J* = 3.0, 9.0, 17.1 Hz, 1 H, HC≡CCH*H*), 3.67 (m, 1 H, C*H*CH_2CH_3), 3.78 (s, 3 H, COOCH_3), 5.31 (s, 1 H, COC*H*=CH), 6.81 (s, 1 H, C*H*C_4H_9), 7.63 (br s, 1 H, COCH=C*H*); ^{13}C NMR δ 11.3, 13.8, 18.4, 21.2, 24.5, 26.9, 39.9, 40.3, 45.6, 54.4, 69.0, 69.2, 69.8, 81.9, 104.9, 139.6, 152.7, 160.1, 164.1, 174.1, 175.3; IR ($CHCl_3$ solution) 3306, 3098, 2257, 1732, 1694, 1680, 1621 cm^{-1}. HRMS calcd for $C_{17}H_{24}O_4N_2$: 320.17372. Found: 320.17412.

(2*S*)-3-[(*S*)-2-Benzylbutyryl]-2-*tert*-butyl-1-carbomethoxy-2,3-dihydro-4(1*H*)-pyrimidinone (35). Following the experimental procedure for **29a**, the sodium enolate of **28** (282 mg, 1.0 mmol) was prepared and treated with benzyl bromide (0.21 g, 0.14 mL, 1.2 mmol, 1.2 equiv) at −78 °C. The mixture warmed to −23 °C and was stirred for 4 h, at which time GC analysis showed a 99:1 ratio of diastereomers. Standard extractive workup and silica gel chromatography (9:1 hexanes/EtOAc) yielded a slightly yellow oil (**35**, 292 mg; 83%) as a single stereoisomer: $[\alpha]_D$ = +141 (*c* 3.44, CH_2Cl_2); ^1H NMR δ 0.77 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 0.85 (s, 9 H, C_4H_9), 1.36–1.49 (m, 1 H, C*H*HCH_3), 1.57–1.76 (m, 1 H, CH*H*CH_3), 2.65 (dd, *J* = 8.4, 14.2 Hz, 1 H, C*H*HC_6H_5), 3.24 (dd, *J* = 6.3, 14.2 Hz, 1 H, CH*H*C_6H_5), 3.8–3.9 (m, 1 H, COC*H*CH_3), 3.88 (s, 3 H, COOCH_3), 5.36 (d, *J* = 7.8 Hz, 1 H, COC*H*=CH), 6.85 (s, 1 H, C*H*C_4H_9), 7.14–7.38 (m, 5 H, aromatic), 7.68 (br s, 1 H, COCH=C*H*); ^{13}C NMR δ 11.9, 24.9, 26.8, 38.7, 40.3, 48.6, 54.4, 69.1, 105.1, 126.2, 127.5, 128.3, 129.5, 139.5, 139.7, 139.9, 152.7, 164.4, 176.8; IR (thin layer) 3086, 3065, 3028, 1744, 1696, 1622 cm^{-1}. HRMS calcd for $C_{21}H_{28}O_4N_2$ − 1: 371.19721. Found: 371.20193.

(*R*)-(−)-2-Methylbutyric Acid (36). Heterocycle **29a** (296 mg, 1.0 mmol, 91:9 ratio of isomers **39a,b**) was dissolved in a 3:1 mixture THF (stabilized with BHT) and water. The mixture was cooled in an ice bath and degassed, and 30% hydrogen peroxide (0.88 mL, 8 mmol, 8 equiv) was added, followed immediately by LiOH (46 mg, 2.0 mmol, 2.0 equiv). TLC showed reaction completion at 20 min, and a 10% excess of aqueous sodium bisulfite solution (1.2 M, 8.8 mmol) was added. The mixture was extracted with EtOAc (5 mL) and brine (5 mL), combined with a back-extraction of the aqueous phase, and dried with anhydrous sodium sulfate. Liberation from solvent yielded 315 mg of clear colorless oil which when subjected to silica gel isolation (Et_2O, then EtOAc) gave **36** (90 mg, 88%) and **1** (180 mg, 85%). The distilled acid (46 mg, 45%) exhibited a rotation consistent with the diastereomeric content of the substrate: $[\alpha]_D$ = −20.7 (*c* 5.30, EtOH) {lit.[49] $[\alpha]_D$ = −18 (*c* 0.77, EtOH)}; ^1H NMR δ 0.94 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.17 (d, *J* = 7.5 Hz, 3 H, $CHCH_3$), 1.42–1.47 (dq, *J* = 7.2, 7.2 Hz, 1 H), 1.63–1.77 (dq, *J* = 7.2, 7.2 Hz, CH_2CH_3), 2.31–2.46 (m, 1 H, C*H*CH_3), 8.9 (br s, 1 H, COO*H*); ^{13}C NMR δ 11.6, 16.5, 26.6, 40.9, 183.0; IR (thin film) 3306, 1708 cm^{-1}.

(2*R*)-2-*tert*-Butyl-3-[(*R*)-2-methylbutyryl]-2,3-dihydro-4(1*H*)-pyrimidinone (38).[59] Compound **29a** (0.331 g, 1.12 mmol) was dissolved in methanol (30 mL) and cooled in an ice bath. Sodium hydroxide (45 mg, 1.12 mmol) was dissolved in water (1 mL), and this solution was added slowly to the heterocycle/methanol solution at 4 °C. The resulting mixture was stirred at 4 °C for 40 min, at which time it was partitioned between water (5 mL) and ether (20 mL). The aqueous layer was washed with ether (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to afford a white solid, which was recrystallized (acetone/H_2O, 215 mg, 81%). ^1H NMR analysis indicated small amounts of a compound presumed to be **38b**: mp 133–135 °C; $[\alpha]_D$ = +104.5 (*c* 1.22, CH_2Cl_2); ^1H NMR δ 0.78 (t, *J* = 7 Hz, 3 H, CH_2CH_3), 0.91 (s, 9 H, C_4H_9), 1.22 (d, *J* = 7 Hz, 3 H, $CHCH_3$), 1.28 (m, 1 H, C*H*HCH_3), 1.62 (m, 1 H, CH*H*CH_3), 3.43 (m, 1 H, COC*H*), 4.80 (d, *J* = 6.2 Hz, 1 H, COC*H*=CH), 5.81 (br s, 2 H, C*H*C_4H_9 and N*H*), 7.02 (m, 1 H, COCH=C*H*); ^{13}C NMR δ 12.2, 17.6, 26.2, 27.5, 40.0, 42.1, 69.0, 94.7, 146.6, 167.2, 179.8; IR ($CHCl_3$ solution) 3121, 1740, 1634 cm^{-1}; UV λ_{max} = 230, 320 nm. HRMS calcd for $C_{21}H_{28}N_2O_4$ − 1: 371.19721. Found: 371.20193.

(2*R*)-2-*tert*-Butyl-3-[(*S*)-2-methyl-3-phenylpropionyl]-2,3-dihydro-4-(1*H*)-pyrimidinone (39). Following the procedure above for **29a**, compound **32** (300 mg, 0.833 mmol) was treated with an equivalent molar amount of NaOH solution (1 mL). Isolation and recrystallization (acetone/H_2O) afforded **39** as a single isomer: mp 156–158 °C: $[\alpha]_D$ = +243 (*c* 1.12, CH_2Cl_2); ^1H NMR δ 0.91 (s, 9 H, C_4H_9), 0.99 (d, *J* = 7.0 Hz, 3 H, COCHCH_3), 2.50 (m, 1 H, C*H*C_6H_5), 3.40 (m, 1 H, C*H*C_6H_5), 3.94 (m, 1 H, COC*H*CH_3), 4.82 (d, *J* = 6.2 Hz, 1 H, COC*H*=CH), 5.86 (d, *J* = 5.0 Hz, 1 H, C*H*C_4H_9), 5.93 (br s, 1 H, N*H*), 7.01 (m, 1 H, COCH=C*H*), 7.27 (m, 5 H, aromatic); ^{13}C NMR δ 16.4, 25.5, 40.1, 40.5, 41.3, 68.9, 92.7, 126.1, 128.2, 129.4, 140.1, 146.6, 165.9, 178.1; IR ($CHCl_3$ solution) 3065, 1748, 1690 cm^{-1}. HRMS calcd for $C_{18}H_{24}N_2O_2$: 300.18392. Found: 300.18450.

(*S*)-2-Methyl-3-phenylpropionic acid (37). (a) Heterocycle **32** (346 mg, 1.0 mmol) was deacylated under conditions identical to those described above for **36**. Chromatographic isolation (9:1 hexanes/EtOAc) yielded **37** as a yellowish oil (157 mg; 95%) and the auxiliary as a slightly

(59) Compound **38a** is the enantiomer of **12**.

off-white oily solid (88%). Distillation of the acid gave a colorless liquid (128 mg; 77%): $[\alpha]_D$ = +17.7 (c 2.37, EtOH) {lit.[49] $[\alpha]_D$ = +17.87 (c 5.30, EtOH)}; ^{1}H NMR δ 1.22 (d, J = 6.9 Hz, 3 H, CH_3CHCOOH), 2.67-2.86 (m, 2 H, $C_6H_5CH_2$), 7.23-7.35 (m, 5 H, aromatic), 11.08 (br s, 1 H, COOH); ^{13}C NMR δ 16.6, 39.4, 41.4, 126.5, 128.5, 129.1, 139.2, 182.9; IR (thin film) 3400, 1703 cm^{-1}. HRMS (EI) calcd for $C_{10}H_{12}O_2$: 164.08376. Found: 164.08382.

(b) Heterocycle **39** (100 mg, 0.331 mmol) was deacylated under conditions identical to those described above for **36**. TLC showed the reaction to be complete in 30 min, and methyl chloroformate (28 μL, 0.36 mmol) was added; the resulting mixture was allowed to stir at room temperature for 4 h. Workup as described for **36** preceded drying of the organic layer ($MgSO_4$), filtration, and evaporation of solvent to afford **1** (530 mg, 76%). The aqueous layer was acidified with HCl and extracted with CH_2Cl_2. Drying of the organic layer ($MgSO_4$), filtration, and evaporation of solvent gave **37** (48 mg, 85%).

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Supplementary Material Available: Crystallographic data for **1** and **11** (14 pages). Ordering information is given on any current masthead page.

Triethylamine-Photosensitized Reduction of a Ketone via a Chemical Sensitization Mechanism[1]

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Abstract: Photolysis of acetonitrile solutions of 3β-hydroxy-5α-androstan-17-one (**1**), or its 3β-methoxy analogue (**5**), and triethylamine (TEA) with 254-nm light leads to reduction of the 17-keto group with high stereoselectivity. By contrast, Norrish type I products are exclusively observed when the photolysis is carried out in cyclohexane, and products from both α-cleavage and reduction are observed in ether or THF. Excitation of TEA in acetonitrile results in the photoionization of the amine to form a radical cation and a solvent radical anion. Several possible mechanisms for reduction of ground-state ketones by these species, or radicals derived therefrom, are outlined. The limiting quantum efficiency for reduction of **1** is 0.17. The results observed in cyclohexane are explained by singlet-singlet energy transfer from the TEA excited state to the ketone, while both photoionization and energy transfer appear to be operating in the ethereal solvents.

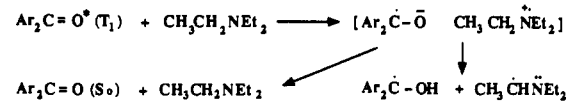
The photoreduction of aromatic ketones by aliphatic amines has been a subject of extensive investigation.[2-4] Early studies by Cohen and co-workers,[5-7] as well as more recent studies,[8-11] have demonstrated that a radical ion pair is generated through electron transfer from the ground-state amine to the photoexcited ketone, followed by proton transfer from the amine radical cation to the ketyl species (Scheme I). Tertiary amines, such as triethylamine (TEA), have frequently been used in these reactions.[12,13]

However, amines are themselves readily excited in the near UV, and although the photophysics of aliphatic amines has been thoroughly investigated,[14-16] very little attention has been paid to the photochemical consequences of *amine* excitation in the presence of other functionalities, such as ketones.[17,18] We now report a new mechanism for the photoreduction of ketones involving photoexcitation of an amine followed by ionization of the amine (i.e., for triethylamine: formation of $TEA^{\bullet+}$). Photoinduced reductions wherein the target functionality reacts through ground-state chemistry have been referred to as proceeding through "chemical sensitization",[19,20] as exemplified by the benzophenone-sensitized photoreduction of aryl-*N*-alkylimines,[19,21a] dibenzoylethylene,[21b] and acridine.[21c]

Results and Discussion

Photoreduction of Steroidal Ketones via Excitation of TEA. When 3β-hydroxy-5α-androstan-17-one (**1**) and TEA are irradiated with 254-nm light, using a ca. 10:1 ratio of amine to ketone such that the TEA absorbs 99% of the incident light,[22] one obtains

Scheme I. Mechanism for Reduction of a Ketone Excited State by an Amine



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