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Convergent First Total Synthesis of Melovinone: A Densely Substituted 3-Methoxy-4-quinolone Isolated from *Melochia tomentosa* L.

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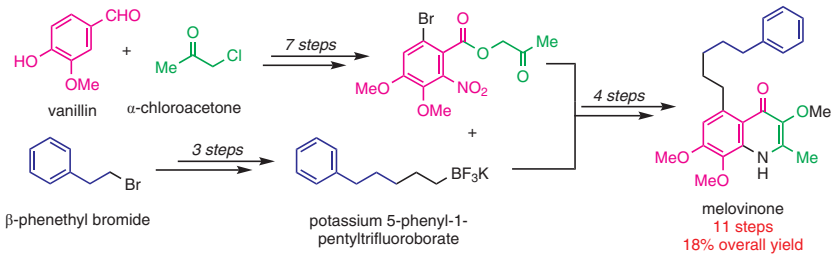

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Abstract The first total synthesis of melovinone, a nonrutaceous 3-methoxy-4-quinolone alkaloid isolated from *Melochia tomentosa* L., is reported. The target was acquired in a convergent fashion through the Suzuki–Miyaura cross-coupling reaction between an *ortho*-nitrobenzoic acid acetonyl ester derivative prepared from vanillin and potassium 5-phenyl-1-pentyltrifluoroborate, obtained from β-phenethyl bromide. The coupling was followed by a chemoselective reduction of the nitro group and a microwave-assisted and AcOH-promoted cyclization with rearrangement of the resulting acetonyl anthranilate. This afforded a pseudane intermediate, which was selectively methylated on the 3-OH. The synthetic pathway enabled to reach the objective in 11 steps and 18% overall yield. The ^{1}H NMR spectra of the synthetic and natural product were in full agreement.

Key words melovinone, total synthesis, natural products, nonrutaceous alkaloids, 3-methoxy-4-quinolones

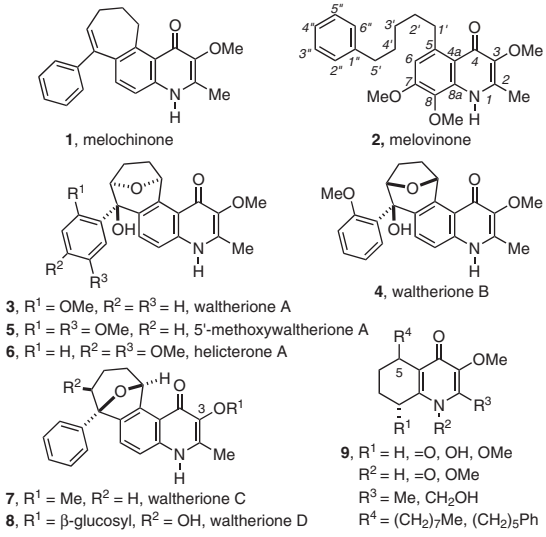

Figure 1 Chemical structures of melovinone (**2**) and related 4-quinolones

During the last decades, a small family of bioactive 3-methoxy-4-quinolones has emerged; however, unlike the structurally related rutaceous alkaloids, its members display a pendant C-5 (ar)alkyl group or a seven-membered ring fused to C-5 and C-6, to form a cyclohepta[*f*]quinolinone core, decorated with an unsaturation or oxygen functionalities.

The first examples (Figure 1) were melochinone (**1**),[1a] and its plausible biogenetic precursor melovinone (**2**), isolated from the Colombian shrub *Melochia tomentosa* L. (Sterculiaceae).[1b] Recently, the related waltheriones A (**3**)[2a] and B (**4**)[2b] were isolated from the root bark of *Waltheria douradinha* St.-Hil. Waltherione A was also isolated from *M. chamaedrys* A. St.-Hil, which grows in southern Brazil,[3a] and from *M. odorata* L. f., harvested in New Caledonia.[3b]

In addition, 5′-methoxywaltherione A (**5**) and helicterone A (**6**) were obtained from the woody herb *Triumfetta grandidens*[4a–c] and from the Chinese tree *Helicteres angustifolia* L., respectively.[4d] The waltheriones C (**7**) and D (**8**) were isolated from *M. odorata* collected in Papua New Guinea.[4e] The family was enlarged with the isolation of the waltheriones E–Q and others[5] from the roots of the Nigerian plant *Waltheria indica* L., most of which share the common core **9**.

Interestingly, the alkaloids **3**, **5**, and **7** inhibited the growth of various nematodes.[4a–c] In addition, waltherione A (**3**) has broad-spectrum antifungal activity,[3b] whereas compound **7** exhibited potent and selective activity against *Trypanosoma cruzi*,[6a–c] and cytotoxicity against P-388 murine leukemia cells,[4e,6a] being also cancer chemopreventive,[6d] and cytoprotective against HIV infection.[4e] Other waltheriones

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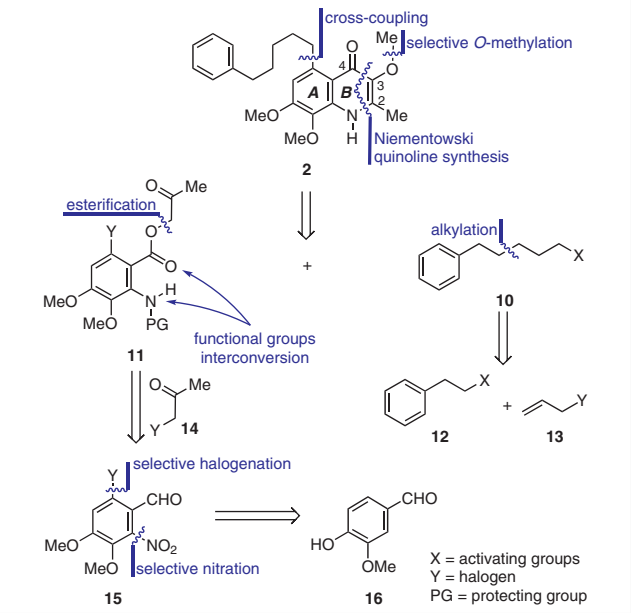
also behaved as potent antifungal and cytotoxic agents.[5b] The bioactivities of the extracts of *W. indica* L. have been recently reviewed.[7]

Constrastingly, few synthetic efforts to access these compounds have been recorded to date. These include a study toward **7**,[8a] the elaboration of the oxabicyclic core of **7** and **8**,[8b] and the total synthesis of waltherione F.[8c,d]

We are interested in the synthesis of heterocyclic natural products[9] and the development of analogues, to assess their structure and bioactivity profile.[10] In pursuit of these interests, herein we disclose the first total synthesis of melovinone (**2**), based on the retrosynthetic analysis depicted in Scheme 1.



Scheme 1 Retrosynthetic analysis of melovinone (**2**)

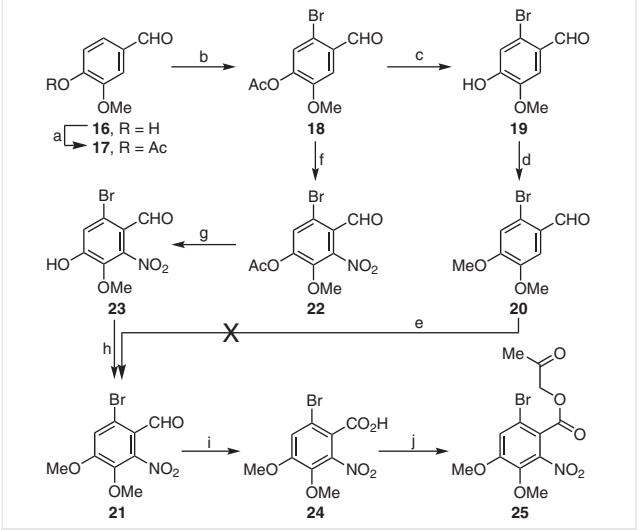
The initial disconnections of melovinone were carried out at the C-3 methyl ether, the aralkyl side chain and between the C-3–C-4 and N–C-2 bonds of the B-ring. These scissions were performed considering that a Niementowski reaction[11] could be a viable means toward the 3-hydroxyquinolone core, which could be further *O*-methylated at a later stage. On the other hand, the side chain was strategically dissected, having in mind a cross-coupling reaction between a properly substituted ω-phenylpentyl derivative **10** and an activated benzenoid. These speculations revealed the anthranilate acetonyl ester **11** as a suitable precursor.

In turn, **10** was disconnected into the β-phenethyl derivative **12** and the allyl component **13**, under the conjecture that the ω-phenylpentyl moiety could result from the alkylation of an activated form of β-phenethyl halide **12** and a three-carbon atoms species like **13**. An additional disconnection was also performed on the ester moiety of **11**, unveiling an *ortho*-halobenzaldehyde derivative as its proper precursor, on the assumption that the haloarene could be a successful scaffold to install the aralkyl side chain, whereas the acetonyl ester could be easily accessible from the formyl group and an activated acetone equivalent **14**.

Further, it was inferred that the amine feature of the key anthranilate could result from a nitro group, through functional group interconversion. Therefore, the 2-nitrobenzaldehyde derivative **15** was assumed as a convenient forerunner of **11**. This approach offered the possibility to perform a convergent synthesis of the natural product by joining **10** and **11**, as well as a stepwise alternative, which should entail coupling **11** to **13** and then react their coupling product with a species like **12**.

Additional simplifications were performed on **15**, by disconnecting both substituents *ortho* to the formyl moiety, under the premise that the directing effects of the different functional groups will enable the selective functionalization of the aromatic ring. These thoughts uncovered the economical and easily available vanillin (**16**) as a logical starting point.

With the above strategy in mind, the synthesis of **2** began with the acetylation of vanillin (required to avoid *ortho*-phenol bromination)[12] under conventional conditions (Ac_2O, DMAP), to give **17** in 93% yield (Scheme 2). Without purification, this material was subjected to bromination with Br_2 and KBr in $MeCN/H_2O$,[13] providing the bromoarene **18** in almost quantitative yield. Next, basic hydrolysis of the acetate **18** furnished the intermediate **19** (85% yield), which was submitted to a Williamson *O*-methylation with MeI in MeCN, employing Cs_2CO_3 as base, to afford the veratraldehyde derivative **20** in 72% overall yield from **18**.



Scheme 2 *Reagents and conditions*: a) Ac_2O, DMAP, 40 °C, 2 h (93%); b) Br_2, KBr, $MeCN/H_2O$ (1:1 v/v), rt 12 h (95%); c) aq 3 M NaOH, rt (85%); d) MeI, Cs_2CO_3, MeCN, reflux, 5 h (85%); e) HNO_3 (d = 1.52 g·cm^{-3}), 0–6 °C, 10 min (polynitrated products); f) HNO_3 (d = 1.52 g·cm^{-3}), 0–6 °C, 10 min (99%); g) aq 0.5 M KOH, 1,4-dioxane, 40 °C, 1 h (81% from **18**); h) MeI, K_2CO_3, DMF, 50 °C 5 h (91%); i) CrO_3, H_2SO_4, acetone, 0 °C → rt, 1 h (99%); j) 1. K_2CO_3, DMF, 40 °C, 1 h; 2. $ClCH_2C(O)Me$, DMF, 20–50 °C, 1 h (99%).

The subsequent step involved installation of the nitro moiety; however, when nitration of **20** was carried out with red fuming nitric acid, only polynitrated materials were observed and **21** could not be detected. Other nitration conditions such as mixtures of HNO_3 with H_2SO_4, AcOH and Ac_2O were also tested, but all of them met with failure.

Conjecturing that the acetate **18** should be a less reactive substrate than the related methyl ether **20**,[14a,b] the nitration of the former with fuming HNO_3 was explored, observing the exclusive formation of the desired nitro derivative **22** in 99% yield. Then, the acetate was hydrolyzed with KOH in 1,4-dioxane and the resulting phenol **23** was methylated, providing the benzaldehyde **21** in 81% overall yield from **18**.[14c,d]

Next, the benzaldehyde **21** was conveniently oxidized with Jones' reagent to the related benzoic acid **24** in 99% yield. The proper aromatic substitution pattern of **24** was assessed by NMR spectroscopy and the molecular structure was also confirmed by single crystal X-ray diffraction (Figure 2).[15]

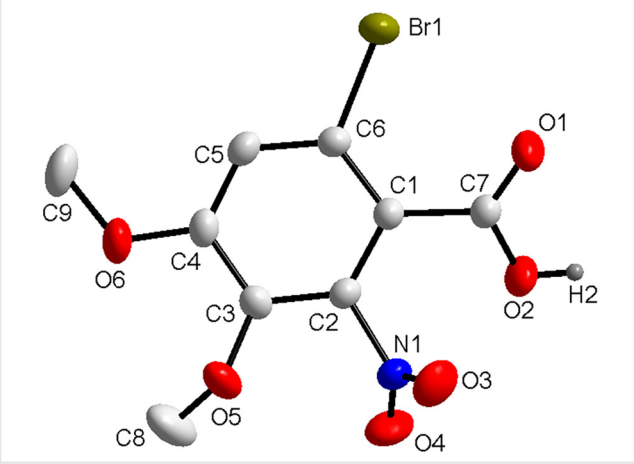
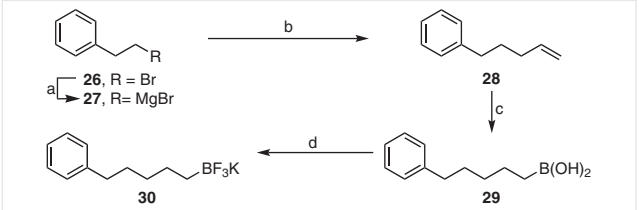


Figure 2 Molecular structure of **24**. The displacement ellipsoids were drawn at the 50% probability level and hydrogen atoms were omitted for the sake of clarity, excepting the OH group.

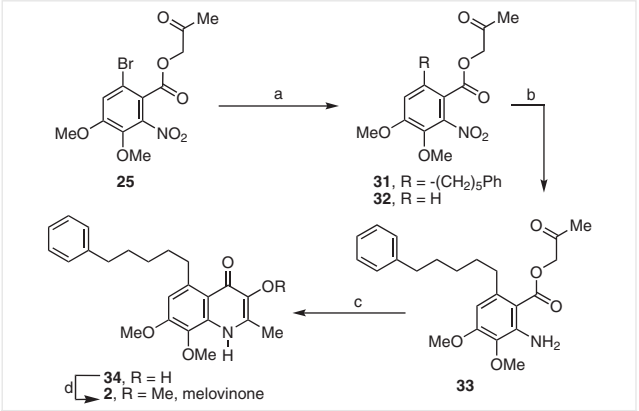
Without additional purification, the acid **24** was treated with chloroacetone and K_2CO_3 in DMF, to give the acetonyl ester **25** in 99% yield, setting the stage for the installation of the C-5 side chain. A Suzuki–Miyaura strategy was chosen to fulfil the task, because this is a leading methodology which tolerates a broad range of functional groups and is increasingly used to create new Csp^3–Csp^2 bonds.[16]

Among different alternatives, the synthesis of the trifluoroborate salt **30** as the boron component was next undertaken, through the intermediacy of 5-phenyl-1-pentene (**28**). Therefore, β-phenethyl bromide (**26**) was exposed to Mg^0 in Et_2O to give the Grignard reagent **27**, and this was made to react with allyl bromide to afford **28** in 95% yield (Scheme 3).[17]



Scheme 3 *Reagents and conditions*: a) Mg^0, I_2, Et_2O, rt; b) $BrCH_2CH{=}CH_2$, Et_2O, 15 °C, 1 h (95% from **26**); c) 1. 1.4 M $BH_3{\cdot}SMe_2$ in toluene, CCl_4, 0 °C, 30 min. Then rt, 3 h; 2. aq 2 M HCl, H_2O, rt (83%); d) sat. aq KHF_2, MeOH, rt, 3 h (22%).

Then, the terminal alkene was submitted to a hydroboration with excess $BH_3{\cdot}SMe_2$ in CCl_4,[18a] to afford 83% yield of the alkylboronic acid intermediate **29** after acid hydrolysis.[18b] Final treatment of the latter with KHF_2 in MeOH, gave the required potassium 5-phenyl-1-pentyltrifluoroborate (**30**).[19] The Suzuki–Miyaura reaction of **30** with the bromoarene **25** was executed in the presence of the hindered phosphine ligand di-*tert*-butyl phosphinoferrocene (dtbpf) to minimize competitive β-hydride elimination.[20] The transformation proceeded smoothly to afford the cross-coupled product **31** in 93% yield (Scheme 4), accompanied by 5% of the debrominated compound **32**.



Scheme 4 *Reagents and conditions*: a) $Ph(CH_2)_5BF_3K$ (**30**), $Pd(AcO)_2$, dtbpf, K_2CO_3, toluene/H_2O (10:1), 80 °C 18 h (**31**, 93%; **32**, 5%); b) Ni_2B, H_2 (1 atm), 1 M HCl, MeOH, 70 °C, 30 min (81%); c) glacial AcOH, MW (150 °C, 60 W), 25 min; d) MeI, *i*-PrOH, K_2CO_3, 50 °C, 3.5 h (40%, from **33**).

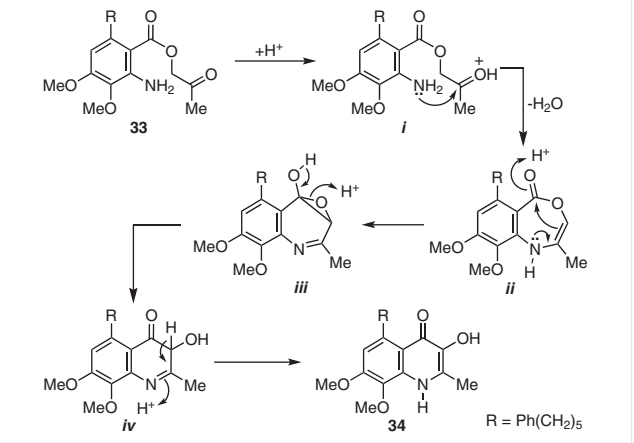
Construction of the heterocyclic B-ring was subsequently undertaken. Hence, the reduction of the nitro group of **31** was pursued, with freshly prepared nickel boride in MeOH, gently affording the acetonyl anthranilate **33** in 81% isolated yield.[21]

Then, the latter was submitted to an intramolecular Niementowski cyclization/rearrangement protocol,[22] involving the microwave irradiation (150 °C, 60 W) of a dilute solution of the ester in glacial AcOH.

Formation of the sought pseudane key intermediate **34** took place smoothly, as first evidenced during TLC monitoring of the reaction, where the heterocycle exhibited a characteristic fluorescence when irradiated with long wavelength (365 nm) UV-light and a blue colored spot, when the plate was sprayed with a $FeCl_3$ solution.

Various alternative mechanisms have been suggested for the classical Niementowski quinoline synthesis, all of which involve N–C-2 and C-3–C-4 bond formation in different order.[23]

Although the actual sequence of transformations leading to **34** remains unknown, a mechanistic picture can be proposed on the basis of analogous processes[22b,c] (Scheme 5). The reaction could be initiated by protonation of the ketone moiety of **33** and intramolecular nucleophilic attack by the amino group on the protonated carbonyl ***i*** to afford a 1,4 oxazepin-5(1*H*)-one derivative ***ii*** after dehydrative cyclization.



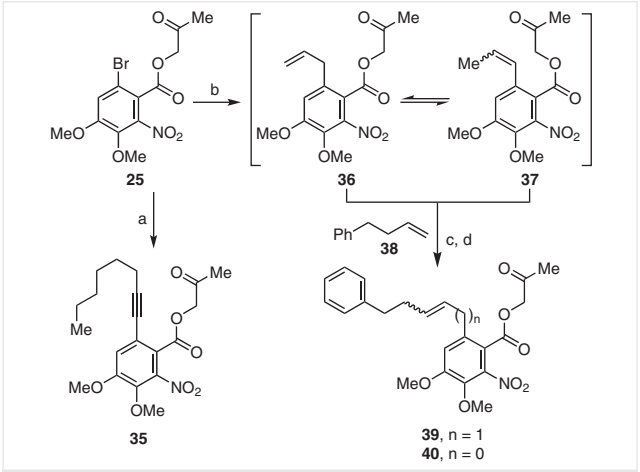
Scheme 5 Proposed mechanism for the Niementowski type cyclization/rearrangement of **33** toward **34**

Subsequent formation of the oxa-azabicyclo[4.1.0] heptadiene-type intermediate ***iii*** by intramolecular attack of the enamine motif to the ester carbonyl under the assistance of the free electronic pair of the nitrogen, could be followed by rearrangement with concomitant oxirane ring opening to the α-hydroxyketonic intermediate ***iv***, which in turn could undergo a 1,3-proton shift to afford **34**.

The chromatographic purification of **34** proved troublesome.[24] Therefore, the crude material was carried forward to the final methylation step (Scheme 4). Based on our experience on the selective alkylation of quinolones,[8c,25] **34** was treated with MeI and K_2CO_3 in anhydrous *i*-PrOH, and the system was refluxed in a closed vessel for 3.5 hours, to give 40% of melovinone (**2**). Delightfully its ^{1}H NMR spectrum was in full agreement with that of the natural product.[1b]

Additional confirmation of the suitability of the Suzuki–Miyaura approach for the key step of joining of the ω-phenylpentyl side chain to the polysubstituted aromatic core **39** was obtained after developing and testing alternative strategies based on other proven cross-coupling schemes, such as the Sonogashira and Stille reactions.

In the first case, the model **35** was prepared by joining **25** with 1-octyne; however, the reaction product demonstrated to be too unstable for further manipulation and had to be abandoned (Scheme 6). On the other hand, in the Stille-based strategy, it was expected to convert **25** into the allylbenzene derivative **36**, which after olefin cross-metathesis with 4-phenyl-1-butene (**38**) should provide the proper intermediate **39**. Therefore, as planned the bromoarene **25** was submitted to Stille cross-coupling conditions with allyltributyltin in toluene under $Pd(Ph_3P)_4$ catalysis, affording the allylbenzenoid **36** in 92% yield.



Scheme 6 *Reagents and conditions*: a) *n*-$C_6H_{13}C{\equiv}CH$, $[Pd(PhP_3)_4]$, CuI, DMF, 70 °C, 15 h (78%); b) $CH_2{=}CHCH_2SnBu_3$, $Pd(Ph_3P)_4$, LiCl, toluene, 80 °C, 18 h (92%); c) **36**, Grubbs II, toluene, 40 °C, 6 h (53%); d) **36**, Hoveyda–Grubbs II, 1,4-benzoquinone, CH_2Cl_2, reflux, 2.5 h (95%).

Sadly enough, however, compound **36** proved to be too labile, easily suffering partial isomerization to the related β-methylstyrenes **37**. It was further observed that the reaction was promoted by the acidity of the silica gel during the chromatographic purification step, as well as by the residual acidity of the $CDCl_3$, as assessed when running long NMR experiments in this solvent. These undesired by-products were also detected when the Stille reaction was allowed to proceed during extended periods of time, and its facile formation was attributed to the presence of the electron-withdrawing groups in **36**.[26]

In an attempt to solve this drawback, the crude compound **36** was carried to the next stage, the cross-metathesis reaction with 4-phenyl-1-butene (**38**).[27] However, TLC monitoring of the reaction revealed a complex series of spots, corresponding to compounds, which could not be separated chromatographically. The mixture was examined by ^{1}H and ^{13}C NMR spectroscopy, concluding that its components included the desired product **39**, and the

corresponding lower homologue **40** (53% combined yield). Furthermore, both compounds (**39**:**40** = 1.8:1) were present as mixtures of their geometric isomers, complicating the analysis and their separation. Presumably, compound **40** arose from the cross-coupling reaction between **38** and the β-methylstyrenes **37**.

Several experiments were carried out with the aim to suppress this undesired reaction. These included changing the catalyst (from Grubbs II to Hoveyda–Grubbs II)[28a] and solvent (from toluene to CH_2Cl_2), as well as adding 1,4-benzoquinone to inhibit the isomerization reaction.[28b,c] In addition, a 'two-steps one-pot' Stille–Grubbs protocol was also explored.[29] However, no significant improvements were observed.

In conclusion, the first total synthesis of the nonrutaceous alkaloid melovinone was accomplished on 11 steps and 18% overall yield from commercially available vanillin, α-chloroacetone and β-phenethyl bromide, by means of a convergent strategy, with minimum use of protecting groups.

The sequence toward the natural product entailed the preparation of the key 2-nitro-3,4-dimethoxy-6-bromobenzoic acid acetonyl ester, and its subsequent cross-coupling under Suzuki–Miyaura conditions, with potassium 5-phenylpentyl trifluoroborate and palladium catalysis, with dtbpf as ligand.

Building of the heterocyclic ring was accomplished by the chemoselective nitro group reduction with Ni_2B, a microwave-promoted cyclization of the so formed acetonyl anthranilate and final methylation of the 3-OH moiety of the resulting pseudane.

The convergent approach to access melovinone employing a Suzuki–Miyaura cross-coupling proved to be a highly suitable alternative toward the total synthesis of the natural product. It paves the route toward acquisition of more complex targets and may find application in the synthesis of other members of this family of heterocycles, such as the polycyclic waltheriones.

All the reactions were carried out under dry N_2 or argon atmospheres, employing oven-dried glassware. Anhyd THF was obtained from a M. Braun solvent purification and dispenser system; anhyd DMF was obtained by heating the PA grade product over BaO for 4 h, followed by distillation under reduced pressure; anhyd toluene, THF, and Et_2O were distilled from blue Na^0/benzophenone ketyl; anhyd Et_3N was prepared by distillation of the commercial product from CaH_2; anhyd MeOH and 2-propanol were prepared by distillation after refluxing the solvent for 24 h over I_2-activated Mg^0 turnings; anhydrous solvents were stored in dry Young ampoules.[30] EtOH refers to the 96° product. All other solvents and reagents were used as received.

Flash chromatographies were carried with silica gel 60 H (particle size <55 μm). Elution of the compounds was carried out with hexanes/EtOAc or EtOAc/EtOH mixtures, under positive pressure and employing gradient of solvent polarity techniques. All new compounds gave single spots on TLC plates run in different hexane/EtOAc and EtOAc/EtOH solvent systems.

The chromatographic spots were detected by exposure to 254 and 365 nm UV light, followed by spraying with Dragendorff reagent (Munier and Macheboeuf modification),[31] with $FeCl_3$ 2.5% in H_2O (to detect pseudane like molecules) or with ethanolic *p*-anisaldehyde/H_2SO_4 reagent and final careful heating of the plates for improving selectivity.

The melting points were measured on an Ernst Leitz Wetzlar model 350 hot-stage microscope and are uncorrected. The FT-IR spectra were acquired on a Shimadzu Prestige 21 spectrophotometer, with the samples prepared as solid dispersions in KBr disks or as thin films held between NaCl cells. The NMR spectra were acquired at 300.13 MHz (^{1}H), 75.48 MHz (^{13}C) MHz, 96.29 MHz (^{11}B) and 282.38 MHz (^{19}F) on a Bruker Avance 300 spectrometer in $CDCl_3$ as solvent, unless stated otherwise. The residual resonance of $CHCl_3$ in $CDCl_3$ (δ_{ref} ^{1}H = 7.26), $BF_3{\cdot}OEt_2$ (δ_{ref} ^{11}B = 0.00) as well as the signals of $CDCl_3$ (δ_{ref} ^{13}C = 77.16) and $CFCl_3$ for (δ_{ref} ^{19}F = 0.00) were used as the corresponding standards. Chemical shifts are reported in parts per million in the δ scale and *J*-values are given in hertz (Hz). In special cases, NOE and 2D-NMR experiments (COSY, HMBC and HMQC) were also employed. Pairs of signals marked with an asterisk or hash signs (* or #) indicate that their assignments may be exchanged. Samples for NMR spectra were dissolved in $CDCl_3$ unless otherwise stated. The high-resolution mass spectra were obtained with a Bruker microTOF-Q IIT instrument (Bruker Daltonics, Billerica, MA) employing sodium formate as reference. Detection of the ions was performed in electrospray ionization, positive ion mode unless otherwise stated.

For single-crystal structure determination the data were collected with a Bruker D8 Venture diffractometer. The equipment was operated using a graphite monochromator with Mo-Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods using SHELXS and refined with SHELXL on F^2 using anisotropic temperature parameters for all non-hydrogen atoms.[32] The positions of the hydrogen atoms were calculated starting from the idealized positions. Microwave-assisted reactions were performed in a CEM Discover microwave oven.

4-Acetoxy-3-methoxybenzaldehyde (Acetylvanillin, 17)

A solution of vanillin (**16**; 4.0 g, 26.29 mmol) and DMAP (22 mg, 0.180 mmol) in Ac_2O (5 mL) was heated at 40 °C during 2 h with vigorous stirring. After verifying complete consumption of the starting material, the mixture was poured over crushed ice (30 g). The resulting white precipitate was recovered by filtration and washed with H_2O (3 × 100 mL). This solid material was dissolved in EtOAc (50 mL), the organic solution was successively washed with H_2O (2 × 50 mL) and brine (2 × 50 mL), dried ($MgSO_4$) and concentrated to afford **17** as a white solid; yield: 4.8 g (93%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.94 (s, 1 H, CHO), 7.51 (d, *J* = 1.8 Hz, 1 H, H-2), 7.49 (dd, *J* = 7.8, 1.8 Hz, 1 H, H-6), 7.21 (d, *J* = 7.8 Hz, 1 H, H-5), 3.89 (s, 3 H, 3-OCH_3), 2.34 (s, 3 H, 2′-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.2 (CHO), 168.5 (1′-CO_2), 152.1 (C-3), 145.1 (C-4), 135.4 (C-1), 124.9 (C-5), 123.5 (C-6), 111.0 (C-2), 56.2 (3-OCH_3), 20.8 (2′-CH_3).

These data were in accordance with the literature values.[33]

4-Acetoxy-6-bromo-3-methoxybenzaldehyde (18)

Br_2 (9.52 g, 59.9 mmol) was cautiously dropped into a solution of **17** (3.90 g, 19.9 mmol) and KBr (8.03 g, 67.5 mmol) in MeCN/H_2O (1:1, v/v, 150 mL). The system was firmly closed and stirred for 20 h at rt, when complete consumption of the starting material was assessed. Then, the mixture was poured onto crushed ice (100 g), the solids were filtered, washed with H_2O, and further dissolved in EtOAc (300 mL). The organic solution was washed with H_2O (250 mL) and brine (2 × 100 mL), and dried ($MgSO_4$). The volatiles were removed in vacuo to afford **18** as an orange solid; yield: 5.13 g (95%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.27 (s, 1 H, CHO), 7.51 (s, 1 H, H-2), 7.36 (s, 1 H, H-5), 3.89 (s, 3 H, 3-OCH_3), 2.33 (s, 3 H, 2′- CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.0 (CHO), 168.1 (1′-CO_2), 151.4 (C-3), 145.1 (C-4), 131.7 (C-1), 128.1 (C-5), 118.0 (C-6), 112.3 (C-2), 56.4 (3-OCH_3), 20.7 (2′-CH_3).

These data were in accordance with the literature values.[33]

4-Acetoxy-6-bromo-3-methoxy-2-nitrobenzaldehyde (22)

The solid acetate **18** (524 mg, 1.92 mmol) was gradually added in small portions over a period of 10 min and under vigorous stirring to concd red fuming HNO_3 (d = 1.52 g·cm^{-3}, 1.9 mL) kept at 0–6 °C. Once the addition was finished and the dissolution of the solid was visually complete, the mixture was poured onto crushed ice (50 g). When the ice melted, the products were extracted with Et_2O (3 × 20 mL), and the combined organic phases were washed with brine (30 mL) and dried ($MgSO_4$). After removal of the volatiles under reduced pressure, the nitro derivative **22** was obtained as a bright yellow amorphous solid; yield: 613 mg (99%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.19 (s, 1 H, CHO), 7.63 (s, 1 H, H-5), 3.91 (s, 3 H, 3-OCH_3), 2.39 (s, 3 H, 2′-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.4 (CHO), 167.2 (1′-CO_2), 148.9 (C-4), 145.1 (C-2), 144.2 (C-3), 130.6 (C-5), 123.0 (C-1), 120.6 (C-6), 63.2 (3-OCH_3), 20.9 (2′- CH_3).

These data were in accordance with the literature values.[34]

6-Bromo-4-hydroxy-3-methoxy-2-nitrobenzaldehyde (23)

Method A: The acetate **22** (600 mg, 1.88 mmol) was suspended in aq 3 M NaOH (10 mL). The system was heated at 40 °C for 1 h with vigorous stirring under a N_2 atmosphere. Once complete hydrolysis was confirmed by TLC, the aqueous solution was washed with Et_2O (2 × 5.0 mL), then made acidic with aq 6 M HCl (ca. 5 mL), and the products were extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), and concentrated under vacuum. The desired phenol **23** was obtained as a pale brownish solid; yield: 448 mg (86%).

^{1}H NMR (300 MHz, acetone-d_6): δ = 10.09 (s, 1 H, CHO), 7.46 (s, 1 H, H-5), 3.94 (s, 3 H, 3-OCH_3).

^{13}C NMR (75 MHz, acetone-d_6): δ = 188.1 (CHO), 158.3 (C-4), 146.3 (C-2), 140.7 (C-3), 123.2 (C-5), 123.1 (C-6), 117.7 (C-1), 62.6 (3-OCH_3).

The spectroscopic data were in agreement with the literature.[34]

Method B: The bromoacetate **18** (2.98 g, 10.95 mmol) was portionwise added to concd red fuming HNO_3 (d = 1.52 g·cm^{-3}, 1.9 mL) at 0–6 °C during a period of 10 min under vigorous stirring. Once the addition was finished and dissolution of the solid was complete, the bright yellow solution was poured onto crushed ice (100 g). The product was extracted with Et_2O (3 × 250 mL), washed with brine (30 mL), and dried ($MgSO_4$). After removal of the volatiles, the thus obtained solid nitro derivative was treated with aq 0.5 M KOH (150 mL) and heated at 40 °C during 1 h. Once saponification was completed, the mixture was driven to pH ~1 by addition of aq 6 M HCl (50 mL) and the aqueous phase was extracted with Et_2O (3 × 150 mL), the combined organic phases were washed with brine (30 mL), and dried ($MgSO_4$). Removal of the solvent afforded the free phenol **23** as a pale brown solid; yield: 2.40 g (81%). The ^{1}H NMR spectrum was in agreement with that of the solid obtained by application of Method A.

6-Bromo-3,4-dimethoxy-2-nitrobenzaldehyde (21)

The phenol **23** (2.2 g, 8.03 mmol) was dissolved in anhyd DMF (25 mL) and the solution was sequentially treated with K_2CO_3 (2.2 g, 16.1 mmol) and MeI (2.5 mL, 40.0 mmol). The resulting slurry was heated at 50 °C for 5 h under N_2 atmosphere. Once complete consumption of the starting material was assessed, the solids were filtered off, and the remaining DMF solution was diluted with H_2O (100 mL). The products were extracted with Et_2O (3 × 50 mL), the combined organic phases were washed with aq 3 M NaOH (2 × 25 mL), H_2O (3 × 30 mL) and brine (30 mL), and dried ($MgSO_4$). After filtration and concentration under reduced pressure, the veratraldehyde derivative **21** was obtained as a yellow oil; yield: 2.12 g (91%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.12 (s, 1 H, CHO), 7.23 (s, 3 H, H-5), 4.02 (s, 3 H, 4-OCH_3), 3.91 (s, 3 H, 3-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.5 (CHO), 158.6 (C-4), 145.1 (C-2), 141.1 (C-3), 123.1 (C-1),* 118.0 (C-5), 117.6 (C-6),* 62.3 (3-OCH_3), 57.1 (4-OCH_3).

The ^{1}H NMR data were in accordance with the literature.[14c]

6-Bromo-3,4-dimethoxy-2-nitrobenzoic Acid (24)

A solution of the veratraldehyde derivative **23** (1.93 g, 6.80 mmol) in acetone (50 mL) was cooled to 0 °C (ice bath) and Jones reagent (2.0 mL) was slowly added dropwise. The system was warmed to rt and stirred for 1 h until the starting aldehyde was fully consumed. Then, 2-propanol was added in order to quench the excess of reagent, the solvent was cautiously removed under vacuum, the remaining suspension was treated with sat. aq Na_2CO_3 (5 mL) and extracted with Et_2O (3 × 50 mL). The organic phase was washed with brine (2 × 50 mL), dried ($MgSO_4$) and the volatiles evaporated to give the benzoic acid derivative **24** as a yellowish solid; yield: 2.0 g (99%); mp 197–195 °C (from $CHCl_3$/MeOH 9:1, v/v) (Lit.[14d] mp 199–198 °C (dil EtOH).

^{1}H NMR (300 MHz, acetone-d_6): δ = 7.56 (s, 1 H, H-5), 4.07 (s, 3 H, 4-OCH_3), 3.94 (s, 3 H, 3-OCH_3).

^{13}C NMR (75 MHz, acetone-d_6): δ = 164.3 (CO_2H), 155.8 (C-4), 146.3 (C-2), 141.5 (C-3), 121.6 (C-1), 120.3 (C-5), 115.5 (C-6), 63.2 (3-OCH_3), 57.9 (4-OCH_3).

Single crystals suitable for X-ray analysis were obtained after slow solvent evaporation from a $CHCl_3$/MeOH (9:1, v/v) solution.[15]

2′-Oxopropyl 6-Bromo-3,4-dimethoxy-2-nitrobenzoate (25)

The benzoic acid **24** (500 mg, 1.63 mmol) was dissolved in anhyd DMF (5.0 mL) and treated with anhyd K_2CO_3 (293 mg, 2.12 mmol). The system was heated at 40 °C for 1 h under argon, and treated with freshly distilled α-chloroacetone (328 μL, 4.08 mmol) at 20 °C, over a 30 min period. The slurry was heated at 50 °C during additional 30 min, when it was poured onto crushed ice (10 g) and left during 10 min. The products were extracted with EtOAc (3 × 25 mL), the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated to dryness. The brownish oil obtained was chromatographed to afford the acetonyl ester **25** as a brownish solid; yield: 585 mg (99%); mp 71–73 °C (from hexanes/EtOAc 1:1, v/v).

IR (KBr): 2922, 2854, 1751, 1724, 1616, 1548, 1420, 1375, 1281, 1148, 1043, 718 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.26 (s, 1 H, H-5), 4.78 (s, 2 H, H-1′), 3.97 (s, 3 H, 4-OCH_3), 3.95 (s, 3 H, 3-OCH_3), 2.23 (s, 3 H, 3′-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.0 (C-2′), 162.4 (ArCO_2CH_2), 156.0 (C-4), 145.9 (C-2), 141.7 (C-3), 119.4 (C-1), 119.1 (C-5), 116.3 (C-6), 69.9 (C-1′), 62.5 (3-OCH_3), 57.3 (4-OCH_3), 26.6 (3′- CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{12}BrNO_7Na$: 383.9689; found: 383.9682.

Potassium 5-Phenyl-1-pentyltrifluoroborate (30)

A solution of 2-phenyl-1-bromoethane (**26**; 2.07 mL, 15.1 mmol) in anhyd Et_2O (6.0 mL) was transferred to an addition funnel and slowly added to a stirred suspension of Mg^0 (405 mg, 16.5 mmol) in Et_2O (2.0 mL) containing a crystal of I_2 under argon. The reaction was initiated by addition of an ethereal solution of phenethyl bromide (0.5 mL), which caused the system to reflux; this condition was kept by continuous dropping of the phenethyl bromide solution. Once the addition was completed, the system was heated to reflux for an additional 1 h period. Then, the reaction system was allowed to cool to rt, placed in a cooled water-bath at 15 °C and the Grignard reagent **27** was treated dropwise during 1 h with a recently distilled solution of allyl bromide (1.8 mL, 15.2 mmol) in anhyd Et_2O (6.0 mL). After this, sat. aq NH_4Cl (5.0 mL) was cautiously added to quench the reaction, and the aqueous phase was extracted with Et_2O (3 × 5.0 mL). The combined organic phases were dried ($MgSO_4$), the volatiles were evaporated off under reduced pressure to afford 5-phenyl-1-pentene **28** as an oily residue; yield: 2.36 g (95%).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.14 (m, 5 H), 5.83 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1 H, H-1), 5.06–4.95 (m, 2 H, H-2), 2.62 (t, *J* = 7.7 Hz, 2 H, H-5), 2.13–2.06 (m, 2 H, H-3), 1.77–1.67 (m, 2 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.6 (C_{ipso}), 138.8 (C-2), 128.6 (2 C, C_{ortho}), 128.4 (2 C, C_{meta}), 125.8 (C_{para}), 114.8 (C-1), 35.5 (C-5), 33.4 (C-3), 30.8 (C-4).

These data were in accordance with the literature,[17a] and the crude material was used in the next step without further purification.

A recently titrated solution of $BH_3{\cdot}SMe_2$ (1.4 M in toluene, 3.2 mL, 4.45 mmol) dissolved in anhyd CCl_4 (5.0 mL) at 0 °C was treated dropwise during 30 min with a solution of alkene **28** (500 mg, 3.42 mmol) in CCl_4 (10 mL), while the diborane evolving from the reaction was quenched by bubbling in an acetone/H_2O solution. Once the addition was completed, the reaction was warmed to rt, and stirred under an argon atmosphere during an additional 3 h period, when the thus formed alkylboranes were cautiously hydrolyzed at 0 °C by dropwise addition of a solution of MeOH (2.0 mL) in CH_2Cl_2 (5.0 mL) over 30 min. Once the gas evolution ceased, aq 2 N HCl (3.42 mL) was added in order to complete the boronic acid formation.[20b] The organic phase was separated, washed with sat. aq $NaHCO_3$ (5.0 mL) and brine (5.0 mL), dried (Na_2SO_4), and concentrated under reduced pressure until dryness, to afford the crude boronic acid intermediate **29**; yield: 549 mg (83%). This material (549 mg, 2.84 mmol) was dissolved in MeOH (6.0 mL) and reacted with sat. aq KHF_2 (4.3 mL) at rt during 3 h. The volatiles were removed under vacuum to give a whitish solid material, which was extracted with hot acetone (4 × 5.0 mL). Evaporation of the solvent furnished the desired potassium salt **30** as a white solid; yield: 161.2 mg (22%); mp >200 °C (from acetone).

IR (NaCl): 2922, 2853, 1300, 1082, 1058, 1031, 959, 741, 696 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.26–7.10 (m, 5 H, C_6H_5), 2.56 (t, *J* = 7.8 Hz, 2 H, H-5), 1.62–1.51 (m, 2 H, H-4), 1.32–1.27 (m, 4 H, H-2, H-3), 0.17–0.14 (m, 2 H, H-1).

^{13}C NMR (75 MHz, acetone-d_6): δ = 144.1 (C_{ipso}), 129.1 (2 C, C_{ortho}), 128.9 (2 C, C_{meta}), 126.2 (C_{para}), 36.8 (C-5), 34.1 (C-4), 32.9 (C-3), 26.2 (C-2). Note: the C-1 peak could not be observed in the ^{13}C NMR spectrum.

^{19}F NMR (282 MHz, acetone-d_6): δ = –141.1.

^{11}B NMR (96 MHz, acetone-d_6): δ = 5.7.

HRMS (ESI, negative mode): *m*/*z* [M]$^-$ calcd for $C_{12}H_{18}BO_2$: 205.1400, found: 205.1390. The mass corresponds to the *O*-monomethylboronate anion, resulting from solvolysis of **30** in the MeOH/HCO_2NH_4 medium used for HRMS sample dissolution.

2′-Oxopropyl 3,4-Dimethoxy-2-nitro-6-(5-phenylpentyl)benzoate (31) and 2′-Oxopropyl 3,4-Dimethoxy-2-nitrobenzoate (32)

A slurry composed by 2′-oxopropyl 6-bromo-3-methoxy-2-nitrobenzoate (**25**; 80 mg, 0.22 mmol), potassium 5-phenyl-1-pentyltrifluoroborate (**30**; 89.8 mg; 0.35 mmol), K_2CO_3 (91.5 mg, 0.66 mmol), $Pd(OAc)_2$ (2.0 mg, 0.009 mmol), and dtbpf (6.3 mg, 0.013 mmol) in toluene (2.4 mL) was purged with argon for 5 min. Freshly distilled H_2O (200 μL, 0.011 mmol) was added, the tube was closed, and the system was heated to 80 °C during 18 h. Once assessed that the starting arene was fully consumed, the mixture was diluted with H_2O (5 mL) and extracted with Et_2O (3 × 30 mL). The organic phase was washed with aq 1 M HCl (10 mL), brine (20 mL), and dried ($MgSO_4$). The volatiles were removed in vacuo and the remaining oily material was chromatographed to afford the desired coupled product **31** as a yellowish oil; yield: 120 mg (93%).

IR (NaCl): 3024, 2932, 2855, 1738, 1730, 1608, 1537, 1454, 1371, 1281, 1157, 1047, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.16 (m, 5 H, C_6H_5), 6.84 (s, 1 H, H-5), 4.74 (s, 2 H, H-1′), 3.93 (s, 3 H, 4-OCH_3), 3.92 (s, 3 H, 3-OCH_3), 2.85–2.80 (m, 2 H, H-1″), 2.62 (td, *J* = 7.9, 2.6 Hz, 2 H, H-5″), 2.18 (s, 3 H, C-3′), 1.71–1.58 (m, 4 H, H-2″, H-4″), 1.47–1.38 (m, 2 H, H-3″).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.7 (C-2′), 163.7 (ArCO_2CH_2), 155.3 (C-4), 145.8 (C-2), 142.6 (C_{ipso}), 140.9 (C-6), 139.5 (C-3), 128.4 (2 C, C_{ortho}),[#] 128.2 (2 C, C_{meta}),[#] 125.6 (C_{para}), 116.3 (C-1), 115.3 (C-5), 69.3 (C-1′), 62.3 (3-OCH_3), 56.4 (4-OCH_3), 35.8(C-5″), 33.9 (C-1″), 31.8 (C-2″), 31.2 (C-4″), 29.1 (C-3″), 26.1 (C-3′).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{27}NO_7Na$: 452.1680; found: 452.1677.

Increasing solvent polarity gave the proto-debrominated benzoate **32** as a colorless solid; yield: 3.3 mg (5%); mp 87–89 °C (from hexanes/EtOAc 3:7, v/v).

IR (KBr): 2943, 2851, 1741, 1724, 1616, 1541, 1458, 1284, 1150, 1043, 893, 740 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.8 Hz, 1 H, H-6), 7.03 (d, *J* = 8.8 Hz, 1 H, H-5), 4.80 (s, 2 H, H-1″), 3.99 (s, 3 H, 3-OCH_3), 3.92 (s, 3 H, 4-OCH_3), 2.19 (s, 3 H, 3′-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.1 (C-2′), 162.0 (ArCO_2CH_2), 157.9 (C-3), 146.5 (C-2), 141.3 (C-4), 127.7 (C-6), 144.0 (C-1), 112.6 (C-5), 69.3 (C-1′), 62.7 (3-OCH_3), 57.2 (4-OCH_3), 26.3 (C-3′).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{13}NO_7Na$: 306.5084; found: 306.5090.

2′-Oxopropyl 2-Amino-3,4-dimethoxy-6-(5-phenylpentyl)benzoate (33)

A mixture of **31** (40.0 mg, 0.093 mmol) and freshly prepared Ni_2B (35.8 mg, 0.279 mmol) in anhyd MeOH (1.3 mL) was stirred while a vigorous stream of H_2 was bubbled in during 5 min. The reaction

mixture was treated with aq 1 M HCl (310 μL, 0.31 mmol), and the reaction tube was tightly closed and placed in a pre-heated bath at 70 °C for 30 min. After confirming the complete consumption of the starting material, a 0.4% aq solution of $NaHCO_3$ (5.0 mL) was added and the products were extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford the acetonyl anthranilate **33**, which was used in the next step without further purification; yield: 30 mg (81%).

IR (NaCl): 3491, 3377, 3024, 2928, 2851, 1717, 1599, 1452, 1369, 1265, 1139, 1043, 804, 737 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.16 (m, 5 H, C_6H_5), 6.15 (s, 1 H, H-5), 5.50 (br s, $w_{½}$ = ~12.5 Hz, 2 H, NH_2), 4.86 (s, 2 H, H-1′), 3.86 (s, 3 H, 4-OCH_3), 3.79 (s, 3 H, 3-OCH_3), 2.79–2.74 (m, 2 H, H-1″), 2.65-2.59 (m, 2 H, H-5″), 2.20 (s, 3 H, H-3′), 1.69–1.56 (m, 4 H, H-2″, H-3″), 1.46–1.34 (m, 2 H, H-4″).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.0 (C-2″), 167.5 (ArCO_2CH_2), 154.3 (C-4), 144.0 (C_{ipso}), 142.9 (C-2), 141.9 (C-6), 133.2 (C-3), 128.5 (2 C, C_{ortho}),* 128.3 (2 C, C_{meta}),* 125.7 (C_{para}), 106.9 (C-1), 103.6 (C-5), 68.3 (C-1′), 59.8 (3-OCH_3), 55.8 (4-OCH_3), 36.0 (C-5″), 35.8 (C-1″), 32.0 (C-2″), 31.4 (C-4″), 29.5 (C-3″), 26.1 (C-3′).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{30}NO_5$: 400.2119; found 400.2105.

3,7,8-Trimethoxy-2-methyl-5-(5′-phenyl-1′-pentyl)quinoline-4(1*H*)-one (Melovinone, 2)

The anthranilate **33** (30.0 mg, 0.08 mmol) was weighed in a microwave vial and dissolved in glacial AcOH (1.0 mL). The system gas purged with argon, capped, and irradiated at 150 °C (power = 60 W) for 25 min. The reaction was controlled by TLC, confirming complete consumption of the starting material and product formation by its characteristic fluorescence UV (360 nm), an orange spot after spraying with the Dragendorff–Munier reagent and an intense blue colored spot obtained after exposure to aq 1% $FeCl_3$ solution. Removal of the solvent under high vacuum gave the crude pseudane **34** as a solid, which was used for the next step without purification; yield: 29 mg (ca. 88%).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{28}NO_4$: 382.2013; found: 382.2011.

Compound **34** (28.5 mg, 0.07 mmol) and K_2CO_3 (41.3 mg, 0.30 mmol) were suspended in anhyd 2-propanol (1.4 mL) contained in a screw capped tube. After purging with argon, the mixture was stirred for 15 min at rt, and further treated with MeI (95 μL, 1.5 mmol). The reaction vessel was tightly closed and heated at 50 °C for 3.5 h. The reaction was then quenched with H_2O (5 mL) and the products were extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under vacuum. The remaining oily material was chromatographed to afford melovinone (**2**) as a white amorphous solid; yield: 10.8 mg (40% overall yield from anthranilate **33**); mp 130–128 °C (from EtOAc/EtOH ~9:1) (Lit.[1b] mp 136–134 °C (from PE/benzene).

IR (NaCl): 3414, 2935, 2918, 2839, 1618, 1560, 1526, 1420, 1319, 1250, 1138, 1005, 899, 746, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.11 (br s, $w_{½}$ = ~6.6 Hz, 1 H, NH), 7.29–7.12 (m, 5 H, C_6H_5), 6.61 (s, 1 H, H-6), 3.97 (s, 3 H, 8-OCH_3), 3.95 (s, 3 H, 7-OCH_3), 3.85 (s, 3 H, 3-OCH_3), 3.32 (dd, *J* = 6.2, 2.8 Hz, 2 H, H-1′), 2.60 (dd, *J* = 7.0, 1.9 Hz, 2 H, H-5′), 2.40 (s, 3 H, 2-CH_3), 1.73–1.60 (m, 4 H, H-2′, H-4′), 1.56–1.46 (m, 2 H, H-3′).

The ^1H NMR spectrum of **2** was in full agreement with that reported by Kapadia et al. for the natural product.[1b]

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.1 (C-4), 151.5 (C-7), 143.4 (C_{ipso}), 142.0 (C-5), 141.2 (C-3), 138.2 (C-2), 134.7 (C-8a), 132.7 (C-8), 128.6 (2 C, C_{ortho}), 128.3 (2 C, C_{meta}), 125.6 (C_{para}), 118.3 (C-4a), 110.4 (C-6), 61.2 (8-OCH_3), 59.8 (3-OCH_3), 56.2 (7-OCH_3), 36.2 (C-5′), 35.9 (C-1′), 32.2 (C-2′), 31.7 (C-4′), 29.8 (C-3′), 15.2 (2-CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{30}NO_4$: 396.2169; found: 396.2164.

2′-Oxopropyl 3,4-Dimethoxy-2-nitro-6-(oct-1-yn-1-yl)benzoate (35)

A mixture of [Pd(PPh_3)$_4$] (6.5 mg, 0.009 mmol), CuI (1.64 mg, 0.008 mmol), and **25** (50 mg, 0.170 mmol) in anhyd DMF (2.0 mL) contained in a screw capped tube under argon was sequentially treated with Et_3N (100 mL, 0.715 mmol) and 1-octyne (36 mL, 0.210 mmol). The system was purged with an intense stream of argon for 1 min, screw capped, and placed in a preheated bath (70 °C) for 15 h. Then, the volatiles were removed under reduced pressure and the remaining oily residue was dissolved in EtOAc (10 mL) and filtered through a Florisil® pad, affording the crude coupling product **35**; yield: 53 mg (78%). This oily material was unstable to chromatographic conditions.

IR (NaCl): 2930, 2861, 2230, 1736, 1729, 1615, 1542, 1360, 1241, 1129, 820 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.07 (s, 1 H, H-5), 4.72 (s, 2 H, H-1′), 3.94 (s, 3 H, 4-OCH_3), 3.93 (s, 3 H, 3-OCH_3), 2.39 (t, *J* = 7.2 Hz, 2 H, H-3″), 2.21 (s, 2 H, H-3′), 1.44–1.25 (m, 6 H, H-4″ to H-7″), 0.89 (t, *J* = 6.9 Hz, 3 H, H-8″).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.9 (C-2′), 162.7 (ArCO_2CH_2), 155.4 (C-4), 141.1 (C-2), 132.2 (C-3), 128.7 (C-6), 121.4 (C-1), 118.0 (C-5), 97.6 (C-2″), 77.3 (C-1″), 69.7 (C-1′), 62.6 (3-OCH_3), 56.7 (4-OCH_3), 31.4 (C-6″), 28.7 (C-5″), 28.4 (C-4″), 26.5 (C-3′), 22.6 (C-7″), 19.7 (C-3″), 14.1 (C-8″).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{25}NO_7Na$: 414.1523; found 414.1520.

2′-Oxopropyl 6-Allyl-3,4-dimethoxy-2-nitrobenzoate (36) and 2′-Oxopropyl (*E*)-3,4-Dimethoxy-2-nitro-6-(prop-1-en-1-yl)benzoate (37)

A mixture of bromoarene **25** (25 mg, 0.07 mmol), LiCl (11.7 mg, 0.280 mmol), Pd(Ph_3P)$_4$ (8.0 mg, 0.007 mmol), and allyltri(*n*-butyl)stannane (40 μL, 0.140 mmol) in anhyd toluene (1.5 mL) contained in a screw capped tube was purged with argon for 5 min. The system was tightly closed with a screw cap and placed in a preheated oil bath at 80 °C for 18 h. Then, the mixture was diluted with EtOAc (5.0 mL) and filtered through Celite. The volatiles were removed under vacuum and the oily residue was chromatographed to give the allylbenzene derivative **36** as a clear oil; yield: 12.3 mg (92%).

^1H NMR (300 MHz, acetone-d_6): δ = 7.25 (s, 1 H, H-5), 5.96 (ddd, *J* = 16.8, 10.3, 6.5 Hz, 1 H, H-2″), 5.13 (dt, *J* = 10.3, 1.5 Hz, 1 H, H-3″$_a$), 5.09 (ddd, *J* = 16.8, 2.9, 1.5 Hz, 1 H, H-3″$_b$), 4.92 (s, 2 H, H-1′), 4.02 (s, 3 H, 4-OCH_3), 3.90 (s, 3 H, 3-OCH_3), 3.69 (dd, *J* = 6.5, 1.5 Hz, 2 H, H-1″), 2.19 (s, 3 H, 3-CH_3).

^{13}C NMR (75 MHz, acetone-d_6): δ = 201.0 (C-2′), 164.4 (ArCO_2CH_2), 156.4 (C-4), 146.6 (C-2), 140.5 (C-3), 138.9 (C-6), 137.5 (C-2″), 117.1 (C-1), 117.0 (C-5),* 116.9 (C-3″), 70.2 (C-1′), 63.5 (3-OCH_3), 57.5 (4-OCH_3), 38.4 (C-1″), 26.0 (C-3′).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{17}NO_7Na$: 346.0897; found: 346.0900.

When longer reaction times were used or simply after standing some time in solution, a mixture consisting by the allyl derivative and its isomerized by-product **37** was observed (**36**:**37** = ~10:1).

37

^{1}H NMR (300 MHz, $CHCl_3$): δ = 7.12 (s, 1 H, H-5), 6.86 (dq$_b$, *J* = 15.6, 1.7 Hz, 1 H, H-1″), 6.21 (dq, *J* = 15.6, 6.6 Hz, 1 H, H-2″), 4.77 (s, 2 H, H-1′), 3.97 (s, 3 H, 4-OCH_3), 3.92 (s, 3 H, 3-OCH_3), 2.20 (s, 3 H, H-3′), 1.93 (dd, *J* = 6.6, 1.7 Hz, 3 H, H-3″).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.0 (C-2′), 163.7 (ArCO_2CH_2), 155.5 (C-4), 140.0 (C-6), 134.3 (C-3), 131.1 (C-2″), 128.6 (C-2), 127.4 (C-1″), 116.5 (C-1), 111.3 (C-5), 69.7 (C-1′), 62.5 (3-OCH_3), 56.5 (4-OCH_3), 26.3 (C-3′), 18.8 (C-3″).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{17}NO_7Na$: 346.0897; found: 346.0900.

2′-Oxopropyl (*E*)-3,4-Dimethoxy-2-nitro-6-(5-phenylpent-2-en-1-yl)benzoate (39) and 2′-Oxopropyl (*E*)-3,4-Dimethoxy-2-nitro-6-(4-phenylbut-1-en-1-yl)benzoate (40)

Method A: A solution of allylbenzene derivative **25** (20.3 mg, 0.063 mmol) and 4-phenyl-1-butene (38 μL, 0.253 mmol) in anhyd toluene (1.0 mL) was purged with argon and treated with Grubbs II catalyst (2.7 mg, 0.003 mmol). The system was closed and heated at 40 °C for 6 h. Once the reaction was judged complete, the solution was filtered through a cotton plug, washed with CH_2Cl_2, and evaporated to dryness. The remaining oil was chromatographed affording an equimolar inseparable mixture of **39** and **40**; yield: 14.3 mg (53%).

39

^{1}H NMR (300 MHz, acetone-d_6): δ = 7.35–7.09 (m, 4 H, H$_{ortho}$, H$_{meta}$), 7.23 (s, 1 H, H-5), 7.18–7.11 (m, 1 H, H$_{para}$), 5.62 (m, 2 H, H-2″, H-3″), 4.90 (s, 2 H, H-1′), 3.97 (s, 3 H, 4-OCH_3), 3.89 (s, 3 H, 3-OCH_3) 3.60 (m, 2 H, H-1″), 2.68 (t, *J* = 7.2 Hz, 2 H, H-5″), 2.3 (m, 2 H, H-4″), 2.17 (s, 3 H, H-3′).

^{13}C NMR (75 MHz, acetone-d_6): δ = 201.1 (C-2′), 164.4 (ArCO_2CH_2), 156.3 (C-4), 146.5 (C-2), 142.7 (C-3), 139.6 (C$_{ipso}$), 132.8 (C-3″), 129.6 (C-6), 129.3 (2 C, C$_{meta}$), 129.0 (2 C, C$_{ortho}$, C-2″), 127.4 (C-1), 126.6 (C$_{para}$), 116.8 (C-5), 70.2 (C-1′), 62.5 (3- CH_3O), 57.1 (4- CH_3O), 37.1 (C-1″), 36.4 (C-5″), 35.0 (C-4″), 26.0 (C-3′).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{25}NO_7Na$: 450.1523; found: 450.1518.

40

^{1}H NMR (300 MHz, acetone-d_6): δ = 7.45 (s, 1 H, H-5), 7.35–7.09 (m, 4 H, H$_{ortho}$, H$_{meta}$), 7.18–7.11 (m, 1 H, H$_{para}$), 7.02 (dt, *J* = 15.7, 1.5 Hz, 1 H, H-1″), 6.55 (m, 1 H, H-2″), 4.92 (s, 2 H, H-1′), 4.05 (s, 3 H, 4-OCH_3), 3.91 (s, 3 H, 3-OCH_3), 2.80 (br s, $w_{½}$ = ~3.2 Hz, 2 H, H-4″), 2.52 (m, 2 H, H-3″), 2.17 (s, 3 H, H-3′).

^{13}C NMR (75 MHz, acetone-d_6): δ = 201.2 (C-2′), 164.4 (ArCO_2CH_2), 156.3 (C-4), 146.2 (C-2), 142.5 (C-3), 140.1 (C$_{ipso}$), 135.9 (C-2″), 130.0 (C-6), 129.5 (2 C, C$_{meta}$), 129.2 (2 C, C$_{ortho}$), 127.4 (C-1″), 126.7 (C$_{para}$), 126.6 (C-1), 112.3 (C-5), 70.3 (C-1′), 62.6 (3- CH_3O), 57.1 (4- CH_3O), 35.9 (C-4″), 35.7 (C-3″), 26.0 (C-3′).

HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{23}NO_7Na$: 436.1367; found: 436.1356.

Method B: A solution of Hoveyda–Grubbs II catalyst (5.0 mg, 0.006 mmol) in CH_2Cl_2 (2.0 mL) was infused at 2.5 mL/h into a refluxing mixture of allylbenzene **36** (40 mg, 0.124 mmol), 4-phenyl-1-butene (37 μL, 0.248 mmol), and 1,4-benzoquinone (1.3 mg, 0.012 mmol) in anhyd CH_2Cl_2 (2.0 mL). The mixture was further refluxed for 2.5 h. Once the reaction was completed, the solution was filtered through a cotton plug, the solids were washed with CH_2Cl_2, and the combined organic solutions were evaporated to dryness. The resulting oil was chromatographed, affording **39** and **40** as an inseparable mixture in a 1.8:1 molar ratio; yield: 50 mg (ca. 95%). The NMR spectra of **39** and **40** were in agreement with those of the product obtained after Method A.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690164.

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