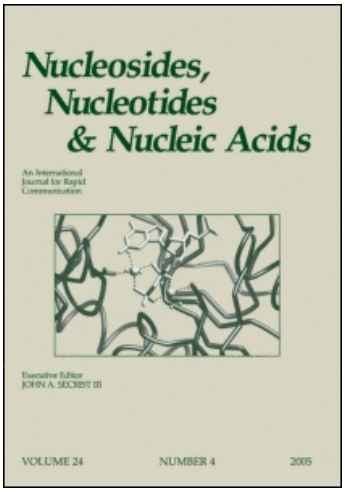


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of Modified Nucleosides for Incorporation of Formyletheno and Carboxyetheno Adducts of Adenine Nucleosides into Oligonucleotides

Niangoran Koissi[a]; Harri Lönnberg[a]
[a] Department of Chemistry, University of Turku, Turku, Finland

To cite this Article Koissi, Niangoran and Lönnberg, Harri(2007) 'Synthesis of Modified Nucleosides for Incorporation of Formyletheno and Carboxyetheno Adducts of Adenine Nucleosides into Oligonucleotides', Nucleosides, Nucleotides and Nucleic Acids, 26: 8, 1203 — 1206
To link to this Article: DOI: 10.1080/15257770701527836
URL: http://dx.doi.org/10.1080/15257770701527836

Nucleosides, Nucleotides, and Nucleic Acids, 26:1203–1206, 2007

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770701527836

Taylor & Francis
Taylor & Francis Group

SYNTHESIS OF MODIFIED NUCLEOSIDES FOR INCORPORATION OF FORMYLETHENO AND CARBOXYETHENO ADDUCTS OF ADENINE NUCLEOSIDES INTO OLIGONUCLEOTIDES

Niangoran Koissi and Harri Lönnberg □ *Department of Chemistry, University of Turku, Turku, Finland.*

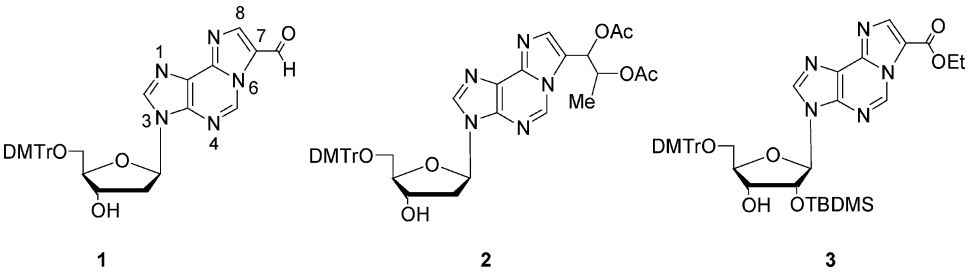
□ *Three protected derivatives of 1,N^6-ethenoadenine nucleosides, viz. 3-[5-O-(4,4′-dimethoxytrityl) of 7-formyl- (**1**) and 7-(1,2-diacetyloxypropyl)-2′-deoxyadenosine (**2**), and 3-[5-O-(4,4′-dimethoxytrityl)-2-O-(tert-butyldimethylsilyl)-7-(ethoxycarbonyl)adenosine (**3**), expected to allow introduction of formyletheno and carboxyethenoadenine adducts into oligonucleotides by the conventional phosphoramidite chemistry, have been synthesized.*

Keywords DNA base modifications; etheno adducts

INTRODUCTION

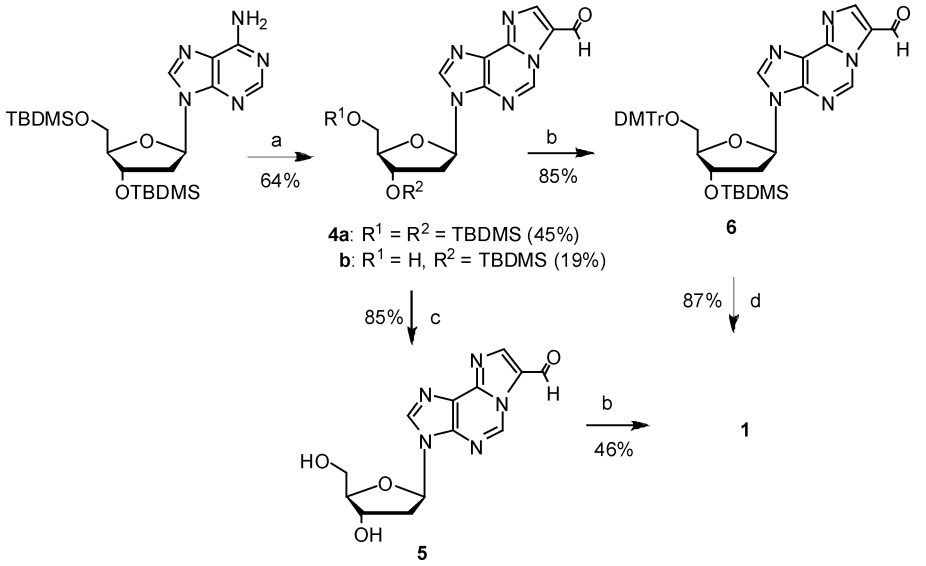
Lipid peroxidation (LPO) generates several aldehydes α,β-unsaturated aldehydes that generate a variety of DNA adducts, many of which are cyclic adducts bearing an extra ring. This additional ring prevents normal hydrogen bonds formation upon hybridization and, hence, interferes with the transfer of genetic information. While the cyclic adducts as such may be classified as mutagenic DNA lesions, those bearing an additional functional group that is able to interfere with the base-pairing and form cross-links, are of particular interest. A major hurdle for evaluation of the mutagenic potential or genotoxicity of this kind of adducted bases is their site-specific incorporation into oligonucleotides.[1,2] We now report on synthesis of three appropriately protected 1,N^6-ethenoadenine nucleosides (**1–3**) that are aimed at allowing introduction of formyletheno and carboxyetheno adducts of adenine into oligonucleotides by conventional phosphoramidite chemistry.

Address correspondence to Niangoran Koissi, Department of Chemistry, University of Turku, FIN 20014, Turku, Finland. E-mail: koissi@gmail.com

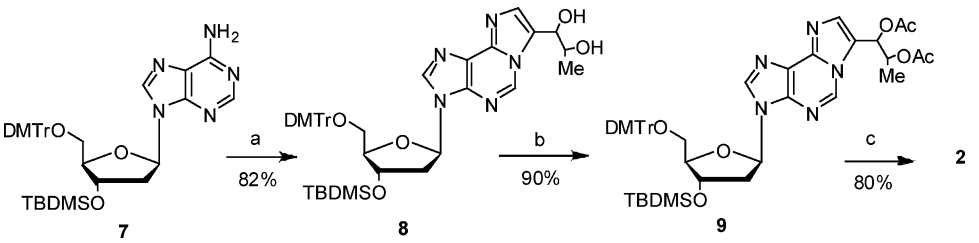


RESULTS AND DISCUSSION

Previous studies on 3-formylindole 2′-deoxyribonucleoside phosphoramidites suggest that the chain assembly without any protection at the aldehyde group is possible.[3] Accordingly, nucleoside **1** could be used for introduction of the formyletheno adduct. This nucleoside was obtained by the reaction of appropriately protected 2′-deoxyadenosine with bromomalonaldehyde (BMA), a reaction shown to compete with formation of 1,N^6-etheno-2′-deoxyadenosine in aqueous solution.[4] When 3′,5′-di-*O*-*tert*-butyldimethylsilyl-2′-deoxyadenosine was allowed to react in DMF with 6 equiv. of BMA in the presence of formic acid (1 equiv) and 2,6-lutidine (4.5 equiv), the formyletheno adduct was obtained in 64% yield (Scheme 1). The 5′-silyl protection was, however, partially removed under these conditions: the 3′,5′-disilylated (**4a**) and 3′-monosilylated (**4b**) adducts were obtained in



SCHEME 1 (a) BMA, HCOOH/2,6-lutidine, 3 hours at 70°C; (b) DMTrCl (1.1 equiv), Py, 3 hours; (c) TBAF, THF, rt, 6 hours; (d) $Et_3N.3HF$/THF, 3 hours.

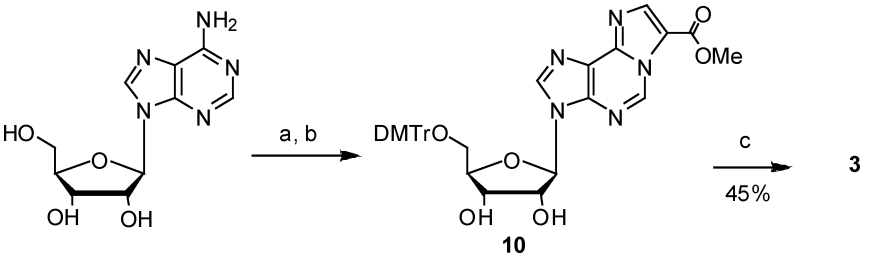


SCHEME 2 (a) HPE/H_2O_2/THF, 3 hours at 70°C; (b) Ac_2O/DMAP, pyr, 3 hours; (c) TBAF/THF, rt, 6 hours.

3:1 ratio. No depurination was observed. **4a** was desilylated with tetrabutylammonium fluoride (TBAF) in THF to obtain **5** and the 5′-hydroxy group was protected with 4,4-dimethoxytrityl chloride in pyridine. **4b** was, in turn, first tritylated to obtain **6** and the 3′-silyl protection was then selectively removed with triethylamine trihydrofluoride in THF.[5] It is worth noting that **1**[6] withstood overnight ammonolysis at room temperature. The imine formation of the formyl group was fully reversible.

In case protection of the formyl group turns out to be necessarry, nucleoside **2** may be used for the same purpose: The 1,2-diol exposed upon ammonolysis readily can be oxidized to formyl group by sodium periodate under very mild conditions.[7,8] The method described recently[9] for preparation of (1-hydroxyhexyl)etheno adduct of 2′-deoxyadenosine was applied to the synthesis of nucleoside **2**. The key step of that approach is the reaction of adenine base with an appropriate formyl epoxide obtained from an α,β-unsaturated aldehyde by treatment with a mixture of trifluoroacetone, Oxone and EDTA in aqueous MeCN. Accordingly, 4-hydroxy-2-pentenal (HPE) was oxidized with hydrogen peroxide to 2,3-epoxy-4-hydroxypentenal and this was allowed to react with 5′-*O*-(4,4′-dimethoxytrityl)-2′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (**7**) to obtain the (1,2-dihydroxypropyl)etheno adduct **8** (Scheme 2). The hydroxy functions were then acetylated with acetic anhydride in pyridine (**9**) and the 3′-silyl protection was removed with TBAF in THF to obtain **2**.[10]

Nucleoside **3** allows introduction of a carboxyetheno adduct into oligonucleotides, providing that after the chain assembly the ethyl ester function is subjected to hydroxide ion catalyzed hydrolysis prior to ammonolysis. This nucleoside was prepared by reacting 5′-*O*-(4,4′-dimethoxytrityl)adenosine with methyl 2-bromo-3-oxopropanoate in dioxane to obtain **10** and protecting the 2′-hydroxy function of with a TBDMS group (Scheme 3). Silylation with 1 equiv. of TBDMSCl in THF expectedly gave a mixture of **3** and its 3′-silylated isomer, which was resolved by silica gel chromatography to obtain **3**.[11] Reaction of 5′-*O*-(4,4′-dimethoxytrityl)adenosine with 2-bromo-3-oxopropanoate was also attempted, but it turned out to be less efficient. 2-Bromo-3-oxopropanoate



SCHEME 3 (a) DMTrCl, Py; (b) OHC-CHBr-COOEt,[12] dioxane, 2 hours reflux, yield; (c) TBDMSCl/Im, 24 hours, chromatographic separation.

was synthesized from ethyl bromoacetate and ethyl formate as described previously.[12]

REFERENCES

1. Iwai, S. *Nucleosides, Nucleotides, and Nucleic Acids* **2006**, 25, 561.
2. Barbin, A. *Mutat. Res.* **2000**, 462, 55.
3. Okamoto, A.; Tainaka, K.; Saito, I. *Tetrahedron Lett.* **2002**, 43, 4581.
4. a) Nair, V.; Offerman, R.J.; Turner, G.A. *J. Org. Chem.* **1984**, 49, 4021; b) Kronberg, L.; Sjöholm, R.; Karlsson, S. *Chem. Res. Toxicol.* **1992**, 5, 852; c) Mikkola, S.; Koissi, N.; Ketomäki, K.; Rauvala, S.; Neuvonen, K.; Lönnberg, H. *Eur. J. Org. Chem.* **2000**, 12, 2315.
5. Pirrung, M.C.; Shuey, S.W.; Lever, D.C.; Fallon, L. *Bioorg. Med. Chem. Lett.* **1994**, 4, 1345.
6. Compd. **1**: ^{1}H NMR ($CDCl_3$): δ 10.04 (CHO, s, 1H), 10.01 (H-5, s, 1H), 8.39 (H-2, s, 1H), 8.27 (H-8, s, 1H), 7.43–7.21 (DMTr, m, 9H), 6.81 (DMTr, dd, J = 4.0 and 9.5 Hz, 4H), 6.58 (H-1′, d, J = 6.4, 1H), 4.77 (H-3′, m, 1H), 4.23 (H-4′, m, 1H), 3.78 (2 × OMe, s, 6H), 3.50 (H-5′, dd, J = 4.7 and 10.2 Hz, 1H), 3.43 (H-5″, dd, J = 5.3 and 10.2 Hz, 1H), 2.88 (H-2′, m, 1H), 2.65 (H-2″, m, 1H); HRMS (FAB) MH^+: found 606.2352, calcd for $C_{34}H_{31}N_5O_6$ 606.2351.
7. Trevisiol, E.; Renard, A.; Defrancq, E.; Lhomme, J. *Tetrahedron Lett.* **1997**, 38, 8687.
8. Karino, N.; Ueno, Y.; Matsuda, A. *Nucleic Acids Res.* **2001**, 29, 2456.
9. Carvalho, V.M.; Gasparutto, D.; Di Mascio, P.; Medeiros, M.H.G.; Cadet, J. *Bioorg. Med. Chem.* **2003**, 11, 2445.
10. Compd. **2**: ^{1}H NMR ($CDCl_3$) 7.98 (H-5, s, 1H), 7.83 (H-2, s, 1H), 7.20–7.35 (DMTr, m, 9H), 6.85 (H-8, s, 1H), 6.69-6.77 (DMTr, m, 4H), 6.30 (H-1, dd, J = 8.0 and 5.6 Hz, 1H), 5.35 [-CH(OAc)-C*H*(OAc)Me, m, 1H], 4.27 [H-3 & -CH(OAc)-C*H*(OAc)Me, m, 2H), 3.99 (H-4, m, 1H), 3.71 (2 × OMe, s, 6H,), 2.88 (H-5′ & H-5″, m, 2H), 2.51 (H-2′ & H-2″, m, 2H), 2.04 & 2.00 (2 × Ac, s, 2 × 3H), 1.18 (s, 3H, Me).
11. Compd. **3**: δ 7.98 (H-5, s, 1H), 7.97 (H-2, s, 1H), 7.20-7.32 (DMTr, m, 9H), 6.95 (H-8, s, 1H), 6.77-6.79 (DMTr, m, 4H), 5.88 (H-1, d, J = 6.0 Hz, 1H), 4.38 (H-2, m, 1H), 3.77 (3 × OMe, s, 9H), 3.72-2.83 (H-3′& H-4′,m, 2H), 3.42-3.46 (H5, dd, J = 13.0 and < 2 Hz, 1H), 3.16-3.20 (H-5, dd, J = 13.0 and < 2 Hz, 1H), 0.72 (C-Me_3, s, 6H), 0.51 (C-Me_3, s, 3H), −0.08 (Si-Me, s, 6H).
12. Gangjee, A.; Vidwands, A.; Elzein, E.; McGuire, J.J.; Queener, S.F.; Kisliuk, R.L. *J. Med. Chem.* **2001**, 44, 1993.