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# Synthesis of 4'-C-Phenylselenated Deoxyribonucleosides by Radical Epimerization

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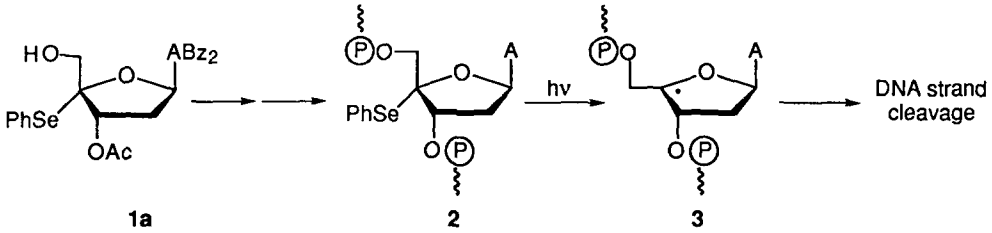
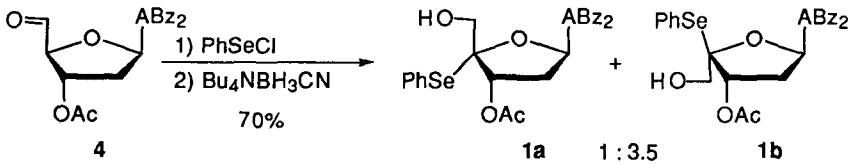
***Abstract***: *Selenides 7b and 8b can be epimerized by irradiation in the presence of $(PhSe)_2$. Intermediates are 4'-deoxyribonucleotide radicals that react with $(PhSe)_2$ and yield isomers 7a and 8a, respectively, in reversible reaction steps.* © 1997 Elsevier Science Ltd.

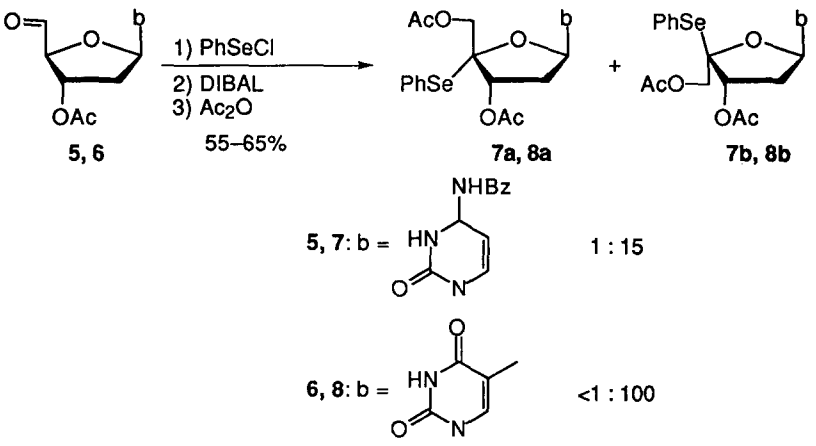
Recently, we have shown that the 4'-selenated 2'-deoxyadenosine **1a** is a building block for the synthesis of modified oligonucleotides **2**.[1] Photolysis of **2** generates the 4'-oligonucleotide radical **3** that induces the cleavage of the DNA strand in a spontaneous or $O_2$-dependent reaction.[2]



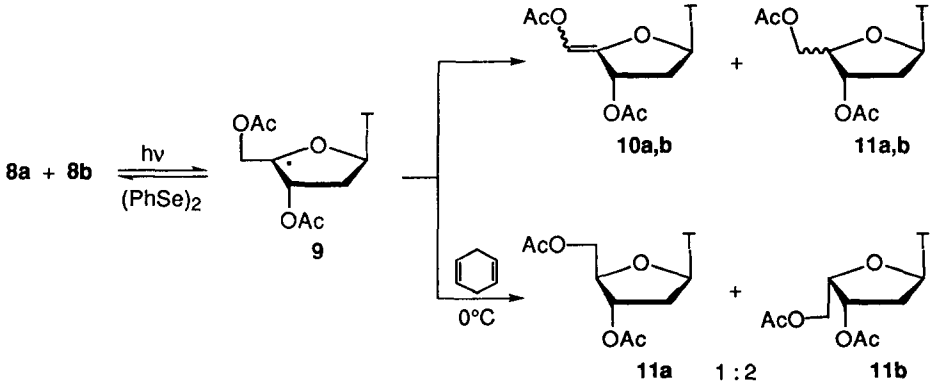

The modified nucleoside **1a** was synthesized by phenylselenation of aldehyde **4** which yielded a 1:3.5 mixture of epimers **1a** and **1b**.[1] The *ribo* isomer **1a**, which is required for the oligonucleotide synthesis, could be separated from this mixture by flash chromatography.




We have now applied this synthetic method to aldehydes **5** and **6** with a benzoylated cytosine (**5**) or a thymine (**6**) as heterocycle.[3] Unfortunately, the phenylselenation of aldehydes **5** and **6** gave mainly or exclusively the selenides **7b** and **8b** with the wrong configuration at the 4'-position.[4,5]




Since the deoxyribo isomers **7a** and **8a** are required for the synthesis of modified oligonucleotides like **2**, we tried to epimerize the isomers **7b** and **8b**, respectively. This turned out to be possible if the selenides were irradiated in the presence of $(PhSe)_2$. Figure 1 shows that photolysis of **8b** with a 1.5fold excess of $(PhSe)_2$ led to a 2.5:1 mixture of **8a**:**8b**. This ratio remained constant during further irradiation but the overall amount of **8a** + **8b** slowly decreased. Among the compounds formed after extended photolysis were the disproportionation products **10** and **11**.[6] If the irradiation was carried out in the presence of 1,4-cyclohexadiene as a radical trap, the hydrogen abstraction products **11a,b** were formed in 78% yield (**11a**:**11b** = 1:2). This is a convincing indication that the epimerization occurs via radical **9** as intermediate. In the presence of $(PhSe)_2$[7] radical **9** can be trapped in a reversible reaction so that an equilibrium mixture of **8a** and **8b** is generated (**8a**:**8b** = 2.5:1).[8] Thus, this photoinduced epimerization **8a** $\rightleftharpoons$ **8b** is a radical counterpart[9] of the base induced isomerization of C,H-acidic compounds.[10]



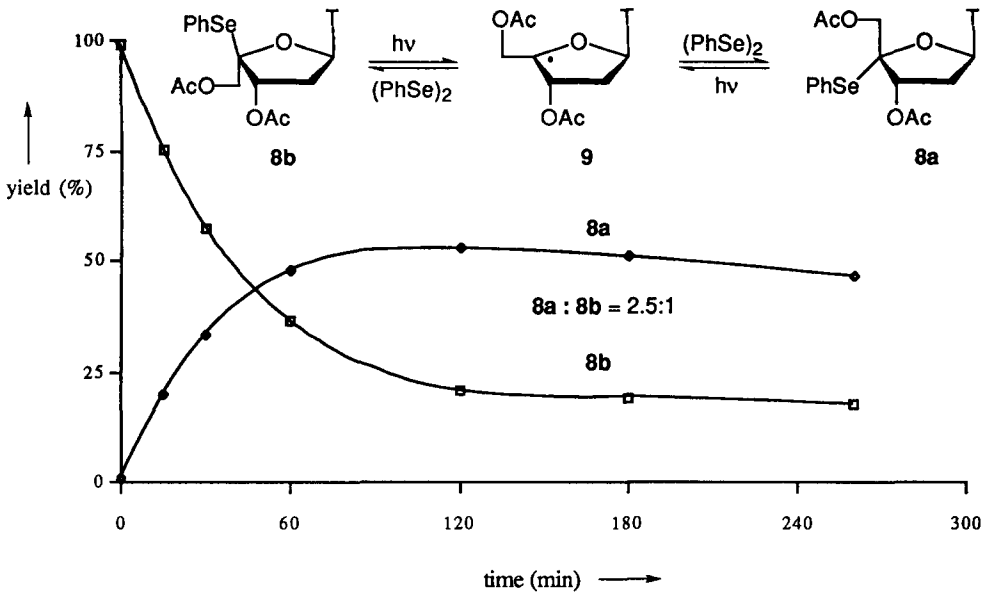



**Fig. 1**: Photolysis (500W Oriel Hg-high pressure lamp; 320 nm cut-off filter) of **8b** (19 µmol) in the presence of $(PhSe)_2$ (29 µmol) in toluene (1.5 ml) at 0°C. After 2h the equilibrium mixture **8a**:**8b** = 2.5:1 is reached.

For synthetic purposes it was best to stop the photoinduced isomerization of **7b** and **8b** before the equilibrium was reached. The selenated deoxyribonucleosides **7a** and **8a** were separated by flash chromatography and the unwanted isomers **7b** and **8b** could be epimerized again.[11]

The modified deoxyribonucleosides **7a** and **8a** were converted into the corresponding phosphoramides and used for the synthesis of modified oligonucleotides following our recently described procedure for the modified adenosine **1a**.[1,12] In order to evaluate the influence of the 4'-phenylselenyl groups on the DNA:DNA duplex stability, we prepared the double stranded oligonucleotides with one modification (**12**,**13**) and a duplex **14** with two modifications at nucleotides that are base-paired.

| | 5'–CAGTTAGT CGAA–3'<br>3'–GTCAATCA*GCTT–5' | 5'–CAGTTAGT*CGAA–3'<br>3'–GTCAATCA GCTT–5' | 5'–CAGTTAGT*CGAA–3'<br>3'–GTCAATCA*GCTT–5' |
|---|---|---|---|
| | **12** | **13** | **14** |
| melting point ($T_m$) depression | – 2.0°C | – 2.6°C | – 4.5°C |

Compared to the unmodified DNA double strand ($T_m$ = 44.4°C), the duplexes with one modification decreased the melting points ($T_m$ values) by 2.0°C (**12**, A* = modified A like in **2**) and 2.6°C (**13**, T* = modified T like in **7a**).[13] Interestingly, this decrease of the $T_m$ value is only additive in duplex **14** where each strand is modified and the modified nucleosides are base-paired.

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## References and Notes

1. B. Giese, A. Dussy, C. Elie, P. Erdmann, U. Schwitter, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1861. B. Giese, P. Erdmann, T. Schäfer, U. Schwitter, *Synthesis* **1994**, 1310.
2. B. Giese, X. Beyrich-Graf, P. Erdmann, M. Petretta, U. Schwitter, *Chem. & Biol.* **1995**, *2*, 368.
3. The phenylselenation of **5** and **6** followed the procedure described for aldehyde **4**.[1] In the subsequent reduction DIBAL turned out to be superior to $Bu_4NBH_3CN$ as we had already shown for a differently protected thymidine derivative.[4]
4. B. Giese, P. Erdmann, L. Giraud, T. Göbel, M. Petretta, T. Schäfer, M. von Rauner, *Tetrahedron Lett.* **1994**, *35*, 2683.
5. The configuration of **7a,b** and **8a,b** was proven by NOE experiments. Only compounds **7b** and **8b** showed an enhancement of 1'-H on irradiation of 5'-H. A further difference between the epimers is the high field shift in $^1H$ NMR (0.25–0.55 ppm) of the pyrimidine proton 6-H in the deoxyribonucleosides **7a** and **8a** compared to **7b** and **8b**, respectively.
6. Extended irradiation of **8b** yielded 5 new peaks in HPLC. By separation of 3 peaks the disproportionation products **10a,b** and **11a,b** were identified (NMR). The two remaining HPLC peaks might correspond to the recombination products.
7. Alkyl radicals are trapped very rapidly by $(PhSe)_2$. The rate coefficients are about $10^7$ $M^{-1}s^{-1}$: M. Newcomb, *Tetrahedron* **1993**, *49*, 1151; G. A. Russell, H. Tashtoush, *J. Am. Chem. Soc.* **1983**, *105*, 1398. Because of the low steady state concentration of the PhSe radical, the formation of the selenides **7a,b** and **8a,b** via combination of the 4'-alkyl radicals with the PhSe radical seems to be less important.
8. The epimeric selenides exhibit the same UV spectra so that the thermal and not the photochemical equilibrium is reached.
9. A prerequisite of a radical epimerization is the reversible formation of the C,X-bond. This is the case for example for C,Co- and C,I-bonds: A. Ghosez, T. Göbel, B. Giese, *Chem. Ber.* **1988**, *121*, 1807; H. Sugiyama, K. Fujimoto, I. Saito, *J. Am. Chem. Soc.* **1995**, *117*, 2945.
10. J. March in *Advanced Organic Chemistry*, J. Wiley, New York, 1985, p.528.
11. A solution of selenides **7b** or **8b** (0.9 mmoles) and $(PhSe)_2$ (0.9 mmoles) in toluene (80 ml) was saturated with Ar and irradiated (150 W, Heraeus Hg-high pressure lamp) at 15°C. After 5–7h of irradiation the solvent was evaporated and the isomers separated by flash chromatography (silicagel; AcOEt:hexane = 2:1 to 3:1 as eluent). Under these conditions the isomer ratio (**7a**:**7b** and **8a**:**8b**) was about 1:1. The yields for each of the isolated isomers were 35–47%.
12. Compounds **7a** and **8a** were hydrolyzed with $K_2CO_3$ in MeOH. The 5'-OH group was tritylated with DMTrCl in pyridine, with cytosine as heterocycle the free $NH_2$ group was benzoylated, and the 3'-OH converted into the phosphoramidites.
13. The concentration of the unmodified and modified dodecamers were 3.6 μM each. The melting points ($T_m$) were determined in medium salt buffer (100 mM NaCl; 10 mM phosphate buffer pH=7; 0.1 mM EDTA; $\lambda$ = 260 nm) as the maximum of the first derivative of the melting curve. A temperature gradient of 1°C/min was applied.

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