2-STYRYLCHROMONES: BIOLOGICAL ACTION, SYNTHESIS AND REACTIVITY

William A. Price[§], Artur M. S. Silva, and José A. S. Cavaleiro*

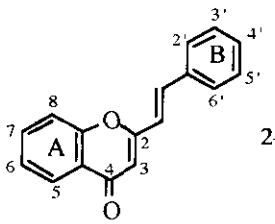
Deparment of Chemistry, University of Aveiro, 3800 Aveiro, Portugal

[§]Department of Chemistry and Biochemistry, La Salle University, Philadelphia, Pennsylvania 19141, USA

Abstract - A brief discussion of the natural occurrence and biological action of 2-styrylchromones is considered in this review; for these compounds and their 3-isoanalogues a thorough description of the successful synthetic strategies is presented. Structural characterization (nmr and mass spectra) and reactivity in Diels-Alder and photooxidation reactions are other important features of 2-styryl-chromones to be considered.

INTRODUCTION

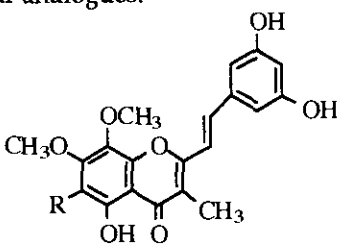
Chromones (4*H*-1-benzopyran-4-ones) and their 2-phenyl derivatives (flavones) are abundantly distributed throughout the plant kingdom[1,2] and are known to exhibit a wide variety of biological activity.[3,4] In 1925, Robinson[5] reasoned through the association of benzoyl and cinnamoyl natural products, that the abundance of flavones in nature makes it probable that representative 2-styrylchromones are naturally occurring as well. Although Venkataraman suggested the opposite, ("the occurrence of 2-styrylchromone derivitives in nature is doubtful"[6]) there was little debate over their potential pharmacological activity. Thus the synthesis of 2-styrylchromones was underway some six decades prior to the isolation of the first natural product.



2-Styrylchromone

ISOLATION AND BIOLOGICAL ACTIVITY

Although one of the rarest classes of natural chromones,[7,8] both natural and synthetic 2-styryl-chromones have shown a remarkable variety of biological activities.[7-10] Only two naturally occurring 2-styrylchromones are known: Hormothamnione (**1a**, characterized in 1986[7]) and 6-desmethoxy-hormothamnione (**1b**, characterized in 1991[8]); both were found in extracts from blue-green algae, *Chrysophaeum taylori* in 1984 off the northern coast of Puerto Rico.[8] Originally identified as *Hormothamnion enteromorphoides* , the taxonomy of these natural styrylchromones has since been revised. Specifically, **1a** has shown cytotoxicity toward P388 leukemia and HL-60 human promyelocytic cells *in vitro* and appears to operate by inhibiting the synthesis of RNA.[7] This potent biological activity has stimulated interest in practical synthetic strategies toward these compounds and has resulted in three syntheses of **1a** as well as preparations of dozens of unnatural analogues.



1a, R=OCH_3 Hormothamnione
1b, R=H 6-Desmethoxyhormothamnione

Prior to the isolation of hormothamnione (**1a**), studies were carried out on numerous synthetic 2-styrylchromones as allergy inhibitors. Several compounds, all substituted at C-6 with a carboxylic acid group, have exhibited significant levels of anti-allergic activity when taken orally.[9]

More recently, synthetic 2-styrylchromone derivatives have shown anti-tumor activity against colon 38 tumors.[10] Carboxylate substitution at C-6 again appears to be crucial for activity. 2-Styryl-chromone-8-acetic acid derivatives have also shown anticancer activity.[10]

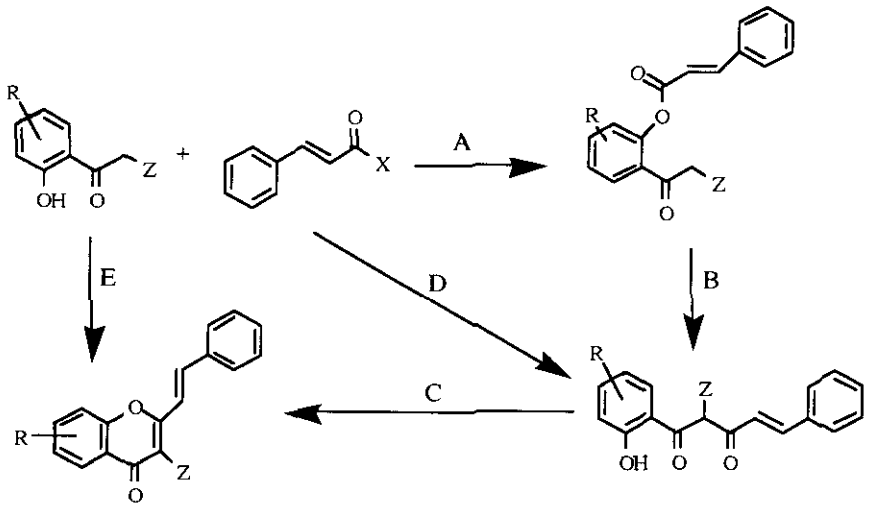
SYNTHESIS

The syntheses of 2-styrylchromones fall into several categories, all having a key carbon-carbon bond forming step. All of the strategies rely on classic, high-yielding convergent reactions. The approaches used are: 1) Baker-Venkataraman rearrangement, 2) Allan-Robinson condensation,

3) aldol condensation / oxidative ring closure, 4) intramolecular Wittig reaction and 5) 2-methylchromone / benzaldehyde condensation. A sixth approach, although not generally used, utilizes an acid catalyzed ring closure of an acetylenic ketone in the preparation of unsubstituted 2-styrylchromone. The preparation of 3-styrylchromones, although not naturally occurring and rarely cited in the literature, will be addressed in this section as well. In the schemes that follow, the different substituents on the A and B rings are generally identified by R and R'.

1) Baker-Venkataraman Rearrangement Approach:

The most common method for the construction of the 2-styrylchromone ring system relies on the *O*-acylation of a substituted *o*-hydroxyacetophenone with any of a number of cinnamic acid derivitives. Base-induced Baker-Venkataraman rearrangement[11,12] (or a modification of this method) to the 2-cinnamoyl-*o*-hydroxyacetophenone preceeds an oxidative ring closure to the 2-styrylchromone.[13-17] Depending on the conditions used, the *o*-cinnamoyloxyacetophenone and/or the 2-cinnamoyl-*o*-hydroxyacetophenone may not be isolated. Scheme I summarizes the variations on this approach.

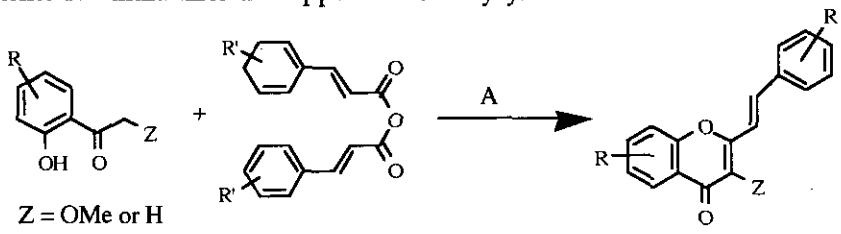


A: Z = H, X = OH; $POCl_3$, pyridine. **B**: KOH, pyridine, room temperature or NaH, DMSO, room temperature. **C**: 2% H_2SO_4 in AcOH, reflux, 1 h or 2% HCl in AcOH, reflux 1 h. **D**: Z = H, X = $-O_2CAr$, $(n\text{-}Bu)_4N^+HSO_4^-$, C_6H_6, K_2CO_3(aq.), 70-80°C. **E**: Z = CH_3 or Ph, X = Cl, K_2CO_3, acetone, reflux, 12 h.

Scheme I

2) Allan-Robinson Approach:

One of the earlier synthetic approaches to 2-styrylchromones involves the condensation of a cinnamoyl anhydride with a polyoxygenated (hydroxy and/or methoxy) *o*-hydroxyacetophenone in the presence of the corresponding sodium or potassium cinnamate.[5,6] In this reaction, *O*-acylation of the *o*-hydroxyacetophenone, subsequent rearrangement to the 2-cinnamoyl-*o*-hydroxyacetophenone, and cyclization occur in one experimental step. Base-induced hydrolysis of any formed cinnamate esters results in the formation of polyhydroxylated 2-styrylchromones.[5] The harsh reaction conditions (180°C, no solvent) place limits on the general applicability of this method. Scheme II summarizes this approach to 2-styrylchromones.

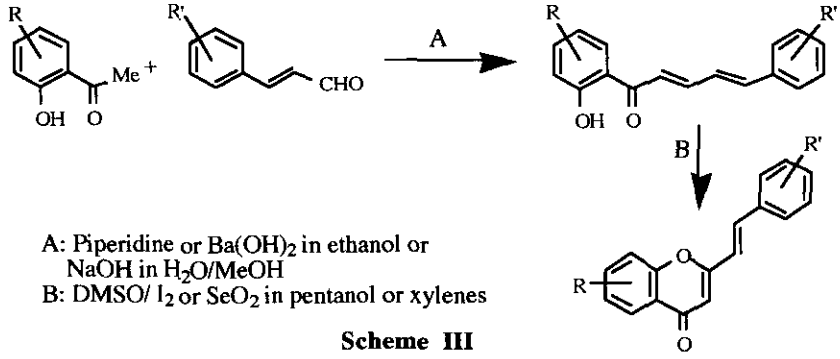


A: $ArCH{=}CHCO_2Na$, fusion, 3-8 h

Scheme II

3) Aldol Condensation/Oxidative Cyclization Approach:

The base-catalyzed condensation of cinnamaldehydes with *o*-hydroxyacetophenones in alcohol solutions affords *o*-hydroxy-2-cinnamylideneacetophenones. These can then be smoothly converted to the 2-styrylchromones using either DMSO with a catalytic amount of iodine,[18,19] or SeO_2.[20] Interestingly, in 1932, Venkataraman[6] successfully condensed cinnamaldehyde with *o*-hydroxyacetophenone but was unable to facilitate the closure to the pyranone ring. This method is summarized in Scheme III.

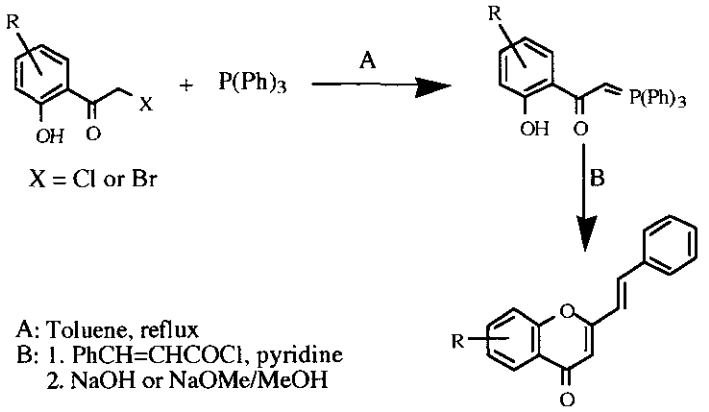


A: Piperidine or $Ba(OH)_2$ in ethanol or NaOH in H_2O/MeOH
B: DMSO/ I_2 or SeO_2 in pentanol or xylenes

Scheme III

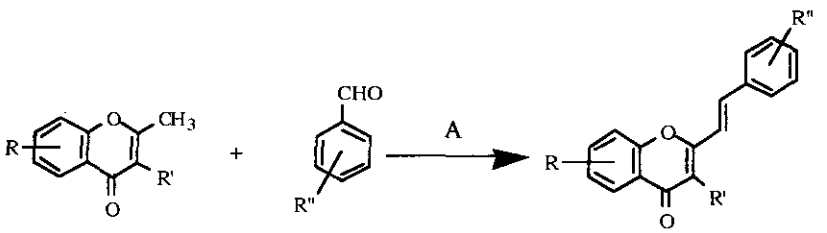
4) Intramolecular Wittig Approach:

A novel approach to 2-styrylchromones utilizes a condensation between [1-(2-hydroxybenzoyl)alkylidene]triphenylphosphoranes and cinnamoyl chloride.[21,22] An intramolecular Wittig reaction of the presumed *o*-cinnamyl ester intermediate provides good yields of the target compounds (Scheme IV).



Scheme IV

5) 2-Methylchromone/Benzaldehyde Condensation Approach. Synthesis of hormothamnione: There are several practical preparations of 2-styrylchromones that rely on the base-induced condensation of a 2-methylchromone with a substitued benzaldehyde (Scheme V).



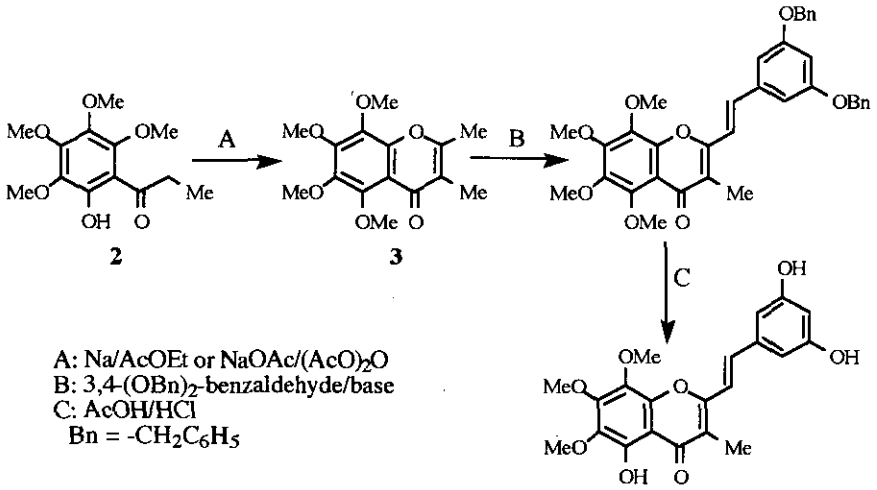
A: NaOEt/EtOH, room temperature, 24 h or piperidine/MeOH or NaOMe/MeOH, reflux, 4 h

Scheme V

Heilbron[23] and Venkataraman[6,24] synthesized several styrylchromones using this approach in the 1920's and 30's and it is through the use of this method that the three syntheses of hormothamnione (**1a**) were achieved.[25-27] Several 3-nitro-2-styrylchromones were also prepared

using this technique and used as precursors to fused pyrrole-benzopyran ring systems.[28] Brion[29] used this method as well in the preparation of several (2-styrylchromon-8-yl)acetic acids.

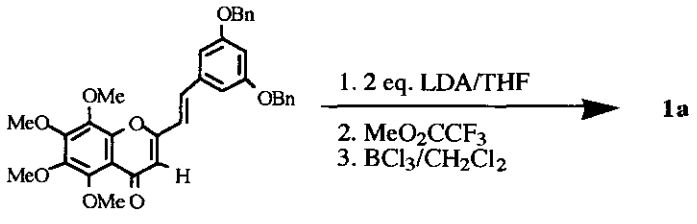
In two syntheses of **1a**, the key intermediate propiophenone (**2**) was cyclized to the corresponding 2,3-dimethylchromone (**3**) as shown in Scheme VI.[25,26] Condensation of this **3** with 3,5-dibenzyloxybenzaldehyde using sodium methoxide and sodium ethoxide respectively, followed by hydrolysis and selective demethylation at C-5 gave **1a** (Scheme VI).



2 **3** **1a**

Scheme VI

McGarry and Detty,[27] in their studies toward the synthesis of **1a**, used this approach for the preparation of 2-styrylchromone (**4**). The selective lithiation of **4** at C-3, using two equivalents of LDA in THF at -78°C, allows for the introduction of C-3 methyl substituents at later stages (Scheme VII). Selective demethylation at C-5 together with debenzylation of the 3' and 5'-benzyloxy groups occurs smoothly in the presence of boron trichloride.

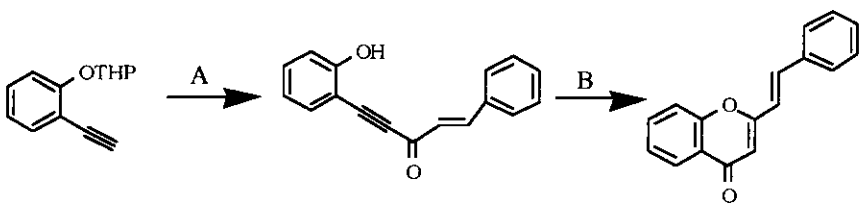


4

Scheme VII

6) Cyclization of Acetylenic Ketones:

Obrecht has modified an acid-catalyzed cyclization of conjugated acetylenic ketones in a synthesis of 2-styrylchromone[30] (Scheme VIII).



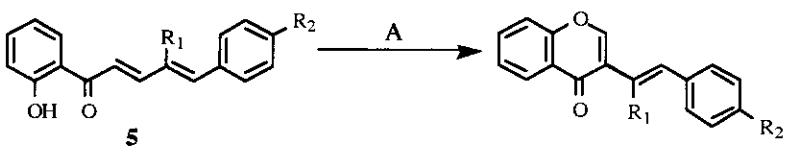
A: 1. n-BuLi, THF 2. PhCH=CHCHO 3. MnO_2 4. Pyridinium *p*-toluenesulfonate/EtOH
B: HBr (aq.), dioxane
THP = tetrahydropyranyl

Scheme VIII

7) Synthesis of 3-Styrylchromones :

There are three methods used for the preparation of 3-styrylchromones. The activation of 3-bromochromones has been effectively demonstrated *via* a Pd^0 insertion into the C-Br bond. Styrylation with styrene gave 3-styrylchromone in high yield.[31] Alonso and Brossi, in their work on the synthesis of **1a**, selectively brominated 2,3-dimethylchromone at the C-3 methyl group. Wittig reaction of the derived phosphonium salt with a MOM-protected 3,5-dihydroxybenzaldehyde, followed by acidification, gave the desired 3-styrylchromone.[25]

The oxidative rearrangement of 2'-hydroxychalcones to isoflavones using thallium (III) nitrate followed by treatment with acid is a well-documented procedure.[32] An analogous reaction involving the rearrangement of 2'-hydroxycinnamylideneacetophones **5**, gives access to 3-styrylchromones (Scheme IX).[33]



A: 1. $Tl(NO_3)_3{\cdot}3H_2O$ / MeOH / TMOF 2. H_3O^+
a) R_1 = Me; R_2 = H b) R_1 = Me; R_2 = Cl c) R_1 = Et; R_2 = Cl
TMOF = Trimethyl orthoformate

Scheme IX

STRUCTURE AND REACTIVITY OF 2-STYRYLCHROMONES

Characterization and Stereochemistry:

The value of the vicinal H_α-H_β coupling constant (^3J = 15-17 Hz) clearly shows a *trans* stereochemistry in every ^1H nmr spectrum reported for 2-styrylchromones. Due to the high degree of conjugation in the dienone portion of 2-styrylchromones, there appears to be a considerable barrier to rotation about the C_2 - C_α bond. The X-ray crystal structure of **1a**[7] as well as detailed nmr experiments using NOE,[18,33] (Figure 1), and NOESY[29] techniques with 2-styryl-chromone indicate that these compounds exist in the s-*trans* conformation as crystalline materials as well as in solution.

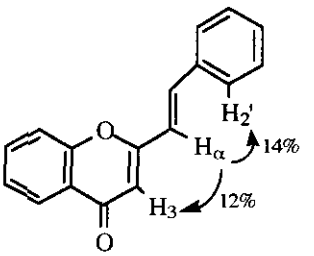


Figure 1 NOE Experiment: Irradiation of H_α of (*E*)–2-styrylchromone

Electron impact (EI) mass spectrometry is also helpful in the characterization of (*E*)-2-styryl-chromones. These mass spectra show the following typical fragmentations: $(M-H)^+$, $(M-OH)^+$, $(M-CO)^{+\cdot}$, $(A_1+H)^+$, $B_1^{+\cdot}$, B_2^+, $(B_3-H)^+$.[34,35] The capital letters A and B indicate fragments containing intact A- and B-rings (as shown in Figure 2); this is in accord with the terminology generally used in the description of EI mass spectra of chromones.[36] The molecular ion ($M^{+\cdot}$) has a typically high intensity and is often the base peak. Those fragments that are most important for structural elucidation are derived from the retro Diels-Alder reaction [$(A_1+H)^+$ and $B_1^{+\cdot}$], B_2^+, and $(B_3-H)^+$.

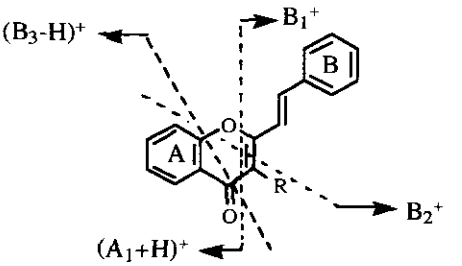


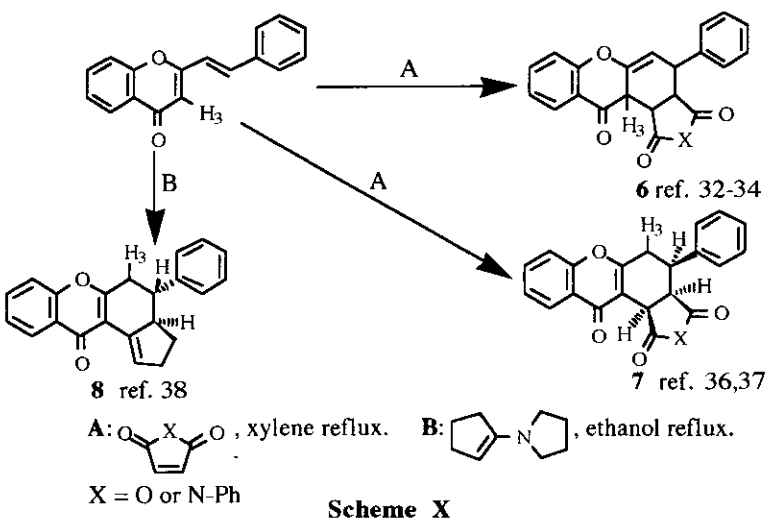
Figure 2 - Mass spectra of (*E*)-2-styrylchromones

Diels-Alder Reactions of 2-Styrylchromones:

Reactions involving the C_2-C_3 double bond in flavones and 2-styrylchromones are exceedingly rare. This is presumably due to the aromatic resonance contribution in the pyranone ring. Under extreme conditions, however, [4+2] cycloaddition reactions between 2-styrylchromones and electron-deficient dienophiles can be carried out. This suggests that the former can adopt an s-*cis* conformation, yet there is some dispute over the actual structure of the adducts. The earliest studies involved Diels-Alder reactions between 2-styrylchromones and maleic anhydride or N-phenylmaleimide in boiling xylene.[37-39] Structural characterization was never carried out on these adducts although elemental analyses clearly showed 1:1 adduct formation. Thus, these products were assumed to have the expected 1,2,3,9a-tetrahydroxanthene (**6**) structure.

Elkashef[40] reacted *o*-, *m*-, and *p*-chlorostyryl-4-chromone with maleic anhydride and suggested the same general structure for the adducts. The proton nmr data provided for the *m*-chlorostyryl adduct (the only one characterized thusly), although not thoroughly interpreted, show a doublet signal at δ 7.78, assigned to H-4.

Letcher has suggested that the xanthene structures derived from these Diels-Alder reactions be revised to 1,2,3,4-tetrahydroxanthenes[41-43] (**7**) (Scheme X). Specifically, studies were carried out on reactions of (*E*)-2-styrylchromones with both electron deficient (path A) and electron rich (path B) dienophiles. All adducts were thoroughly characterized by extensive nmr studies, uv and ir spectroscopies.

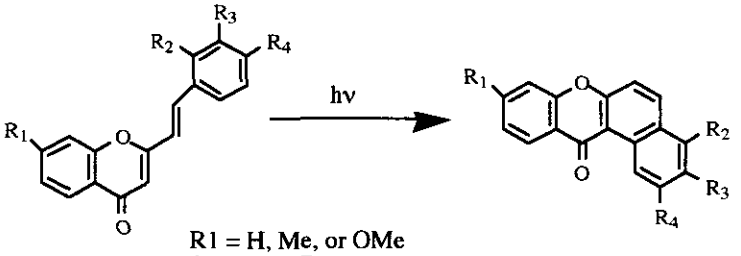


Scheme X

The 1,3-hydrogen shift that must accompany these reactions presumably is facilitated by the stabilized chromone product. In order for 3-methyl-2-styrylchromones to undergo Diels-Alder reactions in this manner, a 1,3-methyl migration is necessary; thus it is not surprising that these reactions have been unsuccessful to date.

Photo-oxidation of 2-Styrylchromones:

Irradiation of 2-styrylchromones facilitates a photo-oxidative cyclization to 12*H*-benzo[a]xanthen-12-ones. Although a facile entry into these fused ring systems, yields are typically between 10 and 20%[44,45] (Scheme XI).



R1 = H, Me, or OMe
R2 = H or Br
R3 = H or OMe
R4 = H, Me, or OMe

Scheme XI

CONCLUSION

A review of the literature reveals seven unique methods for the construction of 2-styrylchromones. Spectroscopic and X-ray analysis of these compounds clearly shows (*E*) stereochemistry as well as s-*trans* conformation about the vinyl portion of the molecule. Extensive work in the characterization of Diels-Alder adducts using (*E*)-2-styrylchromones as dienes, has shown convincing evidence that suggests a reevaluation of previously documented xanthene adducts.

ACKNOWLEDGEMENTS

Thanks are due to the J. William Fulbright Scholarship Foundation for a Fellowship awarded to W.A.P. This work was also partially supported by the University of Aveiro, Portugal.

REFERENCES

1. G. P. Ellis, "Chromenes, Chromanones, and Chromones" ed. by G. P. Ellis, John Wiley & Sons, New York, 1977, p. 455.
2. E. Wollenberger and M. Jay, "The Flavonoids - Advances in Research Since 1980" ed. J. B. Harborne, Chapman and Hall, London, 1988, p. 233.
3. J. W. McClure, "The Flavonoids" eds. J. B. Harborne, T. J. Mabry and H. Mabry, Chapman and Hall, London, 1975, p. 970.
4. G. Atassi, P. Briet, J.-P. Berthelon and F. Collonges, *J. Med. Chem., Chim. Ther.*, **1985**, *20*, 393.
5. R. Robinson and J. Shinoda, *J. Chem. Soc.* , **1925**, *127*, 1973.
6. U. S. Cheema, K. C. Gulati, and K. Venkataraman, *J. Chem. Soc.* , **1932**, 925.
7. W. H. Gerwick, A. Lopez, G. D. Van Duyne, J. Clardy, W. Ortiz, and A. Baez, *Tetrahedron Lett.*, **1986**, *27*, 1979.
8. W. H. Gerwick, *J. Nat. Prod.*, **1989**, *52*, 252.
9. G. Doria, C. Romeo, A. Forgione, P. Sberze, and N. Tibolla, *Eur. J. Med. Chem. - Chim. Ther.*, **1979**, *14*, 347.
10. J. D. Brion, G. Le Baut, F. Zammattio, A. Pierre, G. Atassi, and L. Belachmi, *Eur. Pat. Appl.* , EP 454,587, **1991** (*Chem. Abstr.*, **1992**, *116*, 106092k).
11. W. Baker, *J. Chem. Soc.*, **1933**, 1381.
12. H. S. Mahal and K. Venkataraman, *J. Chem. Soc.*, **1934**, 1767.
13. G. P. Ellis, "Chromenes, Chromanones, and Chromones" ed. by G. P. Ellis, John Wiley & Sons, New York, 1977, p. 581.
14. H. L. Gaggad, K. N. Wadodkar, and B. J. Ghiya, *Indian J. Chem.*, **1985**, *24B*, 1244.
15. C. R. Reddy, G. L. D. Krupadanam, and G. Srimannarayana, *Indian J. Chem.*, **1987**, *26B*, 974.
16. A. K. D. Mazumdar, D. P. Sarbagya, K. Rangachari, and K. D. Banerji, *J. Indian. Chem. Soc.*, **1990**, *67*, 255.
17. J. K. Makrandi and V. Kumari, *Synth. Commun.*, **1989**, *19*, 1919.
18. J. A. S. Cavaleiro, J. Elguero, M. L. Jimeno, and A. M. S. Silva, *Chem. Lett.*,, **1991**, 445.
19. J. K. Makrandi and Seema, *Indian. J. Chem.* **1991**, *30B*, 788.
20. G. B. Marini-Bettòlo, *Gazz. Chim. Ital.*,, **1942**, *72*, 201.
21. A. Hercouet, M. Le Corre, and Y. Le Floc'h, *Synthesis*, **1982**, 597.

22. F. Zammattio, J. D. Brion, P. Ducrey, and G. Le Baut, *Synthesis*, **1992**, 375.

23. I. M. Heilbron, H. Barnes, and R. A. Morton, *J. Chem Soc.*, **1923**, 2559.

24. K. C. Gulati, S. R. Seth, and K. Venkataraman, *J. Chem. Soc.*, **1934**, 1765.

25. R. Alonso and A. Brossi, *Tetrahedron Lett.*, **1988**, *29*, 735.

26. N. R. Ayyangar, R. A. Khan, and V. H. Deshpande, *Tetrahedron Lett.*, **1988**, *29*, 2347.

27. L. W. McGarry and M. R. Detty, *J. Org. Chem.*, **1990**, *55*, 4349.

28. C. Paparao, K. V. Rao, and V. Sundaramurthy, *Synthesis*, **1981**, 234.

29. F. Zammattio, J. D. Brion, L. Belachmi, and G. Le Baut, *J. Heterocycl. Chem.*, **1991**, *28*, 2013.

30. D. Obrecht, *Helv. Chim. Acta*, **1989**, *72*, 447.

31. S. G. Davies, B. E. Mobbs, and C. J. Goodwin, *J. Chem. Soc., Perkin Trans. I*, **1987**, 2597.

32. L. Farkas and W. Wagner, "The Flavonoids", ed. J. B. Harborne, T. Mabry, and H. Mabry, Chapman and Hall, London, 1975, p. 127.

33. A. M. S. Silva, Ph.D. Thesis, 1993, University of Aveiro, 3800 Aveiro, Portugal.

34. R. Tonani, *Org. Mass Spectrom.*, **1980**, *15*, 275.

35. G. Sollazzo and R. Tonani, *Org. Mass Spectrom.*, **1983**, *18*, 89.

36. T. J. Mabry and K. R. Markham, "The Flavonoids" ed. J. B. Harborne, T. Mabry, and H. Mabry, Chapman and Hall, London, 1975, p. 78.

37. A. Schönberg, A. Mustafa, and G. Aziz, *J. Am. Chem. Soc.*, **1954**, *76*, 4576.

38. A. Mustafa and M. I. Ali, *J. Org. Chem.*, **1956**, *21*, 849.

39. G. Aziz, *J. Org. Chem.*, **1962**, *27*, 2954.

40. M. A.-F. Elkaschef, F. M. E. Abdel-Megeid, K.-E. M. Mokhtar, and F. A. Gad, *Acta Chim. Acad. Sci. Hung.*, **1975**, *84*, 319.

41. R. M. Letcher and T.-Y. Yue, *J. Chem. Res. (S)*, **1992**, 248.

42. R. M. Letcher and T.-Y. Yue, *J. Chem. Res. (M)*, **1992**, 2078.

43. R. M. Letcher and T.-Y. Yue, *J. Chem. Soc., Chem. Commun.*, **1992**, 1310.

44. K. A. Kumar and G. Srimannarayana, *Indian J. Chem.*, **1980**, *19B*, 615.

45. I. Yokoe, K. Higuchi, Y. Shirataki, and M. Komatsu, *Chem. Pharm. Bull.*, **1981**, *29*, 2670.

Received, 23nd June, 1993