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Department of Organic chemistry

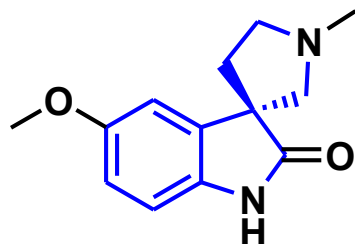
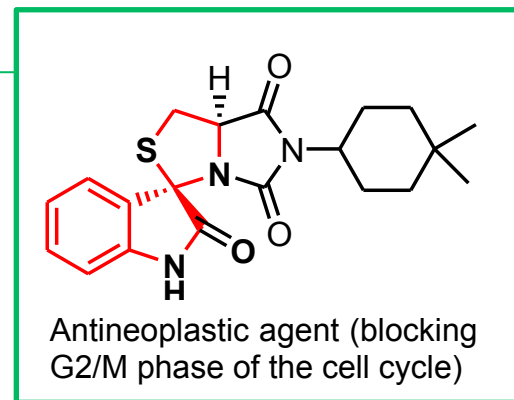
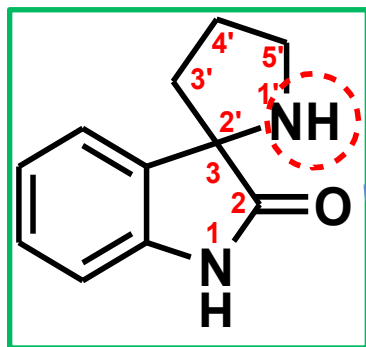


Synthesis and chemical property of spiro[indol-3,2'-pyrrolidine]-2-ones

Master thesis of
levgeniia Kovalova

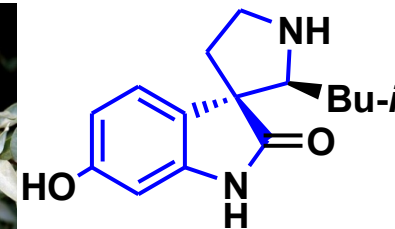
Kharkiv, 2013

Distribution of Spirooxindoles in nature



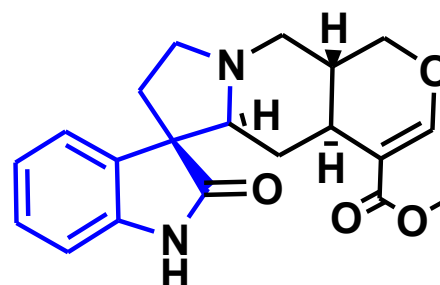
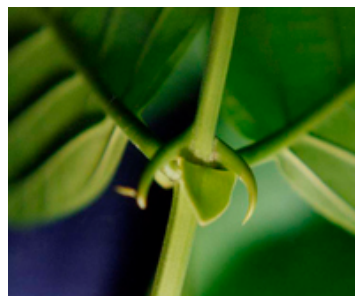
Horsfieldia superba

(-)-Horsfilin



Eleagnus commutata

(+)-Elakomin

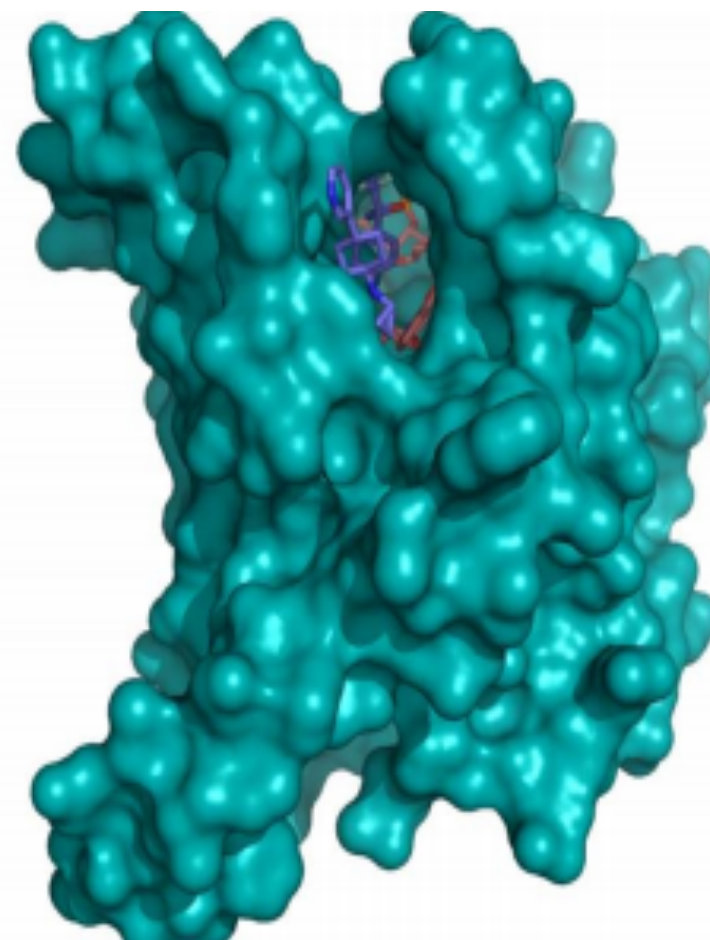
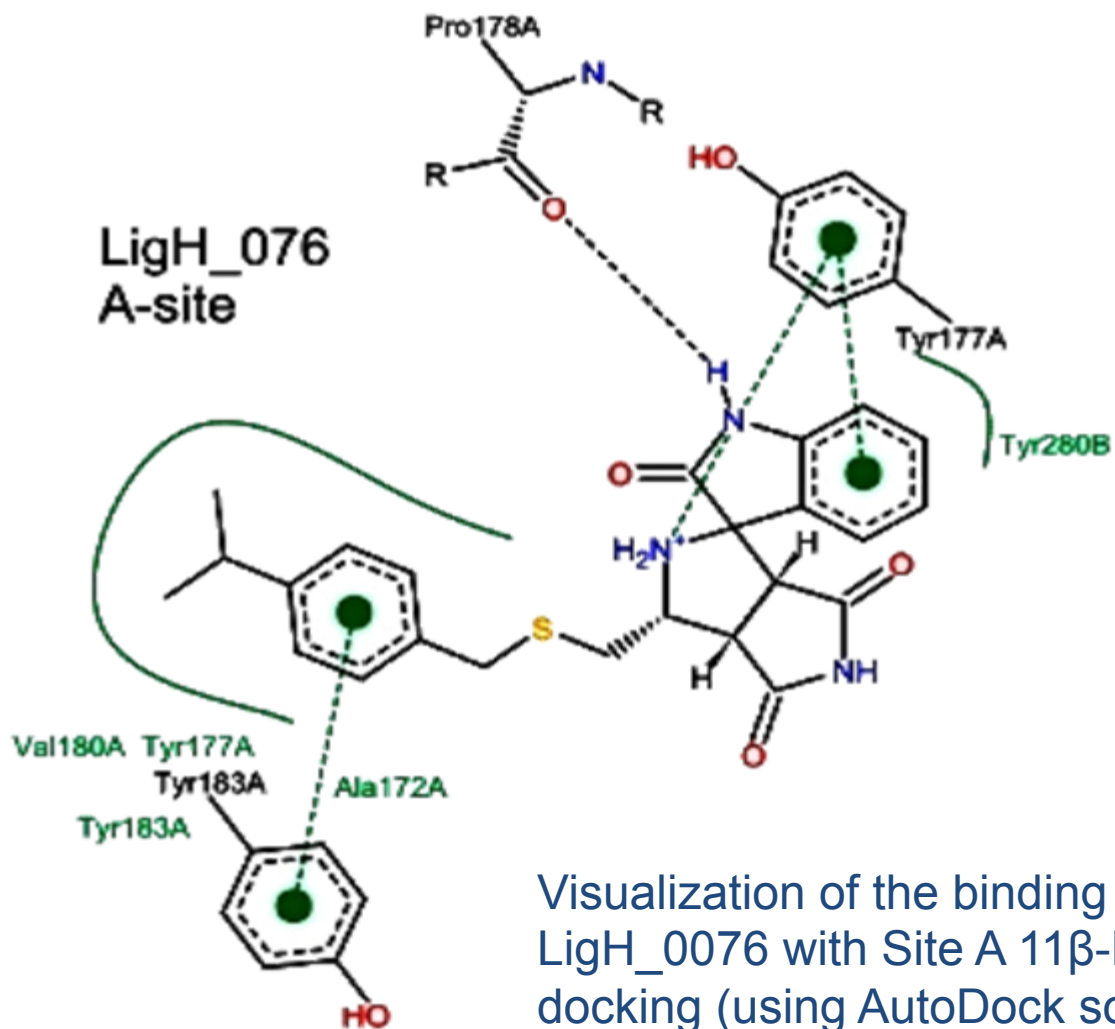


Uncaria tomentosa

Mitrafillin

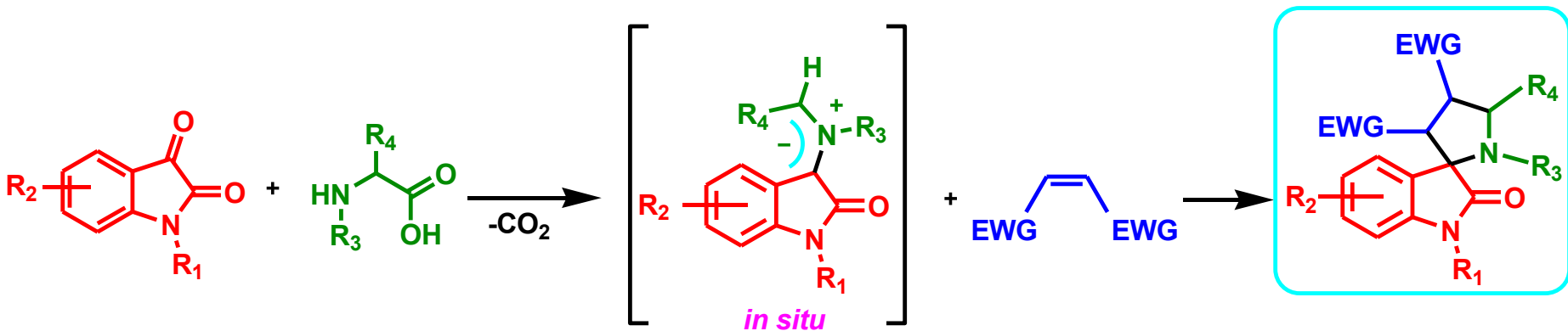
Spiropyrrolidine-3,2'-oxindoles as potential inhibitors of 11 β -HSD1

Estimated Free Energy of Binding = -11.37 kcal/mol
Estimated Inhibition Constant, K_i = 4.67 nM (nanomolar)
[Temperature = 298.15 K]

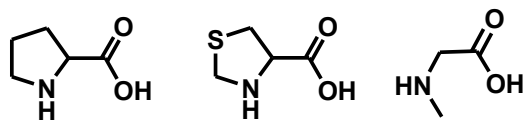


Visualization of the binding molecule compounds LigH_0076 with Site A 11 β -HSD1 on the results of docking (using AutoDock software)

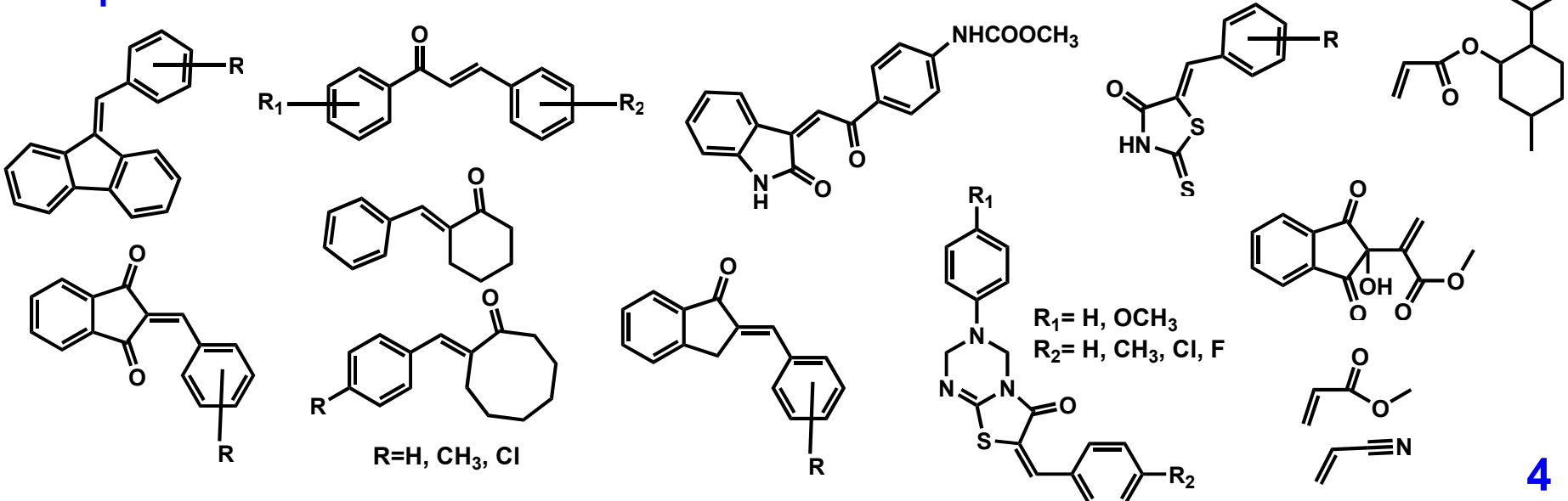
Three-compound reaction of izatines, α -aminoacids and dipolarofiles



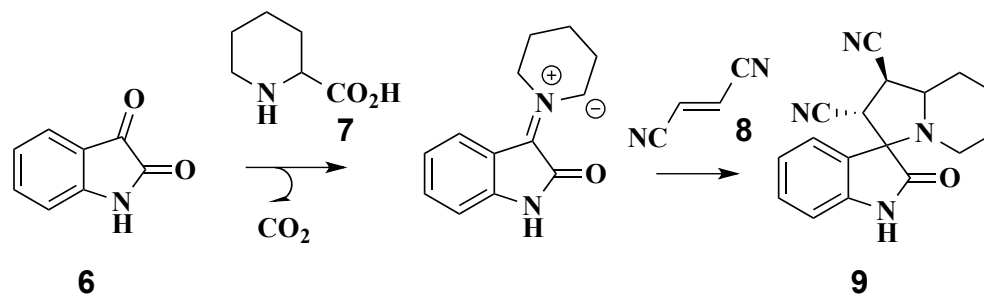
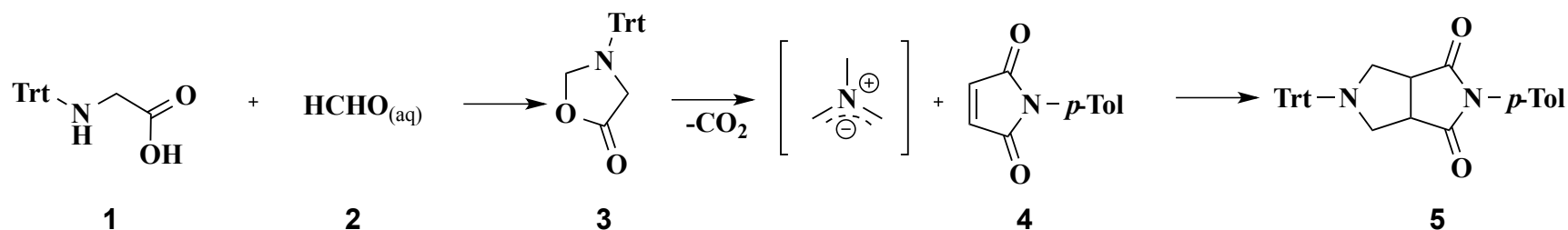
α -aminoacids



Dipolarofiles



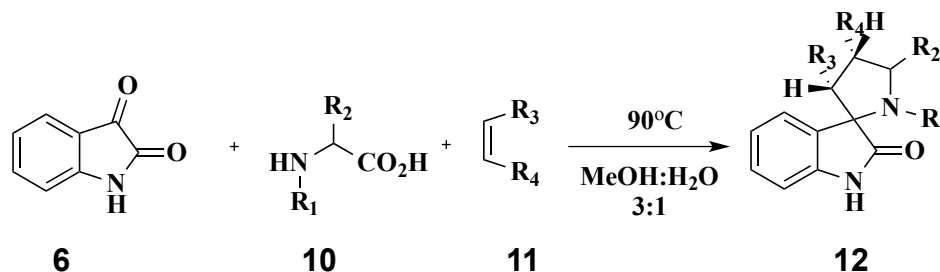
Intermolecular reaction of 1,3-dipolar cycloaddition



Grigg, R.; Aly, M.F.; Sridharan, V.; Thianpatanagul, S. *J. Chem. Soc.; Chem. Commun.* **1984**, 182.

Lown J. W. Wiley: New York, 1984; Vol. 1, p 653.

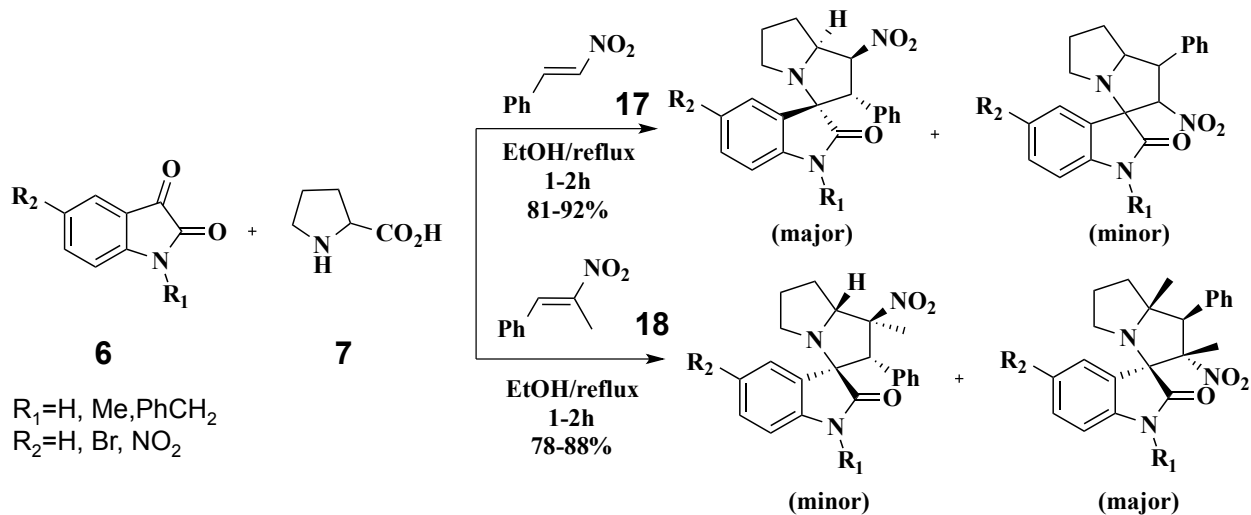
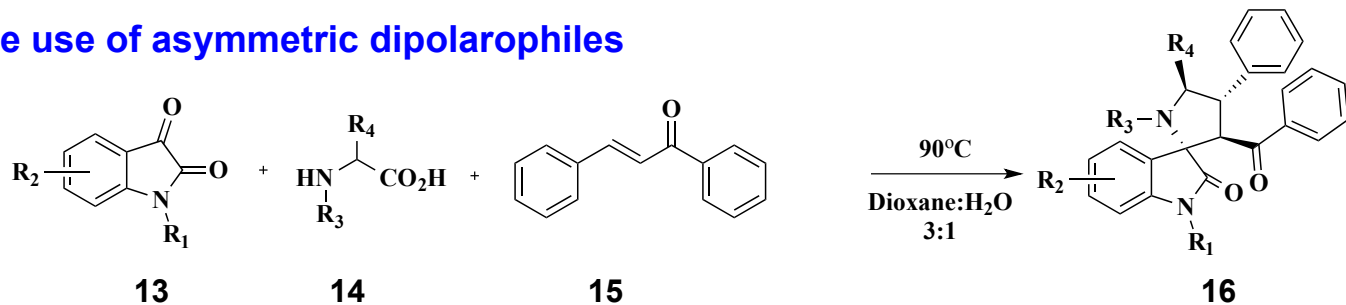
Obtaining of Spirooxindoles



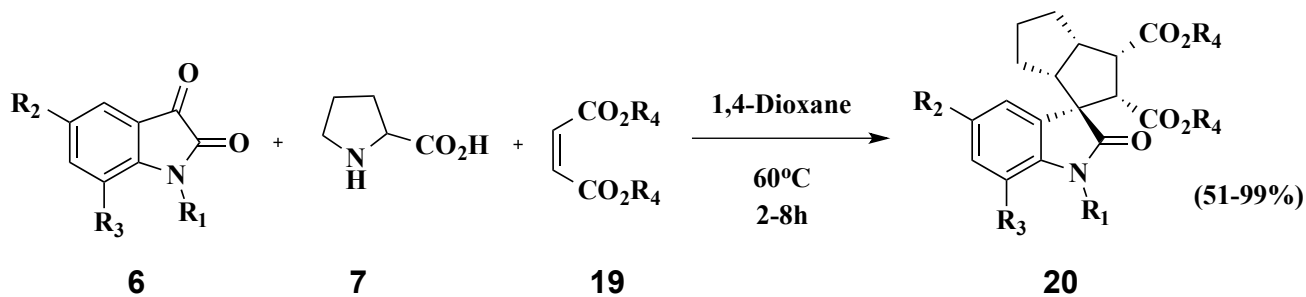
Product	R1	R2	R3	R4	Time, (h)	Yield, (%)
12a	Me	H	-C(O)NBnC(O)-		18	92
12b	Me	H	-C(O)NBnC(O)-		18	82
12c	Bn	H	-C(O)NBnC(O)-		18	77
12d	Me	Me	-C(O)NBnC(O)-		18	79
12f	H	CH(CH ₃) ₂	-C(O)NBnC(O)-		2	94
12g	H	Me	-C(O)NBnC(O)-		18	95
12h	H	H	-C(O)NBnC(O)-		2	39
12i	-CH ₂ SCH ₂ -		-C(O)NBnC(O)-		2	95
12j	CH ₂ CH ₂ CH ₂		-C(O)NBnC(O)-		0.5	87
12h	Bn	H	CO ₂ Me	H	18	38
12k	-CH ₂ SCH ₂ -		CO ₂ Me	H	2	69

The use of symmetric and asymmetric dipolarophiles in 1,3-dipolar cycloaddition reactions

1. The use of asymmetric dipolarophiles

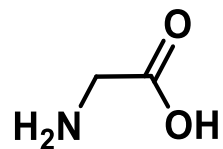
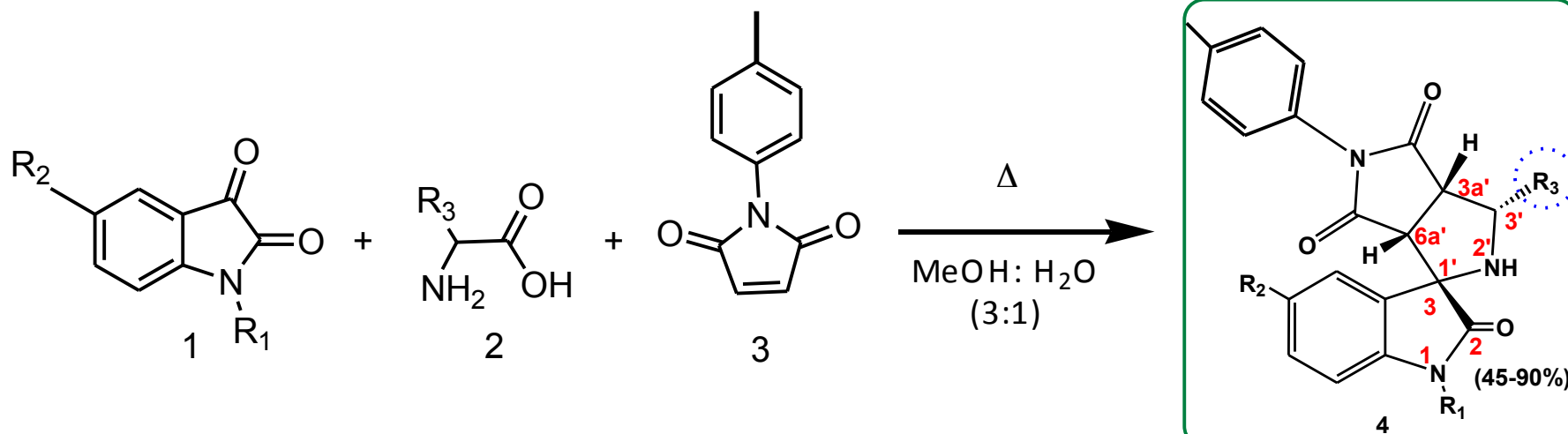


2. The use of symmetric dipolarophiles

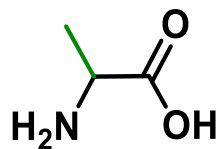


Experimental section

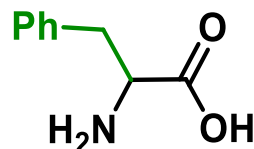
Cycloaddition of symmetric dipolarophiles



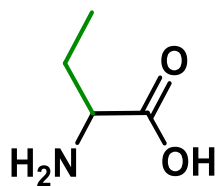
Gly



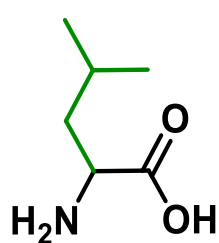
Ala



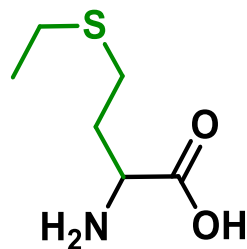
Phe



alpha-Aminobutyric acid



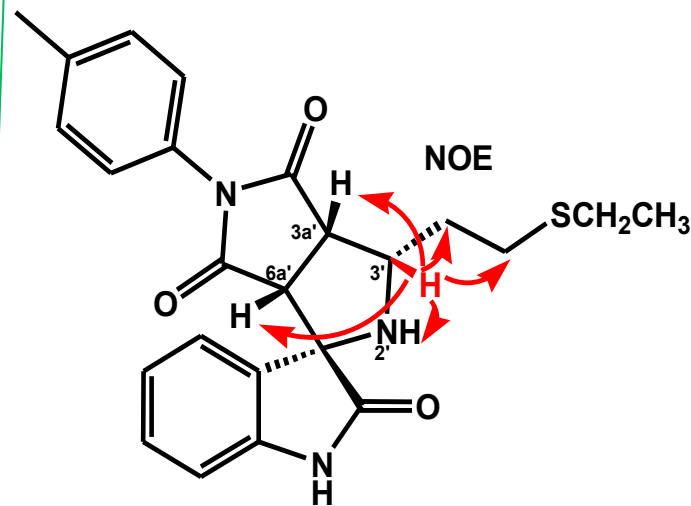
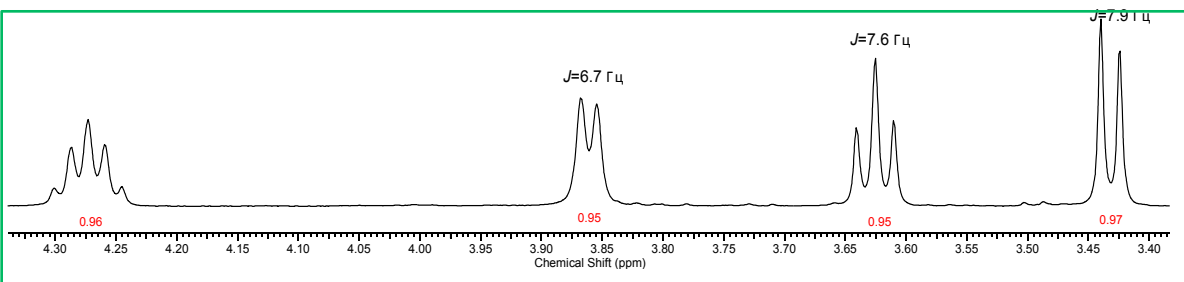
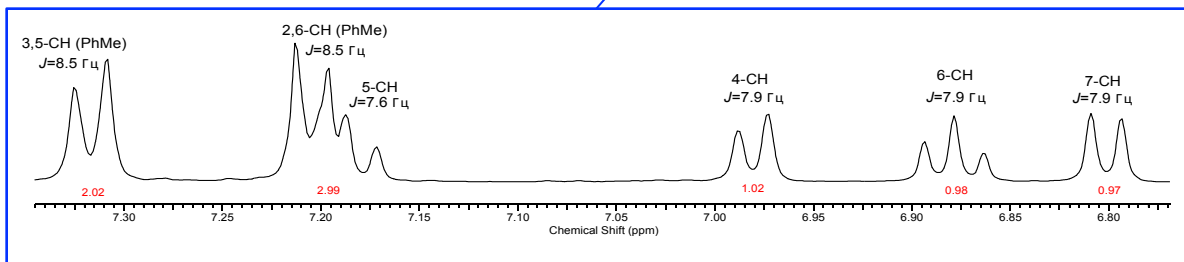
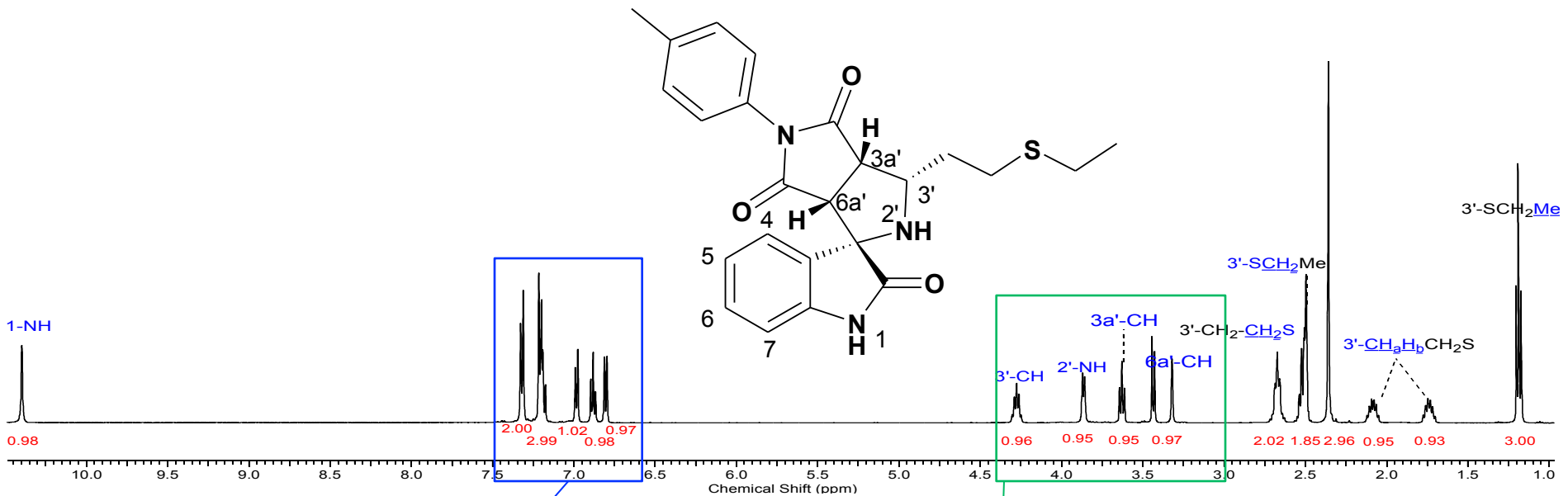
Leu



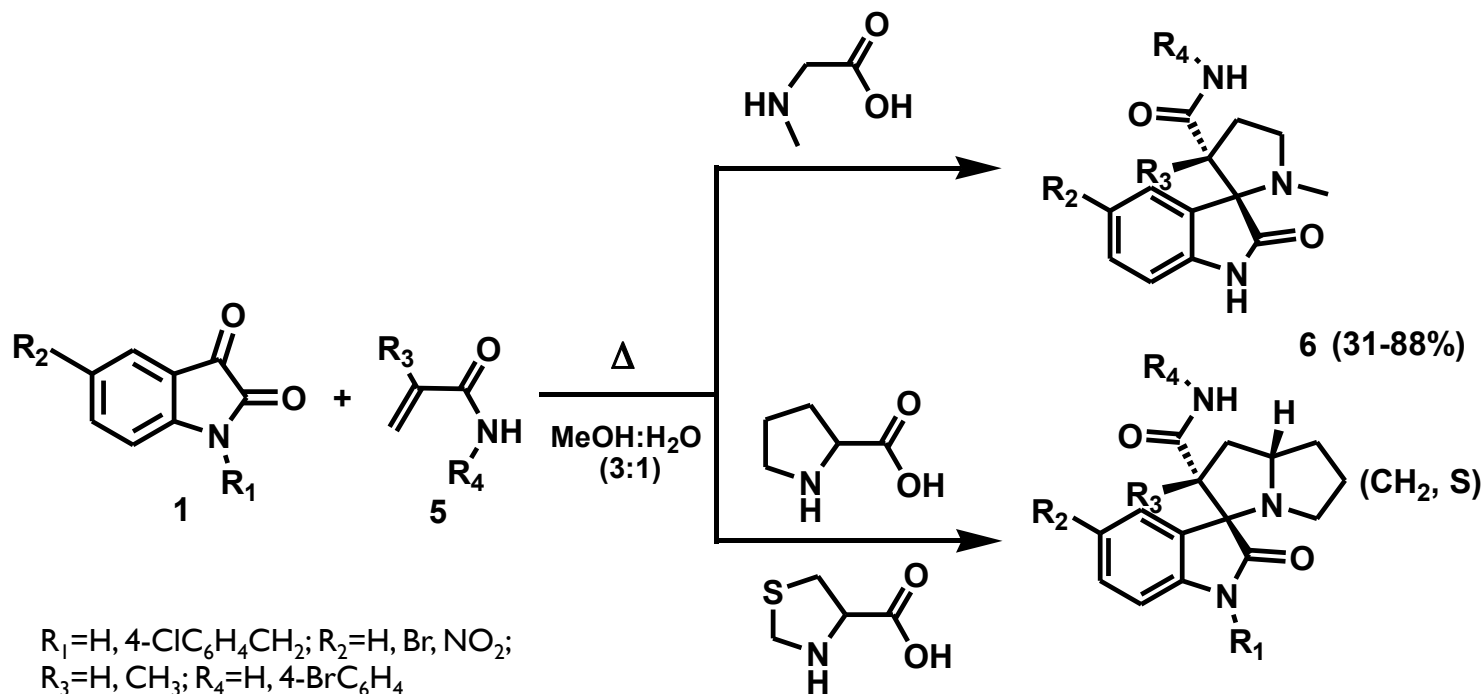
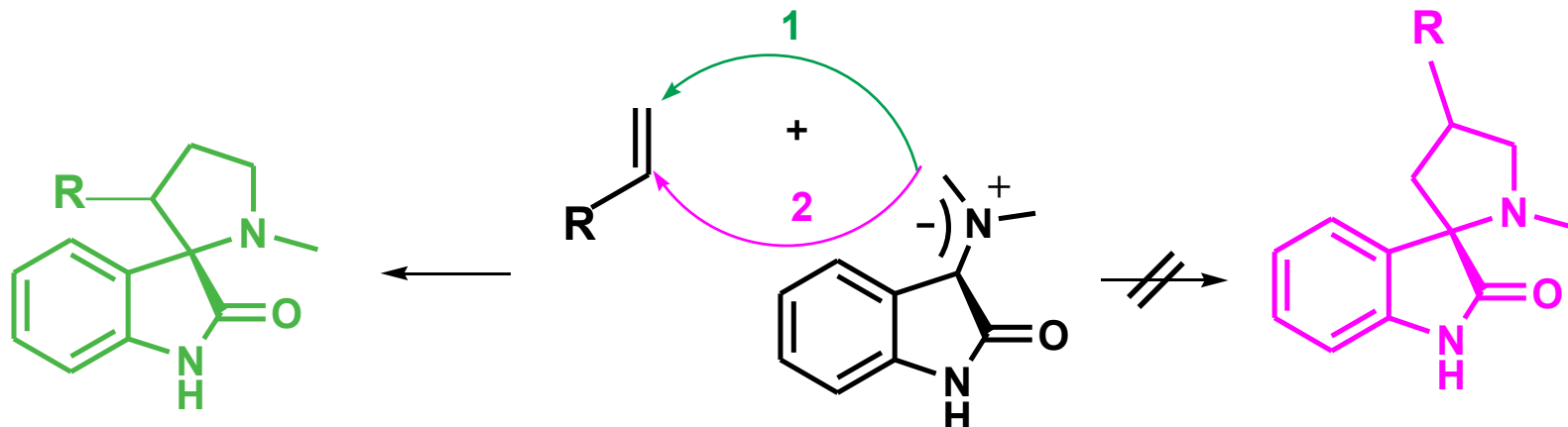
Ethionine

R₁=H, CH₃; R₂=H, Br

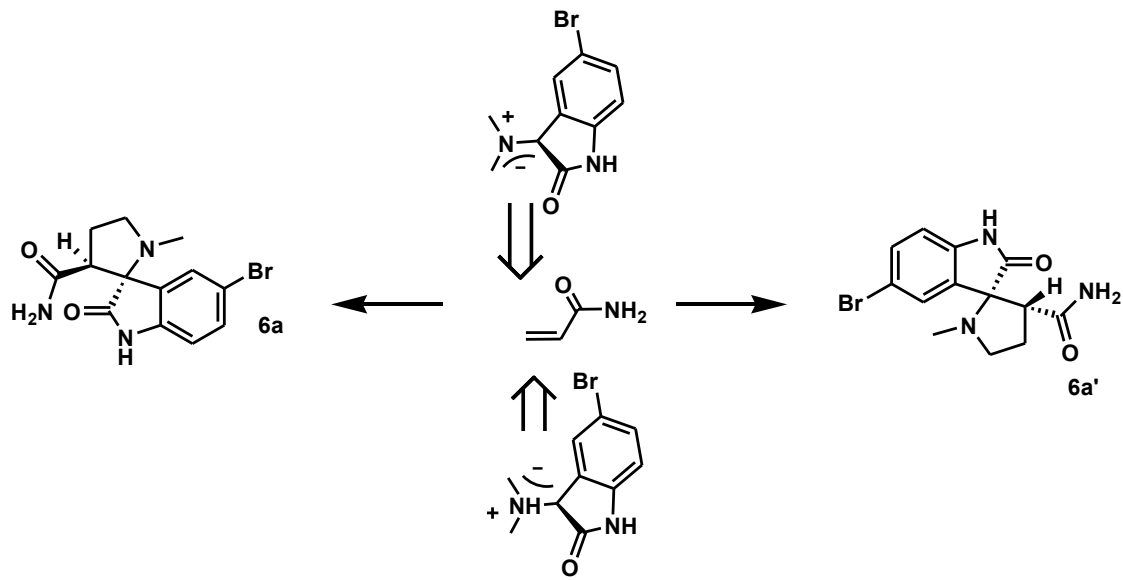
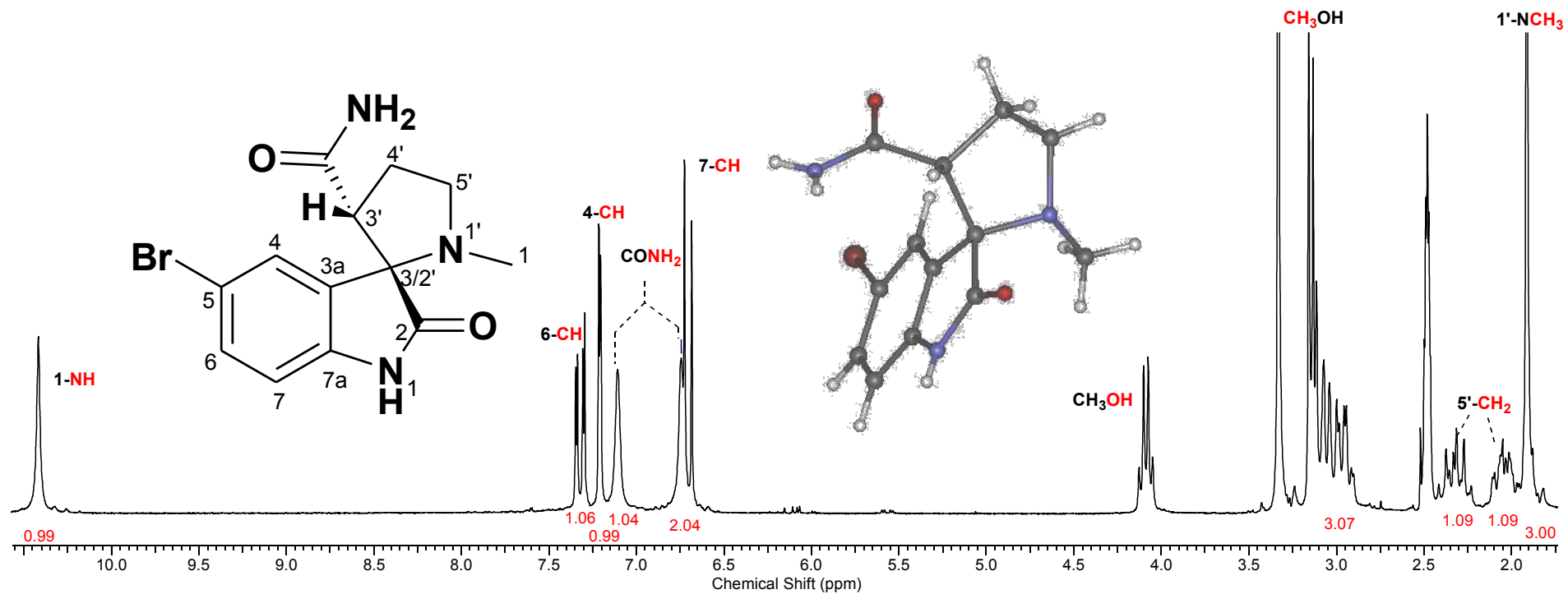
¹H-NMR and NOE data for one of spiropyrrolidines

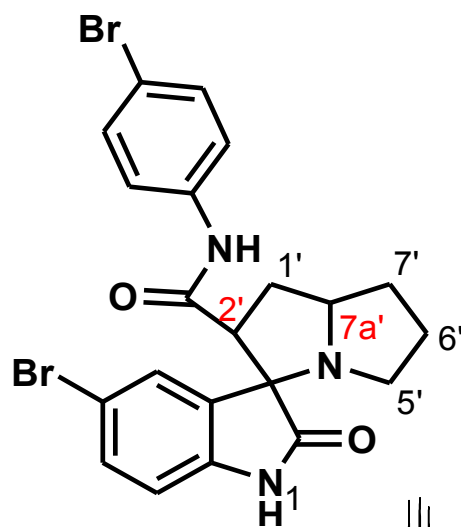


Cycloaddition of asymmetric dipolarophiles

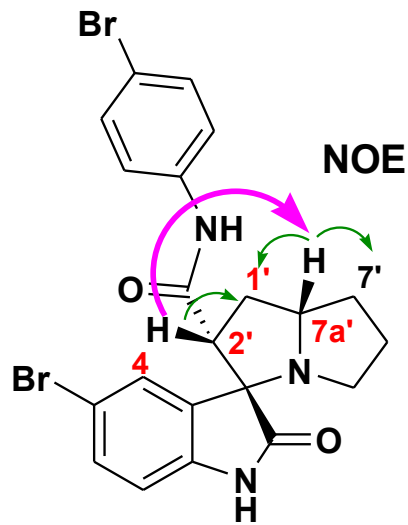
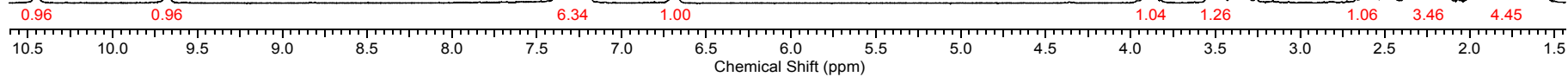


¹H-NMR and X-ray analysis



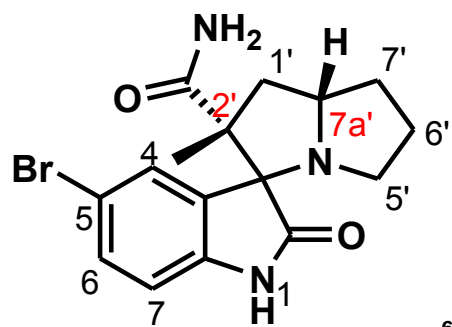


1-NH
NH-акриламид

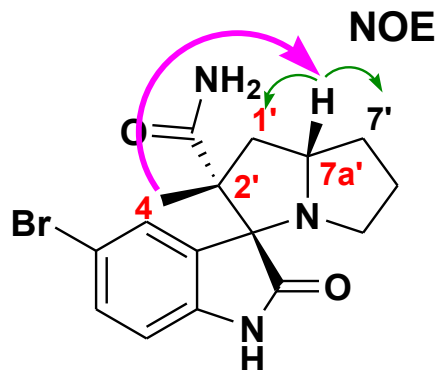
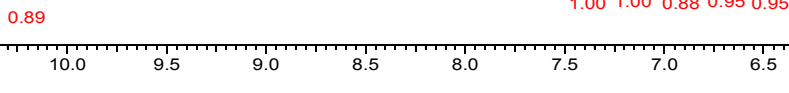


NOE

7a'-CH 2'-CH
5'-CH₂ 1'-CH₂ 6', 7'-CH₂



1-NH
4-CH 6-CH CONH₂ 7-CH

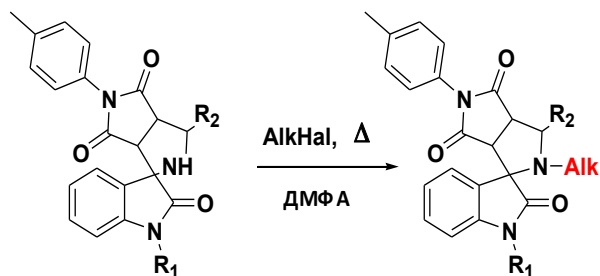


NOE

7a'-CH
1'-CH₂ 6', 7'-CH₂
2'-CH 5'-CH₂ 2'-CH₃

Chemical properties of spirooxindoles

Alkylation



4b: $R_1=H$, $R_2=Bn$;

4c: $R_1=CH_3$, $R_2=CH_3$;

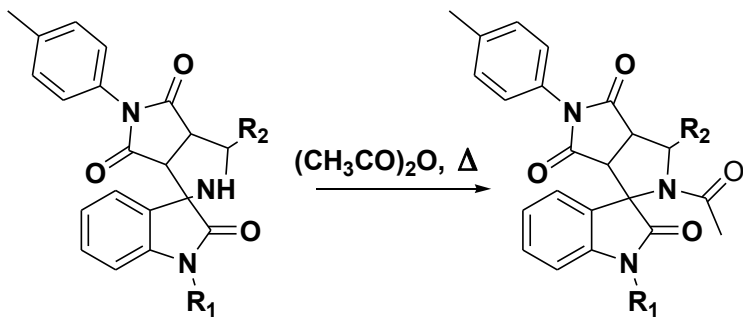
4e: $R_1=H$, $R_2=CH_2CH_3$

7a: $R_1=CH_3$, $R_2=CH_3$, Alk= 4- C_6H_4Cl , 64%;

7b: $R_1=H$, $R_2=CH_2CH_3$, Alk= CH_3 , 85%;

7c: $R_1=CH_3$, $R_2=Bn$, Alk= CH_3 , 94%

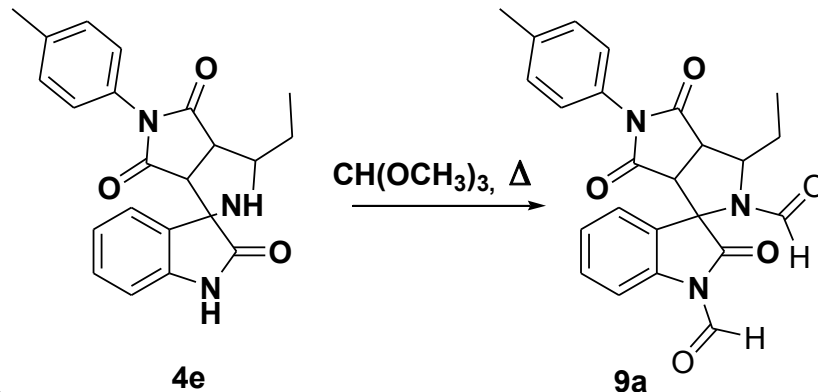
Acylation



4a: $R_1=R_2=H$; 4d: $R_1=4-C_6H_4Cl$,
 $R_2=CH_2CH(CH_3)_2$

8a: $R_1=COCH_3$, $R_2=H$, 96%;

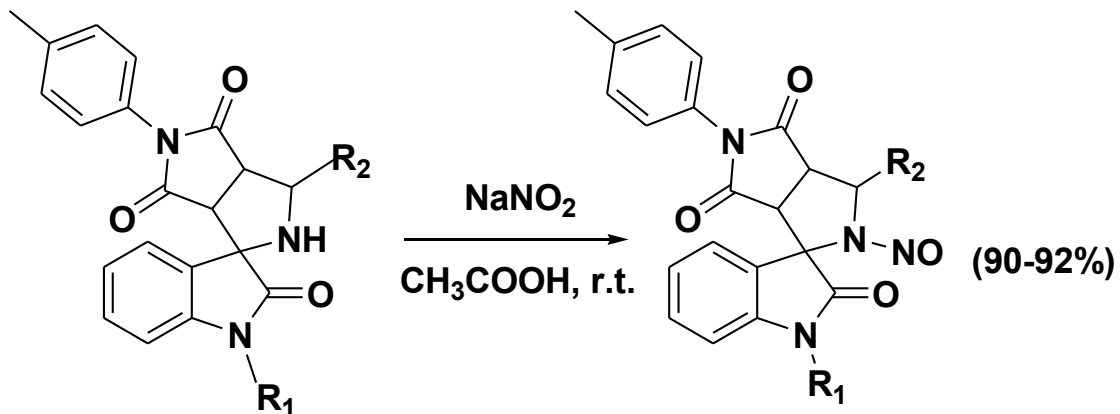
8b: $R_1=4-C_6H_4Cl$, $R_2=CH_2CH(CH_3)_2$, 95%



4e

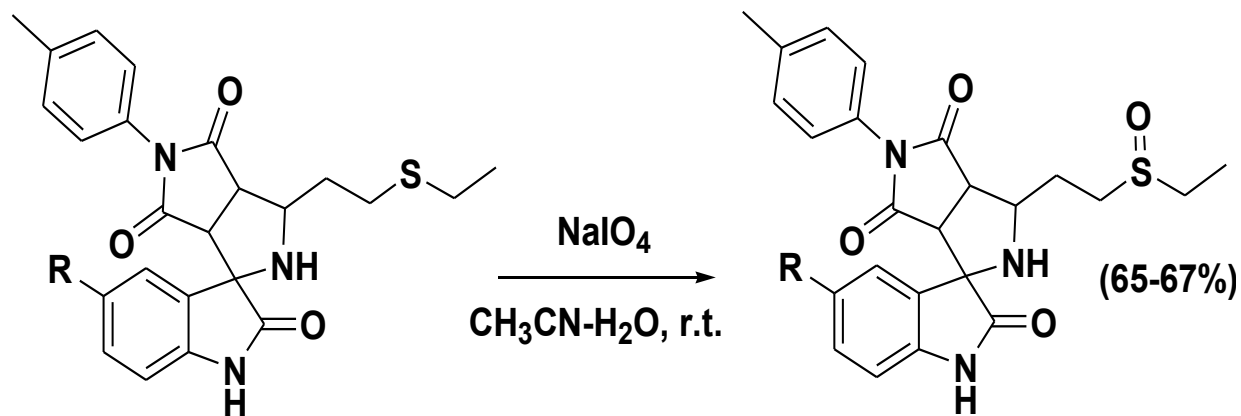
9a

Nitrozilation



4c, 10a: R₁=R₂=CH₃; 4e, 10b: R₁=H, R₂=Et

Oxidation



4f, 11a: R=H; 4g, 11b: R=Br

Thank you for your attention!