α-Alkylation of (*S*)-Asparagine with Self-Regeneration of the Stereogenic Center: Enantioselective Synthesis of α-Substituted Aspartic Acids[1,2]

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A convenient method for the α-alkylation of (*S*)-asparagine with "self-regeneration of the stereogenic center" is described. The synthetic protocol involves stereoselective conversion of (*S*)-asparagine into enantiopure imino ether (2*S*,6*S*)-**9**, which is then alkylated with complete diastereoselectivity to give trans products **10**−**13** in good yields. Hydrolysis of these alkylated heterocycles is accomplished under mild acidic conditions to give the desired, enantiopure α-alkyl aspartic acids in excellent yields.

Introduction

In recent years, the preparation of enantiopure α,α-dialkylated α-amino acids has attracted considerable attention in view of the interesting chemical and biological properties exhibited by these compounds. For example, α,α-dialkylated derivatives of proteinogenic amino acids are efficient inhibitors of those enzymes that metabolize the natural substrates.[3] Furthermore, incorporation of α,α-dialkylated α-amino acids into peptides leads to modified backbone conformations,[4] with increased lipophilicity[5] and increased resistance to both enzymatic and chemical hydrolysis.[6]

Because of their relevant role in physiological events, aspartic acid derivatives are especially interesting subjects for study. Indeed, several methods have been reported that describe the enantioselective synthesis of α-alkylated aspartic acids. Fadel and Salaün[7,8] achieved this goal via the alkylation of oxazolidinones, **1**, with ethyl bromoacetate. Aebi and Seebach[9] alkylated instead imidazolidinones, **2**, whereas Crich and co-workers[10] employed (*S*)-tryptophan derivatives, **3**. Finally, Georg and co-workers[11] demonstrated that the Schmidt rearrangement of α,α-bis-alkylated β-keto esters, **4**, provides an alternative method (Scheme 1).[12]

Recently, (*S*)-asparagine was condensed with pivalaldehyde to afford pyrimidinone **5**,[13] which was then protected, decarboxylated, and hydrogenated to give (*S*)-**6**, a chiral derivative of β-amino propionic acid and a useful synthon for the enantioselective synthesis of α-alkylated β-amino acids[14] (Scheme 2). The present paper describes a convenient application of suitable derivatives of heterocycle **5** in the preparation of enantiopure α-alkylated aspartic acids.

Results and Discussion

Condensation of (*S*)-asparagine with isobutyraldehyde[15] according to the literature procedure[1,13,14] was followed by in situ benzoylation with benzoyl chloride to afford crystalline **7**, in 50% yield for the two steps. The relative configuration in this heterocycle was assigned from the X-ray crystallographic analysis of the methyl ester derivative, **8**, obtained by reaction with 1 equiv of silver oxide and methyl iodide. The resulting structure presented a cis disposition of the isopropyl and carboxylate groups (Figure 1).[16] Thus, the absolute configuration is securely determined as (2*S*,6*S*)-**7** [and (2*S*,6*S*)-**8**] (Scheme 3).

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(1) Enantioselective synthesis of β-amino acids. 8. For part 7 see: Juaristi, E.; Quintana, D.; Balderas, M.; García-Pérez, E. *Tetrahedron*: *Asymmetry* **1996**, *7*, 2233−2246.

(2) Presented in part during the Fifth Chemical Congress of North America, Cancún, México, November 13, 1997. Special Topics in Organic Chemistry. In *Book of Abstracts*, Paper No. 1476.

(3) See, for example: Jung, M. J. In *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: New York, 1985; p 227.

(4) Paul, P. K. C.; Sukumar, M.; Bardi, R.; Piazzesi, A. M.; Valle, G.; Toniolo, C.; Balaram, P. *J. Am. Chem. Soc.* **1986**, *108*, 6363−6370.

(5) See, for example: Christensen, H. N.; Handlogten, M. E.; Vadgama, J. V.; de la Cuesta, E.; Ballesteros, P.; Trigo, G. C.; Avendaño, C. *J. Med. Chem.* **1983**, *26*, 1374−1378.

(6) See, for example: Turk, J.; Panse, G. T.; Marshall, G. R. *J. Org. Chem.* **1975**, *40*, 953−955.

(7) Fadel, A.; Salaün, J. *Tetrahedron Lett.* **1987**, *28*, 2243−2246.

(8) See, also: Altmann, E.; Nebel, K.; Mutter, M. *Helv. Chim. Acta* **1991**, *74*, 800−806.

(9) Aebi, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1507−1518.

(10) Chan, C.-O.; Crich, D.; Natarajan, S. *Tetrahedron Lett.* **1992**, *33*, 3405−3408.

(11) Georg, G. I.; Guan, X.; Kant, J. *Tetrahedron Lett.* **1988**, *29*, 403−406.

(12) More recently, Obrecht and co-workers described the availability of (*R*)- and (*S*)-α-alkyl aspartic acids using L-phenylalanine as resolving agent: Obrecht, D.; Bohdal, U.; Daly, J.; Lehmann, C.; Schönholzer, P.; Müller, K. *Tetrahedron* **1995**, *51*, 10883−10900.

(13) (a) Chu, K. S.; Negrete, G. R.; Konopelski, J. P. *J. Org. Chem.* **1991**, *56*, 5196−5202. (b) See, also: Konopelski, J. P. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997; Chapter 12, pp 249−259.

(14) (a) Juaristi, E.; Quintana, D. *Tetrahedron: Asymmetry* **1992**, *3*, 723−726. (b) See, also: Juaristi, E.; Seebach, D. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997; Chapter 13, pp 261−277.

(15) Owing to the high price of pivalaldehyde, we have substituted this aldehyde with isobutyraldehyde in the synthesis of some chiral analogues of pyrimidinone **6**: Madrigal, D. Ph.D. Thesis, CINVESTAV-IPN: México, 1996.

(16) The authors have deposited atomic coordinates for structures *cis*-**8** and (2*S*,6*S*)-**13** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, CB2 IEZ, U.K.

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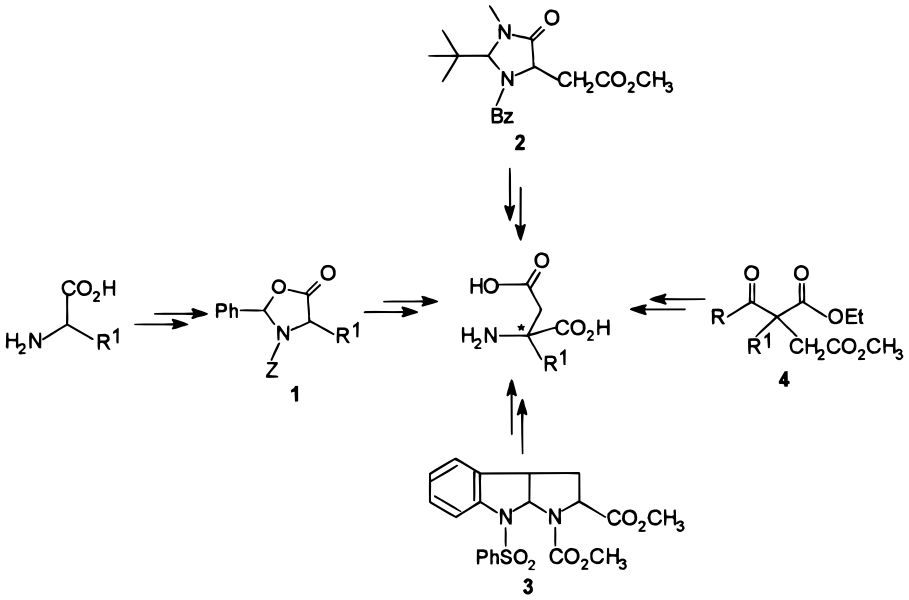
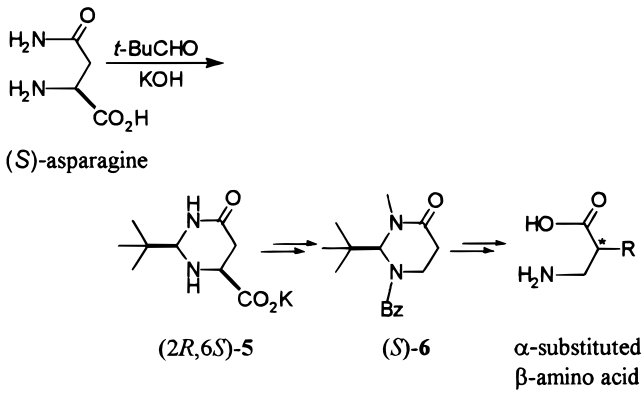
Scheme 1[a]

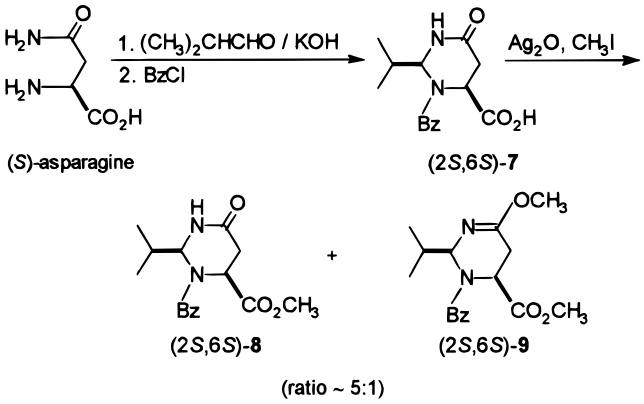


[a] Stereochemistry not indicated.

Scheme 2



Scheme 3



As shown in Scheme 3, in addition to the expected methyl carboxylate derivative **8**, imino ether (2*S*,6*S*)-**9** was produced in low yield (ca. 14.6%). It was realized that imino ether **9** could be a useful precursor of α-alkylated aspartic acids via alkylation at C(6), the most acidic position in the heterocycle, followed by hydrolysis (Scheme 4). In this regard, hydrolysis and isolation of the desired amino acids would be facilitated by the presence of the labile imino group.[17]

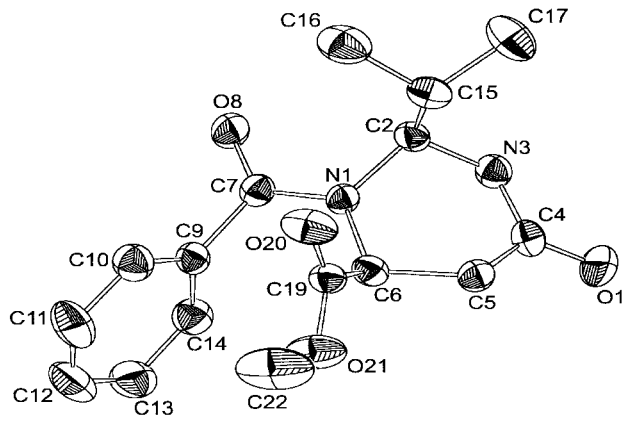


Figure 1. Structure and solid-state conformation of *cis*-1-benzoyl-2-isopropyl-6(*S*)-methyl carboxylate-tetrahydropyrimidin-4-one (*cis*-**8**).[16]

To obtain imino ether **9** as the main product, carboxylic acid **7** was treated with 2 equiv of silver oxide and 3 equiv of methyl iodide. As expected, the desired *O*-methylated ester **9** was obtained in 74% yield.

Fully characterized, enantiopure imino ether (2*S*,6*S*)-**9** was then examined as a potentially general, convenient substrate for the enantioselective synthesis of α-substituted aspartic acids. To this end, enolate (2*S*,6*S*)-**9**-Li was generated upon treatment of the heterocycle with lithium diisopropylamide (LDA), in THF solvent and under nitrogen atmosphere. The electrophile (methyl iodide, ethyl iodide, *n*-buthyl iodide, or benzyl bromide) was then added at −78 °C to afford the trans-alkylated products, apparently with complete diastereoselectivity.[18]

(17) (a) Compare mild conditions employed to hydrolyze bislactimethers: Schöllkopf, U.; Tiller, T.; Bardenhagen, J. *Tetrahedron* **1988**, *44*, 5293−5305. (b) Compare mild conditions used to hydrolyze dihydroimidazoles: Hoffmann, M.; Seebach, D. *Chimia* **1997**, *51*, 90−91. Blank, S.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1765−1766. (c) For related papers, see: Seebach, D.; Hoffmann, M.; Sting, A. R.; Kinkel, J. N.; Schulte, M.; Küsters, E. *J. Chromatogr. A* **1998**, *796*, 299−307. Hoffmann, M.; Blank, S.; Seebach, D.; Küsters, E.; Schmid, E. *Chirality* **1998**, *10*, 217−222.

Scheme 4

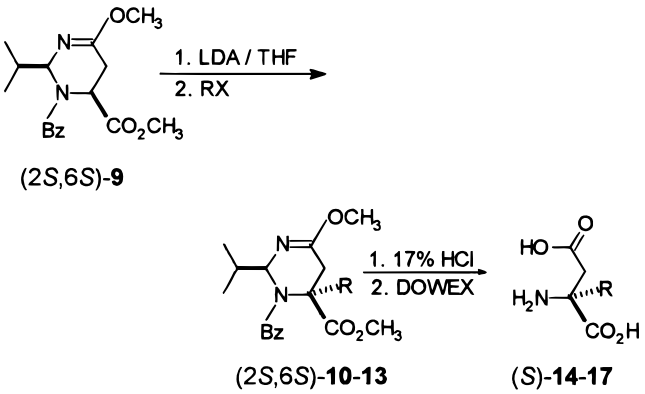
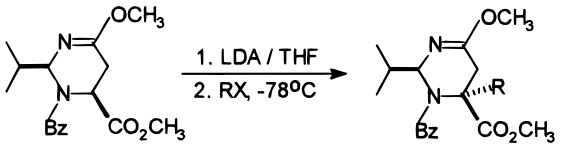


Table 1. Diastereoselectivity of Enolate (2*S*,6*S*)-9-Li Alkylations



product	RX	ds (%)	mp (°C)	$[\alpha]_D^{28°C}$	isolated yield (%)
(2*S*,6*S*)-**10**	CH_3I	>97	*a*	−47.0	52.4
(2*S*,6*S*)-**11**	CH_3CH_2I	>97	158−159	−67.0	61.8
(2*S*,6*S*)-**12**	*n*-C_4H_9I	>97	*a*	−20.0	59.7
(2*S*,6*S*)-**13**	$PhCH_2Br$	>97	122−124	+90.0	64.2

[a] Oil.

The trans configuration of the alkylated products [(2*S*,6*S*)-**10**−**13**; Scheme 4] was assigned by chemical correlation to known α-methyl and α-benzyl aspartic acids (see Experimental Section). Furthermore, an X-ray crystallographic structure of (2*S*,6*S*)-**13** (R = $PhCH_2$; Figure 2)[16] confirms the trans relative configuration between the benzyl and isopropyl groups. Table 1 summarizes the chemical yields and diastereoselectivities observed in the alkylation reaction, as well as some physical properties of the isolated products.

The high stereoselectivity encountered in the addition of (2*S*,6*S*)-**9**-Li to electrophiles is probably due to the steric hindrance generated by the isopropyl group at C(2), which directs addition on the opposite enolate face.[19] Indeed, $A^{1,3}$ strain in (2*S*,6*S*)-**9**-Li is responsible for the axial orientation of the isopropyl group, which effectively hinders syn addition.[20]

The final step of the overall conversion of (*S*)-asparagine to enantiopure (*S*)-α-alkyl aspartic acids (with self-regeneration of the stereogenic center[21]), the hydrolysis of the alkylated heterocycles **10**−**13**, was achieved by heating with 17% HCl in a sealed tube at 95 °C. The free amino acids **14**−**17** were purified by chromatography on an ion-exchange column (Table 2).

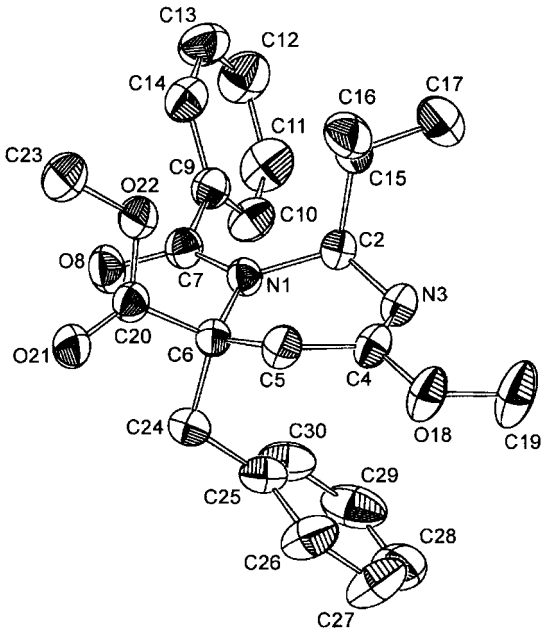
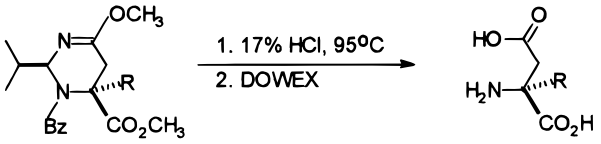


Figure 2. Structure and solid-state conformation of 1-benzoyl-2(*S*)-isopropyl-4-methoxy-6(*S*)-benzyl-6(*S*)-carbomethoxy-(1,2),(5,6)-tetrahypyrimidin-4-one [(2*S*,6*S*)-**13**].[16]

Table 2. Hydrolysis of Products 10−13 to Give α-Alkyl Aspartic Acids 14−17



R	yield of free amino acid (%)	mp of **14**−**17**	$[\alpha]_D^{28°C}$ of **14**−**17**
CH_3	83.8	175−176	+43.0
CH_3CH_2	80.0	165−167	+35.1
n-C_4H_9	88.3	180−182	+26.7
$PhCH_2$	95.4	240−242	+50.0

In summary, (*S*)-asparagine, an inexpensive chiral amino acid, was converted into the enantiopure pyrimidinone imino ether (2*S*,6*S*)-**9**, which was then alkylated with very high diastereoselectivity to give the products of trans addition of various electrophiles. Hydrolysis of the alkylated derivatives **10**−**13** was accomplished under mild acidic conditions to afford enantiopure α-alkyl aspartic acids **14**−**17**.

The present synthetic protocol constitutes a useful application of the so-called "self-regeneration of stereogenic centers" concept.

Experimental Section

General. Flasks, stirring bars, and hypodermic needles used for the generation and reactions of organolithiums were dried for about 12 h at 120 °C. Anhydrous THF was obtained by distillation from benzophenone ketyl.[22] The *n*-butyllithium

(18) A single product was detected by both ^1H and ^{13}C NMR spectroscopy (400 and 100 MHz, respectively).

(19) Compare (a) Juaristi, E.; Escalante, J.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1992**, *57*, 2396−2398. (b) Juaristi, E.; Escalante, J. *J. Org. Chem.* **1993**, *58*, 2282−2285. (c) Escalante, J.; Juaristi, E. *Tetrahedron Lett.* **1995**, *36*, 4397−4400.

(20) Compare (a) Juaristi, E.; Quintana, D.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 2553−2557. (b) Seebach, D.; Lamatsch, B.; Amstutz, R.; Beck, A. K.; Dobler, M.; Egli, M.; Fitzi, R.; Gautschi, M.; Herradón, B.; Hidber, P. C.; Irwin, J. J.; Locher, R.; Maestro, M.; Maetzke, T.; Mouriño, A.; Pfammatter, E.; Plattner, D. A.; Schickli, C.; Schweizer, W. B.; Seiler, P.; Stucky, G.; Petter, W.; Escalante, J.; Juaristi, E.; Quintana, D.; Miravitlles, C.; Molins, E. *Helv. Chim. Acta* **1992**, *75*, 913−934.

(21) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708−2748.

(22) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley: New York, 1975; p 256.

employed was titrated according to the method of Juaristi et al.[23] (4-biphenylmethanol indicator).

TLC. F_{254} silica gel plates; detection by UV light or iodine vapor. Flash column chromatography:[24] silica gel (230−400 mesh). All melting points are uncorrected. ^{1}H NMR spectra: JEOL FX-90Q (90 MHz), JEOL GSX-270 (270 MHz), and JEOL Eclipse-400 (400 MHz) spectrometers. ^{13}C NMR spectra: JEOL FX-90Q (22.5 MHz), JEOL GSX-270 (67.8 MHz), and JEOL Eclipse-400 (100 MHz) spectrometers. Optical rotations were measured in a Perkin-Elmer Model 241 polarimeter, using the sodium D-line (589 nm).

Elemental analyses were performed by Galbraith Laboratories, Inc., TN. The purity of new compounds **9**, **10**, **12**, **15**, and **16**, for which elemental analyses are not provided, was judged to be >97%, as evidenced by ^{1}H and ^{13}C NMR spectra (see Supporting Information).

1-Benzoyl-2(*S*)-isopropyl-6(*S*)-carboxy-1,3-perhydropyrimidin-4-one [(2*S*,6*S*)-7]. In a 1.0 L round-bottom flask was placed 15.0 g (113.5 mmol) of (*S*)-asparagine in 150 mL of dry methanol. A methanolic solution of KOH [6.4 g (113.5 mmol) in 35 mL of CH_3OH] was added, and the resulting solution was stirred at ambient temperature until complete dissolution of the amino acid (ca. 10 min). Isobutyraldehyde (10.8 mL, 113.5 mmol) was then added slowly, and the reaction mixture was heated to reflux for 10 h. The reaction flask was submerged in an ice−water bath before the addition of 4.76 g (67 mmol) of sodium bicarbonate and, dropwise, 13.2 mL (113.5 mmol) of benzoyl chloride. The reaction mixture was stirred at ambient temperature overnight, before treatment with 6 N HCl, until pH = 3.0. The precipitate that formed was filtered, and the solvent was removed at reduced pressure to give a pale yellow oil, which was dissolved in 500 mL of CH_2Cl_2, washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated. Crystallization from ethyl ether−hexane (95:5) gave 14.3 g (50% yield) of (2*S*,6*S*)-**7**, mp 175−177 °C. $[\alpha]_D^{28°C}$ = +156.0 (*c* = 1.0, CH_3OH). ^{1}H NMR (DMSO-d_6; 120 °C; 400 MHz) δ 0.81 (d, *J* = 7.0 Hz, 3 H, C**H$_3$**CHCH$_3$), 0.90 (d, *J* = 6.6 Hz, 3 H, CH$_3$CHC**H$_3$**), 2.04 (m, 1 H, CH$_3$C**H**CH$_3$), 2.71 (dd, J^1 = 8.4 Hz, J^2 = 16.9 Hz, 2 H, C**H$_2$**CO), 4.76 (t, *J* = 8.4 Hz, 1 H, NC**H**CO$_2$H), 4.88 (d, *J* = 9.9 Hz, 1 H, NC**H**N), 7.43 (m, 5 H, C$_6$**H$_5$**CO), 8.25 (s, 1 H, N**H**).^{13}C NMR (DMSO-d_6, 120 °C; 100 MHz), δ 19.2, 19.6, 32.3, 34.0, 53.5, 70.7, 126.9, 128.9, 130.1, 136.1, 168.2, 171.2, 172.3. Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.24. Found: C, 61.73; H, 6.46.

1-Benzoyl-2(*S*)-isopropyl-6(*S*)-carbomethoxy-1,3-perhydropyrimidin-4-one [(2*S*,6*S*)-8]. In a 25 mL round-bottom flask provided with magnetic stirrer, was placed 1.0 g (3.4 mmol) of carboxylic acid (2*S*,6*S*)-**7** and 0.82 g (3.4 mmol, 1.0 equiv) of silver oxide in 15 mL of dry THF. The resulting mixture was stirred at ambient temperature for 30 min, 0.32 mL (5.1 mmol, 1.5 equiv) of methyl iodide was added, and stirring was continued for 12 h. The reaction mixture was filtered over Celite (eluting with CH_2Cl_2) and concentrated at reduced pressure, and the product was purified by flash chromatography (hexanes−ethyl acetate, 2:1) to give 0.85 g (82.0% yield) of (2*S*,6*S*)-**8**, mp 158−159 °C. $[\alpha]_D^{28°C}$ = −149 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 60 °C, 400 MHz) δ 0.92 (d, *J* = 8.3 Hz, 3 H, C**H$_3$**CHCH$_3$), 0.99 (d, *J* = 8.3 Hz, 3 H, CH$_3$-CHC**H$_3$**), 2.0 (m, 1 H, CH$_3$C**H**CH$_3$), 2.71 (dd, J^1 = 4.6 Hz, J^2 = 4.2 Hz, 1 H, C**H**H′), 2.86 (dd, J^1 = 4.5 Hz, J^2 = 4.2 Hz, 1 H, CH**H**′), 3.7 (s, 3 H, OC**H$_3$**), 4.94 (b, 1 H, NC**H**CO$_2$), 5.1 (b, 1 H, NC**H**N), 7.4 (s, 5 H, C$_6$**H$_5$**), 7.44 (s, 1 H, N**H**). ^{13}C NMR ($CDCl_3$, 60 °C, 100 MHz), δ 18.8, 19.0, 32.0, 34.4, 52.5, 53.1, 70.8, 126.7, 128.7, 130.1, 135.1, 168.2, 171.1, 171.2. Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.13; H, 6.62. Found: C, 62.75; H, 6.70.

1-Benzoyl-2(*S*)-isopropyl-4-methoxy-6(*S*)-carbomethoxy-(1,2)(5,6)-tetrahydro-1,3-pyrimidine [(2*S*,6*S*)-9]. In a 100 mL round-bottom flask provided with magnetic stirrer was placed 5.0 g (17.2 mmol) of carboxylic acid (2*S*,6*S*)-**7** and 8.2 g (35.3 mmol, 2.05 equiv) of silver oxide in 50 mL of dry THF. The resulting mixture was stirred at ambient temperature for 30 min, 3.2 mL (51.6 mmol, 3 equiv) of methyl iodide was added, and stirring was continued for 72 h. The reaction mixture was filtered over Celite (eluting with CH_2Cl_2) and concentrated at reduced pressure, and the product was purified by flash chromatography (hexanes−ethyl acetate, 9:1) to give 4.1 g (74.2% yield) of imino ether (2*S*,6*S*)-**9** as a viscous oil. $[\alpha]_D^{28°C}$ = −71.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 100 °C, 400 MHz) δ 0.95 (d, *J* = 6.4 Hz, 3 H, C**H$_3$**CHCH$_3$), 0.97 (d, *J* = 7.7 Hz, 3 H, CH$_3$CHC**H$_3$**), 1.56 (m, 1 H, CH$_3$C**H**CH$_3$), 2.54 (ddd, J^1 = 17.2 Hz, J^2 = 8.1 Hz, J^3 = 1.4 Hz, 1 H, C**H**H′), 2.64 (dd, J^1 = 17.2 Hz, J^2 = 3.3 Hz, 1 H, CH**H**′), 3.64 (s, 3 H, OC**H$_3$**), 3.69 (s, 3 H, OC**H$_3$**), 4.97 (ddd, J^1 = 7.5 Hz, J^2 = 2.2 Hz, 1 H, NC**H**CO$_2$), 5.39 (d, *J* = 9.2 Hz, 1 H, NC**H**N), 7.44 (s, 5 H, C$_6$**H$_5$**). ^{13}C NMR (DMSO-d_6, 100 °C, 67.8 MHz) δ 19.8, 20.0, 26.5, 34.8, 51.5, 52.3, 52.6, 73.3, 126.9, 128.9, 129.9, 136.8, 159.2, 171.2, 171.4.

General Procedure for the Reaction of Pyrimidine Enolate [(2*S*,6*S*)-9-Li] with Electrophiles. A solution of (*i*-Pr)$_2$NH (1.0 equiv) in THF was cooled to −20 °C before the slow addition of 1.0 equiv of *n*-BuLi (ca. 1.8 M in hexane). The resulting solution was stirred at −20 °C for 20 min and then cooled to −78 °C before the dropwise addition of 1.0 equiv of imino ether (2*S*,6*S*)-**9** in THF. Stirring was continued for 1 h at −78 °C in order to secure the complete formation of the enolate. The alkylating agent (1.15 equiv) was then added dropwise via syringe, and the reaction mixture was stirred at −78 °C for 2 h and at ambient temperature overnight. At this point the reaction was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with three portions of CH_2Cl_2. The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated at reduced pressure, maintaining the temperature below 30 °C.

1-Benzoyl-2(*S*)-isopropyl-4-methoxy-6(*S*)-carbomethoxy-6(*S*)-methyl-(1,2),(5,6)-tetrahydro-1,3-pyrimidine [(2*S*,6*S*)-10]. The general procedure was followed with 1.0 g (3.14 mmol) of imino ether (2*S*,6*S*)-**9** in 20 mL of THF and 0.22 mL (3.49 mmol) of methyl iodide. The crude product was purified by flash column chromatography (hexanes−ethyl acetate, 9:1) to give 0.55 g (52.4% yield) of (2*S*,6*S*)-**10** as a viscous oil. $[\alpha]_D^{28°C}$ = −47.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.82 (d, *J* = 6.6 Hz, 6 H, (C**H$_3$**)$_2$CH), 1.62 (s, 3 H, C**H$_3$**C(6)), 2.00 (m, 1 H, (CH$_3$)$_2$C**H**), 2.43 (d, *J* = 15.2 Hz, 1 H, C**H**H′), 2.94 (d, *J* = 15.2 Hz, 1 H, CH**H**′), 3.77 (s, 3 H, OC**H$_3$**), 3.82 (s, 3 H, OC**H$_3$**), 5.29 (d, *J* = 9.2 Hz, 1 H, NC**H**N), 7.39 (s, 5 H, C$_6$**H$_5$**). ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 19.1, 19.6, 22.6, 35.0, 35.7, 52.3, 53.0, 60.0, 77.3, 127.3, 128.1, 129.6, 136.2, 163.7, 170.4, 173.1.

1-Benzoyl-2(*S*)-isopropyl-4-methoxy-6(*S*)-carbomethoxy-6(*S*)-ethyl-(1,2),(5,6)-tetrahydro-1,3-pyrimidine [(2*S*,6*S*)-11]. The general procedure was followed with 0.5 g (1.57 mmol) of imino ether (2*S*,6*S*)-**9** in 20 mL of THF and 0.19 mL (2.3 mmol) of ethyl iodide. The crude product was purified by flash column chromatography (hexanes−ethyl acetate, 9:1) to give 0.34 g (61.8% yield) of (2*S*,6*S*)-**11**, mp 158−159 °C. $[\alpha]_D^{28°C}$ = −67.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.81 (d, *J* = 6.8 Hz, 3 H, C**H$_3$**CHCH$_3$), 0.82 (*J* = 6.8 Hz, 3 H, CH$_3$CHC**H$_3$**), 0.87 (t, *J* = 7.7 Hz, 3 H, C**H$_3$**CH$_2$), 1.94 (dq, J^1 = 14.8 Hz, J^2 = 7.3 Hz, CH$_3$C**H**H′), 2.02 (m, 1 H, CH$_3$C**H**CH$_3$), 2.44 (d, *J* = 16.0 Hz, 1 H, N=C−C**H**H′), 2.66 (ddq, J^1 = 14.8 Hz, J^2 = 7.3 Hz, J^3 = 1.3 Hz, 1 H, CH$_3$CH**H**′), 2.87 (dd, J^1 = 16.0 Hz, J^2 = 1.3 Hz, 1 H, N=C−CH**H**′), 3.74 (s, 3 H, OC**H$_3$**), 3.79 (s, 3 H, OC**H$_3$**), 5.38 (d, *J* = 9.5 Hz, 1 H, NC**H**N), 7.40 (m, 5 H, C$_6$**H$_5$**). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.4, 19.6, 20.0, 28.2, 33.8, 35.4, 52.5, 53.3, 62.8, 77.8, 128.2, 128.4, 130.0, 136.5, 163.6, 170.9, 173.9. Anal. Calcd for $C_{19}H_{26}O_4N_2$: C, 65.87; H, 7.56. Found: C, 65.62; H, 7.50.

1-Benzoyl-2(*S*)-isopropyl-4-methoxy-6(*S*)-carbomethoxy-6(*S*)-*n*-butyl-(1,2), (5,6)-tetrahydro-1,3-pyrimidine [(2*S*,6*S*)-12]. The general procedure was followed with 1.0 g (3.14 mmol) of imino ether (2*S*,6*S*)-**9** in 20 mL of THF and 0.42 mL (3.70 mmol) of *n*-butyl iodide. The crude product was purified by flash column chromatography (hexanes−ethyl acetate, 9:1) to give 0.71 g (59.7% yield) of (2*S*,6*S*)-**12** as a viscous oil.

(23) Juaristi, E.; Martínez-Richa, A.; García-Rivera, A.; Cruz-Sánchez, J. S. *J. Org. Chem.* **1983**, *48*, 2603−2606.

(24) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

$\alpha]_D^{28°C} = -20.0$ ($c = 1.0$, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.77 (d, $J = 6.6$ Hz, 6 H, $(CH_3)_2CH$), 0.84 (t, $J = 6.6$ Hz, 3 H, $(CH_2)_3CH_3$), 1.22 (m, 4 H, $CH_2CH_2CH_3$), 1.84 (dt, $J^1 = 11.7$ Hz, $J^2 = 4.8$ Hz, 1 H, $CH_3(CH_2)_2CHH'$), 1.99 (m, 1 H, $(CH_3)_2CH$), 2.42 (d, $J = 16.1$ Hz, 1 H, N=C−CHH′), 2.56 (dt, $J^1 = 13.7$ Hz, $J^2 = 4.0$ Hz, 1 H, $CH_3(CH_2)_2CHH'$), 2.83 (d, $J = 15.8$ Hz, 1 H, N=C−CHH′), 3.70 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 5.33 (d, $J = 9.5$ Hz, 1 H, NCHN), 7.36 (m, 5 H, C_6H_5). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 19.4, 20.0, 22.9, 26.1, 34.1, 35.1, 35.5, 52.4, 53.2, 62.5, 77.8, 128.1, 128.4, 129.9, 136.6, 163.5, 170.7, 173.9.

1-Benzoyl-2(*S*)-isopropyl-4-methoxy-6(*S*)-carbomethoxy-6(*S*)-benzyl-(1,2),(5,6)-tetrahydro-1,3-pyrimidine [(2*S*,6*S*)-13]. The general procedure was followed with 1.07 g (3.35 mmol) of imino ether (2*S*,6*S*)-**9** in 20 mL of THF and 0.43 mL (3.66 mmol) of benzyl bromide. The crude product was purified by flash column chromatography (hexanes−ethyl acetate, 9:1) to give 0.95 g (69.4% yield) of (2*S*,6*S*)-**13**, mp 122−123 °C. $[\alpha]_D^{28°C} = +90.0$ ($c = 1.0$, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.66 (d, $J = 6.6$ Hz, 3 H, CH_3CHCH_3), 0.68 (d, $J = 6.2$ Hz, 3 H, CH_3CHCH_3), 1.87 (m, 1 H, CH_3CHCH_3), 2.69 (d, $J = 16.5$ Hz, 1 H, N=C−CHH′), 2.84 (d, $J = 16.1$ Hz, 1 H, N=C−CHH′), 3.17 (d, $J = 14.3$ Hz, 1 H, PhCHH′), 3.27 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.03 (d, $J = 13.9$ Hz, 1 H, PhCHH′), 5.26 (d, $J = 9.2$ Hz, 1 H, NCHN), 7.25 (m, 10 H, H_{arom}). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2, 20.1, 34.0, 35.6, 40.3, 52.5, 52.6, 63.0, 77.3, 127.0, 127.7, 128.2, 128.5, 130.0, 131.1, 135.7, 136.2, 162.3, 170.5, 173.6. Anal. Calcd for $C_{24}H_{28}O_4N_2$: C, 70.56; H, 6.90. Found: C, 70.75; H, 7.02.

General Procedure for the Hydrolysis of the Alkylated Pyrimidines 10−13. A suspension of approximately 1 mmol of adduct in 10 mL of 17% HCl was heated in a sealed ampule to 95 °C (in a Thermolyne 21100 oven). The solution was then allowed to cool to ambient temperature and was extracted three times with CH_2Cl_2. The aqueous phase was evaporated to afford the crude amino acid hydrochloride, which was adsorbed to acidic ion-exchange resin Dowex 50W X 8. The resin was washed with distilled H_2O until the washings came out neutral, and then the free amino acid was recovered with 1 N aqueous NH_3. Evaporation afforded the crystalline amino acid, which was dried under vacuum at 40 °C.

α-Methyl Aspartic Acid [(*S*)-14]. Derivative (2*S*,6*S*)-**10** (500 mg, 1.5 mmol) was hydrolyzed according to the general procedure to afford 200 mg (83.8% yield) of pure, free amino acid (*S*)-**14**, mp 175−176 °C [(lit.[12] mp 131−134 °C), (lit.[9] mp 254.0−256.0 °C)]. $[\alpha]_D^{28°C} = +43.0$ ($c = 1.0$, H_2O) [lit.[12] $[\alpha]_D^{28°C} = +36.0$ ($c = 0.18$, H_2O), lit.[9] $[\alpha]_D^{RT} = +55.3$ ($c = 0.57$, H_2O)]. ^1H NMR (D_2O, 270 MHz) δ 1.45 (s, 3 H, CH_3), 2.55 (d, $J = 17.2$ Hz, 1 H, CHH′), 2.83 (d, $J = 17.8$ Hz, 1 H, CHH′). ^{13}C NMR (D_2O, 100 MHz) δ 36.7, 52.3, 59.2, 177.0, 177.7.

α-Ethyl Aspartic Acid [(*S*)-15]. Derivative (2*S*,6*S*)-**11** (100 mg, 0.29 mmol) was hydrolyzed according to the general procedure to afford 40 mg (80.0% yield) of pure, free amino acid (*S*)-**15**, mp 165−167 °C. $[\alpha]_D^{28°C} = +35.1$ ($c = 0.79$, H_2O). ^1H NMR (D_2O, 400 MHz) δ 0.90 (t, $J = 7.4$ Hz, 3 H, CH_2CH_3), 1.79 (m, 2 H, CH_2CH_3), 2.60 (d, $J = 17.6$ Hz, 1 H, CHH′), 2.85 (d, $J = 17.3$ Hz, 1 H, CHH′). ^{13}C NMR (D_2O, 100 MHz) δ 7.5, 29.4, 41.0, 63.1, 175.8, 177.1.

α-*n*-Butyl Aspartic Acid [(*S*)-16]. Derivative (2*S*,6*S*)-**12** (130 mg, 0.35 mmol) was hydrolyzed according to the general procedure to afford 62 mg (88.3% yield) of pure, free amino acid (*S*)-**16**, mp 180−182 °C. $[\alpha]_D^{28°C} = +26.7$ ($c = 0.86$, H_2O). ^1H NMR (D_2O, 400 MHz) δ 0.82 (t, $J = 7.0$ Hz, 3 H), 1.15 (m, 1 H), 1.28 (m, 3 H), 1.70 (m, 2 H), 2.54 (d, $J = 17.2$ Hz, 1 H), 2.79 (d, $J = 17.2$ Hz, 1 H). ^{13}C NMR (D_2O, 100 MHz) δ 13.2, 22.2, 25.2, 35.2, 41.4, 62.8, 175.9, 177.3.

α-Benzyl Aspartic Acid [(*S*)-17]. Derivative (2*S*,6*S*)-**13** (200 mg, 0.49 mmol) was hydrolyzed according to the general procedure to afford 104 mg (95.4% yield) of pure, free amino acid (*S*)-**17**, mp 240−242 °C (lit.[7] mp 235 °C). $[\alpha]_D^{28°C} = +50.0$ ($c = 0.66$, H_2O) [lit.[7] $[\alpha]_D^{28°C} = +50.9$ ($c = 0.8$, H_2O)]. ^1H NMR (D_2O, 270 MHz) δ 2.59 (d, $J = 17.2$ Hz, 1 H, $CHH'CO_2$), 2.90 (d, $J = 17.2$ Hz, 1 H, $CHH'CO_2$), 2.97 (d, $J = 13.9$ Hz, 1H, CHH′Ph), 3.16 (d, $J = 13.9$ Hz, 1 H, CHH′Ph), 7.2−7.3 (m, 5 H, C_6H_5). ^{13}C NMR (D_2O, 100 MHz) δ 41.2, 41.7, 63.3, 128.0, 129.0, 130.3, 133.8, 175.0, 177.4.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for **9**, **10**, **12**, **15**, and **16** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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