ARTICLE

OBC
www.rsc.org/obc

A versatile, non-biomimetic route to the preussomerins: syntheses of (±)-preussomerins F, K and L

Ernesto Quesada, Martin Stockley, Jacques P. Ragot, Michael E. Prime, Adrian C. Whitwood and Richard J. K. Taylor*

Department of Chemistry, University of York, Heslington, York, UK YO10 5DD.
E-mail: rjkt1@york.ac.uk; Fax: +44 (0) 1904 432523; Tel: +44 (0) 1904 432606

Received 26th May 2004, Accepted 5th July 2004
First published as an Advance Article on the web 9th August 2004

The first total syntheses of the *title* fungal metabolites preussomerins F, K and L are described and their structures confirmed thereby. The syntheses were achieved following a versatile, unified, non-biomimetic approach, which is easily extendable to prepare other known and novel members of this family. Key steps include the functionalisation of a 2-arylacetal anion, tandem one-pot Friedel–Crafts cyclisation–deprotection, regioselective substrate-directable hydrogenation and reductive-opening of epoxides.

Introduction

In the past two decades, an extensive number of novel bis-naphthalene-based bioactive natural products have been isolated from fungi.[1] Biosynthetically, all these metabolites have a common origin, being generated by radical oxidative dimerisation of two naphthalene units *via* the 1,8-dihydroxynaphthalene (DHN) pathway.[2] These growing new families of spirobisnaphthalene natural products have a unique structural feature involving two or three oxygen atoms acting as bridges connecting the original naphthalene subunits, which additionally exhibit an elaborate range of functionality patterns, generally involving partial saturation and further oxidation of the original aromatic cores.

Most of these metabolites exhibit significant antifungal and antibacterial properties as a consequence of the interspecies competition among dung-inhabiting fungi in nature. However, the main biological interest concerns their capability to inhibit farnesyl-protein transferase (FTPase) in a highly selective fashion. This enzyme plays a critical role in the post-translational modification of a huge range of different proteins involved in intracellular signalling.[3] In particular, FTPase attaches a farnesyl group to the thiol of a cysteine side chain of the Ras proteins. The cysteine residue belongs to a characteristic carboxy-terminal consensus sequence known as the CAAX box, whose prenylation is of great importance in cellular proliferation through membrane-binding processes. One of the substrates of the FTPase is the protein GTPase Ras, whose oncologically mutated form is found in over 30% of human cancers, particularly colon, lung, thyroid, bladder and pancreatic carcinomas, as well as in several types of leukaemias. As a result, FTPase inhibitors have been developed as potential antitumour therapeutic drugs, blocking the growth of human cancers.[4] Recent studies have demonstrated that these compounds also constitute an efficient alternative therapy for the treatment of parasitic infections, especially against malaria.[5]

These achievements have been mainly based on the screening of natural products. Among the main representative groups of spiro-bisnaphthalene-derived naturally occurring substances with FTPase inhibitory activity are the diepoxins,[6] palmarumycins,[7] spiroxins[8] and preussomerins. Fig. 1 illustrates a representative example of each family.

This paper is concerned with the preussomerin family of natural products, which currently consists of 13 known fungal metabolites (Fig. 2).[9] Preussomerin A was the first member of the family to be isolated from the coprophilous fungus *Preussia isomera* by Gloer and co-workers in 1990.[9a] Subsequently, closely related preussomerins B–F were isolated from the same organism.[9b] Preussomerin D was also later isolated from the endophytic fungus *Hormonema dematioides* recovered from living plant tissue of a coniferous tree.[9c] New additions to this family of natural products came in 1994, when

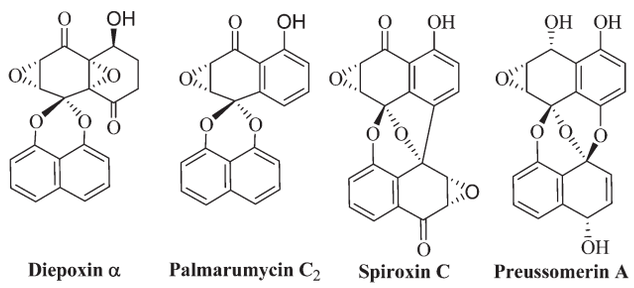


Fig. 1 Representative members of the structurally-related naturally occurring substances with FTPase inhibitory activity.

Singh *et al.* isolated preussomerins G, H, and I from an unidentified dung-inhabiting coelomycetous fungus (MF5916).[9d] An unusual new preussomerin analogue, characterised as 3′-*O*-desmethyl-1-epi-preussomerin C, was next isolated from cultures of the coprophilous fungus *Sporormiella vexans*.[9e] Most recently, the latest additions to the family were reported by Krohn *et al.*, who isolated three new representatives, preussomerin J, K and L from a non-taxonomically characterised endophytic fungi (*Mycelia sterila*) from the roots of *Atropa belladonna*, confirming their absolute configuration by elegant comparison of experimental and theoretical CD spectra.[9f] Preussomerin K, as well as preussomerins E–I, were also isolated independently by Isaka and co-workers from a lichenicolous fungus *Microsphaeropsis* sp. BCC 3050.[9g] These authors have suggested that preussomerin I could be a by-product generated during the isolation protocol by Michael addition of MeOH to preussomerin G, while preussomerins J and K look to be real metabolites present in the crude strain extract before purification.[9f,g]

All of the preussomerins showed pronounced antifungal activity as well as inhibiting Gram-positive bacteria. However, the most important discovery regarding the biological activity of this family of natural products was carried out by Singh *et al.*, who demonstrated that preussomerins are able to inhibit FTPase, preussomerin G and D being the most active (IC_{50} 1.2 μM).[9d]

From the structural point of view, all the members of the preussomerin family are characterised by the same key structural feature, having the original naphthalene units linked by three oxygen atoms, generating a bis-spiroacetal functionality. This remarkable head-to-tail trioxabicyclo[3.3.1]nonane bis-acetal nucleus represents a unique and unexpectedly stable core in the natural kingdom, and constitutes an extremely challenging target for total synthesis.

In all cases, the original naphthalene subunits have been partially reduced and oxidised. The original double bonds can be epoxidised, the epoxides then reductively opened or the carbonyl groups reduced to hydroxyl groups.

DOI: 10.1039/b407895k

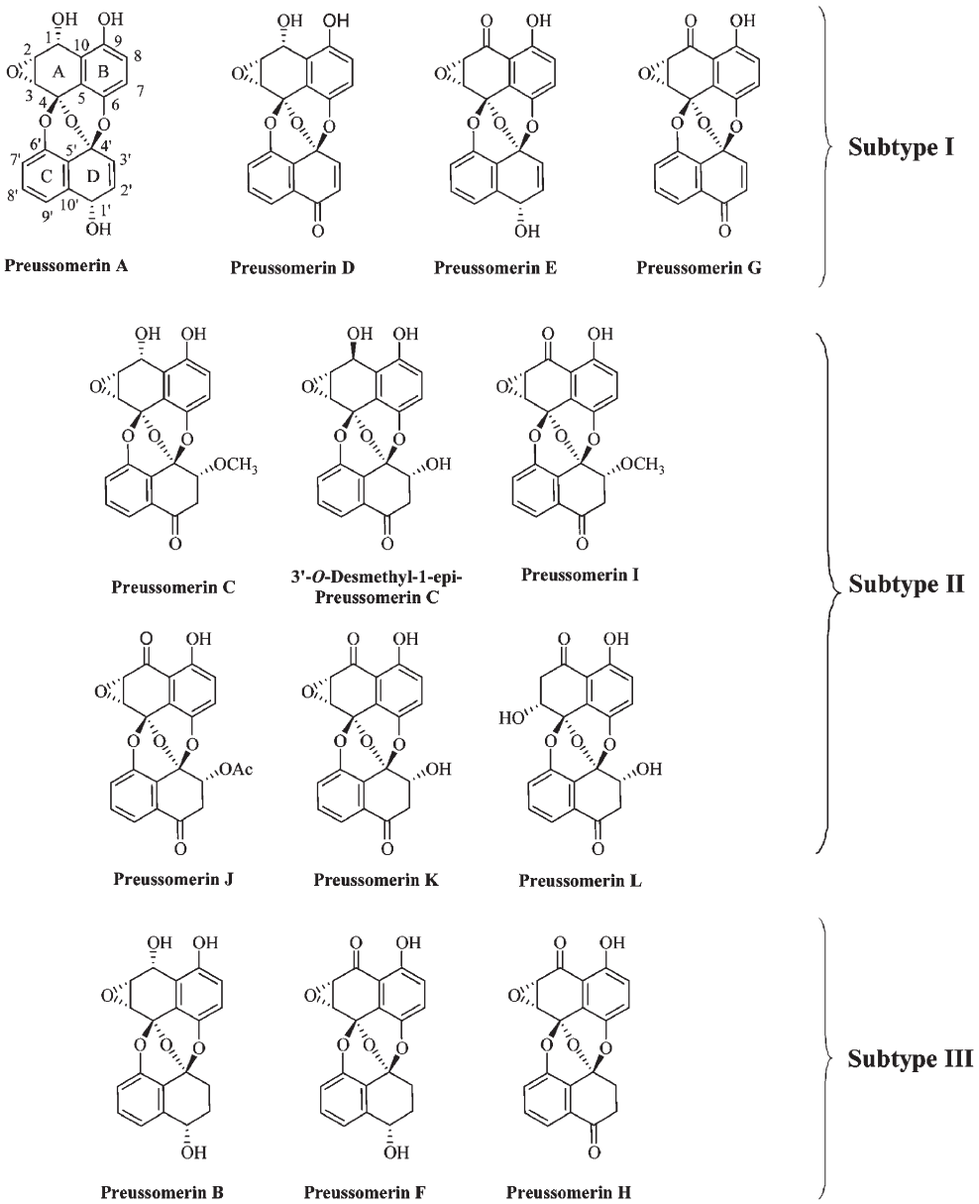
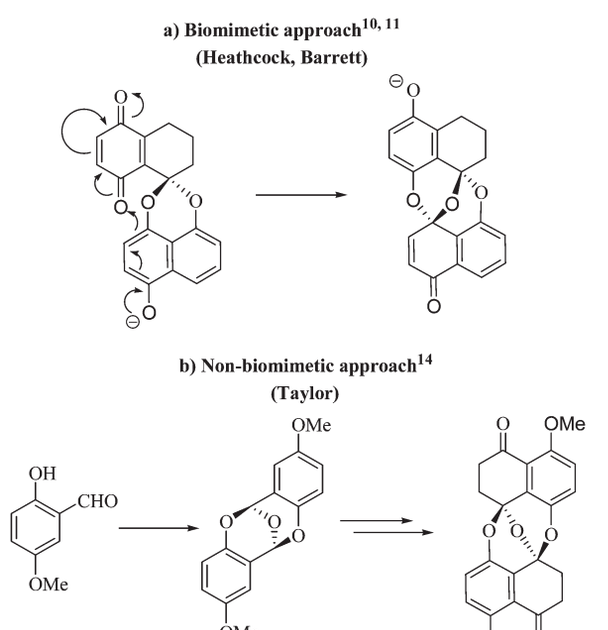


Fig. 2 The currently known members of the preussomerin family of natural products.

As can be seen from Fig. 2, preussomerins share a common bis-acetal skeleton. However, on the basis of the specific structural features of each member of the family, these compounds can be grouped into different subtypes. As a general rule, the northern hemisphere exhibits a common α,β-epoxyketone or α,β-epoxy-alcohol unit. The differences dwell in the southern hemisphere of the molecule. The first set of compounds contain a conjugated ketone or allylic alcohol on this bottom subunit (**Subtype I**, preussomerins A, D, E, and G). An additional subgroup can be formed by preussomerin C, 3′-*O*-desmethyl-1-epi-preussomerin C, and preussomerins I, J, K and L, which could be generated from the subtype I compounds by conjugate addition of oxygenated nucleophiles to the double bond or reductive-opening of a pre-existing epoxide on the subunit (**Subtype II**). A final subtype of preussomerins can be characterised by the presence of a ketone or alcohol function on the benzylic position of the bottom hemisphere, without further functionality (**Subtype III**, preussomerins B, F and H).

The first synthesis of any member of the preussomerin family was carried out by Heathcock and Chi, who reported an elegant total synthesis of (±)-preussomerins G and I.[10] This approach followed an elegant putative biomimetic pathway based on the spontaneous oxidative dimerisation of naphthalenediol monoacetal (Scheme 1a). Further work by Barrett *et al.* described a unified synthesis of the palmarumycin and preussomerin natural products based again on a potentially biomimetic oxidative spirocyclisation as the key



Scheme 1 Key steps from the bio-mimetic approaches[10,11] and *via* a bis-acetal intermediate.[14]

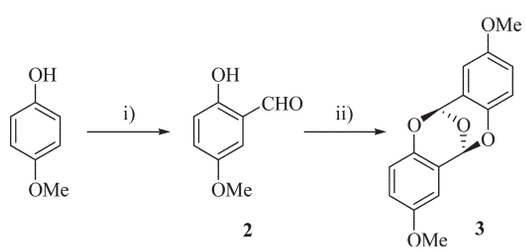
step. A previous asymmetric epoxidation of a palmarumycin-type intermediate enone allowed them access to enantiomerically pure (−)-preussomerin G.[11]

The interest of our own group in preussomerins began as part of a program to prepare a range of different FTPase inhibitors for biological screening (*e.g.* manumycin A,[12] palmarumycins CP_1, CP_2, and C_{11}, CJ-12371 and deoxypreussomerin A[13]). Our approach is based on a novel, non-biomimetic strategy involving the use of 2-arylacetal anions obtained from a simplified bis-acetal (Scheme 1b).

The proposed synthetic pathway described herein involves the formation of the bis-ketal in a single step and at an early stage of the synthesis, with subsequent elaboration of the outer fringes of the molecule. We initially investigated the use of this methodology for the construction of advanced synthetic preussomerin analogues containing the full carbon skeleton of the natural products[14] and subsequently we applied these methods in the total syntheses of preussomerin K and L.[15] Now, in this paper, we describe full details of our optimised and extended approach towards the total syntheses of preussomerins K and L as well as reporting the first synthesis of preussomerin F.

Results and discussion

Our approach is novel in that the bis-acetal nucleus of the preussomerins is formed at the start of the synthesis. Thus, the inexpensive and readily available 4-methoxyphenol was converted into multigram quantities of 5-methoxysalicylaldehyde **2** by an easy, magnesium methoxide-mediated *ortho*-specific formylation in good yield (>90% in a 30 g scale).[16] Subsequent dimerisation of **2** smoothly provided the key racemic bis-acetal **3** in excellent yield following our previously described methodology (Scheme 2).[14] A simplification of this earlier procedure allowed us to isolate **3** without extractive work-up by direct filtration and washing with petrol, avoiding the large scale recrystallisation from diethyl ether previously employed. We were then in a position to elaborate **3** into the full preussomerin skeleton.

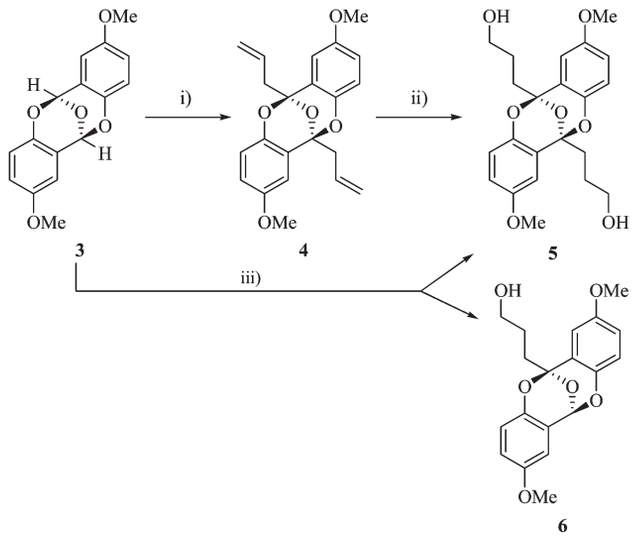


Scheme 2 *Reagents and conditions*: i) $Mg(OMe)_2$, paraformaldehyde, toluene, 90 °C (>90%); ii) pivalic anhydride, H_2SO_4, rt, 1 h (90%).

Acetal protons from the key intermediate **3** were predicted to be acidic due to donation of the resulting negative charge into the adjacent σ* anti-bonding orbitals, thus allowing sequential alkylation of the 2- and 2′-positions. Construction of the saturated rings A and D of the preussomerin skeleton should then be possible by further elaboration of newly introduced alkyl groups.

We needed to introduce a functionalised alkyl group, which would allow us to subsequently elaborate the A and D rings of preussomerins. We chose first to utilise the allyl group. From the practical point of view, model studies demonstrated that the first deprotonation of the bis-acetal **3** could be achieved with n-BuLi. This carbanion was allylated easily in high yield. However, the second deprotonation was found to be more complex, and required the use of a stronger base. s-BuLi gave a significant improvement for this second deprotonation, allowing the introduction of a second allyl group. The sequential deprotonation–alkylation of intermediate **3** allowed us to introduce a double allyl functionality giving **4**, which was further converted into the bis-primary alcohol **5** using 9-BBN followed by oxidative work-up (Scheme 3).

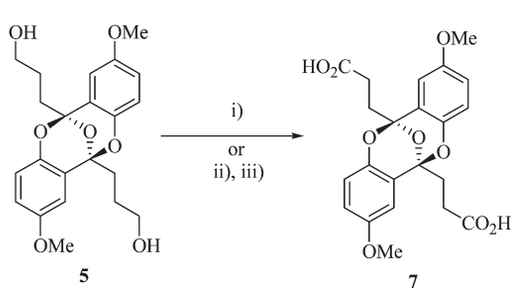
Despite the success of the conversion of **4** into **5**, we found that this procedure was practically difficult and gave variable yields. A higher yielding and more direct way of accessing diol **5** involving



Scheme 3 Sequential functionalisation of the bis-acetal core. *Reagents and conditions*: i) a) n-BuLi, THF, −78 °C; b) allyl bromide; c) s-Buli, THF, −78 °C; d) allyl bromide (52%); ii) a) 9-BBN, THF, 0 °C; b) NaOH, H_2O_2 (62%). One-pot procedure. *Reagents and conditions*: iii) n-BuLi, THF, −78 °C, 30 min; then oxetane, $BF_3{\cdot}Et_2O$, from −100 to −40 °C over 90 min; then s-BuLi, THF, −78 °C, 30 min; then oxetane, $BF_3{\cdot}Et_2O$, from −100 to −40 °C over 4 h (52% **5**, 32% **6**).

a *one-pot* deprotonation–alkylation sequence using oxetane as the electrophile was thus developed. The first alkylation proceeded smoothly using n-BuLi as base giving **6**. The second alkylation used s-BuLi as base. This latter alkylation must be carried out in the presence of a Lewis acid, such as $BF_3{\cdot}$etherate, to allow reasonable yields. The reaction was further improved by adding the oxetane–$BF_3{\cdot}$etherate system sequentially at low temperature (−100 °C) and by using an excess of the electrophile for the second alkylation (Scheme 3). Under these conditions, the symmetrical diol **5** was provided in a moderate 52% overall yield, along with monoalcohol **6** (32% yield).

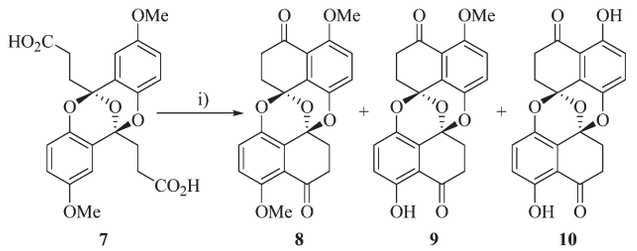
Our next step was to convert diol **5** into its diacid derivative **7** with the aim of then carrying out a double Friedel–Crafts acylation on to the neighbouring aromatic cores, constructing the new rings A and D simultaneously. Oxidation of diol **5** was achieved by two procedures. We initially oxidised **5** using the Swern oxidation, giving the corresponding intermediate dialdehyde, which in a second step was oxidised further to the required diacid **7**. The second oxidation was conducted using silver oxide, generated *in situ* from silver nitrate and potassium hydroxide (Scheme 4). However, an optimised transformation was achieved by direct Jones oxidation, which provided the diacid **7** in higher yields (95%) and shorter time and for a fraction of the cost.



Scheme 4 *Reagents and conditions*: i) Jones' reagent, acetone rt, 10 min (95%); ii) $(COCl)_2$, DMSO, dichloromethane, −70 °C, then Et_3N, −60 °C; iii) $AgNO_3$, aq. KOH, MeOH, THF (85%, two steps).

After activating the diacid **7** *in situ* as the acid chloride, treatment with a homogenous solution of $AlCl_3$ in nitromethane at room temperature produced the Friedel–Crafts adduct **8** in good yield (75%) after 30 min. However, if the reaction was allowed to stand for a longer time in the presence of an excess of $AlCl_3$, two new compounds, characterised as **9** and **10**, began to appear, indicating that after a rapid cyclisation (less than 1 h to completion), the

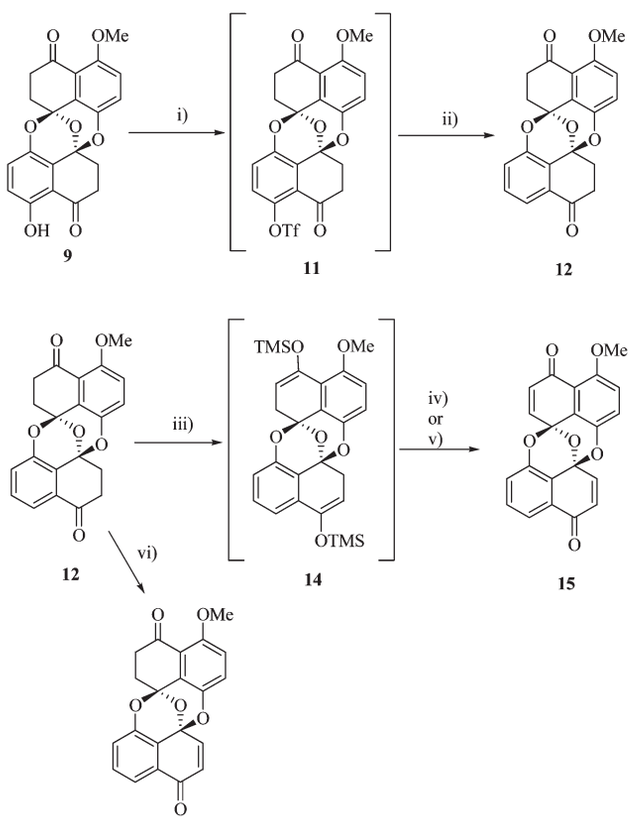
remaining Lewis acid slowly carried out the cleavage of the phenolic methoxy groups (Scheme 5). Compounds **8**–**10** all contain the full preussomerin hydrocarbon skeleton but, additionally, in compound **9** the symmetry has been broken. Thus, in a *one-pot* fashion both the critical intramolecular cyclisation as well as the monodeprotection of one the phenolic moieties has been achieved. The reaction has proved to be easily scalable to provide a 44% yield of compound **9**. Both by-products **8** and **10** are easily separable from **9** and can be recycled to improve the overall yield.



Scheme 5 *Reagents and conditions*: i) a) $(COCl)_2$, DMF (cat), dichloromethane, 0 °C to rt, 1 h; b) $AlCl_3$, $MeNO_2$, dichloromethane, 20 h, then 20% aq. Rochelle's salt (10% **8**; 44% **9**; 33% **10**).

We next investigated the deoxygenation of the free phenol group on intermediate **9**. This transformation was accomplished by an initial activation of the phenol group as the triflate **11**, which was removed by hydrogenation using Pearlman's catalyst to provide **12** in good overall yield (Scheme 6).

Having established an easily scalable route to **12**, our attention became focused on its conversion into dienone **15**. Early investigations regarding the direct dehydrogenation were unsuccessful (*e.g.* benzeneseleninic anhydride,[13] DDQ, *etc.*). When we applied the IBX-mediated direct dehydrogenation method recently described by Nicolaou *et al.*,[17] we found that the monounsaturated compound



Scheme 6 *Reagents and conditions*: i) Tf_2O, pyridine, dichloromethane, −10 °C to rt; ii) H_2, 20% $Pd(OH)_2/C$, Et_3N, MeOH/EtOAc (3 : 1) v/v (82%, two steps); iii) TMSOTf, 2,6-lutidine, 0 °C to rt, 1 h; iv) $Pd(OAc)_2$ (2.2 equiv.), CH_3CN, rt, 16 h (91%, two steps); v) IBX-MPO (3 equiv.), DMSO, rt, 90 min (41%) (61% based on recovered **12**); vi) IBX, toluene, DMSO, 80 °C, 3 d (10%).

13 was the main product, while most of the starting material remained unreacted (or was finally degraded if reaction conditions were forcing or the time prolonged) (Scheme 6).

This problem was circumvented by preparation of the disilyl enol ether **14**, which was converted into dienone **15** (Scheme 6). We again investigated the use of the IBX-MPO complex,[18] which generated the dienone **16**, but only in moderate 41% yield (plus 20% recovered **12**). However, the same transformation could be accomplished efficiently under the classical conditions of the Saegusa reaction,[19] yielding dienone **15** in 91% yield using super-stoichiometric $Pd(OAc)_2$ (2.2 equiv.). Catalytic conditions were unsuccessful for this reaction.[20]

At this stage, we focused our attention on preussomerins K and L. The special structural features of these molecules (Subtype II targets) lie in the characteristic β-hydroxyketone moiety. Two approaches were examined to install this moiety. We first investigated the conjugate addition of oxygenated nucleophiles onto the enone systems (Scheme 7).

Conjugate addition of methanol was achieved cleanly converting **15** into its β-methoxy adduct **16**.[10] It must be noted at this point that the conjugate addition of the oxygenated nucleophiles proceeded with complete stereoselectivity on the less hindered faces of the dienone **15**. The strong steric hindrance provided by the β-(O3)oxygen makes the top face of the preussomerin core inaccessible to nucleophiles due to the unique spatial disposition of the two planar subunits of the molecule, which are almost perpendicular to each other.

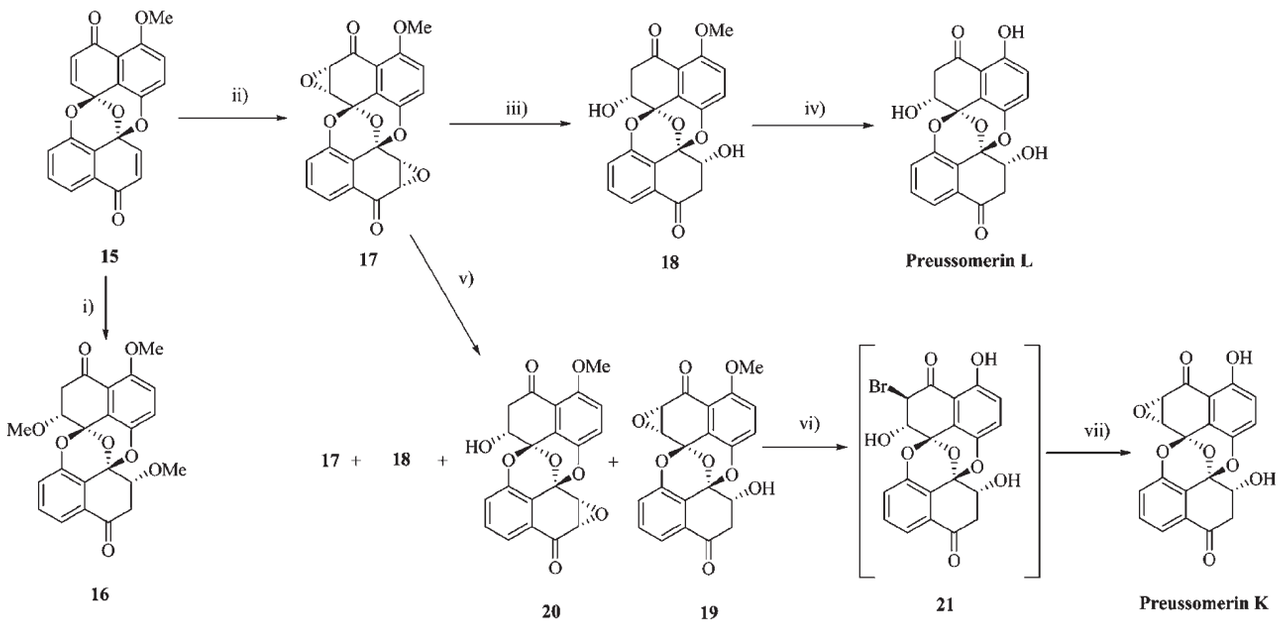
Unfortunately, demethylation of the adduct **16** resulted in extensive degradation of the starting material due to the remarkable resistance of the β-methoxy group to cleavage under all conditions attempted. For this reason, we investigated the epoxidation of dienone **15**. This was successfully carried out using excess *tert*-butyl hydroperoxide (TBHP) in presence of the guanidine base 1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-a]pyrimidine (TBD) following our own methodology[21] to yield the bis-α,β-epoxyketone **17** in excellent yield with total stereoselectivity. In the subsequent step, ring-opening of the diepoxide using a selenium-mediated process[22] proved straightforward and the bis-β-hydroxyketone **18** could be obtained in good yield by a regio- and stereo-selective transformation. Removal of the methyl ether group on the phenolic oxygen in **18** was achieved successfully under very mild conditions using 9-I-BBN[23] affording the first of the natural products, preussomerin L.

The structural identities of **17** and **18** were confirmed by X-ray crystallographic analysis. The ORTEP[24] representations are shown in Fig. 3.[25] It should be noted that both structures are exactly in accordance with those reported for the natural products (with the two aromatic rings almost perpendicular to each other).

The epoxide pathway was also used to access preussomerin K. We anticipated that the α,β-epoxyketones from each subunit of the intermediate **17** would have a different reactivity. The presence of an electron-donating methoxy group on the northern hemisphere of the molecule influences the electronic behaviour of the vicinal carbonyl group, making it less electron-deficient than the carbonyl in the southern hemisphere of the molecule. We therefore treated **17** with a sub-stoichiometric amount of organoselenide and, as predicted, reduction of diepoxide **17** generated predominantly compound **19** (54%). The monoepoxide **20** and recovered **17** could be recycled to afford additional amounts of diol **18** (needed for preussomerin L synthesis).

Attempts to demethylate **19** (9-I-BBN, bromocatechol borane, *etc.*) resulted in extensive degradation of the extremely sensitive epoxide moiety. We circumvented this limitation by using excess boron tribromide, which provided the intermediate bromohydrin **21**. The epoxide was then regenerated by basic treatment of **21** affording preussomerin K (Scheme 7).

The data from the synthetic samples of preussomerin K and L matched with those obtained by analysing authentic samples of the natural compounds kindly provided by Professor K. Krohn. Table 1 shows the ^{13}C NMR shifts found from synthetic preussomerin K and those reported for the natural product.[9g]



Scheme 7 *Reagents and conditions*: i) LiOMe, MeOH, rt, 5 min (quantitative); ii) TBHP, TBD, toluene, 0 °C to rt, 1 h (90%); iii) $(PhSe)_2$ (2.5 equiv.), $NaBH_4$, EtOH, 0 °C to rt, 1 h (67%); iv) 9-I-BBN, dichloromethane, 0 °C to rt, 1 h (42%) (69% based on recovered **18**); v) $(PhSe)_2$ (0.9 equiv.), $NaBH_4$, EtOH, AcOH, 0 °C to rt, 1 h (54% **19**); vi) BBr_3 (4 equiv.), dichloromethane, −78 °C to rt, 1 h; vii) LiOMe, t-BuOH, rt, 10 min (50%, plus 17% preussomerin L).

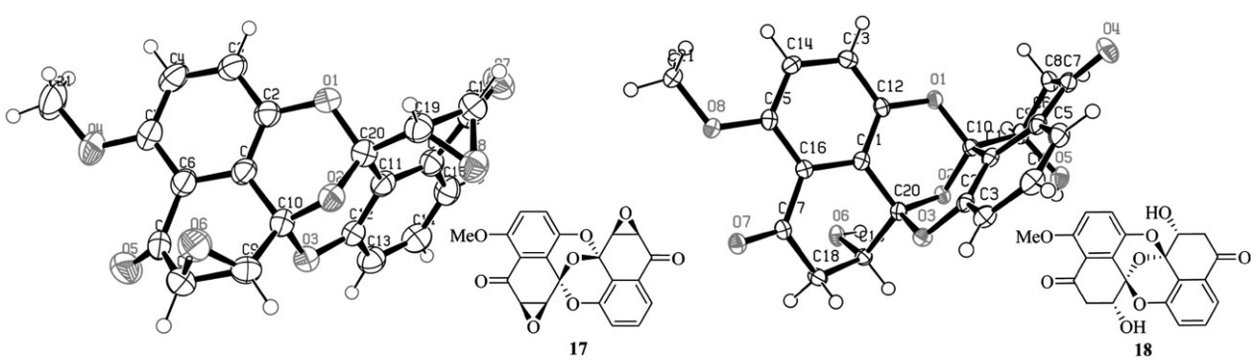


Fig. 3 ORTEP drawing of compound **17** and **18** (50% probability thermal ellipsoids).

Table 1 ^{13}C NMR data[a] comparison of natural and synthetic preussomerin K[9g]

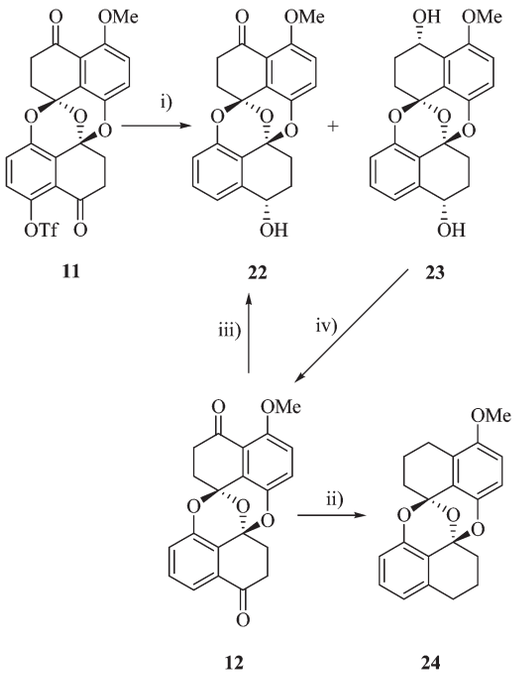
	Chemical shift	
Position	Natural	Synthetic
1	195.4	195.4
2	52.1	52.1
3	53.5	53.5
4	93.6	93.7
5	115.6	115.6
6	142.8	142.8
7	126.4	126.5
8	121.4	120.8
9	156.1	156.2
10	110.1	110.2
1′	193.1	193.1
2′	41.3	41.2
3′	70.1	70.2
4′	94.4	94.4
5′	119.2	119.2
6′	149.8	149.8
7′	121.5	121.5
8′	131.3	131.3
9′	120.8	121.4
10′	130.7	130.7

[a] Data in ppm. Spectra recorded in $CDCl_3$ (100 MHz).

Next, we wished to extend this methodology to access Subtype III preussomerins. This required the regioselective reduction of the carbonyl on the southern hemisphere of the molecule. In our case, we found that the catalytic hydrogenation was the key method for a simple and practical solution to this problem. During the deoxygenation of triflate **11**, we found that a new, more polar compound began to appear after prolonged reaction times (>24 h). This compound was characterised as **22** (Scheme 8). Over-reduction occurred in a regioselective fashion at the southern carbonyl group. This serendipitous finding allowed us to access a new key intermediate from which we were able to synthesise a Subtype III preussomerin.

We therefore concentrated our attention on the development of the optimal conditions for the efficient conversion of **11** into **22**. The original conditions (Pearlman's catalyst) were very slow. Only extended reaction times (>5 d) allowed **22** to be obtained in moderate yield. We therefore screened different catalysts, finding that 5% Pd on activated charcoal produced an efficient over-reduction and generated **22** in 50% yield after 20 h. Another product of over-reduction was found to be formed under these conditions, being characterised as the diol **23**. Its amount increased as the reaction time was extended, but by limiting the reaction time to 20 h less than 10% was obtained (see Scheme 8).

This transformation is quite versatile in terms of reuse of the over-reduced products. Compound **23** can be straightforwardly oxidised to form **12** by Jones oxidation and **12** can be hydrogenated to give **22** with Et_3N/MeOH/EtOAc as solvent. However, hydrogenation of **12** under standard conditions afforded an unexpected result. In the absence of triethylamine, the rapid deoxygenation of both carbonyls occurred, affording **24** in quantitative yield (Scheme 8). The use of triethylamine as co-solvent allowed controlled reduction, giving **22**



Scheme 8 *Reagents and conditions*: i) H_2 (1 atm), 5% Pd/C, Et_3N, MeOH/EtOAc (3 : 1) v/v, 20 h, (50% **22**); ii) H_2 (1 atm), 5% Pd/C, MeOH/EtOAc (3 : 1) v/v, 24 h (quantitative yield); iii) as i), but Et_3N used as co-solvent (50%); iv) Jones' reagent, acetone, rt, 10 min (>90%).

in 50% yield (8–12 h). The role of triethylamine still remains unclear, but is probably related to a poisoning effect on the catalyst.

With the key intermediate **22** in hand, we embarked on a synthesis of preussomerin F. The approaches followed are shown in Scheme 9. First, protection of the benzylic hydroxyl group was carried out to preclude any risk of elimination during the subsequent reactions. Protection as the MOM derivative proceeded smoothly affording **25a** in high yield.

The next step involved generation of the enone. Taking advantage of our previous experience in this field, we attempted the Saegusa reaction *via* the silyl enol ether derived from **25a**. Surprisingly, the mild method used before (TMSOTf, 2,6-lutidine) failed when it was applied to **25a**. The best results were obtained using sodium hexamethyldisilazane in THF (1.1 equiv.) at −40 °C, trapping the enolate *in situ* with excess TMSCl. The intermediate silyl enol ether proved to be extremely sensitive. Removal of the solvent without work-up, redissolving the crude product in acetonitrile and treatment with $Pd(OAc)_2$ without additional purification gave enone **26a** in 54% yield with **25a** being recovered in 25% yield (this could be recycled increasing the overall yield). Epoxidation of enone **26a** proceeded efficiently using the guanidine base-mediated epoxidation affording **27a** in high yield.

The structure of **27a** was confirmed by X-ray crystallographic analysis. The ORTEP[24] representation is shown in Fig. 4.[26] As in the previous series, the two quasi-planar subunits are almost perpendicular to each other.

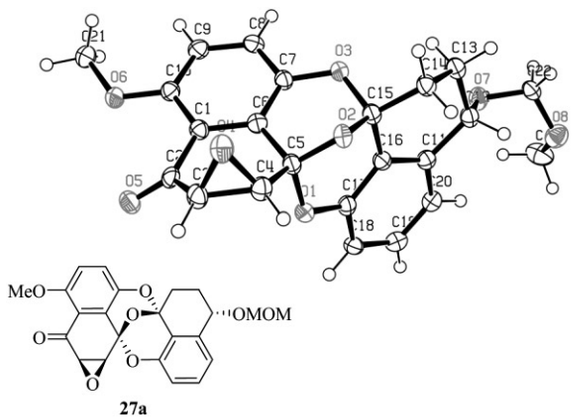
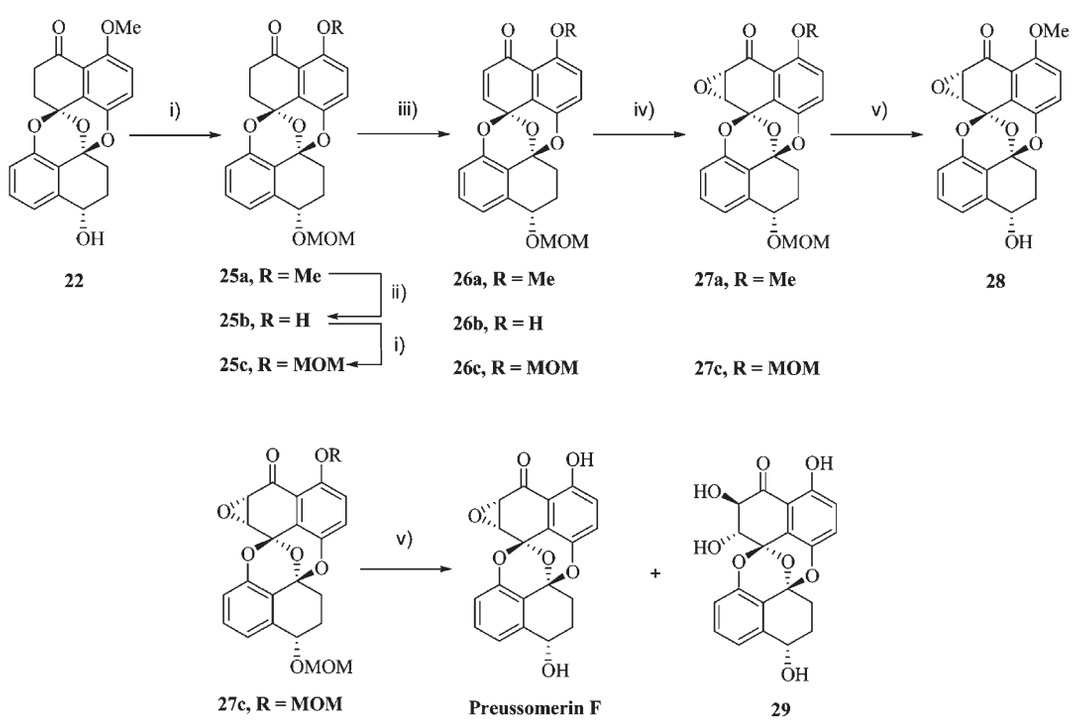


Fig. 4 ORTEP drawing of compound **27a** (50% probability thermal ellipsoids).

Deprotection of the MOM group in **27a** proceeded smoothly under mild conditions providing 9-*O*-methoxy preussomerin F (**28**). Removal of the methoxy protecting group of **28** was attempted using the same strategy described earlier *via* the intermediate bromohydrin and subsequent epoxide regeneration with base. Unfortunately, treatment of **28** with boron tribromide produced extensive degradation of the epoxide without formation of the desired bromohydrin. No method employed gave clean demethylation of the phenol without degrading the epoxide.



Scheme 9 *Reagents and conditions*: i) MOMCl, Hunig's base, dichloromethane, 0° to rt, 2–24 h (**25a** 94%, **25c** 85%); ii) LiI (5 equiv.), pyridine, reflux, 20 h (93%); iii) a) NaHMDS, THF, −40 °C; b) TMSCl; c) $Pd(OAc)_2$, CH_3CN, 16–18 h (50–75%); iv) TBHP, TBD, toluene, 0 °C to rt (90–93%); v) HCl, i-PrOH, 50 °C, 5–8 h (66–75%).

We therefore turned our attention to a modified route in which the methyl ether protecting group was removed prior to the generation of the epoxide.

Demethylation was carried out on **25a** using lithium iodide in refluxing pyridine, affording **25b** in 93% yield. The Saegusa reaction was repeated with this substrate producing enone **26b** in 68% yield. Unfortunately, epoxidation failed on this substrate despite extensive experimentation. We therefore realised the need for protecting the phenol group for the epoxidation. For that we reason introduced on **25b** a second MOM group, converting it cleanly into **25c** (85%). Saegusa reaction on **25c** allowed the preparation of enone **26c** and epoxidation now efficiently afforded **27c**.

The final acid-catalysed deprotection of MOM groups in **27c** proved to be troublesome due to the high lability of epoxide. While the phenol-protecting MOM is easily and rapidly removed, the benzylic MOM removal requires heating and longer reaction times to be completed, thus damaging the sensitive epoxide. However, after extensive experimentation, we were able to develop optimised conditions, which afforded preussomerin F in good yield (66%) with diol **29** as the only by-product in 34% yield (Scheme 9). The authenticity of preussomerin F was established by full characterisation and comparison of spectroscopic data with those reported [*e.g.* signals due to epoxide: δ_H (methanol-d_4) 4.25 (J = 4.2 Hz, C2–C*H*) and 3.84 (J = 4.0 Hz, C3–C*H*); δ_C (methanol-d_4) 54.9 (C2) and 53.2 (C3); lit.,[9b] δ_H (methanol-d_4) 4.27 (J = 4.2 Hz, C2–C*H*) and 3.84 (J = 3.9 Hz, C3–C*H*); δ_C (methanol-d_4) 54.8 (C2) and 53.2 (C3)].

Conclusion

In summary, we have successfully synthesised the racemic natural products preussomerin F (3% overall yield, 13 steps) and preussomerins K and L (4% overall yields in both cases, 11 and 10 steps, respectively) from very simple, inexpensive and easily available starting materials through the application of a straightforward, non-biomimetic strategy with the functionalisation of 2-arylacetal anions, simultaneous one-pot Friedel–Crafts cyclisation–deprotection and substrate-regiocontrolled hydrogenation as the key steps of the syntheses. The above methodology is extremely versatile and could be used for the preparation of a range of preussomerin analogues by simple functional group interconversion. Further studies to develop asymmetric approaches to enantiomerically pure compounds are currently under investigation and will be reported in due course.

Experimental

General information

All reactions were carried out in oven-dried glassware under an inert atmosphere (argon or nitrogen) unless stated otherwise. All solvents were freshly distilled prior to use when anhydrous conditions were required. THF was distilled from sodium/benzophenone, and acetonitrile, dichloromethane, methanol, ethanol and toluene from CaH_2. Chemicals were purchased from commercial suppliers and were used as received without further purification. Analytical thin-layer chromatography (TLC) was performed on precoated aluminium silica gel plates (Merck *60F254*, 0.25 mm). Product spots were visualised under UV light (lamp at 254 or 360 nm), or dipped into any of the following solutions: phosphomolybdic acid (PMA), 2,4-dinitrophenylhydrazine (DNP) or vanillin, followed by heating with a hot air gun. Flash column chromatography was performed on silica gel (Merck, 230–400 mesh). Melting points were measured on an electrothermal IA9100 digital melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on an ATI Mattson Genesis FT-IR spectrometer; deposited samples were prepared by dissolving solids in a small volume of $CHCl_3$ and forming a thin film on a NaCl plate by allowing the solvent to evaporate. ^1H and ^{13}C NMR spectra were taken at room temperature (21 °C unless otherwise noted) in $CDCl_3$, acetone-d_6 or methanol-d_4 on Jeol GX-270, GX-400 or Brücker AMX 500 MHz spectrometers. Chemical shifts are reported in parts per million (ppm) using as internal reference the residual peaks of chloroform (δ 7.26 and 77.0 ppm), acetone-d_6 (δ 2.04 and 29.8 ppm) or methanol-d_4 (δ 3.35 and 49.3 ppm). J values are given in Hz. Carbon and proton assignments were based on ^{13}C–^1H Heteronuclear Singlet Quantum Correlation (HSQC), Heteronuclear Multiple Quantum Correlation (HMQC) and gradient-COSY experiments including large range correlation experiments (HMBC). Stereochemical configuration of key intermediates was determined by selective NOE irradiation of the selected peaks. Low resolution electron impact mass spectra were recorded on a Kratos MS 25 spectrometer. Both low and accurate mass measurement with CI and FAB techniques were carried out on a Micromass Autospec spectrometer. The following abbreviations were used for solvents: PE (petroleum ether bp 60–40 °C), EtOAc (ethyl acetate), DCM (dichloromethane), THF (tetrahydrofuran) and DMF (dimethylformamide). All products were stored at −20 °C under argon. 2-Hydroxy-5-methoxybenzaldehyde (**2**) was prepared from 4-methoxyphenol and paraformaldehyde according to the reported method.[16] Numbering of the preussomerins is in accordance with the numbering of the original reference (see Fig. 2).[9a]

6*H*,12*H*-2,8-Dimethoxy-6,12-epoxydibenzo[b,f][1,5]dioxocin 3

To a solution of 2-hydroxy-5-methoxybenzaldehyde (**2**) (16.92 g, 111 mmol) in pivalic anhydride (20.7 g, 22.6 mL, 111 mmol) at 0 °C (ice bath), under efficient stirring, was added three drops of concentrated H_2SO_4 (catalytic amount). A white precipitate was formed almost immediately. After 1 h, the crude reaction was filtered and repeatedly washed with cold PE. The white precipitate was pressed between two pieces of filter paper and crushed with a spatula until it was finely dispersed as a white solid, which was dried overnight *in vacuo* affording a white powder (14.2 g, 89% yield). Recrystallisation from hot diethyl ether afforded the *title compound* **3** as large translucid crystals; R_f = 0.51 [PE/EA (1 : 1)]; mp 113–114 °C; (Found: C, 67.03; H, 4.79%; required for $C_{16}H_{14}O_5$, C, 67.13; H, 4.93%); ν_{max}(film)/cm^{-1} 1498, 1430, 1262, 1220, 1158, 1060, 1035, 985, 963; δ_H (270 MHz; $CDCl_3$): 3.75 (6 H, s, 2 × OC*H*$_3$), 6.26 (2 H, s, C7-C*H*, C7′-C*H*) and 6.85–6.8 (6 H, m, C2-C*H*, C3-C*H*, C5-C*H*, C2′-C*H*, C3′-C*H*, C5′-C*H*); δ_C (67.5 MHz; $CDCl_3$) 55.6 (2 × OMe), 90.1 (C7, C7′), 111.1 (C2, C2′), 117.3 (C3, C3′), 117.7 (C5, C5′), 120.3 (C6, C6′), 144.3 (C4, C4′) and 154.1 (C1, C1′); *m*/*z* (EI) Calc. for $C_{16}H_{14}O_5$ [M$^+$] 286.08412; Found: 286.08414 (+0.1 ppm); 286 [M$^+$] (80), 150 (100).

6*H*,12*H*-6,12-Di-(3′-hydroxypropyl)-2,8-dimethoxy-6,12-epoxydibenzo[b,f][1,5]dioxocin 5 and 6*H*,12*H*-6-(3′-hydroxypropyl)-2,8-dimethoxy-6,12-epoxydibenzo[b,f][1,5]dioxocin 6

A solution of bis-acetal **3** (1.72 g, 6.0 mmol) in THF (40 mL) was cooled to −78 °C under constant pass of a stream of nitrogen and treated with n-BuLi (2.3 M in hexanes, 2.9 mL, 6.7 mmol). The reaction mixture was stirred at −78 °C for 30 min to provide a deep purple solution. The flask was cooled further to −100 °C (ethanol/liquid nitrogen mixture) and treated with oxetane (0.4 mL, 6.0 mmol), followed by slow addition of $BF_3{\cdot}Et_2O$ (830 μL, 6.6 mmol), maintaining the temperature below −90 °C. The flask was allowed to warm slowly to −40 °C over 90 min and the resultant orange solution stirred at −40 °C for a further hour. The mixture was cooled then again to −78 °C and slowly treated with *s*-BuLi (1.3 M in hexanes, 6.0 mL, 7.8 mmol) to provide a very dark solution. After stirring at −78 °C for 30 min, the solution was cooled to −100 °C and oxetane added (1.2 mL, 18 mmol), followed by slow addition of $BF_3{\cdot}Et_2O$ (2.4 mL, 19 mmol), maintaining the temperature below −90 °C. The flask was allowed to warm to −40 °C over 3 h and the resultant orange solution was stirred at −40 °C for a further hour. The reaction mixture was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (50 mL) and ethyl acetate (80 mL). The layers were separated, the organic layer washed with additional saturated $NaHCO_3$ solution (40 mL) and brine (40 mL) and dried over sodium sulfate. The organic extracts were filtered and the solvent evaporated *in vacuo*. The crude mixture was purified by flash column chromatography on silica gel (eluting with a polar gradient PE/EtOAc 50 to 90% EtOAc), to provide first the *mono-*

alcohol **6** (0.66 g, 32%), followed by the *title compound diol* **5** (1.25 g, 52%). Both compounds were isolated as extremely viscous oils and subsequently converted to pale yellow stable foams by repeated evaporation from DCM and high vacuum drying.

5, R_f = 0.57 (EtOAc); ν_{max}(film)/cm^{-1} 3339, 2943, 1496, 1427, 1276, 1226, 1174, 1039, 1005, 953; δ_H (270 MHz; $CDCl_3$) 1.67 (4H, m, C9-CH_a, C9′-CH_b, 2 × OH), 1.82 (2 H, m, C9-CH_a, C9′-CH_a), 2.27 (2 H, m, C8-CH_b, C8′CH_b), 2.46 (2 H, m, C8-CH_a, C8′-CH_a), 3.68 (4 H, m, C10-CH_2, C10′-CH_2), 3.72 (6 H, s, 2 × OCH_3) and 6.8–6.7 (6 H, m, C2-CH, C3-CH, C5-CH, C2′-CH, C3′-CH, C5′-CH); δ_H (270 MHz; acetone-d_6) 1.85–1.45 (4 H, m, C9-CH_2, C9′-CH_2), 2.5-2.3 (4 H, m, C8-CH_2, C8′-CH_2), 3.65–3.58 (4 H, m, C10-CH_2, C10′-CH_2), 3.70 (6 H, s, 2 × OCH_3), 6.72 (2 H, dd, J = 9 and 1, C2-CH, C2′-CH), 6.79 (2 H, dd, J = 9 and 2.5, C3-CH, C3′-CH), and 6.95 (2 H, d, J = 2.5, C5-CH, C5′-CH); δ_C (67.5 MHz, acetone-d_6) 27.4 (C9, C9′), 34.9 (C8, C8′), 55.9 (2 × OMe), 62.2 (C10, C10′), 98.3 (C7, C7′), 111.0 (C2, C2′), 117.3 (C3, C3′), 117.8 (C5, C5′), 123.8 (C6, C6′), 147.2 (C4, C4′) and 155.1 (C1, C1′); m/z (FAB) Calc. for $C_{22}H_{26}O_7Na$ [M + Na$^+$] 425.15762; Found: 425.15780 (+0.4 ppm).

6, R_f = 0.20 [PE/EtOAc (1 : 1)]; mp 116–117 °C; ν_{max}(film)/cm^{-1} 1497, 1466, 1428, 1274, 1229, 1201, 1059, 1036, 999, 953; δ_H (270 MHz, $CDCl_3$) 1.79 (1 H, m, C9-CH_a), 1.66 (1 H, m, C9-CH_b), 2.13 (1 H, br s, OH), 2.28 (1 H, ddd, J = 14, 9.5 and 5, C8-CH_b), 2.46 (1 H, ddd, J = 14, 9.5 and 5, C8-CH_a), 3.66 (2 H, m, C10-CH_2), 6.23 (1 H, s, C7′-CH), 3.69 (6 H, s, 2 × OCH_3), 6.77 (6 H, m, C2-CH, C3-CH, C5-CH, C2′-CH, C3′-CH, C5′-CH); δ_H (270 MHz; acetone-d_6) 2.5–2.3 (2 H, m, C8-CH_2), 1.77–1.42 (2 H, m, C9-CH_2), 3.718 (3 H, s, OCH_3), 3.61–3.56 (2 H, m, C10-CH2), 3.722 (3 H, s, OCH_3), 6.37 (1 H, s, C7′-CH), 6.74 (1H, d, J = 8.5, C2-CH or C2′-CH), 6.77 (1 H, d, J = 8.5, C2-CH or C2′-CH), 6.83 (1 H, dd, J = 8.5 and 3 Hz, C3-CH or C3′-CH), 6.84 (1 H, dd, J = 8.5 and 3, C3-CH or C3′-CH), 6.92 (1 H, d, J = 3, C5-CH or C5′-CH), 6.95 (1 H, d, J = 3, C5-CH or C5′-CH); δ_C (67.5 MHz; acetone-d_6) 27.3 (C9), 34.6 (C8), 55.8 (2 × OMe), 62.1 (C10), 91.4 (C7′), 97.8 (C7), 111.1 (C2 or C2′), 112.1 (C2 or C2′), 117.5 (C3 or C3′), 117.6 (C3 or C3′), 118.0 (C5 or C5′), 118.1 (C5 or C5′), 121.2 (C6 or C6′), 121.2 (C6 or C6′), 124.1 (C6 or C6′), 145.6 (C4 or C4′), 146.8 (C4 or C4′), 154.9 (C1 or C1′) and 155.3 (C1 or C1′); m/z (CI) Calc. for $C_{19}H_{21}O_6$ [M + H$^+$] 345.13381; Found: 345.13381 (0 ppm).

6*H*,12*H*-6,12-Di-(3′-carboxypropyl)-2,8-dimethoxy-6,12-epoxydibenzo[b,f][1,5]dioxocin 7

A pre-cooled (ice bath) solution of Jones' reagent was slowly added dropwise over an efficiently stirred solution of diol **5** (2.42 g, 6 mmol) in acetone (80 mL) at rt, maintaining a dropping rate such that the temperature did not rise above 30 °C. A green viscous precipitate is formed immediately. When the characteristic red-orange colour of the Jones' reagent persists in the supernatant solution (TLC analysis shows total consumption of the starting material *ca.* 10 min), the reaction was stirred for additional 5 min at rt, quenched by the addition of propan-2-ol (30 mL) and stirred until the precipitate became eventually a finely dispersed suspension (*ca.* 15 min). The crude product was filtered through a short Celite® pad (sintered glass), washing with acetone and EtOAc. The solvent was removed under reduced pressure and re-dissolved in EtOAc, washed with 10% HCl (2 × 50 mL), brine (50 mL) and dried over $MgSO_4$. After filtration and removal of the solvent, the crude diacid was repeatedly evaporated with dichloromethane and finally triturated from PE to form a white, amorphous solid of *di-acid* **7** (2.45 g, 95%); R_f = 0.4 (EtOAc); ν_{max}(film)/cm^{-1} 3000, 2952, 1705, 1497, 1425, 1277, 1225, 1173, 1080, 1037, 933, 879, 818; δ_H (270 MHz; acetone-d_6) 2.4 (2 H, m), 2.71 (2 H, m), 2.47 (4 H, m), 3.73 (6 H, s, 2 × OCH_3), 6.75 (2 H, d, J = 9, C2-CH, C2′-CH), 6.83 (2 H, dd, J = 9 and 3, C3-CH, C3′-CH) and 6.98 (2 H, d, J = 3, C5-CH, C5′-CH); δ_C (125 MHz; acetone-d_6) 27.5 (C8, C8′), 32.5 (C9, C9′), 55.0 (2 × OMe), 96.7 (C7, C7′), 109.8 (C2, C2′), 116.9 (C3, C3′), 117.1 (C5, C5′), 122.2 (C6, C6′), 146.0 (C4, C4′), 155.4 (C1, C1′) and 173.2 (C10, C10′); m/z (FAB) HRMS Calc. for $C_{22}H_{22}O_9Na$ [M + Na$^+$] 453.11615; Found: 453.11559 (+1.2 ppm).

One-pot Friedel–Crafts acylation–desymmetrisation. General procedure

A solution of diacid **7** (0.22 g, 0.5 mmol) in dry dichloromethane (15 mL) was cooled to 0 °C (ice bath) under nitrogen and treated with DMF (1 drop, catalytic amount), followed by the slow addition of oxalyl chloride (0.1 mL, 1.2 mmol). The mixture was warmed to room temperature and stirred for 1 h. Then, the solution was cooled again in an ice bath and diluted with DCM (15 mL), followed by dropwise addition of a freshly prepared solution of aluminium chloride (0.49 g, 3.6 mmoL) in nitromethane (20 mL). The mixture was stirred at room temperature for 20 h and then quenched with a 20% w/v aqueous solution of potassium sodium tartrate (50 mL) and stirred for an additional 1 h. The mixture was diluted with DCM (15 mL) and extracted. The aqueous layers were diluted with 10% HCl for helping during separation of the layers, and the aqueous phase was washed with additional DCM (2 × 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and solvent evaporated *in vacuo*. The crude product was loaded onto Celite® and purified by column chromatography on silica gel [eluting with a polar gradient, PE/EtOAc (7 : 3) to (1 : 1), (1 : 6) and finally (0 : 1)] to provide first the bis-phenolic compound **10** (0.060 g, 33%), followed by **9** (0.083 g, 44%) and finally the dimethoxy compound **8** (0.020 g, 10%). All products were isolated as dark-reddish to pale pink powders after evaporation from cold diethyl ether.

(a) **4*H*,11*H*-5,6,12,13-Tetrahydro-3,10-dimethoxy-6a,13a-epoxydinaphtho[1,8-bc:1′,8′-fg][1,5]dioxocin-4,11-dione 8.** R_f = 0.28 [PE/EtOAc (1 : 6)]; mp 227–229 °C; ν_{max}(film)/cm^{-1} 2937, 1685, 1590, 1481, 1438, 1238, 1184, 1048, 1006, 928, 869, 821; δ_H (270 MHz; $CDCl_3$) 2.40 (2 H, ddd, J = 19, 6.5 and 1, C2-CH_b, C2′-CH_b); 2.65 (2 H, ddd, J = 13, 6.5 and 1, C3-CH_a, C3′-CH_a), 2.84 (2 H, ddd, J = 19, 6.5 and 1, C2-CH_b, C2′-CH_b), 3.16 (2 H, ddd, J = 19, 13 and 6.5, C2-CH_a, C2′-CH_a), 3.86 (6 H, s, 2 × OCH_3), 6.96 (2 H, d, J = 9, C8-CH, C8′-CH), 7.02 (2 H, d, J = 9, C7-CH, C7′-CH); δ_C (67 MHz; $CDCl_3$) 31.81 (C3, C3′), 34.33 (C2, C2′), 56.61 (2 × OMe), 93.3 (C4, C4′), 115.2 (C8, C8′), 118.9 (C), 122.9 (CH), 123.7 (CH_2), 142.7 (C9, C9′), 154.5 (C6, C6′) and 194.9 (C1, C1′); m/z (CI) Calc. for $C_{22}H_{19}O_7$ [M + H$^+$] 395.113078; Found: 395.112735 (+0.9 ppm).

(b) **4*H*,11*H*-5,6,12,13-Tetrahydro-3-methoxy-10-hydroxy-6a,13a-epoxydinaphtho[1,8-bc:1′,8′-fg][1,5]dioxocin-4,11-dione 9.** R_f = 0.5 [PE/EtOAc (1 : 6)]; mp 213–214 °C; ν_{max}(film)/cm^{-1} 2963, 2839, 1686, 1648, 1591, 1478, 1298, 1274, 1184, 1046, 1007, 930, 905; δ_H (270 MHz; $CDCl_3$) 2.44 (2 H, m), 2.67 (2 H, m), 2.85 (2H, m), 3.18 (1 H, ddd, J = 19, 13 and 6.5), 3.34 (1 H, ddd, J = 19, 13 and 5.5), 3.87 (3H, s), 6.89 (1 H, d, J = 9), 6.98 (1 H, d, J = 9), 7.0 (1 H, d, J = 9), 7.05 (1 H, d, J = 9) and 11.68 (1 H, s); δ_C (67 MHz; $CDCl_3$) 31.8 (CH_2), 32.7 (CH_2), 33.9 (CH_2), 34.2 (CH_2), 56.6 (CH_3), 92.7 (C), 93.5 (C), 113.1 (C), 115.2 (CH), 119.1 (C), 120.1 (C), 120.5 (CH), 122.7 (CH), 123.6 (C), 126.0 (CH), 141.7 (C), 142.3 (C), 154.5 (C), 157.2 (C), 194.7 (CO) and 202.3 (CO); m/z (CI) Calc. for $C_{21}H_{17}O_7$ [M + H$^+$] 381.097428; Found: 381.096977 (+1.2 ppm).

(c) **4*H*,11*H*-5,6,12,13-Tetrahydro-3,10-dihydroxy-6a,13a-epoxydinaphtho[1,8-bc:1′,8′-fg][1,5]dioxocin-4,11-dione 10.** R_f = 0.68 [PE/EtOAc (1 : 6)]; mp 232–234 °C; ν_{max}(film)/cm^{-1} 2975, 1644, 1621, 1593, 1469, 1326, 1317, 1264, 1227, 1187, 1084, 1050, 898, 836; δ_H (270 MHz; $CDCl_3$) 2.46 (2 H, ddd, J = 13, 13 and 5.5), 2.70 (2 H, ddd, J = 13, 5.5 and 1.5), 2.87 (2 H, ddd, J = 19, 5.5 and 1.5), 3.33 (2 H, ddd, J = 19, 13 and 5.5), 7.03 (2 H, d, J = 9), 6.91 (2 H, d, J = 9) and 11.69 (2 H, s); δ_C (67 MHz; $CDCl_3$) 32.2 (CH_2), 33.4 (CH_2), 92.6 (C), 112.6 (C), 119.7 (C), 120.2 (CH), 125.5 (CH), 140.9 (C), 156.8 (C) and 201.9 (CO); m/z (CI) Calc. for $C_{20}H_{15}O_7$ [M + H$^+$] 367.081778; Found: 367.081395 (+1.0 ppm).

4*H*,11*H*-5,6,12,13-Tetrahydro-3-methoxy-6a,13a-epoxydinaphtho[1,8-bc:1′,8′-fg] [1,5]dioxocin-4,11-dione 12

(a) A solution of phenol **9** (300 mg, 0.79 mmol) in DCM (6 mL) was cooled to −10 °C (ice–salt bath) and treated with pyridine (0.60 mL, 7.4 mmol), followed by slow addition of triflic anhydride

(0.25 mL, 1.5 mmol). After stirring at room temperature for 4 h, the reaction mixture was diluted with DCM (20 mL) and washed with saturated $NaHCO_3$ solution (2 × 10 mL), 10% HCl (2 × 10 mL) and brine (10 mL). The organic extract was dried over Na_2SO_4, filtered and the solvent evaporated *in vacuo*, to provide the crude *triflate* **11**, which was triturated from DCM/EtOAc/PE to afford a white amorphous solid which was used without further purification in the next step; R_f = 0.57 [PE/EtOAc (1 : 6)]; δ_H (500 MHz; $CDCl_3$) 2.45 (1 H, ddd, *J* = 13, 13 and 6.5), 2.50 (1 H, ddd, *J* = 13, 13 and 6.5), 2.68 (1 H, ddd, *J* = 13, 6 and 1), 2.73 (1 H, ddd, *J* = 13, 6 and 1), 2.86 (1 H, ddd, *J* = 19, 6 and 1), 2.93 (1 H, ddd, *J* = 19, 6 and 1), 3.18 (1 H, ddd, *J* = 19, 13 and 6.5), 3.27 (1 H, ddd, *J* = 19, 13 and 6.5), 3.87 (3H, s), 7.01 (1 H, d, *J* = 9.2), 7.08 (1 H, d, *J* = 9.2), 7.1 (1 H, d, *J* = 9.2) and 7.21 (1 H, d, *J* = 9.2).

(b) A suspension of the above crude triflate **11** in ethyl acetate/methanol (1 : 3 v/v, 24 mL) was treated with triethylamine (0.60 mL, 4.3 mmol) at rt. Under nitrogen, Pearlman's catalyst (20% palladium hydroxide on activated charcoal, 100 mg) was added. The flask was then purged with hydrogen and a sequential cycle vacuum–hydrogen atmosphere was repeated several times. The mixture was stirred at room temperature for 24 h under a hydrogen atmosphere (light overpressure). The black suspension was bubbled with nitrogen and filtered through a short pad of Celite®, washing with ethyl acetate. The filtrate was washed with 10% hydrochloric acid (2 × 10 mL) and brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo* after filtration. The crude product was loaded onto Celite® and purified by flash column chromatography on silica gel [eluting with an PE/EtOAc (1 : 1)] to provide the *title compound* **12** as a pale white solid (0.236 g, 82%); R_f = 0.53 [PE/EtOAc (1 : 6)]; mp 162–165 °C; ν_{max}(film)/cm^{-1} 2952, 2933, 2854, 1689, 1590, 1481, 1440, 1331, 1310, 1287, 1240, 1206, 1185, 1091, 1050, 1010, 996, 898, 807, 734; δ_H (500 MHz; $CDCl_3$) 2.45 (1 H, ddd, *J* = 13.4, 13.2 and 6.7, C3-CH_b), 2.47 (1 H, ddd, *J* = 13.4, 13 and 5.5, C3′-CH_b), 2.68 (1 H, ddd, *J* = 13.4, 6.5 and 1.2, C3-CH_a), 2.73 (1 H, ddd, *J* = 13.4, 5.8 and 1.5, C3′-CH_a), 2.83 (1 H, ddd, *J* = 19, 6.5 and 1.2, C2-CH_b), 2.88 (1H, ddd, *J* = 19, 5.5 and 1.5, C2′-CH_b), 3.20 (1 H, ddd, *J* = 19, 13 and 6.5, C2-CH_a), 3.26 (1 H, ddd, *J* = 19, 13.4 and 5.8, C2′-CH_a), 3.87 (3 H, s, OCH_3), 6.97 (1 H, d, *J* = 9.2, C8-C*H*), 7.043 (1 H, d, *J* = 9.2, C7-C*H*), 7.045 (1 H, dd, *J* = 8 and 1, C7′-C*H*), 7.36 (1 H, t, *J* = 8, C8′-C*H*) and 7.59 (1 H, dd, *J* = 7.6 and 1, C9′-C*H*); δ_C (100 MHz, $CDCl_3$) 31.8, 32.7, 33.7, 34.2, 56.5, 93.0, 93.7, 115.2, 120.5, 121.5, 122.5, 122.8, 123.5, 130.77, 130.79, 130.9, 142.3, 149.6, 154.4, 194.6 and 195.9; *m*/*z* (EI) Calc. for $C_{21}H_{16}O_6$ [M$^+$] 364.094688; Found: 364.094803 (−0.3 ppm).

4*H*,11*H*-3-Methoxy-6a,13a-epoxydinaphtho[1,8-bc:1′,8′-fg] [1,5]dioxocin-4,11-dienone 15

(a) A solution of **12** (345 mg, 1 mmol) in DCM (12 mL) under argon was treated with 2,6-lutidine (390 µL, 3.3 mmol) and TMSOTf (515 µL, 2.8 mmol) and stirred for 15 min at 0 °C (ice bath) and then 1 h at rt. The reaction was quenched by dilution with DCM (10 mL) and then washed with saturated $NaHCO_3$ solution (10 mL). The aqueous layers were extracted with DCM (3 × 10 mL) and dried over $MgSO_4$, filtered and the solvent evaporated at reduced pressure. The remaining traces of 2,6-lutidine were removed by azeotropic distillation under vacuum with toluene. The brownish oil **14** so generated was dried by azeotropic removal of the water traces with acetonitrile, dried under high vacuum and used without further purification in the next step; R_f = 0.67 [PE/EtOAc (7 : 3)]; δ_H (400 MHz; $CDCl_3$) 0.23 (9 H, s, Si*Me*$_3$), 0.28 (9 H, s, Si*Me*$_3$), 2.85–2.75 (3 H, m), 2.89 (1 H, dt, *J* = 16.8 and 6.4), 3.73 (3 H, s, OCH_3), 5.23 (1 H, dd, *J* = 6.4 and 2.8, C2-C*H*), 5.27 (1 H, dd, *J* = 6 and 3.5, C2′-C*H*), 6.64 (1 H, d, *J* = 9), 6.67 (1 H, d, *J* = 8), 6.79 (1 H, d, *J* = 9), 7.01 (1 H, dd, *J* = 7.6 and 1) and 7.18 (1 H, t, *J* = 8.2 and 7.6, C8′-CH); δ_C (100 MHz; $CDCl_3$) 0.0 ($SiMe_3$), 0.16 ($SiMe_3$), 32.9 (CH_2), 33.2 (CH_2), 56.7 (OMe), 93.6, 94.7, 101.8, 103.7, 115.3, 115.5, 115.9, 116.2, 116.3, 117.8, 120.7, 130.1, 133.1, 144.1, 147.5, 147.8, 150.34 and 150.45.

(b) A solution of the crude bis-silyl enol ether **14** (1 mmol) in dry acetonitrile (12 mL) at rt under argon was treated with $Pd(OAc)_2$ (470 mg, 2.1 mmol) and stirred for 18 h. After filtration through a short Celite® pad (eluting $CHCl_3$), the crude product was purified by column chromatography on silica gel [eluting with a polar gradient PE/EtOAc (7 : 3) to (1 : 1)], affording the *dienone* **15** (312 mg, 91%) as a bright yellow solid; R_f = 0.38 [PE/EtOAc (1 : 1)]; mp 206–208 °C; ν_{max}(film)/cm^{-1} 1671, 1634, 1589, 1484, 1475, 1432, 1339, 1291, 1246, 1139, 1025, 943, 914, 833; δ_H (400 MHz; $CDCl_3$) 3.91 (3 H, s, OCH_3), 6.54 (1 H, d, *J* = 10, C2-C*H*), 6.59 (1 H, d, *J* = 9.8, C2′-C*H*), 7.05–6.95 (4 H, m, C3-C*H*, C7′-C*H*, C7-C*H*, C8-C*H*), 7.18 (1 H, d, *J* = 10, C3′-C*H*), 7.38 (1 H, dd, *J* = 8.2 and 7.6, C8′-C*H*) and 7.61 (1 H, dd, *J* = 7.6 and 1.2, C9′-C*H*); δ_C (100 MHz; $CDCl_3$) 56.7, 89.7, 90.5, 115.5, 120.0, 120.2, 121.0, 121.2, 122.9, 129.8, 130.8, 133.4, 135.2, 137.7, 140.8, 142.8, 149.8, 154.1, 182.5 and 183.5; *m*/*z* (EI) Calc. for $C_{21}H_{12}O_6$ [M$^+$] 360.063388; Found: 360.063536 (−0.4 ppm).

4*H*,11*H*-5,6,12,13-Tetrahydro-3,6,13-trimethoxy-6a,13a-epoxydinaphtho[1,8-bc:1′,8′-fg] [1,5]dioxocin-4,11-dione 16

Lithium methoxide (4.4 mg, 0.12 mmol) was added in one portion at rt under argon over a suspension of dienone **15** (7 mg, 0.02 mmol) in dry MeOH (1 mL) and stirred until complete solubilisation of the crude (*ca.* 5 min) and further the beginning of the formation of a white precipitate. The reaction was quenched by addition of Celite® and elimination of the solvent. The residue was filtered in a sintered glass funnel and washed with dichloromethane. Elimination of solvent afforded the *title compound* **16** (8.2 mg, quantitative) as a white wax; R_f = 0.51 [PE/EtOAc (1 : 6)]; ν_{max}/(film) cm^{-1} 2928, 2846, 1690, 1591, 1480, 1335, 1284, 1114, 1093, 1042, 952, 917, 730; δ_H (400 MHz; $CDCl_3$) 3.03 (1 H, dd, *J* = 18.6 and 2, C2′-CH_b), 3.07 (1 H, dd, *J* = 18 and 2.4, C2-CH_b), 3.34 (1 H, dd, *J* = 18.3 and 3.6, C2′-CH_a), 3.41 (1 H, dd, *J* = 18.3 and 3.3, C2-CH_a), 3.526 (3 H, s, OCH_3), 3.533 (3 H, s, OCH_3), 3.87 (3 H, s, ArOCH_3), 4.27 (1 H, dd, *J* = 3.3 and 2, C3′-C*H*), 4.34 (1 H, dd, *J* = 3 and 2.7, C3-C*H*), 6.98 (1 H, d, *J* = 9.2, C8-C*H*), 7.04 (1 H, dd, *J* = 8.2, C7′-C*H*), 7.04 (1 H, d, *J* = 9.2, C7-C*H*), 7.37 (1 H, t, *J* = 8, C8′-C*H*) and 7.63 (1 H, dd, *J* = 7.6 and 1, C9′-C*H*); δ_C (100 MHz; $CDCl_3$) 40.6, 41.2, 56.4, 59.3, 59.4, 78.5, 79.4, 94.0, 94.7, 115.5, 118.5, 120.0, 120.4, 121.1, 121.7, 123.1, 131.0, 143.2, 150.3 (×2), 154.7, 192.4 and 193.8; *m*/*z* (CI) Calc. for $C_{23}H_{21}O_8$ [M + H$^+$] 425.123643; Found: 425.122927 (+1.7 ppm).

4*H*,11*H*-5,6,12,13-Tetrahydro-3-methoxy-5,13-dioxiran-6a,13a-epoxydinaphtho[1,8-bc:1′,8′-fg] [1,5]dioxocin-4,11-dione 17

TBD (39.4 mg, 0.28 mmol) was added to a suspension of the dienone **15** (170 mg, 0.47 mmol) in dry toluene (15 mL) under argon at rt. After cooling to 0 °C (ice bath), TBHP (5–6 M solution in decane, 1 mL) was added *via* microsyringe and the reaction warmed at rt. The original yellow suspension generated a pale brown solution. After 50 min, the reaction was quenched by the addition of a saturated solution of sodium sulfite (15 mL) and diluted with EtOAc. The organic phase was separated and washed with brine. The combined aqueous layers were extracted with EtOAc (3 × 50 mL) and the organic extracts were dried over $MgSO_4$ and filtered. After removal of the solvent, the residue was purified by flash column chromatography on silica gel [eluting with PE/EtOAc (1 : 1)]. *Diepoxide* **17** was isolated as a viscous oil which was triturated from dichloromethane and excess PE affording a white fine powder (165 mg, 89%); R_f = 0.51 [PE/EtOAc (1 : 1)]; mp 116–118 °C; ν_{max}(film)/cm^{-1} 2940, 1702, 1592, 1486, 1336, 1289, 1252, 1160, 1034, 1011, 965, 878; δ_H (400 MHz; $CDCl_3$) 3.85 (3 H, s, OCH_3), 3.89 (1 H, d, *J* = 4, C2-C*H*), 3.89 (1 H, d, *J* = 4.3, C2′-C*H*), 4.26 (1 H, d, *J* = 4.3, C3-C*H*), 4.3 (1 H, d, *J* = 4, C3′-C*H*), 6.99 (1 H, d, *J* = 9.2, C8-C*H*), 7.04 (1 H, d, *J* = 9.2, C7-C*H*), 7.06 (1 H, dd, *J* = 7.9 and 1, C7′-C*H*), 7.42 (1 H, t, *J* = 8, C8′-C*H*) and 7.46 (1 H, dd, *J* = 7.6 and 1.5, C9′-C*H*); δ_C (100 MHz; $CDCl_3$) 52.3, 52.95, 53.1, 53.3, 56.6, 93.6, 94.3, 115.8, 116.0, 120.9, 122.0, 122.9, 128.7, 131.9, 142.7, 149.9, 153.7, 190.6 and 192.1; *m*/*z* (CI) Calc. for $C_{21}H_{13}O_8$ [M + H$^+$] 393.061043; Found: 393.061039 (+0 ppm).

Reductive-opening of α,β-epoxy ketone 17

(a) $NaBH_4$ (37 mg, 1 mmol) was added in small portions to a suspension of $(PhSe)_2$ (152 mg, 0.5 mmol) in absolute ethanol (4 mL) with stirring at room temperature under nitrogen. After the vigorous evolution of hydrogen had ceased, the colourless faint solution of $Na[PhSeB(OEt)_3]$ so generated was cooled to 0 °C (ice bath), and AcOH (67 μL, 1.2 mmol) was added *via* a microsyringe. The resulting mixture was further stirred for 5 min in the cold and then used without additional treatment.

(b) **4*H*,11*H*-5,6,12,13-Tetrahydro-3-methoxy-6,13-dihydroxy-6a,13a-epoxydinaphtho[1,8-bc:1′,8′-fg] [1,5]dioxocin-4,11-dione 18.** A solution of the bis-α,β-epoxy ketone 17 (76 mg, 0.2 mmol) in EtOH/AcOH (1 : 1) v/v (2 mL) was added to the above solution at 0 °C under nitrogen. The mixture was stirred at 0 °C for 10 min and further for 45 min at rt. The reaction mixture was then opened to air for 15 min and diluted with EtOAc. Brine was added and the aqueous layer extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* after filtration. The crude residue was washed with 10 mL portions of PE and decanted and further purified by column chromatography on silica gel [using a polar gradient during the elution PE/EtOAc from (1 : 0) to (1 : 6)], affording *9-O-methoxy preussomerin L* (18) as a pale yellow oil which was converted into a white solid by triturating from PE (51.4 mg, 67%); R_f = 0.22 [PE/EtOAc (1 : 6)]; mp 203–205 °C; ν_{max}(film)/cm^{-1} 3336, 1695, 1677, 1588, 1481, 1432, 1332, 1274, 1083, 1037; δ_H (400 MHz; $CDCl_3$, 40 °C) 2.32 (2 H, br s, 2 × O*H*), 2.98 (1 H, dd, *J* = 18.9 and 2.1, C2-CH_b), 3.03 (1 H, dd, *J* = 18.6 and 2.4, C2′-CH_b), 3.35 (1 H, dd, *J* = 18.9 and 4, C2-CH_a), 3.41 (1 H, dd, *J* = 18.6 and 3.4, C2′-CH_a), 3.87 (3 H, s, OCH_3), 4.69 (1 H, m, C3-C*H*), 4.77 (1 H, m, C3′-C*H*), 7.02 (1 H, d, *J* = 9.2, C8-C*H*), 7.08 (1 H, d, *J* = 9.2, C7-C*H*), 7.08 (1H, dd, *J* = 8.2 and 1, C7′-C*H*), 7.40 (1 H, t, *J* = 8, C8′-C*H*) and 7.66 (1 H, dd, *J* = 7.6 and 1, C9′-C*H*); δ_C (125 MHz; $CDCl_3$) 41.4, 42.2, 56.5, 69.2, 70.1, 93.8, 94.5, 115.8, 118.4, 119.2, 120.3, 120.7, 121.7, 123.1, 130.9, 131.3, 143.4, 150.6, 154.8, 192.0 and 193.45; *m*/*z* (CI) Calc. for $C_{21}H_{17}O_8$ [M + H$^+$] 397.09234; Found: 397.09182 (+1.1 ppm).

(c) **4*H*,11*H*-5,6,12,13-Tetrahydro-3-methoxy-5-oxiran-13-hydroxy-6a,13a-epoxydinaphtho[1,8-bc:1′,8′-fg] [1,5]dioxocin-4,11-dione 19.** The above solution (2 mL, 0.25 mmol) was added to a suspension of bis-α,β-epoxy ketone 17 (53 mg, 0.14 mmol) in EtOH/AcOH (1 : 0.2) v/v (1.2 mL) at rt under argon. After 25 min, the reaction was opened to air for 10 min, diluted with EtOAc (10 mL) and washed with brine. Aqueous layers were extracted with EtOAc (3 × 10 mL) and the combined organic fractions were dried over $MgSO_4$, filtered and the solvent eliminated *in vacuo*. The residue was purified by column chromatography on silica gel [eluting with a polar gradient PE/EtOAc (7 : 3) to (1 : 6)], affording the starting material 17 (10 mg, 20%), *epoxyalcohol* 19 (29 mg, 54%), epoxyalcohol 20 (3.4 mg, 7%) and diol 18 (5.7 mg, 11%), all as yellow waxy solids. The *title compound* 19 was converted into a white solid by triturating from PE; R_f = 0.35 [PE/EtOAc (1 : 1)]; mp 268 °C; ν_{max}(film)/cm^{-1} 3471, 2917, 2848, 1694, 1592, 1485, 1439, 1337, 1285, 1246, 1157, 1031, 1016, 954, 815; δ_H (400 MHz; $CDCl_3$) 2.43 (1 H, br s, 3′-O*H*), 3.04 (1 H, dd, *J* = 18.6 and 2.7, C2′-CH_b), 3.57 (1 H, dd, *J* = 18.6 and 3.4, C2′-CH_a), 3.86 (3 H, s, OCH_3), 3.89 (1 H, d, *J* = 4.3, C3-C*H*), 4.22 (1 H, d, *J* = 4.3, C2-C*H*), 4.80 (1 H, m, C3′-C*H*), 7.0 (1 H, d, *J* = 9.2, C8-C*H*), 7.07 (1 H, d, *J* = 9.2, C7-C*H*), 7.06 (1 H, dd, *J* = 8.2 and 1, C7′-C*H*), 7.41 (1 H, dd, *J* = 8.2 and 7.6, C8′-C*H*) and 7.67 (1 H, dd, *J* = 7.6 and 1, C9′-C*H*); δ_C (100 MHz; $CDCl_3$) 41.2, 53.0, 53.2, 56.6, 70.1, 94.13, 94.18, 115.93, 115.98, 118.4, 119.1, 120.8, 121.6, 123, 130.8, 131.3, 143.1, 150.2, 153.7, 190.6 and 193.3; *m*/*z* (CI) Calc. for $C_{21}H_{15}O_8$ [M + H$^+$] 395.07681; Found: 395.07625 (+1.1 ppm).

4*H*,11*H*-5,6,13,13-Tetrahydro-3-methoxy-6-hydroxy-12-oxiran-6a,13a-epoxydinaphtho[1,8-bc:1′,8′-fg] [1,5]dioxocin-4,11-dione 20

R_f = 0.2 [PE/EtOAc (1 : 1)]; ν_{max}(film)/cm^{-1} 3458, 2916, 2848, 1687, 1591, 1480, 1336, 1200, 1183, 1087, 1032, 962, 887, 735; δ_H (400 MHz; $CDCl_3$) 3.0 (1 H, dd, *J* = 18.9 and 1.8, C2-CH_b), 3.34 (1 H, dd, *J* = 18.9 and 4, C2-CH_a), 3.88 (3 H, s, OCH_3), 3.94 (1 H, d, *J* = 4.3, C3-C*H*), 4.27 (1 H, d, *J* = 4.3, C2-C*H*), 4.74 (1 H, dd, *J* = 4 and 1.8, C3-C*H*), 7.01 (1 H, d, *J* = 9.2, C8-C*H*), 7.06 (1 H, d, *J* = 9.2, C7-C*H*), 7.09 (1 H, dd, *J* = 7.6 and 1.5, C7′-C*H*), 7.42 (1 H, t, *J* = 7.6, C8′-C*H*) and 7.46 (1 H, dd, *J* = 7.6 and 1.5, C9′-C*H*); δ_C (100 MHz; $CDCl_3$) 42.1, 52.4, 53.4, 56.5, 69.3, 93.3, 94.6, 115.78, 115.90, 118.4, 120.3, 120.8, 122.0, 122.9, 128.8, 131.9, 143.1, 150.2, 154.9, 191.7 and 192.1.

Preussomerin L (4*H*,11*H*-5,6,12,13-tetrahydro-3,6,13-trihydroxy-6a,13a-epoxydinaphtho[1,8-bc:1′,8′-fg] [1,5]dioxocin-4,11-dione)

9-I-BBN (1.0 M solution in hexanes, 62 μL, 0.062 mmol) was added dropwise at 0 °C (ice bath) under argon to a stirred suspension of the 9-methoxy-protected preussomerin L (**18**) (24.8 mg, 0.062 mmol) in dry dichloromethane (5 mL). After 60 min, the reaction was quenched by the addition of water (few drops). Stirring was continued and after 5 min, the crude was diluted with dichloromethane and brine and extracted. Aqueous layers were extracted further with dichloromethane. The combined organic fractions were dried over anhydrous $MgSO_4$, filtered, concentrated under reduced pressure and the resultant residue purified by column chromatography on silica gel [polar gradient PE/EtOAc = (1 : 1) to (1 : 6)] to afford preussomerin L (9.8 mg, 42%) and the recovered starting material **18** (6.6 mg, 27%). Preussomerin L was a pale yellow, viscous, waxy solid which was converted into an amorphous white solid by solubilisation in dichloromethane followed by addition of PE and triturating. Analytically pure samples were prepared by recrystallisation from methanol affording colourless needles; R_f = 0.35 [PE/EtOAc (1 : 6)]; mp 173–174 °C; ν_{max}(film)/cm^{-1} 3432, 2917, 2849, 1689, 1648, 1469, 1085, 1041, 730; δ_H (400 MHz; $CDCl_3$) 2.26 (1 H, br s, 3′-O*H*), 2.33 (1 H, br s, 3-O*H*), 3.03 (1 h, dd, *J* = 18.3 and 2.7, C2′-CH_b), 3.05 (1 H, dd, *J* = 18.3 and 2.7, C2-CH_b), 3.41 (1 H, dd, *J* = 18.3 and 3.2, C2′-CH_a), 3.47 (1 H, dd, *J* = 18.3 and 3.2, C2-CH_a), 4.76 (1 H, m, C3-C*H*), 4.77 (1 H, m, C3′-C*H*), 6.96 (1 H, d, *J* = 9.2, C8-C*H*), 7.05 (1 H, d, *J* = 9.2, C7-C*H*), 7.11 (1 H, dd, *J* = 8.2 and 1, C7′-C*H*), 7.44 (1 H, dd, *J* = 8, C8′-C*H*), 7.69 (1 H, dd, *J* = 7.6 and 1, C9′-C*H*) and 11.61 (1 H, br s, 9-O*H*); δ_C (125 MHz; $CDCl_3$) 41.2 (C2/C2′), 41.4 (C2′/C2), 70.0 C3/C3′), 70.2 (C3′/C3), 94.06 (C4), 94.13 (C4′), 112.8 (C10), 117.1 (C5), 119.2 (C8), 120.8 (C9′/C8′), 121.3 (C8′/C9′), 121.6 (C7′), 126.0 (C7), 130.9 (C5′/C10′), 131.3 (C10′/C5′), 142.5 (C6), 150.3 (C6′), 157.3 (C9), 193.3 (C1′) and 199.6 (C1); *m*/*z* (CI) Calc. for $C_{20}H_{15}O_8$ [M + H$^+$] 383.07669; Found: 383.07583 (+2.2 ppm).

Preussomerin K (4*H*,11*H*-5,6,12,13-tetrahydro-3,13-dihydroxy-5-oxiran-6a,13a-epoxydinaphtho[1,8-bc:1′,8′-fg] [1,5]dioxocin-4,11-dione)

(a) Boron tribromide was added dropwise at −78 °C under argon in three different portions every 15 min (two portions of 66 μL and a final portion of 200 μL; 0.33 mmol, 5 equiv.) to a solution of epoxyalcohol **19** (26 mg, 0.066 mmol) in dry dichloromethane (5 mL). After every addition of the Lewis acid, the reaction vessel was warmed at room temperature for 10 min and monitored by TLC. Once the TLC analysis showed total consumption of the starting material, the reaction was quenched with water (1 mL) and diluted with dichloromethane (10 mL). The aqueous layer was extracted with dichloromethane (3 × 10 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was eliminated *in vacuo* and dried under high vacuum. The crude material was analysed by NMR and was shown to be a mixture of *bromohydrin* **21** and preussomerin L in the proportions 8 : 2.

Intermediate *bromohydrin* **21**, δ_H (400 MHz; $CDCl_3$) 2.35 (1 H, br s, 3′-O*H*), 2.8 (1 H, br s, 3-OH), 3.04 (1H, dd, J = 18.3 and 3.4, C2′-CH_a), 3.39 (1H, dd, J = 18.3 and 3.4, C2′-CH_b), 4.76 (1 H, d, *J* = 2, C2-C*H*), 4.77 (1 H, m, C3′-C*H*), 4.95 (1 H, d, J = 2, C3-CH), 7.0 (1 H, d, *J* = 11.5, C8-C*H*), 7.12 (1 H, d, *J* = 11.5, C7-C*H*), 7.2 (1 H, dd, *J* = 10 and 1, C7′-C*H*), 7.45 (1 H, t, *J* = 10, C8′-C*H*), 7.7 (1 H, dd, *J* = 10 and 1, C9′-C*H*) and 11.45 (1 H, br s, 9-O*H*).

(b) The above crude material was dissolved in absolute ethanol (1 mL) at room temperature under argon. Potasium *tert*-butoxide was added in one portion. The pale yellow solution turned dark brown immediately. After 45 min, TLC analysis showed complete transformation of the bromohydrin. The reaction was then quenched by the addition of a 10% HCl solution (2 mL) and partitioned between water and dichloromethane. Aqueous layer was repeatedly washed with additional dichloromethane and finally the combined organic fractions were dried over $MgSO_4$. After filtration and evaporation of the solvent, the subsequent residue was purified on silica gel [eluting with PE/EtOAc (1 : 1)], providing preussomerin L (4.4 mg, 17%), R_f = 0.1 [PE/EtOAc (1 : 1)], and *preussomerin K* (12.3 mg, 50%), R_f = 0.35 [PE/EtOAc (1 : 1)] as a yellowish wax; ν_{max}(film)/cm^{-1} 3362, 2916, 2848, 1692, 1662, 1594, 1470, 1270, 1088, 1023, 794; δ_H (400 MHz; $CDCl_3$) 2.41 (1 H, br s, 3′-O*H*), 3.05 (1 H, dd, *J* = 18.3 and 2.5, C2-CH_b), 3.37 (1 H, dd, J = 18.3 and 3.4, C2′-CH_a), 3.86 (1 H, d, *J* = 4, C3-C*H*), 4.27 (1 H, d, *J* = 4, C2-C*H*), 4.80 (1 H, m, C3′-C*H*), 6.97 (1 H, d, *J* = 9.2, C8-C*H*), 7.06 (1 H, d, *J* = 9.2, C7-C*H*), 7.09 (1 H, dd, *J* = 8.2 and 1, C7′-C*H*), 7.43 (1 H, t, *J* = 8, C8′-C*H*), 7.69 (1 H, dd, *J* = 7.7 and 1, C9′-C*H*) and 10.16 (1 H, br s, 9-O*H*); δ_C (125 MHz, $CDCl_3$) 41.2 (C2′), 52.1 (C3), 53.5 (C2), 70.2 (C3′), 93.7 (C4), 94.4 (C4′), 110,2 (C10), 115.6 (C5), 119.2 (C5′), 120.8 (C7), 121.41 (C9′), 121.46 (C7′), 126.5 (C8), 130.7 (C10′), 131.3 (C8′), 142.77 (C6), 149.8 (C6′), 156.2 (C9), 193.1 (C1′) and 195.4 (C1); *m*/*z* (CI) Calc. for $C_{20}H_{13}O_8$ [M + H$^+$] 381.061043; Found: 381.060608 (+1.1 ppm).

4*H*,11*H*-5,6,11,12,13-Pentahydro-3-methoxy-11-hydroxy-6a,13a-epoxydinaphtho[1,8-bc:1′,8′-fg] [1,5]dioxocin-4-one 22

A suspension of the crude triflate **11** (0.65 mmol) in EtOAc/methanol (1 : 3 v/v, 24 mL) was treated with triethylamine (550 μL). Under nitrogen, Pd/C (5% palladium on activated charcoal, 200 mg) was added. The flask was then purged with hydrogen and committed to a sequential cycle vacuum–hydrogen atmosphere repeated several times. The mixture was stirred at room temperature for 20 h under a hydrogen atmosphere (balloon). The black suspension was then purged with nitrogen and filtered through a short Celite® pad, washing with EtOAc. The filtrate was loaded onto Celite® and purified by flash column chromatography on silica gel [eluting with a polar gradient PE/EtOAc (1 : 1) to (1 : 6)] to provide the *title compound* **22** as an white solid (117 mg, 50%); R_f = 0.43 [PE/EtOAc (1 : 6)]; mp 132–134 °C; ν_{max}(film)/cm^{-1} 3426, 2962, 2884, 1680, 1590, 1480, 1285, 1187, 1048, 1009, 916, 808; δ_H (400 MHz; $CDCl_3$) 2.11 (1 H, m, C2′-CH_b), 2.6–2.3 (4 H, m, C3-CH_b, C3′-CH_a, C3′-CH_b, C2′-CH_a), 2.62 (1 H, ddd, *J* = 13, 6.5 and 1.5, C3-CH_a), 2.82 (1 H, ddd, *J* = 19, 6.7 and 1.5, C2-CH_b), 3.20 (1 H, ddd, *J* = 19, 13 and 6, C2-CH_a), 3.86 (3 H, s, OCH_3), 4.85 (1 H, m, C1′-C*H*), 6.73 (1 H, dd, *J* = 8.2 and 1, C7′-C*H*), 6.95 (1 H, d, *J* = 9.2, C8-C*H*), 7.03 (1 H, d, *J* = 9.2, C7-C*H*), 7.08 (1 H, ddd, *J* = 7.6, 1 and 0.6, C9′-C*H*) and 7.25 (1 H, dd, *J* = 8.2 and 7.6, C8′-C*H*); a selective 1D-NOESY was found at peak δ 7.08 ppm (C9′-CH, 4.1%) when irradiating at δ 4.85 ppm (C1′-C*H*); δ_C (100 MHz; $CDCl_3$) 194.9, 154.3, 149.7, 142.3, 139.3, 130.75 (C8′), 123.9, 122.6 (C7), 121.2 (C9′), 118.7, 117.8, 115.4 (C7′), 115.0 (C8), 94.2, 93.2, 68.2 (C1′), 56.5 (OMe), 34.3 (C2), 31.93 (C3), 31.88 (C2′), 28.2 (C3′); *m*/*z* (CI) Calc. for $C_{21}H_{19}O_6$ [M + H$^+$] 367.118164; Found: 367.118239 (−0.2 ppm).

4*H*,11*H*-5,6,11,12,13-Pentahydro-3-methoxy-11-(methoxy-methoxy)-6a,13a-epoxydinaphtho[1,8-bc:1′,8′-fg] [1,5]dioxocin-4-one 25a

A solution of **22** (95 mg, 0.26 mmol) in dry dichloromethane (10 mL) was cooled to 0 °C under argon and treated with Hunig's base (160 μL, 0.91 mmol). Then, chloromethyl methyl ether (**CAUTION**: cancer suspected agent, 60 μL, 0.78 mmol) was added portionwise. The reaction was stirred at 0 °C for 1 h. The crude was warmed to rt and stirred until completion (TLC analysis, *ca.* 1 h), quenched by the addition of saturated NH_4Cl solution (30 mL) and extracted with DCM (3 × 25 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and the solvent eliminated under reduced pressure. The crude product was purified by column chromatography on silica gel [eluting with a polar gradient PE/EtOAc (1 : 1) to (1 : 6)] affording the *title compound* **25a** as a white wax (100 mg, 94%); R_f = 0.54 [PE/EtOAc (1 : 6)]; ν_{max}(film)/cm^{-1} 2934, 1683, 1591, 1480, 1464, 1285, 1239, 1149, 1101, 1037, 1007, 919, 810, 746; δ_H (400 MHz; $CDCl_3$) 2.11 (1 H, m, C2′-CH_b), 2.7–2.3 (5 H, m, C3-CH_a, C3-CH_b, C3′-CH_a, C3′-CH_b, C2′-CH_a), 2.81 (1 H, ddd, *J* = 19, 6.5 and 1.5, C2-CHb), 3.5 (3 H, s, MOM-CH_3), 3.19 (1 H, ddd, *J* = 19, 13 and 6, C2-CH_a), 3.86 (3 H, s, OCH_3), 4.78 (1 H, d, *J* = 7, MOM-CH_b), 4.84 (1 H, m, C1′-C*H*), 4.9 (1 H, d, *J* = 7, MOM-CH_a), 6.71 (1 H, dd, *J* = 8.2 and 1, C7′-C*H*), 6.94 (1 H, d, *J* = 9.2, C8-C*H*), 7.04 (1 H, d, *J* = 9.2, C7-C*H*), 7.06 (1 H, ddd, *J* = 7.6, 1 and 0.6, C9′-C*H*) and 7.23 (1 H, t, *J* = 8, C8′-C*H*); δ_C (100 MHz; $CDCl_3$) 25.8 (C3′), 32.0 (C2′), 32.6 (C3), 34.4 (C2), 55.8 (OCH_3), 56.5 (MOM-CH_3), 73.0 (C1′), 93.1, 93.7, 95.4 (MOM-CH_2), 114.9 (C8), 115.2 (C7′), 118.5, 121.8 (C9′), 122.9 (C7), 123.8, 130.3 (C8′), 136.9, 142.5, 149.7, 154.1 and 195.0 (C1); *m*/*z* (CI) Calc. for $C_{23}H_{23}O_7$ [M + H$^+$] 411.144378; Found: 411.144043 (+0.8 ppm).

4*H*,11*H*-5,6,11,12,13-Pentahydro-3-hydroxy-11-(methoxy-methoxy)-6a,13a-epoxydinaphtho[1,8-bc:1′,8′-fg] [1,5]dioxocin-4-one 25b

A solution of ketone **25a** (26 mg, 0.06 mmol) was dissolved in dry pyridine (2 mL) under argon and was treated with LiI (42 mg, 0.31 mmol) and heated under reflux for 20 h protected from direct light (aluminium foil). After cooling to rt, the reaction was quenched by the addition of water and acidified carefully with 10% HCl solution. The aqueous layer was extracted with DCM (3 × 25 mL), the combined organic layers washed with brine and dried over $MgSO_4$, filtered and the solvent eliminated *in vacuo*. The residue was purified by column chromatography on silica gel [PE/EtOAc (1 : 1)], affording *title compound* **25b** (23.2 mg, 93%) as a waxy solid; R_f = 0.63 [PE/EtOAc (1 : 1)]; ν_{max}(film)/cm^{-1} 2938, 2889, 2771, 1648, 1622, 1593, 1469, 1365, 1324, 1300, 1276, 1225, 1184, 1148, 1100, 1037, 1006, 917, 808, 750, 733; δ_H (400 MHz; $CDCl_3$) 2.07 (1 H, m, C3′-CH_b), 2.65–2.35 (4 H, m, C3-CH_b, C2′-CH_a, C2′-CH_b, C3′-CH_a), 2.64 (1 H, ddd, *J* = 13.2, 5.6 and 1.8, C3-CH_a), 2.84 (1 H, ddd, *J* = 18.5, 5.2 and 1.8, C2-CH_b), 3.33 (1 H, ddd, *J* = 18.5, 13.7 and 5.6, C2-CH_a), 3.51 (3 H, s, MOM-OCH_3), 4.79 (1 H, d, J = 7, CH_2-MOM), 4.83 (1 H, m, C1′-C*H*), 4.9 (1 H, d, *J* = 7, CH_2-MOM), 6.73 (1 H, d, *J* = 8.2, C7′-C*H*), 6.87 (1 H, d, *J* = 9.1, C8-C*H*), 7.03 (1 H, d, *J* = 9.1, C7-C*H*), 7.08 (1 H, d, *J* = 7.6, C9′-C*H*), 7.24 (1 H, t, *J* = 8, C8′-C*H*) and 11.7 (1 H, s, C9-O*H*); δ_C (100 MHz; $CDCl_3$) 25.5 (C3′), 32.3 (C2′), 32.6 (C3), 33.6 (C2), 55.7 (OCH_3-MOM), 73.1 (C1′), 92.7, 94.1, 95.6 (CH_2-MOM), 113, 115.3 (C7′), 118.7, 120.3, 120.5, 122 (C8), 126.4, 130.6, 137.3 (C7), 141.8, 149.7, 157.2 (C8′) and 203.1 (C1); *m*/*z* (CI) Calc. for $C_{22}H_{21}O_7$ [M + H$^+$] 397.128728; Found: 397.128037 (+1.7 ppm).

4*H*,11*H*-5,6,11,12,13-Pentahydro-3,11-di(methoxy-methoxy)-6a,13a-epoxydinaphtho[1,8-bc:1′,8′-fg] [1,5]dioxocin-4-one 25c

A solution of **25b** (34 mg, 0.085 mmol) in dry dichloromethane (4 mL) was cooled to −10 °C under argon and treated with Hunig's base (52 μL, 0.3 mmol). Then, chloromethyl methyl ether (**CAUTION**: cancer suspected agent; 20 μL, 0.26 mmol) was added portionwise. The reaction was stirred at 0 °C for 1 h and then warmed to rt and stirred for 12 h. More Hunig's base (52 μL, 0.3 mmol) and chloromethyl methyl ether (20 μL, 0.26 mmol) were added and stirred at rt for a further 12 h, then quenched by the addition of saturated NH_4Cl solution (20 mL) and extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvent eliminated under reduced pressure. The crude product was purified by column chromatography on silica gel [eluting with PE/EtOAc (1 : 1)], affording the *title compound* **25c** as a white wax (32 mg, 75%); R_f = 0.43 [PE/EtOAc (1 : 1)]; ν_{max}(film)/cm^{-1} 2953, 2899, 1689, 1591, 1476, 1284, 1192, 1150, 1036, 1006, 990, 919, 810, 733; δ_H (400 MHz; $CDCl_3$) 2.07 (1 H, m, C3′-CH_b), 2.65–2.35 (5 H, m, C3-CH_a, C3-CH_b, C2′-CH_a, C3′-CH_a, C3′-CH_b), 2.8 (1 H, ddd, *J* = 18.8, 6.4 and 1.3, C2-CH_b), 3.18 (1 H, ddd, *J* = 18.8, 13.2 and 6.3, C2-

CH_a), 3.487 (3 H, s, MOM-OCH_3), 3.494 (3 H, s, MOM-OCH_3), 4.76 (1 H, d, J = 7, CH_b-MOM), 4.83 (1 H, m, C1′-CH), 4.87 (1 H, d, J = 7, CH_a-MOM), 5.15 (1 H, d, J = 6.9, CH_b-MOM–Ar), 5.19 (1 H, d, J = 6.9, CH_a-MOM–Ar), 6.71 (1 H, d, J = 7.9, C7′-CH), 7.0 (1H, d, J = 9.1, C8-CH), 7.06 (1 H, d, J = 7.6, C9′-CH), 7.15 (1 H, d, J = 9.1, C7-CH) and 7.23 (1 H, t, J = 8, C8′-CH); δ_C (100 MHz; $CDCl_3$) 25.4, 31.8, 32.3, 34.2, 55.7, 56.3, 72.9, 93.0, 93.9, 95.4, 96.3, 115.5, 118.7, 120.3, 120.8, 122.4, 122.9, 123.7, 130.2, 137.2, 144.3, 150.0, 151.8 and 195.4; *m/z* (CI) Calc. for $C_{24}H_{25}O_8$ [M + H^+] 441.154943; Found: 441.154622 (+0.7 ppm).

4*H*,11*H*-11,12,13-Trihydro-3,11-di(methoxy-methoxy)-6a,13a-epoxydinaphtho[1,8-bc:1′,8′-fg] [1,5]dioxocin-4-one 26c

(a) Sodium hexamethyldisilazane (1.0 M solution in THF, 28 μL, 0.028 mmol) was added portionwise *via* microsirynge to a solution of the protected intermediate **25c** (10.2 mg, 0.023 mmol) in dry THF (2 mL) under argon at −40 °C and stirred for 15 min. The deep orange solution of the enolate so generated was trapped with TMSCl (6 μL, 0.05 mmol) and slowly warmed to −10 °C, then to 0 °C and finally to rt over 5 h. Reaction crude was concentrated under reduced pressure and the crude product was efficiently dried under high vacuum, affording a yellow, viscous oil which was used without further purification in the next step.

(b) The above crude silyl enol ether was dissolved (solubilisation assisted by sonication) in dry acetonitrile (2 mL) at rt under argon and $Pd(OAc)_2$ (6.2 mg, 0.028 mmol) was added in one portion. The reaction was stirred for 15 h. After filtration through a short Celite® pad (EtOAc washings), the solvent was eliminated and the residue purified by column chromatography on silica gel [eluting PE/EtOAc (7 : 3)], affording the hydrolysed starting material **25c** (2.5 mg, 25%) and the *title enone* **26c** (7.6 mg, 75%) as a waxy viscous solid; R_f = 0.4 [PE/EtOAc (1 : 1)]; ν_{max}(film)/cm^{-1} 2951, 2913, 1675, 1591, 1480, 1338, 1287, 1244, 1201, 1150, 1085, 1036, 1006, 990, 918, 808; δ_H (400 MHz; $CDCl_3$) 2.07 (1 H, m, C3′-CH_b), 2.6-2.4 (3 H, m, C2′-CH_a, C2′-CH_b, C3′-CH_a), 3.50 (3 H, s, MOM-OCH_3), 3.51 (3 H, s, MOM-OCH_3), 4.82 (1 H, d, J = 7, CH_b-MOM), 4.93 (1 H, d, J = 7, CH_a-MOM), 4.83 (1 H, m, C1′-CH), 5.19 (1 H, d, J = 6.9, CH_b-MOM–Ar), 5.24 (1 H, d, J = 6.9, CH_a-MOM–Ar), 6.47 (1 H, d, J = 10, C2-CH), 6.72 (1 H, d, J = 8, C7′–CH), 6.98 (1 H, d,J = 9.2, C8–CH), 7.0 (1 H, d, J = 10, C3-CH), 7.09 (1 H, d, J = 7.7, C9′-CH), 7.16 (1 H, d, J = 9.2, C7-CH) and 7.24 (1 H, t, J = 8, C8′-CH); δ_C (100 MHz; $CDCl_3$) 25.6, 32.3, 55.7, 56.4, 73.2, 94.4, 95.8, 96.6, 115.6, 118.1, 119.2, 121.0, 121.7, 122.8, 130.7, 134.9, 137.1, 139.5, 144.7, 150.0, 151.8 and 183.7; *m/z* (CI) Calc. for $C_{24}H_{23}O_8$ [M + H^+] 439.139293; Found: 439.139026 (+0.6 ppm).

4*H*,11*H*-5,6,11,12,13-Pentahydro-3,11-di(methoxy-methoxy)-5-oxiran-6a,13a-epoxydinaphtho[1,8-bc:1′,8′-fg] [1,5]dioxocin-4-one 27c

TBD (1 mg, 0.006 mmol) was added to a solution of the enone **26c** (9.4 mg, 0.02 mmol) in dry toluene (1.2 mL) under argon at rt. After cooling at 0 °C (ice bath), TBHP (5–6 M solution in decane, 24 μL) was added *via* microsyringe and the reaction warmed to rt. The original yellow solution turned to a colourless solution. After 40 min, the reaction was quenched by the addition of a saturated solution of sodium sulfite (2 mL) and diluted with EtOAc. The organic phase was separated and washed with brine. The combined aqueous layers were extracted with EtOAc (3 × 10 mL) and the combined organic extracts dried over $MgSO_4$ and filtered. After removal of the solvent, the residue was purified by flash column chromatography on silica gel [eluting with PE/EtOAc (7 : 3)]. *Epoxide* **27c** was isolated as a colourless wax (8.5 mg, 89%); R_f = 0.39 [PE/EtOAc (1 : 1)]; ν_{max}(film)/cm^{-1} 2959, 2944, 2926, 2825, 1704, 1591, 1483, 1287, 1153, 1037, 923, 808, 733; δ_H (400 MHz; $CDCl_3$) 2.11 (1 H, m, C3′-CH_b), 2.65–2.4 (3 H, m, C2′-CH_a, C2′-CH_b, C3′-CH_a), 3.48 (3 H, s, MOM-OCH_3), 3.50 (3 H, s, MOM-OCH_3), 3.83 (1 H, d, J = 4.4, C2-CH), 4.12 (1 H, d, J = 4.4, C3-CH), 4.78 (1 H, d, J = 7, MOM-CH_b), 4.83 (1 H, m, C1′-CH), 4.89 (1 H, d, J = 7, MOM-CH_a), 5.13 (1 H, d, J = 6.9, CH_b-MOM–Ar), 5.18 (1 H, d, J = 6.9, CH_a-MOM–Ar), 6.7 (1 H, d, J = 8.2, C7′-CH), 7.01 (1 H, d, J = 9.2, C7-CH), 7.1 (1 H, d, J = 7.6, C9′-CH),7.19 (1 H, d, J = 9.2, C7-CH), 7.25 (1 H, t, J = 7.9, C8′-CH); δ_C (100 MHz; $CDCl_3$) 25.0, 31.8, 52.8, 53.3, 55.5, 56.2, 72.9, 93.6, 94.5, 95.8, 96.3, 115.8, 117.8, 118.9, 121.1, 122.9, 123.5, 131.3, 135.4, 137.9, 145.9, 149.8 and 192.7; *m/z* (CI) Calc. for $C_{24}H_{22}O_9$ [M + H^+] 454.126383; Found: 455.126429 (−0.1 ppm).

Preussomerin F (4*H*,11*H*-5,6,11,12,13-pentahydro-3,11-didihydroxy-5-oxiran-6a,13a-epoxydinaphtho[1,8-bc:1′,8′-fg] [1,5]dioxocin-4-one)

A dilute solution of HCl in isopropyl alcohol was prepared prior to use by dropping concentrated HCl (3 drops, *ca* 60 μL) in isopropyl alcohol (10 mL). The MOM-protected epoxyketone **27c** (4.8 mg, 0.01 mmol) was dissolved in 2 mL of this freshly prepared solution and heated at 50 °C for 8 h under argon. The reaction was quenched by the addition of solid $NaHCO_3$, diluted with EtOAc and filtered through a short cotton pad, washing with additional EtOAc. The solvent was eliminated and the residue purified further by column chromatography on silica gel [eluting PE/EtOAc polar gradient (7 : 3) to (1 : 1)] affording the desired deprotected *title compound* preussomerin F (2.4 mg, 66%) and diol **29** (1.3 mg, 34%) as waxy solids; preussomerin F, R_f = 0.32 [PE/EtOAc (1 : 1)]; ν_{max}(film)/cm^{-1} 3435, 3374, 2961, 2929, 2860, 1659, 1633, 1592, 1469, 1363, 1315, 1262, 1091, 1023, 801, 734; δ_H (400 MHz; $CDCl_3$) 2.11 (1 H, ddd, J = 17.7, 13.2 and 6.4, C2′-CH_b), 2.5–2.45 (2 H, m, C3′-CH_a, C3′-CH_b), 2.61 (1 H, ddd, J = 17.7, 13.2 and 4.4, C2′-CH_a), 3.80 (1 H, d, J = 4.0, C2-CH), 4.16 (1 H, d, J = 4.0, C3-CH), 4.86 (1 H, m, C1′-CH), 6.74 (1 H, d, J = 8, C7′-CH), 6.92 (1 H, d, J = 9.1, C7-CH), 7.04 (1 H, d, J = 9.1, C8-CH), 7.17 (1 H, d, J = 7.6, C9′-CH), 7.28 (1 H, t, J = 7.9, C8′-CH) and 10.16 (1 H, s, C9-OH); δ_H (400 MHz; methanol-d_4) 2.1–2.0 (1 H, m, C2′-CH_b), 2.5–2.3 (3 H, m, C2′-CH_a, C3′-CH_a, C3′-CH_b), 3.84 (1 H, d, J = 4, C3-CH), 4.26 (1 H, d, J = 4, C3-CH), 4.8 (1 H, m, C1′-CH), 6.72 (1 H, d, J = 7.6, C7′-CH), 6.91 (1 H, d, J = 9.2, C7-CH), 7.08 (1 H, d, J = 9.2, C8-CH), 7.17 (1 H, d, J = 8, C9′-CH) and 7.24 (1 H, d, J = 8, C8′-CH); δ_C (100 MHz; $CDCl_3$) 28.4, 32.1, 52.1, 53.8, 68.2, 93.1, 94.9, 110.1, 115.2, 115.9, 127.8, 120.8, 121.6, 126.4, 130.9, 139.2, 143.2, 148.6, 155.6 and 195.8; δ_C (100 MHz; methanol-d_4) 29.4 (C3′), 30.8 (C2′), 53.2 (C3), 54.9 (C2), 68.4 (C1′), 94.6 (C4′), 96.2 (C4), 111.6 115.6 (C7′), (C5), 116.6 (C10), 118.9 (C9′), 119.2 (C5′), 121.7 (C7), 127.2 (C8), 131.9 (C8′), 141.4 (C10′), 144.7 (C6), 150.0 (C6′), 156.3 (C9) and 197.4 (C1); *m/z* (EI) Calc. for $C_{20}H_{14}O_7$ [M^+] 366.073953; Found: 366.074153 (−0.5 ppm).

Acknowledgements

We acknowledge Professor Karsten Krohn (University of Paderborn) for providing authentic comparison samples of preussomerins K and L.

References

1 For a recent review, see: K. Krohn, in *Progress in the Chemistry of Organic Natural Products*, W. Herz, H. Falk and G. W. Kirby, ed., Springer, Wien, 2003, vol. 85, pp. 1–49.
2 H. B. Bode, B. Wegner and A. Zeeck, *J. Antibiot.*, 2000, **53**, 153–157; H. B. Bode and A. Zeeck, *Phytochemistry*, 2000, **55**, 311–316.
3 J. Ohkanda, D. B. Knowles, M. A. Blaskovich, S. M. Sebti and A. D. Hamilton, *Curr. Top. Med. Chem.*, 2002, **2**, 303–323; D. M. Leonard, *J. Med. Chem.*, 1997, **40**, 2971–2990; A. D. Cox and C. J. Der, *Curr. Opin. Pharmacol.*, 2002, **2**, 388–393; W. T. Purcell and R. C. Donehower, *Curr. Oncol. Rep.*, 2002, **4**, 29–36.
4 H.-W. Fu and P. J. Casey, *Recent Prog. Horm. Res.*, 1999, **54**, 315–343; A. Wittinghofer and H. Waldmann, *Angew. Chem., Int. Ed.*, 2000, **39**, 4192–4214.
5 J. Wiesner, K. Kettler, R. Sakowski, R. Ortmann, A. M. Katzin, E. A. Kimura, K. Silber, G. Klebe, H. Jomaa and M. Schlitzer, *Angew. Chem., Int. Ed.*, 2004, **43**, 251–254.
6 G. Schlingmann, R. R. West, L. Milne, C. J. Pearce and G. T. Carter, *Tetrahedron Lett.*, 1993, **34**, 7225–7228; G. Schlingmann, S. Matile, N. Berova, K. Nakanishi and G. T. Carter, *Tetrahedron*, 1996, **52**, 435–446.

7 K. Krohn, A. Michel, U. Florke, H. J. Aust, S. Draeger and B. Schulz, *Liebigs Ann. Chem.*, 1994, 1099–1108; K. Krohn, A. Michel, U. Florke, H. J. Aust, S. Draeger and B. Schulz, *Liebigs Ann. Chem.*, 1994, 1093–1097; K. Krohn, K. Beckmann, U. Florke, H. J. Aust, S. Draeger, B. Schulz, S. Busemann and G. Bringmann, *Tetrahedron*, 1997, **53**, 3101–3110.

8 L. A. McDonald, D. R. Abbanat, L. R. Barbieri, V. S. Bernan, C. M. Discafani, M. Greenstein, K. Janota, J. D. Korshalla, P. Lassota, M. Tischler and G. T. Carter, *Tetrahedron Lett.*, 1999, **40**, 2489–2492.

9 (*a*) H. A. Weber, N. C. Baenziger and J. B. Gloer, *J. Am. Chem. Soc.*, 1990, **112**, 6718–6719; (*b*) H. A. Weber and J. B. Gloer, *J. Org. Chem.*, 1991, **56**, 4355–4360; (*c*) J. D. Polishook, A. W. Dombrowski, N. N. Tsou, G. M. Salituro and J. E. Curotto, *Mycologia*, 1993, **85**, 62–64; (*d*) S. B. Singh, D. L. Zink, J. M. Liesch, R. G. Ball, M. A. Goetz, E. A. Bolessa, R. A. Giacobbe, K. C. Silverman, G. F. Bills, F. Pelaez, C. Cascales, J. B. Gibbs and R. B. Lingham, *J. Org. Chem.*, 1994, **59**, 6296–6302; (*e*) A. G. Soman, J. B. Gloer, B. Koster and D. Malloch, *J. Nat. Prod.*, 1999, **62**, 659–661; (*f*) K. Krohn, U. Flörke, M. John, N. Root, K. Steingröver, H. J. Aust, S. Draeger, B. Schulz, S. Antus, M. Simonyi and F. Zsila, *Tetrahedron*, 2001, **57**, 4343–4348; (*g*) P. Seephonkai, M. Isaka, P. Kittakoop, P. Palittapongarnpim, S. Kamchonwongpaisan, M. Tanticharoen and Y. Thebtarononth, *Planta Med.*, 2002, **68**, 45–48.

10 S. Chi and C. H. Heathcock, *Org. Lett.*, 1999, **1**, 3–5.

11 A. G. M. Barrett, F. Blaney, A. D. Campbell, D. Hamprecht, T. Meyer, A. J. P. White, D. Witty and D. J. Williams, *J. Org. Chem.*, 2002, **67**, 2735–2750.

12 L. Alcaraz, G. Macdonald, J. P. Ragot, N. Lewis and R. J. K. Taylor, *J. Org. Chem.*, 1998, **63**, 3526–3527.

13 J. P. Ragot, C. Steeneck, M.-L. Alcaraz and R. J. K. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1073–1082.

14 J. P. Ragot, M. E. Prime, J. Archibald and R. J. K. Taylor, *Org. Lett.*, 2000, **2**, 1613–1616.

15 E. Quesada, M. Stockley and R. J. K. Taylor, *Tetrahedron Lett.*, 2004, **45**, 4877–4881.

16 R. Aldred, R. Johnston, D. Levin and J. Neilan, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1823–1828.

17 K. C. Nicolaou, T. Montagnon and P. S. Baran, *Angew. Chem., Int. Ed.*, 2002, **41**, 993–996; K. C. Nicolaou, Z.-L. Zhong and P. S. Baran, *J. Am. Chem. Soc.*, 2002, **112**, 7596–7597.

18 K. C. Nicolaou, D. L. F. Gray, T. Montagnon and S. T. Harrison, *Angew. Chem., Int. Ed.*, 2002, **41**, 996–1000.

19 Y. Ito, T. Hirao and T. Saegusa, *J. Org. Chem.*, 1978, **43**, 1011–1013.

20 R. C. Larock, T. R. Hightower, G. A. Kraus, P. Hahn and D. Zheng, *Tetrahedron Lett.*, 1995, **36**, 2423–2426.

21 T. Genski, G. Macdonald, X. Wei, N. Lewis and R. J. K. Taylor, *Synlett*, 1999, 795–797.

22 M. Miyashita, T. Suzuki, M. Hoshino and A. Yoshikoshi, *Tetrahedron*, 1997, **53**, 12 469–12 486.

23 A. Fürstner and G. Seidel, *J. Org. Chem.*, 1997, **62**, 2332–2336; A. Lewis, I. Stefanuti, S. A. Swain, S. A. Smith and R. J. K. Taylor, *Org. Biomol. Chem.*, 2003, **1**, 104–116.

24 C. K. Johnson, *ORTEP, Report ORNL-5138*, Oak Ridge National Laboratory, Oak Ridge, TN, 1976.

25 Crystallographic data for **17**: $C_{21}H_{12}O_8$, $M = 392.31$, orthorhombic, $a = 7.9269(17)$, $b = 9.360(2)$, $c = 22.044(5)$ Å, $U = 1635.5(6)$ Å^3, $T = 115(2)$ K, space group *Pna*2(1), $Z = 4$, $\mu = 0.124$ mm^{-1}, 7933 reflections measured. CCDC reference number 239166. For **18**: $C_{21}H_{16}O_8$, CH_4O (methanol solvate), $M = 428.38$, orthorhombic, $a = 12.2619(6)$, $b = 14.5570(8)$, $c = 21.1566(11)$ Å, $U = 3776.4(3)$ Å^3, $T = 115(2)$ K, space group *Pbca*, $Z = 8$, $\mu = 0.118$ mm^{-1}, 20 342 reflections measured. CCDC reference number 230613. See http://www.rsc.org/suppdata/ob/b4/b407895k/ for crystallographic data in .cif or other electronic format.

26 Crystallographic data for **27a**: $C_{23}H_{20}O_8$, $M = 424.39$, monoclinic, $a = 10.5753(8)$, $b = 7.6628(6)$, $c = 12.0215(10)$ Å, $U = 945.49(13)$ Å^3, $T = 115(2)$ K, space group *P*2(1), $Z = 2$, $\mu = 0.114$ mm^{-1}, 3211 reflections measured. CCDC reference number 269167. See http://www.rsc.org/suppdata/ob/b4/b407895k/ for crystallographic data in .cif or other electronic format.