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The behaviour of the natural pyranonaphthoquinone pentalongin in alcoholic solvents

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Abstract—Pentalongin, the major constituent of the roots of the East African medicinal plant *Pentas longiflora* Oliv., undergoes degradation reactions when dissolved in alcoholic solvents. Although these reactions were thought initially to be of a photochemical nature, it is proven that degradation occurs also in the dark. These degradation reactions result in four new derivatives of pentalongin, which were elucidated as 3,4-dihydro-3-methoxypentalongin **4**, 3,4-dihydro-*trans*-3,4-dimethoxypentalongin **5**, 10b-hydroxy-3-methoxy-2a,3,6,10b-tetrahydro-2*H*,5*H*-furo[2,3,4-*ed*]naphtho-[2,3-*c*]pyran-6-one **6** and 3,4-dihydro-*trans*-3,4-diethoxypentalongin **7**.

1. Introduction

Pentas longiflora Oliv. (Rubiaceae), a woody herb from oriental intertropical Africa (Rwanda, Kenia), locally known as Isagara or Nekilango is used in the African traditional medicine to treat scabies and the skin mycosis pityriasis versicolor.[1] The two major constituents of the root bark of *P. longiflora*, pentalongin **1** and mollugin **2** were previously isolated[1,2] and a bioassay-guided fractionation revealed that pentalongin was the antifungal principle.[3] Pentalongin is a member of the family of naturally occurring pyranonaphthoquinone antibiotics, which are the subject of many synthetic studies.[4] Mollugin is an important benzisochromene antibiotic isolated the first time from *Gallium mollugo*.[5] Recently, a new type of tetracyclic naphthoquinone was isolated from the hexane extract of the root bark of *P. longiflora*, which was named isagarin **3** (Fig. 1).[6,7]

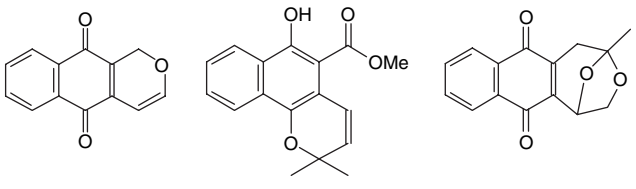

Figure 1. Isolated compounds from *P. longiflora*.

In continuation of the study of the chemical constituents of this plant, several new pyranonaphthoquinones **4**, **5** and **6**, originating from the intrinsic instability of pentalongin **1** towards the eluting solvent, are described. These results are important in view of the fact that pentalongin **1** is the active principle of the medicinal plant *P. longiflora* and that its instability in alcoholic solvents compromises its isolation.

2. Results and discussion

Previously, pentalongin **1** was synthesised in our group via several synthetic methods.[7a,b] It was observed that pentalongin **1** is not a very stable compound when dissolved in methanol. A change in colour appeared by which the intense red colour of pentalongin changes to yellow due to degradation upon standing. In contrast, crystalline pentalongin is not harmed by irradiation, even after a prolonged irradiation of 5 days. Due to the fact that pentalongin was discovered as the active principle of *P. longiflora*, the stability of this lead compound is important.

Indeed, during the fractionation of the hexane extract of the roots of *P. longiflora* on silica gel by MPLC and by elution with methanol, pentalongin **1** and other methoxylated derivatives **4**–**6** were obtained in small quantities. Similarly, when ethanol was used for elution over silica gel, a diethoxylated derivative **7** was isolated. These compounds are so-called artefacts from the isolation procedure of pentalongin and are a consequence of the instability of pentalongin towards the eluting solvent (Fig. 2).

Keywords: Pentalongin; Pyranonaphthoquinone; Natural products; *Pentas*.
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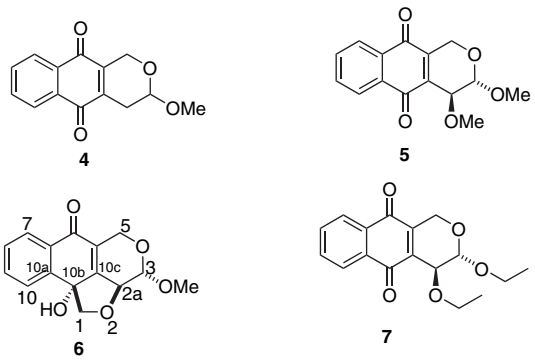


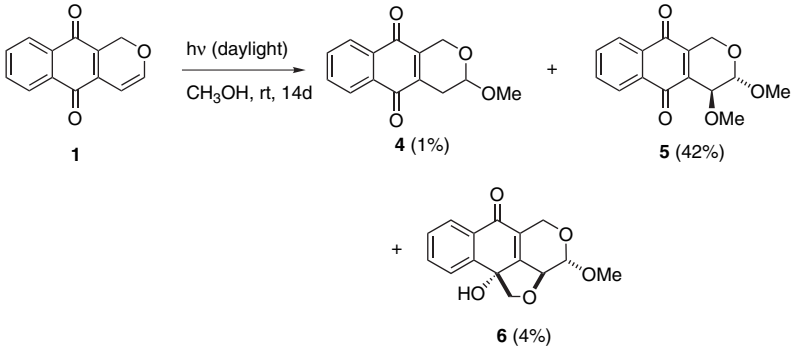
Figure 2. Artefacts in the isolation of pentalongin.

At first, the instability of pentalongin was thought to be of a photochemical nature. Based on the proposal that compounds **4**, **5** and **6** could be obtained by light irradiation of pentalongin, the photochemical reaction of pentalongin in methanol under daylight irradiation was carried out (Scheme 1).

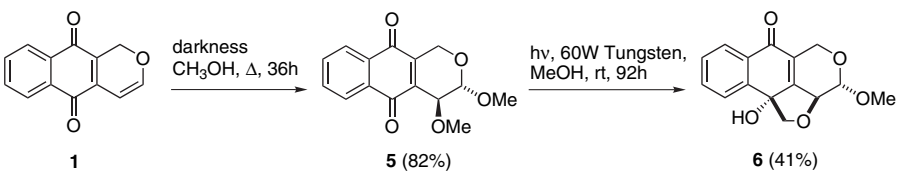
A solution of pentalongin in methanol was left in daylight at room temperature for 14 days in a glass vial. Chromatographic separation of the reaction mixture led to compounds **4**, **5** and **6** in 1%, 42% and 4% yield, respectively. This result does not exclude the possibility that pentalongin reacts with the solvent, i.e., methanol, in the absence of daylight. Therefore, a solution of pentalongin in methanol was heated under reflux in complete darkness (Scheme 2). The reaction was monitored on TLC and revealed the complete disappearance of pentalongin after 36 h. Spectroscopic analysis made clear that 3,4-dihydro-*trans*-3,4-dimethoxypentalongin **5** was formed in 82% yield. No trace of compound **4** or compound **6** was found. In order to exclude the influence of radicals, the reaction was repeated in a degassed solution under a nitrogen atmosphere and with the addition of 20 mol % hydroquinone as a radical scavenger. Again, using these reaction conditions and after 64 h of reflux in methanol in the dark, all pentalongin was consumed and compound **5** was formed (isolated yield 76%).

In an attempt to explain the formation of the tetracyclic compound **6** in the daylight, the dimethoxy compound **5** was exposed to radiation. A solution of 3,4-dihydro-*trans*-3,4-dimethoxypentalongin **5** in methanol in a glass vial was irradiated by means of a 60 W tungsten lamp while being cooled in an ice-bath. The reaction was monitored by UV-analysis (Fig. 3). Compound **5** showed a typical absorption at 260 nm and 446 nm. After 36 h the absorption pattern was significantly different. After 96 h, no further change appeared and the reaction was stopped. Spectroscopic analysis revealed the absence of compound **5** and the presence of tetracylic compound **6** in 41% yield together with some unidentified material. In order to exclude the influence of the solvent, the reaction was repeated in hexane and this resulted in the same compound **6** in a similar yield of 37% together with unidentified material.

These findings make it possible to propose the following reaction mechanism (Scheme 3). The fact that the formation of 3,4-dihydro-*trans*-3,4-dimethoxypentalongin **5** is possible in complete absence of light, in a nitrogen atmosphere and in the presence radical scavengers strongly suggests a non-radicalar mechanism. A Michael addition is feasible at the C-3 carbon, which results in the adduct **8**. Bearing in mind the anomeric effect, it leaves the methoxy moiety to end up in a pseudoaxial manner.[8] In the next step, there are two possibilities. Keto–enol tautomerisation results in the formation of compound **4**, which can be found back in minor quantities (1%). More likely, a second Michael addition occurs across enone **8** to afford intermediate **9**, which results in the dimethoxy compound **5** after spontaneous oxidation by air. This compound **5** is isolated as the major fraction in an 82% yield. By reason of steric hindrance the methoxy group attacks from the *anti*-side. The reasoning behind the relative



Scheme 1.



Scheme 2.

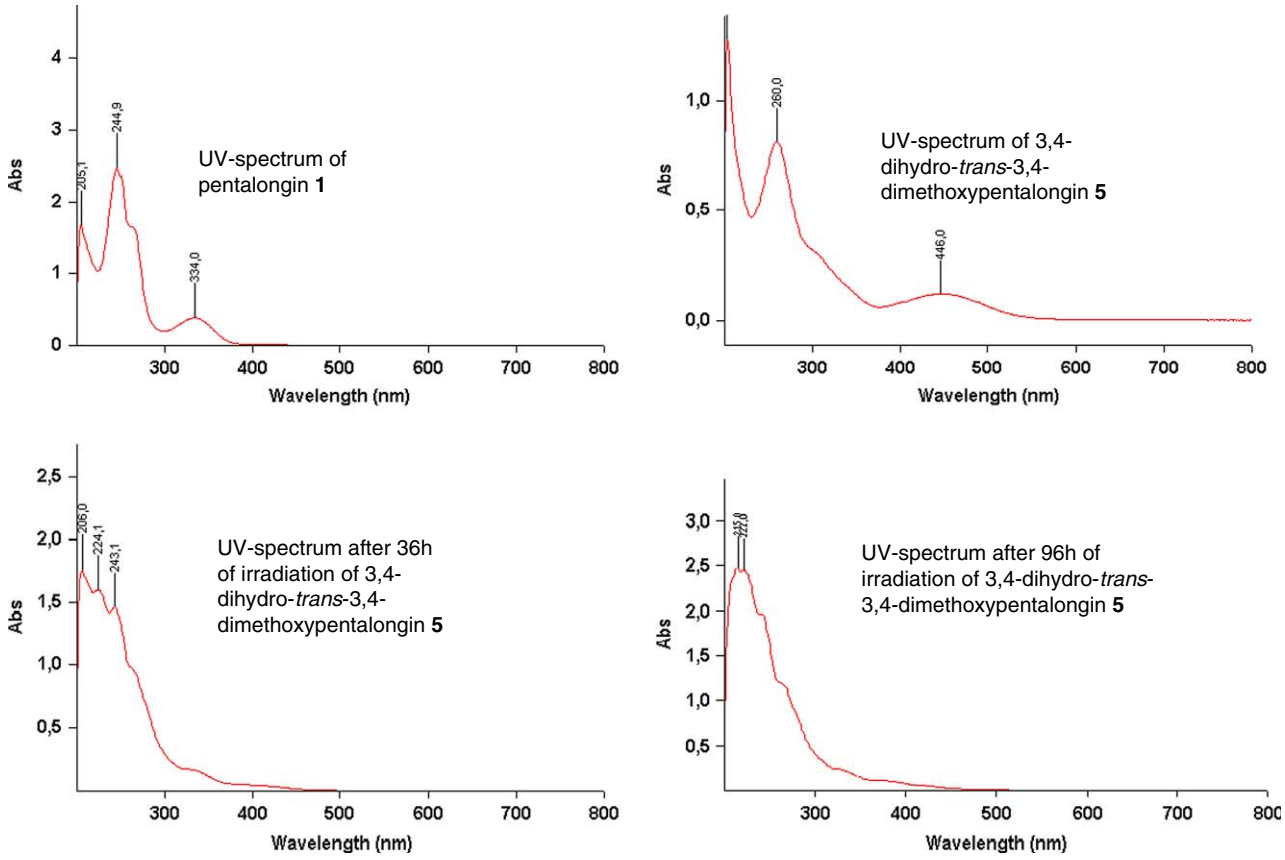
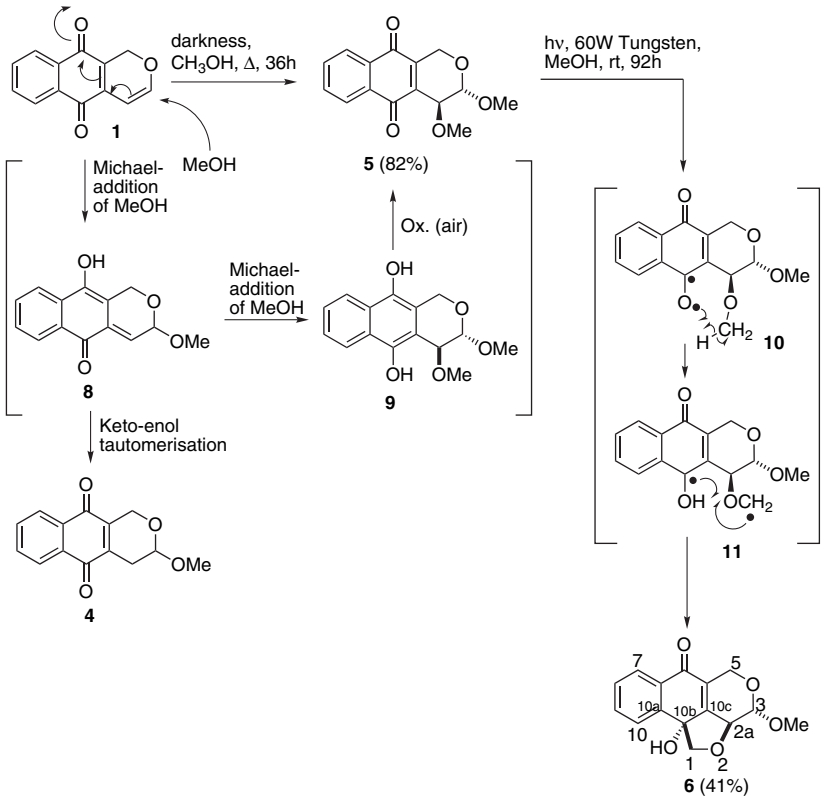


Figure 3. UV-spectra of the reaction mixture of the reaction of pentalongin **1** in methanol in the dark.



Scheme 3.

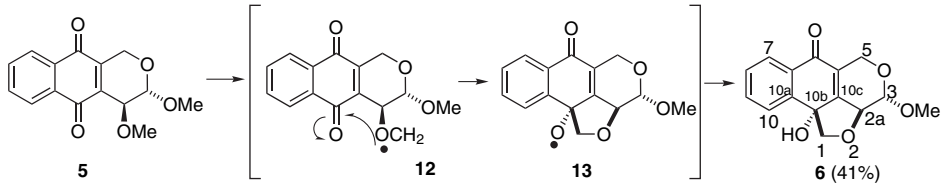
stereochemistry of 3,4-dihydro-*trans*-3,4-dimethoxypentalongin **5** was experimentally confirmed by ^{1}H NMR. The very small value of 0.9 Hz for the coupling constant ($J_{3,4}$=0.9 Hz) in the ^{1}H NMR spectrum of compound **5** indicates a pseudoequatorial–equatorial position for H-4 and H-3 in the half-chair conformation. In addition, the confirmation of the pseudoequatorial orientation of H-4 is based on the axial orientation of methoxy group at C-3, favoured by the anomeric effect.[8] Furthermore, the pseudoequatorial orientation of H-4 could be confirmed by long-range coupling between H-1 and H-4 with $J_{1,4}$=1.3 Hz ($Ja'a'>Ja'e'=Je'a'>Je'e'<0.5$ Hz).[9]

The formation of the tetracyclic compound **6** in the irradiation reaction can be explained by a Norrish type II photocyclisation. This type II photocyclisation has been observed before in the unusual photocyclisation of 2-alkoxy-1,4-naphthoquinones.[10] An intramolecular H-abstraction of the methoxy group at C-4 by the oxygen radical of the carbonyl results in radical **11**. This biradical undergoes a cyclisation reaction resulting in the final product **6**.[11] An alternative cyclisation mechanism is depicted in Scheme 4. Intermolecular H-abstraction of a proton at the methoxy group at C-4 results in compound **12**. This will result in a ring closure at the carbon of the carbonyl to form the intermediate radical **13**, which will result in the final compound **6** after intermolecular H-abstraction.

In addition, the trans-configuration of the two protons H-2a and H-3 of the tetracyclic compound **6** was determined by NOE-experiments. The coupling constant ($J_{2a,3}$=6.3 Hz) in the ^{1}H NMR spectrum is an insufficient indication for the stereochemistry of the compound. Therefore, NOE-experiments were performed (Fig. 4). Irradiation of the methoxy group at 3.59 ppm ($CDCl_3$) resulted in a NOE (4.6%) for the signal of H-2a at 4.20 ppm and a NOE (3.4%) for the signal of H-5 at 4.52 ppm. Irradiation of the signal at 4.20 ppm gave a substantial NOE (5.8%) for the methoxy peak at 3.59 ppm. These findings can only be explained if the compound adopts a structure in which H-2a and H-3 have a trans-configuration.

In order to check the influence of the alcoholic solvent on the isolation of natural products from *P. longiflora*, chromatographic separation of a pentalongin-rich fraction with silica gel was performed with ethanol. *trans*-3,4-Diethoxy-3,4-dihydropentalongin **7** was isolated by MPLC on silica gel by elution with EtOH to give a light yellow oil (3.1% yield). The mass spectrum (EIMS) displayed a molecular ion (M^+; 3%) at *m*/*z* 302, which is consistent with the molecular formula $C_{17}H_{18}O_5$. The isolated compound showed a close resemblance to *trans*-3,4-dihydro-3,4-dimethoxypentalongin **5** as demonstrated by the same pattern of IR, ^{1}H NMR and ^{13}C NMR spectral data. Only the two methoxy signals in **5** were replaced by two ethoxy signals. Accordingly, the structure of the isolated compound was deduced as *trans*-3,4-diethoxy-3,4-dihydropentalongin **7**. The trans-configuration for H-3 and H-4 was determined by ^{1}H NMR. The very small coupling constant ($J_{3,4}$=1.0 Hz) in the ^{1}H NMR spectrum ($CDCl_3$) of compound **7** indicates a pseudoequatorial–equatorial relationship of H-4 and H-3. In addition, the pseudoequatorial configuration was confirmed by long-range coupling of H-4 and H-1 ($J_{4a'1a'}$=1.8 Hz), which indicated the trans-configuration for H-3 and H-4. All signals of the IR spectrum, DEPT spectrum, 2D-COSY spectrum and the HETCOR spectrum were in accordance with the assigned structure **7**.

To verify the conversion of pentalongin to *trans*-3,4-diethoxy-3,4-dihydropentalongin **7**, pentalongin **1** was dissolved in absolute ethanol and left in daylight at room temperature for 14 days (Scheme 5). This reaction was much more complex as compared to the same reaction in methanol from which these compounds were isolated in a total yield of 47%. However, the reaction of pentalongin **1** in EtOH led to the formation of *trans*-3,4-diethoxy-3,4-dihydropentalongin



Scheme 4.

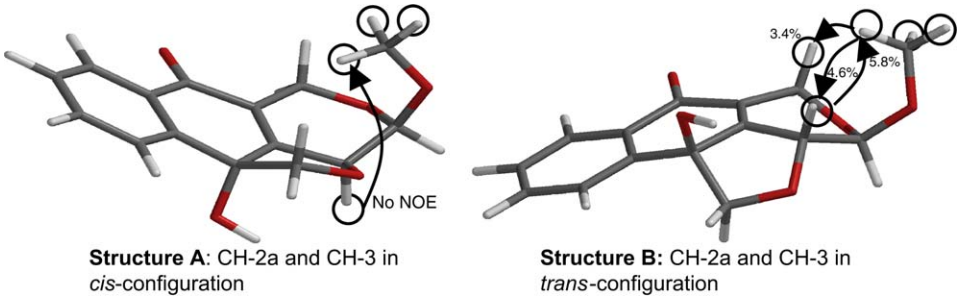
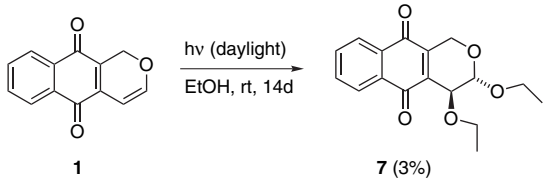


Figure 4. NOE analysis of the tetracyclic compound **6** ($CDCl_3$).

7 in only 3% yield. A range of unidentified compounds were noted by TLC analysis and by NMR spectroscopy. Apparently, several unidentified, not specific reactions took place and it was decided not to examine further this complex reaction.



Scheme 5.

3. Conclusion

Crystalline pentalongin **1** is not harmed by irradiation. Pentalongin **1** in methanol is easily transformed into compounds **4**, **5** and **6**. Pentalongin **1** can also be converted into the diethoxy analogue **7** in a low yield by treating it with ethanol. These compounds are new derivatives of the naturally occurring pentalongin **1**. Irradiation of 3,4-dihydro-*trans*-3,4-dimethoxypentalongin **5** results in the tetracyclic compound **6**, which is a novel compound with a novel heterocyclic skeleton.

4. Experimental

4.1. General

Melting points were determined on a Buchi 535 apparatus. ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded with a Jeol JNM-EX 300 NMR spectrometer. IR spectra were measured with a Perkin Elmer Model 983 spectrophotometer. Mass spectra were recorded with a Varian MAT 112 mass spectrometer (70 eV).

4.2. Plant material

The roots of *P. longiflora* were collected in the Menengai Crater (Nakuru District, Kenya) at an altitude of 2400 m on July 24, 1996. G. M. Mungai and D. O. Nyakundi (National Museum of Nairobi, Kenya) identified the plant and voucher herbarium species were deposited in the East African Herbarium at the National Museum in Nairobi (Kenya) (Mungai and Nyakundi no. 464). The roots were dried in a ventilated oven at 45 °C during 3 days and powdered mechanically (Retsch GmbH, type SK1, 1100 W, 2840 rpm, ∅ 2 mm).

4.3. Extraction

The powdered roots of *P. longiflora* (4.1 kg) were successively extracted in a percolator until exhaustion with *n*-hexane (C_6H_{12}), dichloromethane (CH_2Cl_2), ethyl acetate (EtOAc) and methanol (MeOH). The extracts were filtered over a filter paper (Schleicher and Schuell, 5951/2 folded filters, ∅ 240 mm) and concentrated under reduced pressure at 40 °C yielding a dark red residue (44.0 g, yield 1.07%).

4.4. Isolation of pentalongin derivatives

The hexane extract (44 g) was absorbed on silica gel (440 g) and submitted to medium pressure liquid chromatography MPLC (glass column 460×100 mm ∅) on silica gel. Sample application was executed with a Prep Elute dry application column from Büchi (230×23 mm ∅). Solvent delivery was performed with a chromatography pump. Flow rate: ≅110 ml/min, corresponding to ≅25 bar backpressure. The elution was performed using an *n*-hexane/EtOAc gradient: Hex/EtOAc 5% (180 min), Hex/EtOAc 10% (60 min), Hex/EtOAc 25% (30 min), Hex/EtOAc 50% (30 min), EtOAc 100% (30 min), and finally washed with MeOH 100% (60 min). After monitoring by TLC, 26 fractions were obtained. Fraction 9 (Hex/EtOAc 5%) afforded a pure compound (5.870 g, 0.143% yield) that was identified as pentalongin **1**, based on its spectral data and its physical properties. Spectral data of pentalongin have been described previously.[1,2]

4.5. Reaction of pentalongin 1 in alcoholic solvents in daylight

Pure pentalongin **1** (700 mg) was dissolved in 35 ml of absolute methanol, and this solution was subjected to daylight (sunlight) during a period of two weeks. The solvent was removed in vacuo to give the crude product, which was chromatographed on silica gel by MPLC at pressure from 20 to 30 bar. Flow rate: ≅90 ml/min corresponding to ≅25 bar backpressure to give compounds **4** (1%), **5** (42%) and **6** (4%).

4.5.1. 3-Methoxy-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (3-methoxy-3,4-dihydropentalongin) 4. Yellow crystals, mp 125.6–126.3 °C (from $CHCl_3$). IR (KBr) ν_{max}: 1655 (C=O), 1650 (C=O), 1590 (C=C), 1330, 1290, 1220, 1130, 1050, 1005, 860, 790 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.74–2.78 (2H, m, CH_2-4), 3.48 (3H, s, OMe), 4.56 (1H, d×t, J_d=18.5 Hz, J_t=3.3 Hz, C*H*H-1), 4.70 (1H, d×t, J_d=18.5 Hz, J_t=2.0 Hz, CH*H*-1) 5.02 (1H, t, J=3.0 Hz, CH-3), 7.70–7.74 (2H, m, =CH-7 and =CH-8), 8.05–8.10 (2H, m, =CH-6 and =CH-9). ^{13}C NMR (68 MHz, $CDCl_3$): δ 27.42 (CH_2-4), 55.39 (OMe), 56.51 (CH_2-1), 96.63 (O–*C*H–OMe), 126.39 and 126.64 (=CH-6 and =CH-9), 131.76 and 131.98 (2×=C_q), 133.69 and 133.76 (=CH-7 and =CH-8), 139.22 and 141.14 (2×=C_q), 183.33 and 183.46 (2×C=O). EIMS *m*/*z* (rel int.): 244 (M^+; 9), 213 (8), 184 (100), 156 (27), 128 (38), 104 (12), 76 (17), 50 (8). Anal. Calcd $C_{14}H_{12}O_4$: C 68.85, H 4.95; found C 68.98, H 5.12.

4.5.2. *trans*-3,4-Dimethoxy-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (*trans*-3,4-dimethoxy-3,4-dihydropentalongin) 5. Yellow sticky compound, mp 90.4–91.1 °C (from MeOH). IR (KBr) ν_{max}: 1665 (C=O), 1650 (C=O), 1595 (C=C), 1330, 1290, 1252, 1190, 1180, 1150, 1110, 900, 700 cm^{-1}. ^{1}H NMR (270 MHz $CDCl_3$): δ 3.48 (3H, s, OMe), 3.59 (3H, s, OMe), 4.23 (1H, d×d, J=1.3, J=0.9 Hz, CH-4), 4.49 (1H, d×d, J_d=19.5 Hz, J_d=1.3 Hz, C*H*H-1), 4.75 (1H, d, J=19.5 Hz, CH*H*-1), 5.02 (1H, d, J=0.9 Hz, CH-3), 7.72–7.76 (2H, m, =CH-7 and =CH-8), 8.05–8.14 (2H, m, =CH-6 and =CH-9). ^{13}C NMR (68 MHz, $CDCl_3$): δ 55.97 (OMe), 56.38 (CH_2-1), 59.08 (OMe), 68.60 (CH-4), 97.78 (CH-3), 126.16 and 126.55

(=CH-6 and =CH-9), 131.69 and 131.92 (2×=C_q), 133.79 and 134.10 (=CH-7 and =CH-8), 136.99 and 142.96 (2×=C_q), 182.94 and 183.66 (2×C=O). EIMS *m/z* (rel int.): 274 (M^+; 3), 242 (16), 227 (12), 214 (35), 197 (27), 183 (13), 163 (9), 155 (8), 141 (11), 127 (16), 115 (21), 97 (21), 85 (38), 71 (58), 57 (100). Anal. Calcd $C_{15}H_{14}O_5$: C 65.69, H 5.15; found C 65.87, H 5.27.

4.5.3. 10b-Hydroxy-3-methoxy-2a,3,6,10b-tetrahydro-2*H*,5*H*-furo[2,3,4-*ed*]naphtho[2,3-*c*]pyran-6-one 6. Light yellow solid compound, mp 194.4–195.3 °C. IR (KBr) ν_{max}: 3400 (OH), 1650 (C=O), 1600 (C=C), 1450, 1400, 1390, 1300, 1120, 1230, 1175, 1150, 1105, 1075, 1045, 1015, 990, 935, 870, 810, 775, 710 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 3.58 (3H, s, OCH_3), 3.72 (1H, d, *J*=9.4 Hz, C*H*H-1), 4.19 (1H, d×t, *J*=6.3 Hz, *J*=2.3 Hz, CH-2a), 4.48 (1H, d×d, *J*=17.2 Hz, *J*=2.6 Hz, C*H*H-5), 4.51 (1H, d, *J*=9.4 Hz, CH*H*-1), 4.75 (1H, d, *J*=6.3 Hz, CH-3), 4.84 (1H, d×d, *J*=17.2, *J*=2.1 Hz, CH*H*-5), 7.50–7.70 (2H, m, =CH-8 and =CH-9), 8.09–8.75 (2H, m, =CH-7 and =CH-10). ^{13}C NMR (68 MHz, $CDCl_3$): δ 181.88 (C=O), 151.80 (=C_q-10c), 140.6 (=C_q-10a), 133.72 (=CH-7), 130.15 (=C_q-6a), 129.36 (=CH-9), 128.83 (=C_q-5a), 127.85 (=CH-10), 127.14 (=CH-8), 102.76 (OCO), 77.33 (CH_2-1), 73.92 (CH-2a), 72.18 (C_q-10b), 63.70 (CH_2-5), 56.69 (OCH_3). EIMS *m/z* (rel int.): no M^+, 258 (M^+-16; 1), 214 (47), 197 (100), 169 (10), 141 (15), 128 (13), 115 (14), 101 (4), 85 (7), 77 (11). Anal. Calcd $C_{15}H_{14}O_5$: C 65.69, H 5.15; found C 65.41, H 5.06.

4.5.4. *trans*-3,4-Diethoxy-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (*trans*-3,4-diethoxy-3,4-dihydropentalongin) 7. Pure pentalongin **1** (100 mg) was dissolved in 35 ml of absolute ethanol and this solution was subjected to daylight (sunlight) during a period of two weeks. The solvent was removed in vacuo to give the crude product, which was chromatographed on silica gel by MPLC at a pressure from 20 to 30 bar. Flow rate: ≅90 ml/min corresponding to ≅25 bar backpressure to afford compound **7** as a light yellow oil (3.1% yield). IR (KBr) ν_{max}: 1665 (C=O), 1650 (C=O), 1590 (C=C), 1480, 1450, 1430, 1410, 1330, 1290, 1250, 1180, 1150, 1110, 1100, 1070, 900, 880, 850, 790 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 1.21 (3H, t, *J*=7.3 Hz, CH_3), 1.25 (3H, t, *J*=7.3 Hz, CH_3), 3.48–3.73 (2H, m, OCH_2), 3.78–3.97 (2H, m, OCH_2), 4.30 (1H, dd, *J*=1.8 Hz, *J*=1.0 Hz, =CH-3), 4.47 (1H, d×d, *J*=19.4 Hz, *J*=1.8 Hz, C*H*H-1), 4.75 (1H, d, *J*=19.4 Hz, CH*H*-1), 5.09 (1H, d, *J*=1.0 Hz, CH-4), 7.73–7.76 (2H, m, =CH-7 and =CH-8), 8.06–8.14 (2H, m, =CH-6 and =CH-9). ^{13}C NMR (68 MHz, $CDCl_3$): δ 14.98 (CH_3), 15.61 (CH_3), 56.33 (CH_2-1), 64.06 (OCH_2), 67.25 (OCH_2), 67.54 (CH-4), 97.03 (CH-3), 126.12 and 126.52 (CH-6 and CH-9), 131.7 and 132.09 (2×=C_q), 133.7 and 134.05 (=CH-7 and =CH-8), 137.4 and 142.9 (2×=C_q), 182.9 and 183.8 (2×C=O). EIMS *m/z*: 302 (M^+; 3), 257 (7), 228 (100), 221 (8), 212 (10), 200 (31), 194 (64), 187 (10), 186 (15), 173 (13), 172 (90), 144 (23). Anal. Calcd $C_{17}H_{18}O_5$: C 67.54, H 6.00; found C 67.69, H 5.88.

4.6. Reaction of pentalongin 1 in the absence of daylight

Absolute methanol (20 ml) was degassed by nitrogen and 20 mg hydrochinon was added. The solution was stirred for 30 min under a nitrogen atmosphere. Then 100 mg of pentalongin **1** was added in complete darkness. After 64 h of refluxing, the solution was cooled and the solvent was evaporated taking care to avoid daylight irradiation. Flash chromatography using Hex/EtOAc 85/15 as eluents resulted in 105 mg (82%) of *trans*-3,4-dimethoxy-3,4-dihydropentalongin) **5** as a yellow sticky compound (R_f-value: 0.2). Spectral data are as previously described, vide supra.

4.7. Reaction of *trans*-3,4-dimethoxy-3,4-dihydropentalongin 5 under irradiating conditions

A solution of 40 mg of *trans*-3,4-dimethoxy-3,4-dihydropentalongin **5** in 5 ml of absolute methanol in a glass vial was put in a reflexion chamber and a tungsten lamp of 60 W was used to irradiate the sample. The glass vial was put at a sufficient distance of the tungsten lamp taking care-not to heat the reaction. When the temperature reached 35 °C the glass vial was cooled down in an ice-bath. The reaction was monitored by UV and after 96 h the solvent was evaporated. Thin layer chromatography was applied to purify the mixture using Hex/EtOAc 9/1 as eluent, which resulted in 16 mg (41%) of a yellow solid compound, i.e., 10b-hydroxy-3-methoxy-2a,3,6,10b-tetrahydro-2*H*,5*H*-furo[2,3,4-*ed*]-naphtho[2,3-*c*]pyran-6-one **6** (R_f-value: 0.48). Spectral data are as previously described, vide supra.

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