



Synthesis and photochemistry of oligopeptides functionalized by quinone methide precursor and their binding to polynucleotides

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Laboratory of Synthetic Organic Chemistry

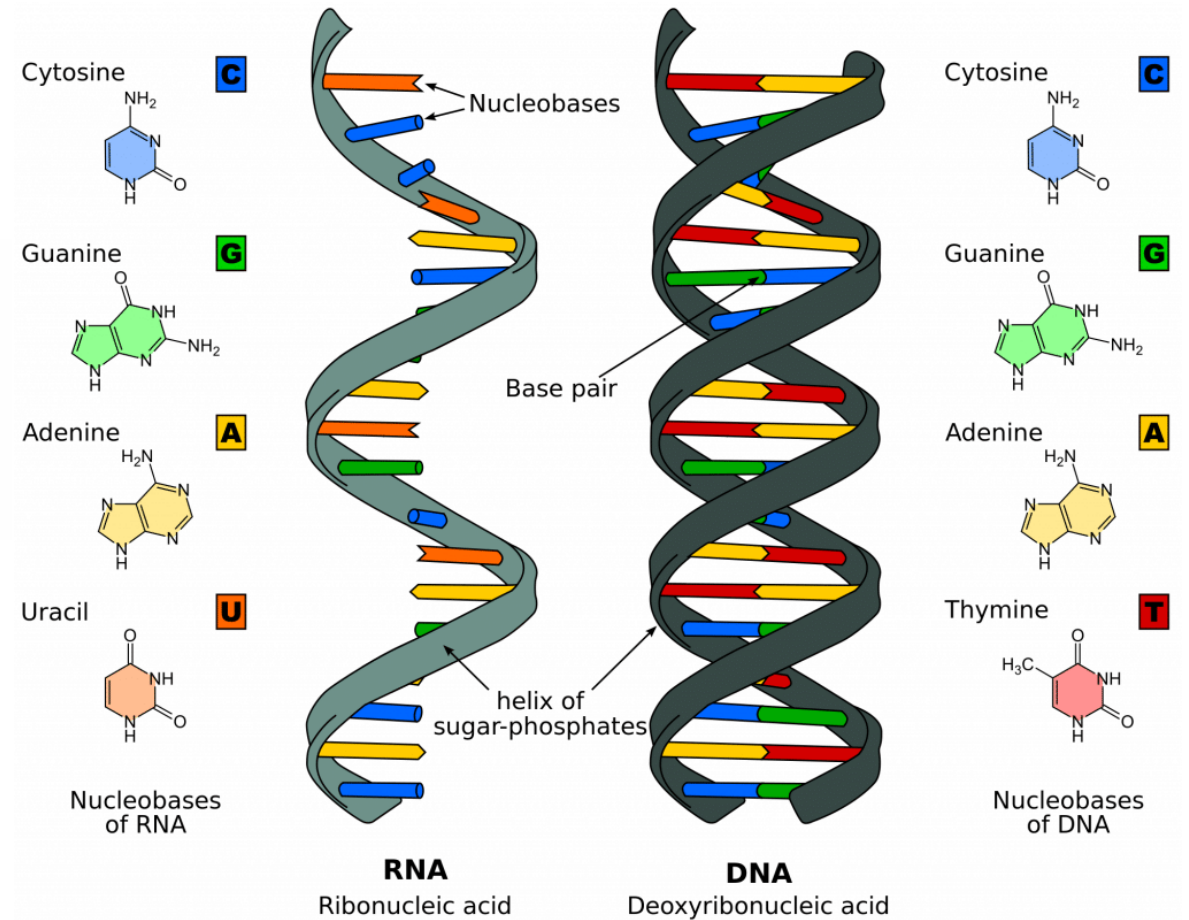
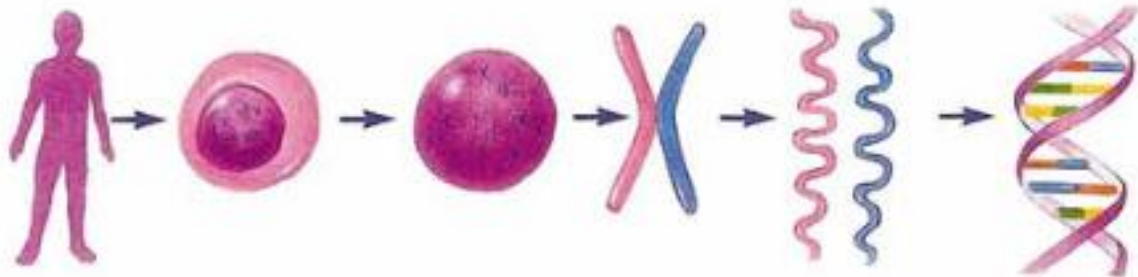
Ruđer Bošković Institute

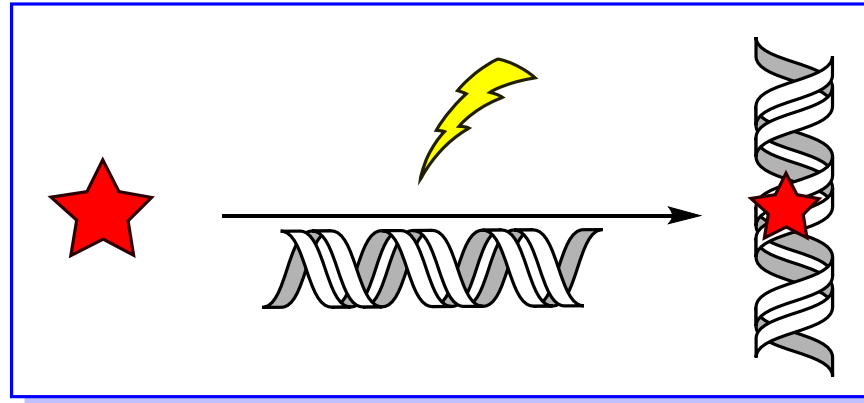
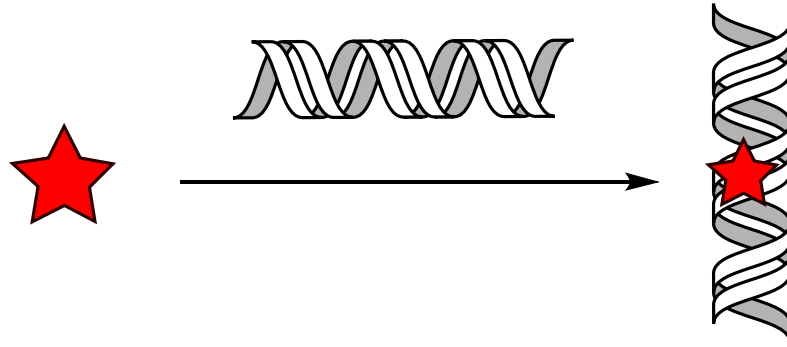
Zagreb, Croatia

Project: HrZZ-IP-2019-04-8008

4.9.2023.

Stare Jablonki, Poland

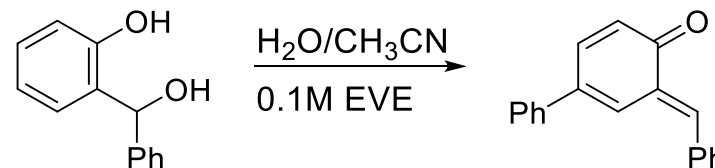
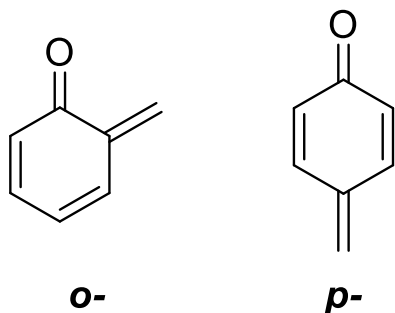




Photochemical reactions:

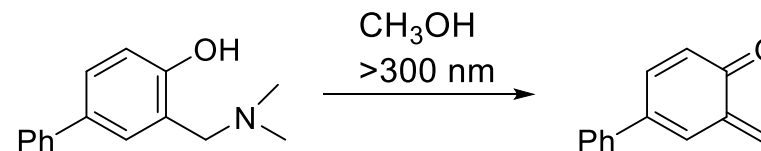
1. dehydration of hydroxymethyl substituted phenols

Quinone methide (QM)



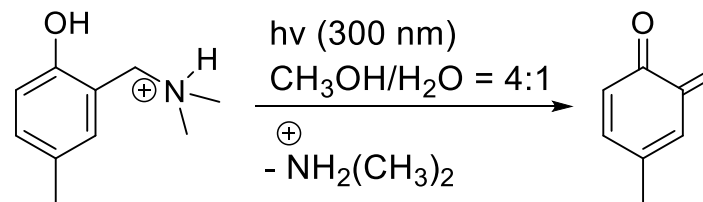
Wan *et al.*, *J. Am. Chem. Soc.* **117** (1995) 5369 – 5370.

2. deamination of aminomethyl

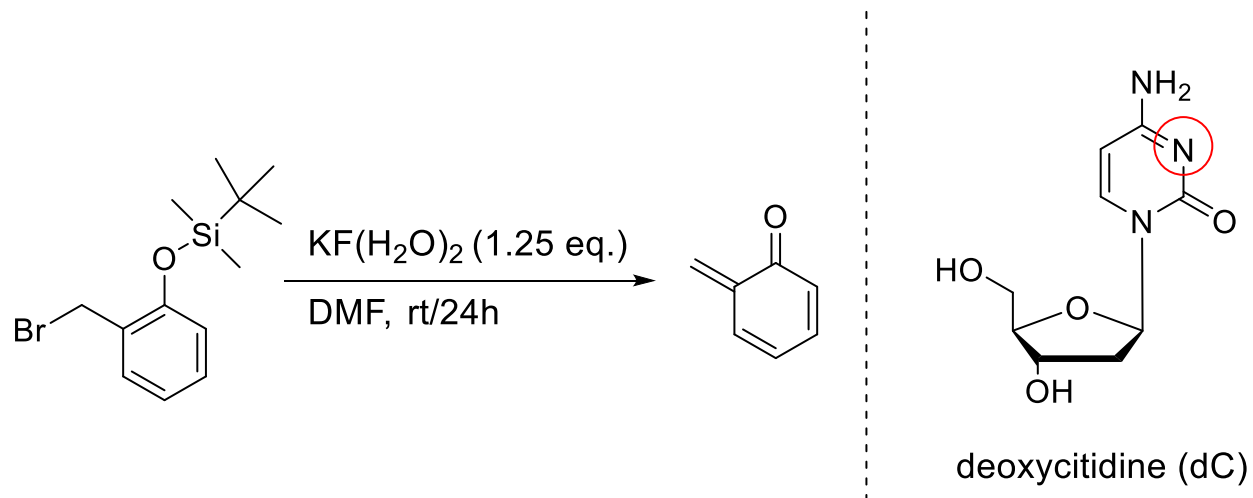


Nakatani *et al.*, *Tetrahedron Lett.* **28** (1997) 5005 – 5008.

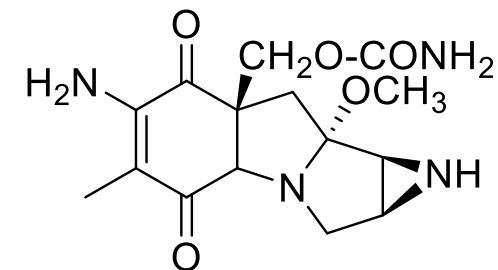
3. photodeamination from the Mannich salt of the corresponding phenol



Škalamera *et al.*, *J. Org. Chem.* **80** (2015) 10817 – 10828.



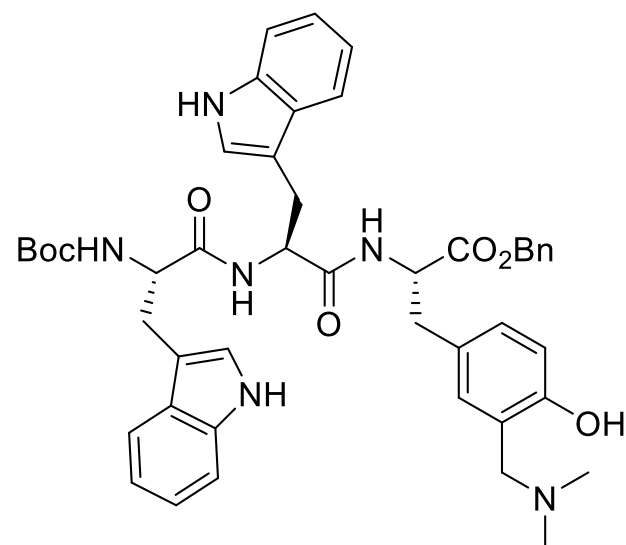
Rokita *et al.*, *J. Org. Chem.* **62** (1997) 3010 – 3012.



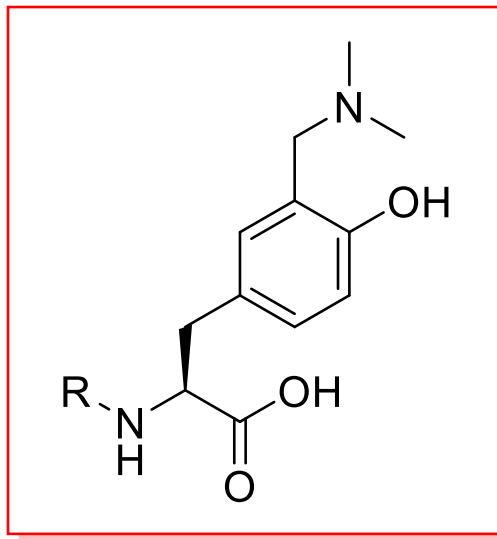
mitomycin

Jelmyto, Mitosol, Mutamycin

Tomasz *et al.*, *J. Am. Chem. Soc.* **120** (1998) 11581 – 11593.;
 V.-S. Li, H. Kohn, *J. Am. Chem. Soc.* **113** (1991) 275 – 283.;
 Han *et al.*, *J. Org. Chem.* **57** (1992) 1799 – 1807.

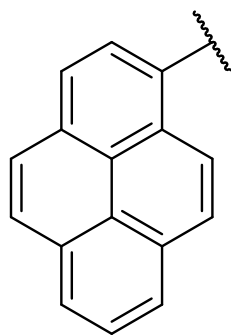


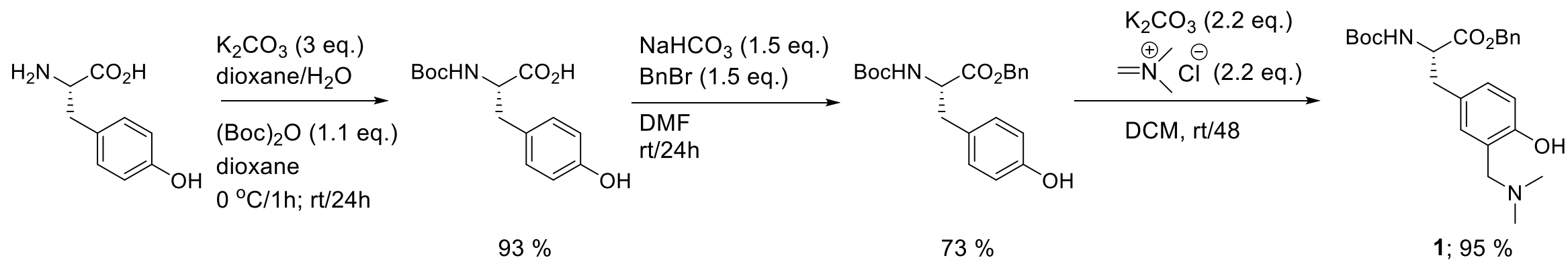
Erben, A.; Sviben, I.; Mihaljević, B.; Piantanida, I.; Basarić, N., *Molecules* **26** (2021) 4315.

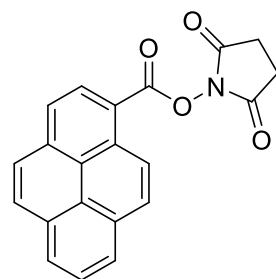
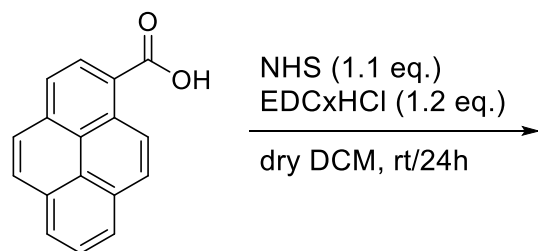


Dipeptide
R = Ala
R = Lys

Tripeptide
R = Arg-Arg

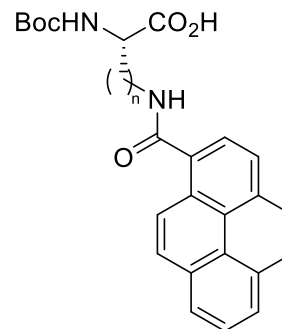






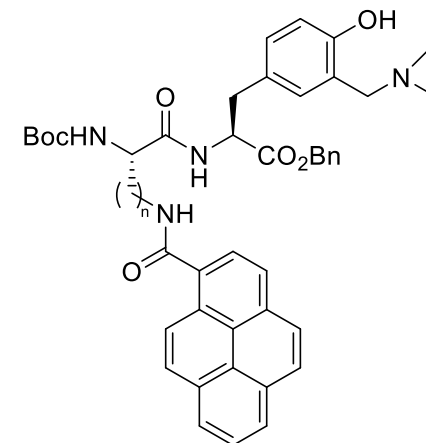
2; 85 %

Boc-Lys (1 eq.) or
Boc-Ala(NH₂)
KHCO₃ (1.1 eq.)
dry DMF, rt/24h



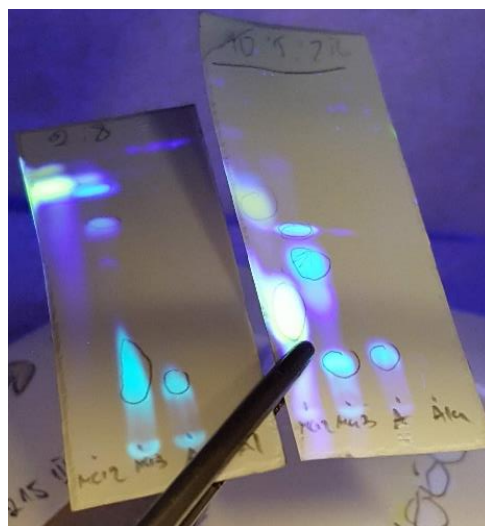
3; n = 4; Lys 82 %
4; n = 1; Ala 64 %

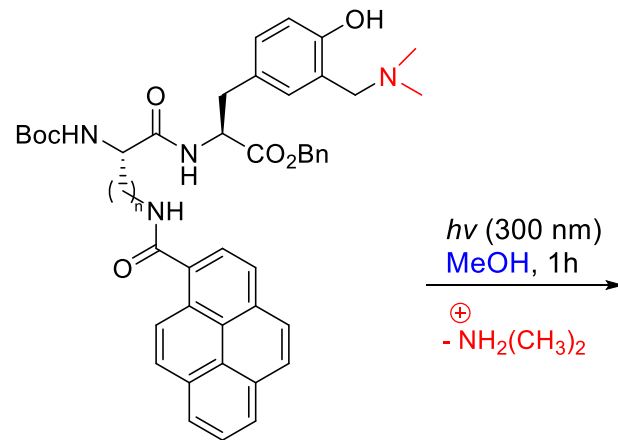
1. Boc-Tyr(*m*-CH₂N(CH₃)₂)-OBn (1 eq.)
TFA/DCM, rt/1h
2. HBTU (1.1 eq.)
HOBt (1.1 eq.)
TEA (4 eq.)
dry DMF, rt/48h



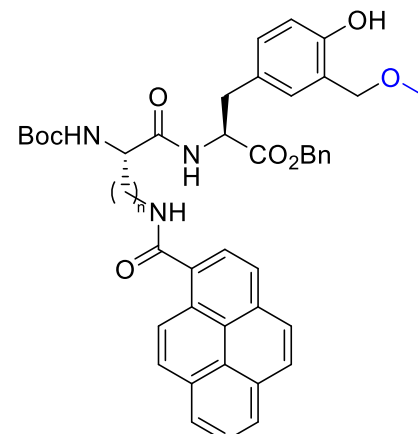
5; n = 4; Lys 37 %
6; n = 1; Ala 23 %

PLC purification

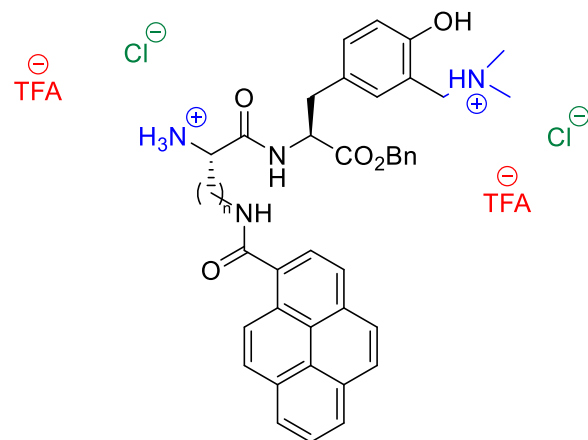
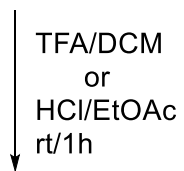




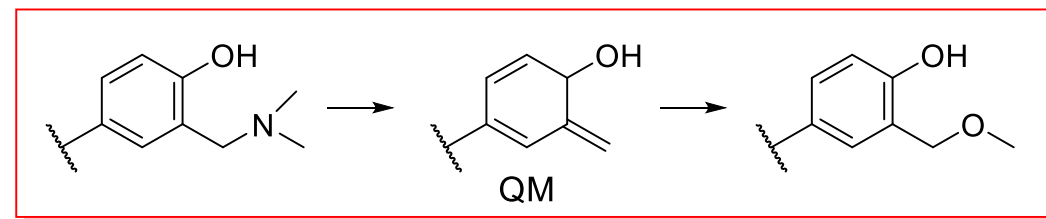
5; n = 4; Lys
6; n = 1; Ala

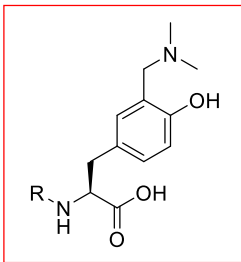


7; n = 4; Lys 33% (HPLC 89%)
8; n = 1; Ala 21% (HPLC 70%)

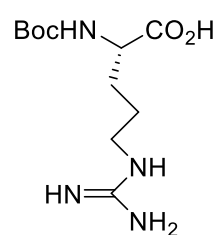


9; n = 4; Lys
10; n = 1; Ala

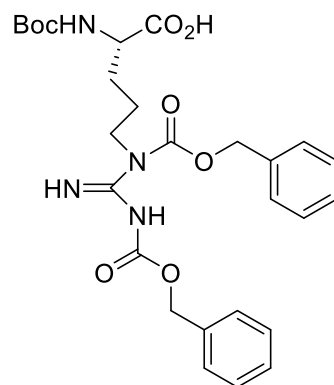




R = Arg-Arg

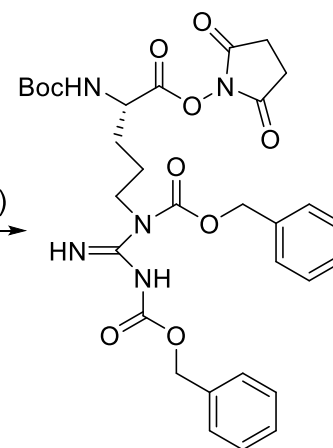


1. TMSCl (8 eq.)
DIPEA (8 eq.)
DCE, rt - 40 °C/24h, N₂
2. DIPEA (4 eq.)
benzyl chloroformate (4 eq.)
0 °C - rt/24h, N₂



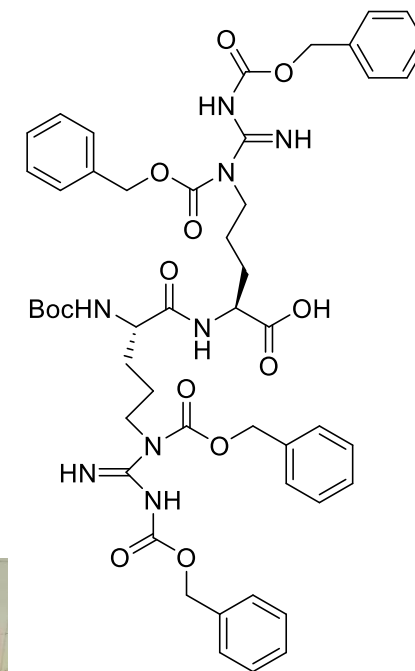
11; 51 %

NHS (1.1 eq.)
EDC·HCl (1.2 eq.)
dry DCM, N₂
0 °C/2h; rt/24h



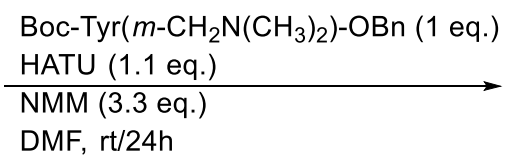
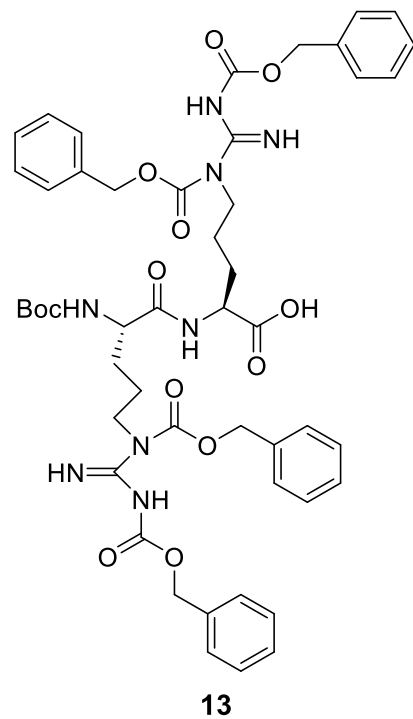
12; 85 %

1. Boc-Arg(2Z) (1.1 eq.)
TFA/DCM, rt/1h
2. KHCO₃ (5 eq.)
dry DMF, N₂, rt/96h

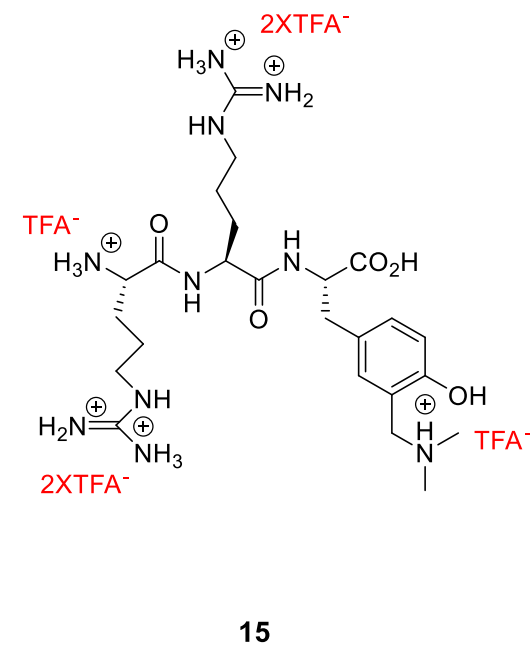
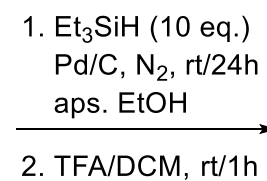
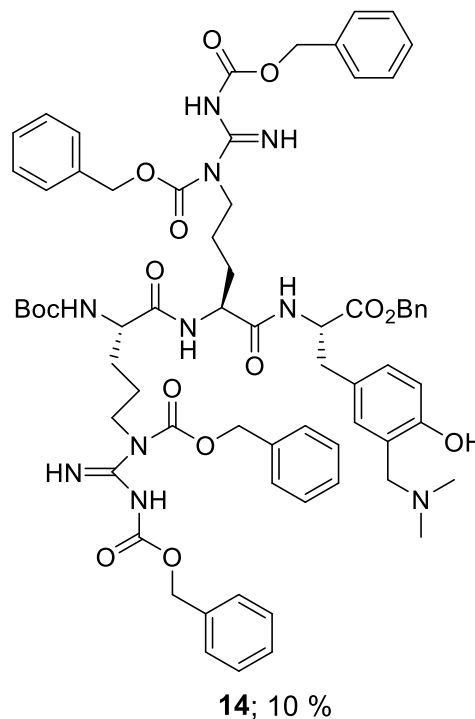


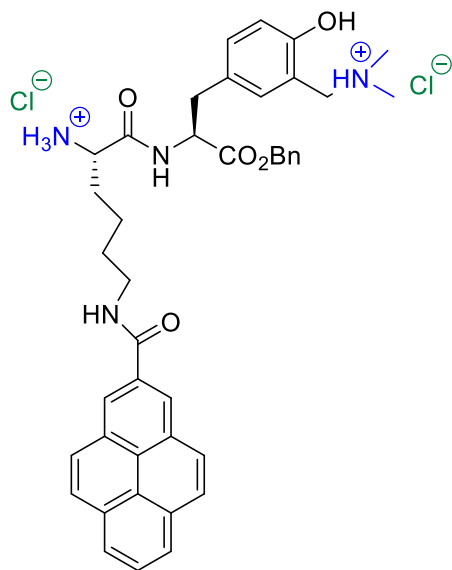
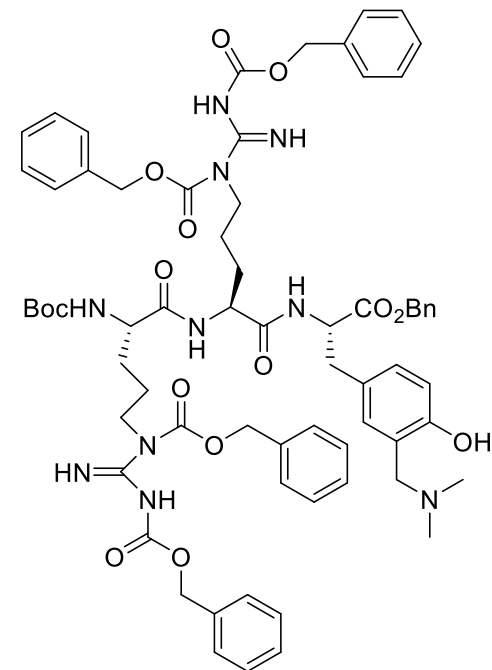
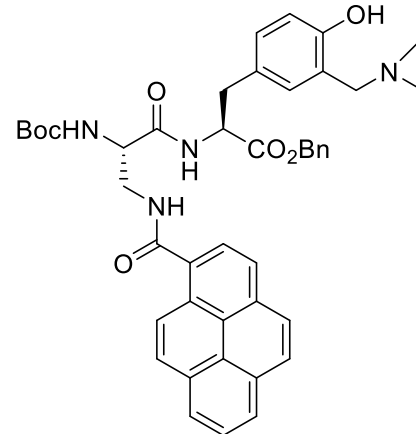
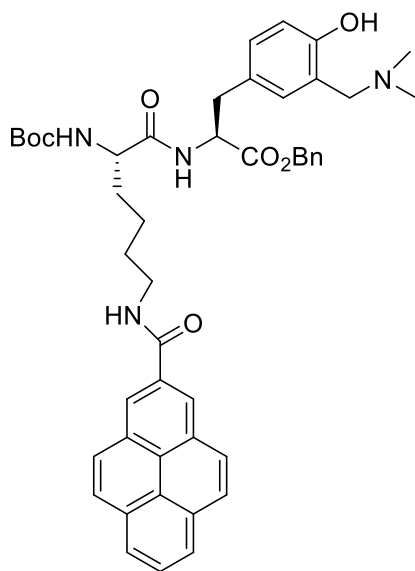
13; 75 %



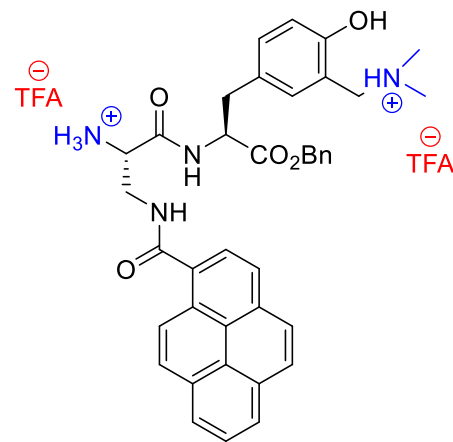


PLC purification

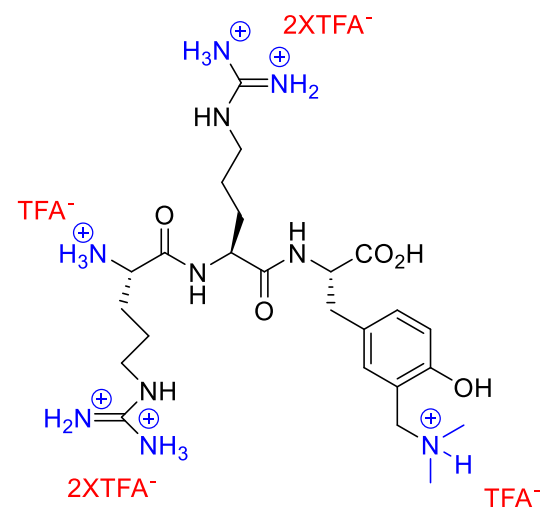




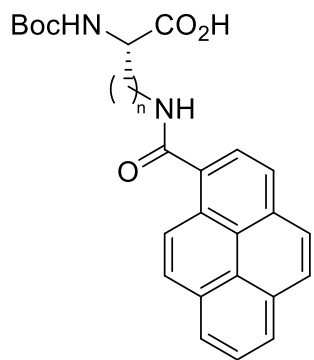
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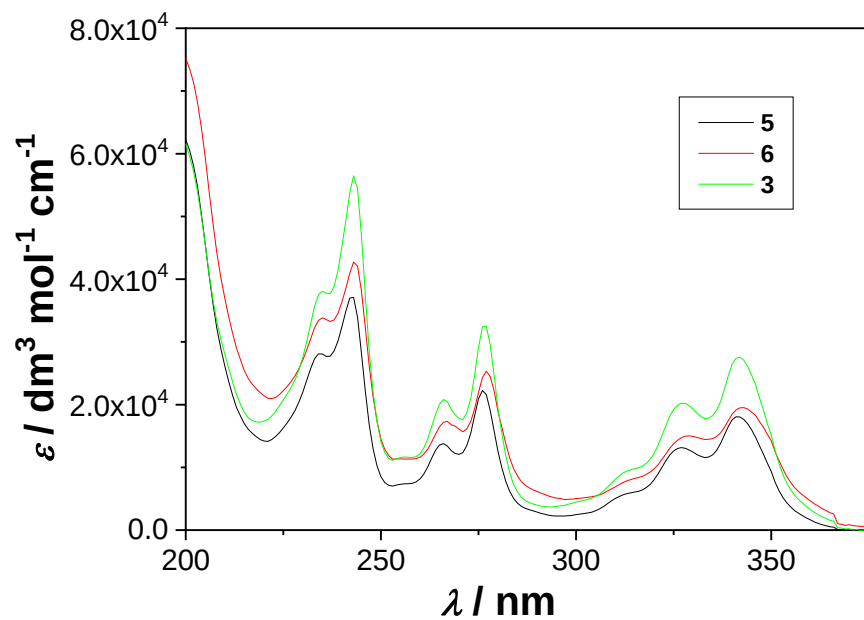
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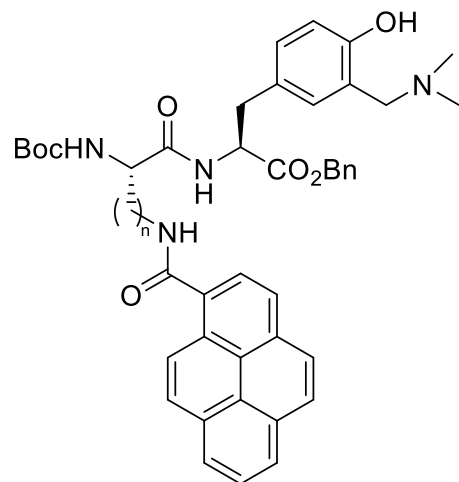
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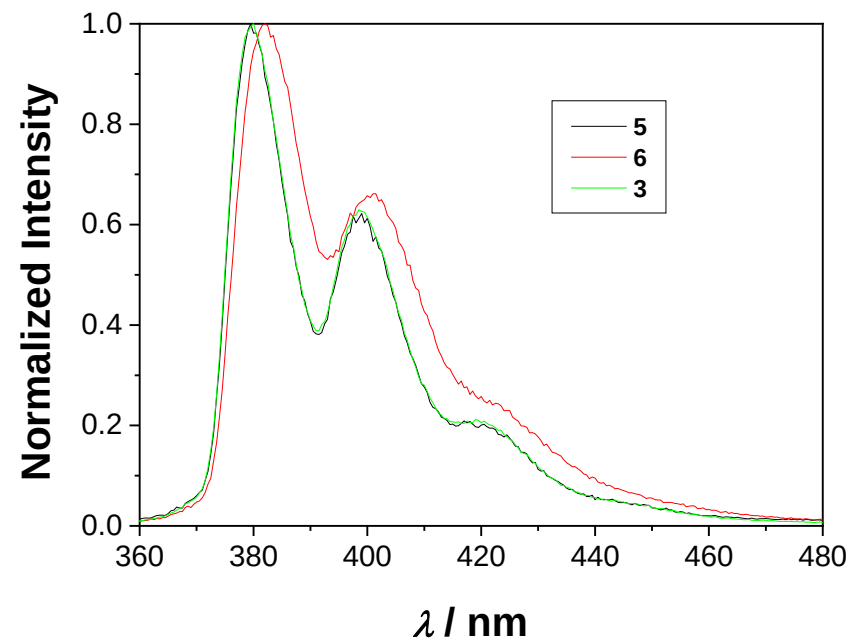
3; $n = 4$; Lys



Absorption spectra in CH_3CN



5; $n = 4$; Lys
6; $n = 1$; Ala

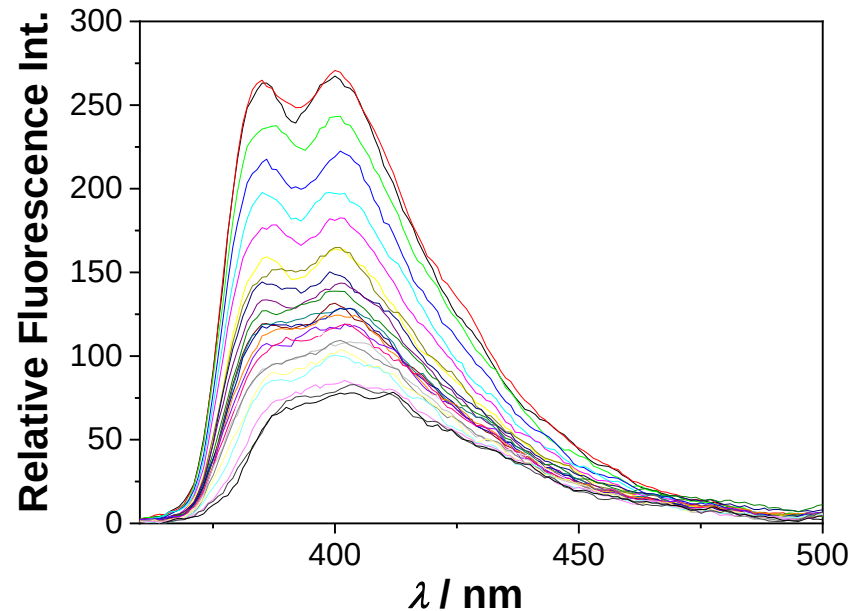


Normalized emission spectra in CH_3CN ($\lambda_{\text{ex}} = 310 \text{ nm}$)

Compound.	Φ_f
6	0.4 ± 0.1
5	0.3 ± 0.1
3	0.5 ± 0.1

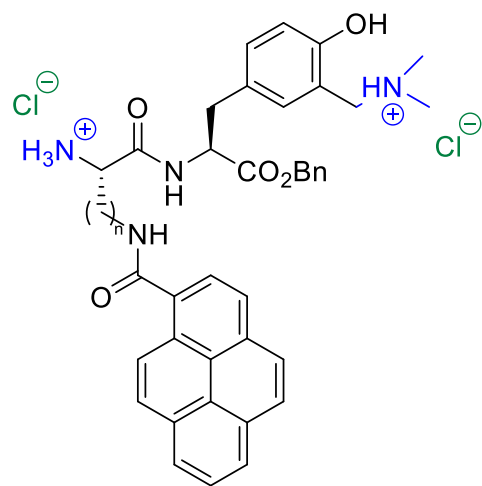
reference: quinine sulfate in $\text{H}_2\text{O}/\text{H}_2\text{SO}_4$ ($\Phi_f = 0.546$)

ct-DNA
 p(dAdT)₂
 p(dGdC)₂
 pApU



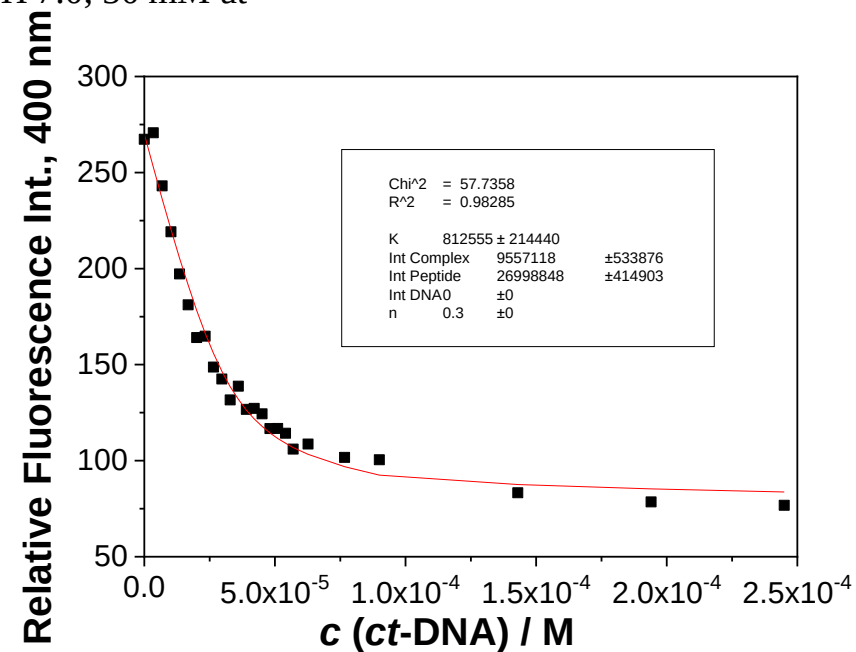
	<i>ct</i> -DNA
10	5.58 ± 0.03
9	5.98 ± 0.07

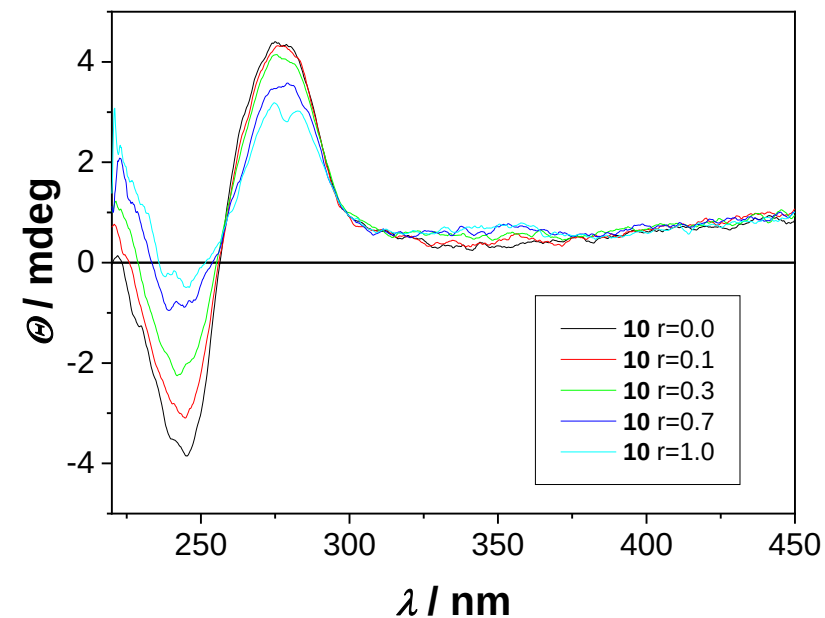
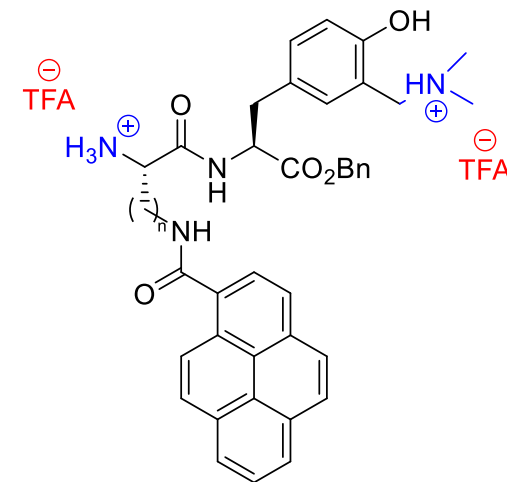
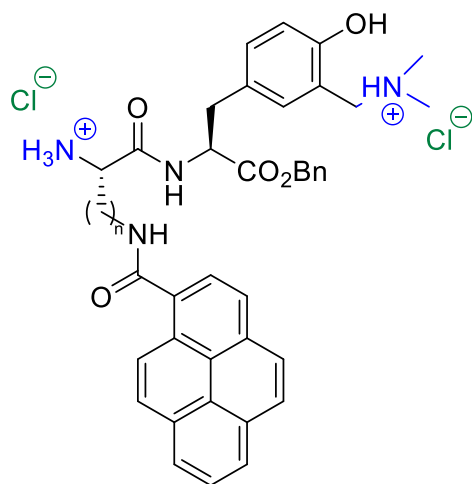
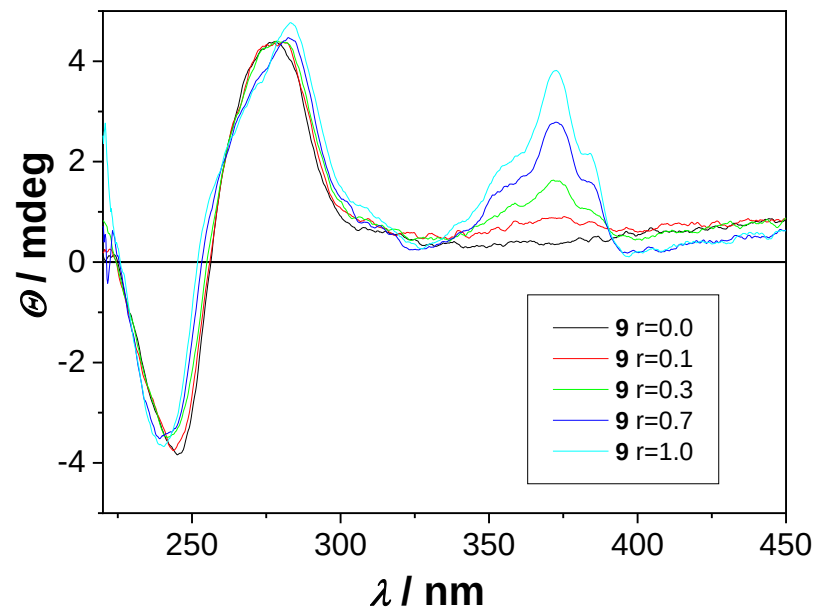
$$\log K_A \approx 6$$

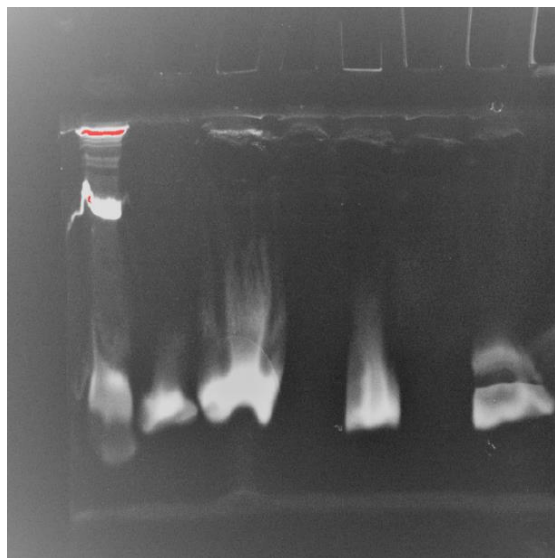
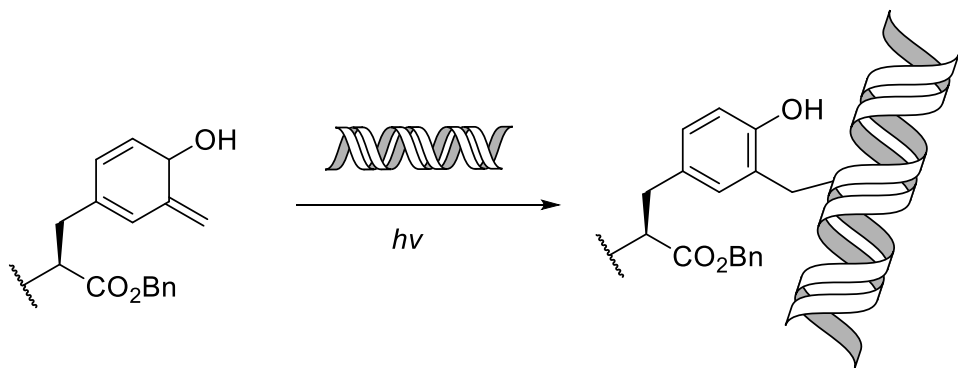


9; $n = 4$; Lys

Fluorescence titration ($c = 1 \times 10^{-5} \text{ M}$, $\lambda_{\text{exc}} = 330 \text{ nm}$) with *ct*-DNA ($c = 0 - 2.5 \times 10^{-4} \text{ M}$) in cacodylate buffer (pH 7.0, 50 mM at 25°C) containing 0.5% DMSO

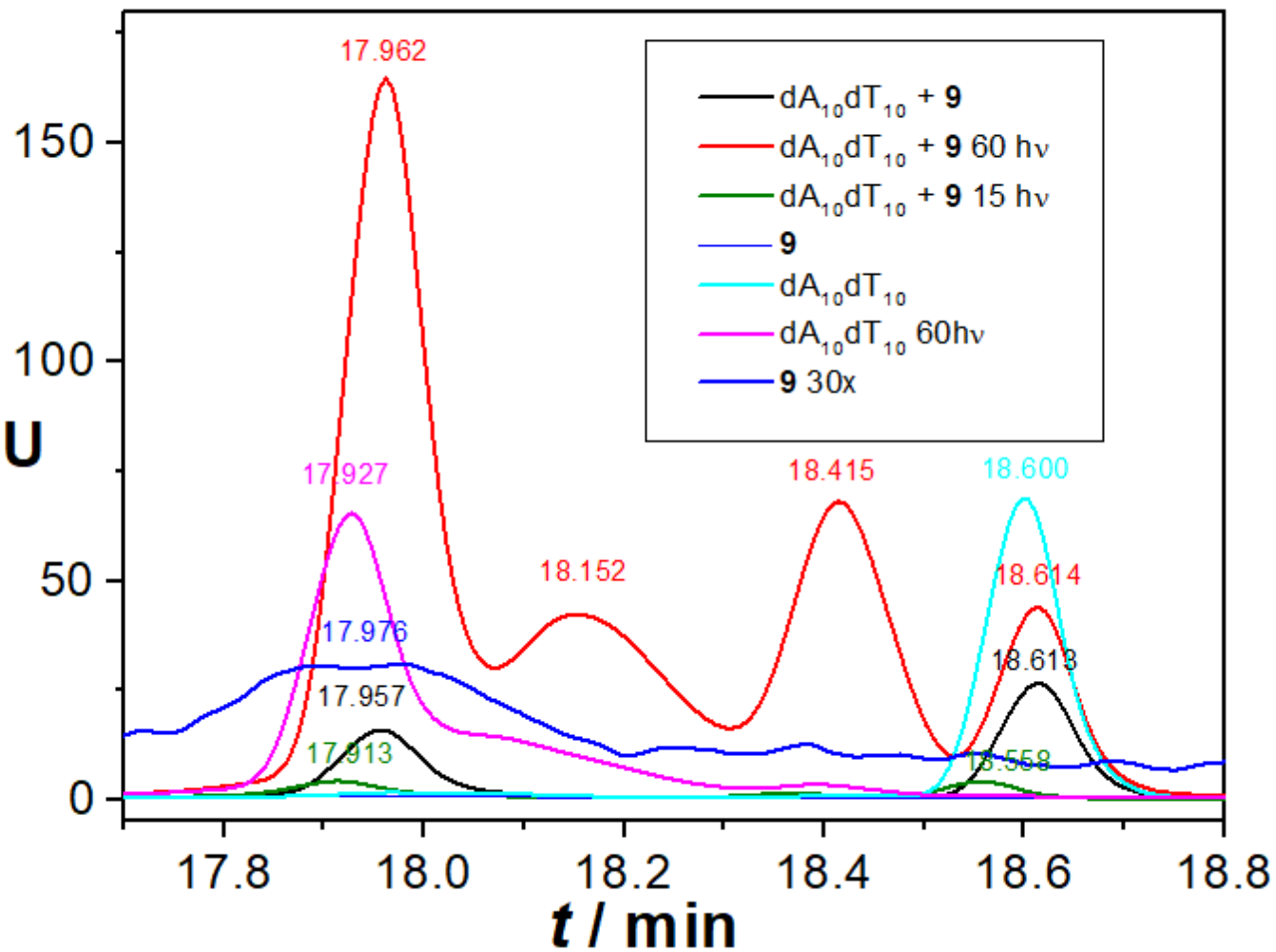






- 1: marker
 2: **9** + dA₁₀dT₁₀
 4: dA₁₀dT₁₀ *hν*
 5: **9** *hν*
 6: empty
 7: **9** + dA₂₅dT₂₅ *hν*

mAU





Members of LSOC:

Nikola Basarić, PhD (Head of LSOC)

Igor Sviben, PhD

Margareta Sohora, PhD

Marija Alešković, PhD

Tatjana Šumanovac, PhD

Marina Šekutor, PhD

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Josip Draženović, PhD student

Antonija Erben, PhD student

Nataša Burić, PhD student

Enidija Rajaković

Antonela Šimunić

Ivo Piantanida, PhD

Dijana Pavlović Saftić, PhD

Antonija Karakaš

Thomas Bachelart

Croatian Science Foundation

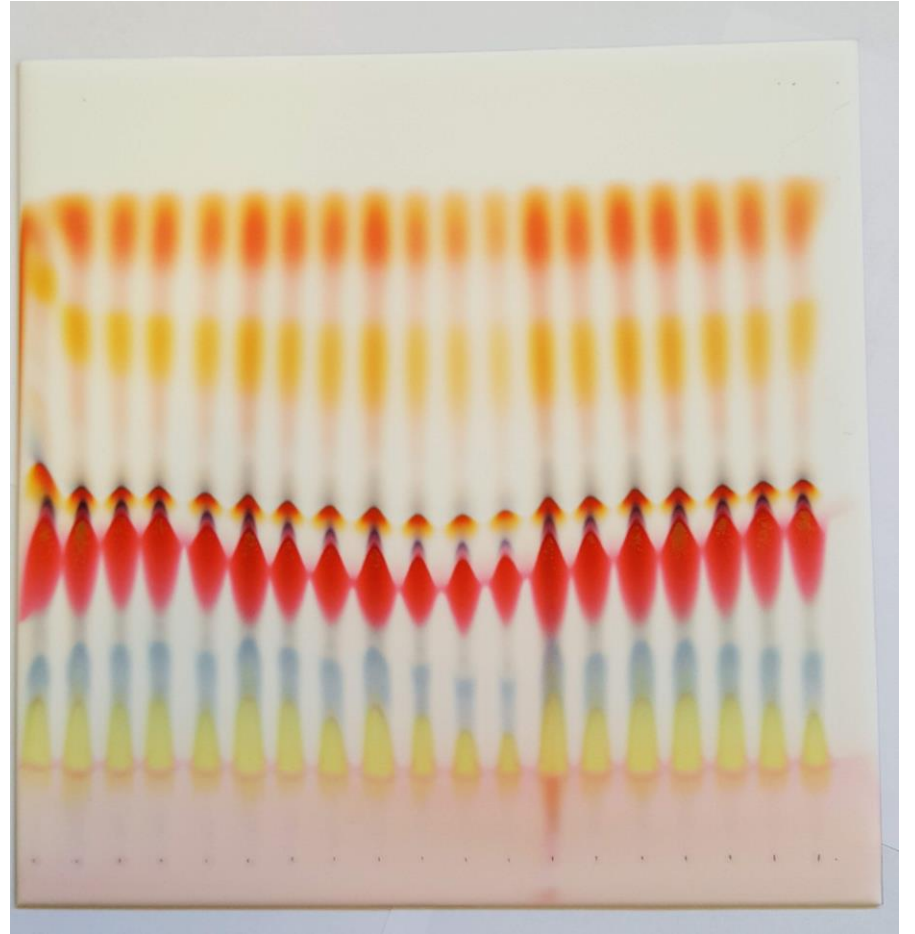
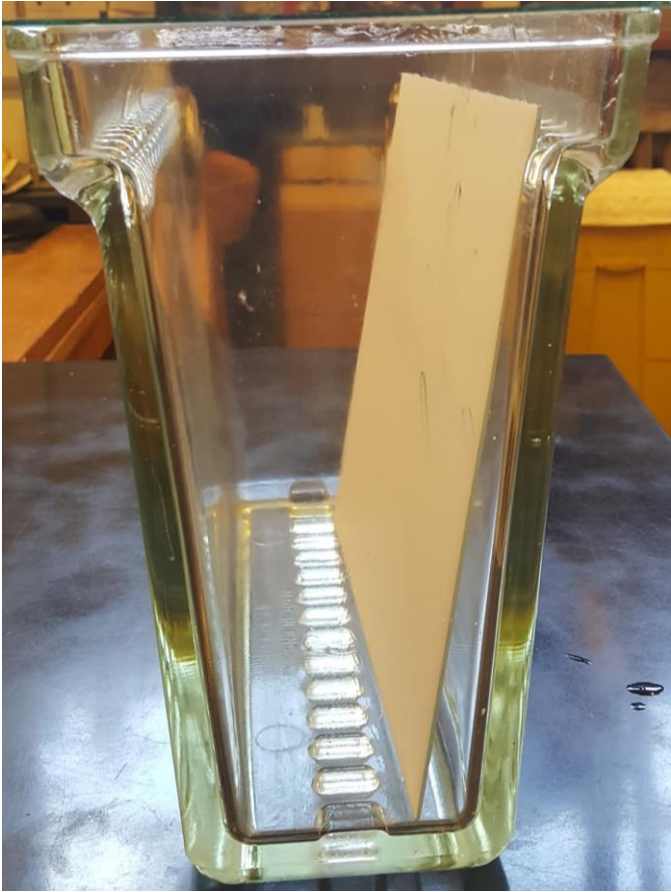
Photochemistry: Reaction mechanisms and
applications in organic synthesis and biology

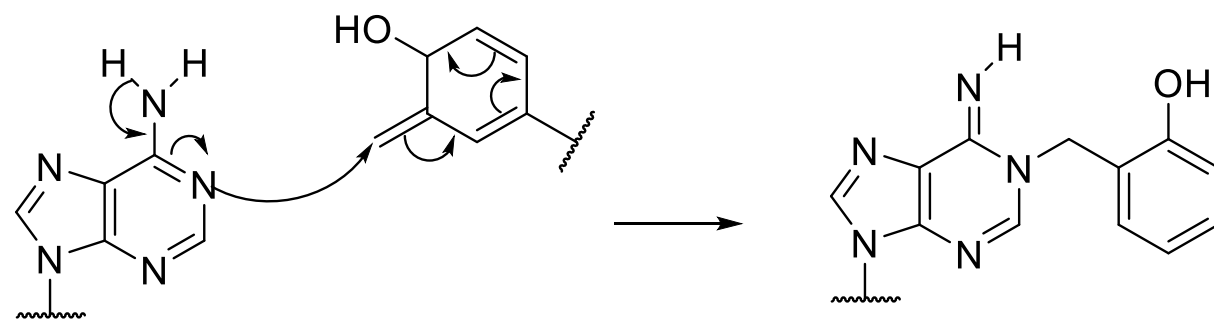
IP-2019-04-8008



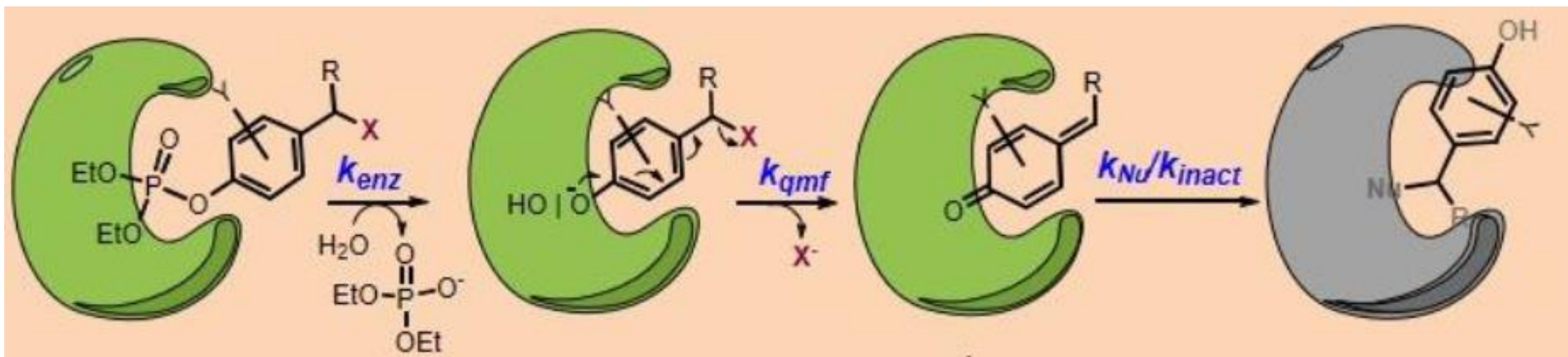
Thank you!



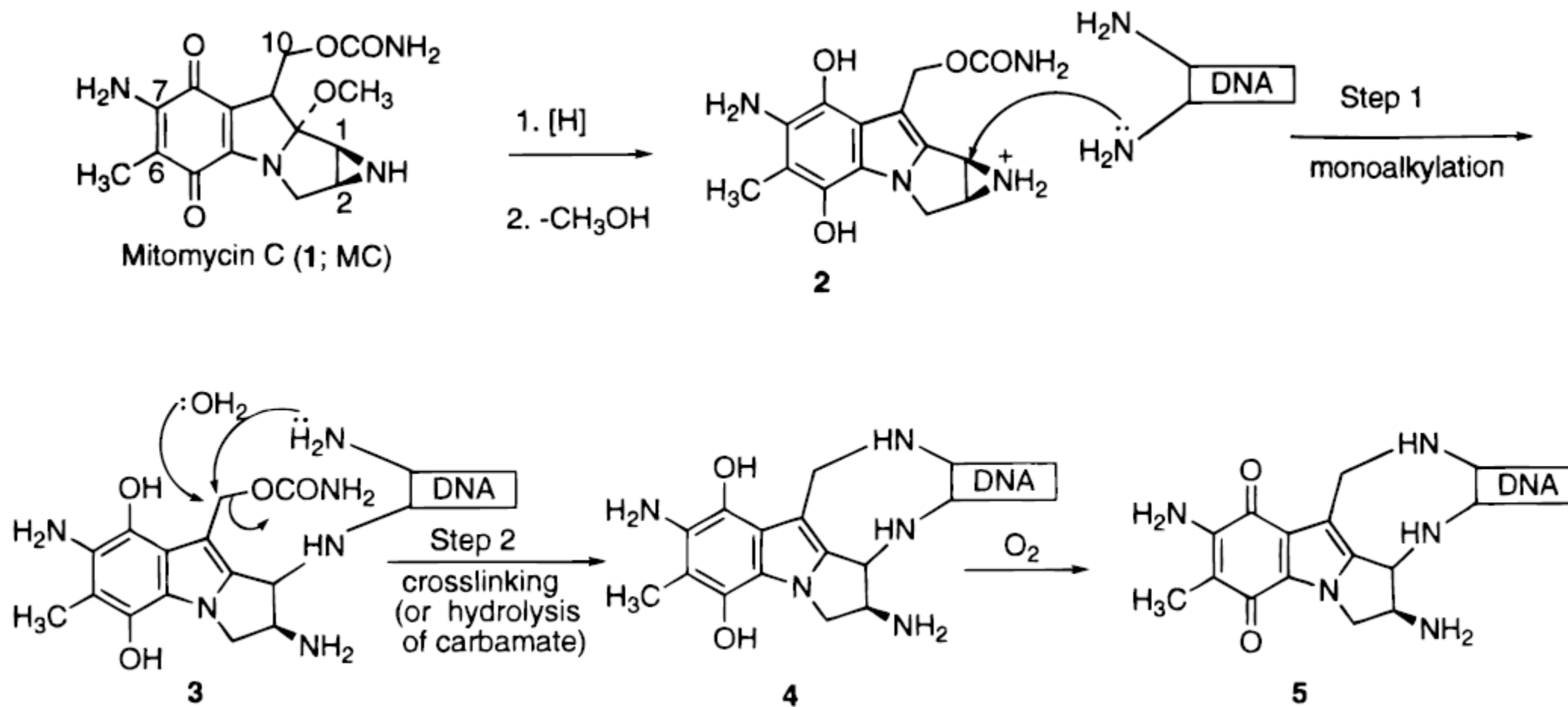




Rokita *et al.*, *J. Org. Chem.* **62** (1997) 3010 – 3012.



Dubovetsky *et al.*, *Chem. Bio. Chem.* **22** (2021) 894 – 903.



Tomasz *et al.*, *J. Am. Chem. Soc.* **120** (1998) 11581 – 11593.;
 V.-S. Li, H. Kohn, *J. Am. Chem. Soc.* **113** (1991) 275 – 283.;
 Han *et al.*, *J. Org. Chem.* **57** (1992) 1799 – 1807.