Tetrahedron Vol. 49, No. 41, pp. 9183-9190, 1993
Printed in Great Britain

0040-4020/93 \$6.00+.00

Self-Reproduction of Chirality. Asymmetric Synthesis of β-Alkyl-β-Amino Acids From Enantiomerically Pure Dihydropyrimidinones

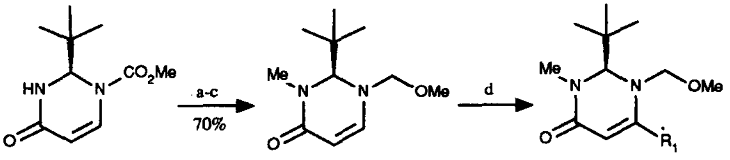
Kent S. Chu and Joseph P. Konopelski*‡

Department of Chemistry and Biochemistry
University of California, Santa Cruz, CA 95064

(*Received in USA* 8 *February* 1993; *accepted* 1 *June* 1993)

Abstract: Enantiomerically pure heterocycle **2** is deprotonated at C6 with *tert*-butyllithium at -78 °C. The resulting carbanion reacts with alkyl halides and aldehydes to give the corresponding alkylated products. Reduction of the double bond followed by hydrolysis affords enantiomerically pure β-alkyl-β-amino acids.

Interest in the synthesis of β-amino acids is due largely to their presence in biologically active natural products[1] and their use as precursors to β-lactams.[2] As part of our synthetic effort toward (+)-jasplakinolide,[3] which contains the β-amino acid (*R*)-β-tyrosine,[4] we became intrigued with the prospect of a synthetic method in which introduction of the desired *carbon substituent* at the β-site could be achieved in an enantioselective manner. This approach contrasts with other methodologies, which develop the chiral center via conjugate addition of an amine to an α,β-unsaturated system,[5] reduction of a C=C or C=N functionality,[6] C-C bond formation involving imines and carbon nucleophiles,[7] or manipulation of an α-amino acid.[1f,8] In previous papers we described the synthesis of enantiomerically pure dihydropyrimidinone **1**,[9] which can be used both as a reagent for the synthesis of β-aryl-β-amino acids[10] and as a chiral auxiliary in asymmetric alkylation reactions.[11,12] We have now found that C6 of modified heterocycle **2** can be deprotonated at low temperature. Reaction of the resulting vinyl carbanion with electrophiles affords the corresponding alkylated products which, after reduction and hydrolysis, give β-amino acid derivatives. Herein we report our results.



1 **2** **3** R_1 = R or CH(OH)R

a) 1) *n*-BuLi, THF, -78 °C, 3h; 2) MeI, -78-23 °C, 3h; b) NaOH, MeOH-H_2O, 0 °C, 2h; c) 1) *n*-BuLi, THF, -78 °C, 3h; 2) $MeOCH_2Cl$, -78 °C, 3h; d) 1) 1.5 *t*-BuLi, THF, -78 °C, 2.5h; 2) 5 RX or RCHO, -78-23 °C, 12 h

‡ Dedicated to Professor Carl Djerassi on the occasion of his 70th birthday.

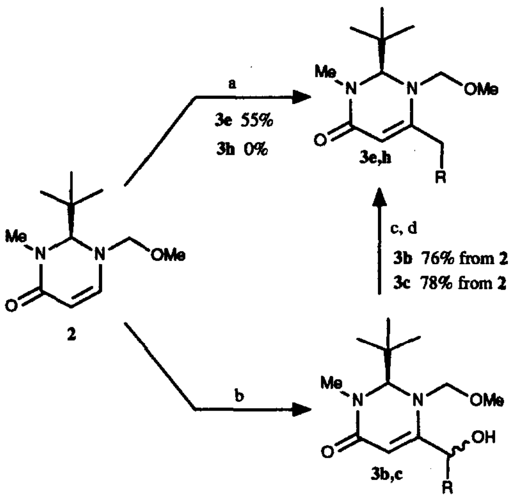
Compound **2** is derived from **1** by protecting the nitrogen atoms of the heterocycle with base-stable groups. First, the amide is deprotonated with *n*-butyllithium, followed by methylation with methyl iodide. This reaction requires at least three hours at room temperature. The carbomethoxy group in **1** is then cleaved with sodium hydroxide. The resulting amine is protected with the MOM group with an overall 70% yield from **1**. Excess chloromethyl methyl ether is to be avoided in this step for maximum yield.[13]

Compound **2** can be directly lithiated with *tert*-butyllithium at -78 °C in a manner similar to the β-aminoacrylic acid derivatives reported by Schmidt and coworkers.[14] The vinyl anion so formed is treated with electrophiles such as alkyl halides and aldehydes to give C6-substituted heterocycles. Results of these reactions are summarized in the table below. Methylation is quite successful. Other alkyl halides afford yields that, while not as high, are still useful. Arylation with phenyl iodide affords modest amounts of product.[15] Treatment of **3d** with *tert*-BuLi/MeI afforded **3f**.[16,17]

Entry	Electrophile	yield of 3
a	CH_3CHO	81%
b	$(CH_3)_2CHCHO$	85%
c	PhCHO	84%
d	CH_3I	95%
e	$PhCH_2Br$	55% (78%[a])
f	CH_3CH_2I	55%
g	PhI	27%
h	$(CH_3)_2CHCH_2I$	0% (76%[b])

a) Substrate prepared from **3c**, see adjacent sketch

b) Substrate prepared from **3b**, see adjacent sketch

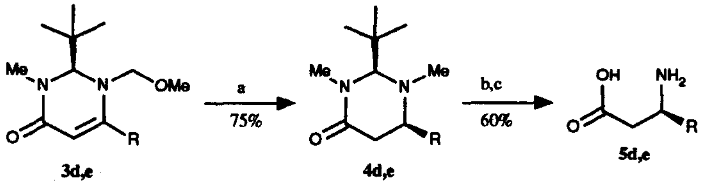


a) *t*-BuLi, RX; b) *t*-BuLi, RCHO; c) $(AcO)_2O$, pyridine; d) $NaBH_4$

Aldehydes are excellent electrophiles in this reaction. The product alcohols (as a mixture of diastereomers which can be separated on column chromatography[18]) can be converted to their corresponding acetates by treatment with acetic anhydride. The acetate group can then be reduced with sodium borohydride in high yield to afford the C6-alkylated heterocycles. Thus, whereas direct alkylation of the anion of **2** with isobutyl bromide is unsuccessful, the formation of **3b** and subsequent reduction of the derived acetate affords **3h** in 76% yield from **2** in enantiomerically pure form (*vide infra*). Likewise, the overall yield of **3e** is improved by this three step protocol.

Completion of the C6 alkylation studies of **2** indicated success in the production of β-alkyl-β-amino acids, inasmuch as the previous work from this laboratory on the production of enantiomerically pure β-aryl-β-amino acids had verified two important points. First, the *tert*-butyl group at C2 functions as an efficient steric barrier to reagent approach. Second, the product amino acids did not undergo racemization under strong acid treatment for amide and acetal cleavage. The production of known β-amino acids (*S*)-3-aminobutyric acid and (*S*)-3-amino-4-phenylbutyric acid was undertaken to exemplify these facts.

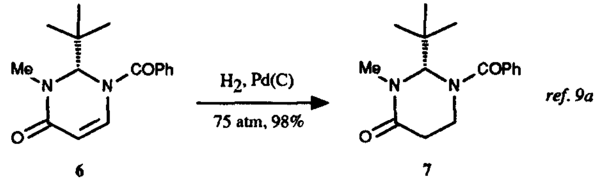
Although there are a few reports of reductions of similar substrates,[9a,19] hydrogenation of compound **3** was not straightforward. Attempted hydrogenation of **3d** using $Pd(OH)_2$, Pd-C, PtO_2, Raney Ni, and Rh on alumina as catalyst and with hydrogen pressure up to 50 psi gave no reaction. However, compounds **3d** and **3e** were cleanly reduced in good yield with sodium cyanoborohydride[19c] to corresponding saturated heterocycles **4**. The cis relationship between the *tert*-butyl group at C2 and the new chiral center at C6 was established by NMR (NOESY). High diastereomeric selectivity (>95%) was consistently observed. The temperature of this reduction is important; at higher temperatures (≥ 0 °C) the carbonyl group is also reduced. Unexpectedly, the MOM group is also reduced.[20]



a) $NaBH_3CN$, HCl, -30 °C, 2h; b) 3 CH_2=CHOCOCl, $ClCH_2CH_2Cl$, reflux, 5 h;
c) 6 *N* HCl, 100 °C, 2h

Demethylation of the amine nitrogen and hydrolysis were combined in the last step to give the desired β-amino acids **5**.[21] The heterocycle is first treated with vinyl chloroformate in refluxing 1,2-dichloroethane. The resulting carbamate is then refluxed with ethanolic HCl to achieve dealkylation, and after removal of the solvent the reaction mixture is hydrolyzed with 6*N* HCl to liberate the β-amino acids.[21]

In conclusion, the above route to β-alkyl-β-amino acids, coupled with the approach to β-aryl-β-amino acids already described,[10,12] allows for the production of diverse members of this important class of compounds in enantiomerically pure form. The present work offers the facility of adding what is likely to be a strategically important fragment (i.e., the β-carbon alkyl or aryl group) as an electrophile to an enantiomerically pure nucleophilic template late in the synthesis, thus simplifying the production of large numbers of related compounds. Recently, Enders[22] has published a strategically complementary approach involving an electrophilic chiral template/nucleophilic alkyl (aryl) coupling. In addition, Juaristi[9a] has recently published the stereospecific catalytic hydrogenation of **6** to **7** with hydrogen pressure of 75 atmospheres in 98% yield. The application of this protocol to **3**, followed by hydrolysis, would afford **5** in a shorter sequence in higher yield. Further work on the transformation of **3** to **5** and on the chemistry of **1** is in progress and will be reported in due course.



EXPERIMENTAL SECTION

General. Melting point determinations are reported uncorrected. Proton (^1H NMR) and carbon (^{13}C NMR) magnetic resonance spectra were recorded (in $CDCl_3$ unless otherwise noted) at 300 MHz and 75.5 MHz respectively. Ultraviolet (UV) spectra were recorded in methanol. Combustion analysis for carbon and hydrogen were performed by the staff at Atlantic MicroLabs, Norcross, Georgia.

Tetrahydrofuran (THF) and diethyl ether were distilled from sodium metal/benzophenone immediately prior to use. For anhydrous reactions, $ClCH_2CH_2Cl$ was distilled from CaH_2 immediately prior to use. Pyridine was distilled from calcium hydride and stored over KOH.

Alkyllithium reagents were titrated with 1,10-phenanthroline by the method of Watson and Eastham.[23] *n*-Butyllithium and *tert*-butyllithium were purchased as solutions in hexane. Unless otherwise indicated, all other reagents were used as received. All chromatographic separations were performed on silica gel.

(*S*)-2-*tert*-Butyl-1-methoxymethyl-3-methyl-2,3-dihydro-4(1*H*)-pyrimidinone (2). (*S*)-2-*tert*-Butyl-1-carbomethoxy-2,3-dihydro-4(1*H*)-pyrimidinone (**1**, 32.0 g, 0.15 mol) was dissolved in freshly distilled THF (750 mL) and cooled to -78 °C. *n*-Butyllithium (2.5 *M*, 60 mL, 0.15 mol) was added dropwise and the reaction was continued at -78 °C for 3 h. Methyl iodide (11.3 mL, 0.18 mol) was added slowly and the reaction was warmed to room temperature over 3 h. The resulting mixture was washed with brine (100 mL) and solvent was removed by evaporation.

The crude methylated heterocycle was dissolved in MeOH (200 mL) and cooled to 4 °C. Sodium hydroxide solution (prepared by dissolving 9.0 g NaOH in 150 mL water, 0.22 mol) was added dropwise. The reaction was stirred at that temperature for 40 min and checked by TLC to ensure complete reaction. Aqueous hydrochloric acid solution (6.0 *N*, 36 mL, 0.22 mol) was carefully added to the reaction mixture (with cooling) to bring the solution to a final pH of 7. The mixture was extracted with ether, dried over $MgSO_4$, and evaporated to afford 20.5 g (82%).

The product from the above reaction (18.6 g, 0.11 mol) was dissolved in THF (500 mL) and cooled to -78 °C. *n*-Butyllithium (2.5 *M*, 44 mL, 0.11 mol) was added. The reaction was continued at that temperature for 3 h. Chloromethyl methyl ether (8.46 mL, 0.11 mol) was added and the reaction was stirred at -78 °C for 3 h. The mixture was washed with brine and solvent evaporated at below 40 °C under reduced pressure. The residue was purified by chromatography [EtOAc/hexanes/MeOH (50/45/5)] twice, yielding the product as a slightly yellow crystalline solid: mp: 84-5 °C; $[\alpha]_D$ = +441 (c 0.78, EtOAc); ^1H NMR: δ 0.96 (s, 9H, CC_4H_9), 3.10 (s, 3H, NMe), 3.26 (s, 3H, OMe), 4.33 (d, *J* = 1.5 Hz, 1H, NC*H*N), 4.45 (AB system, 2H, $-CH_2-$), 5.00 (d, *J* = 7.3 Hz, 1H, C*H*=C-N), 6.68 (dd, *J* = 7.3, 1.5 Hz, 1H, C=C*H*); ^{13}C NMR: δ 26.4, 37.7, 42.5, 55.8, 82.9, 86.3, 99.2, 136.6, 144.6; UV: λ_{max} = 235, 290 nm; IR(KBr): 2950, 1700, 1378 cm^{-1}. Anal. calcd for $C_{11}H_{20}N_2O_2$: C, 62.24; H, 9.50. Found: C, 62.33; H, 9.53.

General procedure for the alkylation of 2. (*S*)-2-*tert*-Butyl-6-(1-hydroxyethyl)-1-methoxymethyl-3-methyl-2,3-dihydro-4(1*H*)-pyrimidinone (3a). Compound **2** (77 mg, 0.36 mmol) was dissolved in THF (5 mL) and cooled to -78 °C. *tert*-Butyllithium (1.7 *M*, 0.32 mL, 1.5 equiv) was added dropwise and the reaction was stirred at that temperature for 2.5 h. Acetaldehyde (0.1 mL, 5 equiv) was added dropwise and the reaction was allowed to warm to room temperature overnight. Saturated sodium bicarbonate solution was added and the mixture was extracted with ethyl ether (20 mL). The ether layer was washed with saturated NaCl solution and dried over $MgSO_4$. Purification by chromatography (EtOAc) afforded the desired material (78 mg, 81%): major isomer: $[\alpha]_D$ = +31 (c 0.2, EtOAc); ^1H NMR: δ 0.95 (s, 9H, CC_4H_9), 1.41 (d, *J* = 6 Hz, 3H, $-CHCH_3$), 3.07 (s, 3H, NMe), 3.26 (s, 3H, OMe), 4.23 (s, 1H, NC*H*N), 4.48 (m, 1H, -C*H*OH), 4.26 (d, *J* = 10.7 Hz, 1 H, $-CH_2$), 5.07 (d, *J* = 10.7 Hz, 1 H, $-CH_2$), 5.21 (s, 1H, C*H*=C-N); ^{13}C NMR: δ 20.4, 26.5, 37.2, 42.1, 55.4, 66.4, 84.1, 85.8, 101.3, 156.2, 161.0; IR (thin film): 3325, 2950, 1630, 1285 cm^{-1}; HRMS (EI): calcd for $C_{13}H_{24}N_2O_3$-1: 255.17099. Found: 255.17098.

(*S*)-2-*tert*-Butyl-6-(1-hydroxy-2-methylpropyl)-1-methoxymethyl-3-methyl-2,3-dihydro-4(1*H*)-pyrimidinone (3b). Analysis by ^1H and ^{13}C NMR of the crude product indicated a 3:2 mixture of isomers at the new chiral center. The product was purified by chromatography (EtOAc), giving the pure isomers as colorless oils: isomer 1: $[\alpha]_D$ = +45 (c 0.3, EtOAc); ^1H NMR: δ 0.93 (s, 9H, CC_4H_9), 0.98 (d, *J* = 6.7 Hz, 3H, $-CHCH_3$), 1.08 (d, *J* = 6.7 Hz, 3H, $-CHCH_3$), 1.90 (m, 1H, -C*H*-), 3.04 (s, 3H, NMe), 3.24 (s, 3H, OMe), 3.95 (m, 1H, -C*H*OH), 4.23 (s, 1H, NC*H*N), 4.22 (d, *J* = 10.7 Hz, 1 H, $-CH_2$), 5.02 (d, *J* = 10.7 Hz, 1 H, $-CH_2$), 5.42 (s, 1H, C*H*=C-N); ^{13}C NMR: δ 16.4, 20.9, 26.5, 32.0, 37.2, 41.4, 55.5, 73.5, 83.0, 85.7, 99.9, 158.1, 165.2; IR (thin film): 3330, 2954, 1631, 1484, 1468, 1390, 1161, 1067 cm^{-1}; HRMS (EI): calcd for $C_{14}H_{24}N_2O_2$ (M^+-CH_3OH): 252.1832. Found: 252.1837.

isomer 2: $[\alpha]_D$ = +22 (c 0.2, EtOAc); ^1H NMR: δ 0.97 (s, 9H, CC_4H_9), 1.00 (d, *J* = 6.7 Hz, 3H, $-CHCH_3$), 1.03 (d, *J* = 6.7 Hz, 3H, $-CHCH_3$), 2.03 (m, 1H, -C*H*-), 3.10 (s, 3H, NMe), 3.27 (s, 3H, OMe), 3.99 (m, 1H, -C*H*OH), 4.24 (s, 1H, NC*H*N), 4.17 (d, *J* = 10.6 Hz, 1 H, $-CH_2$), 4.88 (d, *J* = 10.6 Hz, 1 H, $-CH_2$), 5.23 (s, 1H, C*H*=C-N); ^{13}C NMR: δ 17.4, 20.4, 26.6, 30.3, 37.2, 41.7, 55.4, 75.3, 83.9, 85.6, 102.1, 154.9, 164.9. IR (thin film): 3335, 2950, 1633, 1165 cm^{-1}.

(*S*)-2-*tert*-Butyl-6-(1-hydroxybenzyl)-1-methoxymethyl-3-methyl-2,3-dihydro-4(1*H*)-pyrimidinone (3c). Analysis by ^{1}H and ^{13}C NMR of the crude product indicated a 3:2 mixture of isomers at the new chiral center. The product was purified with silica gel (EtOAc), giving the pure isomers as colorless oils: isomer 1: $[\alpha]_D$ = +75 (c 0.4, EtOAc); ^{1}H NMR: δ 0.89 (s, 9H, CC_4H_9), 3.03 (s, 3H, NMe), 3.22 (s, 3H, OMe), 4.20 (s, 1H, NC*H*N), 4.16 (d, *J* = 10.6 Hz, 1 H, -CH_2), 5.10 (d, *J* = 10.6 Hz, 1 H, -CH_2), 4.87 (s, 1H, C*H*=C-N), 5.43 (s, 1H, -C*H*OH), 7.31 (m, 5H, aromatics); ^{13}C NMR: δ 26.5, 37.1, 41.9, 55.4, 73.3, 83.7, 85.4, 103.7, 127.1, 128.2, 128.5, 139.9, 154.4, 165.1; IR (thin film): 3295, 2943, 1642, 1537, 1454, 1396, 1237, 1049 cm^{-1}; HRMS (EI): calcd for $C_{18}H_{24}N_2O_2$ (M^+-H_2O): 300.1838. Found: 300.1838.
isomer 2: $[\alpha]_D$ = +42 (c 0.2, EtOAc); ^{1}H NMR: δ 0.68 (s, 9H, CC_4H_9), 3.02 (s, 3H, NMe), 3.16 (s, 3H, OMe), 4.14 (s, 1H, NC*H*N), 4.16 (d, *J* = 10.6 Hz, 1 H, -CH_2), 4.92 (d, *J* = 10.6 Hz, 1 H, -CH_2), 5.51 (s, 1H, C*H*=C-N), 5.65 (s, 1H, -C*H*OH), 7.35 (m, 5H, aromatics); ^{13}C NMR: δ 26.1, 37.0, 41.4, 55.5, 71.2, 83.0, 84.9, 100.5, 126.5, 127.9, 128.4, 140.8, 158.5, 165.5; IR (thin film): 3285, 2940, 1640, 1100 cm^{-1}.

(*S*)-2-*tert*-Butyl-1-methoxymethyl-3,6-dimethyl-2,3-dihydro-4(1*H*)-pyrimidinone (3d). The product is a white crystalline solid: mp: 90-93 °C; $[\alpha]_D$ = +394 (c 0.6, EtOAc); ^{1}H NMR: δ 0.88 (s, 9H, CC_4H_9), 1.94 (s, 3H, -CH_3), 3.04 (s, 3H, NMe), 3.20 (s, 3H, OMe), 4.19 (s, 1H, NC*H*N), 4.17 (d, *J* = 11.2 Hz, 1 H, -CH_2), 4.84 (d, *J* = 11.2 Hz, 1 H, -CH_2), 4.94 (s, 1H, C*H*=C-N); ^{13}C NMR: δ 18.5, 26.4, 37.1, 42.1, 55.2, 82.8, 85.3, 101.6, 151.7, 164.9; MS(EI): 226, 209, 169, 129, 96; IR (KBr): 2935, 1703, 1281 cm^{-1}; HRMS (EI): calcd for $C_{12}H_{22}N_2O_2$: 226.1681. Found: 226.1681.

(*S*)-6-Benzyl-2-*tert*-Butyl-1-methoxymethyl-3-methyl-2,3-dihydro-4(1*H*)-pyrimidinone (3e). Procedure 1: The general procedure for the alkylation of **2** was employed. The product was purified by chromatography (EtOAc) as a colorless oil.
Procedure 2: Compound **3c** (1.01 g, 3.18 mmol, mixture of isomers) was dissolved in THF (2 mL) and acetic anhydride (0.3 mL, 3.49 mmol) was added. After stirring at room temperature for 2 h, the reaction mixture was diluted with ether (20 mL) and washed with saturated $NaHCO_3$ solution. The organic portion was dried ($MgSO_4$) and solvent was removed by evaporation. The residue was dissolved in MeOH (15 mL) and sodium borohydride (0.60 g, 15.6 mmol) was added. The reaction mixture was stirred at room temperature for 4 h, extracted with ether and purified by chromatography (EtOAc), affording **3e** as a colorless oil: $[\alpha]_D$ = +284 (c 0.3, EtOAc); ^{1}H NMR: δ 0.83 (s, 9H, CC_4H_9), 3.07 (s, 3H, NMe), 3.22 (s, 3H, OMe), 3.58 (m, 2H, -CH_2-Ph), 4.18 (s, 1H, NC*H*N), 4.12 (d, *J* = 11.2 Hz, 1 H, -CH_2), 4.95 (d, *J* = 11.2 Hz, 1 H, -CH_2), 4.97 (s, 1H, C*H*=C-N), 7.23 (m, 5H, aromatic); ^{13}C NMR: δ 26.5, 36.2, 38.5, 41.9, 55.4, 83.0, 85.5, 102.8, 127.1, 128.3, 129.1, 136.2, 165.0; IR (thin film): 2950, 2920, 1685, 1135 cm^{-1}; HRMS (EI): calcd for $C_{18}H_{26}N_2O_2$+1: 303.2072. Found: 303.2072.

(*S*)-2-*tert*-Butyl-6-ethyl-1-methoxymethyl-3-methyl-2,3-dihydro-4(1*H*)-pyrimidinone (3f). The product is isolated as a colorless oil: $[\alpha]_D$ = +341 (c 0.2, EtOAc); ^{1}H NMR: δ 0.90 (s, 9H, CC_4H_9), 1.11 (t, *J* = 7.1 Hz, 3H, -CH_2CH_3), 2.32 (m, 2H, -CH_2CH_3), 3.06 (s, 3H, NMe), 3.22 (s, 3H, OMe), 4.20 (s, 1H, NC*H*N), 4.17 (d, *J* = 11.2 Hz, 1 H, -CH_2), 4.82 (d, *J* = 11.2 Hz, 1 H, -CH_2), 5.05 (s, 1H, C*H*=C-N); ^{13}C NMR: δ 11.9, 24.9, 26.5, 37.2, 42.1, 55.4, 82.6, 85.1, 100.6, 151.7; IR (thin film): 2940, 1698, 1280 cm^{-1}; HRMS (EI): calcd for $C_{13}H_{24}N_2O_2$+1: 241.1960. Found: 241.1952.

(*S*)-2-*tert*-Butyl-1-methoxymethyl-3-methyl-6-phenyl-2,3-dihydro-4(1*H*)-pyrimidinone (3g). The product was isolated as a colorless oil: $[\alpha]_D$ = +290 (c 1.2, EtOAc); ^{1}H NMR: δ 1.05 (s, 9H, CC_4H_9), 3.16 (s, 3H, NMe), 3.18 (s, 3H, OMe), 4.39 (s, 1H, NC*H*N), 4.38 (AB system, 2H, -CH_2-), 5.45 (s, 1H, C*H*=C-N), 7.43 (m, 5H, phenyl); ^{13}C NMR: δ 26.6, 36.9, 41.7, 56.4, 82.8, 84.3, 104.4, 128.4, 129.1, 130.4, 135.2, 155.5; IR (KBr): 2925, 1665 cm^{-1}; HRMS (EI): calcd for $C_{17}H_{24}N_2O_2$+1: 289.1916. Found: 289.1916.

(*S*)-2-*tert*-Butyl-1-methoxymethyl-3-methyl-6-(2-methylpropyl)-2,3-dihydro-4(1*H*)-pyrimidinone (3h). Procedure 1: the general procedure for the alkylation of **2** was employed. No desired material was obtained. Procedure 2: following procedure 2 for the synthesis of **3e** given above, the desired material was obtained in 88% yield from **3b** following chromatography (EtOAc): $[\alpha]_D$ = -23 (c 0.2, EtOAc); ^{1}H NMR: δ 0.95 (s, 9H, CC_4H_9), 0.99 (d, *J* = 6.5 Hz, 3H, $-CHCH_3$), 1.00 (d, *J* = 6.5 Hz, 3H, $-CHCH_3$), 1.88 (m, 1H, $CH(CH_3)_2$), 2.16 (m, 2H, CH_2CH), 3.10 (s, 3H, NMe), 3.26 (s, 3H, OMe), 4.24 (s, 1H, NC*H*N), 4.16 (d, *J* = 11.2 Hz, 1 H, $-CH_2$), 4.84 (d, *J* = 11.2 Hz, 1 H, $-CH_2$), 5.05 (s, 1H, C*H*=C-N); ^{13}C NMR: δ 22.6, 23.3, 26.3, 26.6, 37.2, 41.2, 55.4, 75.8, 82.4, 85.4, 101.8; IR (thin film): 2954, 1650, 1485, 1466, 1370 cm^{-1}; HRMS (EI): calcd for $C_{15}H_{28}N_2O_2$-1: 267.20725 Found: 267.20770.

(*S,S*)-2-*tert*-Butyl-1,3,6-trimethyl-4-pyrimidinone (4d). Compound **3d** (36.6 mg, 0.173 mmol) was dissolved in EtOH (3 mL) and cooled to -30 °C. Aqueous HCl (2 *N*, 1 equiv) was added. The mixture was allowed to stirred while $NaBH_3CN$ (40 mg, 4 equiv) was added. After stirring at that temperature for 4 h, the reaction was carefully neutralized with 2 *N* NaOH and extracted with ether. The product was purified by chromatography (1:1 EtOAc/hexanes) giving a colorless oil (30 mg, 75%): $[\alpha]_D$ = -26 (c 0.4, EtOAc); ^{1}H NMR: δ 0.92 (s, 9H, CC_4H_9), 1.1 (d, *J* = 6 Hz, 3H, $-CHCH_3$), 2.28 (AB part of ABX system, 2H, $-CH_2CH-$), 2.49 (s, 3H, NMe), 2.57 (X of ABX system, 1H, $-CH_2CH-$), 3.04 (s, 3H, CONMe), 3.55 (s, 1H, NC*H*N); ^{13}C NMR: δ 22.1, 27.1, 27.5, 39.2, 39.7, 46.1, 55.0, 90.6; IR (thin film): 2910, 1640, 1210 cm^{-1}; HRMS (EI): calcd for $C_{11}H_{22}N_2O$+1: 199.1810. Found: 199.1810.

(*S,S*)-6-Benzyl-2-*tert*-butyl-1,3-dimethyl-4-pyrimidinone (4e). Following the procedure for **4d** above, **4e** was obtained in 75% yield as a colorless oil: $[\alpha]_D$ = -38 (c 0.3, EtOAc); ^{1}H NMR: δ 0.84 (s, 9H, CC_4H_9), 2.23 (AB part of ABX system, 2H, $-CH_2CH-$), 2.62 (s, 3H, NMe), 2.72 (m, 1H, $-CH_2CH-$), 2.80 (AB part of ABX system, 2H, $-CH_2CH-$), 3.03 (s, 3H, CONMe), 3.58 (s, 1H, NC*H*N), 7.21 (m, 5H, aromatic); ^{13}C NMR: δ 27.1, 29.0, 36.5, 39.1, 41.1, 41.9, 46.6, 61.2, 90.6, 126.4, 128.2, 129.8, 137.6, 171.1; IR (thin film): 2935, 2900, 1640, 1180 cm^{-1}; HRMS (EI): calcd for $C_{17}H_{26}N_2O$+1: 275.2239. Found: 275.2123.

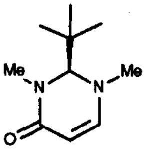
(*S*)-3-Aminobutyric acid (5d). Compound **5d** (100 mg, 0.51 mmol) was dissolved in 1,2-dichloroethane (30 mL) and Proton Sponge® (0.209 g, 1.0 mmol) was added, followed by vinyl chloroformate (0.128 mL, 1.5 mmol). After refluxing for 5 h, the solvent was evaporated under reduced pressure and the residue was dissolved in ether and washed with 1 *N* HCl, $NaHCO_3$, and brine. The urethane was taken up in EtOH (20 mL) and treated with saturated HCl/ethanol solution (20 mL). The resulting solution was then refluxed for 3 h, after which the solvent was removed and replaced with 6 *N* HCl. Heating was continued for 4 h at 100 °C. After cooling to 0 °C, the mixture was carefully neutralized with 2 *N* NaOH to pH 7. The desired product was obtained as a white solid (31 mg, 61%): mp: 196-7 °C; $[\alpha]_D$ = +38.2 (c 0.7, H_2O), literature[24] $[\alpha]_D$ = +38.8 (H_2O); ^{1}H NMR (MeOH-d_4): δ 1.24 (d, *J* = 7.4 Hz, 3H, $-CH_3$), 2.32 (m, AB of ABX, 2H, $-CH_2-$), 3.43 (m, X of ABX, 1H, -C*H*-); ^{13}C NMR: δ 18.8, 41.2, 46.7, 177.7; IR (KBr): 3300, 1680 cm^{-1}; MS (EI): 102, 86, 70, 58.

(*S*)-3-Amino-4-phenylbutyric acid (5e). Following the procedure above for **5d**, compound **5e** was obtained as a white solid (35 mg, 60%): mp: 230-2 °C; $[\alpha]_D$ = +8.2 (c 0.3, H_2O), literature[25] $[\alpha]_D$ = +8.5 (c 0.2, H_2O); ^{1}H NMR (D_2O): δ 2.55 (m, 2H, $-CH_2-$), 3.00 (m, 2H, $-CH_2-$), 3.80 (m, 1H, -C*H*-), 7.40 (aromatics, 5H); ^{13}C NMR: δ 39.5, 41.7, 57.1, 126.1, 128.0, 129.8, 144.2, 172.1; IR (KBr): 3040, 2930, 2880, 1568, 1535, 1419, 1403; MS (EI): 162, 117, 91, 88.

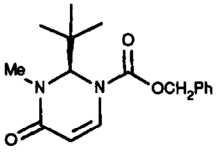
Acknowledgments. Research support by the National Institutes of Health (GM 45015) and the Donors of The Petroleum Research Fund, administered by the American Chemical Society (22854-AC1), is gratefully acknowledged.

NOTES AND REFERENCES

1. Some examples of natural products containing β-amino acids are: a) Blasticidin S: Yonehara, H.; Otake, N. *Tetrahedron Lett.* **1966**, 3785-91. b) Bleomycin: Hecht, S. M. *Acc. Chem. Res.* **1986**, *19*, 383-91. c) Bottromycin: Waisvisz, J. M.; van der Hoeven, M. G.; Nijenhuis, B. *J. Am. Chem. Soc.* **1957**, *79*, 4524-7. Kaneda, M. *J. Antibiot.* **1992**, *45*, 792-6, and references therein. d) Edeine: Hettinger, T. P.; Craig, L. C. *Biochemistry* **1966**, *7*, 4147-53. e) Scytonemin A: Helms, G. L.; Moore, R. E.; Niemczura, W. P.; Patterson, G. M. L.; Tomer, K. B.; Gross, M. L. *J. Org. Chem.* **1988**, *53*, 1298-1307. f) Taxol: Denis, J.-N.; Correa, A.; Greene, A.E. *J. Org. Chem.* **1991**, *56*, 6939-42.
2. a) Montgomery, J.; Wieber, G.M.; Hegedus, L.S. *J. Am. Chem. Soc.* **1990**, *112*, 6255-63. b) Liebeskind, L. S.; Welker, M. E.; Fengl, R. W. *J. Am. Chem. Soc.* **1986**, *108*, 6328-43.
3. Chu, K.S.; Negrete, G.R.; Konopelski, J.P. *J. Org. Chem.* **1991**, *56*, 5196-5202.
4. Parry, R.J.; Kurylo-Borowska, Z. *J. Am. Chem. Soc.* **1980**, *102*, 836-7.
5. a) Davies, S.G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183-6. b) Hawkins, J.M.; Lewis, T.A. *J. Org. Chem.* **1992**, *57*, 2114-21.
6. a) Lubell, W.D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543-54. b) Potin, D.; Dumas, F.; d'Angelo, J. *J. Am. Chem. Soc.* **1990**, *112*, 3483-6.
7. a) Davis, F.A.; Reddy, R.T.; Reddy, R.E. *J. Org. Chem.* **1992**, *57*, 6387-9. b) Laschat, S.; Kunz, H. *J. Org. Chem.* **1991**, *56*, 5883-9. c) Corey, E.J.; Decicco, C.P.; Newbold, R.C. *Tetrahedron Lett.* **1991**, *32*, 5287-90. d) Hua, D.H.; Miao, S.W.; Chen, J.S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4-6.
8. a) El Marini, A.; Roumestant, M.L.; Viallefont, Ph., Razafindramboa, D.; Bonato, M.; Follet *Synthesis*, **1992**, 1104-8. b) Dondoni, A.; Perrone, D.; Merino, P. *J. Chem. Soc., Chem. Commun.* **1991**, 1313-4. c) Gmeiner, P. *Tetrahedron Lett.* **1990**, *31*, 5717-20.
9. For other examples of pyrimidinones in the synthesis of β-amino acids, see: a) Juaristi, E.; Quintana, D. *Tetrahedron: Asymmetry* **1992**, *3*, 723-6, and references therein. b) Amoroso, R.; Cardillo, G,; Tomasini, C. *Tetrahedron Lett.* **1992**, *33*, 2725-8, and references therein.
10. Konopelski, J. P.; Chu, K. S.; Negrete, G. R. *J. Org. Chem.* **1991**, *56*, 1355-6.
11. Negrete, G. R.; Konopelski, J. P. *Tetrahedron: Asymmetry* **1991**, *2*, 105-8.
12. For a full account of the chemistry of **1**, see: Chu, K. S.; Negrete, G. R.; Konopelski, J. P.; Lakner, F. J.; Woo, N.-T.; Olmstead, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 1800-12.
13. A general, one-pot transformation of **1** to derivatives with different groups on the two nitrogen atoms has been developed (see reference 12). Inferior yields of **2** are obtained by this route; hence the multistep approach reported herein.
14. a) Schmidt, R. R.; Speer, H. *Tetrahedron Lett.* **1981**, *22*, 4259-62. b) Schmidt, R. R.; Hirsenkorn, R. *Tetrahedron* **1983**, *39*, 2043-54. c) Schmidt, R. R.; Talbiersky, J. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 853-4. d) Schmidt, R. R.; Talbeirsky, J. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 171-2. e) Schmidt, R. R. *Bull. Soc. Chim. Belg.* **1983**, *92*, 825-36.
15. The reaction may involve a benzyne intermediate. See House, H. O. *Modern Synthetic Reactions*, Second Edition; W. A. Benjamine: Menlo Park, 1972; 537-40.
16. (*S*)-2-*tert*-Butyl-1,3-dimethyl-2,3-dihydro-4(1*H*)-pyrimidinone (**i**) also undergoes this C6 methylation reaction (*tert*-BuLi, MeI). In contrast, (*S*)-2-*tert*-butyl-1-carbobenzoxy-3-methyl-2,3-dihydro-4(1*H*)-pyrimidinone (**ii**) affords a variety of undesired materials under identical conditions.
17. Seebach, D.; Misslitz, U.; Uhlmann, P. *Angew. Chem., Int Ed. Engl.* **1989**, *28*, 472-3.
18. Diastereomeric ratios varied from 4:1 for **3a** to 3:2 for **3b** and **3c**.



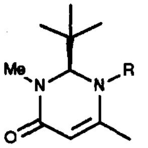
i



ii

19. a) Pizzorono, M. T.; Albonico, S. M. *J. Org. Chem.* **1974**, *39*, 731-2. b) R. Augustine, R.; Bellina, R.; Gustavsen, A. *J. Org. Chem* **1968**, *33*, 1287-8. c) Furukawa, M.; Okawara, T.; Noguchi, Y.; Terawaki, Y. *Chem. Pharm. Bull.* **1979**, *27*, 2223-6. d) Dietrich, R. F.; Sakurai, T.; Kenyon, G. *J. Org. Chem.* **1979**, *44*, 1894-6. e) Kim, S.; Oh, C.H.; Ko, J.S.; Ahn, K.H.; Kim, Y.J. *J. Org. Chem.* **1985**, *50*, 1927-32.

20. We briefly explored the deprotection of N1 prior to $NaBH_3CN$ reduction. When compound **3d** was treated with 1 equivalent $AlBr_3$/EtSH in an attempt to remove the MOM group, compound **iii** was obtained quantitatively. However, with excess reagents compound **iv** was isolated in low yield.



iii R = $CH_2SCH_2CH_3$
iv R = H

21. a) Mitch, C. H.; Zimmerman, D. M.; Snoddy, J. D.; Reel, J. K.; Cantrell, B. E. *J. Org. Chem.* **1991**, *56*, 1660-3. b) Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, 1567-70.
22. Enders, D. Klatt, M.; Funk, R. *Synlett* **1993**, 226-8.
23. Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165-8.
24. Balenovic, K.; Cerar, D.; Fuks, Z. *J. Chem. Soc.* **1952**, 3316-7.
25. Plucińska, K; Liberek, B. *Tetrahedron* **1987**, *43*, 3509-17.