XXI.
EUROPEAN COLLOQUIUM
ON
HETEROCYCLIC CHEMISTRY
BOOK OF ABSTRACTS

Sopron
HUNGARY
2004
Sept. 12-15th

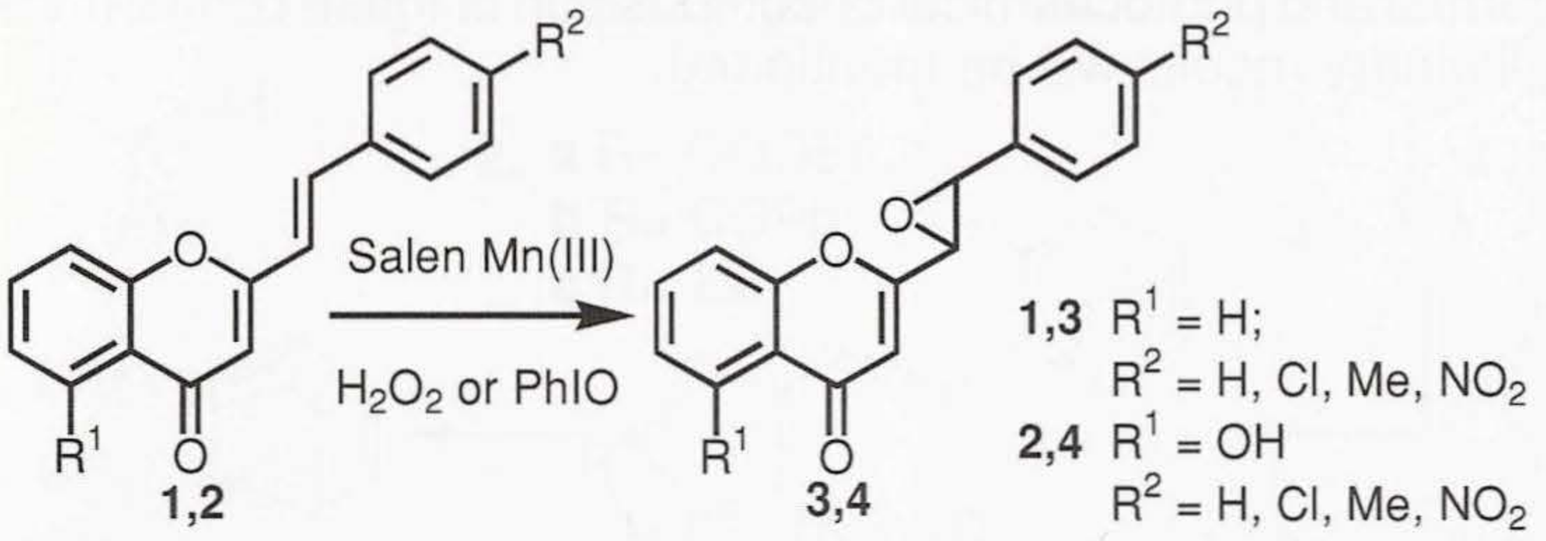
SEPTEMBER 12-15TH, 2004
LISZT FERENC CONGRESS AND CULTURE CENTER
SOPRON, HUNGARY

EPOXIDATION OF 2-STYRYLCHROMONE DERIVATIVES

Clementina M. M. Santos,[a,b] Artur M. S. Silva,[b]
José A. S. Cavaleiro,[b] Tamás Patonay,[c] and Albert Levai,[c]

[a]*Department of Agro-Industries, Escola Superior Agrária de Bragança, 5301-855 Bragança, Portugal*
[b]*Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal*
[c]*Department of Organic Chemistry, University of Debrecen, H-4010 Debrecen, Hungary*

2-Styrylchromones constitute a small group of natural heterocyclic compounds with significant biological properties. Certain natural and synthetic hydroxyl derivatives have shown important pharmacological and mainly antioxidant activities [1,2].
We are interested in the design of new 2-styrylchromones analogues containing hydroxyl groups at C-3 and in the Cα=Cβ systems because they could increase the antioxidation activity of these type of compounds [2]. Our first approach is the preparation of epoxy systems and then we will try to open the epoxy ring to give the desired hydroxyl derivatives. We studied the epoxidation of 2-styryl-chromones **1** with hydrogen peroxide and iodosylbenzene using [salen Mn(III)] as catalyst, and the epoxy products **2** were obtained in moderate yields. Since the best results were obtained with iodosylbenzene, we applied oxidant to compounds **3** in order to prepare **4**. In this communication, we will report the synthetic details and the structural characterisation of the epoxides **3** and **4**.



Acknowledgements: Thanks are due to the University of Aveiro, FCT and FEDER for funding the Organic Chemistry Research Unit and the project POCTI/QUI/38394/2001. One of us (C.M.M. Santos) is also grateful to PRODEP 5.3 for financial support.

1. (a) Doria G, Romeo C, Forgione A, Sberze P, Tibolla N, Corno ML, Cruzzola G, Cadelli G, *Eur. J. Med. Chem. - Chim. Ther.* **1979**, *14*, 347. (b) Gerwick WH, Lopez A, Van Duyne GD, Clardy J, Ortiz W, Baez A, *Tetrahedron Lett.*, **1986**, *27*, 1979; (c) Gerwick WH, *J. Nat. Prod.* **1989**, *52*, 252; (d) Desideri N, Conti C, Mastromarino P, Mastropaolo F, *Antiviral Chem. Chemother.* **2000**, *11*, 373.
2. *e.g.* (a) Fernandes E, Carvalho F, Silva AMS, Santos CMM, Pinto DCGA, Cavaleiro JAS, Bastos ML, *J. Enz. Inhib.*, **2002**, *17*, 45; (b) Fernandes E, Carvalho M, Carvalho F, Silva AMS, Santos CMM, Pinto DCGA, Cavaleiro JAS, Bastos ML, *Arch. Toxicol.*, **2003**, *77*, 500.

XXIst
EUROPEAN COLLOQUIUM
ON
HETEROCYCLIC CHEMISTRY

SOPRON, SEPTEMBER 12-15TH, 2004

CERTIFICATE
OF
ATTENDANCE

WE HAVE THE PLEASURE TO CONFIRM
THE ATTENDANCE OF

SANTOS, CLEMENTINA
PORTUGALIA

DR. GYÖRGY HAJÓS
CHAIRMAN

DR. PÉTER MÁTYUS
CO-CHAIRMAN

Epoxidation of 2-styryl

Clementina M. M. Santos,[a,b] Artur M. Tamás Patonay [c]

[a]Department of Agro-Industries, Escola

5301-855 Bragança,

[b]Department of Chemistry, University of

[c]Department of Organic Chemistry, University of

chromones derivatives

S. Silva,[b] José A. S. Cavaleiro,[b] and Albert Levaí[c]

Superior Agrária de Bragança, Portugal

Aveiro, 3810-193 Aveiro, Portugal

Debrecen, H-4010 Debrecen, Hungary

Introduction

❋ 2-Styrylchromones constitute a small group of natural heterocyclic compounds with significant biological properties such as pharmacological and antioxidant activities [1,2].

❋ We are interested in the design of new 2-styrylchromone analogues containing hydroxy groups because they could increase the antioxidation activity of this type of compounds [2].

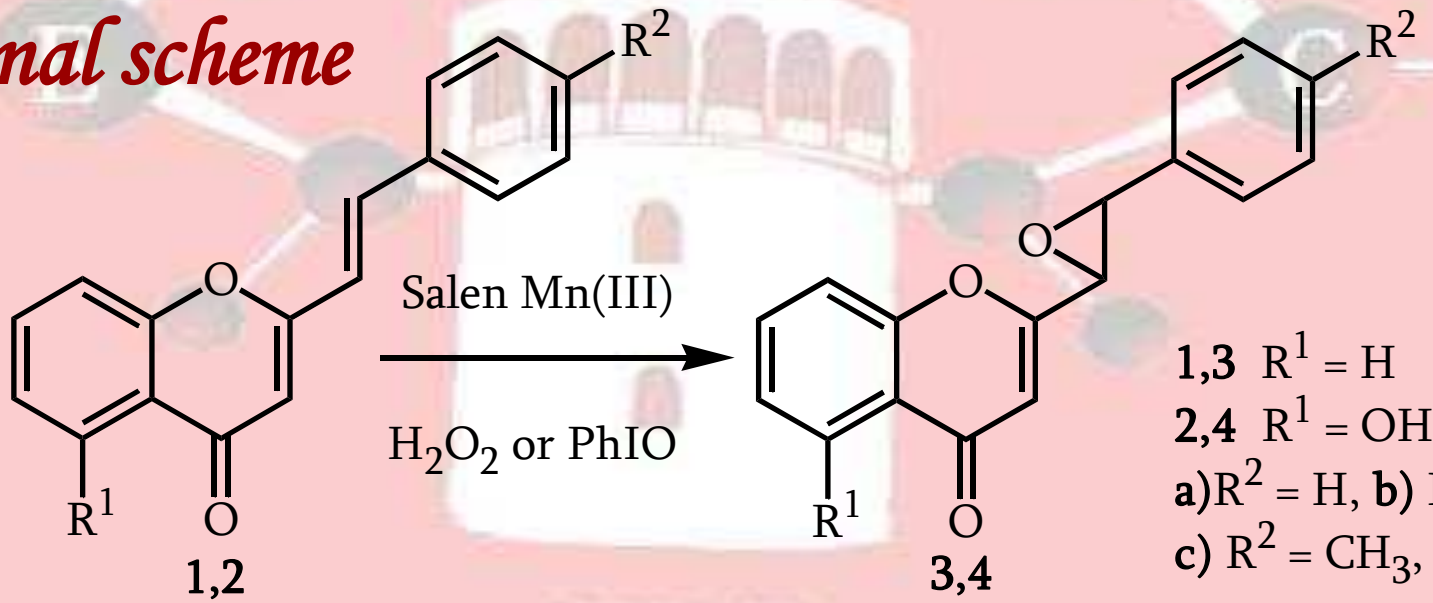
❋ Our first approach is the preparation of epoxy systems and then we will try to open the epoxy ring to give the desired hydroxy derivatives.

❋ In this communication, we will report the synthetic details and the structural characterisation of the epoxides **3** and **4**.

Epoxidation studies of 2-styrylchromones

- In order to prepare epoxides 3 and 4, we started our study with the epoxidation of 2-styrylchromone **1a** (R=H) with different experimental conditions.
- We have used hydrogen peroxide (method A) and iodosylbenzene (method B) as oxidants and [salen Mn(III)] as catalyst.

Reaccional scheme



1,3 R^1 = H
2,4 R^1 = OH
a) R^2 = H, **b)** R^2 = Cl,
c) R^2 = CH_3, **d)** R^2 = NO_2

Yields obtained in the epoxidation of 2-styrylchromone **1a** in different experimental conditions:

Method A

Exp.	Catal. (equiv)	Ligand (equiv)	Oxidant (equiv)	Solvent	Conditions	η (%)	Efec. η (%)
1 A	0.05	1-MeIm 0.7	H_2O_2 aq 30% 30	CH_2Cl_2/CH_3OH 3.0 ml	40 C ; N_2 19h	No reac.	0.0
2 A	0.05	1-MeIm 0.7	H_2O_2 aq 30% 60	CH_2Cl_2/CH_3OH 4.0 ml	40 C ; N_2 2 days	**3a** 26.7 **1a** 62.4	70.9
3 A	0.05	1-MeIm 0.7	H_2O_2 aq 30% 60	CH_3CN 4.0 ml	60 C ; N_2 20h	**3a** 5.1 **1a** 63.4	13.9
4 A	0.05	PyNO 0.7	H_2O_2 aq 30% 60	CH_2Cl_2/CH_3OH 4.0 ml	40 C ; N_2 15h	No reac.	0.0
5 A	0.05	NH_4OAc 0.4	H_2O_2 aq 30% 60	CH_2Cl_2/CH_3OH 4.0 ml	r.t. ; N_2 8h	No reac.	0.0
6 A	0.05	1-MeIm 0.3	H_2O_2 aq 30% 60	CH_2Cl_2/CH_3OH 4.0 ml	40 C ; N_2 2 days	No reac.	0.0
7 A	0.05 (4x)	1-MeIm 0.7 (4x)	H_2O_2 aq 30% 60 (4x)	CH_2Cl_2/CH_3OH 4.0 ml (4x)	40 C ; N_2 2 days	**3a** 6.0 **1a** 41.9	10.3

Legend:

Salen: *N,N'*-bis(3,5-di-*tert*-butylsalicylidine) -1,2-cyclohexanediaminomanganese (III) chloride

1-MeIm: 1-methylimidazol

NH_4OAc: ammonium acetate

r.t.: room temperature

Method B

Exp.	Catalis. (equiv.)	Ligand (equiv.)	Oxidant (equiv.)	Solvent	Conditions	η (%)	Efec. η (%)
1 B	0.05	PyNO 0.5	PhIO 2	CH_3CN 4.0 ml	r.t. ; N_2 4 days	**3a** 15.6 **1a** 40.1	36.2
2 B	0.05	PyNO 0.5	PhIO 2	CH_3CN 4.0 ml	60 C ; N_2 16h	**3a** 21.2 **1a** 46.3	39.5
3 B	0.05	PyNO 0.5	PhIO 2	CH_3CN 4.0 ml	0 →80 C ; N_2 2 days	**3a** 11.6 **1a** 44.0	15.3
4 B	0.1	---	PhIO 1+1	CH_2Cl_2 5.0 ml	r.t.→reflux ; N_2 3 days	**3a** 3.8 **1a** 80.2	19.4
5 B	0.05 (4x)	PyNO 0.5 (4x)	PhIO 1 (4x)	CH_3CN 4.0 ml	60 C ; N_2 3 days	**3a** 9.8 **1a** 25.7	13.2
6 B	0.05	PyNO 0.5	PhIO 2	Py 4.0 ml	r.t.→reflux ; N_2 2 days	No reac.	0.0
7 B	0.05	PyNO 0.5	PhIO 2	CH_3CN 4.0 ml	r.t. ; N_2 4 h	**3a** 14.6 **1a** 47.9	29.8
8 B	0.05	PyNO 0.5	PhIO ; 2 (4x0.5 eq.)	CH_3CN 4.0 ml	r.t. ; N_2 4 h	**3a** 22.9 **1a** 25.1	30.6

Legend:

PyNO: pyridine *N*-oxide

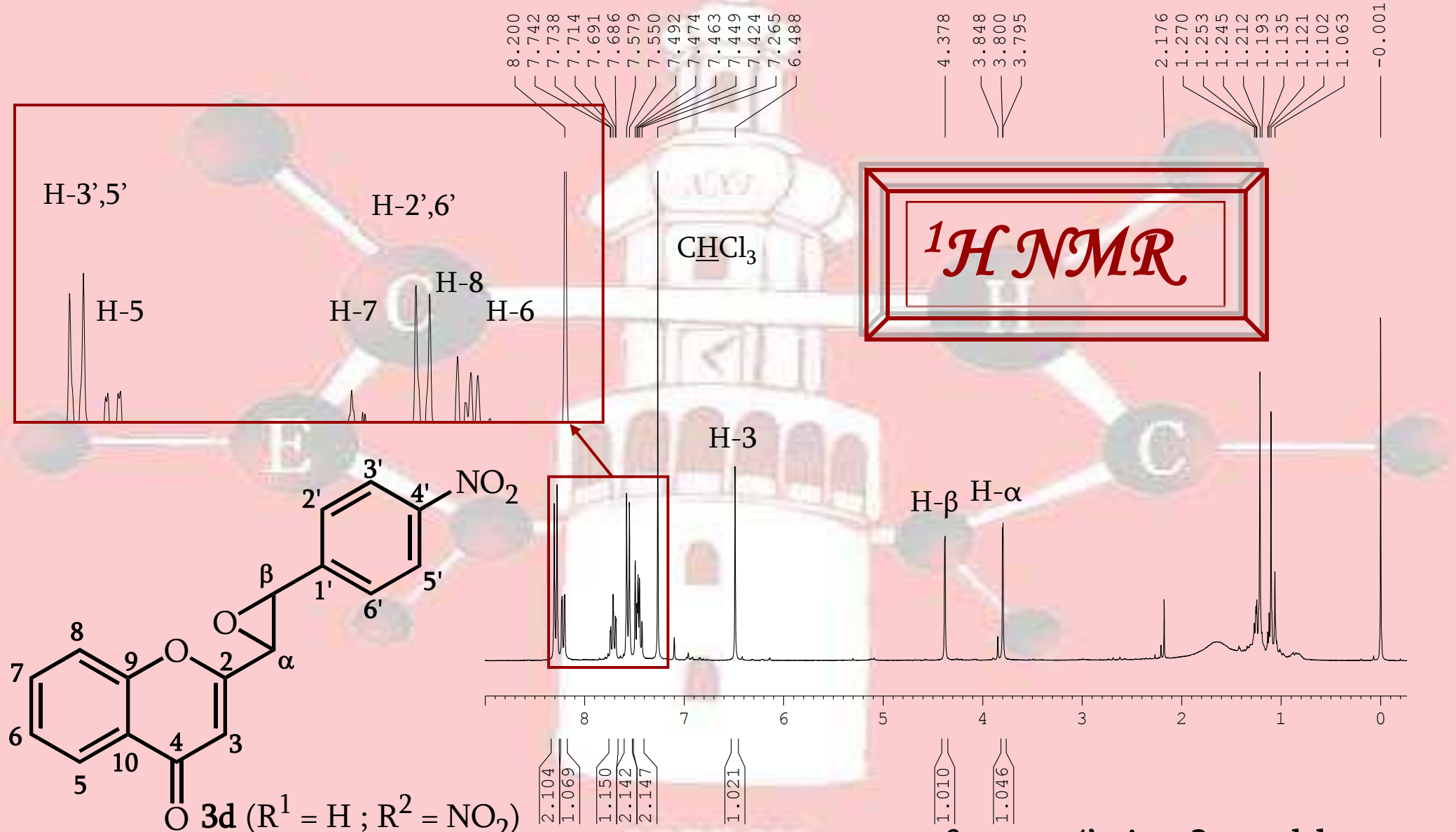
PhIO: iodosylbenzene

The best conditions obtained in the two methods are marked in grey.

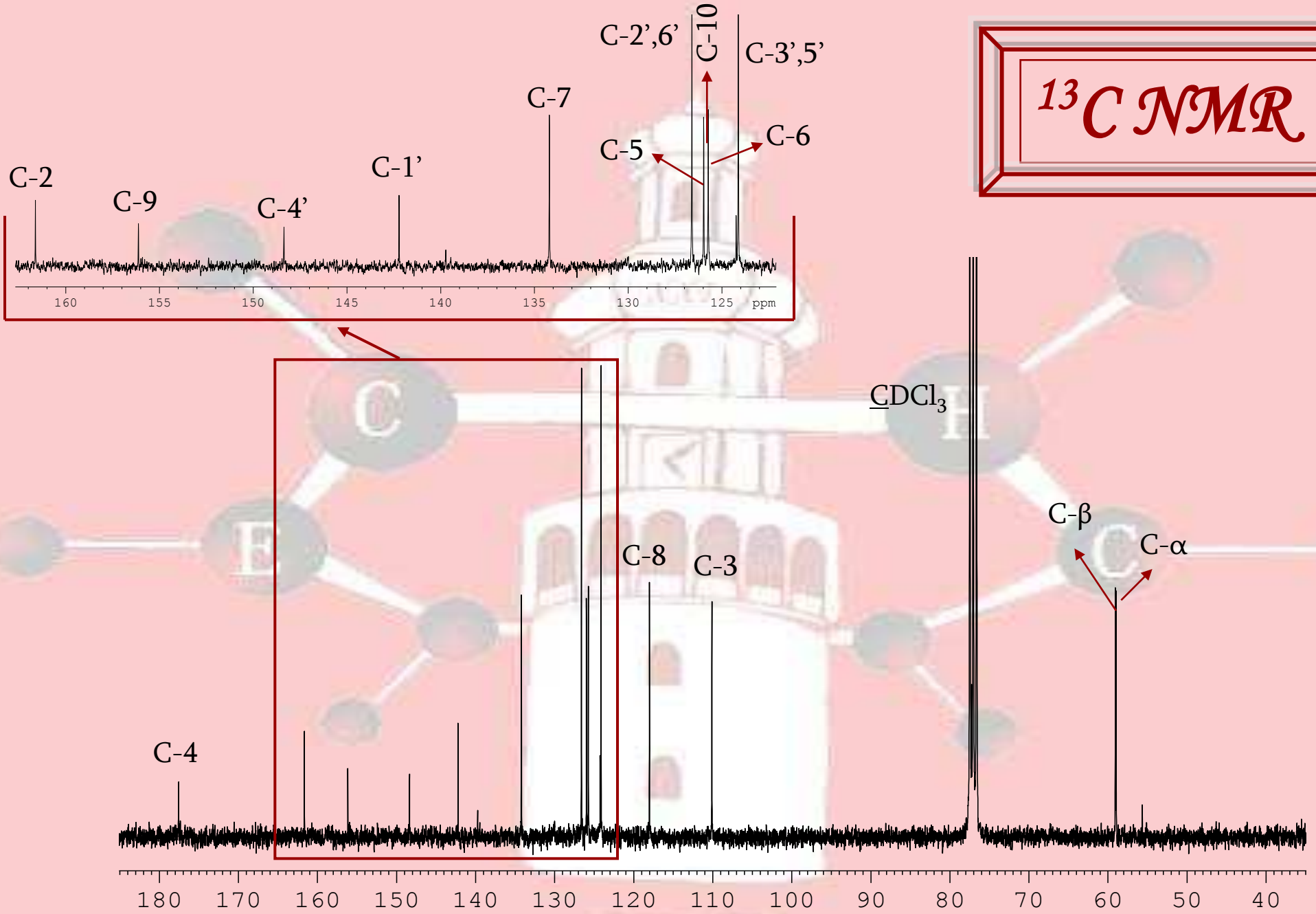
Taking into consideration the best yields obtained, we applied the conditions to the other 2-styrylchromones and the epoxy products **3** and **4** were obtained in moderate yields.

Products		H_2O_2 aq. 30% / 1-MeIm		PhIO / PyNO	
		Yield (%)	Efec. Yield (%)	Yield (%)	Efec. Yield (%)
3	a) R^2 = H	26.7	70.9	21.2	39.5
	b) R^2 = Cl	4.0	32.3	9.7	36.2
	c) R^2 = CH_3	7.6	34.7	15.3	27.0
	d) R^2= NO_2	2.7	37.2	4.4	13.1
4	a) R^2 = H	2.9	13.5	22.2	39.3
	b) R^2 = Cl	3.4	38.0	11.8	21.8
	c) R^2 = CH_3	3.3	26.6	3.8	16.2
	d) R^2 = NO_2	2.6	4.3	7.3	20.1

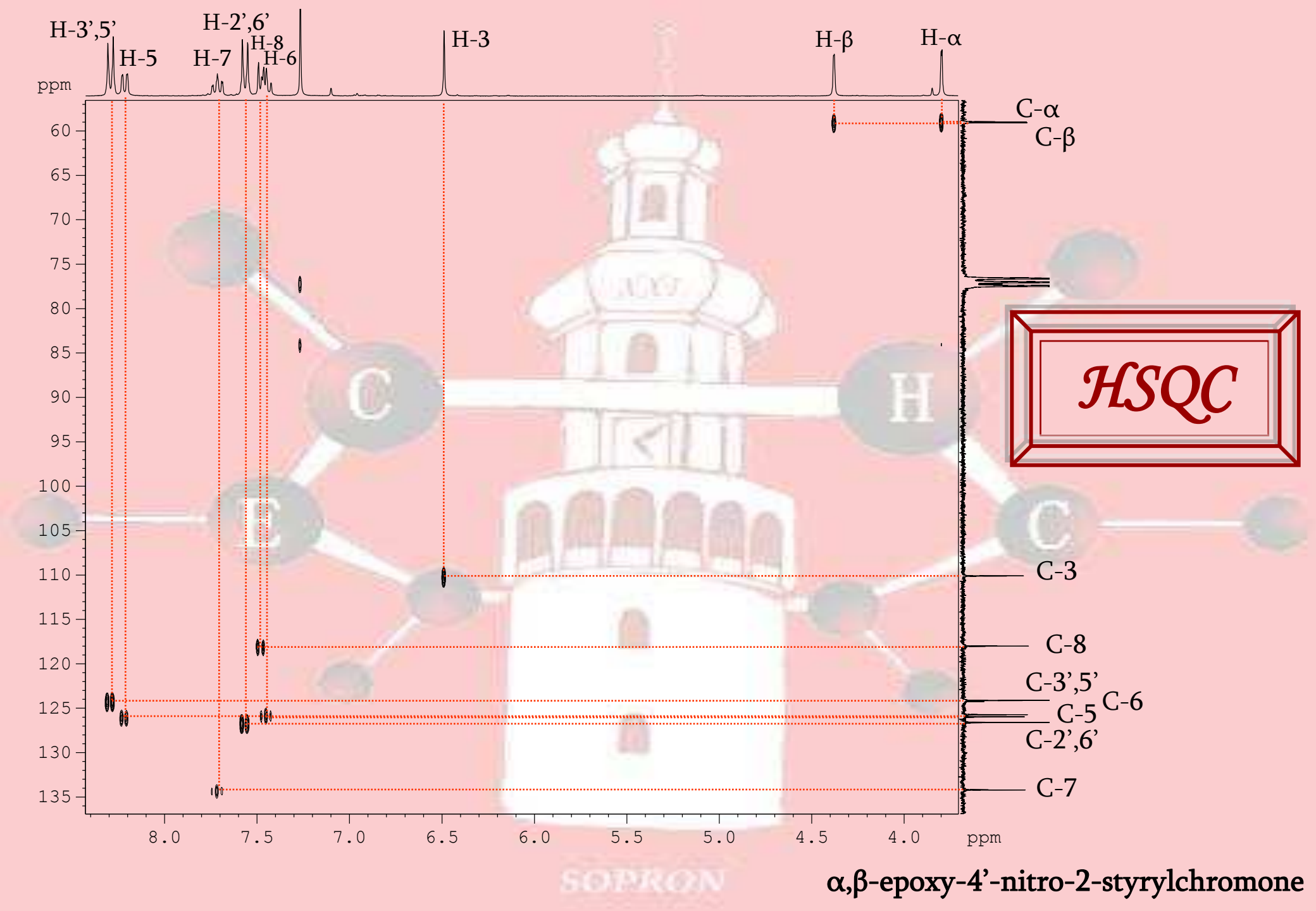
Structural elucidation



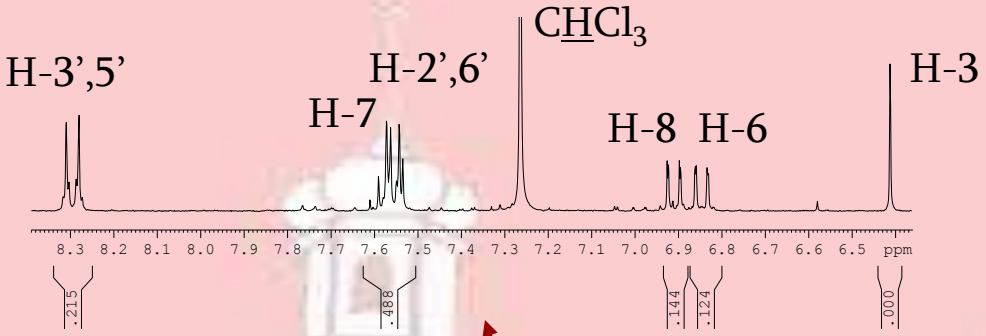
^{13}C NMR

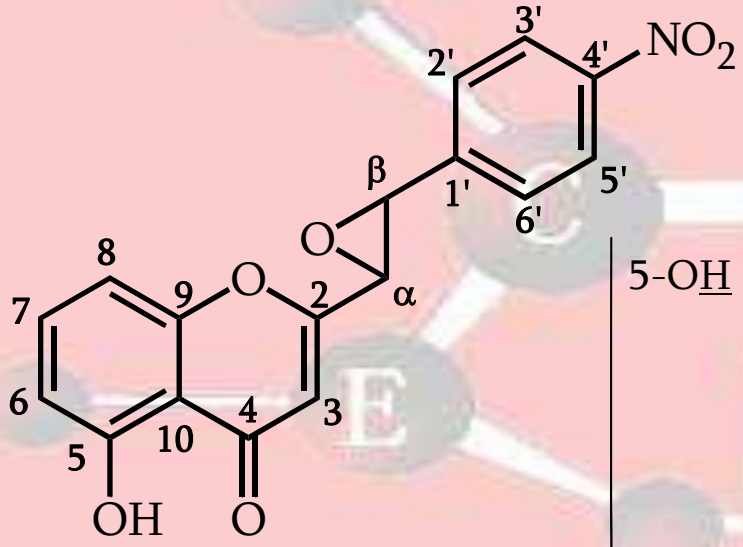


α,β-epoxy-4'-nitro-2-styrylchromone


H-3',5'
H-5
H-7
H-2',6'
H-8
H-6
H-3
H-β
H-α
ppm
C-α
C-β
C-3
C-8
C-3',5'
C-6
C-5
C-2',6'
C-7
HSQC
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
ppm
α,β-epoxy-4'-nitro-2-styrylchromone

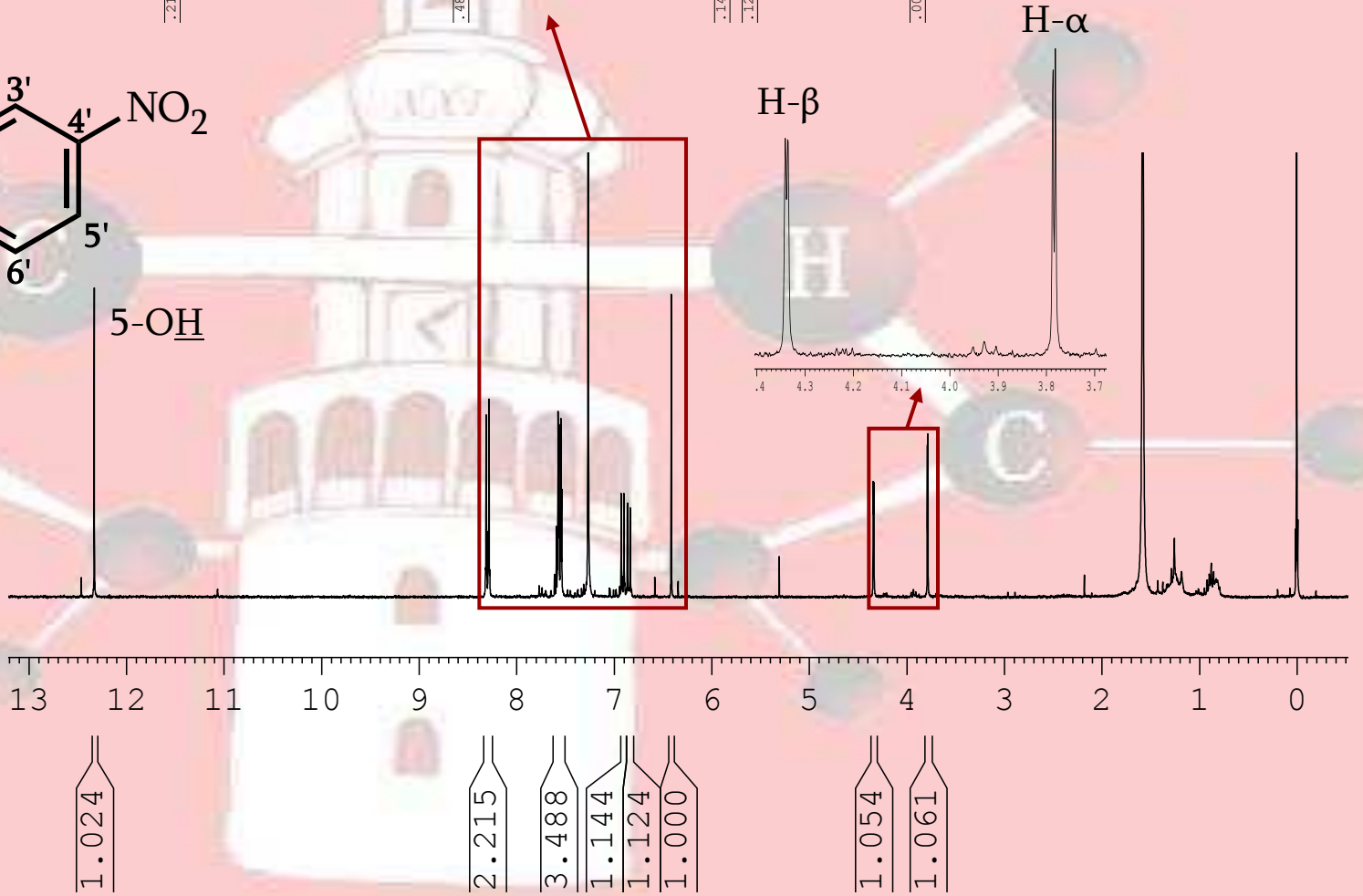
^1H NMR





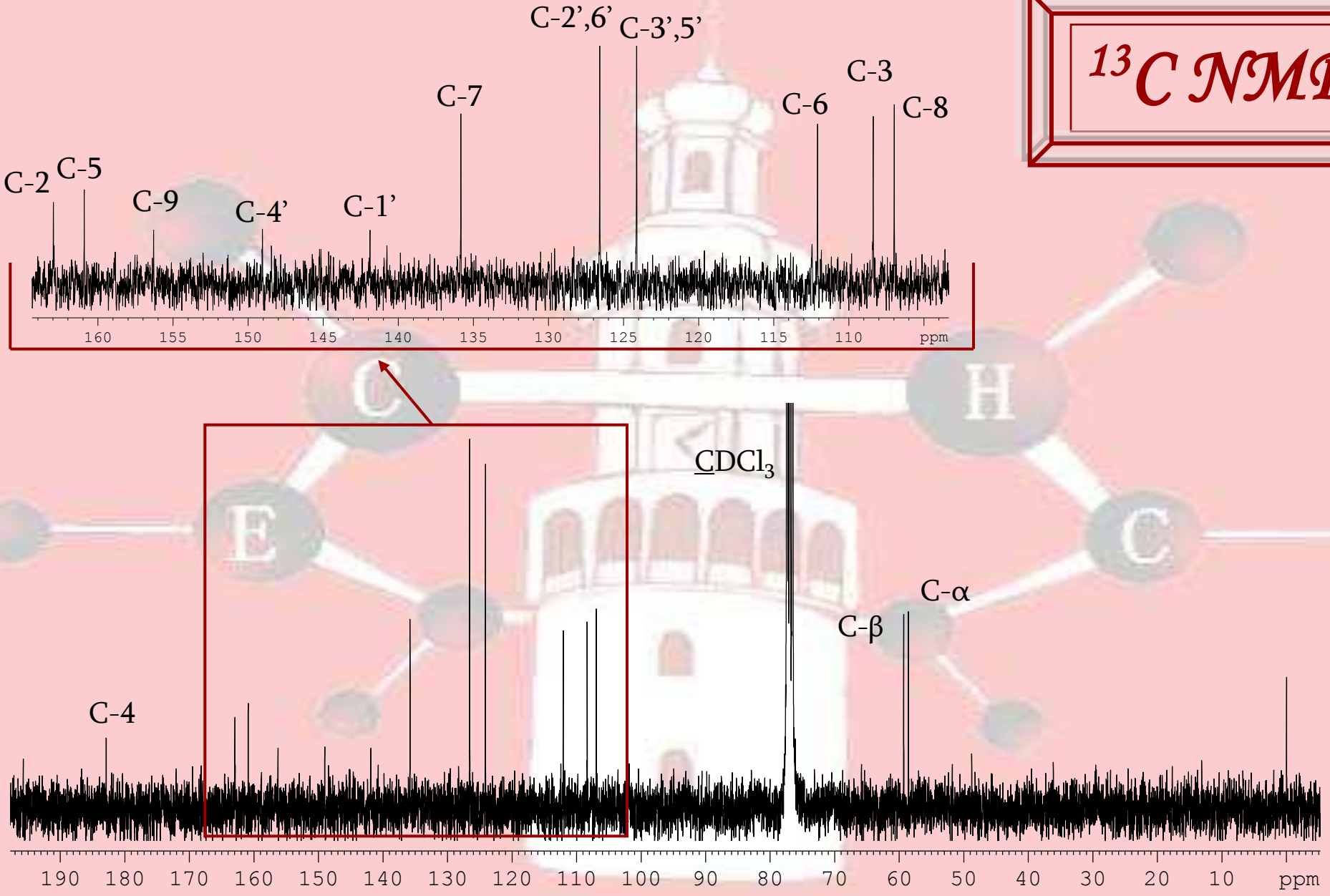
4d

(R^1 = OH ; R^2 = NO_2)

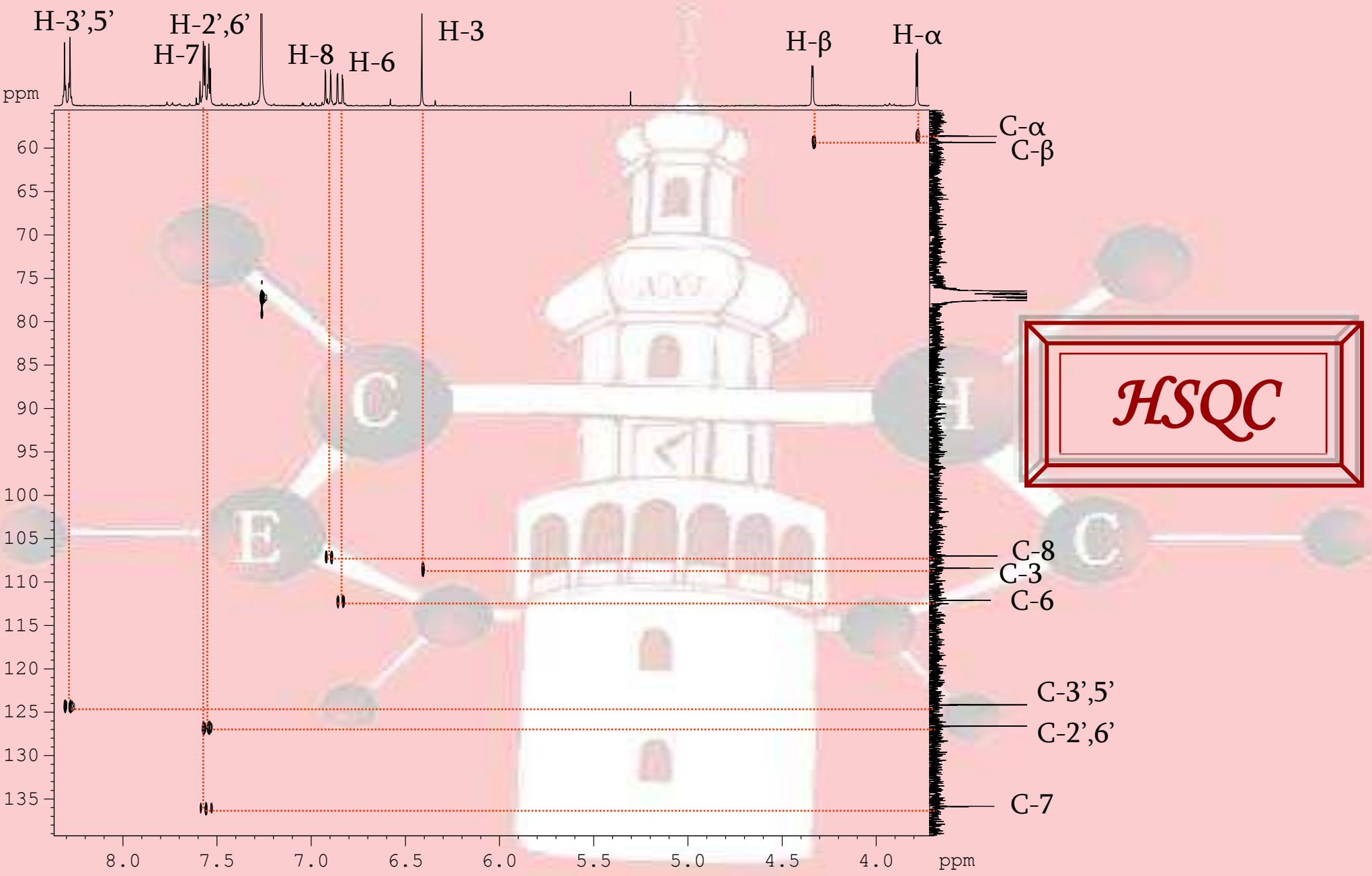


α,β-epoxy-5-hydroxy-4'-nitro-2-styrylchromone

^{13}C NMR



α,β-epoxy-5-hydroxy-4'-nitro-2-styrylchromone



α,β-epoxy-5-hydroxy-4'-nitro-2-styrylchromone

Conclusion

- The most appropriated ligant for the epoxidation with hydrogen peroxide is 1-methylimidazol while with iodosylbenzene is pyridine *N*-oxide.
- With hydrogen peroxide we used a biphasic system as solvent while with iodosylbenzene we used an organic system.
- In general, the best yields for the epoxidation of 2-styrylchromones are obtained using iodosylbenzene as oxidant but the more effective in the conversion of the substracts are the method using hydrogen peroxide.

Acknowledgements

Thanks are due to the University of Aveiro, FCT and FEDER for funding the Organic Chemistry Research Unit and the project POCTI/QUI/38394/2001. One of us (C.M.M. Santos) is also grateful to PRODEP 5.3 for finantial support.

References

1. (a) Doria G., Romeo C., Forgione A., Sberze P., Tibolla N., Corno M.L., Cruzzola G., Cadelli G., *Eur. J. Med. Chem. - Chim. Ther.* **1979**, *14*, 347. (b) Gerwick W.H., Lopez A., Van Duyne G.D., Clardy J., Ortiz W., Baez A., *Tetrahedron Lett.*, **1986**, *27*, 1979; (c) Gerwick W.H., *J. Nat. Prod.* **1989**, *52*, 252; (d) Desideri N., Conti C., Mastromarino P., Mastropaolo F., *Antiviral Chem. Chemother.* **2000**, *11*, 373.

2. (a) Fernandes E., Carvalho F., Silva A.M.S., Santos C.M.M., Pinto D.C.G.A., Cavaleiro J.A.S., Bastos M.L., *J. Enz. Inhib.*, **2002**, *17*, 45; (b) Fernandes E., Carvalho M., Carvalho F., Silva A.M.S., Santos C.M.M., Pinto D.C.G.A., Cavaleiro J.A.S., Bastos M.L., *Arch. Toxicol.*, **2003**, *77*, 500; c) Filipe P., Silva A.M.S., Morliére P., Brito C.M., Patterson, L.K., Hug G.L., Silva J.N., Cavaleiro J.A.S., Maziére, J-C, Freitas J.P., Santus R., *Biochem. Pharmacol.*, **2004**, *67*, 2207.