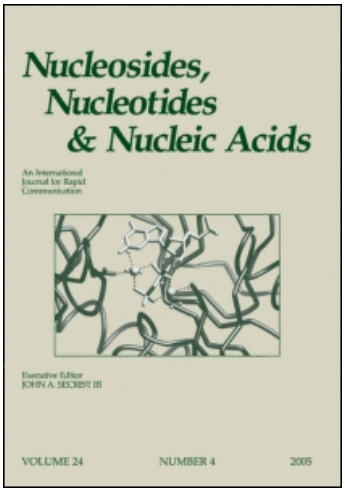

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The "Corey's Reagent," 3,5-di-tert-butyl-1,2-Benzoquinone, as a Modifying Agent in the Synthesis of Fluorescent and Double-Headed Nucleosides

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THE "COREY'S REAGENT," 3,5-DI-TERT-BUTYL-1,2-BENZOQUINONE, AS A MODIFYING AGENT IN THE SYNTHESIS OF FLUORESCENT AND DOUBLE-HEADED NUCLEOSIDES

Victor A. Timoshchuk and Richard I. Hogrefe

TriLink Biotechnologies, Inc., San Diego, California, USA

□ *A new method for the synthesis of fluorescent nucleosides has been developed. It has been shown that a reaction of benzoquinone with aminopropenyl group at C-5-position of 2′-deoxyuridine or 2′-deoxycytidine and aminopropynyl group at the C-7-position of 8-aza-7-deazaadenosine under extremely mild conditions affords conjugated benzoxazole derivatives of nucleosides, which possess strong fluorescent properties. In a similar reaction 5′-amino-5′-deoxy-nucleosides form double-headed nucleoside derivatives with benzoxazole attached at C-4′-position.*

Keywords Fluorescent nucleosides; Corey's reagent; benzoxazoles; labeling; double-headed nucleosides

INTRODUCTION

It was shown that 3,5-di-tert-butyl-1,2-benzoquinone (**1**) is an extremely versatile reagent.[1] Corey[2] showed more than 20 years ago that sec-alkyl primary amines (**2**) underwent oxidative deamination with quinone **1** to form an aminophenol (**3**) and a ketone (**4**) (Scheme 1).

At the same time n-alkyl primary amines (**5**) react with benzoquinone **1** in a different way. Quinonemonoimine (**6**) is formed at the first stage of the reaction and transformed into a Schiff's base (**7**) as a result of a sigmatropic shift. Existing equilibrium between this base and benzoxazoline (**8**) makes it possible to oxidize **8** with an excess of **1** into substituted benzoxazole (**9**)[1] (Scheme 2).

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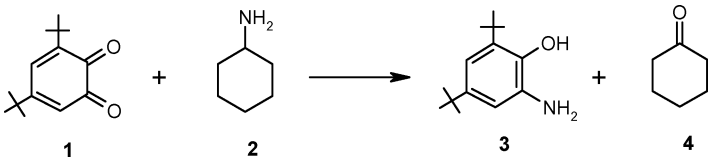
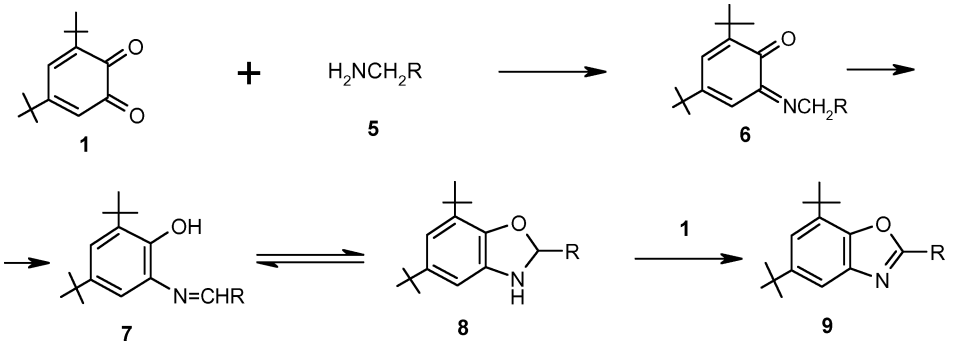


SCHEME 1 Oxidative deamination of amines with 3,5-di-tert-butyl-1,2-benzoquinone.



SCHEME 2 Transformation of primary amines into benzoazoles.

This chemistry led us to consider the possibility that this reaction could be used to develop a novel class of fluorescent nucleosides which are formed in situ, using a quinone with the appropriately modified nucleosides that would react under extremely mild conditions. This would open up the possibility of forming fluorescently labeled DNA from "black" monomers. One significant problem with in situ DNA labeling techniques is that the dyes used to label the DNA can lead to background fluorescence if not completely washed away. This is particularly troublesome with highly sensitive techniques like some microarray assays. The approach we are proposing would completely remove background since the labeling reagent is not fluorescent until it reacts with the desired nucleoside.

To the best of our knowledge the reaction of benzoquinone **1** with nucleosides bearing aminomethyl functionalities has never been reported for use in nucleoside chemistry. At the same time it is very well known that 5-(3-aminopropenyl)- and 5-(3-aminopropynyl)-2′-dUTP and dCTP are widely used for coupling with amine-reactive fluorescent labels.[3,4] These triphosphates and C-7 modified 7-deaza-dATP and 7-deaza-dGTP with aminopropynyl side chain have been tested as substrates for *Taq* polymerase during PCR. All of these modifications are tolerated by this enzyme.[5,6]

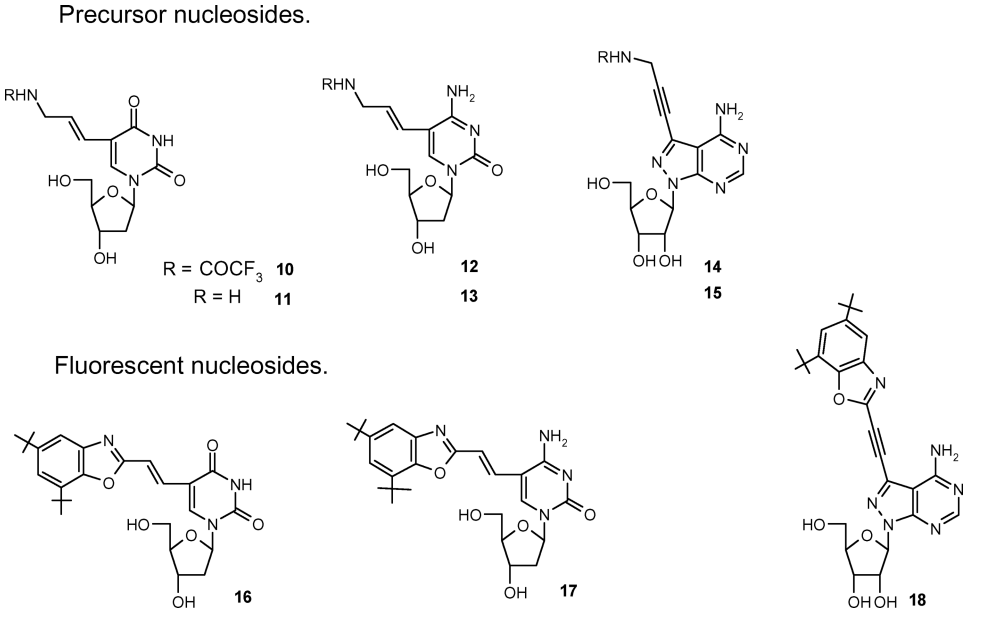
Therefore, it seems reasonable to try to modify this reaction of 5-(E)-(3-aminopropenyl)-dU and dC and 8-aza-7-deaza-7-(3-aminopropynyl)-dA with quinone to form fluorescently labeled oligonucleotides in situ.

RESULTS AND DISCUSSION

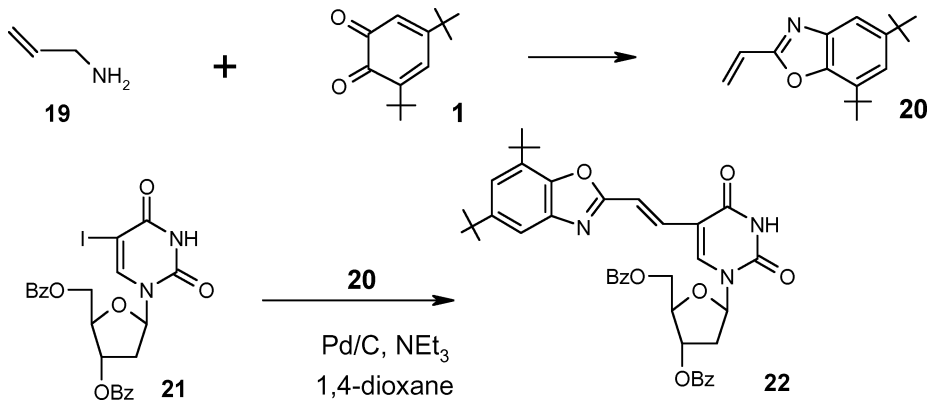
Trifluoroacetamides **10, 12** and **14**[7] of nucleosides **11**, **13,** and **15** were chosen as candidates for reaction with benzoquinone. They were treated first with methanolic ammonia to remove the trifluoroacetyl group, and then (after vacuum evaporation) reacted with 2 equivalents of benzoquinone **1** at room temperature in methanol. The progress of reaction was monitored by TLC and after completion the fluorescent nucleosides **16**, **17,** and **18** were purified by column chromatography on silica gel (Scheme 3).

3,5-Di-tert-butyl-1,2-benzoquinone is commercially available, but still quite expensive in comparison with its precursor 3,5-di-tert-butylcatechol. A number of oxidants were used for preparation of **1** [1] but most of them are not very convenient. We have developed a very simple method, which consists in the treatment of 3,5-di-tert-butylcatechol using acetic acid with the solution of sodium nitrite in water. Solid benzoquinone **1** was obtained in 85% yield by adding an excess of water, filtration, and drying. It is soluble in the mixture of DMF:H_2O = 1:1 v/v (1.4 mg/mL) and MeOH:H_2O = 3:2 v/v (3 mg/mL).

Another more traditional route for the synthesis of nucleoside **16** was used to prepare an authentic sample of the desired product. The treatment of allylamine **19** with quinone **1** gave us 2-vinyl-4,6-di-tert-butylbenzoxazole (**20**). Two equivalents of benzoxazole **20** were coupled with 5-iodo-3′,



SCHEME 3 Synthesis of the fluorescent nucelosides **16–18**.



SCHEME 4 Alternative synthesis of the protected nucleoside **22**.

5′-di-*O*-benzoyl-2′-deoxyuridine (**21**) in the Heck reaction.[8,9] This reaction was carried out in boiling 1,4-dioxane with 10% Pd/C as a catalyst to give 3′,5′-di-O-benzoyl-5-(E)-[2-(4,6-di-tertbutylbenzoxazol-2-yl)ethenyl] –2′-deoxyuridine (**22**) in 75% yield (Scheme 4).

Although this route gave a relatively high yield of the product **22**, it is much more time consuming and laborious then direct reaction of benzoquinone with aminopropenyl and aminopropynyl nucleoside derivatives and obviously not amenable for in situ labeling of DNA.

Photophysical properties of the nucleosides **16**, **17**, and **18** were examined in ethanol due to their poor solubility in methanol and water (Figure 1).

Their spectra were recorded and compared with one of the most efficient dyes, Cy-3. It was found that fluorescence of compounds **16**, **17**, and **18** is only 5–10% of Cy-3 labeled 5-derivative of dU fluorescence (λ_{em} = 575 nm). Further, their emission was observed at about 400 nm while the most of microarray scanners detect the emission at 532 nm and above, which somewhat decreases the applications of this approach using this particular benzoquinone to derivatized nucleosides. Our next goal is the synthesis of nucleoside derivatives of conjugated aryloxazoles with a longer wavelength emission using water-soluble arylquinones.

Another part of the present communication concerns the modification of 5′-amino-5′-deoxy-nucleosides into their benzoxazole derivatives. The reaction of 5′-amino-5′-deoxy-2′,3′-*O*-isopropylideneuridine (**23**)[10] with benzoquinone **1** produced the so called "double-headed"[11,12] nucleoside (**24**) with two bases approximated in space. Nucleoside **25** was obtained by acidic deprotection of isopropylidene group. 5′-Amino-2′,5′-dideoxyadenosine (**26**)[13] was converted into (**27**) in the same way in 60% yield (Scheme 5).

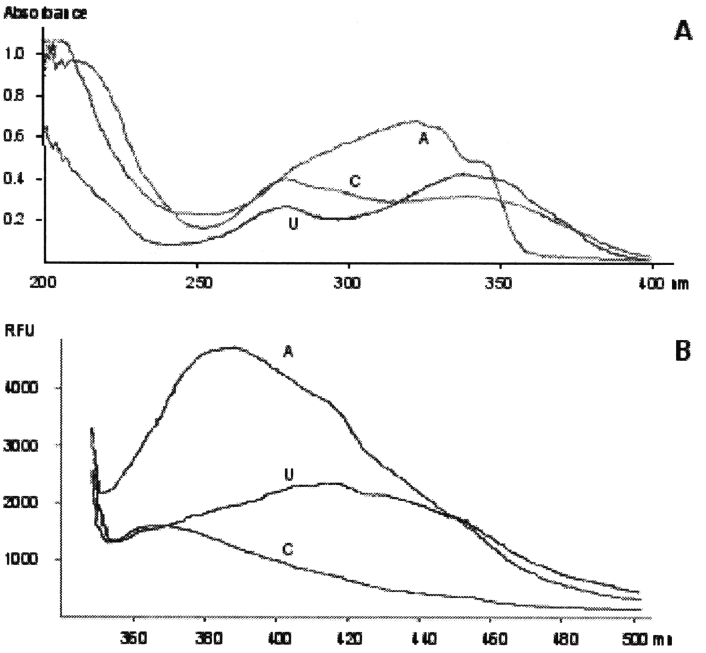
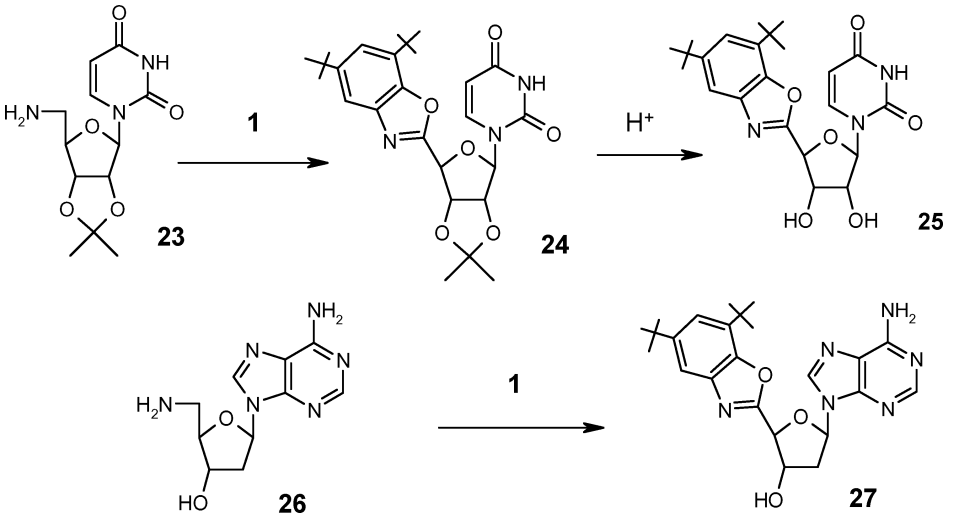


FIGURE 1 Absorption (A) and fluorescent spectra (B, $\lambda_{ex} = 345$ nm) of modified nucleosides **16** (U), **17** (C), and **18** (A) in ethanol at 0.5 μM concentration at room temperature.

A few attempts were undertaken to introduce another heterocyclic base at the 4′-position of the nucleoside.[14–16] Nucleosides with such substituents as CI, OAc, OAlk, NH_2, and N_3 groups at 4′-position were synthesized,



SCHEME 5 Synthesis of double-headed nucelosides **24, 25, 27**.

but the synthesis of nucleosides with two nucleobases failed.[16] We believe this method will prove successful for the synthesis of C-1 nucleoside analogs[17,18] and adenosine receptor agonists[19] and warrants further attention.

CONCLUSION

Fluorescent nucleosides were synthesized by simple interaction of aminopropenyl and aminopropynyl groups of 5-modified pyrimidine and 8-aza-7-deaza-7-modified purine nucleosides with 3,5-di-tert-butyl-1,2-benzoquinone. The possibility of the transformation of 5′-amino-5′-deoxynucleosides into double-headed nucleosides has been discussed. This publication reports the preliminary effort toward creating a novel in situ labeling technique that will benefit the development of highly sensitive microarray procedure. We believe this was a very successful first step.

EXPERIMENTAL

Reagents were purchased from Sigma Aldrich (St. Louis, MO, USA) and used as such. ^{1}H NMR spectra were obtained at 500 MHz (Bruker AM 500, Billerica, MA, USA) and are reported on δ scale. Fluorescence spectra were obtained at 350 nm excitation using a microplate Gemini XS spectrofluorophotometer (Molecular Dynamics, Sunnyvale, CA, USA). Low-resolution ES mass spectra (LRMS) were recorded with an ionization voltage of 70 eV. TLC was performed with Merck 60 F_{254} silica, and flash column chromatography with Silica Gel 60 Geduran (40–63 μm, Merck, Lawrence, KS, USA) in the solvent systems A ($CHCl_3$:MeOH = 9:1 v/v), B ($CHCl_3$:MeOH = 98:2 v/v), and C (Hexanes:EtOAc = 95:5 v/v). Nucleosides **10** and **12** are TriLink's commercial products.

Synthesis of 3,5-di-tert-butyl-1,2-benzoquinone (1)

The solution of sodium nitrite (1.4 g, 20 mmol) in water (5 mL) was added dropwise (foaming) to a stirred solution of 3,5-di-tert-butylcatechol (2.2 g, 10 mmol) in acetic acid (10 mL). After stirring for **1** hour at room temperature, water (20 mL) was added for precipitation of benzoquinone. It was filtered off, washed and dried to give **1** as a brown solid (1. 9 g, 85%).

General Procedure for Preparation of Benzoxazoles from Primary Amines

Nucleosides **10**, **12**, and **14**[7] with trifluoroacetyl protective groups were treated with ammonia (7 N solution in methanol) until full deprotection (TLC). The volatiles were evaporated in vacuum and the crude nucleosides **16**, **17**, and **18** were used in the reaction with quinone **1** without preliminary

purification. Their 4% solutions in methanol were treated with two equivalents of quinone **1** at room temperature overnight. After evaporation, crude products were purified by flash chromatography in an appropriate solvent systems.

5-(E)-[2-(4,6-Di-tert-butylbenzoxazol-2-yl)ethenyl)-2′-deoxyuridine (16). System A (78% yield). ^{1}H NMR (DMSO-d_6): 11.69 (s, 1H, NH), 8.46 (s, 1H, H-6), 7.54 (d, 1H, J = 16.0 Hz, = CH), 7.46 (d, 1H, J = 16.0 Hz, = CH), 7.50 (d,1H, J = 1.8 Hz, Ar) 7.25 (d, 1H, J = 1.8 Hz, Ar), 6.17 (dd, 1H, H-1′), 5.28 (d, 1H, J = 4.5 Hz, 3′-OH), 5.22 (t, 1H, J = 5.4 Hz, 5′-OH), 4.29 (m, 1H, H-3′, 3.81 (m, 1H, H-4′), 3.69 (m, 1H, H-5′a), 3.62 (m, 1H, H-5′b), 2.27 (m, 1H, H-2′a), 2.18 (m, 1H, H-2′b), 1.47 and 1.34 (2s, 18H, 2 t-Bu). LRMS: m/z = 482.5 $[M-H]^-$, 506.5 $[M+Na]^+$. UV: λ_{max} (MeOH) 282 nm, 338 nm, 350 nm (sh.), 370 nm (sh.). λ_{em} (EtOH) 415 nm.

5-(E)-[2-(4,6-Di-tert-butylbenzoxazol-2-yl)ethenyl)-2′-deoxycytidine (17). System A (63% yield). ^{1}H NMR (DMSO-d_6): 8.57 (s, 1H, H-6), 7.64 (d, 1H, J = 16.0 Hz, = CH), 7.60 (br.s, 2H, NH_2), 7.49 (d, 1H, J = 1.8 Hz, Ar), 7.25 (d,1H, J = 1.8 Hz, Ar), 6.89 (d, 1H, J = 16.0 Hz, = CH), 6.17 (dd, 1H, H-1′), 5.25 (t, 1H, J = 5.5 Hz, 5′-OH), 5.23 (d, 1H, J = 4.5 Hz, 3′-OH), 4.28 (m, 1H, H-3′), 3.82 (m, 1H, H-4′), 3.70 (m, 1H, H-5′a), 3.62 (m, 1H, H-5′b), 2.19 (m, 2H, H-2′a, H-2′b), 1.49 and 1.34 (2s, 18H, t-Bu). LRMS: m/z = 481.4 $[M-H]^-$, 483.5 $[M+H]^+$, 505.5 $[M+Na]^+$. UV: λ_{max} (MeOH) 292 nm, 345 nm. λ_{em} (EtOH) 410 nm.

8-Aza-7-deaza-7-[(4,6-di-tert-butylbenzoxazol-2-yl)ethynyl)adenosine (18). System A (42% yield). ^{1}H NMR (DMSO-d_6): 8.33 (s, 1H, H-2), 8.2 (br.s, 1H, NH), 7.66 (d, 1H, J = 1.8 Hz, Ar), 7.43 (d, 1H, J = 1.8 Hz, Ar), 7.2 (br.s, 1H, NH), 6.17 (d, 1H, J = 4.8 Hz, H-1′), 5.48 (d, 1H, J = 5.9 Hz, 2′-OH), 5.21 (d, 1H, J = 5.5 Hz, 3′-OH), 4.86 (t, 1H, J = 5.8 Hz, 5′-OH), 4.63 (m, 1H, H-2′), 4.24 (m, 1H, H-3′), 3.94 (m, 1H, H-4′), 3.60 (m, 1H, H-5′a), 3.47 (m, 1H, H5′b), 1.48 and 1.37 (2s, 18H, t-Bu). LRMS: m/z = 519.6 $[M-H]^-$, 521.5 $[M+H]^+$, 543.6 $[M+Na]^+$, 559.5 $[M+K]^+$. UV: λ_{max} (MeOH) 274 nm, 326 nm. λ_{em} (EtOH) 390 nm, 415 nm (sh).

2-Vinyl-4,6-di-tert-butylbenzoxazole (20). System C (78% yield). ^{1}H NMR (DMSO-d_6): 7.54 (d, 1H, J = 1.8 Hz, Ar), 7.29 (d, 1H, J = 1.8 Hz, Ar), 6.83 (dd, 1H, J = 11.0 Hz, 17.5 Hz, = CH), 6.41 (dd, 1H, J = 1.0 Hz, 17.5 Hz, = CH), 5.94 (dd, 1H, J = 1.0 Hz, 11.0 Hz, = CH). LRMS: m/z = 256.4 $[M-H]^-$, 280.4 $[M+Na]^+$. UV: λ_{max} (MeOH) 280 nm.

3′,5′-Di-*O*-benzoyl-5-(E)-[2-(4,6-di-tert-butylbenzoxazol-2-yl)ethenyl]-2′-deoxyuridine (22). 3′,5′-Di-O-benzoyl-5-iodo-2′-deoxyuridine **(21)** (562 mg, 1 mmol) was dissolved in 1,4-dioxane (20 mL) and heated together with triethylamine (0.5 mL), 2-vinyl-4,6-di tert-butylbenzoxazole **20** (520 mg, 2 mmol) and 10% Pd/C (100 mg) at 100–110°C for 3 hours. The volatiles were evaporated and the residue was purified by flash chromatography (system B) to give title compound in 75% yield. ^{1}H NMR ($CDCI_3$): 8.85 (s, 1H, NH), 8.08–8.03 (m, 4H, Ar), 7.92 (s. 1H, H-6), 7.65 (d, 1H, J = 16.0

Hz, = CH), 7.62 (d, 1H, J = 16.0 Hz, = CH), 7.60 (d, 1H, J = 1.8 Hz, Ar), 7.48 (t, 3H, Ar), 7.37 (t, 3H, Ar), 7.28 (d, 1H, J = 1.8 Hz, Ar), 6.38 (dd, 1H, H-1′), 5.63 (m, 1H, H-3′), 4.85 (m, 1H, H-5′a), 4.79 (m, 1H, H-5′b), 4.64 (m, 1H, H-4′), 2.87 (m, 1H, H-2′a), 2.35 (m, 1H, H-2′b), 1.49 and 1.38 (2s, 18H, t-Bu). LRMS: m/z = 690.8 $[M-H]^-$, 714.8 $[M+Na]^+$. UV: λ_{max} (MeOH) 228 nm, 281 nm, 338 nm, 370 nm (sh).

***N*^{1}-[4(R)-(4,6-Di-tert-butylbenzoxazol-2-yl)-2,3-*O*-isopropylidene-β-D-erythrofuranosyl)uracil (24).** System B (78% yield). ^{1}H NMR (CCl_4): 9.50 (s, 1H, NH), 7.53 (d, 1H, J = 1.8 Hz, Ar), 7.38 (d, 1H, J = 8.0 Hz, H-6), 7.20 (d, 1H, J = 1.8 Hz, Ar), 5.91 (d, 1H, J = 1.6 Hz, H-1′), 5.51 (d, 1H, J = 8.0 Hz, H-5), 5.47 (dd, 1H, J = 3.0 Hz, J = 6.0 Hz, H-3′), 5.31 (d, 1H, J = 3.0 Hz, H-4′), 5.10 (dd, 1H, J = 1.6 Hz, J = 6.0 Hz, H-2′), 1.58 and 1.36 (2s, 6H, iPr), 1.50 and 1.36 (2s, 18H, t-Bu). LRMS: m/z = 482 $[M-H]^-$, 506 $[M+Na]^+$. UV: λ_{max} (MeOH) 242 nm, 280 nm (sh).

***N*^{1}-[4(R)-(4,6-Di-tert-butylbenzoxazol-2-yl)-β-D-erythrofuranosyl)uracil (25).** Nucleoside **24** was heated with 80% acetic acid for 2 hours. the volatiles were evaporated and crude material was purified by flash chromatography (system B) to give **25** in 80% yield.

^{1}H NMR ($CDCl_3$): 10.56 (s, 1H, NH), 8.13 (d, 1H, J = 8.0 Hz, H-6), 7.60 (d, 1H, J = 1.8 Hz, Ar), 7.32 (d, 1H, J = 1.8 Hz, Ar), 6.21 (d, 1H, J = 4.0 Hz, H-1′), 5.76 (d, 1H, J = 8.0 Hz, H-5), 5.42 (d, 1H, J = 4.0 Hz, H-4′), 4.66 (m, 2H, H-2′, H-3′), 1.45 and 1.34 (2s, 18H, t-Bu). LRMS: m/z = 442.4 $[M-H]^-$, 466.6 $[M+Na]^+$. UV: λ_{max} (MeOH) 240 nm, 268 nm.

***N*^{9}-[4(R)-(4,6-Di-tert-butylbenzoxazol-2-yl)-2-deoxy-β-D-erythrofuranosyl]adenine (27).** System B (60% yield). ^{1}H NMR ($CDCl_3$): 8.57 (s, 1H, H-8), 8.28 (s, 1H, H-2), 7.60 (d, 1H, J = 1.8 Hz, Ar), 7.32 (d, 1H, J = 1.8 Hz, Ar), 6.82 (dd, 1H, J = 6.4 Hz, H-1′), 6.02 (s, 2H, NH_2), 5.39 (d, 1H, J = 1.5 Hz, H-4′), 5.13 (m, 1H, H-3′), 3.0 (m, 1H, H-2′a), 2.81 (m, 1H, H-2′b), 1.42 and 1.37 (2s, 18H, t-Bu). LRMS: m/z = 449.5 $[M-H]^-$, 473.6 $[M+Na]^+$. UV: λ_{max} (MeOH) 251 nm.

REFERENCES

1. Vinsova', J.; Horak V. 3,5-Di-tert-butyl-1,2-benzoquinone as a model compound of pyridoxal. *Chem. Listy* **2003**, 97, 1157–1167.
2. Corey, E.J.; Achiva, K. A new method for the oxidation of primary amines to ketones. *J. Am. Chem. Soc.* **1969**, 91, 1429–1432.
3. Wojczewski, C.; Stolze, K.; Engels, J.W. Fluorescent oligonucleotides–versatile tools as probes and primers for DNA and RNA analysis. *Synlett* **1999**, 1667–1678.
4. Weisbrod, S.H.; Marx, A. Novel strategies for the site-specific covalent labeling of nucleic acids. *Chem. Comm.* **2006**, 5675–5685.
5. Lee, S.E.; Sidorov, A.; Gourlain, T.; Mignet, N.; Thorpe, S.J.; et al. Enhancing the catalytic repertoir of nucleic acids: a systematic study of linker length and rigidity. *Nucleic Acid Res.* **2001**, 29, 1565–1573.
6. Gourlain, T.; Sidorov, A.; Mignet, N.; Thorpe, S.J.; Lee, S.E.; et al. Enhancing the catalytic repertoir of nucleic acids. II. Simultaneous incorporation of amino and imidazolyl functionalities by two modified triphosphate during PCR. *Nucleic Acids Res.* **2002**, 30, 3739–3747.

7. McGall, G.H.; Barone, A.D. Nucleic acid labeling compounds. US patent 7423143, 2008.
8. Nasonov, A.F.; Korshunova, G.A. C-Alkenylation of pyrimidine nucleosides and their analogues. *Russian Chem. Rev.* **1999**, 68, 483–504.
9. Agrofoglio, L.A.; Gillaizeau, I.; Saito, Y. Palladium assisted routs to nucleosides. *Chem. Rev.* **2003**, 103, 1875–1916.
10. Isono, K.; Azuma, T.; Suzuki, S. Polyoxin analogs. I. Synthesis of aminoacyl derivatives of 5′-amino-5′-deoxyuridine. *Chem. Pharm. Bull.* **1971**, 19, 505–512.
11. Wu, T.; Nauwelaerts, K.; Van Aerschot, A.; Froeyen, M.; Lescrinier, E.; Herdewijn, P. Base-base interaction in the minor groove of double-strended DNA. *J. Org. Chem.* **2006**, 71, 5423–5431.
12. Andersen, C.; Sharma, P.K.; Christensen, M.S.; Pedersen, N.S.; Nielsen, P. Synthesis of double-headed nucleosides with the additional nucleobase in the 5′-C-position. *Nucleic Acid Symposium Series* **2008**, 275–276.
13. Wolfe, J.L.; Kawate, T.; Belenky, A.; Stanton, V. Jr. Synthesis and polymerase incorporation of 5′-amino-2′, 5′-dideoxy-5′-*N*-triphosphate nucleotides. *Nucleic Acids Res.* **2002**, 30, 3739–3747.
14. Kim, C.U.; Luh, B.Y.; Martin, J.C. Regiospecific and highly stereoselective electrophilic addition to furanoid glycols: synthesis of phosphonate nucleotide analogues with potent activity against HIV. *J. Org. Chem.* **1991**, 56, 2642–2647.
15. Teng, K.; Cook, P.D. Nucleic acid mimics. Synthesis of ethylene glycol—and propoxy-linked thymidyl-tetrahydrofuranylthymine dimmers via Vorbruggen-type glycosylation reaction. *J. Org. Chem.* **1994**, 59, 278–280.
16. Teng, K.; Bharadwaj, R.; Cook, P.D. Utility of 1-(5′-acetoxy-4′-benzoyltetrahydrofuran-2′-yl)-3-benzyloxymethylthymine for the synthesis of 5′-modified furanoid nucleoside analogs. *Synlett* **1996**, 346–348.
17. Jazouli, M.; Guianvarc'h, D.; Soufiaoui, M.; Bougrin, K.; Vierling, P.; Benhida, R. A short and efficient synthesis of 2′-deoxybenzo- and pyridoimidazole C-nucleosides. *Tetrahedron Lett.* **2003**, 44, 5807–5810.
18. Wu, Q.; Simons, C. Synthetic methodologies for C-nucleosides. *Synthesis* **2004**, 1533–1553.
19. Caddell, J.M.; Chapman, A.M.; Cooley, B.E.; Downey, B.P.; LeBlanc, M.P.; et al. Efficient synthesis of an adenosine A2a agonist: glycosylation of 2-haloadenines and N^2-alkyl-6-chloroguanine. *J. Org. Chem.* **2004**, 69, 3212–3215.