

## Total Synthesis of (±) Carbocyclic Polyoxin C and Its α-Epimer

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Carbocyclic polyoxin C (**2**) and its α-epimer **3** were synthesized in racemic form in an efficient and diastereodivergent fashion from *cis*-4-(*N*-*tert*-butylcarbamoyl)cyclopent-2-en-1-ol (**5a**). This synthesis features a Pd(0)-catalyzed substitution reaction, a novel, mild reduction of an α-nitro ester to an amino acid ester, and an improved procedure for uracil ring formation.

## Introduction

Fungal infections have increased dramatically during the past two decades. Deeply invasive fungal infections are the major cause of morbidity and mortality among immunocompromised patients.<sup>1</sup> While the number of available antifungal drugs is increasing, most of these drugs possess significant side effects and limitations. Thus, more effective and safer antifungal medications are urgently needed. Polyoxins and nikkomycins are peptidyl nucleoside antibiotics isolated from *Streptomyces cacaoi* and *Streptomyces tandemae*.<sup>2–10</sup> They are known antifungal agents that selectively inhibit membrane-bound enzyme chitin synthase from yeast and other fungi, including *Candida albicans*. Inhibition of the biosynthesis of chitin, an essential component of yeast and fungal cell walls, provides an attractive therapeutic target. Because of the absence of chitin synthase in mammalian cells, it is thought that these mechanism-based drugs would potentially be safer therapeutic agents. However, polyoxins and nikkomycins are only weakly active against whole pathogenic fungal cells,<sup>11,12</sup> presumably due to their hydrolytic instability and/or inefficient transport into the cells.

In the course of developing effective and safe antifungal agents, many efforts have been directed toward replacing the amino terminal peptide moiety (R<sup>1</sup>, Figure 1) of polyoxins and nikkomycins but with only limited success.<sup>13–24</sup> Little work has been done to modify the nucleo-

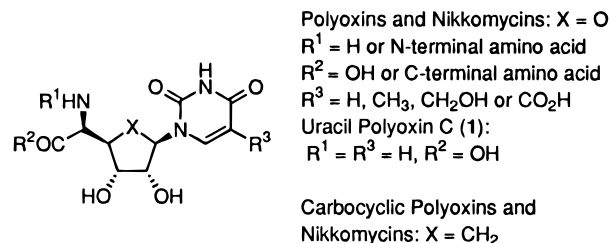
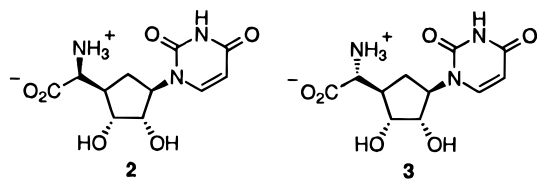
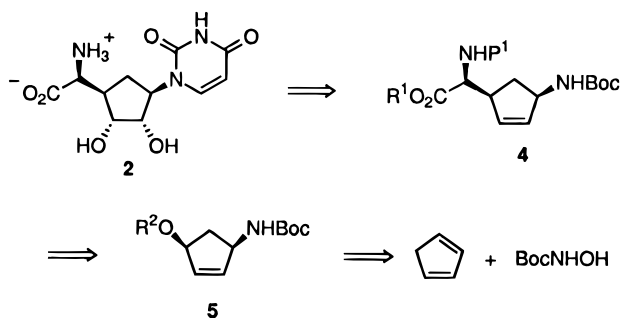
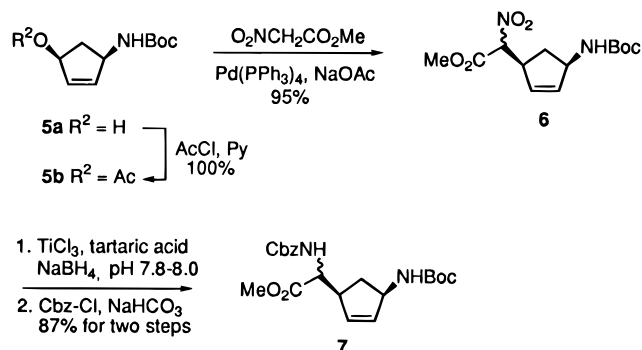


Figure 1. General structure of polyoxins and nikkomycins.

side moiety,<sup>25,26</sup> or to develop other alternate transport systems. Nucleosides in general, display a broad range of biological activities, in particular, antiviral, antifungal, and antitumor activities.<sup>27</sup> Extensive efforts have been made to modify nucleosides to improve their disease-fighting efficacy and lower their toxicity. Among these, isosteric replacement of the furanose ring oxygen with a methylene group is of particular interest, since the resulting *carbocyclic nucleosides* have greater metabolic stability and in some cases, decreased toxicity.<sup>28,29</sup> It would be very interesting to synthesize the carbocyclic version of polyoxins and nikkomycins and evaluate their biological activities. Uracil polyoxin C (**1**) is the simplest member of the polyoxin family and is also a key fragment of some polyoxins and nikkomycins. As part of an ongoing project, we developed and describe here an efficient synthesis of (±)-carbocyclic polyoxin C (**2**) and its epimer **3**.

- (1) Walsh, T. J. In *Emerging Targets in Antibacterial and Antifungal Chemotherapy*; Sutcliffe, J. A., Georgopapadakou, N. H., Eds.; Chapman and Hall: New York, 1992; p 349.
- (2) Isono, K.; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7490.
- (3) Hagenmaier, H.; Keckeisen, A. *Liebigs Ann. Chem.* **1979**, 1494.
- (4) Isono, K.; Suzuki, S. *Heterocycles* **1979**, *13*, 333.
- (5) König, W. A.; Hahn, H.; Rathmann, R.; Hass, W.; Keckeisen, A.; Hagenmaier, H.; Bormann, C.; Dehler, W.; Kurth, R.; Zähler, H. *Liebigs Ann. Chem.* **1986**, 407.
- (6) Uramoto, M.; Kobinata, K.; Isono, K.; Higashijima, T.; Miyazawa, T.; Jenkins, E. E.; McCloskey, J. A. *Tetrahedron Lett.* **1980**, *21*, 3395.
- (7) Uramoto, M.; Kobinata, K.; Isono, K.; Higashijima, T.; Miyazawa, T.; Jenkins, E. E.; McCloskey, J. A. *Tetrahedron* **1982**, *38*, 1599.
- (8) Hori, M.; Kakiki, K.; Suzuki, S.; Misato, T. *Agr. Biol. Chem.* **1971**, *35*, 1280.
- (9) Isono, K.; Nagatsu, J.; Kobinata, K.; Sasaki, K.; Suzuki, S. *Agr. Biol. Chem.* **1967**, *31*, 190.
- (10) Isono, K.; Nagatsu, J.; Kawashima, Y.; Suzuki, S. *Agr. Biol. Chem.* **1965**, *29*, 848.
- (11) Yadan, J.-C.; Gonneau, M.; Sarthou, P.; Goffic, F. L. *J. Bacteriol.* **1984**, *160*, 884.
- (12) Becker, J. M.; Covert, N. L.; Shenbagamurthi, P.; Steinfeld, A. S.; Naider, F. *Antimicrob. Agents Chemother.* **1983**, *23*, 926.
- (13) Krainer, E.; Becker, J. M.; Naider, F. *J. Med. Chem.* **1991**, *34*, 174.
- (14) Fiandor, J.; García-López, M.-T.; De las Heras, F. G.; Méndez-Castrillón, P. P. *Synthesis* **1987**, 978.

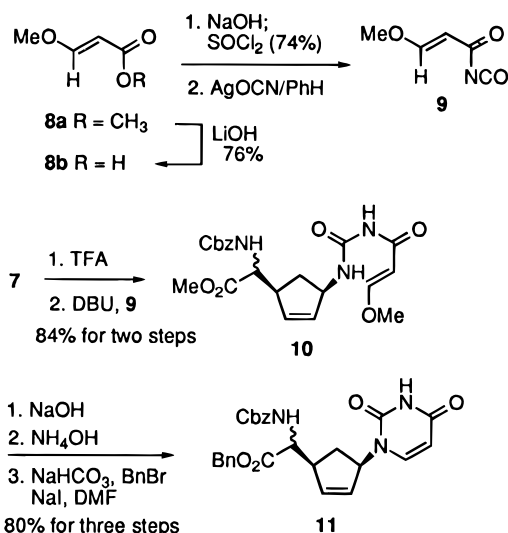
- (15) Emmer, G.; Ryder, N. S.; Grassberger, M. A. *J. Med. Chem.* **1985**, *28*, 278.
- (16) Khare, R. K.; Becker, J. M.; Naider, F. R. *J. Med. Chem.* **1988**, *31*, 650.
- (17) Boehm, J.; Kingsbury, W. D. *J. Org. Chem.* **1986**, *51*, 2307.
- (18) Smith, H. A.; Shenbagamurthi, P.; Naider, F.; Kundu, B.; Becker, J. *Antimicrob. Agents Chemother.* **1986**, *29*, 33.
- (19) Naider, F.; Shenbagamurthi, P.; Steinfeld, A. S.; Smith, H. A.; Boney, C.; Becker, J. M. *Antimicrob. Agents Chemother.* **1983**, *24*, 787.
- (20) Shenbagamurthi, P.; Smith, H. A.; Becker, J. M.; Naider, F. *J. Med. Chem.* **1986**, *29*, 802.
- (21) Shenbagamurthi, P.; Smith, H. A.; Becker, J. M.; Steinfeld, A.; Naider, F. *J. Med. Chem.* **1983**, *26*, 1518.
- (22) Hori, M.; Kakiki, K.; Misato, T. *Agr. Biol. Chem.* **1974**, *38*, 691.
- (23) Hori, M.; Kakiki, K.; Misato, T. *Agr. Biol. Chem.* **1974**, *38*, 699.
- (24) Isono, K.; Suzuki, S.; Azuma, T. *Agr. Biol. Chem.* **1971**, *35*, 1986.
- (25) Baumgartner, H.; Marschner, C.; Pucher, R.; Singer, M.; Griengl, H. *Tetrahedron Lett.* **1992**, *33*, 6443.
- (26) Aggarwal, V. K.; Monteiro, N.; Tarver, G. J.; Lindell, S. D. *J. Org. Chem.* **1996**, *61*, 1192.
- (27) Isono, K. *J. Antibiotics* **1988**, *41*, 1711.
- (28) Bricaud, H.; Herdewijn, P.; De Clercq, E. *Biochem. Pharmacol.* **1983**, 3583.
- (29) De Clercq, E. *Nucleosides Nucleotides* **1994**, *13*, 1271.

**Figure 2.** Target molecules.**Scheme 1****Scheme 2**

Retrosynthetically, carbocyclic polyoxin C (**2**) was anticipated to be obtained from alkene **4** after elaboration of the uracil ring and dihydroxylation (Scheme 1).

**Results and Discussion**

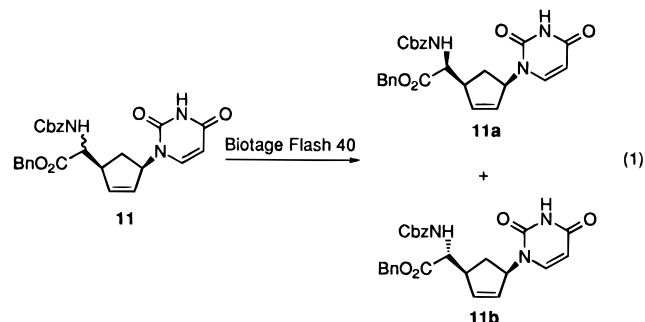
Allylic acetate **5b** was prepared from cyclopentadiene in three steps following our published procedure<sup>30,31</sup> and was subjected to Pd(0)-catalyzed nucleophilic substitution<sup>32,33</sup> with methyl nitroacetate (Scheme 2). Here, nitroacetate was utilized as a synthon<sup>34</sup> for an amino ester which would provide flexibility in controlling the stereochemistry of the newly generated  $\alpha$ -chiral center. Reduction of the nitro group of compound **6** to an amino group without an adverse effect on other functional groups in the molecule was a challenge. Among conditions we tried,  $\text{SnCl}_2$  reduction<sup>35</sup> afforded the desired product in low yield whereas  $\text{NaBH}_4/\text{Pd}$ <sup>36</sup> resulted in C=C bond reduction. Previously, we reported that  $\text{TiCl}_3/\text{NaBH}_4$  in a buffered solution can effectively reduce oximino esters to the corresponding amino esters.<sup>37</sup>  $\text{Ti(III)}$  also has been

**Scheme 3**

reported to convert nitro groups to carbonyls, presumably through an imine intermediate which can be hydrolyzed under acidic conditions.<sup>38,39</sup> Indeed, we found that nitro ester **6** was reduced to the corresponding amino ester with  $\text{TiCl}_3/\text{NaBH}_4$  in a buffered solution (pH 7.8–8.0) in very good yield. The intermediate amine thus generated was protected with Cbz-Cl to generate two diastereomers **7** in a 1:1 ratio. The mixture of these diastereomers was only partially separable by flash chromatography and thus was carried on without separation.

Next, the uracil ring was incorporated using a modification of Shaw's method.<sup>40</sup> Hydrolysis of methyl methoxycarbonyl acrylate (**8a**) generated the corresponding acid, **8b**. The sodium salt of acid **8b** was treated with  $\text{SOCl}_2$  to afford the acyl chloride, which upon treatment with  $\text{AgOCN}$ , generated acyl isocyanate **9**. The free amine, obtained after removal of the Boc protecting group of compound **7**, was reacted with **9** to afford acylurea **10**. Cyclization to produce the uracil moiety was effected by refluxing in aqueous ammonia<sup>25,41,42</sup> to afford **11** after benzyl ester formation (Scheme 3).

Separation of the two diastereomers of **11a,b** proved to be very difficult. An enzymatic resolution of these



(1)

diastereomers using chymotrypsin was attempted but failed to act on these substrates. We eventually found

(30) Zhang, D.; Ghosh, A.; Süling, C.; Miller, M. J. *Tetrahedron Lett.* **1996**, 37, 3799.

(31) Zhang, D.; Süling, C.; Miller, M. J. *J. Org. Chem.* **1998**, 63, in press.

(32) Trost, B. M.; Van Vranken, D. L. *Chem. Rev. (Washington, D.C.)* **1996**, 96, 395.

(33) Frost, C. F.; Howarth, J.; William, J. M. J. *Tetrahedron: Asymmetry* **1992**, 3, 1089.

(34) Wade, P. A.; Morrow, S. D.; Hardinger, S. A. *J. Org. Chem.* **1982**, 47, 365.

(35) Bellamy, F. D.; Ou, K. *Tetrahedron Lett.* **1984**, 25, 839.

(36) Petrini, M.; Ballini, R.; Rosini, G. *Synthesis* **1987**, 713.

(37) Hoffman, C.; Tanke, R. S.; Miller, M. J. *J. Org. Chem.* **1989**, 54, 3750.

(38) McMurry, J. E. *Acc. Chem. Res.* **1974**, 7, 281.

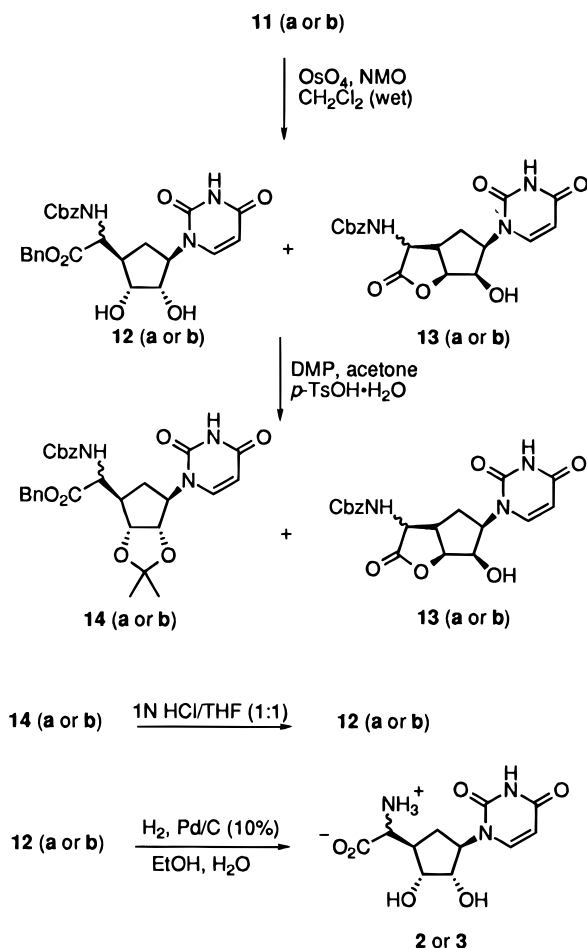
(39) McMurry, J. E.; Melton, J. J. *J. Org. Chem.* **1973**, 38, 4367.

(40) Shaw, G.; Warren, R. N. *J. Chem. Soc.* **1958**, 157.

(41) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, 48, 571.

(42) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, 50, 10611.

Scheme 4



that by using a Biotage Flash 40 system, up to 55% of the originally loaded mixture was separated (eq 1). Repeated chromatography with this system provided both diastereomers on a gram scale. The diastereomeric purity for **11a** and **11b** was determined by HPLC to be 98% and 95%, respectively.

Dihydroxylation of **11a** and **11b** with  $\text{OsO}_4$  was studied under different conditions with variations of solvents,  $\text{OsO}_4$  amount, and pH of the reaction mixture. Under all these conditions, diols **12** and lactones **13** were obtained in an approximately 1:1 ratio, that is presumably due to the possible coordination of nitrogen atoms to the osmium that promotes diol delivery from the upper face (Scheme 4). Due to intrinsic separation difficulties, dihydroxylation products **12** and **13** were treated with dimethoxypropane (DMP) under acidic conditions to convert diols **12** to acetonides **14** while not affecting lactones **13** which, in turn, were easily separated from acetonides **14**. From compound **11a**, diol **12a** also could be separated from lactone **13a** by two consecutive flash chromatographies. The relative stereochemistries of the α-chiral center for the **a** and **b** series were determined through NOESY studies on lactones **13a** and **13b**. The assignments were further confirmed by comparison with published results.<sup>26</sup> From acetonides **14**, regeneration of diols **12**, followed by careful hydrogenolyses, cleanly provided the desired (±) carbocyclic polyoxin C (**2**) and its α-epimer **3**.

### Conclusion

Racemic carbocyclic polyoxin C (**2**) and its α-epimer **3** were synthesized in an efficient and diastereodivergent

fashion. Relative stereochemistries of the chiral centers in the molecules were quickly established from the starting allylic acetate **5a**. The successful reduction of a nitro group to an amino group and subsequent separation of diastereomers make this unified design practical. These features would allow an efficient synthesis of all major carbocyclic polyoxin C analogues in an asymmetric fashion if optically pure allylic acetates were employed.

### Experimental Section

General methods and instruments used have been described previously.<sup>43</sup>

**cis-1-Acetoxy-4-N-(tert-butylcarbamoyl)-2-cyclopentene (5b).** To a solution of alcohol **5a**<sup>30,31</sup> (212 mg, 1.065 mmol) in pyridine- $\text{CH}_2\text{Cl}_2$  (1:1, 4 mL) at 0 °C was added a solution of  $\text{AcCl}$  (109 mg, 1.38 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL). The reaction was stirred at 0 °C overnight. After removal of  $\text{CH}_2\text{Cl}_2$ , the residue was diluted with EtOAc and was washed with 10% citric acid solution. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine and dried. Filtration and concentration in vacuo gave crude product. Flash chromatography (EtOAc:hexanes 1:3) afforded **5b** (256 mg, 100%) as a white solid; mp 56.5–58.5 °C;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  1.37 (s, 9H), 1.45 (dt,  $J = 13.5, 6.0$  Hz, 1H), 1.98 (s, 3H), 2.68 (dt,  $J = 13.5, 7.5$  Hz, 1H), 4.38 (m, 1H), 5.40 (m, 1H), 5.81 (dt,  $J = 5.4, 2.1$  Hz, 1H), 5.90 (m, 1H), 7.11 (d,  $J = 7.5$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  20.8, 28.2, 37.6, 53.3, 77.1, 77.8, 130.9, 137.3, 154.9, 170.1; IR (KBr) 3366, 1734, 1680, 1510  $\text{cm}^{-1}$ ; HRMS [ $\text{M}^+$ ] calcd for  $\text{C}_{12}\text{H}_{20}\text{NO}_4$  242.1392, found 242.1382. Anal. Calcd for  $\text{C}_{12}\text{H}_{19}\text{NO}_4$ : C, 59.73; H, 7.94; N, 5.81. Found: C, 59.81; H, 7.96; N, 5.65.

**Methyl 4-N-(tert-Butylcarbamoyl)-α-nitro-2-cyclopentene-1-acetate (6).** A 100 mL round-bottomed flask under  $\text{N}_2$  was charged with acetate **5b** (1.50 g, 6.22 mmol),  $\text{Pd}(\text{PPh}_3)_4$  (539 mg, 0.47 mmol),  $\text{PPh}_3$  (245 mg, 0.93 mmol),  $\text{NaOAc}$  (560 mg, 6.8 mmol), methyl nitroacetate (1.05 g, 8.7 mmol), and THF (50 mL). The reaction was stirred at 50–55 °C under  $\text{N}_2$  overnight. After removal of volatiles in vacuo, the residue was redissolved in EtOAc and washed with brine and dried. Filtration and concentration in vacuo gave crude product. Flash chromatography (EtOAc:hexanes 3:10) afforded **6** (1.77 g, 95%) as a colorless oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.45 (s, 9H), 1.55 (m, 1H), 2.71 (m, 1H), 3.57 (m, 1H), 3.85 (s, 3H), 4.60 (m, 1H), 4.77 (m, 1H), 5.09 (d,  $J = 7.5$  Hz, 1H), 5.77 (dt,  $J = 5.4, 2.0$  Hz, 1H), 5.87 (dt,  $J = 5.7, 2.1$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  28.3, 34.4, 45.1 (45.4), 53.5, 55.6 (55.9), 79.5, 90.4 (90.6), (130.3) 130.9, 135.7 (136.2), 155.0, 163.88 (163.93); IR (neat) 3338 (br), 2980, 1754, 1700 (br), 1560  $\text{cm}^{-1}$ ; HRMS [ $\text{M}^+$ ] calcd for  $\text{C}_{13}\text{H}_{21}\text{N}_2\text{O}_6$  301.1399, found 301.1402. Anal. Calcd for  $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_6$ : C, 51.99; H, 6.71; N, 9.33. Found: C, 52.25, H, 6.29; N, 9.35.

**Methyl α-[(Benzyloxy)carbonylamino]-4-N-(tert-butylcarbamoyl)-2-cyclopentene-1-acetate (7).** To a solution of L-tartaric acid (53 g, 1.02 mol) and NaOH (102 g, 2.55 mol) in water (620 mL) was added aqueous  $\text{TiCl}_3$  (15%, 124 mL, 112 mmol). The resulting mixture was adjusted to pH 7.8 using 1 N NaOH solution. To this green slurry was added  $\text{NaBH}_4$  (5.14 g, 136 mmol) quickly followed by a solution of **6** (6.78 g, 22.6 mmol) in MeOH (35 mL). The reaction was stirred under  $\text{N}_2$  for 30 min and then exposed to air and stirred overnight. The reaction mixture was saturated with  $\text{K}_2\text{HPO}_4$  and was extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was dried, filtered, and concentrated in vacuo to provide a slightly yellow residue. The residue was diluted with THF, and to this solution was added benzyl chloroformate (3.92 g, 23 mmol) while maintaining the pH at 9 during the reaction. After the reaction was complete, the mixture was adjusted to pH 5–6, and the aqueous layer was extracted with EtOAc three times. The organic layer was dried, filtered, and concentrated in vacuo to provide a crude product. Chromatography (EtOAc:

(43) Teng, M.; Miller, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 548.

hexanes 1:2.6) afforded **7** mainly as a mixture of two diastereomers (1:1, total 7.92 g, 87%). However, a small amount of one diastereomer was obtained in pure form, mp 83–85 °C. <sup>1</sup>H NMR (CD<sub>3</sub>OD, one ds) δ 1.42 (s, 9H), 1.52 (m, 1H), 2.40 (m, 1H), 3.12 (m, 1H), 3.73 (s, 3H), 4.30 (d, *J* = 6.3 Hz, 1H), 4.53 (m, 1H), 5.08 (s, 2H), 5.72 (m, 2H), 7.34 (m, 5H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 28.4, 32.6, 47.4, 52.4, 56.1, 67.0, 67.2, 79.4, 133.1, 134.1, 136.2, 155.2, 156.2, 171.8; IR (KBr) 3350, 1748, 1685, 1674 cm<sup>-1</sup>; HRMS [MH<sup>+</sup>] calcd for C<sub>21</sub>H<sub>29</sub>N<sub>2</sub>O<sub>6</sub> 405.2025, found 405.2017. Anal. Calcd for C<sub>21</sub>H<sub>28</sub>N<sub>2</sub>O<sub>6</sub>: C, 62.36; H, 6.98; N, 6.93. Found: C, 62.15; H, 7.06; N, 7.00.

**Methyl α-[[[(Benzyloxy)carbonyl]amino]-4-[[[(3-methoxyacryloyl)amino]carbonyl]amino]-2-cyclopentene-1-acetate (10).** To a precooled solution of **7** (4.51 g, 11.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (55 mL) was added TFA (33 mL). The solution was stirred at 0 °C for 15 and 45 min more at rt. The solvents were removed in vacuo, the residue was dissolved in THF, and DBU (6.1 g, 40 mmol) was added. The solution was cooled to -30 °C, and to this solution was added acyl isocyanate **9** (prepared by refluxing methoxyacryloyl chloride (3.10 g, 25.76 mmol) and AgOCN (5.54 g, 37 mmol) in benzene (50 mL) for 2.5 h). The reaction was stirred at -30 °C for 30 min and then at rt overnight. The solvent was removed in vacuo, the residue was redissolved in CH<sub>2</sub>Cl<sub>2</sub>, and the mixture was acidified to pH 5 with citric acid. The organic phase was separated, and the aqueous layer was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The organic layers were combined and washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and removal of the solvent in vacuo afforded a residue. Chromatography (EtOAc:hexanes 3:2) gave **10** mainly as a mixture of two diastereomers, but the following data are for single diastereomers obtained from early and late chromatography fractions. First diastereomer eluted: mp 131–3 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.52 (m, 1H), 2.45 (m, 1H), 3.23 (br, 1H), 3.70 (s, 3H), 3.76 (s, 3H), 4.55 (dd, *J* = 4.5, 7.8 Hz, 1H), 4.82 (dd, *J* = 6.6, 14.1 Hz, 1H), 5.06 (d, *J* = 12.3 Hz, 1H), 5.13 (d, *J* = 12.3 Hz, 1H), 5.29 (d, *J* = 12.3 Hz, 1H), 5.80 (m, 3H), 7.34 (m, 5H), 7.61 (d, *J* = 12.3 Hz, 1H), 8.77 (d, *J* = 7.5 Hz, 1H), 9.42 (br, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 32.6, 47.4, 52.4, 55.5, 56.1, 57.7, 67.0, 97.5, 128.0, 128.4, 133.3, 133.6, 136.2, 154.7, 156.2, 163.4, 167.7, 171.7; IR (KBr) 3462, 3266 (br), 1742, 1682 (br), 1616, 1540 cm<sup>-1</sup>; HRMS [MH<sup>+</sup>] calcd for C<sub>21</sub>H<sub>26</sub>N<sub>3</sub>O<sub>7</sub> 432.1771, found 432.1778. The latter diastereomer: mp 180.5–181.5 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.57 (m, 1H), 2.59 (m, 1H), 3.23 (br, 1H), 3.69 (s, 3H), 3.75 (s, 3H), 4.42 (dd, *J* = 4.5, 8.7 Hz, 1H), 4.87 (m, 1H), 5.08 (d, *J* = 12.3 Hz, 1H), 5.14 (d, *J* = 12.0 Hz, 1H), 5.34 (d, *J* = 12.3 Hz, 1H), 5.50 (m, 1H), 5.69 (m, 1H), 5.87 (m, 1H), 7.35 (m, 5H), 7.58 (d, *J* = 12.3 Hz, 1H), 8.79 (d, *J* = 7.8 Hz, 1H), 9.87 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 34.0, 46.7, 52.3, 55.4, 56.3, 57.6, 67.1, 97.5, 127.95, 127.99, 128.4, 131.5, 135.0, 136.1, 154.8, 156.4, 163.2, 167.8, 171.9; IR (KBr) 3312, 1734, 1684, 1618, 1532 cm<sup>-1</sup>; HRMS [MH<sup>+</sup>] calcd for C<sub>21</sub>H<sub>26</sub>N<sub>3</sub>O<sub>7</sub> 432.1771, found 432.1776. Anal. Calcd for C<sub>21</sub>H<sub>25</sub>N<sub>3</sub>O<sub>7</sub>: C, 58.46; H, 5.84; N, 9.74. Found: C, 58.43; H, 5.73; N, 9.50.

**Benzyl α-[[[(Benzyloxy)carbonyl]amino]-4-[3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-2-cyclopentene-1-acetate (11a).** To a solution of **10** (1.40 g, 3.2 mmol) in THF (50 mL) was added aqueous 0.5 N NaOH (8.4 mL, 4.2 mmol). The reaction was allowed to stir at rt overnight. The solvent was removed in vacuo to afford the crude product.

To the residue was added concentrated aqueous ammonia (120 mL). The solution was heated to 85–95 °C for 40 min. Most of the solvent was removed in vacuo, and the residue was redissolved in saturated aqueous NaHCO<sub>3</sub>. The aqueous solution was extracted with EtOAc twice. The aqueous layer was then acidified to pH 3 and extracted with EtOAc twice. The aqueous layer was saturated with NaCl and extracted again with EtOAc twice. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and removal of the solvent afforded a crude residue (1.23 g).

The residue was redissolved in DMF (8 mL), and to this solution was added NaHCO<sub>3</sub> (350 mg, 4.2 mmol). The mixture was stirred for 30 min followed by addition of BnBr (547 mg, 3.2 mmol) and NaI (5 mg, 0.03 mmol). The reaction was allowed to stir at rt overnight. The solvent was removed in

vacuo, and the residue was dissolved in EtOAc/citric acid (pH ~ 3), the aqueous layer was separated and extracted three times with EtOAc. The combined organic layers were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and removal of the solvent afforded a crude product. Chromatography with a Biotage Flash 40 system (EtOAc:CHCl<sub>3</sub> 2:3) provided two diastereomers with diastereomer **11b** eluting first. For **11a**, white solid, mp 178.5–180.5 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.46 (m, 1H), 2.73 (m, 1H), 3.28 (br, 1H), 4.53 (br, 1H), 5.09 (s, 2H), 5.17 (d, *J* = 12.0 Hz, 1H), 5.24 (d, *J* = 12.0 Hz, 1H), 5.43 (d, *J* = 8.7 Hz, 1H), 5.53 (d, *J* = 7.2 Hz, 1H), 5.63 (m, 1H), 5.67 (m, 1H), 5.88 (m, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 7.36 (s, br, 10H), 9.07 (br, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 33.4, 47.4, 56.1, 60.9, 67.5, 102.7, 128.3, 128.5, 128.6, 128.7, 128.8, 132.0, 134.8, 135.7, 135.9, 140.4, 150.8, 156.3, 163.1, 170.9; IR (KBr) 3325 (br), 1743, 1687 (br), 1625, 1517 cm<sup>-1</sup>; HRMS [MH<sup>+</sup>] calcd for C<sub>26</sub>H<sub>26</sub>N<sub>3</sub>O<sub>6</sub> 476.1821, found 476.1833. Anal. Calcd for C<sub>26</sub>H<sub>25</sub>N<sub>3</sub>O<sub>6</sub>: C, 65.67; H, 5.30; N, 8.84. Found: C, 65.48; H, 5.39; N, 8.68. For **11b**, white solid, mp 175.5–177.5 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.29 (m, 1H), 2.47 (m, 1H), 3.29 (br, 1H), 4.72 (br, 1H), 5.16 (m, 4H), 5.44 (d, *J* = 7.5 Hz, 1H), 5.52 (m, 1H), 5.57 (m, 1H), 5.77 (d, *J* = 8.1 Hz, 1H), 6.13 (br, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 7.35 (m, 10H), 9.20 (br, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 31.7, 48.1, 55.6, 61.1, 67.1, 67.6, 102.3, 128.3, 128.40, 128.43, 128.55, 128.66, 128.71, 130.1, 134.8, 136.0, 138.1, 140.7, 151.0, 156.0, 163.5, 170.7; IR (neat) 3300 (br), 3060, 1700, 1684 (br), 1530, 1246 cm<sup>-1</sup>; HRMS [MH<sup>+</sup>] calcd for C<sub>26</sub>H<sub>26</sub>N<sub>3</sub>O<sub>6</sub> 476.1821, found 476.1820. Anal. Calcd for C<sub>26</sub>H<sub>25</sub>N<sub>3</sub>O<sub>6</sub>: C, 65.67; H, 5.30; N, 8.84. Found: C, 65.77; H, 5.22; N, 8.83.

The diastereomeric purity of **11a** and **11b** was determined by HPLC (Waters: column: Microsorb-MV 5 μm, solvent: CH<sub>2</sub>Cl<sub>2</sub>:iPrOH 96:4; flow rate: 1 mL/min; detected at 254 nm).

**Benzyl α-[[[(Benzyloxy)carbonyl]amino]-4-[3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-2,3-di-O-isopropylidenecyclopentaneacetate (14a).** To a solution of **11a** (101 mg, 0.21 mmol) and NMO·H<sub>2</sub>O (43 mg, 0.32 mmol) in wet CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added a catalytic amount of OsO<sub>4</sub> (2 mg, 0.01 mmol). After TLC analysis indicated consumption of the starting material, the reaction was quenched with aqueous 1 M NaHSO<sub>3</sub> and was acidified to pH 5 with aqueous 10% citric acid. The organic layer was separated, and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and removal of the solvent in vacuo afforded a residue.

The residue was redissolved in acetone (5 mL), and to this solution was added dimethoxypropane (66 mg, 0.64 mmol) and *p*TsOH·H<sub>2</sub>O (4 mg, 0.02 mmol). The reaction was stirred overnight. The solvent was removed in vacuo, and the residue was redissolved in EtOAc. The solution was adjusted to pH 8 with saturated aqueous NaHCO<sub>3</sub>. The organic layer was separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and removal of the solvent afforded two crude products. Chromatography (EtOAc:CH<sub>2</sub>Cl<sub>2</sub> 2:3 and CH<sub>2</sub>Cl<sub>2</sub>:iPrOH 10:1) provided acetone **14a** (36 mg, 31%) as an oil and lactone **13a** (32 mg, 38%) as a white solid. Acetone **14a**, <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.22 (s, 3H), 1.43 (s, 3H), 2.04 (m, 2H), 2.49 (m, 1H), 4.41 (d, *J* = 6.9 Hz, 1H), 4.59 (m, 2H), 4.74 (dd, *J* = 5.0, 7.0 Hz, 1H), 5.08 (s, 2H), 5.15 (s, 2H), 5.64 (d, *J* = 7.8 Hz, 1H), 7.29 (m, 10H), 7.49 (d, *J* = 8.1 Hz, 1H); <sup>13</sup>C NMR (CD<sub>3</sub>OD) δ 25.6, 27.9, 33.8, 47.2, 49.9, 56.9, 64.6, 67.8, 68.2, 82.0, 83.7, 102.8, 114.9, 128.8, 129.0, 129.4, 129.46, 129.53, 137.0, 138.0, 145.3, 152.4, 158.5, 166.1, 172.5; IR (neat) 3300 (br), 1700, 1684 (br), 1530 cm<sup>-1</sup>; HRMS [MH<sup>+</sup>] calcd for C<sub>29</sub>H<sub>32</sub>N<sub>3</sub>O<sub>8</sub> 550.2189, found 550.2159. Anal. Calcd for C<sub>29</sub>H<sub>31</sub>N<sub>3</sub>O<sub>8</sub>: C, 63.38; H, 5.69; N, 7.65. Found: C, 63.53; H, 5.71; N, 7.57. Lactone **13a**, mp 225–227 °C dec; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.70 (ddd, *J* = 7.5, 12.0, 14.8 Hz, 1H), 2.13 (pesudo-dd, *J* = 12.3, 23.1 Hz, 1H), 3.04 (m, 1H), 4.13 (dd, *J* = 4.6, 6.6 Hz, 1H), 4.67 (m, 1H), 4.87 (m, 2H), 5.06 (d, *J* = 12.0 Hz, 1H), 5.10 (d, *J* = 12.0 Hz, 1H), 5.55 (2d, *J* = 8.1 Hz, 1H), 5.60 (d, *J* = 5.1 Hz, 1H), 7.37 (m, 5H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.73 (d, *J* = 9.6 Hz, 1H), 11.28 (br, s, 1H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 26.3, 36.3, 51.7, 55.8, 65.9, 68.8, 79.9, 99.7, 127.8, 127.9, 128.4, 136.7, 143.6, 151.3, 156.4, 163.2, 174.9; IR (KBr)

3382, 1776, 1700, 1684 (br), 1524  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_7$ : C, 56.86; H, 4.77; N, 10.47. Found: C, 56.82; H, 4.90; N, 10.26.

**Benzyl  $\alpha$ -[[[(Benzyloxy)carbonyl]amino]-4-[3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-2,3-di-O-isopropylidenecyclopentaneacetate (14b).** A procedure similar to that used for conversion of **11a** was applied to **11b**. Acetonide **14b** was obtained in 37% yield as a white solid and lactone **13b** was obtained in 49% yield as a white solid. Acetonide **14b**, mp 185–187  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  1.21 (s, 3H), 1.43 (s, 3H), 1.98 (m, 1H), 2.16 (m, 1H), 2.43 (m, 1H), 4.37 (d,  $J$  = 8.4 Hz, 1H), 4.61 (m, 2H), 4.72 (dd,  $J$  = 5.0, 7.0 Hz, 1H), 5.06 (br, 2H), 5.14 (s, 2H), 5.65 (d,  $J$  = 8.1 Hz, 1H), 7.30 (m, 10H), 7.52 (d,  $J$  = 8.1 Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  25.6, 27.9, 33.8, 47.3, 57.3, 64.0, 67.9, 68.4, 82.0, 84.0, 102.9, 114.8, 128.9, 129.0, 129.4, 129.46, 129.51, 137.0, 138.0, 145.2, 152.5, 158.6, 166.1, 172.8; IR (KBr) 3320 (br), 1750, 1702, 1684, 1676  $\text{cm}^{-1}$ ; HRMS [ $\text{MH}^+$ ] calcd for  $\text{C}_{29}\text{H}_{32}\text{N}_3\text{O}_8$  550.2189, found 550.2211. Anal. Calcd for  $\text{C}_{29}\text{H}_{31}\text{N}_3\text{O}_8$ : C, 63.38; H, 5.69; N, 7.65. Found: C, 63.26; H, 5.49; N, 7.39. Lactone **13b**, mp 228–230  $^{\circ}\text{C}$  dec;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  2.10 (dt,  $J$  = 5.1, 12.3 Hz, 1H), 2.25 (dt,  $J$  = 12.3, 8.7 Hz, 1H), 2.86 (m, 1H), 4.01 (dd,  $J$  = 3.6, 4.8 Hz, 1H), 4.16 (t,  $J$  = 5.4 Hz, 1H), 4.80 (dt,  $J$  = 2.1, 10.2 Hz, 1H), 4.92 (dd,  $J$  = 3.6, 9.6 Hz, 1H), 5.04 (s, 2H), 5.54 (d,  $J$  = 7.8 Hz, 1H), 6.04 (d,  $J$  = 4.5 Hz, 1H), 7.36 (m, 5H), 7.83 (d,  $J$  = 8.4 Hz, 1H), 7.91 (d,  $J$  = 8.4 Hz, 1H), 11.31 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  30.8, 54.7, 58.0, 65.8, 69.6, 79.8, 100.1, 127.9, 128.4, 136.7, 143.5, 151.3, 155.8, 163.1, 175.7; IR (KBr) 3400 (br), 1780, 1700, 1684 (br)  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_7$ : C, 56.86; H, 4.77; N, 10.47. Found: C, 56.68; H, 4.63; N, 10.22.

**Benzyl  $\alpha$ -[[[(Benzyloxy)carbonyl]amino]-4-[3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-2,3-dihydroxycyclopentaneacetate (12a).** To a solution of acetonide **14a** (126 mg, 0.23 mmol) in THF (4 mL) was added N HCl (4 mL), and the reaction was stirred at rt overnight. The solvent was removed in vacuo and the residue was purified by chromatography ( $\text{CH}_2\text{Cl}_2$ :iPrOH 10:1) to afford the diol **12a** (78 mg, 67%) as a white solid, mp 87–89  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  1.56 (dd,  $J$  = 11.1, 23.1 Hz, 1H), 2.00 (m, 1H), 2.37 (m, 1H), 4.04 (dd,  $J$  = 5.1, 6.3 Hz, 1H), 4.12 (dd,  $J$  = 6.3, 7.8 Hz, 1H), 4.38 (d,  $J$  = 7.2 Hz, 1H), 4.51 (m, 1H), 5.07 (s, 2H), 5.15 (s, 2H), 5.62 (d,  $J$  = 7.8 Hz, 1H), 7.30 (m, 10H), 7.41 (d,  $J$  = 8.1 Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  28.6, 46.4, 57.4, 64.1, 67.8, 68.1, 72.4, 74.2, 102.6, 128.8, 129.0, 129.4, 129.47, 129.50, 129.6, 137.0, 138.0, 144.8, 152.8, 158.6, 166.2, 172.7; IR (neat) 3375 (br), 1720 (br), 1685 (br)  $\text{cm}^{-1}$ ; HRMS [ $\text{MH}^+$ ] calcd for  $\text{C}_{26}\text{H}_{28}\text{N}_3\text{O}_8$  510.1876, found 510.1895.

**Benzyl  $\alpha$ -[[[(Benzyloxy)carbonyl]amino]-4-[3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-2,3-dihydroxycyclopentaneacetate (12b).** Similar treatment of acetonide **14b** afforded diol **12b** in 83% yield as a white solid after purification by chromatography, mp 89–91  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  1.60 (pseudo-dd,  $J$  = 11.0, 23.0 Hz, 1H), 1.95 (dt,  $J$  = 12.9, 8.1 Hz,

1H), 2.49 (m, 1H), 4.02 (pseudo-t,  $J$  = 5.5 Hz, 1H), 4.12 (dd,  $J$  = 6.6, 7.2 Hz, 1H), 4.54 (m, 2H), 5.05 (d,  $J$  = 10.5, 1H), 5.08 (d,  $J$  = 10.5, 1H), 5.12 (d,  $J$  = 12.3 Hz, 1H), 5.17 (d,  $J$  = 12.3 Hz, 1H), 5.63 (d,  $J$  = 7.8 Hz, 1H), 7.29 (m, 10H), 7.48 (d,  $J$  = 8.1 Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  27.5, 46.2, 56.7, 64.2, 67.9, 68.2, 72.4, 74.6, 102.5, 128.8, 129.0, 129.30, 129.32, 129.4, 129.5, 137.0, 137.9, 145.0, 152.8, 158.8, 166.2, 172.8; IR (neat) 3340 (br), 1700, 1685, 1678 (br)  $\text{cm}^{-1}$ ; HRMS [ $\text{MH}^+$ ] calcd for  $\text{C}_{26}\text{H}_{28}\text{N}_3\text{O}_8$  510.1876, found 510.1879.

**$\alpha$ -Amino-4-[3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-2,3-dihydroxycyclopentaneacetic Acid (2).** To a solution of diol **12a** (28 mg, 0.055 mmol) in EtOH/ $\text{H}_2\text{O}$  (2.2 mL, 10:1) was added Pd/C(10%) (7 mg). The system was purged first with Ar and then  $\text{H}_2$ . The reaction was stirred under  $\text{H}_2$  (1 atm) for 75 min at rt. The system was purged with Ar again, and the mixture was diluted in 15 mL of  $\text{H}_2\text{O}$  and filtered. Removal of solvent in vacuo afforded pure product **2** (15.4 mg, 98%) as a white solid, mp 198–202  $^{\circ}\text{C}$  dec;  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$  with 1,4-dioxane)  $\delta$  1.46 (dt,  $J$  = 12.6, 10.9 Hz, 1H), 2.02 (dt,  $J$  = 12.6, 7.5 Hz, 1H), 2.13 (m, 1H), 3.64 (d,  $J$  = 6.6 Hz, 1H), 4.40 (pseudo-dt,  $J$  = 10.9, 7.5 Hz, 1H), 5.64 (d,  $J$  = 8.1 Hz, 1H), 7.42 (d,  $J$  = 8.1 Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$  with 1,4-dioxane)  $\delta$  26.7, 46.6, 56.7, 62.7, 72.3, 73.0, 102.0, 144.5, 152.2, 166.4, 172.9; IR (KBr) 3410 (br), 1720, 1675, 1645  $\text{cm}^{-1}$ ; HRMS [ $\text{MH}^+$ ] calcd for  $\text{C}_{11}\text{H}_{16}\text{N}_3\text{O}_6$  286.1039, found 286.1047.

**$\alpha$ -Amino-4-[3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-2,3-dihydroxycyclopentaneacetic Acid (3).** Similar treatment of diol **12b** (86 mg) with Pd/C (25 mg) in EtOH/ $\text{H}_2\text{O}$  (6.6 mL, 10:1) afforded the product **3** (48 mg, quantitative) as a white solid, mp 200–204  $^{\circ}\text{C}$  dec;  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$  with 1,4-dioxane as internal leble)  $\delta$  1.71 (dt,  $J$  = 12.9, 11.1 Hz, H), 2.04 (dt,  $J$  = 15.9, 8.1 Hz, 1H), 2.25 (m, 1H), 3.65 (d,  $J$  = 5.1 Hz, 1H), 3.95 (t,  $J$  = 6.4 Hz, 1H), 4.02 (dd,  $J$  = 6.3, 6.9 Hz, 1H), 4.40 (pseudo-dt,  $J$  = 10.5, 7.2 Hz, 1H), 5.65 (d,  $J$  = 8.1 Hz, 1H), 7.45 (d,  $J$  = 8.1 Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$  with 1,4-dioxane)  $\delta$  26.7, 43.4, 55.6, 62.5, 70.6, 73.3, 102.0, 144.6, 152.2, 166.3, 172.9; IR (KBr) 3412 (br), 1707, 1656  $\text{cm}^{-1}$ ; HRMS [ $\text{MH}^+$ ] calcd for  $\text{C}_{11}\text{H}_{16}\text{N}_3\text{O}_6$  286.1039, found 286.1026.

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**Supporting Information Available:**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for **12a**, **12b**, **2**, **3**, and the first eluted diastereomer of **10** (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 the ACS; see any current masthead page for ordering information.

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