Biomimetic studies towards the cardinalins: synthesis of (+)-ventiloquinone L and an unusual dimerisation†

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Studies towards the biomimetic synthesis of cardinalin 3 are described. Despite the successful enantioselective synthesis of the monomeric pyranonaphthoquinone ventiloquinone L, it subsequently failed to undergo a proposed biomimetic homodimerisation to cardinalin 3 using a range of oxidants. However, treatment of a related naphthopyran with cerium ammonium nitrate (CAN) facilitated a tandem biaryl bond formation–oxidative demethylation sequence furnishing a dimeric pyranonaphthoquinone that had exclusively dimerised at C6. The nature of this unusual sequence is discussed and the product subsequently converted to the C6 regioisomer of cardinalin 3.

Introduction

Cardinalin 3 (**1**) is a member of a family of dimeric pyranonaphthoquinones[1] contained in the deep-red ethanolic extract of the fresh fruit bodies of the New Zealand toadstool *Dermocybe cardinalis*.[2] Its interesting structure, in particular the tetra-substituted C8–C8′ biaryl bond that results in **1** existing as a single (*aS*)-atropisomer, combined with its significant cytotoxic properties (IC_{50} = 0.47 mg mL^{-1} against P388 murine leukaemia cell line) renders it an attractive target for synthesis (Fig. 1).

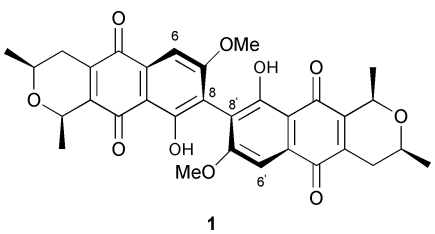

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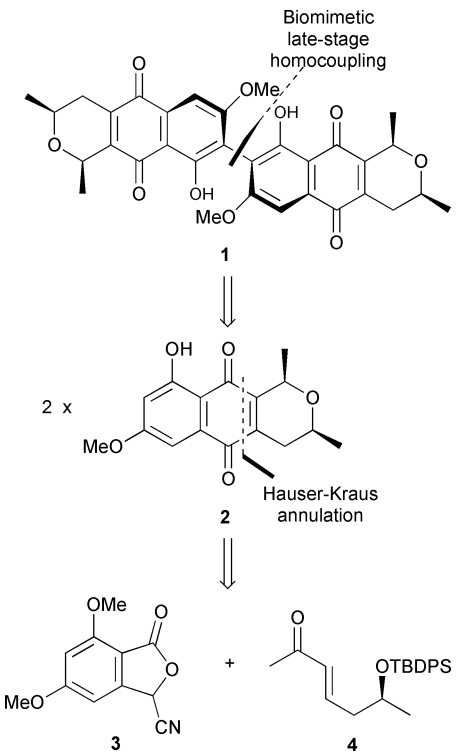
Fig. 1 Cardinalin 3.

Our previous synthetic efforts towards **1** have resulted in the successful enantioselective synthesis of the dimeric pyranonaphthoquinone core using a late stage homocoupling of an aryltriflate.[3] Additionally, de Koning *et al.* have reported a racemic synthesis of **1** using a bidirectional approach in which the biaryl bond was installed at an early stage of the synthesis.[4]

Herein we report our initial studies based on a revised approach that hinges on the late stage biomimetic coupling of the monomer of cardinalin 3 **1**, ventiloquinone L **2**, itself a natural product isolated from the root bark of *Ventilago goughii*.[5] It was hoped that if ventiloquinone L **2** could be made in an enantiopure fashion, the chirality present in **2** may exert some induction during the dimerisation step leading to atroposelective biaryl formation. Adopting a route analogous to our synthesis of the monomeric pyranonaphthoquinone eleutherin,[6] we envisaged ventiloquinone L **2** could be prepared using a Hauser–Kraus annulation[7] between cyanophthalide **3** and (−)-enone **4** (Scheme 1).



Scheme 1 Retrosynthesis of **1**.

Results and discussion

Thus, our initial thoughts turned to the enantioselective synthesis of ventiloquinone L **2**. De Koning *et al.* have reported a racemic synthesis of **2**[8] but to date only a single enantioselective synthesis of **2** exists in the literature, a 10 step procedure employing the Diels–Alder addition of a silyloxybutadiene to a bromoquinone as the key step.[9]

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† Electronic supplementary information (ESI) available: Full experimental data, nOe data and spectra of compounds **2**, **5**, **7**, **8**, **10a** and **10b**. See DOI: 10.1039/b905077a

The synthesis of **2** was hence conducted as shown in Scheme 2. Although the Hauser–Kraus annulation between cyanophthalide **3**[10] and (−)-enone **4**[6] initially proved troublesome, it was eventually found that isolating the crude annulation product after a very short reaction time (3–4 min) and immediately subjecting it to reductive methylation conditions furnished naphthalene **5** in modest overall yield. Treatment of **5** with excess TBAF for 4 days effected silyl group removal with concomitant cyclisation and the resulting crude lactol **6** was stereoselectively reduced with trifluoroacetic acid and triethylsilane delivering the *cis*-1,3-dimethyl pyran **7** as a single diastereomer in good overall yield.

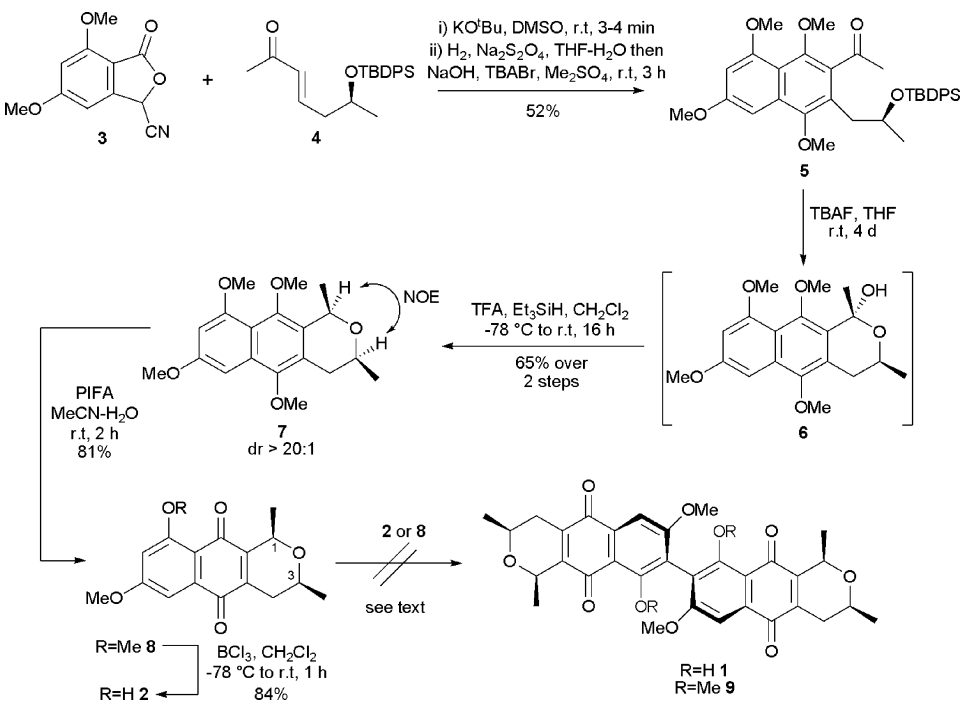
The 1,3-stereochemistry was confirmed unequivocally by the observed NOE correlation between the axial protons at C1 and C3 on the pyran ring, a result expected due to the predicted pseudoaxial delivery of hydride during the reduction step.[11] Oxidative demethylation with phenyliodine bis(trifluoroacetate)[12] in aqueous acetonitrile delivered ventiloquinone L methyl ether (7-methoxyeleutherin) **8** for which the spectroscopic data were identical to that reported for material prepared from a semi-synthesis of **8** *via* oxidation of (+)-karwinaphthol B.[13] Finally, selective monodeprotection of **8** with boron trichloride delivered (+)-ventiloquinone L **2** which was identical in all aspects to the natural (+)-ventiloquinone L[5] and synthetic (+)-ventiloquinone L[9] obtained from the previous synthesis. Based on these results, we further confirm the absolute stereochemistry present in **2** to be 1*R*, 3*S*.

Next, attention turned towards the key dimerisation step. Unfortunately, despite subjecting **2** to a plethora of known phenolic oxidative dimerisation conditions including basic ferricyanide, $FeCl_3$, Pb^{IV} salts, Cu^{I}/O_2, $h\nu/O_2$ and cerium ammonium nitrate (CAN), no cardinalin 3 **1** was ever isolated. Similarly, attempted dimerisation of **8** failed to deliver dimer **9** (Scheme 2).

Undeterred by these disappointing results, it was decided at this stage to attempt the proposed late stage homocoupling of an advanced aromatic intermediate instead of the pyranonaphthoquinone **2**. Naphthopyran **7** was identified as the best candidate.

Thus, upon subjecting the naphthopyran **7** to a similar array of oxidative coupling conditions, the one electron oxidant cerium ammonium nitrate (CAN) proved the most promising.[14] During the CAN oxidation, complete consumption of the starting material **7** was only evident upon addition of three equivalents of the oxidant, resulting in the formation of a very polar product. Upon purification an orange solid was isolated that showed only one aromatic proton by ^{1}H NMR, suggesting dimerisation had occurred. The ^{13}C spectrum showed the requisite amount of peaks required for dimer **9**, several of which had satellite peaks suggesting the existence of diastereomers. Careful separation of the mixture was carried out affording two distinct symmetrical atropisomers **10a** and **10b** in a 1 : 1 ratio suggesting that the chirality present on the pyran ring in **7** had not exerted any chiral induction in the biaryl forming step (Scheme 3).

X-Ray crystallographic analysis was conducted on pure **10a** which revealed the configuration at the C6–C6′ biaryl bond to be *R* but unfortunately the existence of conformers around the pyran area of **10a** precluded a complete crystallographic analysis. Therefore, it should be noted that this study cannot be used to definitively confirm the configuration of the biaryl bond. NOE studies on the (*S*)-atropisomer **10b** established the remaining aromatic proton had a strong correlation with both methoxy groups on the aryl ring, indicating that dimerisation had unfortunately not occurred through C8 as proposed in our biomimetic hypothesis and as is necessary for construction of the cardinalin 3 **1** framework. Rather, naphthopyran **7** had surprisingly dimerised exclusively at C6. Also, the chemical shifts for the aromatic proton in the ^{1}H



Scheme 2 Synthesis of (+)-ventiloquinone L **2** and failed dimerisation.

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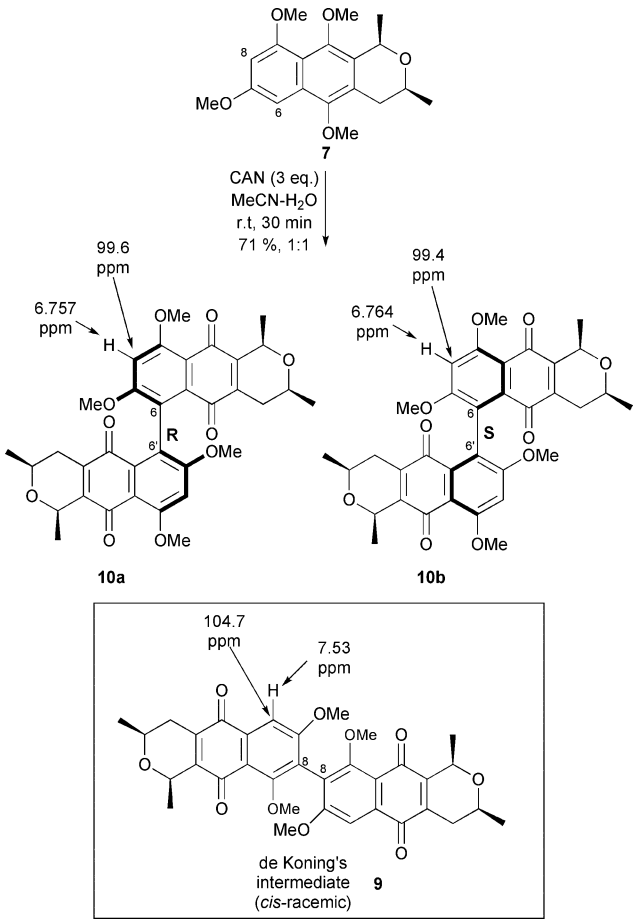


Scheme 3 Homodimerisation of naphthopyran **7**.

NMR of the *aR* and *aS* atropisomers **10a** and **10b** were observed at $\delta = 6.757$ and 6.764 ppm respectively, significantly further upfield than the aromatic protons observed at $\delta = 7.53$ ppm in (±)-cardinalin dimethyl ether **9** synthesised during de Koning's racemic synthesis of **1**.[4] The ^{13}C chemical shifts of the remaining aromatic methine carbons in **10a**, **10b** and **9** also showed significant differences (Scheme 3).

Next, we set out to define the order of events in this interesting dimerisation. Thus, in order to gauge whether biaryl bond formation was occurring before or after the oxidative demethylation, naphthopyran **7** was treated with 1 equivalent of CAN. Surprisingly, only dimers **10a** and **10b** were isolated, again as a 1 : 1 mixture along with substantial amounts of starting material **7**. None of the dimeric naphthopyran **11** was ever observed. However, none of the dimers **10a** or **10b** were isolated when treating ventiloquinone methyl ether **8** with varying amounts of CAN, indicating that the oxidation of **7** to **8** is not the first step in the CAN mediated reaction of **7** to **10a** and **10b**. These results suggest that in the transformation of naphthopyran **7** to **10a** and **10b**, the biaryl bond is formed in the first step followed by immediate oxidation of the resulting electron rich dimeric naphthopyran **11** affording the dimers **10a** and **10b** (Scheme 4).

At this stage it was decided to selectively deprotect **10a** and **10b** in order to complete the total synthesis of a regioisomer of cardinalin 3 **1**. Thus, the 1 : 1 mixture of atropisomers **10a** and **10b** was treated with boron trichloride affording the atropisomers **12a** and **12b** also in a 1 : 1 ratio in good yield. The synthesis of **12a** and **12b** constitutes the total synthesis of the C6 regioisomer of cardinalin 3 **1** (Scheme 5).

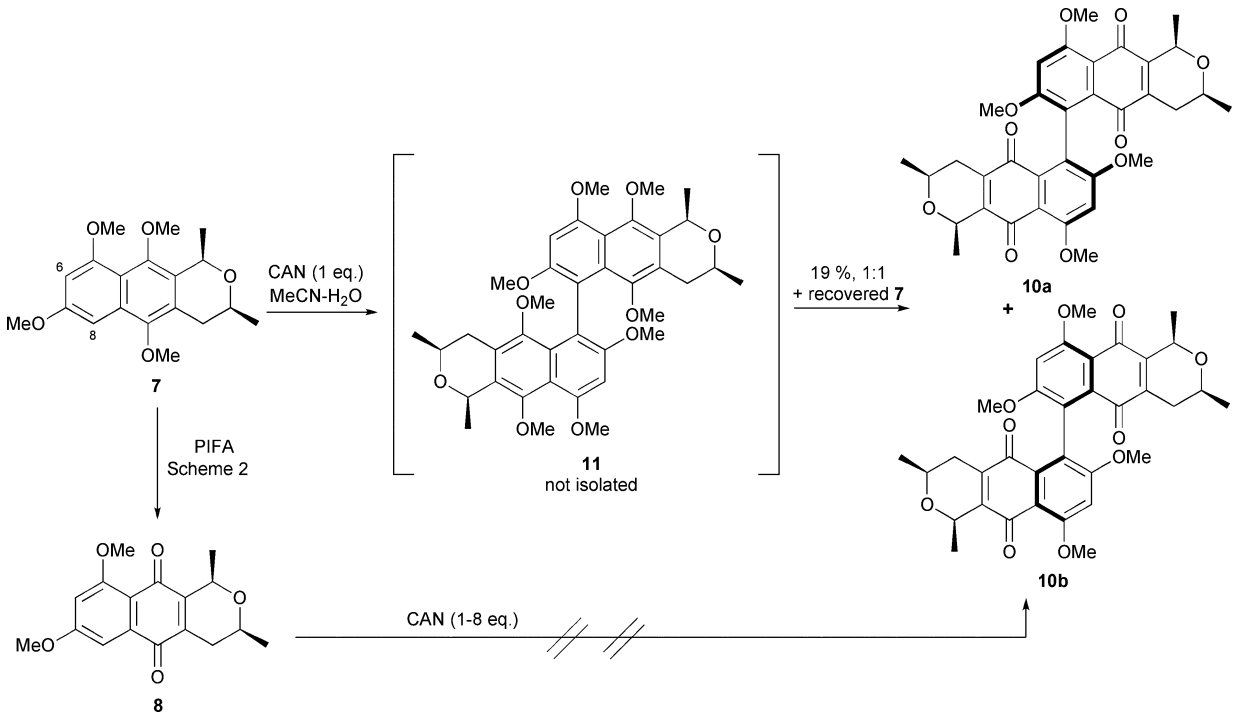
In conclusion, an efficient synthesis of (+)-ventiloquinone L **2** has been achieved with a longest linear sequence of 7 steps further confirming the 1*R*,3*S* stereochemistry of the natural product. Although attempts to dimerise **2** directly were unsuccessful, mild oxidation of naphthopyran **7** triggered homodimerisation at C6 furnishing **10a** and **10b**. To the best of our knowledge, this high yielding oxidative dimerisation of a naphthopyran or pyranonaphthoquinone at C6 is extremely rare and the only other similar reactions are the isolation of traces (2%) of a C6 dimer during a semi-synthesis of actinorhodin from its respective monomer[15] and the borate promoted dimerisation of quinone A.[16] The mild biaryl formation demonstrated herein provides interesting insight into the possible biosynthesis of C6-symmetrical dimeric naphthopyran natural products such as xylindein[17] or viridotoxin[18] from their respective monomers. Furthermore, selective deprotection of **10a** and **10b** delivered **12a** and **12b**, the C6 regioisomer of cardinalin 3 **1**. Our failure to successfully dimerise pyranonaphthoquinones **2** or **8** combined with the high yielding dimerisation of naphthopyran **7** exclusively at C6 somewhat contradicted our proposal that cardinalin 3 **1** is constructed in Nature from a late stage homocoupling of ventiloquinone L **2** or a closely related compound. Also, due to the facile and mild nature of the successful dimerisation of naphthopyran **7** at C6, we propose that pyranonaphthoquinone dimers of type **10a**, **10b**, **12a** and **12b** may well be as yet undiscovered natural products.

Experimental section

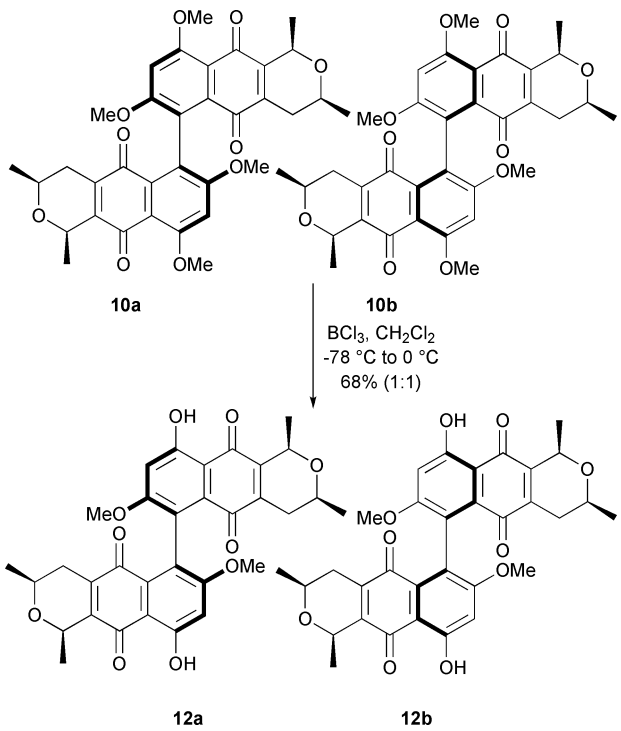
(1*R*,1′*R*,3*S*,3′*S*,6*R*)-7,7′,9,9′-Tetramethoxy-1,1′,3,3′-tetramethyl-3,3′,4,4′-tetrahydro-1*H*,1′*H*-6,6′-bibenzo[*g*]isochromene-5,5′,10,10′-tetraone (10a) and (1*R*,1′*R*,3*S*,3′*S*,6*S*)-7,7′,9,9′-tetramethoxy-1,1′,3,3′-tetramethyl-3,3′,4,4′-tetrahydro-1*H*,1′*H*-6,6′-bibenzo[*g*]isochromene-5,5′,10,10′-tetraone (10b)

Naphthopyran **7** (48 mg, 0.14 mmol) was taken up in acetonitrile (4 mL) and a solution of cerium(IV) ammonium nitrate (245 mg, 0.45 mmol) in distilled water (2 mL) was added. The reaction mixture was stirred for 30 min at rt and water (12 mL) was then added. The aqueous layer was extracted with ethyl acetate (3 × 30 mL) and the combined organic layers dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography eluting with hexanes–ethyl acetate (1 : 3 then 100% ethyl acetate) to give the *title compounds* as an orange solid and a 1 : 1 mixture of atropisomers; (30.7 mg, 0.051 mmol, 71%). Purification of this mixture by further flash chromatography eluting with hexanes–ethyl acetate (1 : 1 then 2 : 3) gave pure (*R*)-atropisomer **10a** (R_f 0.42, ethyl acetate) as a yellow solid (14 mg, 0.023 mmol, 34%) and pure (*S*)-atropisomer **10b** (R_f 0.35, ethyl acetate) as a yellow solid (15 mg, 0.025 mmol, 36%).

10a Mp 270–272 °C; $[\alpha]_D^{24}$ +852.9 (*c* 0.13, CH_2Cl_2); ν_{max} (neat) 2928, 2851, 1737, 1649, 1634, 1582, 1551, 1456, 1433, 1341, 1300, 1253, 1211, 1149 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.27 (6 H, d, *J* 6.3,



Scheme 4 Route for transformation of **7** to **10a** and **10b**.



Scheme 5 Synthesis of the C6 regioisomer of cardinalin 3 **1**.

2 × CH_2CHMe), 1.56 (6 H, d, *J* 6.6, 2 × Me), 1.97 (2 H, ddd, *J* 3.8, 10.2 and 18.2, 2 × $CH_{ax}H$), 2.50 (2 H, dt, *J* 2.6 and 18.2, 2 × $CH_{eq}H$), 3.48 (2 H, m, 2 × H-3), 3.74 (6 H, s, 2 × OMe), 4.05 (6 H, s, 2 × OMe), 4.81 (2 H, m, 2 × H-1), 6.757 (2 H, s, 2 × Ar–H); δ_C (75 MHz, $CDCl_3$) 20.7 (2 × Me), 21.2 (2 × Me), 29.9 (2 × CH_2), 56.1 (2 × OMe), 56.3 (2 × OMe), 68.8 (2 × CH), 70.3 (2 × CH), 99.6 (2 × CH), 114.8 (2 × C), 120.9 (2 × C), 132.3 (2 × C), 139.8 (2 × C), 148.0 (2 × C), 161.3 (2 × C), 161.6 (2 × C), 182.7 (2 × C=O), 184.8 (2 × C=O); *m*/*z* (EI+) 602 (100%, M^+), 587 (10), 260 (10), 43 (80); HRMS (EI+, M^+) found 602.2150, calc for $C_{34}H_{34}O_{10}$ 602.2152.

10b Mp 127–129 °C; $[\alpha]_D^{24}$ +108.1 (*c* 0.16, CH_2Cl_2); ν_{max} (neat) 2928, 2851, 1737, 1649, 1634, 1582, 1551, 1456, 1433, 1341, 1300, 1253, 1211, 1149 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.26 (6 H, d, *J* 6.0, 2 × CH_2CHMe), 1.53 (6 H, d, *J* 6.6, 2 × Me), 1.94 (2 H, ddd, *J* 3.8, 10.3 and 18.1, 2 × $CH_{ax}H$), 2.50 (2 H, t, *J* 2.6 and 18.1, 2 × $CH_{eq}H$), 3.49 (2 H, m, 2 × H-3), 3.73 (6 H, s, 2 × OMe), 4.05 (6 H, s, 2 × OMe), 4.82 (2 H, m, 2 × H-1), 6.764 (2 H, s, 2 × Ar–H); δ_C (75 MHz, $CDCl_3$) 20.6 (2 × Me), 21.2 (2 × Me), 29.8 (2 × CH_2), 56.1 (2 × OMe), 56.3 (2 × OMe), 68.8 (2 × CH), 70.3 (2 × CH), 99.4 (2 × CH), 114.9 (2 × C), 121.4 (2 × C), 131.3 (2 × C), 139.6 (2 × C), 148.2 (2 × C), 161.3 (2 × C), 162.6 (2 × C), 183.1 (2 × C=O), 184.8 (2 × C=O); *m*/*z* (EI+) 602 (100%, M^+), 587 (10), 260 (10), 43 (80); HRMS (EI+, M^+) found 602.2150, calc for $C_{34}H_{34}O_{10}$ 602.2152.

Acknowledgements

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