Formation of Aziridine-2-amides through 5-Halo-6-methylperhydropyrimidin-4-ones. A Route to Enantiopure L- and D-Threonine and *allo*-Threonine

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The synthesis of stereodefined aziridine-2-carboxylates is an area of increasing interest in organic chemistry.[1] These compounds are useful starting materials for the preparation of α- and *β*-amino acids and amino alcohols; indeed, ring-opening performed with a variety of nucleophiles is one of the most interesting features of this class of compounds. We will describe the synthesis of both cis and trans chiral aziridine-2-amides starting from (1′*S*,6*R*)- and (1′*S*,6*S*)-1-benzyloxycarbonyl-3-(1′-phenylethyl)-6-methylperhydropyrimidin-4-ones. These compounds are useful intermediates to α-substituted *β*-amino acids[3] and have easily been prepared starting from (±)-3-aminobutanoic acid, following a known procedure.[2] We tested the reactivity of lithium enolates of both diastereoisomers with *p*-toluenesulfonyl chloride and benzenesulfonyl bromide and iodine as electrophiles.[4]

Indeed (1′*S*,6*R*)-6-methylperhydropyrimidin-4-one **1** was treated with LiHMDS in dry THF at 0 °C for 1 h. The enolate was cooled at −30 °C, and the halogenating agent was then added dropwise.[5] After the scheduled time, the reaction was quenched with water and worked up following the usual procedure. The results obtained are reported in Table 1.

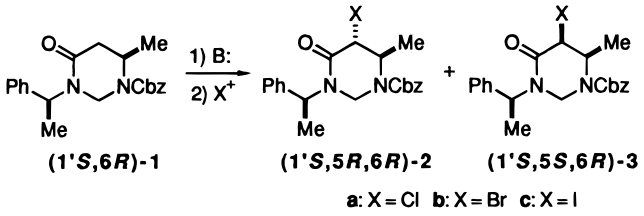

Table 1. Diastereomeric Product Ratios and Chemical Yield for the Halogenation Reactions of 6-Methylperhydropyrimidin-4-one 1

entry	X	reagent (equiv)	temp (°C)	time	yield (%)	diastereomeric ratio **2**:**3**[a]
1	Cl	TsCl (1.5)	−30	15 min	74	10:90
2	Cl	TsCl (1.5)	−30	1 h	85	16:84
3	Cl	TsCl (1.5)	−30 to rt	16 h	87	78:22
4	Br	$PhSO_2Br$ (1.5)	−30	15 min	98	38:62
5	Br	$PhSO_2Br$ (1.5)	−30	1 h	98	41:59
6	Br	$PhSO_2Br$ (1.5)	−30 to rt	16 h	98	61:39
7	I	I_2 (3)	−30	15 min	85	85:15

[a] The diastereomeric ratios were determined by means of HPLC analysis.

Table 1 shows some unexpected results, deserving a few considerations. The chlorination reaction is far more selective than the bromination and, in both cases, the 5,6-cis adducts **3a** and **3b** are preferentially obtained after a short reaction time (entries 1 and 4). After longer reaction times, there is a reversal of diastereoselectivity with both reagents. Thus we can infer that the 5,6-cis adducts **3a** and **3b** are the kinetically preferred products, while the 5,6-trans adducts **2a** and **2b** are the thermodynamically preferred compounds. This assumption was confirmed when we treated pure **3a** or a 1:1 mixture of **2a** and **3a** with gaseous ammonia in ethanol at room temperature: in both cases an equilibrium was reached, and a mixture containing **2a** and **3a** in 3:1 ratio was obtained as established by NMR and HPLC analysis.

By contrast, when the lithium enolate was treated with iodine, we observed the direct preferential formation of the 5,6-trans adduct **2c** (entry 7).[6]

Then *trans*- and *cis*-5-halo-6-methylperhydropyrimidin-4-ones **2** and **3** have been transformed under mild acid conditions into the corresponding 2-carboxyaziridines, synthetic precursors of enantiomerically pure threonines or *allo*-threonines.

allo-Threonines represent one of the most common families of nonproteinogenic amino acids, and they are the building blocks of many bioactive peptides and glycopeptides associated with biological recognition and selectivity.[7] Furthermore, it has been shown that substitution of threonines by *allo*-threonines in peptide sequences can make the molecules more resistant to proteolysis under physiological conditions.[8]

The hydrolysis of **2a** was performed with 11 M HCl in ethanol and was stopped after 2 h to open the heterocycle without destroying the carbon−halogen bond. As the highly reactive *erythro*-halo derivative **4** cannot be isolated, the aziridine **5** was directly recovered pure in 65% yield after concentration, addition of 5 M NaOH, and extraction with ethyl acetate. The coupling constant of

(1) (a) Fanta, P. E. *Heterocyclic Compounds with Three and Four-membered Rings;* Weissemberg, A., Ed.; Wiley-Interscience: New York, 1964; Part 1, p 524. (b) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.

(2) (a) Amoroso, R.; Cardillo, G.; Tomasini, C. *Tetrahedron Lett.* **1992**, *33*, 2725. (b) Braschi, I.; Cardillo, G.; Tomasini, C. *Tetrahedron* **1994**, *50*, 2955. (c) Braschi, I.; Cardillo, G.; Tomasini, C.; Venezia, R. *J. Org. Chem.* **1994**, *59*, 7292. (d) Amoroso, R.; Cardillo, G.; Mobbili, G.; Tomasini, C. *Tetrahedron: Asymmetry* **1993**, *4*, 2241. (e) Cardillo, G.; Tolomelli, A.; Tomasini, C. *Tetrahedron* **1995**, *51*, 11831.

(3) For recent reviews on *β*-amino acids, see: (a) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. (b) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichimica Acta* **1994**, *27*, 3. (c) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117. (d) *Enantioselective Synthesis of β-Amino Acids;* Juaristi, E., Ed.; VCH Publishers: New York, 1996.

(4) (a) Muth, F. Methoden zur Herstellung und Umwandlung von aromatischen Sulfinsauren. In *Methoden der organischen Chemie* (*Houben-Weyl-Muller*); Thieme Publisher: Stuttgart, 1955; 4. Aufl., Board 9, S. 310.; (b) Stotter, P. L.; Hill, K. A. *J. Org. Chem.* **1973**, *38*, 2576. (c) Hirsch, E.; Hunig, S.; Rei*β*ig, H.-U. *Chem. Ber.* **1982**, *115*, 399. (d) Hirsch, E.; Hunig, S.; Rei*β*ig, H.-U. *Chem. Ber.* **1982**, *115*, 3687. (e) Kuhlein, K.; Jensen, H. *Liebigs Ann. Chem.* **1974**, 369.

(5) If the reaction is conducted at −78 °C, similar diastereoselectivities and lower yield are obtained and a larger amount of starting material is recovered.

(6) For compounds **2** and **3** the comparison of the H_5 and H_6 coupling constants were not diagnostic and disagreed with NOEDIFF experiments. The absolute configuration at C_5 was attributed by transforming the 5-haloperhydropyrimidin-4-one into 2-carboxyaziridines; so we ascertained that 5,6-trans derivatives always have smaller coupling constants than 5,6-cis derivatives (2.0−4.4 Hz versus 5.3−5.9 Hz).

(7) (a) Okonya, J. F.; Kolasa, T.; Miller, M. J. *J. Org. Chem.* **1995**, *60*, 1932. (b) Rossner, E.; Zeeck, A.; Konig, W. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 64. (c) Gurjar, M. K.; Saha, U. K. *Tetrahedron Lett.* **1991**, *32*, 6621.

(8) Allen, M. C.; Wade, R. *Int. J. Pept. Protein Res.* **1988**, *32*, 89.

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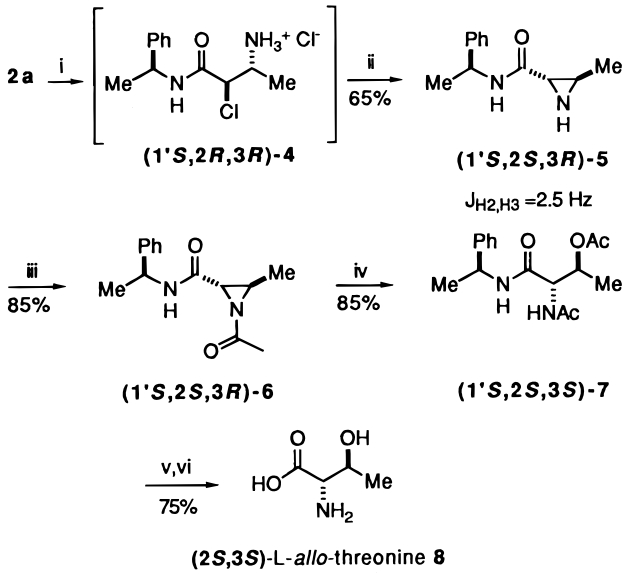
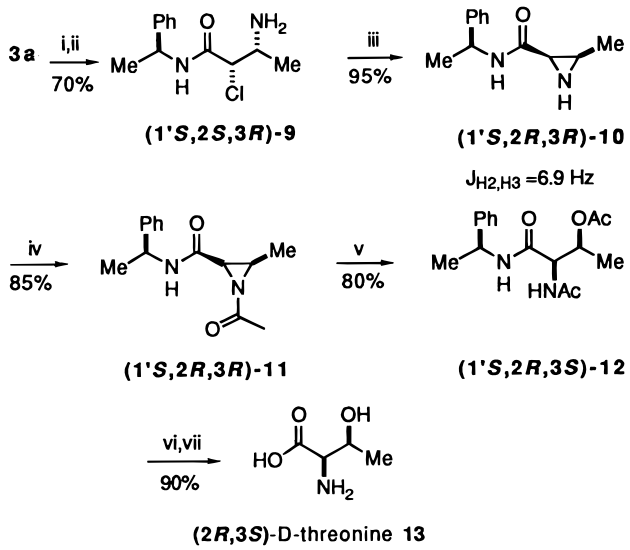
Scheme 1[a]



[a] Reagent and conditions: (i) 11 M HCl/EtOH 1:1, Δ, 2 h; (ii) 5 M NaOH; (iii) Ac_2O (2.5 equiv), Py (2 equiv), DMAP (0.2 equiv), CH_2Cl_2, 1 h; (iv) Ac_2O (10 equiv), Py, Δ, 1 h; (v) 11 M HCl/MeOH 10:1; (vi) cation exchange resin, 0.5 M NH_4OH.

Scheme 2[a]



[a] Reagent and conditions: (i) 11 M HCl/EtOH 1:1, Δ, 2 h; (ii) 5 M NaOH; (iii) NH_3, DMSO, 16 h; (iv) Ac_2O (2.5 equiv), Py (2 equiv), DMAP (0.2 equiv), CH_2Cl_2, 1 h; (v) Ac_2O (10 equiv), Py, Δ, 1 h; (vi) 11 M HCl/MeOH 10:1; (vii) cation exchange resin, 0.5 M NH_4OH.

the aziridine ring hydrogens ($J_{H2,H3}$ = 2.5 Hz) accounts for a trans relationship of the substituent,[9a] thus making it possible to attribute the relative trans configuration to the perhydropyrimidin-4-one **2a**.

It is reported that *N*-acyloylaziridines are easily opened by a range of nucleophiles.[9b−d] Accordingly, to synthesize L-*allo*-threonine **8**, aziridine **5** was transformed into the corresponding *N*-acetyl derivative **6**. Then, on refluxing **6** with acetic anhydride in pyridine for 1 h, the *erythro*-*N*,*O*-diacetyl derivative **7** was isolated in 85% yield and, after acid hydrolysis of product **7** and purification on cation-exchange resin, (2*S*,3*S*)-L-*allo*-threonine **8** was obtained pure in 75% yield (Scheme 1). The specific rotation and the NMR spectrum of **8** are in agreement with the data reported in the literature.[10]

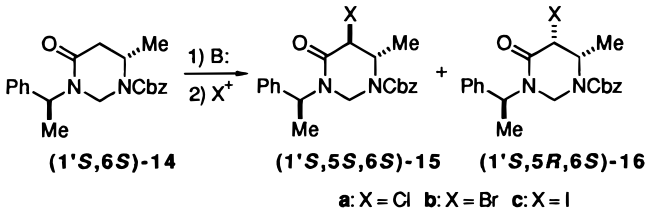
Following the same route, (1′*S*,5*S*,6*R*)-**3a** was hydrolyzed into the corresponding *threo*-α-chloro-*β*-amino amide **9** in 70% yield (Scheme 2). The aziridine **10** was obtained in 95% yield by bubbling gaseous NH_3 in a DMSO solution of **9**. The coupling constant of the aziridine hydrogens ($J_{H2,H3}$ = 6.9 Hz) accounts for a cis relationship of the substituents,[9a] thus confirming the stereochemical assignment of the pyrimidin-4-one **3a**. The aziridine **10** was then subjected to the reactions of *N*-acylation, ring opening, acid hydrolysis, and purification as described above. This made it possible to obtain pure (2*R*,3*S*)-D-threonine[10a] **13** in good yield.

The halogenation reaction was also tested for (1′*S*,6*S*)-6-methylperhydropyrimidin-4-one **14**. The heterocycle reacted under the same conditions held for compound **1**, affording the 5,6-trans adduct (1′*S*,5*S*,6*S*)-5-halo-6-methylperhydropyrimidin-4-one **15** and the 5,6-cis adduct (1′*S*,5*R*,6*S*)-5-halo-6-methylperhydropyrimidin-4-one **16**. The results obtained are reported in Table 2.

Table 2. Diastereomeric Product Ratios and Chemical Yield for the Halogenation Reaction of (1′*S*,6*S*)-6-Methylperhydropyrimidin-4-one 14

entry	X	reagent (equiv)	time	temp (°C)	yield (%)	diastereomeric ratio **15**:**16**[a]
1	Cl	TsCl (1.5)	15 min	−30	82	28:72
2	Cl	TsCl (1.5)	1 h	−30	85	55:45
3	Cl	TsCl (1.5)	16 h	−30 to rt	86	76:24
4	Br	$PhSO_2Br$ (1.5)	15 min	−30	82	25:75
5	Br	$PhSO_2Br$ (1.5)	1 h	−30	98	34:66
6	Br	$PhSO_2Br$ (1.5)	16 h	−30 to rt	98	84:16
7	I	I_2 (3)	15 min	−30	93	82:18

[a] The diastereomeric ratios were determined by means of HPLC analysis.

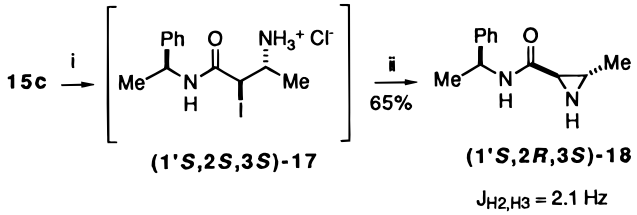


As observed in the halogenation of **1**, both bromination and chlorination reactions proceed with an excess of the kinetically preferred 5,6-cis products **16a** and **16b** (entries 1 and 4). However, in this case, diastereoselectivity is overall less satisfactory. Furthermore, an excess of the thermodynamically preferred 5,6-trans compounds **15a** and **15b** was obtained in both cases after prolonged reaction times.Treatment of a 25:75 mixture of **15a** and **16a** with ammonia in dry ethanol furnishes an increase of the trans adduct **15a** (63:37 trans/cis ratio). Moreover, iodination (entry 7) affords an excess of trans adduct **15c**.[6]

(9) (a) Nagel, D. L.; Woller, P. B.; Cromwell, N. H. *J. Org. Chem.* **1971**, *36*, 3911. (b) Legters, J.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 16. (c) Legters, J.; Willems, J. G. H.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas*, **1992**, *111*, 59. (d) Dauban, P.; Dubois, L.; Tran Huu Dau, M. E.; Dodd, R. H. *J. Org. Chem.* **1995**, *60*, 2035 and references therein.

(10) (a) *Beilstein 4* (3), 1625-9. (b) Genet, J. P.; Juge, S.; Mallart, S. *Tetrahedron Lett.* **1988**, *51*, 6765. (c) Kuzuhara, H.; Watanabe, N.; Ando, M. *J. Chem. Soc., Chem. Commun.* **1987**, 95. (d) Pons, D.; Savignac, M.; Genet, J. P. *Tetrahedron Lett.* **1990**, *35*, 5023.

Scheme 3[a]



[a] Reagents and conditions: (i) 11 M HCl/EtOH 1:1, Δ, 2 h; (ii) 5 M NaOH.

To confirm the absolute configuration assigned to C_5 of compounds **15** and **16**, **15c** was transformed into the corresponding aziridine **18** following the procedure previously described (Scheme 3).

The 2-iodo derivative **17** was not isolated and the aziridine **18** was directly recovered pure in 65% yield, after acid hydrolysis with 11 M HCl and ethanol for 2 h at reflux, elimination of the ethanol under reduced pressure, treatment with 5 M NaOH, and extraction with ethyl acetate. The coupling constant of the aziridine ring hydrogens ($J_{H2,H3} = 2.1$ Hz) accounts for a trans relationship of the substituents, thus confirming the relative trans configuration assigned to the perhydropyrimidin-4-one **15c**. Moreover, the aziridine **18** can easily be transformed into D-*allo*-threonine by acetylation, opening of the aziridine ring, and acid hydrolysis of the adduct, as previously described for aziridine **5**.

In conclusion, *trans*- or *cis*-2-carboxyaziridines can be obtained in good yield by acid hydrolysis of the 5-halo perhydropyrimidin-4-ones and are selectively transformed into enantiomerically pure threonines or *allo*-threonines, depending on the stereochemistry of the starting 5-halo-6-methylperhydropyrimidin-4-one.

Experimental Section

General. ^{1}H NMR spectra were recorded at 300 or 200 MHz. Chemical shifts are reported in ppm relative to the solvent peak of $CHCl_3$, defined to be δ 7.27 ppm. Infrared spectra were recorded with an FT-IR spectrometer. Melting points were determined in open capillaries and are uncorrected. Flash chromatography was performed with Merck silica gel 60 (230−400 mesh). THF was distilled from sodium benzophenone ketyl. Dichloromethane was distilled from P_2O_5. *p*-Toluenesulfonyl chloride was dissolved in methylene chloride and washed with water. Benzenesufonyl bromide was prepared according to ref 11.

General Procedure for the Halogenation of Perhydropyrimidin-4-ones 1 and 14. LiHMDS (1 M solution in THF, 1 mL) was added in one portion under argon at 0 °C to a stirred solution of perhydropyrimidin-4-one **1** or **14** (1 mmol, 0.35 g) in dry THF (20 mL). The formation of the enolate was complete in 30 min and the solution was then cooled to −30 °C and the halogenating agent (1.5 mmol for chlorination and bromination, 3 mmol for iodination) in dry THF (10 mL) was added dropwise. After the scheduled time, the reaction was quenched with water, and the organic solvent was removed under reduced pressure and replaced with ethyl acetate, which was washed twice with water. The organic layer was dried over Na_2SO_4, concentrated, and chromatographed on silica gel (cyclohexane/ethyl acetate 9:1 as eluant). All the products were obtained as oils.

(1′*S*,5*R*,6*R*)-1-Benzyloxycarbonyl-5-chloro-6-methyl-3-(1′-phenylethyl)perhydropyrimidin-4-one (2a): IR (film) 1710, 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C) δ 1.28 (d, 3H, J = 6.6 Hz), 1.55 (d, 3H, J = 7.0 Hz), 4.22 (d, 1H, J = 4.4 Hz), 4.31 (d, 1H, J = 12.5 Hz), 4.38 (m, 1H), 5.02 (d, 1H, J = 12.5 Hz), 5.15 (s, 2H), 5.91 (q, 1H, J = 7.0 Hz), 7.31 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 15.6, 18.5, 50.9, 51.6, 54.0, 58.0, 67.7, 127.2, 127.8, 128.0, 128.2, 128.5, 128.7, 135.9, 138.8, 153.8, 163.8; $[\alpha]_D$ −16.2 (*c* 0.3, $CHCl_3$); HRMS calcd for (M^+) $C_{21}H_{23}N_2O_3Cl$ 386.1397206, found 386.1394773.

(1′*S*,5*S*,6*R*)-1-Benzyloxycarbonyl-5-chloro-6-methyl-3-(1′-phenylethyl)perhydropyrimidin-4-one (3a): IR (film) 1701, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C) δ 1.31 (d, 3H, J = 6.7 Hz), 1.53 (d, 3H, J = 7.1 Hz), 4.37 (d, 1H, J = 12.9 Hz), 4.50 (m, 1H), 4.57 (d, 1H, J = 5.8 Hz), 4.97 (m, 1H), 5.17 (AB, 2H, J = 11.9 Hz), 5.85 (q, 1H, J = 7.1 Hz), 7.31 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 13.8, 15.7, 50.4, 50.9, 51.4, 58.3, 67.7, 126.8, 127.6, 128.1, 128.3, 128.4, 135.6, 138.7, 153.6, 164.4; $[\alpha]_D$ −78.3 (*c* 0.3, $CHCl_3$); HRMS calcd for (M^+) $C_{21}H_{23}N_2O_3Cl$ 386.1397206, found 386.1393392.

(1′*S*,5*R*,6*R*)-1-Benzyloxycarbonyl-5-bromo-6-methyl-3-(1′-phenylethyl)perhydropyrimidin-4-one (2b): IR (film) 1710, 1676 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C), δ 1.25 (d, 3H, J = 6.9 Hz), 1.55 (d, 3H, J = 7.1 Hz), 4.29 (d, 1H, J = 2.7 Hz), 4.40 (d, 1H, J = 11.3 Hz), 4.50 (dq, 1H, J = 2.7 Hz, 6.9 Hz), 5.02 (d, 1H, J = 11.3 Hz), 5.14 (s, 2H), 5.95 (q, 1H, J = 7.1 Hz), 7.34 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 15.3, 19.2, 46.6, 51.0, 52.1, 53.9, 67.8, 127.3, 127.9, 128.1, 128.3, 128.6, 128.8, 136.0, 138.9, 153.9, 163.9; $[\alpha]_D$ +11.6 (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{21}H_{23}N_2O_3Br$: C, 58.48; H, 5.37; N 6.49. Found: C, 58.45; H, 5.36; N 6.52.

(1′*S*,5*S*,6*R*)-1-Benzyloxycarbonyl-5-bromo-6-methyl-3-(1′-phenylethyl)perhydropyrimidin-4-one (3b): IR (film) 1710, 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C), δ 1.36 (d, 3H, J = 6.3 Hz), 1.51 (d, 3H, J = 6.6 Hz), 4.37 (m, 1H), 4.39 (d, 1H, J = 13.4 Hz), 4.65 (d, 1H, J = 5.6 Hz), 4.97 (d, 1H, J = 13.4 Hz), 5.18 (AB, 2H, J = 12.1 Hz), 5.81 (q, 1H, J = 6.6 Hz); 7.30 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 16.0, 19.2, 50.1, 50.2, 50.4, 51.5, 68.1, 127.1, 127.8, 128.1, 128.2, 128.5 128.7, 135.7, 138.9, 154.0, 165.0; $[\alpha]_D$ −67.8 (*c* 0.8, $CHCl_3$). Anal. Calcd for $C_{21}H_{23}N_2O_3Br$: C, 58.48; H, 5.37; N 6.49. Found: C, 58.49; H, 5.39; N 6.45.

(1′*S*,5*R*,6*R*)-1-Benzyloxycarbonyl-5-iodo-6-methyl-3-(1′-phenylethyl)perhydropyrimidin-4-one (2c): IR (film) 1697, 1658 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C) δ 1.22 (d, 3H, J = 6.7 Hz), 1.52 (d, 3H, J = 7.0 Hz), 4.43 (d, 1H, J = 11.7 Hz), 4.46 (m, 1H), 4.49 (d, 1H, J = 1.8 Hz), 4.97 (d, 1H, J = 11.7 Hz), 5.10 (m, 2H), 5.95 (q, 1H, J = 7.0 Hz), 7.30 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 14.6, 19.7, 22.6, 50.8, 52.3, 54.7, 67.6, 127.2, 127.8 128.0, 128.2, 128.5, 128.7, 136.0, 138.8, 153.7, 165.1; $[\alpha]_D$ +35.9 (*c* 2.2, $CHCl_3$). Anal. Calcd for $C_{21}H_{23}N_2O_3I$: C, 52.73; H, 4.85; N 5.86. Found: C, 52.70; H, 4.85; N 5.89.

(1′*S*,5*S*,6*R*)-1-Benzyloxycarbonyl-5-iodo-6-methyl-3-(1′-phenylethyl)perhydropyrimidin-4-one (3c): IR (film) 1695, 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C) δ 1.34 (d, 3H, J = 6.2 Hz), 1.52 (d, 3H, J = 6.9 Hz), 3.84 (false p, 1H, J = 6.3 Hz), 4.33 (d, 1H, J = 13.6 Hz), 4.87 (d, 1H, J = 5.9 Hz), 4.99 (d, 1H, J = 13.6 Hz), 5.17 (AB, 2H, J = 12.3 Hz), 5.80 (q, 1H, J = 6.9 Hz), 7.30 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 14.5, 16.2, 23.9, 50.1, 50.8, 51.8, 68.1, 127.3, 127.8, 128.0, 128.2, 128.5, 128.7, 135.9, 139.1, 154.8, 166.1; $[\alpha]_D$ −78.9 (*c* 0.2, $CHCl_3$). Anal. Calcd for $C_{21}H_{23}N_2O_3I$: C, 52.73; H, 4.85; N 5.86. Found: C, 52.75; H, 4.81; N 5.89.

(1′*S*,5*S*,6*S*)-1-Benzyloxycarbonyl-5-chloro-6-methyl-3-(1′-phenylethyl)perhydropyrimidin-4-one (15a): IR (film) 1709, 1681 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C), δ 1.35 (d, 3H, J = 6.7 Hz), 1.58 (d, 3H, J = 7.0 Hz), 4.24 (d, 1H, J = 3.1 Hz), 4.46 (dq, 1H, J = 3.1 Hz, 6.7 Hz), 4.67 (AB, 2H, J = 12.0 Hz), 5.10 (m, 2H), 5.93 (q, 1H, J = 7.0 Hz), 7.32 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 14.2, 15.6, 50.8, 52.2, 53.9, 57.5, 67.8, 127.1, 127.8, 128.0, 128.3, 128.6, 128.8, 136.0, 138.7, 154.1, 163.9; $[\alpha]_D$ −76.4 (*c* 0.5, $CHCl_3$); HRMS calcd for (M^+) $C_{21}H_{23}N_2O_3Cl$ 386.1397206, found 386.1391934.

(1′*S*,5*R*,6*S*)-1-Benzyloxycarbonyl-5-chloro-6-methyl-3-(1′-phenylethyl)perhydropyrimidin-4-one (16a): IR (film) 1720, 1690 cm$^{-1;}$ ^{1}H NMR ($CDCl_3$, 50 °C), δ 1.38 (d, 3H, J = 6.3 Hz), 1.56 (d, 3H, J = 7.2 Hz), 4.51 (m, 1H), 4.60 (d, 1H, J = 5.4 Hz), 4.76 (AB, 2H, J = 13.3 Hz), 5.08 (m, 2H), 5.90 (q, 1H, J = 7.2 Hz), 7.32 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) d 15.4, 15.9, 51.3, 52.0, 52.1, 58.5, 67.9, 127.1, 127.9, 128.0, 128.3, 128.6, 128.7, 135.8, 139.2, 153.8, 164.7; $[\alpha]_D$ -31.1 (*c* 0.4, $CHCl_3$); HRMS calcd for (M^+) $C_{21}H_{23}N_2O_3Cl$ 386.1397206, found 386.1399492.

(11) Cristol, S. J.; Harrington, J. K.; Singer, M. S. *J. Am. Chem. Soc.* **1966**, *88*, 1529.

(1′*S*,5*S*,6*S*)-1-Benzyloxycarbonyl-5-bromo-6-methyl-3-(1′-phenylethyl)perhydropyrimidin-4-one (15b): IR (film) 1704, 1644 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C), δ 1.36 (d, 3H, J = 6.8 Hz), 1.59 (d, 3H, J = 7.1 Hz), 4.28 (d, 1H, J = 2.4 Hz), 4.55 (dq, 1H, J = 2.4 Hz, J = 6.8 Hz), 4.65 (AB, 2H, J = 11.8 Hz), 5.11 (s, 2H), 5.95 (q, 1H, J = 7.1 Hz), 7.32 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 15.5, 19.2, 45.9, 50.5, 52.4, 53.7, 67.7, 127.0, 127.7, 127.9, 128.2, 128.5, 128.7, 135.9, 138.5, 153.8, 163.9; $[\alpha]_D$ −104.6 (*c* 0.1, $CHCl_3$). Anal. Calcd for $C_{21}H_{23}N_2O_3Br$: C, 58.48; H, 5.37; N 6.49. Found: C, 58.48; H, 5.40; N 6.47.

(1′*S*,5*R*,6*S*)-1-Benzyloxycarbonyl-5-bromo-6-methyl-3-(1′-phenylethyl)perhydropyrimidin-4-one (16b): IR (film) 1712, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C), δ 1.41 (d, 3H, J = 6.9 Hz), 1.52 (d, 3H, J = 7.3 Hz), 4.38 (false p, 1H, J = 5.9 Hz), 4.67 (d, 1H, J = 5.3 Hz), 4.74 (d, 1H, J = 12.6 Hz), 4.89 (d, 1H, J = 12.6 Hz), 5.07 (m, 2H), 5.86 (q, 1H, J = 7.3 Hz), 7.32 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 15.5, 19.3, 46.0, 50.6, 52.4, 53.8, 67.7, 127.1, 127.8, 128.0, 128.2, 128.6, 128.8, 136.0, 138.6, 153.9, 163.9; $[\alpha]_D$ −108.5 (*c* 0.1, $CHCl_3$). Anal. Calcd for $C_{21}H_{23}N_2O_3Br$: C, 58.48; H, 5.37; N 6.49. Found: C, 58.50; H, 5.34; N 6.44.

(1′*S*,5*S*,6*S*)-1-Benzyloxycarbonyl-5-iodo-6-methyl-3-(1′-phenylethyl)perhydropyrimidin-4-one (15c): IR (film) 1690, 1668 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C) δ 1.33 (d, 3H, J = 6.8 Hz), 1.59 (d, 3H, J = 7.2 Hz), 4.48 (d, 1H, J = 2.0 Hz), 4.55 (dq, 1H, J = 2.0 Hz, 6.8 Hz), 4.65 (AB, 2H, J = 11.8 Hz), 5.14 (s, 2H), 5.97 (q, 1H, J = 7.2 Hz), 7.32 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 14.1, 15.4, 21.6, 50.1, 52.3, 54.5, 67.6, 127.1, 127.7, 127.9, 128.2, 128.5, 128.8, 135.7, 138.2, 154.5, 164.1; $[\alpha]_D$ −99.7 (*c* 1.5, $CHCl_3$). Anal. Calcd for $C_{21}H_{23}N_2O_3I$: C, 52.73; H, 4.85; N 5.86. Found: C, 52.73; H, 4.81; N 5.89.

(1′*S*,5*R*,6*S*)-1-Benzyloxycarbonyl-5-iodo-6-methyl-3-(1′-phenylethyl)perhydropyrimidin-4-one (16c): IR (film) 1696, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C) δ 1.39 (d, 3H, J = 6.2 Hz), 1.50 (d, 3H, J = 7.2 Hz), 3.92 (false p, 1H, J = 5.9 Hz), 4.71 (d, 1H, J = 12.7 Hz), 4.90 (d, 1H, J = 5.5 Hz), 4.93 (d, 1H, J = 12.7 Hz), 5.05 (AB, 2H, J = 14.6 Hz), 5.85 (q, 1H, J = 7.2 Hz), 7.31 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 14.1, 15.2, 22.7, 22.9, 50.1, 51.8, 67.6, 127.1, 127.3, 127.9, 128.2, 128.5, 128.6, 135.6, 139.2, 153.9, 166.0; $[\alpha]_D$ +10.6 (*c* 0.3, $CHCl_3$). Anal. Calcd for $C_{21}H_{23}N_2O_3I$: C, 52.73; H, 4.85; N 5.86. Found: C, 52.70; H, 4.85; N 5.83.

Partial Hydrolysis of 1-Benzyloxycarbonyl-5-halo-6-methyl-3-(1′-phenylethyl)perhydropyrimidin-4-ones 2a, 3a, and 15c. A solution of 5-halo-6-methylperhydropyrimidinone (1 mmol) in 11 M HCl (3 mL) and ethanol (3 mL) was refluxed for 2 h. The mixture was then concentrated under reduced pressure to remove ethanol and washed twice with ethyl acetate. Then a 2 M solution of NaOH was added to the aqueous layer until pH 10 was reached, and the mixture was extracted with ethyl acetate. The organic layer, dried over Na_2SO_4 and concentrated, gave compound **5**, **9,** or **18** as an oil. Compounds **5** and **18** were purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 2:8 as eluant).

(1′*S*,2*S*,3*R*)-3-Methyl-2-(1′-phenylethyl)amidoaziridine (5): 65% yield; IR (film) 3278, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3H, J = 5.4 Hz), 1.48 (d, 3H, J = 6.9 Hz), 2.13 (dq, 1H, J = 5.4 Hz, 2.5 Hz), 2.17 (d, 1H, J = 2.5 Hz), 5.10 (false p, 1H, J = 7.4 Hz), 6.6 (bs, 1H), 7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.3, 30.2, 34.7, 38.7, 49.3, 126.6, 127.9, 128.0, 129.2, 143.4, 173.7; $[\alpha]_D$ −60.4 (*c* 0.1, $CHCl_3$). Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.89; N 13.71. Found: C, 70.55; H, 7.87; N, 13.67.

(1′*S*,2*S*,3*R*)-*N*-(1′-Phenylethyl)-3-amino-2-chlorobutanamide (9): 70% yield; IR (film) 3427, 1637 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (d, 3H, J = 6.5 Hz), 1.52 (d, 3H, J = 7.0 Hz), 2.65 (m, 1H), 3.65 (dq, 1H, J = 6.5 Hz, 2.8 Hz), 4.28 (d, 1H, J = 2.8 Hz), 5.10 (false p, 1H, J = 7.4 Hz), 7.30 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 18.8, 21.8, 48.4, 49.5, 51.6, 126.1, 126.9, 127.2, 127.4, 128.5, 128.6, 128.9, 142.5, 166.6; $[\alpha]_D$ −28.2 (*c* 1.4, $CHCl_3$). Anal. Calcd for $C_{12}H_{17}N_2OCl$: C, 59.87; H, 7.12; N 11.64. Found: C, 59.84; H, 7.16; N 11.65.

(1′*S*,2*R*,3*S*)-3-Methyl-2-(1′-phenylethyl)amidoaziridine (18): 65% yield; IR (film) 3277, 1654 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (d, 3H, J = 5.2 Hz), 1.51 (d, 3H, J = 7.0 Hz), 2.11 (dq, 1H, J = 5.2 Hz, J = 2.1 Hz), 2.17 (d, 1H, J = 2.1 Hz), 5.11 (false p, 1H, J = 7.0 Hz), 6.43 (bs, 1H), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.7, 21.9, 34.2, 38.1, 48.7, 126.2, 127.3, 142.8, 169.6; $[\alpha]_D$ −65.3 (*c* 0.3, $CHCl_3$). Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.89; N 13.71. Found: C, 70.54; H, 7.92; N 13.70.

(1′*S*,2*R*,3*R*)-3-Methyl-2-(1′-phenylethyl)amidoaziridine (10). Gaseous NH_3 was bubbled through a solution of chloro derivative **9** (1 mmol, 0.24 g) in dimethyl sulfoxide (10 mL), for 1 h. The reaction mixture was allowed to stir overnight and then was extracted twice with ethyl acetate and water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give compound **10** in 95% yield, after flash chromatography (cyclohexane/ethyl acetate 2:8, as eluant).

10: IR (film) 3378, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (d, 3H, J = 5.7 Hz), 1.51 (d, 3H, J = 6.9 Hz), 1.5 (bs, 1H), 2.35 (dq, 1H, J = 5.7 Hz, 6.9 Hz), 2.72 (d, 1H, J = 6.9 Hz), 5.16 (dq, 1H, J = 6.9 Hz, 8.5 Hz), 6.8 (bs, 1H), 7.23 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.5, 21.3, 323, 36.4, 48.3, 126.2, 127.3, 128.6, 143.0 168.1; $[\alpha]_D$ −10.3 (*c* 0.3, $CHCl_3$). Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.89; N 13.71. Found: C, 70.51; H, 7.87; N 13.74.

General Procedure for the Acetylation of Aziridines 5 and 10. To a stirred solution of aziridine **5** and **10** (1 mmol, 0.2 g) in CH_2Cl_2 (10 mL) at 0 °C were added acetic anhydride (2.5 mmol, 0.24 mL), pyridine (2 mmol, 0.16 mL) and (dimethylamino)pyridine (0.2 mmol, 0.02 g). The reaction mixture was stirred for 3 h and then washed twice with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Compounds **6** and **11** were obtained pure, after flash chromatography on silica gel (ethyl acetate as eluant).

(1′*S*,2*S*,3*R*)-*N*-Acetyl-3-methyl-2-(1′-phenylethyl)amidoaziridine (6): 85% yield; IR (film) 1701, 1634 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (d, 3H, J = 5.2 Hz), 1.49 (d, 3H, J = 6.9 Hz), 2.14 (s, 3H), 2.80 (m, 2H), 5.11 (dq, 1H, J = 6.9 Hz, 7.0 Hz), 6.34 (d, 1H, J = 7.0 Hz), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.1, 21.7, 24.3, 40.0, 43.0, 49.0, 126.2, 127.5, 128.7, 14.6, 166.1, 180.0; $[\alpha]_D$ −90.0 (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.25; H, 7.37; N 11.38. Found: C, 68.23; H, 7.41; N 11.38.

(1′*S*,2*R*,3*R*)-*N*-Acetyl-3-methyl-2-(1′-phenylethyl)amidoaziridine (11): 85% yield; IR (film) 1716, 1656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (d, 3H, J = 5.7 Hz), 1.54 (d, 3H, J = 7.0 Hz), 2.17 (s, 3H), 2.74 (dq, 1H, J = 5.7 Hz, 3.7 Hz), 3.16 (d, 1H, J = 3.7 Hz), 5.17 (dq, 1H, J = 7.0 Hz, 8.7 Hz), 6.45 (d, 1H, J = 8.7 Hz), 7.28 (m, 5H),^{13}C NMR ($CDCl_3$) δ 1.2, 21.4, 2.2, 38.5, 46.0, 48.6, 126.2, 127.6, 128.7, 141.0, 145.8, 166.7, 17.8; $[\alpha]_D$ +26.6 (*c* 0.2, $CHCl_3$). Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.25; H, 7.37; N 11.38. Found: C, 68.24; H, 7.34; N 11.40.

General Procedure for the Synthesis of Diacetates 7 and 12. To a stirred solution of compound **6** or **11** (0.4 mmol, 0.1 g) in pyridine (5 mL) was added acetic anhydride (4 mmol, 0.38 mL) in one portion. The reaction mixture was refluxed for 1 h and washed twice with water and the organic layer concentrated and dried over Na_2SO_4. The solvent was removed under reduced pressure and compounds **7** and **12** were purified by flash chromatography on silica gel (ethyl acetate as eluant).

(1′*S*,2*S*,3*S*)-Diacetate (7): 85% yield; mp 159−161 °C; IR (Nujol) 3284, 1733, 1648, 1594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (d, 3H, J = 6.4 Hz), 1.50 (d, 3H, J = 7.0 Hz), 1.86 (s, 3H), 2.05 (s, 3H), 4.77 (dd, 1H, J = 5.5 Hz, 8.3 Hz), 4.94 (dq, 1H, J = 5.5 Hz, 6.4 Hz), 5.09 (dq, 1H, J = 7.0 Hz, 11 Hz), 6.53 (d, 1H, J = 8.3 Hz), 6.61 (d, 1H, J = 11 Hz), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.4, 20.9, 21.7, 23.2, 49.2, 55.3, 71.1, 126.1, 127.5, 128.7, 142.8, 167.7, 170.2, 170.8; $[\alpha]_D$ −30.1 (*c* 0.2, $CHCl_3$). Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.71; H, 7.24; N, 9.15. Found: C, 62.70; H, 7.21; N, 9.14.

(1*S*′,2*R*,3*S*)-Diacetate (12): 80% yield; mp 157−159 °C; IR (Nujol) 3290, 1729, 1637, 1542 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3H, J = 6.4 Hz), 1.48 (d, 3H, J = 6.9 Hz), 1.96 (s, 3H), 2.05 (s, 3H), 4.64 (dd, 1H, J = 8.5 Hz, 4.7 Hz), 5.07 (dq, 1H, J = 6.9 Hz, 7.7 Hz), 5.36 (dq, 1H, J = 4.4 Hz), 6.43 (d, 1H, J = 8.5 Hz), 6.84 (d, 1H, J = 6.8 Hz), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.6, 21.1, 21.7, 23.1, 49.2, 56.2, 70.0, 126.0, 27.5, 128.7, 142.7, 67.7, 170.0, 170.5; $[\alpha]_D$ −44.1 (*c* 0.3, $CHCl_3$). Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.71; H, 7.24; N, 9.15. Found: C, 62.67; H, 7.23; N, 9.12.

General Procedure for the Hydrolysis of Diacetates 7 and 12. A solution of compound **7** or **12** (0.1 g, 0.33 mmol) in 11 M HCl (10 mL) and MeOH (1 mL) was refluxed for 25 h. The

mixture was then concentrated under reduced pressure and extracted with ethyl acetate/aqueous Na_2CO_3 to separete the (*S*)-1-phenylethylamine. To the aqueous layer was added 6 N HCl until the solution reached pH 1. The solvent was then eliminated and replaced with water (1 mL). The mixture was adsorbed on cation-exchange resin and the resin was washed with distilled water, until the washing came out neutral, then with 0.5 M aqueous NH_4OH to recover the α-amino-*β*-hydroxy acid, which was obtained pure after evaporation.

(2*S*,3*S*)-L-*allo*-Threonine (8): 70% yield; ^{1}H NMR (D_2O+DCl) *δ* 1.04 (d, 3H, *J* = 6.6 Hz), 3.82 (d, 1H, *J* = 3.5 Hz), 4.13 (m, 1H); $[\alpha]_D$ +9.7 (*c* 0.1, H_2O).

(2*R*,3*S*)-D-Threonine (13): 74% yield; ^{1}H NMR (D_2O+DCl) *δ* 1.14 (d, 3H, *J* = 6.6 Hz), 3.72 (d, 1H, *J* = 3.7 Hz), 4.20 (m, 1H), $[\alpha]_D$ +26.1 (*c* 0.1, H_2O).

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