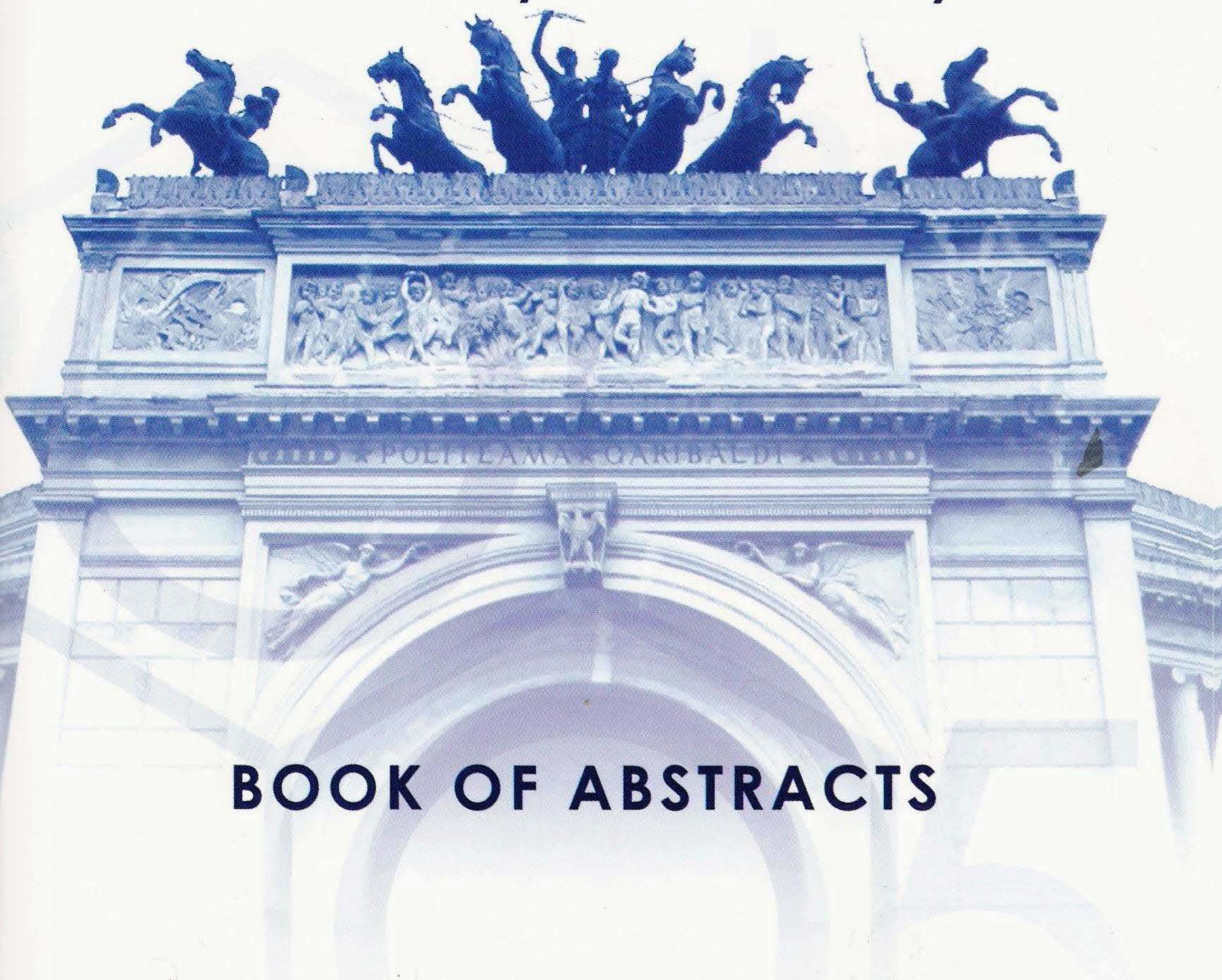
20th ICHC 05 PALERMO

20th International Congress of Heterocyclic Chemistry



BOOK OF ABSTRACTS

July 31 - August 5, 2005

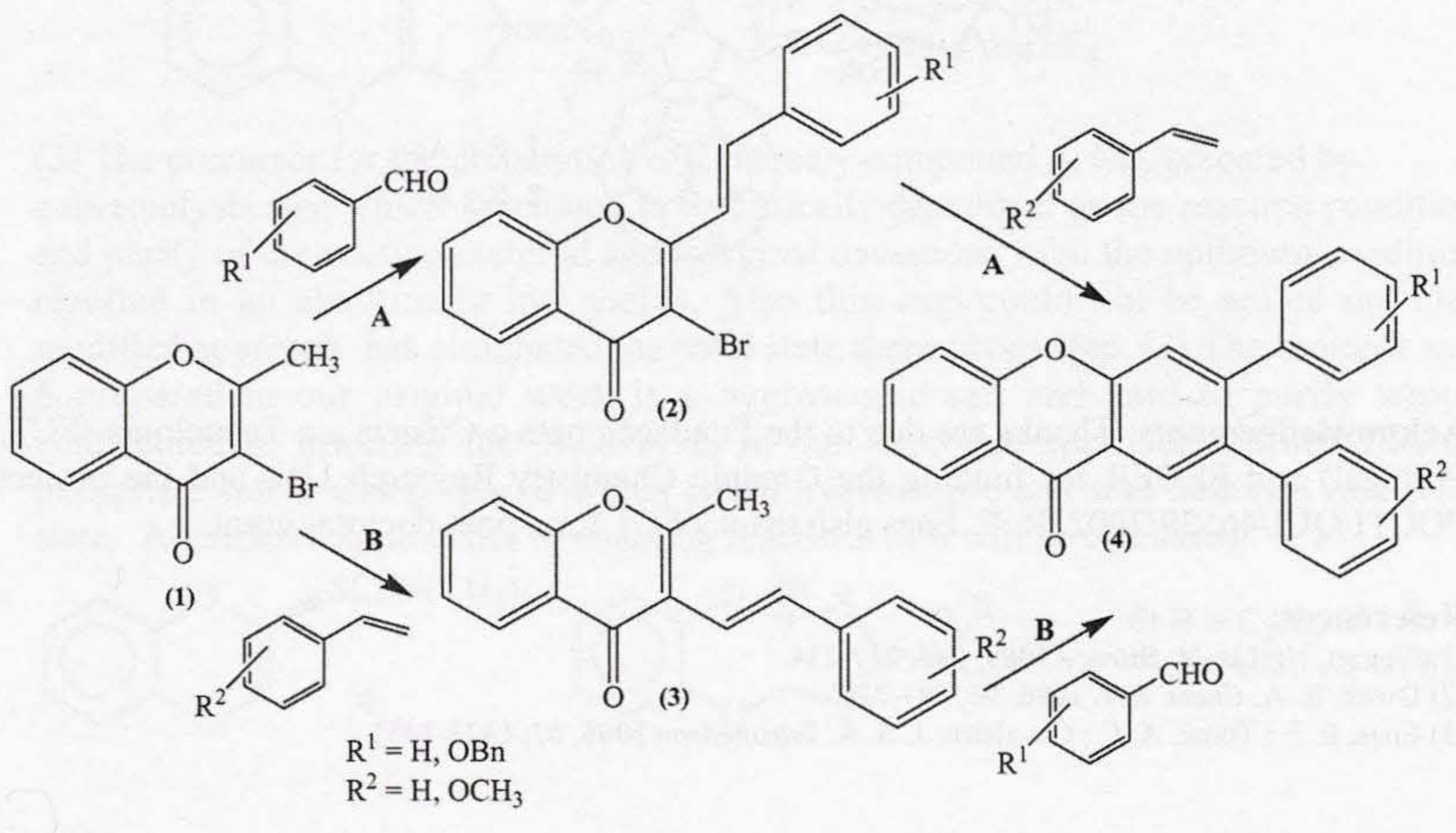
Palermo - ITALY

Syntheses of new xanthone derivatives

[1,2]Clementina M. M. Santos, [2]Artur M. S. Silva, [2]José A. S. Cavaleiro

[1]Department of Agro-Industries, Escola Superior Agrária de Bragança, 5301-855 Bragança, Portugal
[2]Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal
clems@dq.ua.pt

Xanthones are a class of heterocyclic compounds widely distributed in the plant kingdom (1). Since a long time ago, compounds with the xanthone core are of great interest for chemists, biologists and pharmacologists due to their potencial biological properties. Certain natural and synthetic derivatives have shown important anti-fungal, anti-tumour, anti-inflammatory as well as antioxidant activities (1,2).
We report were the synthesis of new xanthones **4** starting from the 3-bromo-2-methylchromone **1** with two different routes: **A**: Aldol condensation of **1** with benzaldeydes leading to the formation of 3-bromo-2-styrylchromones **2** followed of Heck reaction with styrenes, and **B**: Heck reaction of **1** with styrenes leading to the formation of 2-methyl-3-styrylchromones **3** followed of Aldol condensation with benzaldeydes. Experimental procedures and spectroscopic characterization of xanthones **4** and of all the intermediates will be presented and discussed.



R^1 = H, OBn
R^2 = H, OCH_3

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) Hostettman, K.; Hostettman, M. in Methods in Plant Biochemistry, Vol. 1 – Plant Phenolics, Ed. P. M. Dey, J. B. Harbone, Academic Press, **1989**, pp. 493.
(2) (e.g.) Bennett, G. J.; Lee, H.-H. *Phytochemistry* **1989**, *28*, 967-998; Minami, H.; Kinoshita, M.; Fukuyama, Y.; Komoda, M.; Yoshizawa, T.; Sugiura, M.; Nakagawa, K.; Tago, H. *Phytochemistry* **1994**, *36*, 501-511; Abdel-Lateff, A.; Klemke, C.; König, G. M.; Wright, A. D. *J. Nat. Prod.* **2003**, *66*, 706-708; Chiang, Y.-M.; Kuo, Y.-H.; Oota, S.; Fukuyama, Y. *J. Nat. Prod.* **2003**, *66*, 1070-1073.

Syntheses of new xan

Clementina M. M. Santos,[a,b] Artur M.

[a]Department of Agro-Industries, Escola

5301-855 Bragança,

[b]Department of Chemistry, University of

Escola Superior Agrária de Bragança
INSTITUTO POLITÉCNICO DE BRAGANÇA

thones derivatives

S. Silva,[b] José A. S. Cavaleiro,[b]

Superior Agrária de Bragança,

Portugal

Aveiro, 3810-193 Aveiro, Portugal

Introduction

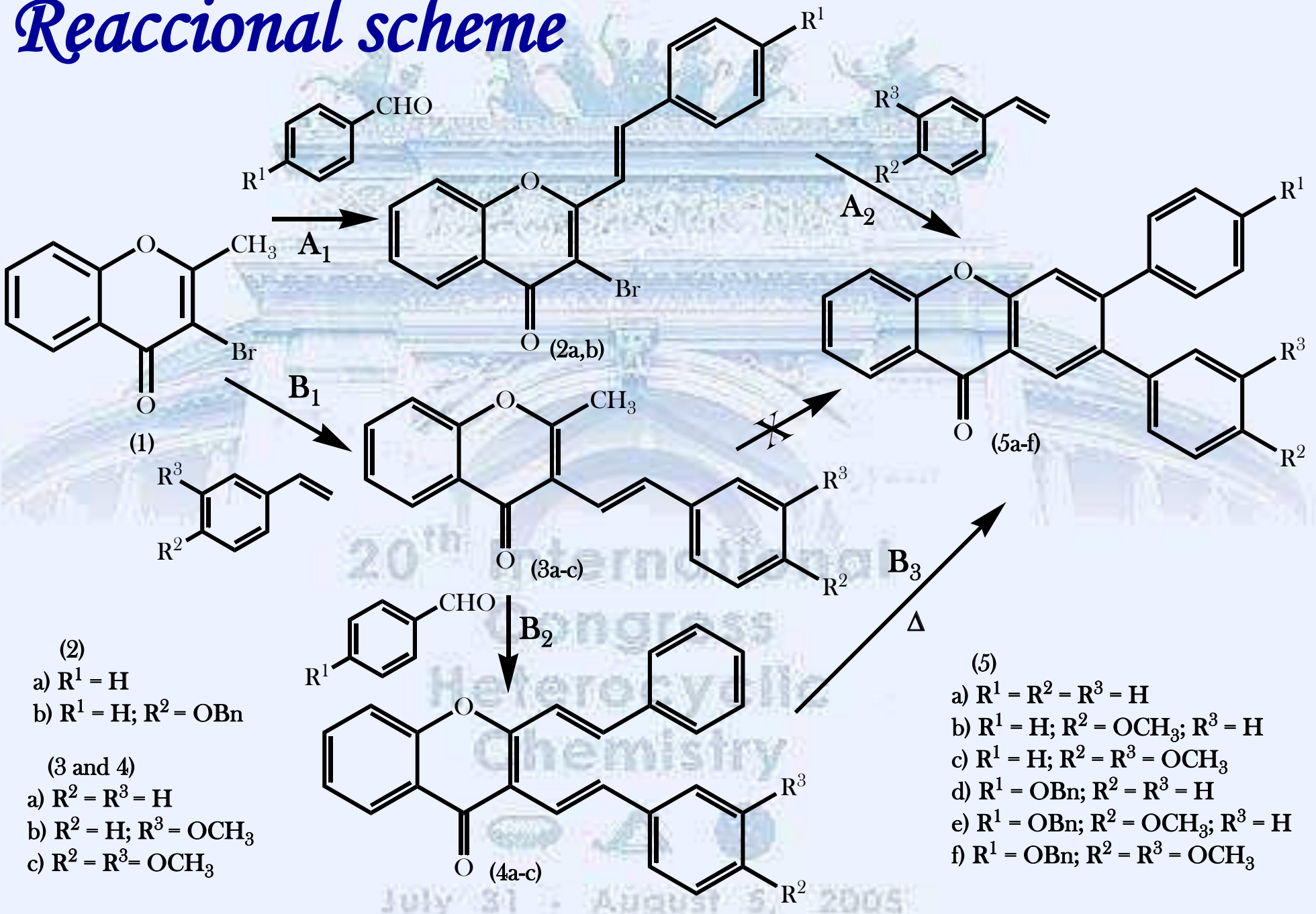
❋Xanthones are a class of heterocyclic compounds widely distributed in the plant kingdom (1). Since a long time ago, compounds with the xanthone core are of great interest for chemists, biologists and pharmacologists due to their potencial biological properties.

❋Certain natural and synthetic derivatives have shown important anti-fungal, anti-tumour, anti-inflammatory as well as antioxidant activities (1,2).

❋We report were the synthesis of new xanthones **5** starting from the 3-bromo-2-methylchromone **1** with two different routes (A and B).

❋Experimental procedures and spectroscopic characterization of xanthones *5* and of all the intermediates are presented and discussed.

Reaccional scheme



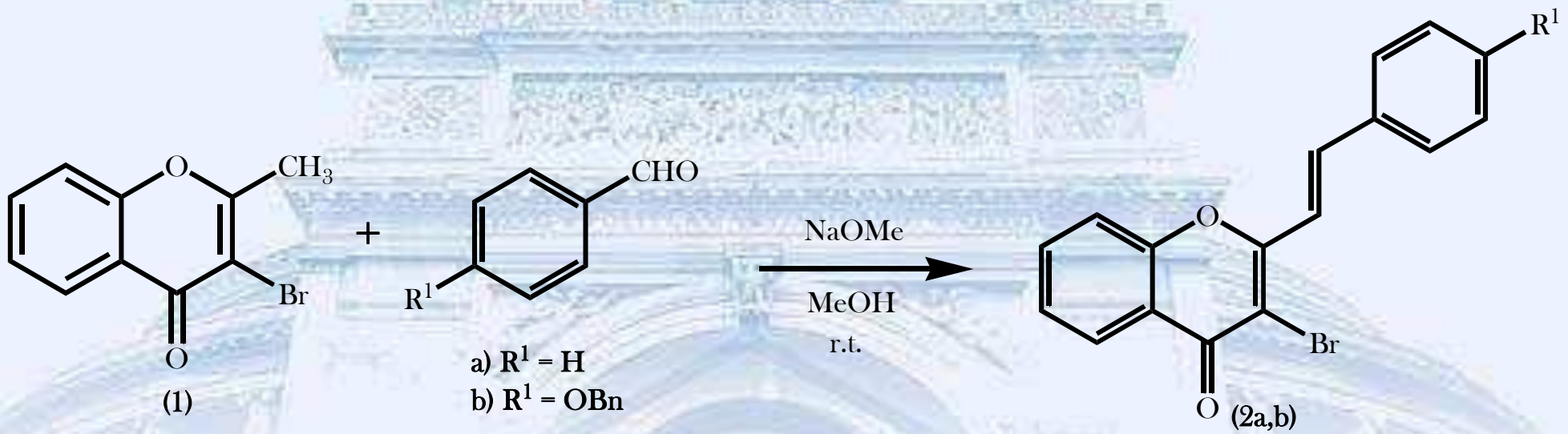
(2)
a) $R^1 = H$
b) $R^1 = H$; $R^2 = OBn$

(3 and 4)
a) $R^2 = R^3 = H$
b) $R^2 = H$; $R^3 = OCH_3$
c) $R^2 = R^3 = OCH_3$

(5)
a) $R^1 = R^2 = R^3 = H$
b) $R^1 = H$; $R^2 = OCH_3$; $R^3 = H$
c) $R^1 = H$; $R^2 = R^3 = OCH_3$
d) $R^1 = OBn$; $R^2 = R^3 = H$
e) $R^1 = OBn$; $R^2 = OCH_3$; $R^3 = H$
f) $R^1 = OBn$; $R^2 = R^3 = OCH_3$

Method A

A_1 – Synthesis of 3-bromo-2-styrylchromones (3a-c)



❋The 3-bromo-2-methylchromone is synthetized according to the literature* and involves 3 steps:

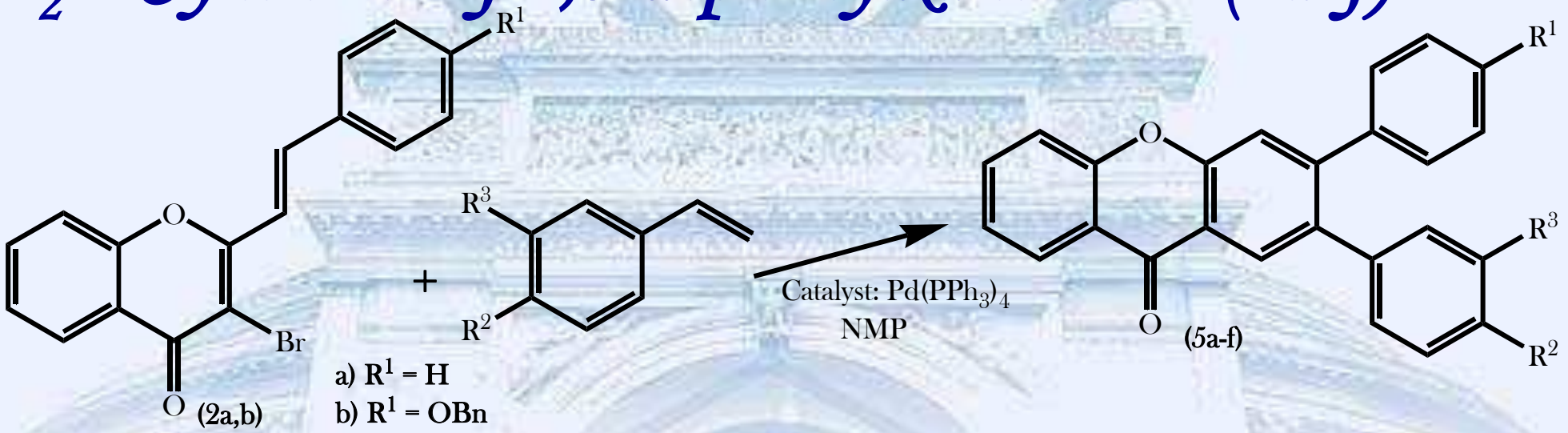
1.Acetylation of 2'-hydroxy-acetophenone
2.Transposition of the acetyl group
3.Bromination and cyclization

❋The hydroxyl group of 4-hydroxybenzaldeyde must be protected. In this case, we used benzyl chloride, K_2CO_3, DMF.

Base (eq.)	Time (h)	2a (%)	2b (%)
4	2	54.8	51.7
4	12	55.8	52.2
4	24	61.2	52.7
4	48	87.3	68.2
4	72	49.0	48.9

*Ind. Eng. Chem. Res., **2001**, *40*, 37-39.

A_2 – Synthesis of 2,3-diphenylxanthones (5a-f)



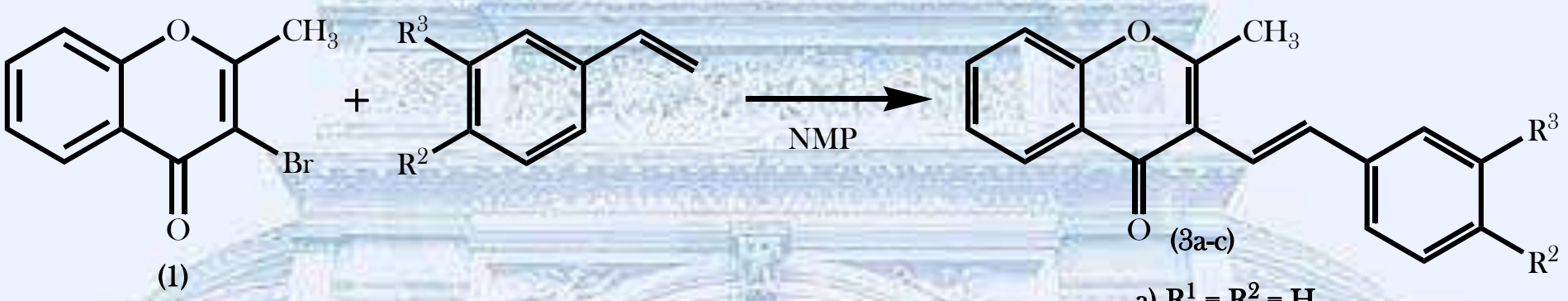
a) R^1 = H
b) R^1 = OBn

After an extensive study of the reacion conditions (base, phosphine, catalyst, solvent) we describe only the best conditions/yields in the Heck reaction:

Compound	Et_3N (eq.)	PPh_3 (eq.)	Catalyst (eq.)	Styrene (eq.)	Conditions	Yield (%)
5a	4	0.1	0.05	5	160°C; 6h	55.6
5b	4	0.1	0.05	5	reflux; 3h	49.1
5c	1	0.1	0.05	2	160°C; 12h	45.2
5d	1	0.1	0.05	5	reflux; 6h	50.7
5e	4	0.1	0.05	5	reflux; 6h	65.8
5f	1	0.1	0.05	5	reflux; 3h	19.5

(5)
a) $R^1 = R^2 = R^3 = H$
b) $R^1 = H$; $R^2 = OCH_3$; $R^3 = H$
c) $R^1 = H$; $R^2 = R^3 = OCH_3$
d) $R^1 = OBn$; $R^2 = R^3 = H$
e) $R^1 = OBn$; $R^2 = OCH_3$; $R^3 = H$
f) $R^1 = OBn$; $R^2 = R^3 = OCH_3$

B_1 – Synthesis of 2-methyl-3-styrylchromones (2a,b)



a) $R^1 = R^2 = H$
b) $R^1 = OCH_3$; $R^2 = H$
c) $R^1 = R^2 = OCH_3$

In this reaction, we also tried several conditions do obtain the 2-methyl-3-styrylchromones (3a-c).

We describe below an interesting study of the catalyst effect in the reaction of (1) with styrene.

Catalyst (0.05 eq.)	Et_3N (eq.)	PPh_3 (eq.)	Styrene (eq.)	Conditions	Yield (%)
$Pd(PPh_3)_4$	1	0.1	5	160°C; 9h	47.9
$Pd(PPh_3)Cl_2$	1	0.1	5	160°C; 9h	38.8
$PdCl_2$	1	0.1	5	160°C; 9h	48.4
$Pd(OAc)_2$	1	0.1	5	160°C; 9h	46.2

Applying the conditions described for the $Pd(PPh_3)_4$ catalyst in the reaction of (1) with the other styrenes, we have the following results.

Compound	Yield (%)
3a	48.4
3b	49.1
3c	51.5

Method B

$B_{2\ and\ 3}$ – Synthesis of 2,3-distyrylchromones (4a-c) and 2,3-diphenylxanthones (5a,b)

In this method, the synthesis of 2,3-diphenylxanthones involves the formation of 2,3-distyrylchromones followed by cyclization of (4a-c) with high temperature.

The oxidative electrocyclization gave the desired 2,3-diphenylxanthones (5a-c).

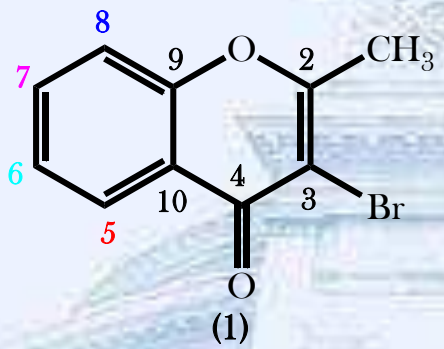
Compound	Yield (%)
4a	52.9
4b	57.6
4c	67.1

Compound	Yield (%)
5a	65.8
5b	54.5
5c	36.8

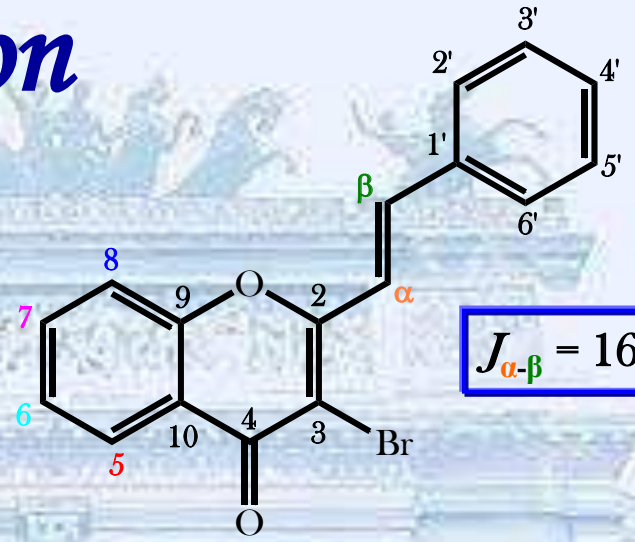
a) $R^1 = R^2 = H$
b) $R^1 = OCH_3$; $R^2 = H$
c) $R^1 = R^2 = OCH_3$

Structural elucidation

^1H NMR



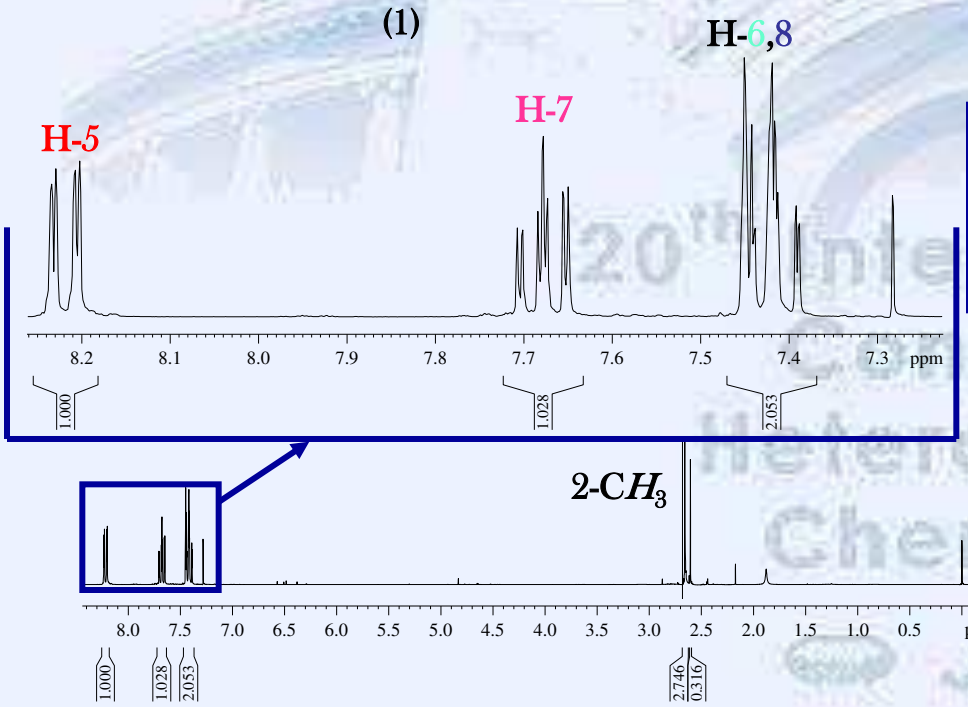
(1)



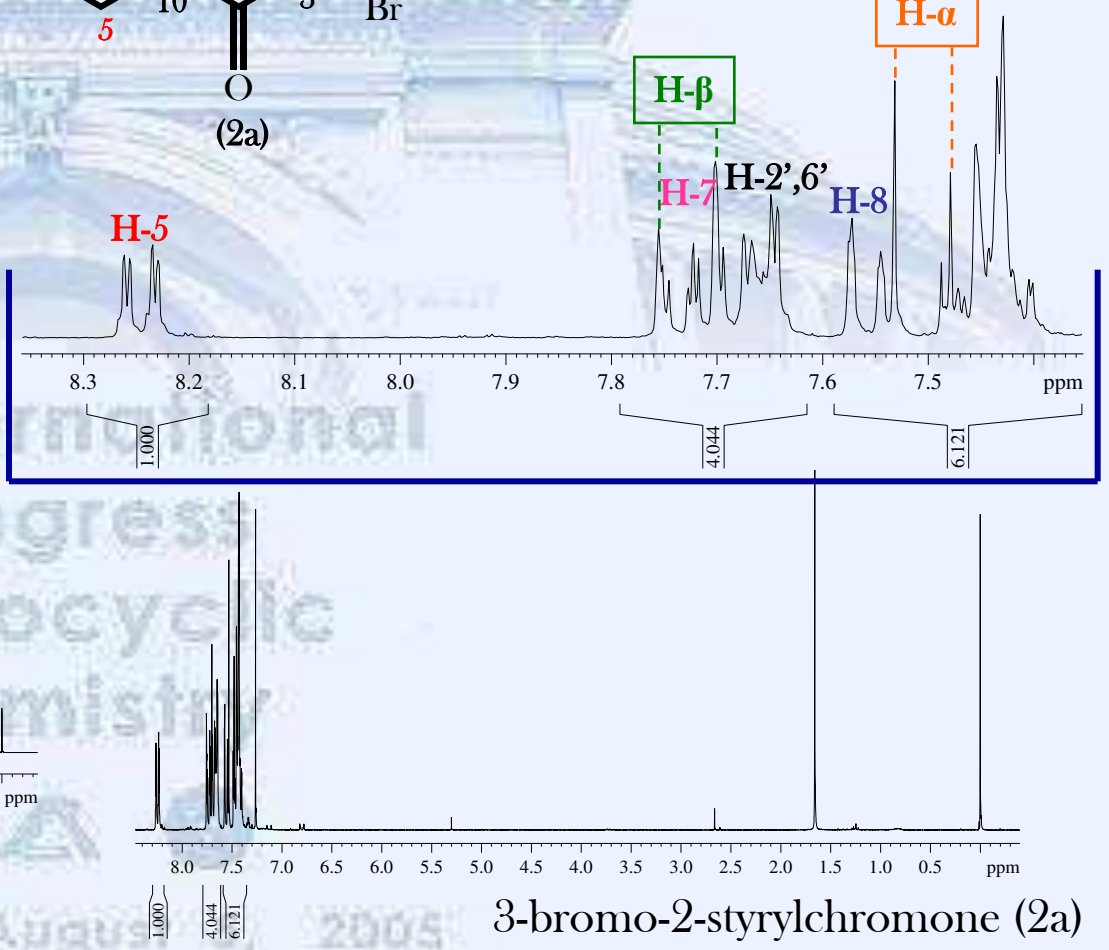
(2a)

E Configuration

$J_{\alpha\text{-}\beta}$ = 16 Hz

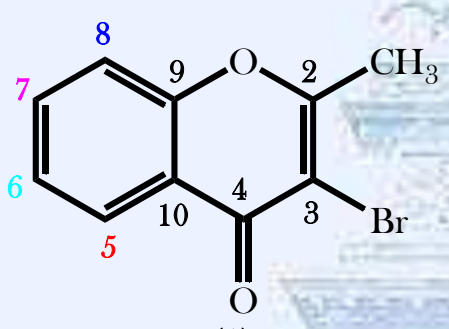


3-methyl-2-bromochromone (1)



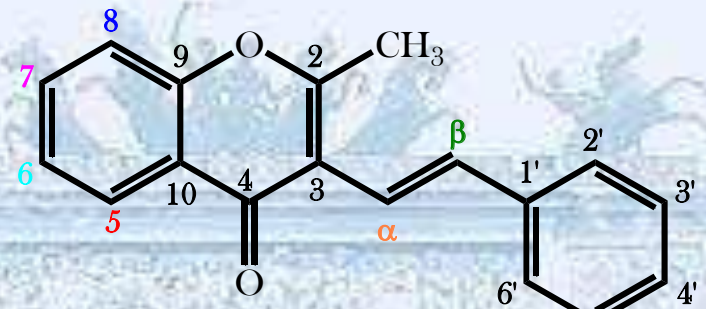
3-bromo-2-styrylchromone (2a)

^1H NMR



(1)

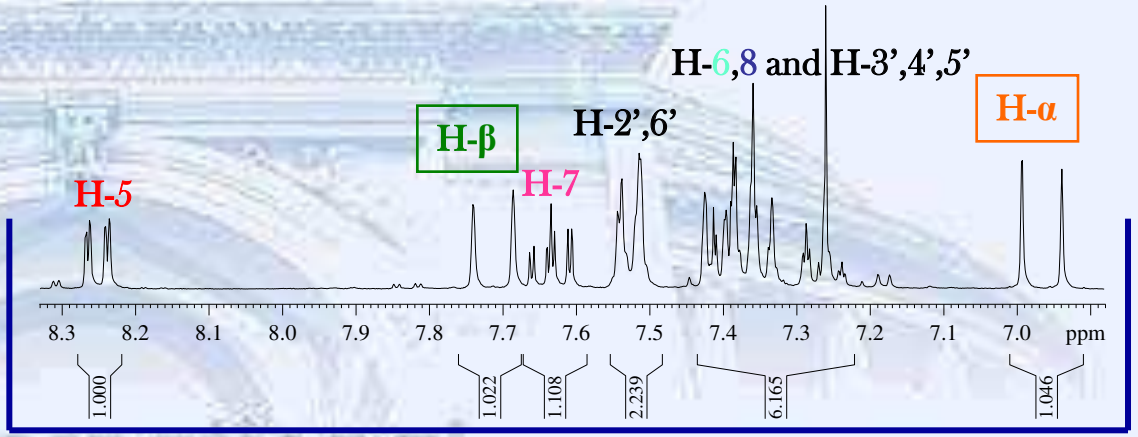
3-methyl-2-bromochromone (1)

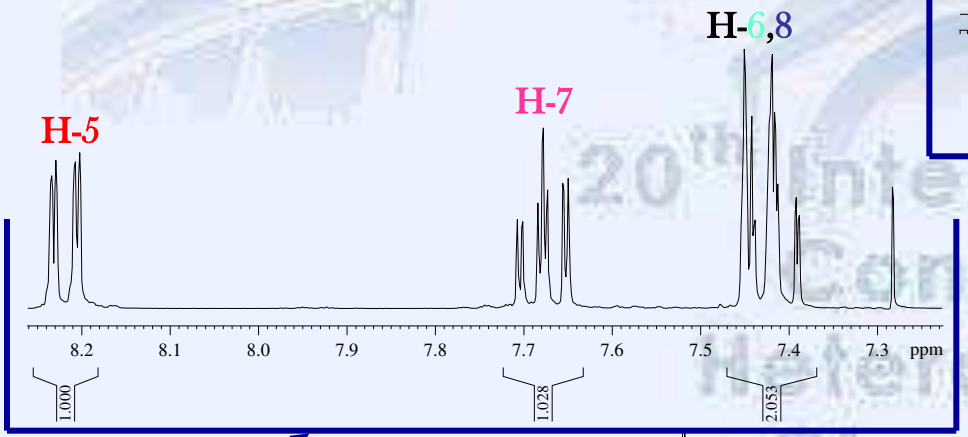


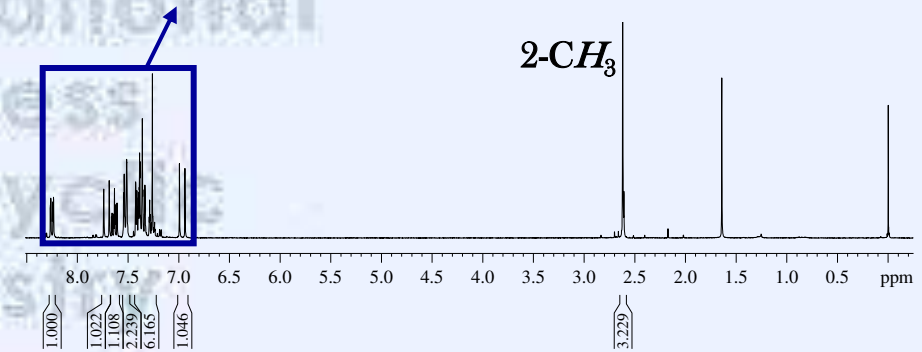
(3a)

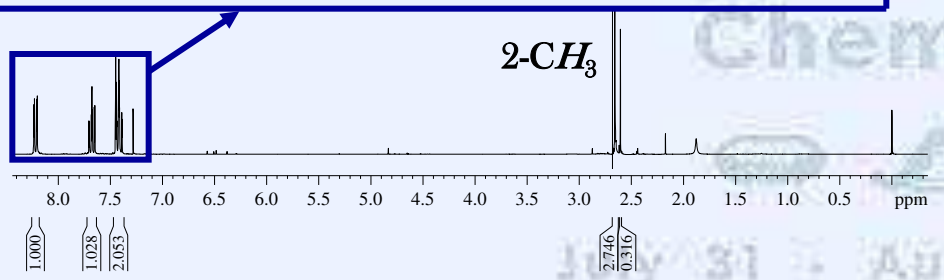
E Configuration

$J_{\alpha\text{-}\beta}$ = 16 Hz

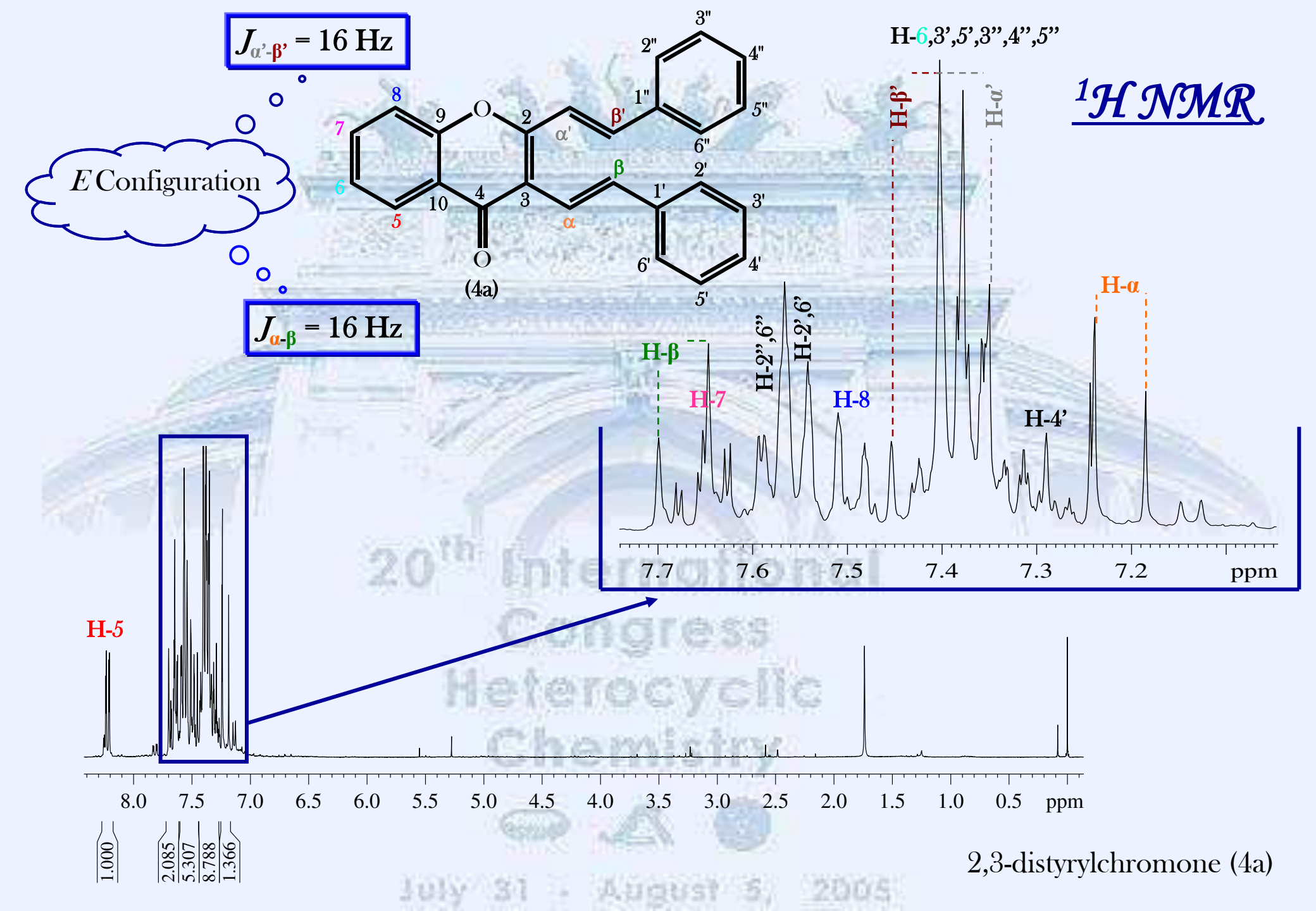








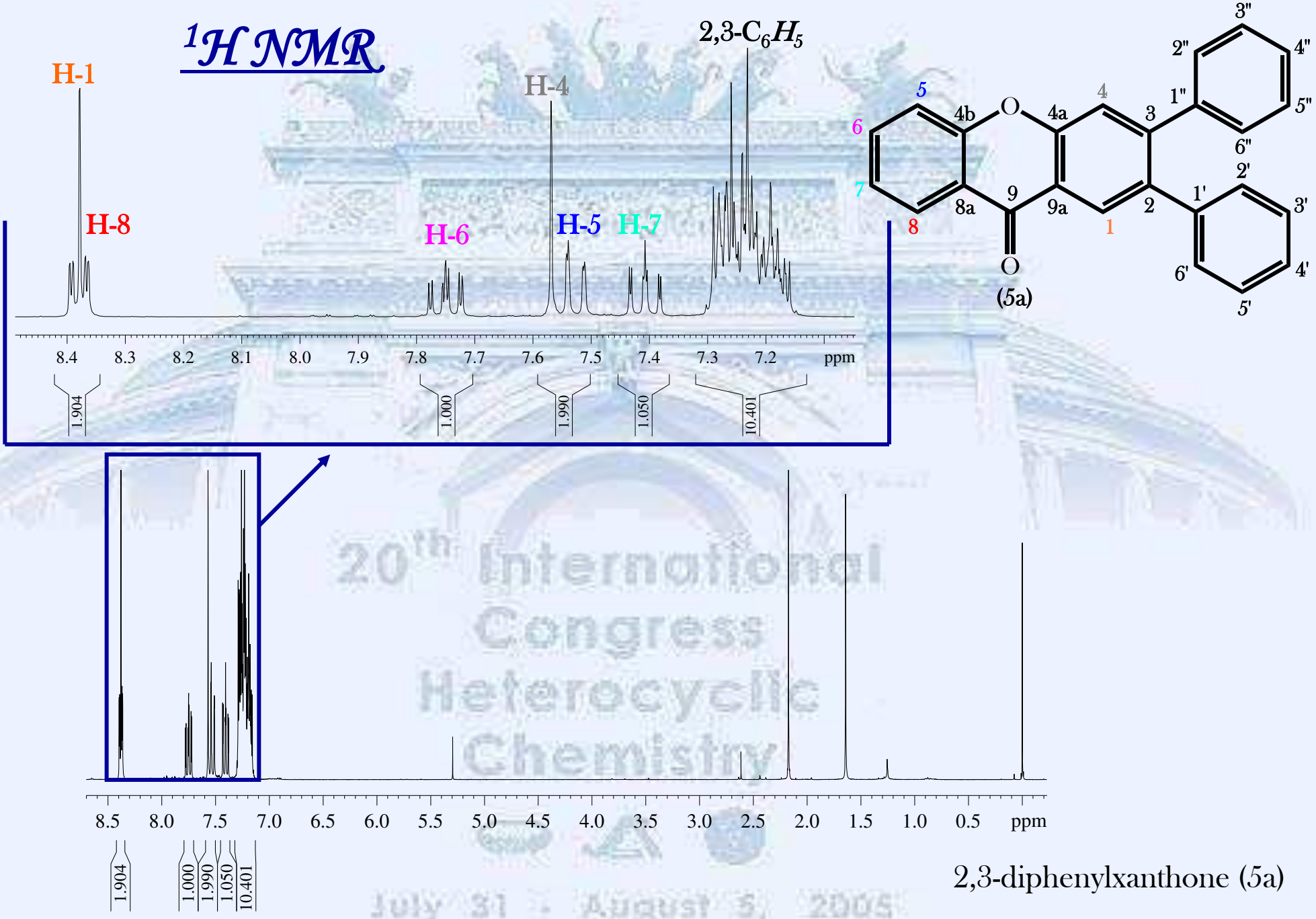
2-methyl-3-styrylchromone (3a)



^1H NMR

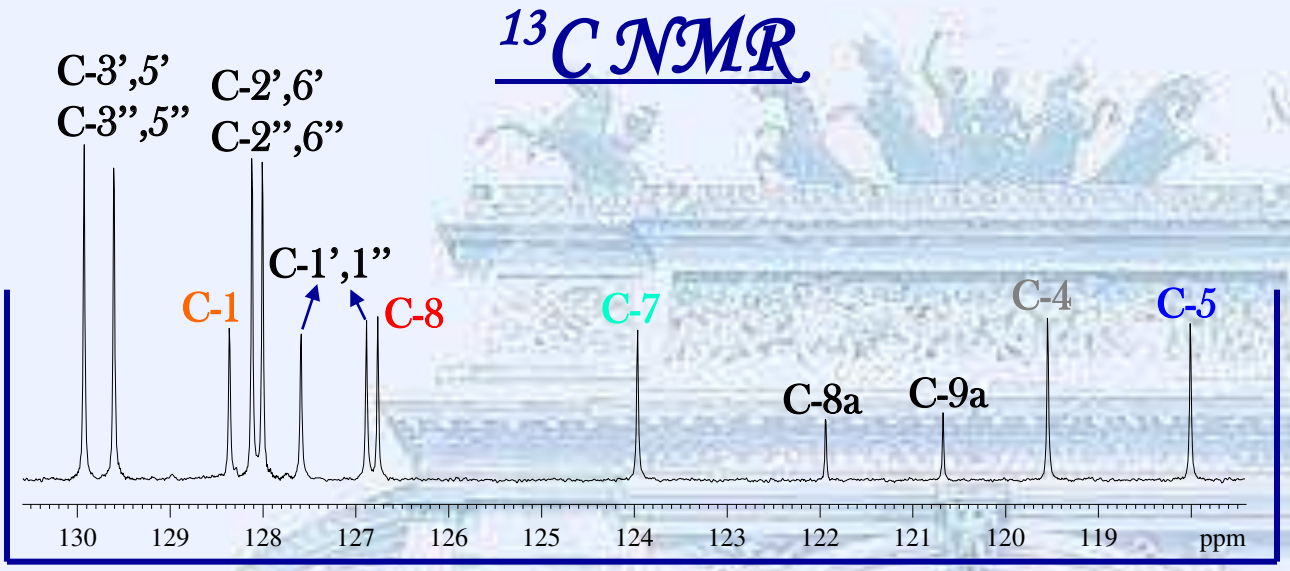
2,3-distyrylchromone (4a)

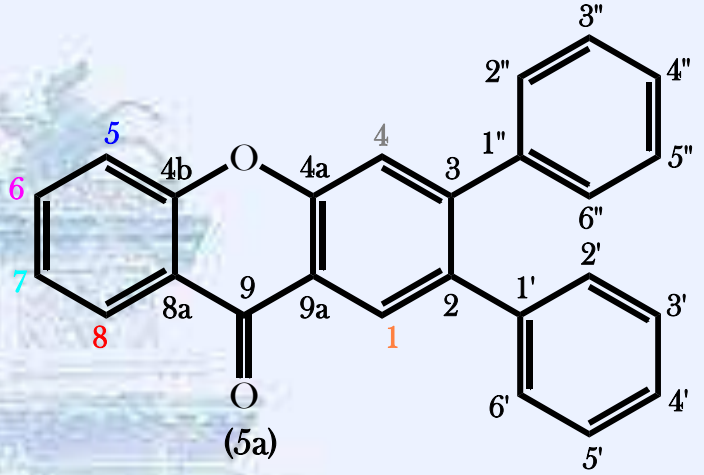
^1H NMR

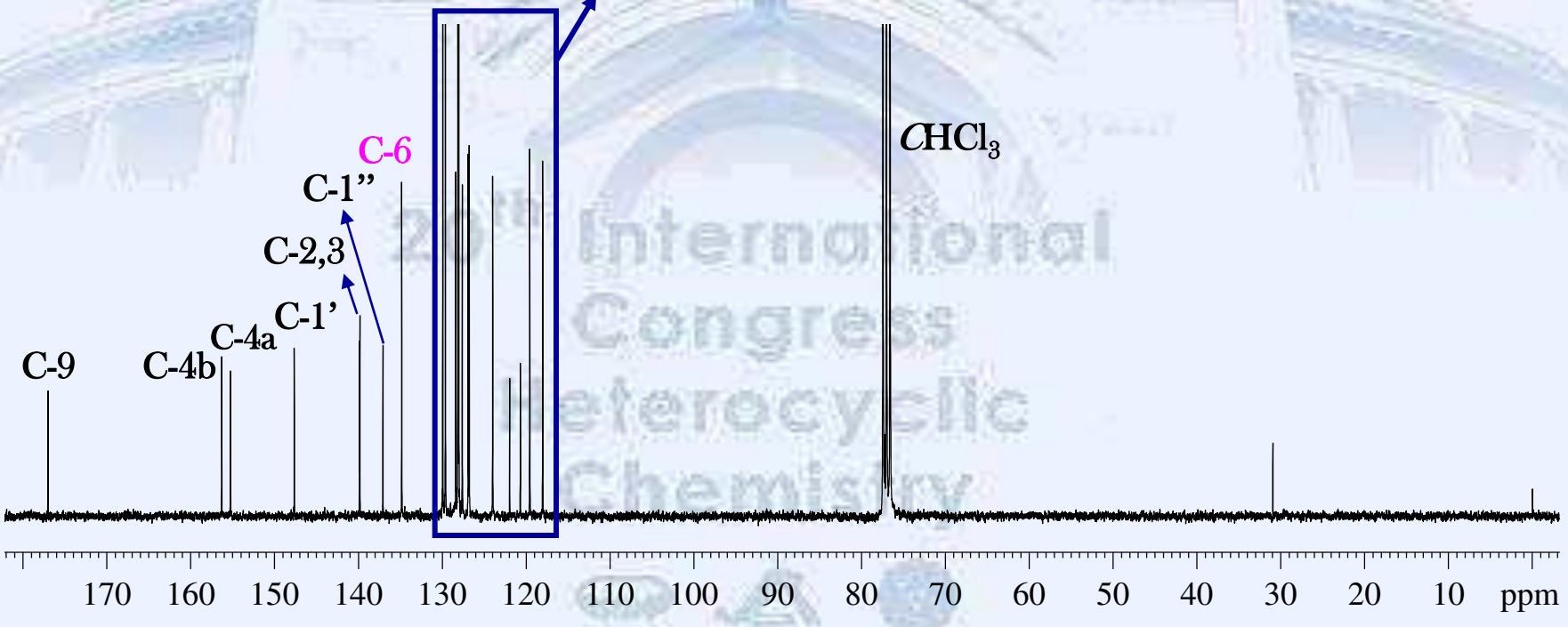


2,3-diphenylxanthone (5a)

^{13}C NMR

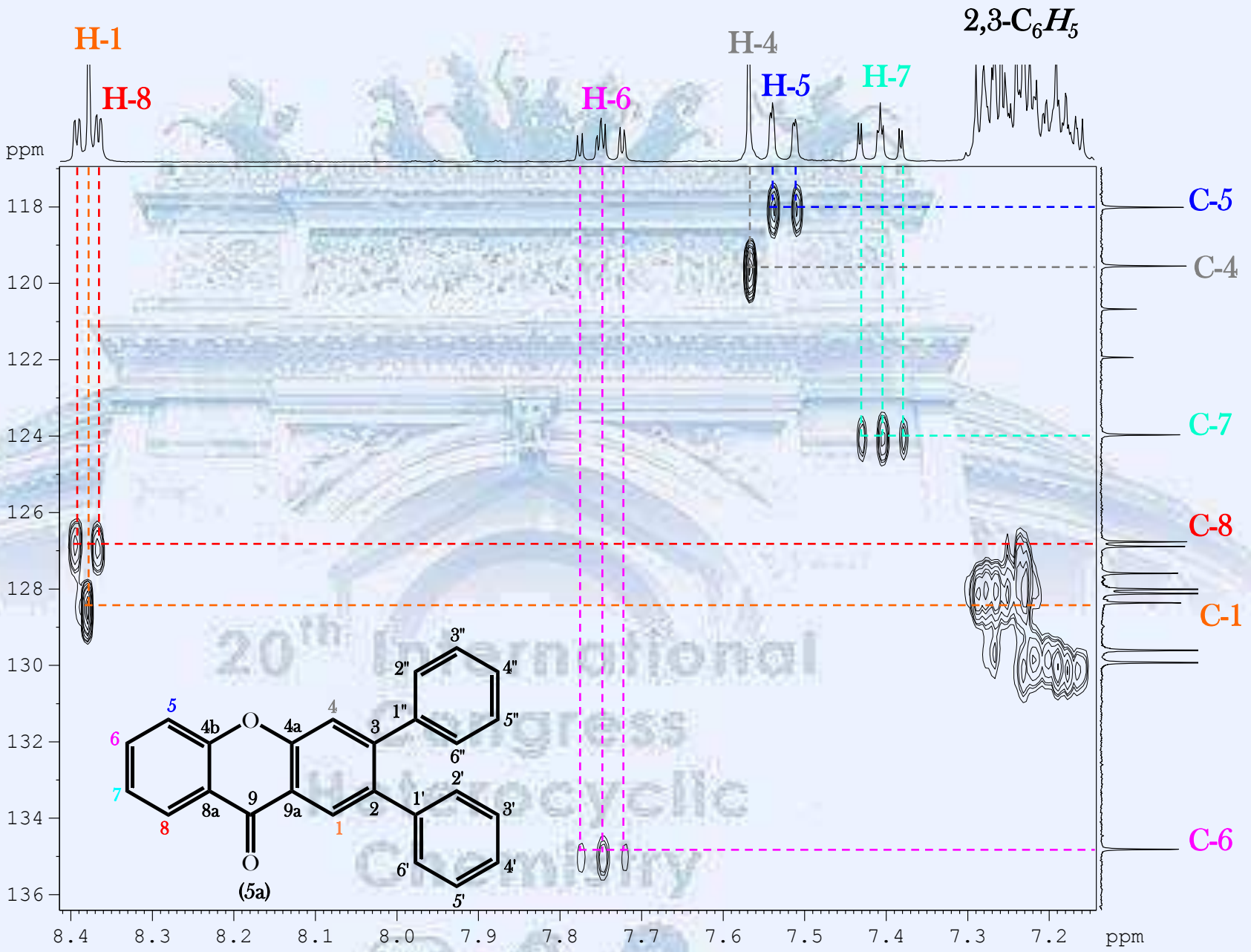




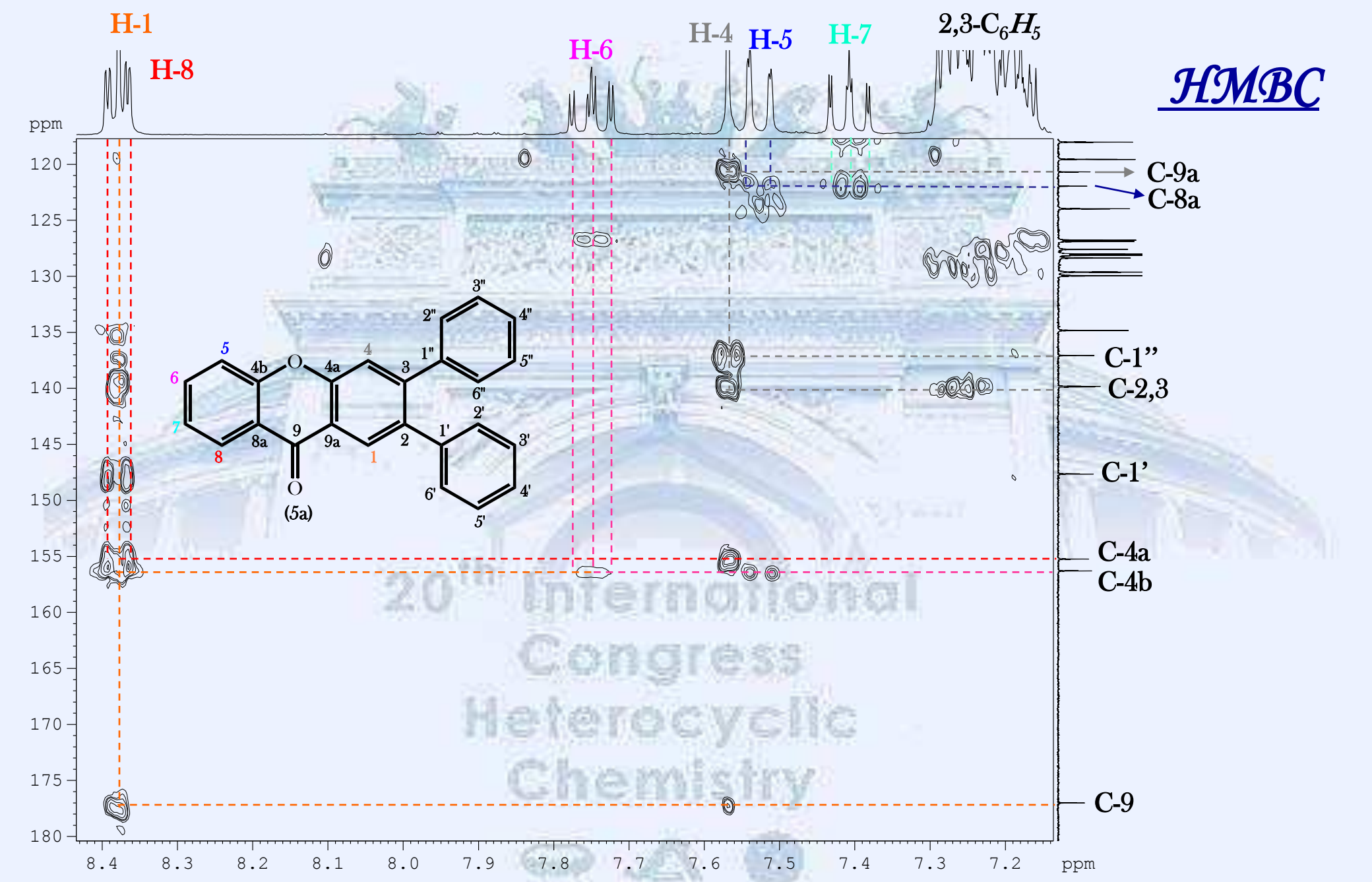


2,3-diphenylxanthone (5a)

HSQC



2,3-diphenylxanthone (5a)


H-1
H-8
H-6
H-4
H-5
H-7
2,3-C6H5
HMBC
ppm
C-9a
C-8a
C-1”
C-2,3
C-1’
C-4a
C-4b
C-9
(5a)
2,3-diphenylxanthone (5a)

References

(1) Hostettman, K.; Hostettman, M. in Methods in Plant Biochemistry, Vol. 1 – Plant Phenolics, Ed. P. M. Dey, J. B. Harbone, Academic Press, **1989**, pp. 493.

(2) (e.g.) Bennett, G. J.; Lee, H.-H. *Phytochemistry* **1989**, *28*, 967-998; Minami, H.; Kinoshita, M.; Fukuyama, Y.; Komoda, M.; Yoshizawa, T.; Sugiura, M.; Nakagawa, K.; Tago, H. *Phytochemistry* **1994**, *36*, 501-511; Abdel-Lateff, A.; Klemke, C.; König, G. M.; Wright, A. D. *J. Nat. Prod.* **2003**, *66*, 706-708; Chiang, Y.-M.; Kuo, Y.-H.; Oota, S.; Fukuyama, Y. *J. Nat. Prod.* **2003**, *66*, 1070-1073.

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.