Nucleosides XIII.[1] Facile Synthesis of 4-Amino-1-(2-deoxy-β-D-ribofuranosyl)quinazolin-2-one as a 2′-Deoxycytidine Analog for Oligonucleotide Synthesis

Tun-Cheng Chien[†] (簡敦誠), Chien-Shu Chen (陳建樹) and Ji-Wang Chern* (陳基旺)
School of Pharmacy, National Taiwan University, Taipei 100, Taiwan, R.O.C.

4-Amino-1-(2-deoxy-β-D-ribofuranosyl)quinazolin-2-one (**4**) was prepared by Barton deoxygenation from 4-amino-1-(β-D-ribofuranosyl)quinazolin-2-one (**3**) as a 2′-deoxycytidine analog.

Keywords: 2′-Deoxycytidine; Cytidine; Quinazolinone; Barton deoxygenation; Markiewicz silylation.

INTRODUCTION

The development of automated solid-phase methods for the synthesis of nucleic acids in the last two decades has prompted the use of synthetic oligonucleotides or modified analogs to study DNA or RNA interactions. Since all nucleic acid helices are formed predominantly by hydrogen bonding and base stacking, strategies designed for improving nucleic acid recognition/interactions have mainly relied on modifications of the nucleic acid structure by chemical synthesis. In attempts of base modification, extending the aromatic domains of aglycons has been considered to increase stacking interactions between planar heterocyclic bases of nucleic acids, which would contribute to the stabilization of the nucleic acid helices.[2] Thus, oligonucleotides containing quinazolines or their derivatives to substitute the corresponding pyrimidine bases have received some attention.[3-8] While maintaining Watson-Crick base pairing properties of pyrimidines, these heterocycles, possessing an extended benzene or naphthalene ring fused to pyrimidines (Fig. 1), may provide additional stacking interactions and enhance the hydrogen bonding. Such an approach could be readily applicable to antisense or antigene research.

Quinazoline nucleosides were first synthesized by Stout and Robins in 1968 as pyrimidine nucleoside analogs[9] and consequent synthetic studies were contributed by Dunkel and Pfleiderer in the 1990s.[10-12] Quinazoline nucleosides were once used as a conformationally restricted model to study the *syn-anti* conformational preference of pyrimidine nucleosides in solution.[3,13,14] More recently, several quinazoline-2,4-dione nucleosides have been incorporated into oligonucleotides as uridine or thymidine substitutes to study the

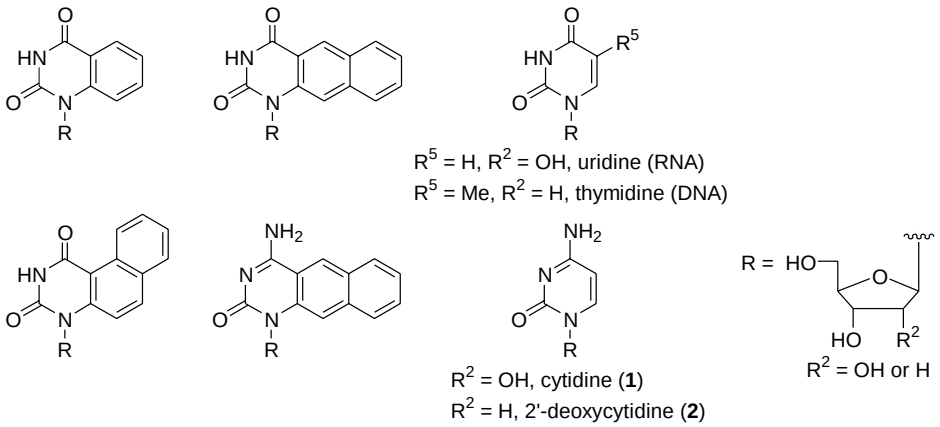


Fig. 1. Quinazolines and benzoquinazolines as pyrimidine analogs.

* Corresponding author. Fax: +886-2-2393-4221; E-mail: chern@jwc.mc.ntu.tw
[†] Current address: Division of Medicinal Chemistry, College of Pharmacy, The University of Texas at Austin, Austin, TX 78712, USA

binding affinity and base-pairing selectivity.[3-5]

4-Aminoquinazolin-2-one nucleosides (**3** and **4**) are our particular interest (Fig. 2). These quinazoline nucleosides were previously synthesized *via* a multi-step procedure from quinazoline-2,4-dione by Stout and Robins.[9] But the use of 4-aminoquinazolin-2-one nucleosides (**3** and **4**) in oligonucleotides has not yet been reported in the literature. Our group has previously reported a convenient synthesis of the 4-amino-1-(β-D-ribofuranosyl)quinazolin-2-one (**3**).[15] In an effort to incorporate 4-aminoquinazolin-2-one into oligodeoxynucleotides, we hereby report a facile synthesis of 4-amino-1-(2-deoxy-β-D-ribofuranosyl)quinazolin-2-one (**4**), which could be used for automated DNA synthesis (Scheme I).

RESULTS AND DISCUSSION

There are two general approaches for the preparation of 2′-deoxy-β-ribonucleosides: (1) the direct glycosylation of the base with a 2′-deoxyribofuranose derivative; and (2) the 2′-deoxygenation from an appropriately protected ribonucleoside. The synthesis of 4-amino-1-(2-deoxy-β-D-ribofuranosyl)quinazolin-2-one (**4**) was previously reported by Stout and Robins[9] *via* a direct glycosylation of quinazoline-2,4-dione with 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-ribofuranosyl chloride[16-18] followed by a multi-step functional group manipulation. The glycosylation was not very stereoselective and the separation of the α/β anomeric mixture was difficult. Therefore, this approach is not practical for large scale synthesis.[3,11] In our preliminary studies, a direct alkylation or glycosylation at the N^1-position of 4-amino-protected 4-aminoquinazolin-2-ones was unsuccessful, which prompted us to investigate the 2′-deoxygenation of 4-amino-1-(β-D-ribofuranosyl)quinazolin-2-one[15] (**3**) as an alternative synthetic route.

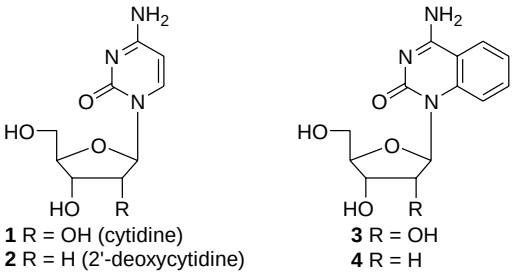
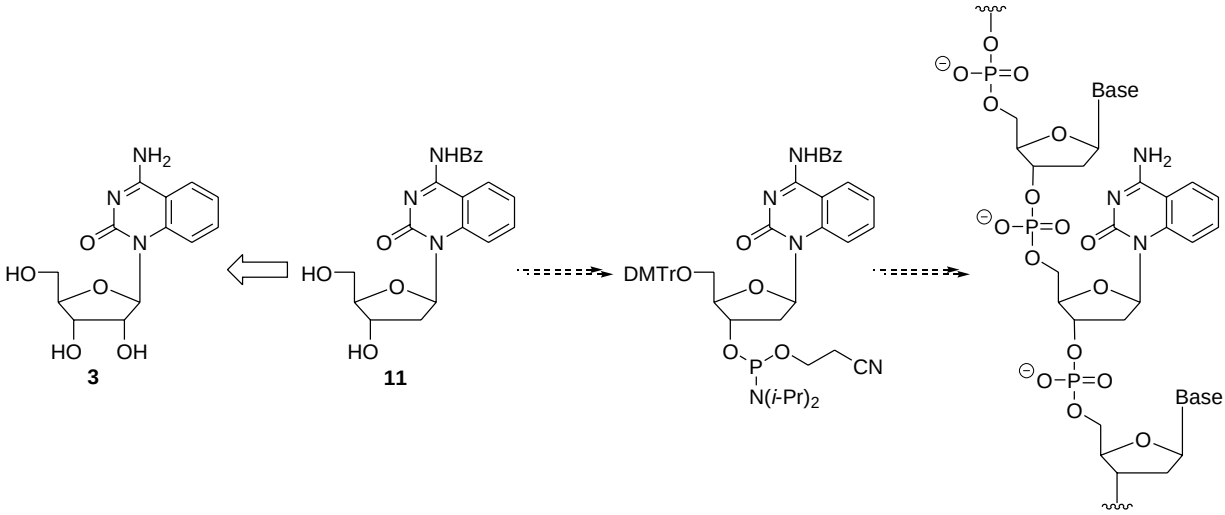


Fig. 2. Cytosine nucleosides (**1** and **2**) and proposed 4-aminoquinazolin-2-one nucleosides (**3** and **4**).

A convenient preparation of 2′-deoxynucleosides from the corresponding ribonucleosides using chemical 2′-deoxygenation was reported by Robins and Wilson.[19,20] This approach was achieved by the phenoxythiocarbonylation of 3′,5′-*O*-protected nucleosides followed by the Barton deoxygenation reaction.[21] However, we have encountered some difficulties when we applied the same synthetic route to the 4-aminoquinazolin-2-one nucleoside (**3**). The 3′,5′-diol of 4-amino-1-(β-D-ribofuranosyl)quinazolin-2-one[15] (**3**) was selectively protected with the Markiewicz reagent[22,23] to give **5** in an excellent yield. But our attempts to introduce the phenoxythiocarbonyl group to the 2′-*O*-position under several conditions were unsuccessful and led to a mixture of unidentified products. We speculated that the free amino group

Scheme I



at the 4-position of the quinazolinone might interfere with the phenoxythiocarbonylation. We first tried to protect the 4-amino group with *N,N*-dimethylformamide dimethyl acetal.[1,15,24] This attempt only had moderate success because the overall yield after the protecting steps was unsatisfactory. Therefore, we decided to introduce a benzoyl group onto the 4-amino group that could serve as a protecting group throughout the oligonucleotide synthesis. Compound **5** was treated with 1.3 equivalents of benozyl chloride in pyridine to give 54% of the monobenzoylated product **7a** and 16% of the dibenzoylated product **7b**. The monobenzoylated product **7a** was identified as the desired 4-amino-benzoylated product. When the reaction was carried out with 1.1 equivalents of benzoyl chloride, the desired 4-amino-benzoylated product **7a** was obtained in 53% yield, and about 24% of the unreacted starting material **5** was recovered. The recovered starting material was treated under the same benzoylation condition. After two reaction cycles, the 4-amino group of **5** was regioselectively protected and the desired 4-amino-benzoylated product **7a** was obtained in 65-73% overall yield.

Phenoxythiocarbonylation of **7a** under a commonly used condition, phenyl chlorothionocarbonate and an excess amount of 4-dimethylaminopyridine in acetonitrile,[11,19,20] gave a single product **8**. Mass spectrometry suggested that **8** is a dehydrated product of **7a**. The 2′-hydroxy group on the sugar, the amide hydrogen on the base, and the desired phenoxythiocarbonyl group were all absent from the ^{1}H NMR spectrum. The structure was consequently assigned as 3′,5′-*O*-protected O^2,2′-anhydronucleoside **8**.[11] It is noticeable that the coupling constant between 1′-H and 2′-H ($J_{1'-2'}$) in **8** is 8.3 Hz. This coupling constant is considerably greater than in other compounds (**5**, **7a-b**) with β-configuration in this series ($J_{1'-2'} \sim 0$ Hz), which results from the *cis*-coupling between the 1′-H and 2′-H.[25] To avoid the intramolecular nucleophilic ring-closure reaction, a modified condition using dichloromethane as the solvent was employed, and the reaction gave exclusively the desired 2′-*O*-phenoxythiocarbonylated product **9** in 87% yield. An excess amount of 4-dimethylaminopyridine (2-3 equivalent) is essential in these reactions.

The deoxygenation was carried out with tri-*n*-butyltin hydride by a homolytic cleavage of the $C^{2'}$-$O^{2'}$ bond followed by a hydrogen transfer in a radical chain reaction to afford **10** in 49% yield. Deprotection of the Markiewicz's disilyl group with tetra-*n*-butylammonium fluoride in tetrahydrofuran gave the 4-amino-benzoylated 2′-deoxynucleoside **11** in 72% yield. Alternatively, the disilyl group could also be deblocked with a mixture of potassium fluoride and 18-crown-6 in tetrahydrofuran.[26] The 4-amino-benzoyl group was removed by treatment of **11** with methanolic ammonia to afford the desired 4-amino-1-(2-deoxy-β-D-ribofuranosyl)quinazolin-2-one (**4**) in 43% yield (Scheme II).

The split patterns of the anomeric protons (1′-H) for **4** and **11** in the ^{1}H NMR spectrums both exhibit as a *pseudo*-triplet. Since the anomeric configuration has previously been established as the β-configuration,[15] this observation is consistent with Townsend's empirical rule that the anomeric protons of the 2′-deoxyribofuranosyl nucleosides displaying a *pseudo*-triplet split pattern mostly possess the β-configuration.[25]

CONCLUSION

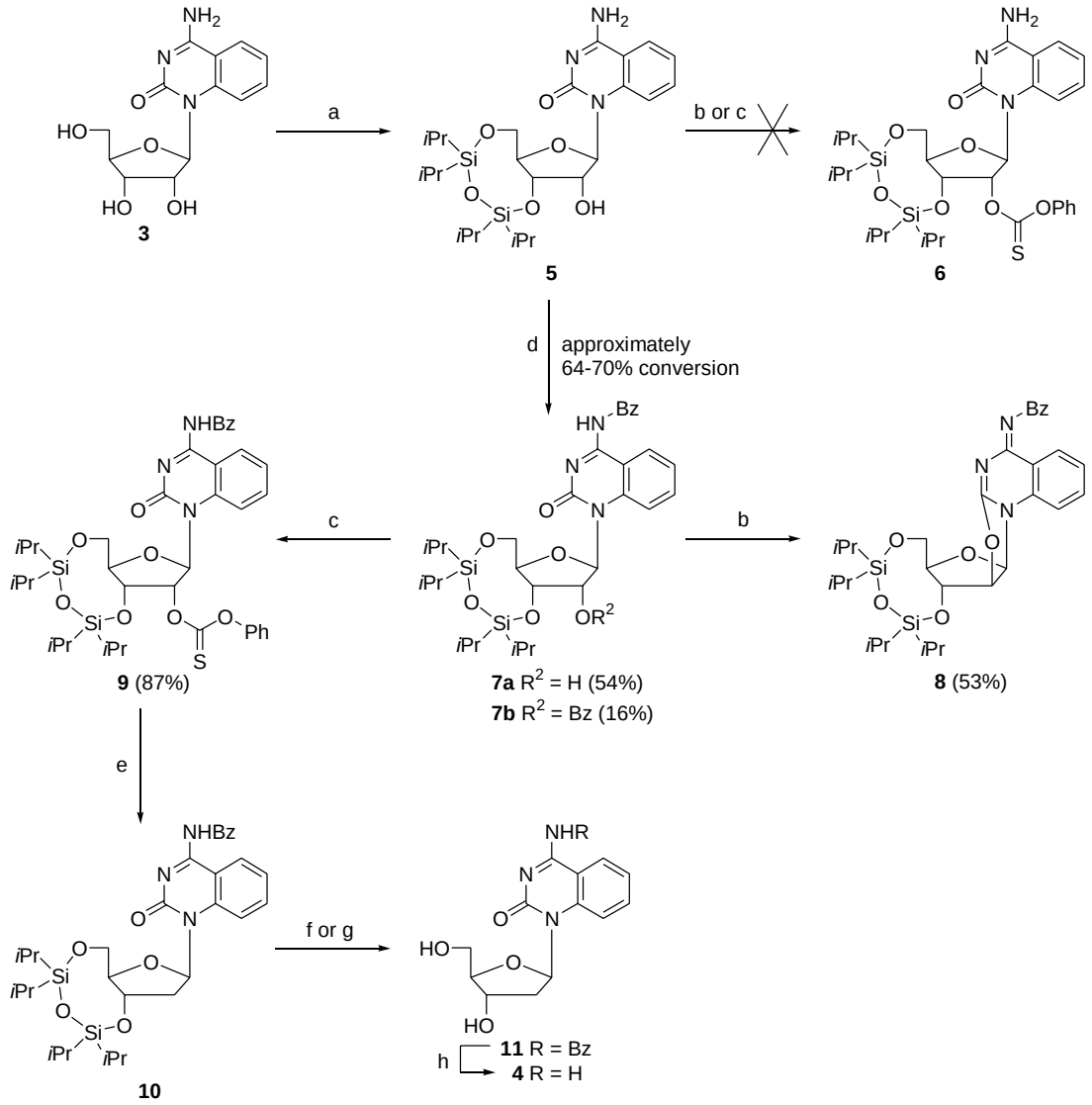
In summary, our investigation has provided a feasible route for the synthesis of 4-amino-1-(2-deoxy-β-D-ribofuranosyl)quinazolin-2-one (**4**). The 3′,5′-diol of 4-amino-1-(β-D-ribofuranosyl)quinazolin-2-one[15] (**3**) was selectively protected with the Markiewicz reagent.[22,23] Regioselective protection of the 4-amino group on the base with benzoyl chloride was accomplished. In an effort to introduce the phenoxythiocarbonyl group to the 2′-*O*-position, we observed the unexpected intramolecular nucleophilic ring-closure reaction. But the undesired reaction can be avoided simply by the solvent effect, i.e. by changing the solvent from acetonitrile to dichloromethane.[11] After phenoxythiocarbonylation at the 2′-hydroxy group, the nucleoside **9** underwent Barton deoxygenation followed by the removal of the protecting groups to give the desired 2′-deoxynucleoside (**4**) as a 2′-deoxycytidine (**2**) analog. Incorporating the 2′-deoxy quinazolinone nucleoside (**4**) into the oligodeoxynucleotide synthesis is in progress.

EXPERIMENTAL SECTION

General Chemical Procedures

Melting points were obtained on an Electrothermal apparatus and are uncorrected. NMR spectra were obtained on Varian Gemini-300, JEOL JNM-EX400 or Bruker DRX-500 spectrometers. Mass spectra were recorded on Finnigan TSQ-46C (EI), JEOL JMS-D300 (EI), VG 70-250S (FAB) or Micromass LCT (ESI) mass spectrometers. Elemental analy-

Scheme II



Reagents and conditions: (a) TiPDS-Cl_2, pyridine, rt, 5 hr, 89%; (b) PTC-Cl, 2-3 eq. DMAP, CH_3CN, rt, overnight; (c) PTC-Cl, 2-3 eq. DMAP, CH_2Cl_2, 0 °C or rt, 3 hr; (d) BzCl, pyridine, 0 °C -rt, overnight; (e) AIBN, *n*-Bu_3SnH, toluene, 80 °C, 3 hr, 49%; (f) KF, 18-crown-6, H_2O, THF, rt, 4 hr, 55%; (g) TBAF, THF, rt, 90 min, 72%; (h) NH_3/MeOH, rt, 24 hr, 43% [TiPDS-Cl_2 = 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane, the Markiewicz reagent; PTC-Cl = phenyl chlorothionocarbonate; AIBN = 2,2′-azobisisobutyronitrile].

ses for C, H, and N were carried out either on a Heraeus elemental analyzer or Perkin-Elmer 240 elemental analyzer and were within ±0.4% of the theoretical values. Thin-layer chromatography (TLC) was performed on Merck plates precoated with silica gel 60 containing fluorescent indicator. Compounds on thin-layer chromatography were visualized by illumination under UV light (254 nm), or dipped into 10% methanolic sulfuric acid followed by charring on a hot plate. Merck silica gel (230-400 mesh) was used for flash column chromatography as described by Still, W. C. et al.[27] Evaporation was carried out with a rotary evaporator under reduced pressure with the bath temperature below 50 °C unless specified otherwise. Materials obtained from commercial suppliers were used without further purification unless otherwise

stated. The solvents (THF, CH_3CN, CH_2Cl_2, pyridine, toluene) and reagents (benzoyl chloride) were purified/dried by distillation according to the standard procedures.[28] The reported yields have not been optimized.

4-Amino-1-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl]quinazolin-2-one (5)

To a suspension of 4-amino-1-(β-D-ribofuranosyl)-quinazolin-2-one[15] (**3**, 3.0 g, 10.2 mmol) in pyridine (50 mL) at room temperature was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (3.6 mL, 3.55 g, 11.25 mmol, 1.1 eq). The mixture was stirred at room temperature for 5 hr. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (100 mL). The organic solution was washed with H_2O (2 × 30 mL), saturated NaCl solution (30 mL), dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography ($CHCl_3$/MeOH = 97.5:2.5) to give **5** (foam, 4.90 g, 9.15 mmol, 89%, Rf = 0.31 ($CHCl_3$/MeOH = 95:5)). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97-1.12 (m, 28H, *i*Pr), 3.57 (br s, 1H, 2′-OH), 3.92-4.06 (m, 3H, 4′ & 5′-H), 4.79 (d, 1H, *J* = 6.5 Hz), 5.04 (t, 1H, *J* = 6.9 Hz), 6.00 (s, 1H, 1′-H), 7.07-7.13 (m, 1H, Ar), 7.41 (br s, 2H, NH_2), 7.48-7.54 (m, 1H, Ar), 7.72-7.74 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.2, 13.7, 13.8, 17.7, 17.8, 17.8, 17.9, 18.0, 18.1, 64.2, 73.2, 73.6, 83.2, 92.8, 110.9, 115.1, 123.0, 125.0, 134.8, 143.2, 155.9, 163.9; MS (FAB) *m/z* 162 (100), 261 (12), 357 (10), 535 (7) (M).

4-Benzamido-1-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl]quinazolin-2-one (7a)

To a mixture of **5** (4.83 g, 9.01 mmol) in pyridine (100 mL) at 0 °C was added dropwise benzoyl chloride (1.14 mL, 1.39 g, 9.91 mmol, 1.1 eq). After the addition was completed, the temperature was allowed to rise to room temperature and the mixture was stirred overnight. The reaction was quenched by adding H_2O (1 mL). The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (100 mL). The organic solution was washed with H_2O (2 × 30 mL) and saturated NaCl solution (30 mL), dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (Hex/EtOAc = 85:15) to give **7a** (foam, 3.06 g, 4.78 mmol, 53%, Rf = 0.27 (Hex/EtOAc = 8:2), also recovered 24% of **5**). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.00-1.26 (m, 28H, *i*Pr), 3.36 (br s, 1H, 2′-OH), 3.96-4.08 (m, 3H, 4′ & 5′-H), 4.82 (d, 1H, *J* = 6.0 Hz), 5.10 (t, 1H, *J* = 6.7 Hz), 5.97 (s, 1H, 1′-H), 7.27-7.74 (m, 6H, Ar), 8.39-8.41 (m, 2H, Ar), 8.66-8.68 (m, 1H, Ar), 13.02 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.2, 13.2, 13.6, 13.7, 13.8, 17.6, 17.8, 17.9, 18.1, 63.6, 72.6, 74.1, 83.1, 92.6, 115.1, 116.8, 124.5, 128.7, 128.8, 130.6, 133.4, 136.3, 137.4, 142.1, 147.6, 158.1, 180.3; MS (FAB) *m/z* 81 (20), 105 (100), 266 (60), 289 (25), 640 (12) (M + 1).

When the reaction was carried out with 1.3 equivalents of benzoyl chloride, the desired product (**7a**) was obtained in 54% yield and approximately 16% of 4-benzamido-1-[2-*O*-benzoyl-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl]quinazolin-2-one (**7b**) (Rf = 0.34 (Hex/EtOAc = 8:2)) was obtained from the reaction mixture.

4-Benzamido-1-[2-*O*-benzoyl-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl]quinazolin-2-one (7b)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87-1.25 (m, 28H, *i*Pr), 4.04-4.15 (m, 3H, 4′ & 5′-H), 5.23 (dd, 1H, *J* = 6.2, 8.4 Hz, 3′-H), 6.16 (s, 1H, 1′-H), 6.22 (d, 1H, *J* = 6.2 Hz, 2′-H), 7.33-7.73 (m, 9H, Ar), 8.06-8.10 (m, 2H, Ar), 8.39-8.43 (m, 2H, Ar), 8.68-8.72 (m, 1H, Ar), 13.06 (br s, 1H, NH); MS (FAB) *m/z* 77 (18), 105 (100), 261 (15), 479 (18), 744 (20) (M + 1).

***O*^{2},2′-Anhydro-4-benzamido-1-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl]quinazolin-2-one (8)**

To a mixture of **7a** (0.65 g, 1.01 mmol) and 4-dimethylaminopyridine (DMAP, 0.41 g, 3.33 mmol, 3.3 eq) in acetonitrile (20 mL) at room temperature was added phenyl chlorothionocarbonate (0.31 mL, 0.38 g, 2.22 mmol, 2.2 eq). The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (30 mL). The organic solution was washed with H_2O (15 mL) and saturated NaCl solution (15 mL), dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (Hex/EtOAc = 7:3) to give **8** (foam, 0.332 g, 0.53 mmol, 53%, Rf = 0.35 (Hex/EtOAc = 6:4)). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.00-1.26 (m, 28H, *i*Pr), 3.83-4.04 (m, 3H, 4′ & 5′-H), 4.50 (dd, 1H, *J* = 4.5, 9.9 Hz, 3′-H), 5.33 (dd, 1H, *J* = 4.5, 8.2 Hz, 2′-H), 6.47 (d, 1H, *J* = 8.2 Hz, 1′-H), 7.19-7.56 (m, 7H, Ar), 8.03-8.10 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.0, 13.2, 13.7,

13.9, 17.5, 17.5, 17.7, 17.8, 18.0, 62.7, 78.4, 83.8, 86.4, 89.7, 114.9, 117.3, 126.1, 128.1, 128.7, 130.2, 132.9, 133.7, 135.4, 135.8, 154.5, 157.6, 181.7; MS (FAB) *m/z* 105 (100), 622 (80) (M + 1).

4-Benzamido-1-[2-*O*-phenoxythiocarbonyl-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl]quinazolin-2-one (9)

To a mixture of **7a** (0.968 g, 1.52 mmol) and 4-dimethylaminopyridine (DMAP, 0.407 g, 3.33 mmol, 2.2 eq) in dichloromethane (10 mL) at 0 °C was added phenyl chlorothionocarbonate (0.26 mL, 0.327 g, 1.89 mmol, 1.25 eq). The mixture was stirred at room temperature for 3 hr. The reaction was quenched by adding H_2O (0.25 mL). The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (100 mL). The organic solution was washed with H_2O (2 × 45 mL) and saturated NaCl solution (45 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (Hex/EtOAc = 9:1) to give **9** (foam, 1.03 g, 1.33 mmol, 87%, Rf = 0.56 (Hex/EtOAc = 8:2)). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.09-1.43 (m, 28H, *i*Pr), 4.01-4.17 (m, 3H, 4′ & 5′-H), 5.32 (dd, 1H, *J* = 5.8, 8.8 Hz, 3′-H), 6.02 (s, 1H, 1′-H), 6.68 (d, 1H, *J* = 5.8 Hz, 2′-H), 7.09-7.72 (m, 11H, Ar), 8.67-8.39 (m, 2H, Ar), 8.63-8.65 (m, 1H, Ar), 11.20 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.6, 12.8, 13.0, 13.2, 14.0, 16.8, 17.0, 17.1, 17.2, 17.4, 22.6, 31.5, 61.0, 70.1, 81.7, 83.4, 89.1, 114.3, 116.3, 121.7, 124.0, 126.5, 128.1, 128.2, 129.4, 130.0, 132.7, 135.7, 136.7, 141.2, 146.8, 153.3, 157.2, 179.7, 194.1; MS (ESI) *m/z* 644 (100) (M + Na - HOC(=S)OPh), 798 (77) (M + Na); HRMS (ESI) Calcd for $C_{39}H_{49}N_3O_8Si_2S \cdot Na$: 798.2677. Found 798.2672; Anal. Calcd for $C_{39}H_{49}N_3O_8Si_2S$: C, 60.36; H, 6.36; N, 5.41. Found: C, 60.39; H, 6.49; N, 5.44.

4-Benzamido-1-[2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl]quinazolin-2-one (10)

To a solution of **9** (2.8715 g, 3.70 mmol) and 2,2′-azobisisobutyronitrile (AIBN, 0.122 g, 0.74 mmol, 0.2 eq) in distilled toluene (80 mL) at room temperature under an argon atmosphere was added tri-*n*-butyltin hydride (3.0 mL, 3.23 g, 11.1 mmol, 3 eq). The mixture was then heated at 80 °C for 3 hr. After cooling to room temperature, the solution was concentrated under reduced pressure and the resulting oil was purified by flash column chromatography (Hex/EtOAc = 10:0-9:1) to give **10** (oil, 1.13 g, 1.81 mmol, 49%, Rf = 0.25 (Hex/EtOAc = 9:1)). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87-1.44 (m, 28H, *i*Pr), 2.41 (ddd, 1H, *J* = 6.9, 9.0, 13.9 Hz, 2′-H), 2.93 (ddd, 1H, *J* = 4.6, 9.0, 13.9 Hz, 2′-H), 3.88 (dd, 1H, *J* = 5.1, 11.0 Hz, 5′-H), 4.00-4.16 (m, 2H, 4′ & 5′-H), 5.00-5.08 (m, 1H, 3′-H), 6.56 (dd, 1H, *J* = 4.6, 9.0 Hz, 1′-H), 7.30-7.69 (m, 6H, Ar), 8.39-8.41 (m, 2H, Ar), 8.67-8.69 (m, 1H, Ar), 13.02 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.1, 13.4, 13.8, 14.0, 14.7, 17.5, 17.6, 17.7, 17.8, 17.9, 18.0. 18.1, 38.0 (2′-CH_2), 63.4 (5′-CH_2), 72.6, 84.5, 85.7, 115.8, 117.2, 124.3, 128.8 (2 × C), 130.6, 133.3, 135.8, 137.5, 141.3, 147.7, 158.0, 180.3; MS (ESI) *m/z* 543 (38), 646 (100) (M + Na); HRMS (ESI) Calcd for $C_{32}H_{45}N_3O_6Si_2 \cdot Na$: 646.2745. Found 646.2732.

4-Benzamido-1-(2-deoxy-β-D-ribofuranosyl)quinazolin-2-one (11)

[Method A]

To a mixture of **10** (1.13 g, 1.81 mmol), potassium fluoride (1.44 g, 24.8 mmol, 8 eq) and 18-crown-6 (0.66 g, 2.48 mmol, 0.8 eq) in THF (20 mL) was added one drop of H_2O. The mixture was stirred at room temperature for 5 hr. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (50 mL). The solution was washed with H_2O (2 × 20 mL) and saturated NaCl solution (20 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography ($CHCl_3$/MeOH = 95:5, Rf = 0.21) to give **11** (378 mg, 0.99 mmol, 55%). An analytical sample of **11** was obtained by recrystallization from EtOAc.

[Method B]

To a solution of **10** (0.195 g, 0.31 mmol) in THF (5 mL) was added 1 M TBAF solution in THF (1.55 mL, 5 eq). The mixture was stirred at room temperature for 90 min. The solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography ($CHCl_3$/MeOH = 95:5, Rf = 0.21) to give **11** (85.1 mg, 0.223 mmol, 72%). The compound was recrystallized from EtOAc to give an analytical sample of **11** (57.2 mg, 0.15 mmol, 48%). mp 170-173 °C (decomp.) (EtOAc); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.99 (ddd, 1H, *J* = 3.7, 7.5, 13.4 Hz, 2′-H), 2.69 (dt, 1H, *J* = 7.9, 13.4 Hz, 2′-H), 3.64-3.77 (m, 3H, 4′ & 5′-H), 4.42 (m, 1H, 3′-H), 4.97 (br s, 1H, OH), 5.27 (br s, 1H, OH), 6.69 (t, 1H, *J* = 7.5 Hz, 1′-H), 7.36-7.40 (m, 1H, Ar), 7.51-7.55 (m, 2H, Ar), 7.60-7.64 (m, 1H, Ar), 7.72-7.76 (m,

1H, Ar), 7.95-7.97 (m, 1H, Ar), 8.26-8.28 (m, 2H, Ar), 8.53-8.55 (m, 1H, Ar), 12.68 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 36.3 (2′-CH_2), 60.8 (5′-CH_2), 69.5, 84.0, 86.7, 115.8, 117.2, 123.7, 127.3, 128.4, 129.6, 132.9, 135.3, 136.2, 139.8, 147.5, 155.9, 178.4; MS (ESI) *m/z* 288 (50), 404 (100) (M + Na); HRMS (ESI) Calcd for $C_{20}H_{19}N_3O_5$·Na: 404.1222. Found 404.1223. Anal. Calcd for $C_{20}H_{19}N_3O_5$: C, 62.99; H, 5.02; N, 11.02. Found: C, 62.71; H, 5.04; N, 11.16.

4-Amino-1-(2-deoxy-β-D-ribofuranosyl)quinazolin-2-one[9] (4)

Compound **11** (378 mg, 0.99 mmol) was dissolved in methanolic ammonia (20 mL) and the solution was stirred at room temperature for 24 hr. The solvent was removed under reduced pressure and the resulting residue was recrystallized from ethanol and H_2O to give **4** (118 mg, 0.43 mmol, 43%). mp 211-213 °C (decomp.) (EtOH/H_2O) [*lit.*[9] 212.5-213 °C (MeOH/H_2O)]; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.86-1.89 (m, 1H, 2′-H), 2.62 (dt, 1H, *J* = 8.2, 13.2 Hz, 2′-H), 3.62-3.70 (m, 3H, 4′-H & 5′-H), 4.39-4.40 (m, 1H, 3′-H), 4.96 (t, 1H, *J* = 4.9 Hz, OH), 5.23 (d, 1H, *J* = 4.9 Hz, OH), 6.75 (t, 1H, *J* = 7.7 Hz, 1′-H), 7.19-7.22 (m, 1H, Ar), 7.57-7.61 (m, 1H, Ar), 7.79-7.81 (m, 1H, Ar), 7.89 (br s, 1H, NH), 8.04-8.06 (m, 2H, 1 × Ar & 1 × NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 37.2 (2′-CH_2), 61.9 (5′-CH_2), 70.8 (CH), 84.7 (CH), 87.2 (1′-CH), 111.3, 117.3 (CH), 122.4 (CH), 125.7 (CH), 134.1 (CH), 142.0, 156.0, 163.8; MS (ESI) *m/z* 184 (30) (4-aminoquinazolin-2-one + Na), 300 (100) (M + Na); HRMS (ESI) Calcd for $C_{13}H_{15}N_3O_4$ · Na: 300.0960. Found 300.0962. Anal. Calcd for $C_{13}H_{15}N_3O_4$ · ¼ H_2O: C, 55.41; H, 5.54; N, 14.91. Found: C, 55.56; H, 5.47; N, 14.87.

ACKNOWLEDGMENTS

This investigation was supported by a research grant (NSC 84-2331-B-016-018) from the National Science Council of the Republic of China, Taiwan.

Received January 18, 2005.

REFERENCES

1. Previous paper in this series: Chien, T.-C.; Kuo, C.-C.; Chen, C.-S.; Chern, J.-W. *J. Chin. Chem. Soc. (Taipei)* **2004**, *51*, 1401-1406.
2. Kool, E. T. *Chem. Rev.* **1997**, *97*, 1473-1487.
3. Bhattacharya, B. K.; Chari, M. V.; Durland, R. H.; Revankar, G. R. *Nucleosides Nucleotides* **1995**, *14*, 45-63.
4. Michel, J.; Toulme, J.-J.; Vercauteren, J.; Moreau, S. *Nucleic Acids Res.* **1996**, *24*, 1127-1135.
5. Michel, J.; Gueguen, G.; Vercauteren, J.; Moreau, S. *Tetrahedron* **1997**, *53*, 8457-8478.
6. Godde, F.; Toulme, J.-J.; Moreau, S. *Biochemistry* **1998**, *37*, 13765-13775.
7. Arzumanov, A.; Godde, F.; Moreau, S.; Toulme, J.-J.; Weeds, A.; Gait, M. J. *Helv. Chim. Acta* **2000**, *83*, 1424-1436.
8. Godde, F.; Toulme, J.-J.; Moreau, S. *Nucleic Acids Res.* **2000**, *28*, 2977-2985.
9. Stout, M. G.; Robins, R. K. *J. Org. Chem.* **1968**, *33*, 1219-1225.
10. Dunkel, M.; Pfleiderer, W. *Nucleosides Nucleotides* **1991**, *10*, 799-817.
11. Dunkel, M.; Pfleiderer, W. *Nucleosides Nucleotides* **1992**, *11*, 787-819.
12. Dunkel, M.; Pfleiderer, W. *Nucleosides Nucleotides* **1993**, *12*, 125-374.
13. Schweizer, M. P.; Witkowski, J. T.; Robins, R. K. *J. Am. Chem. Soc.* **1971**, *93*, 277-279.
14. Schweizer, M. P.; Banta, E. B.; Witkowski, J. T.; Robins, R. K. *J. Am. Chem. Soc.* **1973**, *95*, 3770-3778.
15. Chien, T.-C.; Chen, C.-S.; Yu, F.-H.; Chern, J.-W. *Chem. Pharm. Bull.* **2004**, *52*, 1422-1426.
16. Rolland, V.; Kotera, M.; Lhomme, J. *Synth. Commun.* **1997**, *27*, 3505-3511.
17. Hoffer, M. *Chem. Ber.* **1960**, *93*, 2777-2781.
18. Hoffer, M.; Duschinsky, R.; Fox, J. J.; Yung, N. *J. Am. Chem. Soc.* **1959**, *81*, 4112-4113.
19. Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932-933.
20. Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059-4065.
21. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574-1585.
22. Markiewicz, W. T. *J. Chem. Res. (S)* **1979**, 24-25.
23. Markiewicz, W. T.; Padyukova, N. S.; Samek, Z.; Smrt, J. *Collect. Czech. Chem. Commun.* **1980**, *45*, 1860-1865.
24. Chen, C.-S.; Chern, J.-W. *Nucleosides Nucleotides* **1996**, *15*, 1253-1261.
25. Townsend, L. B. Chapter 7. Nuclear Magnetic Resonance Spectroscopy in the Study of Nucleic Acid Components and Certain Related Derivatives. In *Synthetic Procedures in Nu-*

cleic Acid Chemistry; Zorbach, W. W.; Tipson, R. S. Eds.; Wiley: New York, 1973; Vol. 2, pp 267-398.
26. Kremsky, J. N.; Sinha, N. D. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2171-2174.
27. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.
28. Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*; 4th ed.; Butterworth Heinemann: Oxford, 1997.