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Chemoenzymatic Asymmetric Total Synthesis of Phosphodiesterase Inhibitors: Preparation of a Polycyclic Pyrazolo[3,4-*d*]pyrimidine from an Acylnitroso Diels−Alder Cycloadduct-Derived Aminocyclopentenol

May Xiao-Wu Jiang, Namal C. Warshakoon, and Marvin J. Miller*

Department of Chemistry & Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556-5670

mmiller1@nd.edu

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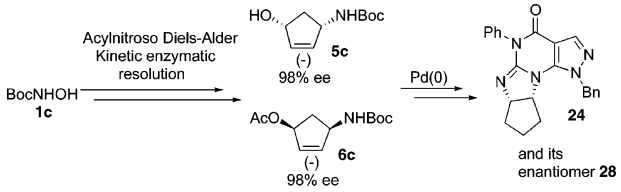
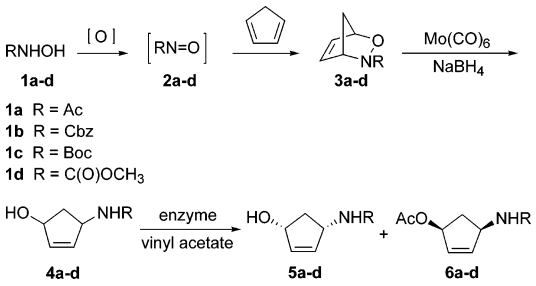


Enzymatic resolution of Boc-protected 4-aminocyclopenten-1-ol **4c** gave both enantiomers **5c** and **6c** in high ee. Boc removal and separate condensation with chloropyrazolopyrimidine **18** provided elaborated 1,4-aminocyclopentenol derivatives **20** and **26**, respectively. Separate treatment of **20** and **26** with Pd(0) under basic conditions induced cyclization to unsaturated polycycles **22** and **27**, which, upon catalytic hydrogenation, were transformed to new cyclopentane-containing pyrazolopyrimidines **24** and **28**, analogues of recently described novel phosphodiesterase inhibitors.

Functionalized cyclopentane derivatives are major constituents of many natural products and analogues,[1] and stereoselective syntheses of cyclopentane derivatives have been especially important for the preparation of a number of carbocyclic nucleosides.[2] Functionalized aminocyclopentenol derivatives are also potential aminoglycosidase inhibitors.[1c,3] We have previously described an efficient enzymatic resolution of 4-aminocyclopentol-1-ol **4**[4] derived from acylnitroso Diels−Alder adducts **3**[5] (Scheme 1).

Using this process, both enantiomers of the Boc-protected 4-aminocyclopenten-1-ol **4** are available in optically pure form by employing different enzymes. The synthetic utility of related aminocyclopentenol derivatives has been

SCHEME 1



highlighted by several recent applications.[6a,b,7] Derivatives of acetate **6** are ideally suited for the introduction of nucleophiles via palladium-mediated π-allyl chemistry.[8] Here we report an application of enantiomerically pure aminocyclopentenol **5** or **6** in the synthesis of phosphodiesterase inhibitor analogues of recent interest. Phosphodiesterases (PDE) are involved in cyclic nucleotide regulation,[9] and PDE inhibition as a target for therapeutic intervention is of considerable interest.[10] More specifically, the beneficial effects of inhibition of the cGMP PDE for the treatment of cardiovascular diseases have been notable.[11] These biological properties resulted in numerous research programs directed toward the synthesis of PDE inhibitors and analogues thereof.[12] Polycyclic guanine derivatives of the general type **7** (Figure 1) were found to be potent inhibitors of PDE1 and PDE5 in vitro and potent antihypertensive agents in vivo.[13] Polyclic pyrazolo[3,4-*d*] analogues of the type **8** and **9** have also been found to have similar activity.[14] As

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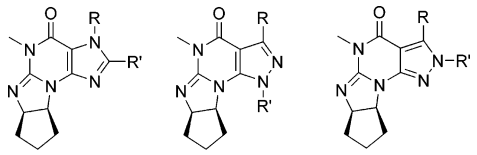
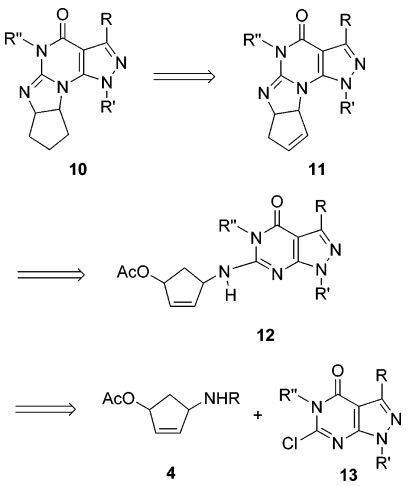


FIGURE 1. Polycyclic guanine PDE inhibitors **7** and pyrazolo[3,4-*d*]pyrimidine analogues **8** and **9**.

SCHEME 2



shown in Scheme 2, we anticipated that related analogues **10** could be prepared by Pd(0)-mediated cyclizations of **12** to **11** followed by the reduction of the remaining double bond. By using enzymatically resolved compound **4**, both enantiomers of **10** could be prepared by similar methods.

As indicated in Scheme 1, our previous publication reported the enzymatic resolution of a number of *N*-protected aminocyclopentenol **4** to provide either **5** or **6** in high ee.[4] The starting material **4** for this resolution was prepared through protection of hydroxylamine, oxidation, and trapping of the transient nitroso intermediate with cyclopentadiene to produce (±)-**3** and N−O bond reduction using substoichiometric (20 mol %) $Mo(CO)_6$ and $NaBH_4$ as we have also previously described.[6] Although this method provided access to large amounts of optically pure **5a** and **6a**, further elaboration of these building blocks for the synthesis of complex carbocyclic nucleosides and other highly functionalized cyclopentane-containing compounds of interest often required the exchange of the *N*-acetyl protecting group for one that could be removed under milder conditions. Therefore, we sought to improve the resolution of Boc-protected aminocyclopentenol (±)-**4c** which, using our reported methodology,[4] gave acetate (−)-**6c** in 81% ee (without recrystallization). To develop a method that would also enable us to recycle the enzyme, immobilized *Candida antarctica B*[15] was used. Racemic aminocyclopentenol (±)-**4c** was mixed with vinyl acetate and enzyme in wet CH_2Cl_2 or heptane/CH_2Cl_2 for 3−4 h at room temperature providing **6c** in 40−50% yield and leaving **5c** unreacted. After chromatographic separation, (−)-**6c** was determined to be significantly optically enriched, the ee was improved from 81% to >90% with the use of the resin-bound enzyme (ee was determined by hydrolysis of the acetate and acylation to give the corresponding Mosher ester as described earlier[4]). A single recrystallization of **6c** provided multigram amounts of (−)-**6c** in >98% ee. The chromatographically separated alcohol was enriched in **5c** and was isolated in 35−45% yield. After a single recrystallization, the compound was determined to be essentially optically pure (>99% ee) by Mosher ester analysis.

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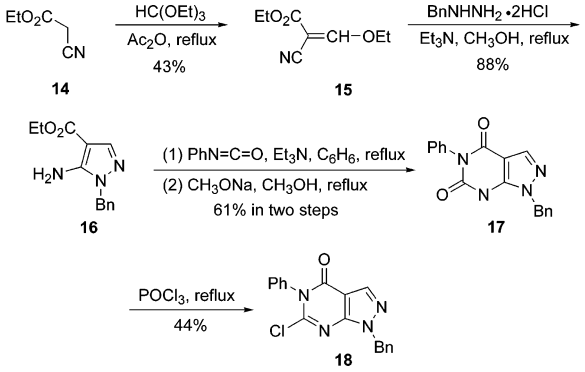
SCHEME 3



Pyrazole **16** was prepared via a modified procedure (Scheme 3).[14] Condensation of ethyl cyanoacetate **14** with triethyl orthoformate generated ethyl (ethoxyethylene)-cyanoacetate **15**, which was then converted to pyrazole **16** by treatment with benzylhydrazine. Condensation of **16** with phenyl isocyanate followed by base-promoted cyclization formed intermediate **17**. Compound **17** was then converted to the desired chloride **18** by treatment with phosphorus oxychloride.

Next, as shown in Scheme 4, enantiopure **5c** was converted to acetate **19**. The Boc group was removed and the resultant TFA salt of **19** was neutralized and condensed with chloride **18** in the presence of triethylamine to afford **20** in 96% yield. Our next task was to perform the crucial palladium(0)-mediated cyclization reaction. Gratifyingly, treatment of **20** with in situ generated palladium(0) in THF induced formation of the desired product, **22**, under basic conditions (Table 1). It was found that this reaction was sensitive to the base used. When the relatively weak base NEt_3 was used, the reaction proceeded slowly, and after overnight, only 20% of the starting material was consumed. When NaH was used, the reaction was complete in 3 h and gave the desired product in 79% yield. When the organic base 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine, **21**, was utilized, the cyclization reaction gave the highest yield (94%) of product **22**. Compound **22** was then subjected to catalytic hydrogenation. It was surprising to find that upon complete reaction of **22**, rather than the desired hydrogenated product **24**, the ring-opened product **23** was generated in 50% yield as the only isolable product after the reaction was carried out with Pd/C and H_2. The structure of **23** was first determined by extensive 1D and 2D NMR analysis. It was further confirmed by synthesizing **23** through the simple coupling reaction of cyclopentylamine **25** with chloride **18** under conditions similar to those used to prepare **20** (Scheme 5).

SCHEME 4

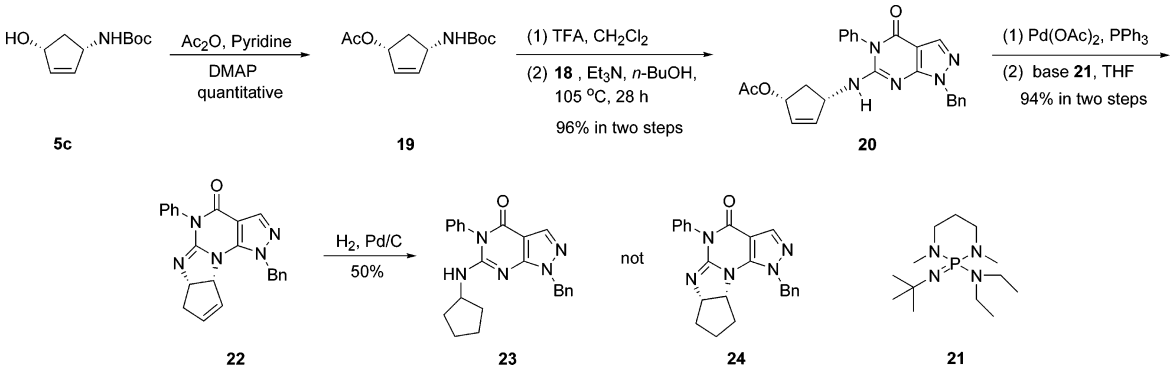


TABLE 1. Pd(0)-Catalyzed Cyclization Reaction of 20 to 22 under Basic Conditions

base	time (*t*)	yield of **22** (%)
NEt_3	overnight	10 (20% conversion)
NaH	3 h	79
21	3 h	94

SCHEME 5

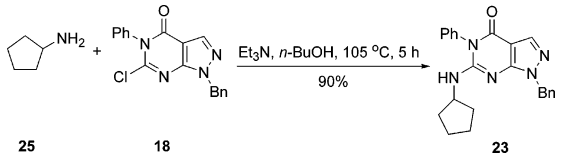
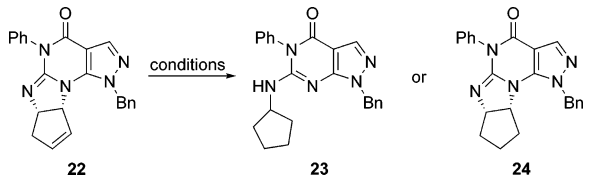


TABLE 2. Hydrogenation Reaction of Compound 22 under Different Conditions



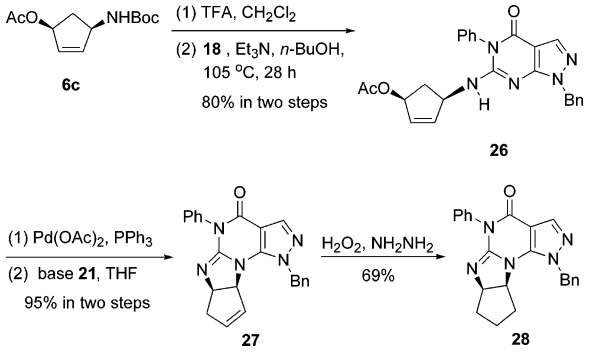
conditions	product, yield (%)
Pt/C, H_2	**23**, 50
PtO_2, H_2	**23**, 50 (90% conversion)
H_2O_2, NH_2NH_2	**24**, 60

The hydrogenation reaction was carried out under different conditions, which are summarized in Table 2. The desired selective reduction was finally achieved by the reaction of **22** with diimide[16] (HNNH, generated in situ by reaction of aqueous hydrogen peroxide and hydrazine in EtOH solution) to give **24** in 50−60% yield. Starting with enantiomerically pure compound **6c**, the enantiomer of **24** also has been synthesized (Scheme 6).

Preliminary determination of phosphodiesterase (PDE1) inhibition at a concentration of 100 μM revealed modest activity of 26% inhibition by precursor **20** and a more significant 71% inhibition by ring-opened product **23**. Both enantiomers of **24** and **28** showed modest PDE1 inhibition, with IC_{50} values of 55.8 and 41.2 μM, respectively.

In conclusion, we were able to develop a mild and potentially general protocol for the construction of polycylic pyrazolo[3,4-*d*]pyrimidines in a highly efficient manner (54% overall yield starting from optically pure Boc-protected aminocyclopentenol **5c** and 52% overall yield from **6c**). In addition to the high chemical efficiency, this route should be compatible with peripheral variation that will allow access to a library of compounds suitable for biological study.

SCHEME 6



Experimental Section

Enzymatic Acetylations. To a solution of **4c** (10 g, 50.25 mmol) in a mixture of wet heptane/dichloromethane (2.8:1, 380 mL) was added vinyl acetate (22.2 mL, 240.9 mmol). The wet heptane was prepared by thoroughly mixing with water in a 1 L bottle, the two layers were allowed to separate, and the organic layer was decanted and used. Resin-bound *C. antarctica* B lipase (CAB*)[15] (1 g) was added, and the resultant mixture was shaken vigorously in an incubator−shaker at room temperature while the reaction was monitored by TLC. The conversion was complete within 3 h, although longer times had no deleterious effect. The mixture was filtered through a filter paper to remove the resin-bound enzyme. The enzyme was recovered and could be used a second time of resolution of **4c**. The solvent was removed from the filtrate, and the mixture was then purified using column chromatography (hexanes/EtOAc 10:1) to afford 5.2 g (43%) of **6c** as a white solid (90% ee, determined by hydrolysis of the acetate (K_2CO_3/MeOH) and derivatization with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetyl chloride for Mosher ester analysis) The product, **6c**, was recrystallized using hexanes to afford 4.6 g of **6c** as a white, crystalline solid (98% ee): $[\alpha]_D = -22.6$ ($c = 0.40$, $CHCl_3$); mp = 57−58 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 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}C NMR (75 MHz, DMSO-d_6) δ 20.8, 28.2, 37.6, 53.3, 77.1, 77.8, 130.9, 137.3, 154.9, 170.1; HRMS [MH^+] calcd for $C_{12}H_{19}NO_4$ 242.1392, found 242.1382. The unreacted alcohol **5c** was recovered in 42% yield with 98% ee after recrystallization from hexanes/EtOAc at 0 °C: $[\alpha]_D = -69.0$

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(c=1.0, $CHCl_3$); mp = 103−104 °C. Spectral data were identical to those previously reported.[4]

1-Benzyl-6-chloro-5-phenyl-1,5-dihydropyrazolo[3,4-*d*]-pyrimidin-4-one (**18**). Compound **17** (1.1 g, 3.45 mmol)[14] was heated with $POCl_3$ (16 mL) at reflux for 48 h. The solution was cooled and diluted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$ (Caution, vigorous exotherm and gas evolution), H_2O, and brine and dried with $MgSO_4$. After filtration and concentration, the residue was purified by column chromotagraphy eluting with hexanes/EtOAc from 10:1 to 5:1 to 3:1 to give 0.51 g (44% yield) of a white solid: mp = 159−161 °C; R_f = 0.65 (hexanes/EtOAc = 1:1); ^{1}H (300 MHz, $CDCl_3$) δ 5.49 (s, 2H), 7.21−7.23 (m, 2H), 7.25−7.39 (m, 5H), 7.48−7.55 (m, 3H), 8.07 (s, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 51.2, 104.3, 128.1, 128.1, 128.3, 128.7, 129.6, 129.6, 135.6, 136.0, 137.2, 148.3, 149.7, 157.2; IR (KBr) 3065, 1723, 1565, 1489, 1284, 1224, 1186, 1031, 712 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{14}N_4O^{35}Cl$ $(M + H)^+$ 337.0856, found 337.0850.

Acetic Acid 4-(1-Benzyl-4-oxo-5-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidinyl-6-amino)cyclopent-2-enyl Ester (**20**). To an ice-cold solution of **19** (50 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (0.17 mL). The mixture was stirred at 0 °C for 20 min, warmed to room temperature, and stirred for another 1 h. The solvent was removed by coevaporation with toluene (2 × 2 mL). The residue was dissolved in *n*-BuOH (2 mL). Chloride **18** (142 mg, 0.42 mmol) was added to the solution followed by Et_3N (0.26 mL, 1.89 mmol). The mixture was heated at 105 °C for 28 h under an Ar atmosphere. After the reaction was cooled, the solvent was removed and the residue was purified by column chromatography eluting with hexanes/EtOAc (3:1 to 1:1) to afford 89 mg (96% yield) of a white foam: mp = 64 °C; R_f = 0.65 (1:1 of hexanes/EtOAc); $[\alpha]_D$ = −7.2 (c = 1.0, $CHCl_3$); ^{1}H (500 MHz, $CDCl_3$) δ 1.44 (dt, J = 4, 14 Hz, 1H), 1.93 (s, 3H), 2.81 (q, J = 7.5 Hz, 1H), 4.23 (d, J = 7.5 Hz, 1H), 5.03−5.05 (m, 1H), 5.39 (s, 2H), 5.50−5.51 (m, 1H), 5.94−5.98 (m, 2H), 7.23−7.38 (m, 6H), 7.50−7.58 (m, 4H), 7.97 (s, 1H); ^{13}C (125 MHz, $CDCl_3$) δ 21.0, 38.5, 50.6, 55.6, 77.2, 100.2, 127.8, 128.1, 128.6, 129.0, 129.1, 129.9, 130.6, 130.6, 133.2, 134.5, 135.9, 136.0, 136.7, 151.9, 152.4, 158.1, 170.3; IR (CH_2Cl_2, NaCl) v 2987, 1765, 1665, 1221, 880 cm^{-1}; HRMS (FAB) calcd for $C_{25}H_{24}N_5O_3$ $(M + H)^+$ 442.1879, found 442.1879.

(6a*S*,9a*R*)-5,6a,7,9a-Tetrahydro-5-phenyl-1-(phenylmethyl)cyclopent[4.5]imidazo[1,2-*a*]pyrazolo[4,3-*e*]pyrimidin-4(1*H*)one (22). Compound **20** (31 mg, 0.07 mmol) was dissolved in dry THF (1 mL). In a separate flask, $Pd(OAc)_2$ (3.1 mg, 0.2 equiv) was mixed with PPh_3 (18.4 mg, 1 equiv) in dry THF (1 mL). The in situ generated Pd(0) was added to the solution of **20**, and the mixture was stirred at room temperature for 5 min. 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine **21** (41 μL, 2 equiv) was added to the mixture, and the reaction was stirred at room temperature for 6 h. Another portion of in situ generated Pd(0) (0.2 equiv) was then added. After 1 h, the reaction was complete. It was then quenched with H_2O and extracted with EtOAc. The organic phase was dried with $NaSO_4$. After filtration and concentration, the residue was purified by column chromatography eluting with hexanes and EtOAc (1:1−1:4) to give 25 mg (94% yield) of an oil: R_f = 0.14 (hexanes/EtOAc = 1:4); $[\alpha]_D$ = −99.7 (c = 0.75, $CHCl_3$); ^{1}H (500 MHz, $CDCl_3$) δ 2.56−2.61 (m, 1H), 2.74−2.79 (m, 1H), 4.72 (t, J = 7 Hz, 1H), 5.23 (d, J = 8 Hz, 1H), 5.43 (d, J = 17 Hz, 1H), 5.60−5.61 (m, 1H), 5.65 (d, J = 17 Hz, 1H), 6.10−6.11 (m, 1H), 7.14−7.49 (m, 10H), 7.95 (s, 1H); ^{13}C (125 MHz, $CDCl_3$) δ 40.8, 53.3, 66.9, 68.1, 99.7, 125.8, 126.1, 128.4, 128.6, 128.8, 129.3, 129.5, 135.9, 136.0, 137.7, 138.5, 142.7, 151.6, 157.7; IR (CH_2Cl_2, NaCl) 2918, 1702, 1632, 1592, 1548, 1426, 731 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{20}N_5O$ $(M + H)^+$ 382.1668, found 382.1651.

1-Benzyl-6-cyclopentylamino-5-phenyl-1,5-dihydropyrazolo[3,4-*d*]pyrimidin-4-one (23). A solution of compound **22** (20 mg, 0.05 mmol) in methanol (5 mL) was charged with Pd/C (10%, 6.6 mg). The mixture was stirred under a balloon filled with H_2. The reaction was monitored by TLC. Upon completion of the reaction, the mixture was diluted with EtOAc and filtered through a thin pad of Celite. The solvent was removed, and the residue was purified by column chromatography eluting with hexanes and EtOAc (1:1) to give 9.4 mg (49% yield) of a white solid: mp = 138−140 °C; R_f = 0.68 (hexanes/EtOAc = 1:4); ^{1}H (500 MHz, $CDCl_3$) δ 1.25−1.33 (m, 2H), 1.56−1.63 (m, 4H), 2.00−2.08 (m, 2H), 4.11 (d, J = 6.5 Hz, 1H), 4.31, 4.32 (td, J = 8.5, 6.5 Hz), 5.44 (s, 2H), 7.28−7.63 (m. 10H), 7.97 (s, 1H); ^{13}C (125 MHz, $CDCl_3$) δ 23.5, 33.0, 50.5, 53.8, 100.0, 127.7, 128.2, 128.6, 129.1, 129.8, 130.5, 134.8, 135.8, 136.8, 152.4, 152.8, 158.2; IR (CH_2Cl_2, NaCl) 3000, 2987, 1554, 1223, 890 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{24}N_5O$ $(M + H)^+$ 386.1981, found 386.1998.

(6a*S*,9a*R*)-5,6a,7,8,9,9a-Hexahydro-5-phenyl-1-(phenylmethyl)cyclopent[4.5]imidazo[1,2-*a*]pyrazolo[4,3-*e*]pyrimidine-4(1*H*)-one (24). To a solution of compound **22** (21 mg, 0.055 mmol) in ethanol (1 mL) were added 35% NH_2NH_2 (0.05 mL, 0.55 mmol) and 30% H_2O_2 (0.07 mL, 0.66 mmol) three times at 8 h intervals. The reaction was quenched with 1 M $Na_2S_2O_3$ solution, extracted with CH_2Cl_2, washed with brine, and dried with $NaSO_4$. After filtration and concentration, the residue was purified by column chromatography eluting with hexanes and EtOAc (1:4) to give 10 mg (50% yield) of an oil: $[\alpha]_D$ = −162 (c = 1.0, $CHCl_3$); ^{1}H (500 MHz, $CDCl_3$) δ 1.61−2.09 (m, 6H), 4.62−4.64 (m, 2H), 5.38 (d, J = 16.5 Hz, 1H), 5.64 (d, J = 17 Hz, 1H), 7.14−7.52 (m, 10H), 7.97 (s, 1H); ^{13}C (125 MHz, $CDCl_3$) δ 23.1, 34.3, 35.1, 53.3, 62.6, 70.7, 99.7, 126.0, 128.4, 128.6, 128.7, 129.2, 129.5, 136.1, 136.2, 138.5, 142.5, 152.3, 157.7; IR (CH_2Cl_2, NaCl) 2960, 1701, 1633, 1591, 1549, 760 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{22}N_5O$ $(M + H)^+$ 384.1824, found 384.1822.

Acetic Acid 4-(1-Benzyl-4-oxo-5-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidinyl-6-amino)cyclopent-2-enyl Ester (26, *ent*-20). The compound was prepared using the same procedure employed for the synthesis of its enantiomer (**20**): $[\alpha]_D$ = +8.1 (c = 1.0, $CHCl_3$); ^{1}H and ^{13}C data were identical to those of its enantiomer **20**; HRMS (FAB) calcd for $C_{25}H_{24}N_5O_3$ $(M + H)^+$ 442.1879, found 442.1852.

(6a*R*,9a*S*)-5,6a,7,9a-Tetrahydro-5-phenyl-1-(phenylmethyl)cyclopent[4,5]imidazo[1,2-*a*]pyrazolo[4,3-*e*]pyrimidin-4(1*H*)-one (27). The compound was prepared using the same procedure employed for the synthesis of its enantiomer (**22**): $[\alpha]_D$ = +100 (c = 1.0, $CHCl_3$); R_f = 0.14 (hexanes/EtOAc = 1:4); ^{1}H and ^{13}C data were identical to its enantiomer **22**; HRMS (FAB) calcd for $C_{23}H_{20}N_5O$ $(M + H)^+$ 382.1668, found 382.1659.

(6a*R*,9a*S*)-5,6a,7,8,9,9a-Hexahydro-5-phenyl-1-(phenylmethyl)cyclopent[4,5]imidazo[1,2-*a*]pyrazolo[4,3-*e*]pyrimidin-4(1*H*)-one (28). The compound was prepared using the same procedure employed for the synthesis of its enantiomer (**24**): $[\alpha]_D$ = +169 (c = 0.93, $CHCl_3$); R_f = 0.14 (hexanes/EtOAc = 1:4); ^{1}H and ^{13}C data were identical to its enantiomer **24**; HRMS (FAB) calcd for $C_{23}H_{22}N_5O$ $(M + H)^+$ 384.1824, found 384.1830.

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Note Added after ASAP Publication. The compound numbers were omitted from the Table of Contents graphic in the version published ASAP March 4, 2005. The corrected version was published March 10, 2005.

Supporting Information Available: ^{1}H and ^{13}C NMR of compounds **20**, **22**, **23**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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