Pergamon

Tetrahedron 54 (1998) 14541–14548

TETRAHEDRON

Novel Cyclobutane Fused Furochromone Oligomers from the Seeds of *Pimpinella monoica* Dalz

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Received 11 June 1998; revised 21 September 1998; accepted 1 October 1998

Abstract: Novel oligomers *viz.* di-, tri-, tetra- and pentamers (**2-5**) of the furochromone visnagin (**1**) were isolated from the chloroform extract of the fresh mature seeds of the plant *Pimpinella monoica*. 1D and 2D NMR studies revealed a linear head-to-tail (2 + 2) pyran-furan fusion for the oligomers. NOE data and molecular modelling suggested that the higher oligomers with all *syn* geometry may have helicity.

INTRODUCTION

The genus *Pimpinella* (N.O. Umbelliferae) comprises annual or perennial herbs which are distributed in Asia, Europe and Africa.[1] Though the plants belonging to the genus are known to contain furocoumarins, our studies showed that *P. monoica* Dalz commonly known as ladies lace,[2] is a rich source for furanochromones.[3] The hexane and methanol extracts of *P. monoica* showed significant feeding deterrency to *Spodoptera litura* F. larvae. The biological activities were found to be due to the furanocoumarins and furanochromones.[3,4] An estimation of the furanochromones in different parts of *P. monoica* revealed higher accumulation of these compounds in the mature seeds and flowers. Recently, we have reported the occurrence of a novel dimer, pimolin (**2**) from the chloroform extracts of *P. monoica*[5] in addition to visnagin (**1**) and khellin (**1a**). The linear pyran-furan fusion in **2** was confirmed by extensive 2D NMR studies. On the basis of solvent induced NMR shifts and molecular modelling, host recognition properties were postulated for **2**. Further investigation on the chloroform extracts of the fresh mature seeds resulted in the isolation of three additional compounds, **3-5**.[6] These compounds showed characteristic fluorescence under UV which was useful for monitoring the isolation by column chromatography and TLC. This paper deals with the isolation, characterisation and stereochemistry of the oligomers.

RESULTS AND DISCUSSION

Fresh mature seeds of the plant *P. monoica* were ground in the dark and then subjected to percolation with chloroform. In addition to **1**, **1a** and **2**, compounds **3** to **5** were isolated from the chloroform extract by repeated column and thin layer chromatography.

Compound 3 was obtained as a solid from hot methanol and analysed for $C_{13}H_{10}O_4$. The UV and the IR spectra of **3** showed close resemblance to those of **2** except that **3** had an additional absorption in the carbonyl region. In the FABMS spectrum, it showed a molecular ion peak (m/z 690) along with fragment ions at 460 (M^+- 230), 230 (M^+- 460) and a base peak at 201. The last three peaks were also present in the MS of **2**. Therefore, it was concluded that **3** could be a trimer of **1** (M^+ 230). The ^{1}H NMR spectrum displayed resonances due to three methyls, three methoxyls, a pair of furan protons, six aliphatic and four olefinic methine protons. Of the three methyl groups, the downfield methyl signal at δ 2.2 could be assigned to a methyl on a sp^2 carbon. The ^{13}C DEPT spectra confirmed the presence of three methyls, three methoxyls and twelve methine carbons. Out of twelve methine carbons, six were in the aromatic/olefinic region while the other six were sp^3 carbons with two of them attached to oxygen (δ 89.2 and 89.4). The presence of 21 quaternary carbons could be accounted for by three carbonyls, ten O-bonded sp^2 (δ 153-167), six aromatic (δ 108 - 115) and two O-bonded sp^3 (δ 79.2 and 79.3) carbons. Based on these data compound **3** could be

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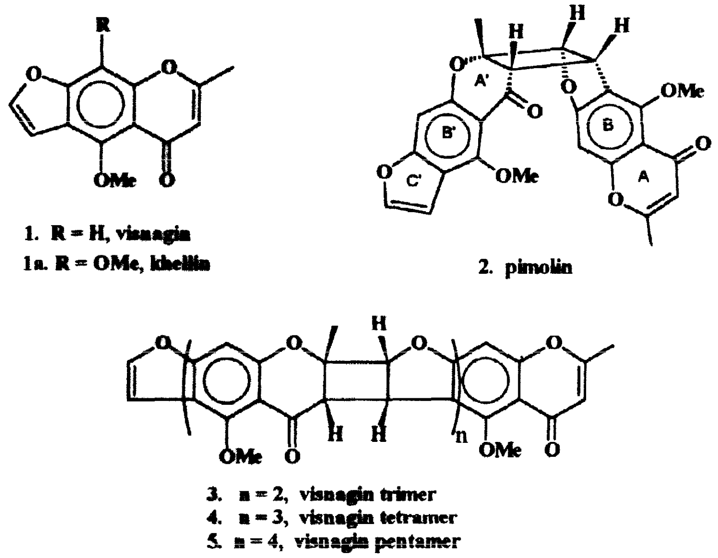
PII: S0040-4020(98)00913-2

visualised as a trimer of **1**. An extensive study by 2D NMR techniques resulted in the unequivocal assignments of all the ^{1}H and ^{13}C resonances which are essential for the determination of stereochemistry.

For convenience, the three rings of the first visnagin moiety in **3** were labelled as A, B and C, starting from the terminal pyranone ring The subsequent visnagin moieties were labelled A', B' and C' and A", B" and C" (*Scheme 2*). The two cyclobutane rings at the pyran-furan junctions were labelled as D and D'. The ^{1}H NMR of **3** follows similar pattern as in **2**.

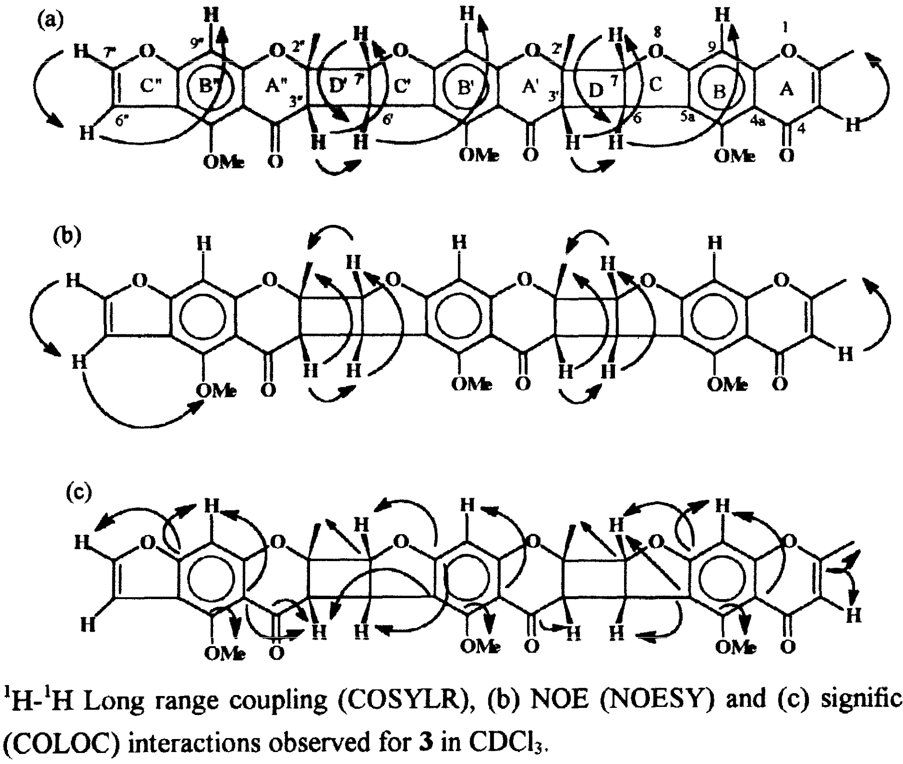


1. R = H, visnagin
1a. R = OMe, khellin

2. pimolin

3. n = 2, visnagin trimer
4. n = 3, visnagin tetramer
5. n = 4, visnagin pentamer

Scheme 1. Visnagin oligomers from the chloroform extracts of the mature seeds of *Pimpinella monoica*.



Scheme 2. (a) ^{1}H-^{1}H Long range coupling (COSYLR), (b) NOE (NOESY) and (c) significant ^{13}C-^{1}H Long range coupling (COLOC) interactions observed for **3** in $CDCl_3$.

The ^1H-^1H COSY displayed cross peaks between the furan protons (ring C"). Careful correlations resulted in the identifications of two sets of AMX spin systems between δ 3.5- 5.4 which were confirmed from the observation of the following COSY interactions (δ_H-δ_H): (3.44 ↔ 4.29), (3.44 ↔ 5.09), (4.29 ↔ 5.09); (3.35 ↔ 4.42), (3.35 ↔ 5.08) and (4.42 ↔ 5.08). The COSYLR experiment established additional four - bond (between 2-Me and 3-H) and five - bond (between 9-H and 6-H; 9'-H and 6'-H; and 9"-H and 6"-H) scalar couplings. Though the coupling constants could not be calculated small magnitudes, these constitute rare examples of five-bond couplings. The COSYLR interactions (*Scheme 2*) described above led to assignments of all the proton resonances in **3**.

Further assignments could be made by the judicious use of NOESY, HETCOR and COLOC experiments.[7] Based on NOESY cross peaks between 6"-H and a signal at δ 3.79, the latter was assigned to the methoxyl group at C-5" position. Although NOESY (*Scheme 2*) was useful for the determination of the stereochemistry of the cyclobutane rings, it could not distinguish between the protons of D and D' rings. This could be done by observing heteronuclear long range coupling (^3J) of the quaternary carbons to the protons of the cyclobutane rings in a COLOC experiment.[7] The assignments of the remaining protons then follows from the COSYLR interactions (*Scheme 2*); these are listed in **Table 1**.

Table 1. ^1H NMR of **3** in $CDCl_3$

H-no	δ (ppm) multiplicity, J (Hz)	H-no	δ (ppm) multiplicity, J (Hz)	H-no	δ (ppm) multiplicity, J(Hz)
7-H	5.08, dd, $J_{6,7} = 6.5$, $J_{3',7} = 1.9$	7'-H	5.09, dd, $J_{6',7'} = 6.8$, $J_{3'',7'} = 1.9$	7"-H	7.35, d, $J = 2.4$
6-H	4.42, dd, $J_{3',6} = 8.5$, $J_{6,7} = 6.5$	6'-H	4.29, dd, $J_{3'',6'} = 8.4$, $J_{6',7'} = 6.8$	6"-H	6.73, dd, $J = 2.4$, 1.1
9-H	6.29, s	9'-H	5.6, s	9"-H	6.65, d, $J = 1.1$
2-Me	2.2, s	2'-Me	1.53, s	2"-Me	1.62, s
3-H	5.85, s	3'-H	3.35, dd, $J_{3',6} = 8.5$, $J_{3',7} = 1.9$	3"-H	3.44, dd, $J_{3'',6'} = 8.4$, $J_{3'',7'} = 1.9$
5-OMe	3.85, s	5'-OMe	3.5, s	5"-OMe	3.79, s

The methyl, methoxyl and the methine protons were correlated to their respective carbons by HETCOR experiment. There were five methine carbons in the region δ 89-95 of which three were assigned to carbons at C-9, C-9' and C-9" on the basis of their HETCOR interactions with the downfield protons (δ 6.29, 5.6 and 6.65) and the other two belonged to C-7 and C-7'. Similarly, of the eight carbons between δ 105-114, those at 111 and 105.5 showed interactions with 3-H and 6"-H and are therefore assigned to C-3 and C-6", respectively. The assignments of other proton-bearing carbons are detailed in **Table 2**.

Table 2. ^{13}C NMR of compound **3** in $CDCl_3$

Carbon	δ (ppm) multiplicity	Carbon	δ (ppm) multiplicity	Carbon	δ (ppm) multiplicity
7	89.2, d	7'	89.4, d	7"	143.4, d
6	41.6, d	6'	41.3, d	6"	105.5, d
5a	114.0, s	5'a	110.8, s	5"a	113.2, s
5	157.6, s	5'	158.4, s	5"	154.2, s
4a	111.8, s	4'a	108.2, s	4"a	108.7, s
4	176.5, s	4'	185.9, s	4"	188.7, s
3	114.0, d	3'	54.6, d	3"	55.9, d
2	162.9, s	2'	79.2, s	2"	79.3, s
9a	159.4, s	9'a	160.3, s	9"a	164.4, s
9	93.4, d	9'	93.1, d	9"	94.7, d
8a	166.8, s	8'a	168.9, s	8"a	159.9, s
2-Me	19.6, q	2'-Me	25.4, q	2"-Me	25.9, q
5-OMe	61.4, q	5'-OMe	59.7, q	5"-OMe	60.6, q

The assignments of all the quaternary carbons and the differentiation between the resonances of the D and D' rings could be made from the long range interactions (*Scheme 2*) obtained from a COLOC experiment. The salient features of the assignments were: (i) 9"-H (unequivocally assigned from COSYLR) showed COLOC interaction (^3J) with the carbon at 108.7 which in turn showed interaction with the proton at δ 3.44. Therefore, this carbon was attributed to C-4"a and the latter proton to 3"-H of A" ring. These assignments were helpful in the identification of the resonances of 6'-H, 7'-H, 2"-Me (D' ring) and 9'-H from those of 6-H, 7-H, 2'-Me (D ring), 9-H and 3'-H by COSYLR correlation. (ii) The carbonyl carbons at δ 188.7 and δ 185.9 were attributed to C-4" and C-4' positions due to their heteronuclear coupling (^2J) with 3"-H and 3'-H respectively. Hence the third carbonyl resonance at δ 176.5 was due to the α,β-unsaturated carbonyl functionality in ring A. (iii) The carbons bearing the methoxyl groups showed prominent interactions with the respective methoxyl protons and thus could be assigned. For example, the carbon at δ 154.2 had COLOC interaction with the methoxyl group of B" ring (δ 3.79, assigned on the basis of NOE with H-6") and attributed to C-5". Similarly, the most downfield methoxyl protons showed interaction with the carbon at δ 157.6 allowing assignment of the latter to C-5. These consequently fixed the resonance at δ 158.4 to C-5'. (iv)

The O-bonded quaternary sp^2 carbons showed interactions (both ^2J and ^3J) with the cyclobutane ring protons and hence were easily assigned. (v) The rest of the quaternary carbons *viz.* C-4a, C-4'a, C-5a, C-5'a and C-5"a were assigned on the basis of their COLOC interactions with 9-H, 9'-H and 9"-H. (vi) The alternative structures with other modes of pyran-furan fusion were ruled out on the basis of observed COLOC interactions *viz.* those between the C-7 and C-7' carbons and the methyl protons at C-2 and C-2' as was done for **2**.[5]

Useful information on the stereochemistry of the molecule could be derived from the NOE interactions between the ring junction protons of D and D' rings. The interactions between 3'-H ↔ 6-H, 6-H ↔ 7-H, 7-H ↔ 2'-Me and 3'-H ↔ 2'-Me indicated the *cis*-disposition of all the methine protons with respect to the dihydropyran methyl group. Likewise, the interactions observed in the D' ring were: 3"-H ↔ 6'-H, 3"-H ↔ 2"-Me, 6'-H ↔ 7'-H, and 7'-H ↔ 2"-Me. The stereochemical arrangements of the cyclobutane ring protons of **3** were thus similar to those in **2**.[5] The J-coupling constants between the protons of cyclobutane rings also reflect *cis*-disposition.

These data characterised compound **3** as the trimer of visnagin where the pyran ring of one is fused with the furan ring of the subsequent monomer linearly in a *head-to-tail* fashion. However, these are not sufficient to define the relative stereochemistry between the two cyclobutane rings D and D'. The optically active visnagin trimer **3** represents a novel example of a naturally occurring oligomer, which could act as a molecular receptor for small organic and metal ion guests.

Compound 4 was obtained as a minor component by preparative TLC. As in the case of **2** and **3** the elemental analysis indicated an empirical formula, $C_{13}H_{10}O_4$. The IR spectrum revealed strong absorptions due to four carbonyl functionalities. UV absorptions at 239.7 and 292.5 were similar to those observed in **2** and **3**. It showed a molecular ion peak at m/z 920 along with low intensity fragment ions, 690 (M^+- 230), 460, 230 and a base peak at 201 in FABMS. The ^1H NMR spectrum (**Figure 1d**) of compound **4**, displayed four methyls (δ 2.2, 1.63, 1.59 and 1.45), four methoxyls (δ 3.94, 3.79, 3.56 and 3.42) and five isolated aromatic/olefinic protons (δ 6.64, 6.2, 5.9, 6.6 and 5.79). In addition, there were three AMX spin systems (δ 3.2-5.2) and a pair of *vicinally* coupled furan protons (δ 7.36 and 6.72). The spectral properties of **4** bore resemblance to those of **2** and **3**. Therefore, compound **4** could be a tetramer of visnagin. Observation of only one pair of coupled furan protons and a downfield methyl at δ 2.2 suggested a similar type of furan-pyran fusion for compound **4** as in **2** and **3**. Three sets of AMX spin systems identified on the basis of COSY spectrum (see Experimental) accounted for the three cyclobutane rings (D, D' and D") in the tetramer. Although paucity of the sample did not permit a detailed 2D NMR study, the fact that **4** is a tetramer of visnagin where the monomers are connected through cyclobutane rings as a result of linear pyran-furan ring fusion has been firmly established.

Compound 5 was obtained in a small quantity as a colourless solid with some inseparable impurity (see **Fig 1**). The UV (238 and 282 nm) and IR spectra of **5** were similar to those of the previous compounds. The IR spectra displayed absorptions for five carbonyl groups between 1665 and 1685 cm^{-1}. It showed a similar pattern of resonances in the ^1H NMR spectrum as in compounds **2-4** along with additional resonances (**Figure 1e**). There were five methyl signals in the region δ 1.45-2.2 with one of them present on a double bond carbon (methyl group of ring A as in **2-4**). The presence of five methoxyl groups (δ 3.4-3.95), six aromatic/olefinic singlets (δ 5.8-6.7) and two coupled furan protons were also inferred from the ^1H NMR spectrum. In addition, overlapping complex multiplets integrating for twelve protons appeared in the region δ 3.1-5.2. The four AMX spin systems accounting for four cyclobutane rings were identified on the basis of COSY interactions. All the data indicated compound **5** to be a pentamer of visnagin. The absolute assignments of these resonances and the stereochemical derivations were difficult due to the complexity of the NMR spectrum, instability of the compound and paucity of the sample.

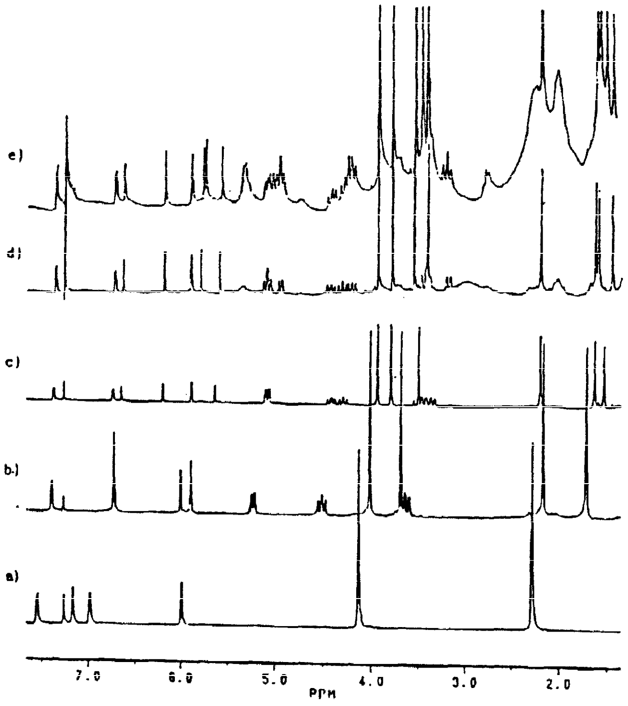


Figure 1. Comparative NMR spectra ($CDCl_3$) of (a) **1**, (b) **2**, (c) **3**, (d) **4** and (e) **5**.

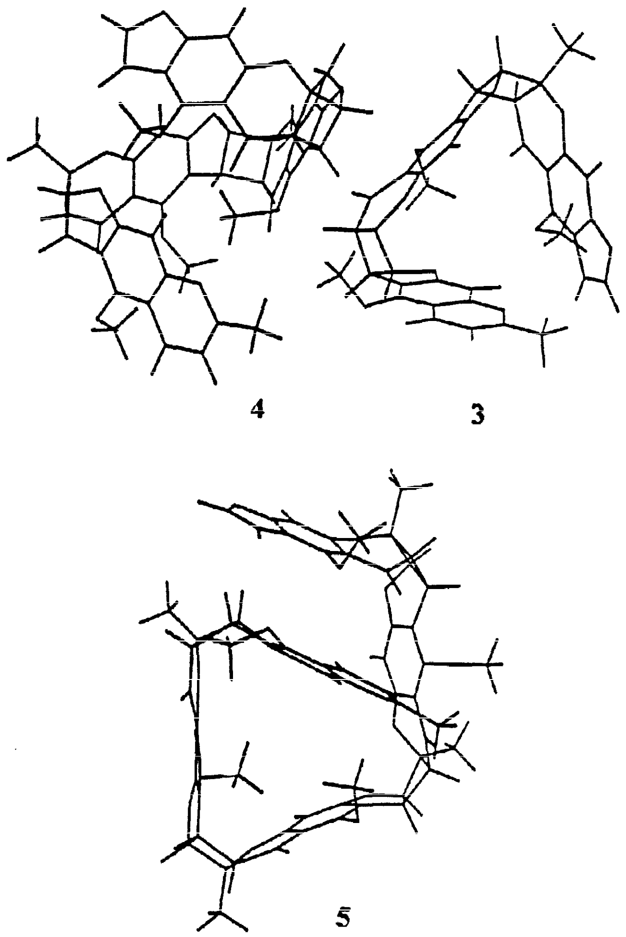


Figure 2. Energy minimised models of the trimer, **3**, tetramer, **4** and the pentamer, **5** using DISCOVER module displaying helicity in **4** and **5**.

The compounds **3-5** represent a novel class of naturally occurring oligomers of visnagin. It is surprising that, despite our repeated search, we were unable to isolate similar oligomers of khellin (**1a**). The oligomers of **1** are sensitive molecules and show sign of decomposition even at room temperature. In fact, compounds **3-5** could not be isolated when the plant material was either dried in sunlight or stored for a long period. All attempts to crystallise **3-5** for X ray crystallography were not successful. A comparative study of the visnagin oligomers (**1-5**) led to interesting generalisation of the ^1H signals in $CDCl_3$ which would be useful for the characterisation of such compounds. The oligomers (n = 1-5) in general displayed the following diagnostic features in the NMR spectra as shown in **Figure 1**. The diagnostic regions are: (i) one methyl on a double bond (~ δ 2.2) and (n-1) methyl on sp^3 carbons (δ 1.4-1.7) and n methoxyl (δ 3.4-4.0) groups, (ii) n isolated aromatic protons (δ 6.0-7.0), (iii) (n-1) AMX spin systems (δ 3.1-5.3), (n-1) cyclobutane rings, (iv) a pair of *vicinal* protons in furan ring and (v) an olefinic singlet (~ δ 5.85).

The novel visnagin oligomers from *P. monoica* have interesting stereochemistry. The *cis* pyran-furan fusion (based on NOE and coupling data) would result in several bends and twists. It has not been possible to obtain direct evidence for the relative stereochemistry of the visnagin moieties around the cyclobutane rings in **3-5**. However, molecular modeling of **3-5** with INSIGHT II (version 2.3.5) interfaced with DISCOVER module[8] suggest the *syn* dispositions of pyrone and furan rings leading to helicity in the molecules (**Figure 2**). The aromatic, pyranone, cyclobutane and the dihydro-furan rings constitute a rigid backbone. Hence, these compounds with appropriately placed oxygen atoms could possibly be molecular receptors for organic compounds or metal ions. They may interact with oligonucleotides due to their possible helical geometry. These aspects are the subject for further investigations.

EXPERIMENTAL

General: Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrophotometer (Model 783). The UV absorption spectra were obtained on a Shimadzu UV/VIS spectrophotometer (Model 240 S). For FABMS, 8 kV Xe gun was used with LiCl as the matrix. Optical rotations were measured on a JASCO Polarimeter (DIP-370). All the 1D and 2D NMR experiments were recorded on a Bruker AC 200 FT-NMR spectrometer with operative frequencies, 200 and 50 MHz for ^1H and ^{13}C nuclei, respectively. In the COSYLR experiment, 64 scans were recorded for each of 256 experiments. The t_1 dimension was then zero filled to 512 w. A delay of 0.12 s was used before the last detection pulse. The NOESY spectra were recorded in $CDCl_3$ with a mixing time of 0.9 s and the 2D matrix was multiplied with the square sine bell (SSB = 8) function before transformation. For HETCOR, 256 scans were recorded for 128 experiments using a ^1H relaxation of 1.5 s. The other delays were d_2 = 0.001 s, d_3 = 0.0032 s and d_4 = 0.0016 s. In COLOC,[7] 512 transients were recorded for each t_1 experiment of 100 increments and 4K t_2 data points. The delays used were: d_1 = 1.5 s, d_2 = 0.03 s and d_3 = 0.16 s. For column chromatography silica gel (100-200 mesh) was used. The ratio between the material to be separated and the adsorbent were 1 : 40 to 1: 100 depending on the Rf of the components. The pre-adsorbed material was loaded on the column which was prepared in petroleum ether (60-80°). The column was eluted with petroleum ether, $CHCl_3$ followed by $CHCl_3$ containing increasing amounts of EtOAc.

Plant Material: Fresh mature seeds of the plant *P. monoica* Dalz, were collected from the nursery of Bhabha Atomic Research Centre, Mumbai in the month of October. Identification of the plant was established by Drs. S. D. Jaywant and V. Abraham of B. A. R. C. The fresh seeds (480 g) were ground in the dark and then subjected to percolation with chloroform. The chloroform extracts were evaporated under vacuum to give a green resinous mass (8.8 g) which was then triturated with ether. The filtrate mainly contained visnagin (**1**) and khellin (**1a**). Careful TLC of the residue on silica gel [$CHCl_3$: MeOH (19:1)] showed two fluorescent spots under UV light. Multiple development in $CHCl_3$: MeOH (12:1) showed two additional fluorescent spots. Extensive column chromatography and preparative TLC on silica gel provided **2** (0.25 g), **3** (0.09 g), **4** (0.042 g) and **5** (0.018 g) along with a mixture of **1** and **1a**.

Pimolin (2): As in Ref. 5.

Visnagin Trimer (3): Colourless solid (hot MeOH), mp 210-216 °C; Analysis: Found C 67.6, H 4.5: calc. C 67.82, H 4.38, O 27.8 for $C_{13}H_{10}O_4$; $[\alpha]_D^{28}$ - 6.5 ^{0}; c = 0.24 in $CHCl_3$); MS (FAB) m/z 690, 461, 460, 230, 216, 201 (100%) and 184; IR (KBr): 2935, 1680, 1674, 1660, 1625, 1615, 1590, 1480, 1430 and 1128 cm^{-1}; UV (MeOH): 243.5 (log ε 4.18) and 289.9 (log ε 3.89) nm; ^1H and ^{13}C NMR ($CDCl_3$) see Tables 1 and 2.

Visnagin Tetramer (4): Colourless solid (hot MeOH), mp 202 °C; Analysis: Found C 67.3, H 4.7: calc. C 67.82, H 4.38, O 27.8 for $C_{13}H_{10}O_4$; $[\alpha]_D^{28}$ = negligible; IR (KBr): 2940, 1690, 1675, 1665, 1660, 1625, 1620, 1615, 1485, 1430, 1360, 1300, 1150,1115 and 1090 cm^{-1}; UV (MeOH): 239.7 (log ε 4.21), 292.5 (log ε 3.9) nm; MS (FAB) m/z 920, 690, 460, 230, 201 (100%), 184 and 160; ^1H NMR ($CDCl_3$): (i) furan protons (two): δ 7.36 and 6.72 (each 1H, d, 2.4 Hz), (ii) aromatic (four): δ 6.64, 6.2, 5.9 and 6.6 (1H each, s), (iii) methyls (four): δ 2.2 (3H, s, 2-Me), 1.63, 1.59 and 1.45 (3H each, s), (iv) methoxyls (four): δ 3.94, 3.79, 3.56 and 3.42 (3H, s), (v) olefinic (one): δ 5.79 (1H, s), (vi) cyclobutane ring protons (nine): AMX [δ 3.50, 4.2 and 4.96 (1H each, dd, $J_{3',6}$ = 8.5, $J_{6,7}$ = 6.8 and $J_{3',7}$ = 1.8 Hz)], A'M'X' [δ 3.42, 4.31 and 5.08 (1H, each, dd, $J_{3'',6'}$ = 8.4, $J_{6',7'}$ = 6.9 and $J_{3'',7'}$ = 1.9 Hz)] and A"M"X" [δ 3.19, 4.43 and 5.11 (1H, each, dd, $J_{3''',6''}$ = 8.6, $J_{6'',7''}$ = 6.6 and $J_{3''',7''}$ = 1.7 Hz)].

Visnagin Pentamer (5): Colourless solid (hot MeOH) contains some amount of impurities, mp 196 ^{0}C (charred); $[\alpha]_D^{28}$ = negligible; IR (KBr): 2980, 1685, 1680, 1670, 1665, 1630, 1580, 1490, 1445, 1400, 1360, 1320 and 1130 cm^{-1}; UV (MeOH): 238 (log ε 4.26), 281.7 (log ε 3.86) nm; ^1H NMR ($CDCl_3$): (i) furan protons (two): δ 7.36 and 6.72 (each 1H, d, 2.4), (ii) aromatic (five): δ 6.64, 6.19, 5.78, 5.75 and 5.58 (1H, each, s), (iii) methyls (five): δ 2.2 (3H, s, 2-Me); δ 1.62, 1.58, 1.52 and 1.45 (3H each, s), (iv) methoxyls (five): δ 3.94, 3.79, 3.56, 3.49 and 3.43 (3H each, s), (v) olefinic (one): δ 5.90 (1H, s), (vi) cyclobutane ring protons (twelve): AMX [δ 3.19, 4.29 and 5.11 (1H, each, dd, $J_{3',6}$ = 8.8, $J_{6,7}$ = 6.5 and $J_{3',7}$ = 1.9 Hz)], A'M'X' [δ 8.40, 4.26 and 5.06 (1H, each, dd, $J_{3'',6'}$ = 8.6, $J_{6',7'}$ = 6.8 and $J_{3'',7'}$ = 1.8 Hz)], A"M"X" [δ 3.49, 4.23 and 4.99 (1H, each, dd, $J_{3''',6''}$ = 8.3, $J_{6'',7''}$ = 5.8 and $J_{3''',7''}$ = 2.0 Hz)] and A"'M"'X"' [δ 3.56, 3.93 and 4.94 (1H, each, dd, $J_{3'''',6'''}$ = 7.3, $J_{6''',7'''}$ = 5.4 and $J_{3'''',7'''}$ = 1.9 Hz)].

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