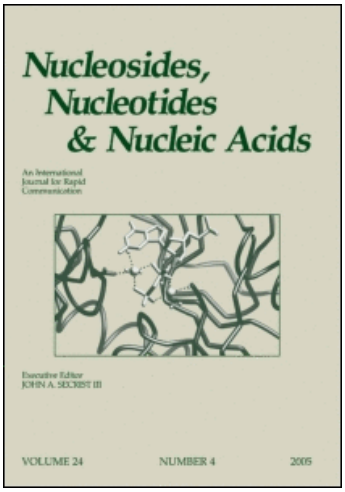

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Enantiospecific Synthesis of Carbocyclic Aminoimidazole Carboxamide Ribonucleotide (C-AICAR), Succinoaminoimidazole Carboxamide Ribonucleotide (C-SAICAR), and a New Intermediate for SAICAR Analogs

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ENANTIOSPECIFIC SYNTHESIS OF CARBOCYCLIC AMINOIMIDAZOLE CARBOXAMIDE RIBONUCLEOTIDE (C-AICAR), SUCCINOAMINOIMIDAZOLE CARBOXAMIDE RIBONUCLEOTIDE (C-SAICAR), AND A NEW INTERMEDIATE FOR SAICAR ANALOGS

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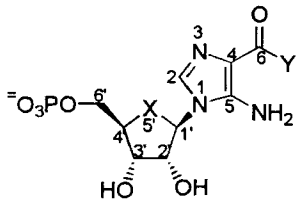
Abstract. The (–)-enantiomer of the carbocyclic analogs of aminoimidazole carboxamide ribonucleotide (C-AICAR[1], **7**), and succinoaminoimidazole carboxamide ribonucleotide (C-SAICAR, **14**) have been prepared. En route, a new intermediate (**19**) for the preparation of SAICAR analogs was developed.

The *de novo* synthesis of purine nucleotides is an important anabolic pathway that has been demonstrated to be an effective target for anti-proliferative therapy. The imidazole nucleotides AICAR and SAICAR are important intermediates in this metabolic pathway. As part of our program to evaluate carbocyclic analogs of *de novo* purine biosynthetic intermediates as substrates and/or inhibitors of the enzymes responsible for their inter-conversion[2-5], we sought to prepare the carbocyclic analogs of AICAR and SAICAR in the enantiomeric form equivalent in absolute configuration to D-ribose, which is the natural precursor to the purine ribonucleotides.

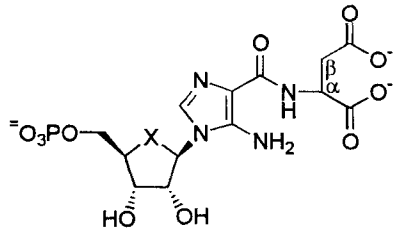


AICAR, X=O, Y=NH_2

C-AICAR, X=CH_2, Y=NH_2

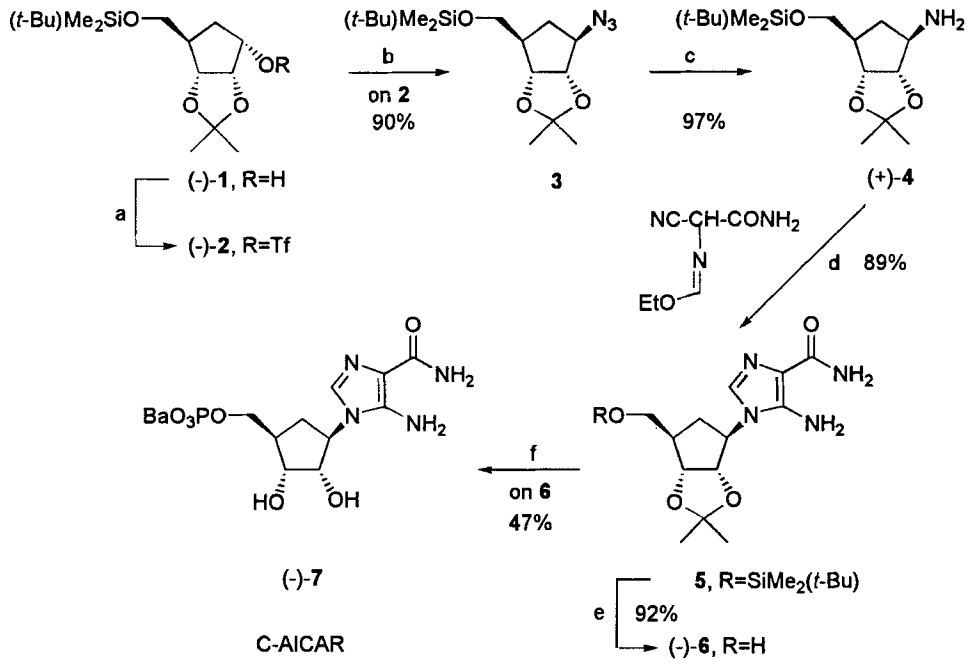
CAIR, X=O, Y=OH

C-CAIR, X=CH_2, Y=OH



SAICAR, X=O

C-SAICAR, X=CH_2

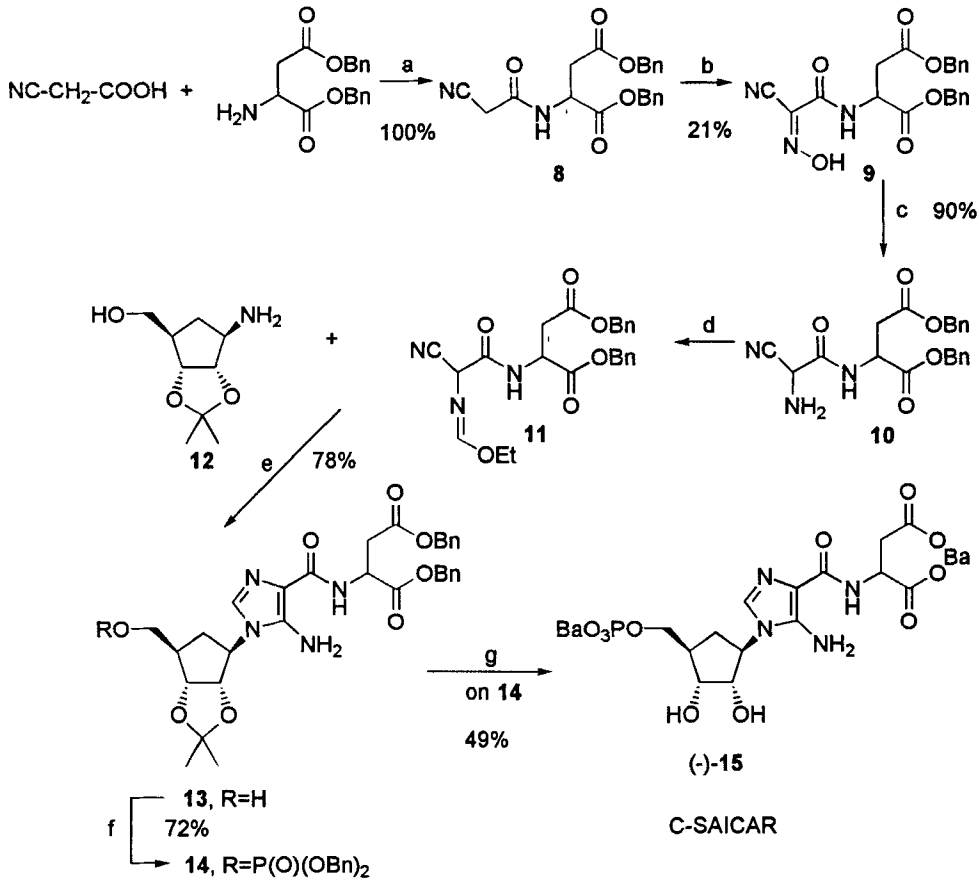


Reaction conditions: a, $(CF_3SO)_2O$, DMAP, pyridine, CH_2Cl_2; b, NaN_3, DMF; c, $SnCl_2$, Et_3N, thiophenol, CH_2Cl_2; d, CH_3CN; e, *n*-Bu_4NF, THF; f, i. $POCl_3$, $(EtO)_3PO$, ii.NH_4HCO_3, iii. CF_3COOH, iv. $BaBr_2$.

Scheme 1

The synthesis of the desired analogs requires the availability of an appropriately functionalized, chiral cyclopentane and methodology for the assembly of the derivatized imidazole ring. A chiral cyclopentane precursor was available from the work of Johnson and Penning[6]. We prepared the requisite amino triol (+)-**4** (Scheme 1) by slight modifications of the published procedure[7,8]. Thus, (–)-**1**[8] was converted to triflate (–)-**2** by treatment with trifluoromethanesulfonic anhydride. The triflate was displaced with sodium azide to afford **3**, which was reduced with stannous chloride and thiophenol[9] to amine **4**, with an $[\alpha]_D$ of +6.05 (c=1.04, $CHCl_3$).

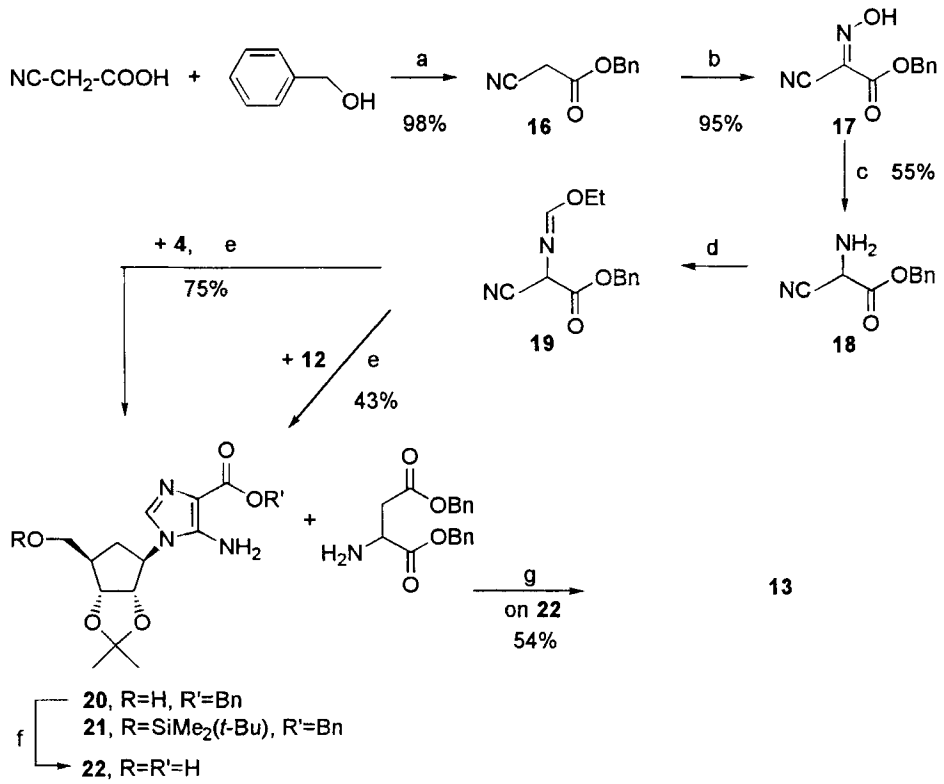
The assembly of the imidazole ring to form C-AICAR ((–)-**7**) was based on the methodology previously employed for the synthesis of AICAR from ribofuranosylamine[10]. Thus, condensation of amine **4** with the formimidate of



Reaction conditions: a, DCC, pyridine, CH_2Cl_2; b, $NaNO_2$, CH_3COOH, dioxane; c, Al/Hg, ether; d, $(EtO)_3CH$, CH_3CN; e, CH_3CN; f, NaH, tetrabenzyl pyrophosphate, THF; g, i. H_2, 10% Pd/C, EtOH, TFA, ii. $BaBr_2$

Scheme 2

α-amino-α-cyanoacetamide[11] afforded the protected C-AICAR nucleoside **5**. Selective removal of the *tert*-butyldimethylsilyl protecting group from the primary alcohol with tetrabutylammonium fluoride afforded (–)-**6**, which has an $[\alpha]_D$ of –20.0 (c=1.06, CH_3OH). (–)-**6** had been prepared previously by ring opening of carbocyclic inosine[12], although its optical rotation was not reported. Phosphorylation of **6** was accomplished with phosphorus oxychloride in triethyl

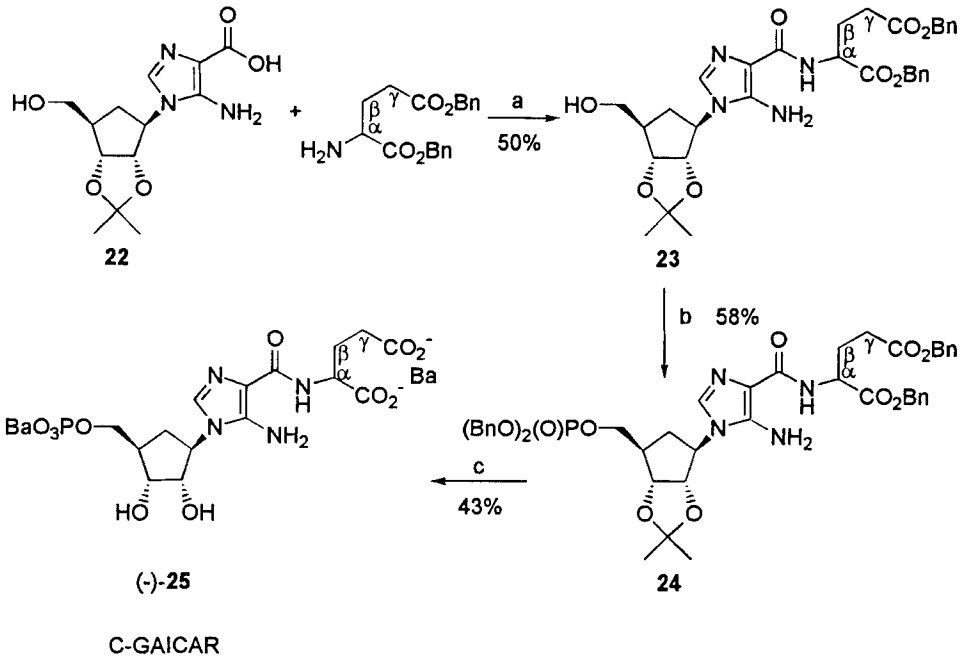


Reaction conditions: a, DCC, pyridine, CH_3CN; b, $NaNO_2$, CH_3COOH, H_2O; c, Al/Hg, ether,; d, $(EtO)_3CH$, CH_3CN, reflux; e, CH_3CN; f, H_2, 10% Pd/C, EtOH; g, DCC, CF_3-HOBT, CH_3CN.

Scheme 3

phosphate, as described for the phosphorylation of AICAR nucleoside[13]. Hydrolysis of the isopropylidene protecting group afforded C-AICAR, **7**, with an $[\alpha]_D$ of –26.4 (c=0.5, H_2O). ^1H and ^{13}C NMR were consistent with the proposed structure. A single phosphorus resonance at δ 5.96 was observed.

Our first approach to C-SAICAR, outlined in Scheme 2, required the preparation of a suitable precursor to the derivatized imidazole ring. It was envisioned that the formimidate of the protected aspartamide of α-amino-α-cyanoacetate (**11**) would serve this purpose. Carbodiimide-mediated[14] coupling



Reaction conditions: a, DCC, CF_3-HOBT, CH_3CN; b, NaH, tetrabenzyl pyrophosphate, THF; c, i. H_2, 10% Pd/C, EtOH, TFA, ii. $BaBr_2$.

Scheme 4

of cyanoacetic acid and dibenzyl aspartate provided amide **8**, which was converted to oxime **9** with sodium nitrite[15]. Reduction of the oxime with aluminum amalgam[16] afforded amine **10**, which was condensed with triethyl orthoformate[10] to yield the requisite formimidate **11**. This, in turn, was condensed with amino alcohol **12,** derived from (+)-**4,** to provide the protected C-SAICAR nucleoside **13**, with $[\alpha]_D$ = –7.3 (c=0.5, $CHCl_3$). Phosphorylation of **13** with tetrabenzyl pyrophosphate[17] yielded **14** [$[\alpha]_D$ = –3.9, (c=0.85, $CHCl_3$)]. Deprotection of **14** afforded C-SAICAR (**15**) with an $[\alpha]_D$ of –3.7 (c=0.57, H_2O). ^1H and ^{13}C NMR were consistent with the structure proposed. A single phosphorus resonance was observed at δ 3.41.

An alternative approach to C-SAICAR is depicted in Scheme 3. This approach, which also provides access to carbocyclic carboxyaminoimidazole ribonucleotide (C-CAIR) and amide analogs of C-SAICAR, was accessible

through the use of the formimidate derived from benzyl α-amino-α-cyanoacetate (**19**). Carbodiimide-mediated[14] coupling of cyanoacetic acid and benzyl alcohol afforded ester **16**. Ester **16** had previously been prepared by phase transfer catalyzed condensation of α-cyanoacetate and benzyl bromide[18]. This, in turn, was converted[10,15,16] to formimidate **19** as described above for the conversion of **8** to **11**. Condensation of **19** with amino alcohol **12** provided ester **20**, with an $[\alpha]_D$ of −17.1 (c=0.55, $CHCl_3$) in moderate (43%) yield. A better yield (75%) was obtained when **19** was condensed with **4** to afford the *tert*-butyldimethylsilyl derivative **21** [$[\alpha]_D$ = −15.8, (c=0.61, $CHCl_3$)]. Acid **22** was generated from **20** by hydrogenolysis and immediately coupled[19] with dibenzyl aspartate to afford (−)-**13** which was identical in all respects to that obtained by the route depicted in Scheme 2.

We also anticipate that benzyl ester **20** can serve as an immediate precursor to C-CAIR, using standard methodology. It should be noted that acid **22** can be coupled with a variety of amines or alcohols to provide analogs of C-SAICAR. For example, we have prepared (Scheme 4) the glutamate analog of C-SAICAR, C-GAICAR (**(−)-25**), by this approach. The spectral data (^1H, ^{13}C, ^{31}P NMR, UV) obtained were consistent with the proposed structure. Moreover, condensation of ribofuranosyl amine[10] with formimidate **19** would permit entry to CAIR and to SAICAR and its analogs.

The enzymology of these carbocyclic nucleotides will be reported elsewhere.

Experimental Section

General

NMR spectra were recorded on a Bruker AC-300 spectrometer. UV spectra were obtained with a Cary 3 spectrophotometer. Concentrations of nucleotide solutions used for the determination of the molar extinction coefficient were determined independently by phosphate analysis[20]. Optical rotations were measured with a Rudolph Autopol III polarimeter at the sodium D line in a 10 cm pathlength cell at 25 °C and concentrations are reported in g/100 mL. TLC was performed with either silica gel plates (Eastman 13181) or cellulose plates (Eastman 13254) for the phosphomonoesters, which were isolated by barium precipitation[21]. Column chromatographic purifications were performed on silica gel 60 (70-230 mesh). Solvents were reagent grade and dried using standard procedures[22]. Reactions, unless otherwise noted, were run under anhydrous conditions under nitrogen.

1-Azido-2,3-O-isopropylidene-4-(*tert*-butyldimethylsilyloxymethyl) cyclopentane (3). A solution of alcohol (–)-**1**[8] (3.0 g, 9.92 mmol), dry pyridine (2.1 mL, 25.79 mmol, 2.6 eq.), and DMAP (121 mg, 0.99 mmol, 0.1 eq.) in CH_2Cl_2 (60 mL) was cooled to 0 °C. To this was added trifluoromethanesulfonic anhydride (2.17 mL, 12.89 mmol, 1.3 eq.) dropwise *via* syringe. After 2 h at 0 ° C, the solvent was evaporated and the residue was dried *in vacuo* for 30 min. The residue was dissolved in DMF (50 mL), this solution was cooled to 0 °C, and NaN_3 (3.22g, 49.6 mmol, 5 eq.) was added. The resulting solution was stirred at 0 °C for 1 h, followed by 15 h at 25 °C. Evaporation of solvent, followed by purification of the residue on silica gel (ether-hexanes, 1:9) gave **3** (2.92 g, 8.91 mmol, 90%) as a clear oil: TLC (silica, ether-hexanes, 1:3) R_f 0.56; ^{1}H NMR ($CDCl_3$, TMS) δ 4.49 (dd, J=6.3 Hz, J=2.2 Hz, 1 H, H-3), 4.39 (dd, J=6.3 Hz, J=2.7 Hz, 1 H, H-2), 3.93 (td, J=6.2 Hz, J=2.7 Hz, 1 H, H-1), 3.60 (ABX, J_{AB}=10.1 Hz, J_{AX}=6.6 Hz, J_{BX}=6.4 Hz, 2 H, H-6), 2.35-2.15 (m, 2 H, H-4, H-5), 1.70 (dt, J=13.3 Hz, J=5.1 Hz, 1 H, H-5), 1.47 (s, 3 H, $C(C\underline{H}_3)_2$), 1.30 (s, 3 H, $C(C\underline{H}_3)_2$), 0.89 (s, 9 H, $(C\underline{H}_3)_3CSi$), 0.05 (s, 6 H, $(C\underline{H}_3)_2Si$); ^{13}C NMR ($CDCl_3$) 111.5 ($(CH_3)_2\underline{C}$), 85.1 (C-3), 81.9 (C-2), 66.9 (C-1), 63.3 (C-6), 46.9 (C-4), 31.5 (C-5), 26.9 ($C(\underline{C}H_3)_2$), 25.9 ($(\underline{C}H_3)_3CSi$), 24.5 ($C(\underline{C}H_3)_2$), 18.3 ($(CH_3)_3\underline{C}Si$), -5.4 ($(\underline{C}H_3)_2Si$).

1-Amino-2,3-O-isopropylidene-4-(*tert*-butyldimethylsilyloxymethyl) cyclopentane ((+)-4). To a stirred solution of anhydrous $SnCl_2$ (3 g, 15.82 mmol) in CH_2Cl_2 (40 mL) was added triethylamine (4.85 mL, 34.8 mmol, 2.2 eq.). This solution was cooled to 0 °C and thiophenol (3.25 mL, 31.64 mmol, 2 eq.) was added. This solution was stirred at 0 °C for 15 min and 2 h at 25 °C. Triethyl-amine (2.2 mL, 15.82 mmol, 1 eq.) and thiophenol (1.6 mL, 15.82 mmol, 1 eq.) were added and the solution was cooled to 0 °C. A solution of azide **3** (2.5 g, 7.63 mmol) in CH_2Cl_2 (10 mL) was added slowly to the cooled solution. This was stirred at 0 °C for 30 min, followed by 18 h at 25 °C. The solution was cooled to 0 °C and a 2% solution of H_2O_2, adjusted to pH 10.5 with solid K_2CO_3, (70 mL) was added. This was stirred at 0 °C for 30 min and then at 25 °C for 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic solution was dried ($MgSO_4$) and evaporated. Purification of the residue on silica gel by elution with CH_2Cl_2, 2% CH_3OH in CH_2Cl_2, and then 10% CH_3OH in CH_2Cl_2 afforded (+)-**4** (2.23 g, 7.39 mmol, 97%) as a clear oil: TLC (silica, CH_2Cl_2-CH_3OH, 95:5) R_f 0.45; $[\alpha]_D$ +6.05 (c=1.04, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS) δ 4.48 (dd, J=6.5 Hz, J=3.1 Hz, 1 H, H-3), 4.15 (dd, J=6.5 Hz, J=3.6 Hz, 1 H, H-2), 3.68 (d, J=4.7 Hz, 2 H, H-6), 3.36

(td, J=6.7 Hz, J=3.8 Hz, 1 H, H-1), 2.25-2.15 (m, 2 H, H-4, H-5), 1.55 (s, 2 H, NH_2), 1.47 (s, 3 H, $C(C\underline{H}_3)_2$), 1.45-1.35 (m, 1 H, H-5), 1.30 (s, 3 H, $C(C\underline{H}_3)_2$), 0.90 (s, 9 H, $((C\underline{H}_3)_3CSi)$, 0.06 (s, 6 H, $((C\underline{H}_3)_2Si)$; ^{13}C NMR ($CDCl_3$) 111.4 ($\underline{C}(CH_3)_2$), 89.1 (C-3), 82.5 (C-2), 64.5 (C-1), 58.1 (C-6), 47.0 (C-4), 36.2 (C-5), 27.3 ($C(\underline{C}H_3)_2$), 25.9 ($(\underline{C}H_3)_3CSi$), 24.9 ($C(\underline{C}H_3)_2$), 18.3 ($(CH_3)_3\underline{C}Si$), -5.4 ($(\underline{C}H_3)_2Si$).

5-Amino-1-[2',3'-O-isopropylidene-4'-(*tert*-butyldimethylsilyloxymethyl)cyclopentyl] imidazole-4-carboxamide (5). A solution of (+)-**4** (0.5 g, 1.66 mmol) in CH_3CN (1 mL) was added to a solution of the formimidate of α-amino-α-cyanoacetamide[10] [prepared[10,11] from oxalic acid di(α-amino-α-cyanoacetate) (0.95 g, 2.5 mmol)] in CH_3CN (10 mL). The resulting solution was stirred at 25 °C for 15 h and precipitate was removed by filtration. Evaporation of solvent left a residue that was purified on Florisil (CH_3OH in CH_2Cl_2, 0→3%) to yield a yellow solid (0.61 g, 1.48 mmol, 89%): TLC (silica, CH_2Cl_2-CH_3OH, 95:5) R_f 0.60; ^1H NMR (CD_3OD, CHD_2OD) δ 7.24 (s, 1 H, H-2), 4.65-4.50 (m, 2 H, H-2', H-3'), 4.35-4.25 (m, 1 H, H-1'), 3.75 (d, J=5.2 Hz, 2 H, H-6'), 2.50-2.30 (m, 2 H, H-4', H-5'), 2.2-2.0 (m, 1 H, H-5'), 1.56 (s, 3 H, $C(C\underline{H}_3)_2$), 1.32 (s, 3 H, $C(C\underline{H}_3)_2$), 0.92 (s, 9 H, $(C\underline{H}_3)_3CSi$), 0.10 (s, 6 H, $(C\underline{H}_3)_2Si$); ^{13}C NMR (CD_3OD) δ 169.3 (C-6), 145.9 (C-5), 129.1 (C-2), 115.2 ($\underline{C}(CH_3)_2$), 113.3 (C-4), 86.2 (C-3'), 82.6 (C-2'), 64.8 (C-6'), 61.8 (C-1'), 46.8 (C-4'), 33.3 (C-5'), 27.6 ($C(\underline{C}H_3)_2$), 26.4 ($(\underline{C}H_3)_3CSi$), 25.2 ($C(\underline{C}H_3)_2$), 19.2 ($(CH_3)_3\underline{C}Si$), -5.3 ($(\underline{C}H_3)_2Si$).

C-AICAR nucleoside ((−)-6). To a stirred solution of **5** (0.61 g, 1.48 mmol) in THF (10 mL) was added a solution of TBAF (1 M in THF-H_2O, 95:5, 1.56 mL, 1.05 eq.). This solution was stirred at 25 °C for 1.5 h. Solvent was evaporated and the residue was purified on silica gel (CH_3OH in CH_2Cl_2, 1→5%) to yield (−)-**6** (0.407 g, 1.37 mmol, 92%) as a white solid: TLC (silica, CH_2Cl_2-CH_3OH, 9:1) R_f 0.34; $[\alpha]_D$ −20.0 (c=1.06, CH_3OH); ^1H NMR (CD_3OD, CHD_2OD) δ 7.27 (s, 1 H, H-2), 4.65-4.50 (m, 2 H, H-2', H-3'), 4.32 (td, J=12.1 Hz, J=6.0 Hz, 1 H, H-1'), 3.67 (d, J=5.5 Hz, 2 H, H-6'), 2.45-2.35 (m, 2 H, H-4', H-5'), 2.09 (td, J=17.2 Hz, J=11.1 Hz, 1 H, H-5'), 1.56 (s, 3 H, $C(C\underline{H}_3)_2$), 1.32 (s, 3 H, $C(C\underline{H}_3)_2$); ^{13}C NMR (CD_3OD) δ 169.3 (C-6), 145.8 (C-5), 129.3 (C-2), 115.3 ($\underline{C}(CH_3)_2$), 113.3 (C-4), 86.2 (C-3'), 82.7 (C-2'), 63.7 (C-6'), 61.8 (C-1'), 46.7 (C-4'), 33.4 (C-5'), 27.6 ($C(\underline{C}H_3)_2$), 25.2 ($C(\underline{C}H_3)_2$).

C-AICAR ((−)-7). To a stirred suspension of alcohol **6** (100 mg, 0.34 mmol) in dry triethyl phosphate (0.6 mL) at 0 °C, was added $POCl_3$ (0.16 mL, 1.7 mmol, 5 eq.) dropwise *via* syringe. After 3.5 h at 0 °C, the solution was poured into ether (20 mL). The ether was decanted and the oily residue was washed

with ether (20 mL). The residual gummy material was dissolved in 0.1 M NH_4HCO_3, pH 7.8 (10 mL) and the pH of the resulting solution was adjusted to 7 and stirred at 25 °C for 2 h. The volume was reduced to approximately 3 mL. 95% Ethanol (3 mL) and TFA (1 drop) were added and the solution was stirred at 25 °C for 15 h. Solvent was evaporated and the residue was dissolved in H_2O (2 mL). 1 M $BaBr_2$ (0.68 mL, 2 eq.) was added and the pH was adjusted to 8.5. Inorganic phosphate precipitated and was removed by centrifugation. The supernatant (3.2 mL) was treated with ethanol (16 mL). The resulting suspension was kept at –20 °C for 2 h. The precipitated organic phosphate was collected by centrifugation, washed with ethanol and ether, and dried *in vacuo* to afford (–)-**7** (75.3 mg, 0.16 mmol, 47%) as a white powder: TLC (cellulose, n-BuOH-H_2O-HOAc, 5:3:2) R_f 0.19; $[\alpha]_D$ –26.4 (c=0.5, H_2O); UV (50 mM Tris, pH 7.5) λ_{max} 266 nm (ε=10.03 mM^{-1}); ^1H NMR (D_2O, HOD) δ 7.56 (s, 1 H, H-2), 4.45-4.25 (m, 2 H, H-1', H-3'), 4.11 (dd, J=5.1 Hz, J=3.0 Hz, 1 H, H-2'), 3.90-3.70 (d, J=15.5 Hz, 2 H, H-6'), 2.50-2.40 (m, 1 H, H-5'), 2.40-2.30 (m, 1 H, H-4'), 1.80-1.65 (m, 1 H, H-5'); ^{13}C NMR (D_2O, CH_3CH_2OH) δ 169.1 (C-6), 159.8 (C-5), 131.3 (C-2), 112.6 (C-4), 76.5 (C-3'), 72.7 (C-2'), 65.6 (C-6'), 58.8 (C-1'), 44.2 (C-4'), 28.6 (C-5'); ^{31}P NMR (D_2O, H_3PO_4 (ext.)) δ 5.96; MS (ion spray) MH^+ 473.0, calcd. for $C_{10}H_{15}N_4PBa$, M 471.57.

Dibenzyl aspartyl-α-cyanoacetamide (8). To a stirred solution of cyanoacetic acid (0.323 g, 3.8 mmol), dibenzyl L-aspartate (1.2 g, 3.8 mmol), and pyridine (0.77 mL, 9.5 mmol, 2.5 eq.) in CH_3CN (5 mL) at 0 °C, was slowly added a solution of DCC (0.862 g, 4.18 mmol, 1.1 eq.) in CH_3CN (2 mL). The resulting solution was stirred at 0 °C for 1 h and 25 °C for 2 h. The suspension was filtered and solvent was evaporated to leave a residue that was purified on silica gel (CH_3OH in CH_2Cl_2, 0→2%) to provide **8** (1.46 g, 3.8 mmol, 100%) as a white solid: TLC (silica, CH_2Cl_2-CH_3OH, 97:3) R_f 0.65; ^1H NMR ($CDCl_3$, TMS) δ 7.40-7.15 (m, 10 H, Ph), 5.14 (s, 2 H, -OC$\underline{H}_2$Ph), 5.06 (s, 2 H, -OC$\underline{H}_2$Ph), 4.90-4.85 (m, 1 H, aspartyl α-H), 3.36 (s, 2 H, NC-C$\underline{H}_2$-CO), 3.01 (ABX, J_{AB}=14.8 Hz, J_{AX}=4.6 Hz, J_{BX}=4.5 Hz, 2 H, aspartyl β-H's); ^{13}C NMR ($CDCl_3$) δ 170.4 (α-$\underline{C}O_2Bn$), 169.6 (β-$\underline{C}O_2Bn$), 161.2 (-$\underline{C}$ONH-), 135.2 (Ph), 128.6 (Ph), 128.5 (Ph), 128.3 (Ph), 114.0 (N$\underline{C}$-), 67.9 (-O$\underline{C}H_2$Ph), 67.0 (-O$\underline{C}H_2$Ph), 49.3 (α-$\underline{C}$H), 35.9 (β-$\underline{C}H_2$), 25.8 (NC-$\underline{C}H_2$-CO).

Dibenzyl aspartyl-α-cyano-α-oximinoacetamide (9). To a cold (0 °C), stirred solution of amide **8** (0.7 g, 1.84 mmol) in dioxane (2 mL) and glacial acetic acid (3 mL), was added a solution of $NaNO_2$ (0.393 g, 5.69 mmol, 3 eq.) in H_2O (0.7 mL). After 1.5 days, the solution was added to ether (50 mL) and

CH_2Cl_2 (15 mL) and washed with saturated $NaHCO_3$ (2 × 20 mL). The organic layer was dried ($MgSO_4$) and evaporated to leave **9** (0.16g, 0.39 mmol, 21%): TLC (silica, ether) R_f 0.60; ^1H NMR ($CDCl_3$, TMS) δ 7.71 (d, J=8.2 Hz, 1 H, CO-NH), 7.35-7.20 (m, 10 H, Ph), 5.13 (s, 2 H, OCH_2Ph), 5.04 (s, 2 H, $-OCH_2Ph$), 5.00-4.90 (m, 1 H, aspartyl α-H), 3.06 (ABX, J_{AB}=17.3 Hz, J_{AX}=4.7 Hz, J_{BX}=4.5 Hz, 2 H, aspartyl β-H's); ^{13}C NMR ($CDCl_3$) δ 170.5 (α-CO_2Bn), 169.6 (β-CO_2Bn), 157.7 (-CONH-), 135.0 (Ph), 134.7 (Ph), 128.5-128.0 (Ph), 127.9 (C=NOH), 107.3 (NC-), 67.8 ($-OCH_2Ph$), 66.9 ($-OCH_2Ph$), 48.8 (α-CH), 35.8 (β-CH_2). This material was used without further purification.

Dibenzyl aspartyl-α-amino-α-cyanoacetamide (10). To aluminum amalgam, prepared[16] from 100 mg of aluminum foil, in ethyl acetate (20 mL) was added a solution of oxime **9** (0.16 g, 0.39 mmol) in ethyl acetate (10 mL). Water (0.5 mL) was added dropwise and the mixture was stirred at 25 °C for 20 min, when water (0.5 mL) was added. Stirring was continued for 30 min. The mixture was filtered, dried ($MgSO_4$), and evaporated to leave amine **10** (0.139 g, 0.35 mmol, 90%): TLC (silica, ether) R_f 0.37. This material was used without further purification or characterization.

1-Amino-2,3-O-isopropylidene-4-hydroxymethyl cyclopentane (12). To a stirred solution of (+)-**4** (0.5 g, 1.66 mmol) in THF (5 mL), was added a solution of TBAF (1 M in THF-H_2O, 95:5, 1.74 mL, 1.05 eq.). The solution was stirred for 1 h at 25 °C. Solvent was evaporated and the residue was purified on silica gel (CH_3OH in CH_2Cl_2, 0→3%) to provide 0.3 g (1.6 mmol, 96%) of **12**: TLC (silica, CH_2Cl_2-CH_3OH, 9:1) R_f 0.25; $[\alpha]_D$ +1.5 (c=0.65, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 4.80 (d, J=5.5 Hz, 1 H, H-3); 4.23 (d, J=5.5 Hz, 1 H, H-2), 3.73 (dd, J=11.4 Hz, J=3.7 Hz, 1 H, H-1), 3.60-3.50 (m, 2 H, H-6), 3.20-3.00 (bs, 3 H, NH_2, OH), 2.55-2.40 (m, 2 H, H-4, H-5), 1.50-1.40 (m, 1 H, H-5), 1.44 (s, 3 H, $C(CH_3)_2$), 1.29 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 109.3 ($C(CH_3)_2$), 87.8 (C-3), 84.5 (C-2), 64.1 (C-1), 57.0 (C-6), 47.7 (C-4), 37.0 (C-5), 26.4 ($C(CH_3)_2$), 23.8 ($C(CH_3)_2$).

5-Amino-1-(2',3'-O-isopropylidene-4'-hydroxymethylcyclopentyl) imidazole-4-dibenzyl aspartyl carboxamide ((–)-13). A solution of amine **10** (0.11 g, 0.278 mmol) and triethyl orthoformate (0.1 mL, 0.556 mmol, 2 eq.) in CH_3CN (1 mL) was refluxed for 45 min. Solvent was evaporated and the residue was dried *in vacuo* for 10 min. The residue was dissolved in CH_3CN (1 mL) and a solution of amine **12** (52 mg, 0.278 mmol) in CH_3CN (1 mL) was added. The resulting solution was stirred at 25 °C for 24 h. Solvent was evaporated to leave an oil which was purified on silica gel (CH_3OH in CH_2Cl_2, 1→3%) to afford (–)-**13**

(130 mg, 0.219 mmol, 78%): TLC (silica, CH_2Cl_2-CH_3OH, 95:5) R_f 0.47; $[\alpha]_D$ –7.3 (c=0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 7.45 (d, J=8.7 Hz, 1 H, CONH), 7.35-7.25 (m, 10 H, Ph), 6.94 (s, 1 H, H-2), 5.55-5.45 (bs, 1 H, NH_2), 5.14 (s, 2 H, -OCH_2Ph), 5.07 (s, 2 H, -OCH_2Ph), 5.20-5.00 (m, 1 H, aspartyl α-H), 4.61 (dd, J=7.5 Hz, J=4.5 Hz, 1 H, H-3'), 4.37 (dd, J=7.3 Hz, J=6.6 Hz, 1 H, H-2'), 4.20 (td, J=12.6 Hz, J=6.3 Hz, 1 H, H-1'), 3.81 (ABX, J_{AB}=10.6 Hz, J_{AX}=4.6 Hz, J_{BX}=4.9 Hz, 2 H, H-6'), 3.03 (ABX, J_{AB}=16.9 Hz, J_{AX}=5.1 Hz, J_{BX}=5.0 HX, 2 H, aspartyl β-H's), 2.50-2.30 (m, 2 H, H-4', H-5'), 2.30-2.10 (m, 1 H, H-5'), 2.00-1.70 (bs, 1 H, -OH), 1.60 (s, 3 H, $C(CH_3)_2$), 1.31 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 171.0 (α-CO_2Bn), 170.5 (β-CO_2Bn), 164.6 (-CONH-), 143.7 (C-5), 135.5 (Ph), 128.5 (Ph), 128.3 (Ph), 128.2 (Ph), 128.1 (Ph), 126.6 (C-2), 114.6 ($C(CH_3)_2$), 112.8 (C-4). 85.5 (C-3'), 81.2 (C-2'), 67.2 (OCH_2Ph), 66.7 (OCH_2Ph), 63.0 (C-6'), 60.6 (C-1'), 47.9 (α-CH), 45.1 (C-4'), 37.0 (β-CH_2), 31.2 (C-5'), 27.2 ($C(CH_3)_2$), 24.9 ($C(CH_3)_2$).

5-Amino-1-(2',3'-O-isopropylidene-4'-dibenzyl phosphoroxymethyl-cyclopentyl) imidazole-4-dibenzyl aspartyl carboxamide ((–)-14). To a cold (0 °C), stirred solution of alcohol **(–)-13** (112 mg, 0.189 mmol) in THF (5 mL), was added NaH (11.3 mg, 0.28 mmol, 1.5 eq.). After 5 min, tetrabenzyl pyrophosphate (153 mg, 0.28 mmol, 1.5 eq.) was added and stirring was continued at 0 °C for 1 h and 25 °C for 7 h. Water (1 drop) was added and solvent was evaporated. The residue was dissolved in brine (5 mL) and the aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL). The organic extract was dried ($MgSO_4$) and evaporated to leave a residue which was purified on silica gel (CH_3OH in CH_2Cl_2, 0→2%) to give 117 mg (0.137 mmol, 72%) of product: TLC (silica, CH_2Cl_2-CH_3OH, 95:5) R_f 0.31; $[\alpha]_D$ –3.9 (c=0.85, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 7.44 (d, J=8.7 Hz, 1 H, -CONH-), 7.40-7.25 (m, 20 H, Ph), 6.80 (s, 1 H, H-2), 5.42 (s, 2 H, NH_2), 5.20-4.95 (m, 9 H, -OCH_2Ph, aspartyl α-H), 4.41 (dd, J=7.4 Hz, J=5.3 Hz, 1 H, H-'), 4.20 (dd, J=7.3 Hz, J=6.6 Hz, 1 H, H-2'), 4.15-4.05 (m, 3 H, H-1', H-6'), 3.03 (ABX, J_{AB}=16.9 Hz, J_{AX}=5.1 Hz, J_{BX}=5.0 Hz, 2 H, aspartyl β-H's), 2.50-2.35 (m, 1 H, H-4'), 2.25-2.15 (m, 1 H, H-5'), 2.10-1.90 (m, 1 H, H-5'), 1.58 (s, 3 H, $C(CH_3)_2$), 1.26 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 171.0 (α-CO_2Bn), 170.5 (β-CO_2Bn), 164.6 (-CONH-), 143.6 (C-5), 135.7 (Ph), 135.5 (Ph), 128.8-127.0 (Ph), 126.4 (C-2), 114.8 ($C(CH_3)_2$), 113.9 (C-4), 85.2 (C-3'), 80.6 (C-2'), 69.7 (C-6'), 69.5 ($POCH_2Ph$), 69.3 ($POCH_2Ph$), 67.2 (CO_2CH_2Ph), 66.7 (CO_2CH_2Ph), 60.1 (C-1'), 48.0 (α-CH), 43.5 (C-4'), 37.1 (β-CH_2), 31.5 (C-5'), 27.2 ($C(CH_3)_2$), 24.9 ($C(CH_3)_2$); ^{31}P NMR ($CDCl_3$, H_3PO_4(ext.)) δ 0.03.

C-SAICAR ((–)-15). A solution of (–)-**14** (110 mg, 0.129 mmol) in 95% ethanol (10 mL)-CH_2Cl_2 (0.2 mL)-TFA (0.1 mL) was hydrogenated (1 atm.) over 10% Pd/C (20 mg) for 12 h. The suspension was filtered through Celite and solvent was evaporated. The residue was dissolved in water (2.2 mL). 1 M $BaBr_2$ (0.52 mL, 0.52 mmol, 4 eq.) was added and the pH was adjusted to pH 8.4. Ethanol (15.5 mL, 5 vol.) was added and the resulting suspension was kept at –20 °C for 1 h. The precipitate was collected by centrifugation, washed with ethanol and ether, and dried *in vacuo* to afford (–)-**15** (113 mg) as a white powder: TLC (cellulose, ethanol-water, 2:1) R_f 0.25; $[\alpha]_D$ –3.7 (c=0.57, H_2O); UV (50 mM Tris, pH 7.5) λ_{max} 268 nm (ε=12.4 mM^{-1}); ^1H NMR (D_2O, HOD) δ 8.58 (s, 1 H, H-2), 4.94 (t, J=5.3 Hz, 1 H, aspartyl α-H), 4.60 (dt, J=17.9 Hz, J=8.9 Hz, 1 H, H-1'), 4.33 (dd, J=8.8 Hz, J=5.7 Hz, 1 H, H-2'), 4.15-4.05 (m, 1 H, H-3'), 4.10-3.80 (dm, J_{HP}=22.8 Hz, 2 H, H-6'), 3.10-2.90 (m, 2 H, aspartyl β-H's), 2.65-2.50 (m, 1 H, H-5'), 2.45-2.30 (m, 1 H, H-4'), 1.83 (dt, J=15.7 Hz, J=10.4 Hz, 1 H, H-5'); ^{13}C NMR (D_2O, CH_3CH_2OH) δ 175.0 (α-$\underline{C}O_2^-$), 174.8 (β-$\underline{C}O_2^-$), 163.7 (-$\underline{C}$ONH-), 144.7 (C-5), 129.7 (C-2), 115.0 (C-4), 76.4 (C-3'), 72.3 (C-2'), 66.4 (C-6'), 60.5 (C-1'), 49.6 (α-$\underline{C}$H), 43.7 (C-4'), 36.4 (β-$\underline{C}H_2$), 27.9 (C-5'); ^{31}P NMR (D_2O, H_3PO_4 (ext.)) δ 3.41; MS (ion spray) MH^+ 722.9, calcd. for $C_{14}H_{17}N_4O_{11}PBa_2$ M 722.9

Benzyl α-cyanoacetate (16). To a cold (0 °C), stirred solution of cyanoacetic acid (2g, 23.5 mmol), dry pyridine (4.75 mL, 58.75 mmol, 2.5 eq.), and benzyl alcohol (2.7 mL, 25.85 mmol, 1.1 eq.) in CH_3CN (20 mL) was added dropwise a solution of DCC (5.34 g, 25.85 mmol, 1.1 eq.) in CH_3CN (10 mL). Stirred at 0 °C for 1 h, followed by 1 h at 25 °C. Filtration, followed by solvent evaporation left a red oil which was purified on silica gel (ether in hexanes, 10→ 30%) to provide 4.07 g (23.23 mmol, 98%) of **16**: TLC (silica, ether-hexanes, 1:2) R_f 0.40; ^1H NMR ($CDCl_3$, TMS) δ7.4-7.3 (m, 5 H, Ph), 5.20 (s, 2 H, O$\underline{C}H_2$Ph), 3.45 (s, 2 H, NC-$\underline{C}H_2$-CO-); ^{13}C NMR ($CDCl_3$) 162.8 (-$\underline{C}O_2$-), 134.3 (Ph), 128.8 (Ph), 128.6 (Ph), 128.5 (Ph), 126.8 (Ph), 112.9 (N$\underline{C}$), 68.4 (-O$\underline{C}H_2$Ph), 24.6 (NC-$\underline{C}H_2$-CO-).

Benzyl α-cyano-α-oximinoacetate (17). To a cold (0 °C), stirred solution of ester **16** (2 g, 11.4 mmol) in glacial acetic acid (1.96 mL) was added slowly a solution of $NaNO_2$ (2.44 g, 34.2 mmol, 3 eq.) in H_2O (4 mL). Stirred at 0 °C for 1.5 h and at 25 °C for 1.5 h. Ether (50 mL) and 1 N HCl (10 mL) were added and the layers were separated. The aqueous layer was extracted once with ether (20 mL). The ethereal solution was washed with saturated $NaHCO_3$ (2 × 10 mL), and brine (20 mL), and dried ($MgSO_4$). Evaporation of solvent left

2.23g (10.92 mmol, 95%) of product: TLC (silica, ether-hexanes, 1:1) R_f 0.4; ^{1}H NMR ($CDCl_3$, TMS) δ 12.9-11.0 (bs, 1 H, NO<u>H</u>), 7.45-7.30 (m, 5 H, Ph), 5.37 (s, 2 h, OC<u>H</u>$_2$Ph); ^{13}C NMR ($CDCl_3$) δ 158.3 (-<u>C</u>O$_2$-), 133.7 (Ph), 129.5-127.4 (Ph), 126.3 (<u>C</u>=NOH), 107.1 (N<u>C</u>-), 69.2 (-O<u>C</u>H$_2$Ph).

Benzyl α-amino-α-cyanoacetate (18). Oxime **17** (0.61 g, 2.98 mmol) was added to aluminum amalgam (prepared[16] from 240 mg of aluminum foil) in ether (30 mL). After stirring for 5 min, H_2O (0.1 mL) was added dropwise. Stirring was continued for 20 min. Filtration and evaporation of solvent left 312 mg (1.64 mmol, 55%) of oil: TLC (silica, ether-hexanes, 2:1) R_f 0.25; ^{1}H NMR ($CDCl_3$, TMS) δ 7.40-7.30 (m, 5 H, Ph), 5.27 (d, J=12.0 Hz, 2 H, -OC<u>H</u>$_2$Ph), 4.69 (s, 1 H, NC-C<u>H</u>-(NH$_2$)-CO), 2.0-1.8 (bs, 2 H, N<u>H</u>$_2$); ^{13}C NMR ($CDCl_3$) δ 166.0 (-<u>C</u>O$_2$-), 134.1 (Ph), 130.0-126.0 (Ph), 116.7 (N<u>C</u>-), 68.9 (-O<u>C</u>H$_2$Ph), 47.0 (NC-<u>C</u>H-(NH$_2$)-CO).

5-Amino-1-(2',3'-O-isopropylidene-4'-hydroxymethylcyclopentyl) imidazole-4-benzyl carboxylate (20). A stirred solution of amine **18** (186 mg, 0.98 mmol) and triethyl orthoformate (0.35 mL, 2 mmol, 2 eq.) in CH_3CN (3 mL) was refluxed for 50 min. The solvent was evaporated and the residue was dried *in vacuo* for 10 min. The residue was dissolved in CH_3CN (1 mL) and a solution of amine **12** (75 mg, 0.4 mmol) in CH_3CN (1 mL) was added and the resulting solution was stirred at 25 °C for 19 h. Evaporation of solvent left a residue which was purified on silica gel (CH_3OH in CH_2Cl_2, 1→5%) to yield 67 mg (0.173 mmol, 43%) of (–)-**20:** TLC (silica, CH_2Cl_2-CH_3OH, 9:1) R_f 0.45; $[\alpha]_D$ –17.1 (c=0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS) δ 7.50-7.20 (m, 5 H, Ph), 7.01 (s, 1 H, H-2), 5.58 (bs, 2 H, N<u>H</u>$_2$), 5.40-5.20 (m, 2 H, -OC<u>H</u>$_2$PH), 4.62 (dd, J=7.4 Hz, J=4.4 Hz, 1 H, H-3'), 4.40 (dd, J=7.2 Hz, J=6.7 Hz, 1 H, H-2'), 4.20-4.10 (m, 1 H, H-1'), 3.81 (ABX, J_{AB}=10.6 Hz, J_{AX}=4.6 Hz, J_{BX}=4.8 Hz, 2 H, H-6'), 2.50-2.35 (m, 2 H, H-4', H-5'), 2.30-2.20 (m, 1 H, H-5'), 2.20-2.00 (bs, 1 H, O<u>H</u>), 1.60 (s, 3 H, C(C<u>H</u>$_3$)$_2$), 1.32 (s, 3 H, C(C<u>H</u>$_3$)$_2$); ^{13}C NMR ($CDCl_3$) δ 164.2 (-(-<u>C</u>O$_2$-), 146.5 (C-5), 136.6 (Ph), 128.4 (Ph), 128.2 (Ph), 127.9 (Ph), 114.4 (<u>C</u>(CH$_3$)$_2$), 111.0 (C-4), 85.4 (C-3'), 81.3 (C-2'), 65.4 (-O<u>C</u>H$_2$Ph), 62.5 (C-6'), 61.0 (C-1'), 44.9 (C-4'), 31.1 (C-5'), 27.2 (C(<u>C</u>H$_3$)$_2$), 24.9 (C(<u>C</u>H$_3$)$_2$).

5-Amino-1-[2',3'-O-isopropylidene-4'-(*tert*-butyldimethylsilyloxy-methyl)cyclopentyl)] imidazole-4-benzyl carboxylate (21). A solution of amine **18** (312 mg, 1.64 mmol) and triethyl orthoformate (0.55 mL, 3.28 mmol) in CH_3CN (5 mL) was stirred at reflux for 1 h. Solvent was evaporated and the residue was dried *in vacuo* for 10 min. The residue was dissolved in CH_3CN (4 mL) and a solution of (+)-**4** (0.28 g, 0.92 mmol) in CH_3CN (2 mL) was added.

The resulting solution was stirred at 25 °C for 15 h. Solvent was evaporated and the residue was purified on silica gel (CH_3OH in CH_2Cl_2, 0→1%) to afford **(-)-21** (346 mg, 0.689 mmol, 75%) as a clear oil: TLC (silica, CH_2Cl_2-CH_3OH, 98:2) R_f 0.34; $[\alpha]_D$ −15.8 (c=0.61, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 7.50-7.25 (m, 5 H, Ph), 7.17 (s, 1 H, H-2), 5.66 (bs, 2 H, $N\underline{H}_2$), 5.35-5.25 (m, 2 H, -$OC\underline{H}_2Ph$), 4.58 (dd, J=7.3Hz, J=3.9 Hz, 1 H, H-3'), 4.37 (dd, J=7.1 Hz, J=6.8 Hz, 1 H, H-2'), 4.20 (td, J=12.6 Hz, J=6.6 Hz, 1 H, H-1'), 3.76 (ABX, J_{AB}=10.2 Hz, J_{AX}=4.0 Hz, J_{BX}=3.2 Hz, 2 H, H-6'), 2.50-2.20 (m, 3 H, H-4', H-5'), 1.61 (s, 3 H, $C(C\underline{H}_3)_2$), 1.32 (s, 3 H, $C(C\underline{H}_3)_2$), 0.90 (s, 9 H, $(C\underline{H}_3)_3CSi$), 0.08 (s, 6 H, $(C\underline{H}_3)_2Si$); ^{13}C NMR ($CDCl_3$) δ 163.7 (-$\underline{C}O_2$-), 146.4 (C-5), 136.6 (Ph), 128.4 (Ph), 128.2 (Ph), 127.9 (Ph), 114.4 ($\underline{C}(CH_3)_2$), 110.2 (C-4), 85.4 (C-3'), 80.9 (C-2'), 65.5 (-$O\underline{C}H_2Ph$), 62.7 (C-6'), 61.3 (C-1'), 44.9 (C-4'), 30.9 (C-5'), 27.3 ($C(\underline{C}H_3)_2$), 25.8 ($(\underline{C}H_3)_3CSi$), 24.9 ($C(\underline{C}H_3)_2$), 18.3 ($(CH_3)_3\underline{C}Si$), −5.4 ($(\underline{C}H_3)_2Si$).

20→13. A solution of **20** (65 mg, 0.168 mmol) in 95% ethanol was hydrogenated (1 atm.) over 10% Pd/C (10 mg). After 4 h, the suspension was filtered through Celite, solvent was evaporated, and the residue was dried *in vacuo*. The residue and CF_3-HOBT (44 mg, 0.22 mmol, 1.3 eq.) were dissolved in CH_3CN (1 mL) and a solution of dibenzyl L-aspartate (72 mg, 0.23 mmol) in CH_3CN (1 mL) was added, followed by DCC (30 mg, 0.34 mmol, 2 eq.). Stirred at 25 °C for 17 h. Filtration, followed by evaporation of solvent, left a residue which was purified by silica gel (CH_3OH in CH_2Cl_2, 1→3%) to afford (−)-**13** (54 mg, 0.91 mmol, 54%). This material was identical in all respects to (−)-**13** reported above.

5-Amino-1-(2',3'-O-isopropylidene-4'-hydroxymethylcyclopentyl) imidazole-4-dibenzyl glutamyl carboxamide ((−)-23). To a solution of acid **22**, prepared from ester **20** (82 mg, 0.21 mmol) as described above, and CF_3-HOBT (65 mg, 0.317 mmol, 1.5 eq.) in CH_3CN (1 mL) was added a solution of dibenzyl L-glutamate (151 mg, 0.462 mmol, 2.2 eq.) in CH_3CN (1 mL), followed by DCC (88 mg, 0.42 mmol, 2 eq.). Stirred at 25 °C for 20 h. Filtration, followed by evaporation of solvent left a residue which was purified on silica gel (CH_3OH in CH_2Cl_2, 0→3%) to afford **23** (64 mg, 0.105 mmol, 50%) as a clear oil: TLC (silica, CH_2Cl_2-CH_3OH, 19:1) R_f 0.49; $[\alpha]_D$ −11.1 (c=0.92, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 7.35-7.25 (m, 10 H, Ph), 7.16 (d, H=8.5 Hz, 1 H, -CO$N\underline{H}$-), 6.92 (2, 1 H, H-2), 5.52 (s, 2 H, $N\underline{H}_2$), 5.17 (s, 2 H, -$OC\underline{H}_2Ph$), 5.07 (s, 2 H, -$OC\underline{H}_2Ph$), 4.80 (dt, J=8.6 Hz, J=5.0 Hz, 1 H, glutamyl α-H), 4.60 (dd, J=7.4 Hz, J=4.4 Hz, 1 H, H-3'), 4.30 (dd, J=6.9 Hz, 1 H, H-2'), 4.15 (td, J=12.7 Hz, J=6.4

Hz), 1 H, H-1'), 3.76 (ABX, J_{AB}=10.7 Hz, J_{AX}=4.6 Hz, J_{BX}=4.8 Hz, 2 H, H-6'), 3.40-3.00 (bs, 1 H, -OH), 2.60-2.00 (m, 7 H, H-4', H-5', glutamyl β- and γ-H's), 1.58 (s, 3 H, $C(CH_3)_2$), 1.29 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 172.4 (α-CO_2), 172.0 (γ-CO_2), 164.7 (-CONH), 143.7 (C-5), 135.7 (Ph), 134.4 (Ph), 128.5 (Ph), 128.2 (Ph), 126.7 (C-2), 114.3 ($C(CH_3)_2$), 113.3 (C-4), 85.4 (C-3'), 81.1 (C-2'), 67.0 (-OCH_2Ph), 66.3 (-OCH_2Ph), 62.5 (C-6'), 60.7 (C-1'), 50.8 (α-CH), 45.0 (C-4'), 31.1 (C-5'), 30.4 (β-CH_2), 27.7 (γ-CH_2), 27.2 ($C(CH_3)_2$), 24.8 ($C(CH_3)_2$).

5-Amino-1-(2',3'-O-isopropylidene-4'-dibenzyl phosphoroxymethyl cyclopentyl) imidazole-4-dibenzyl glutamyl carboxamide ((−)-24). To a cold (0 °C), stirred solution of alcohol **23** (60 mg, 0.099 mmol) in THF (3 mL) was added NaH (5.9 mg, 0.148 mmol, 1.5 eq.). After 5 min, tetrabenzyl pyrophosphate (80 mg, 0.148 mmol, 1.5 eq.) in THF (1 mL) was added. Stirred at 0 °C for 1 h and 25 °C for 12 h. Water (1 drop) was added and the solvent was evaporated. The residue was purified on silica gel (CH_3OH in CH_2Cl_2, 0→3%) to afford 50 mg (0.057 mmol, 58%) of (−)-**24**: TLC (silica, CH_2Cl_2-CH_3OH, 95:5) R_f 0.59; $[\alpha]_D$ −11.2 (c=0.86, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 7.40-7.20 (m, 20 H, Ph), 7.08 (d, J=8.6 Hz, 1 H, -CONH), 6.80 (s, 1 H, H-2), 5.41 (bs, 2 H, NH_2), 5.20-4.95 (m, 8 H, -OCH_2Ph), 4.82 (dt, J=8.6 Hz, J=4.9 Hz, glutamyl α-H), 4.40 (dd, J=7.4 Hz, J=5.2 Hz, 1 H, H-3'), 4.19 (dd, J=6.6 Hz, 1 H, H-2'), 4.15-4.00 (m, 3 H, H-1', H-6'), 2.60-1.90 (m, 7 H, H-4', H-5', glutamyl β- and γ-H's), 1.55 (s, 3 H, $C(CH_3)_2$), 1.25 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 172.4 (α-CO_2), 171.8 (γ-CO_2), 164.7 (-CONH-), 143.4 (C-5), 135.8 (Ph), 135.7 (Ph), 135.6 (Ph), 128.7 (Ph), 127.9 (Ph), 126.2 (C-2), 114.7 ($C(CH_3)_2$), 113.8 (C-4), 85.1 (C-3'), 80.0 (C-2'), 69.5 (C-6'), 69.5-69.4 (-OCH_2Ph), 66.9 (-OCH_2Ph), 66.3 (-OCH_2Ph), 60.0 (C-1'), 50.7 (α-CH), 43.4 (C-4'), 30.9 (C-5'), 30.4 (β-CH_2), 27.8 (γ-CH_2), 27.1 ($C(CH_3)_2$), 24.8 ($C(CH_3)_2$); ^{31}P NMR ($CDCl_3$, H_3PO_4 (ext.)) δ 0.018.

C-GAICAR ((−)-25). A solution of phosphate ester **(−)-24** (50 mg, 0.057 mmol) in 95% ethanol (4 mL) was hydrogenated (1 atm.) over 10% Pd/C (20 mg) at 25 °C for 15 h. Water (1 mL) and TFA (0.2 mL) were added and stirring was continued for 24 h. Filtration and evaporation of solvent left a residue that was dissolved in water (1 mL). 1 M $BaBr_2$ (0.23 mL, 0.23 mmol, 4 eq.) was added and the pH was adjusted to pH 8.4. The precipitate that formed was removed by centrifugation. Ethanol (6 mL) was added to the supernatant and the resulting suspension was kept at −20 °C for 1 h. The precipitate was collected by centrifugation, washed with ethanol and ether, and dried *in vacuo* to afford 18 mg (0.024 mmol, 43%) of (−)-**25** as a white powder: TLC (cellulose, n-BuOH-

H_2O-HOAc, 5:3:2) R_f 0.32; UV (50 mM Tris, pH 7.5) λ_{max} 267 nm (ε=7.9 mM^{-1}); $[\alpha]_D$ –24.6 (c=0.33, H_2O, pH 1); ^1H NMR (D_2O, HOD) δ 7.57 (s, 1 H, H-2), 4.50-4.20 (m, 2 H, H-1', H-2'), 4.20-4.10 (m, 1 H, H-3'), 3.90-3.70 (m, 2 H, H-6'), 2.50-1.70 (m, 7 H, H-4', H-5', glutamyl β- and γ-H's), (glutamyl α-H obscured by HOD); ^{13}C NMR (D_2O) δ 183.0 (α-$\underline{C}O_2$), 179.9 (β-$\underline{C}O_2$), 166.1 (-$\underline{C}$ONH-), 143.9 (C-5), 131.2 (C-2), 113.8 (C-4), 76.6 (C-3'), 72.8 (C-2'), 65.7 (C-6'), 58.8 (C-1'), 54.9 (α-$\underline{C}$H), 44.2 (C-4'), 34.6 (C-5'), 29.6 (β-$\underline{C}H_2$), 28.7 (γ-$\underline{C}H_2$); ^{31}P NMR (D_2O, H_3PO_4 (ext.)) δ 6.93.

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REFERENCES AND NOTES

1. Abbreviations used: AICAR, aminoimidazole carboxamide ribonucleotide; CAIR, carboxyaminoimidazole ribonucleotide; CF_3-HOBT, 6-trifluoromethyl-1-hydroxybenzotriazole; DCC, dicyclohexylcarbodiimide; DMAP, 4-dimethylaminopyridine; DMF, N,N-dimethylformamide; GAICAR, glutaroaminoimidazole carboxamide ribonucleotide; SAICAR, succinoaminoimidazole carboxamide ribonucleotide; TBAF, tetrabutylammonium fluoride; TFA, trifluoroacetic acid.
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