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Step-Economic Total Synthesis of Melosatin A from Eugenol

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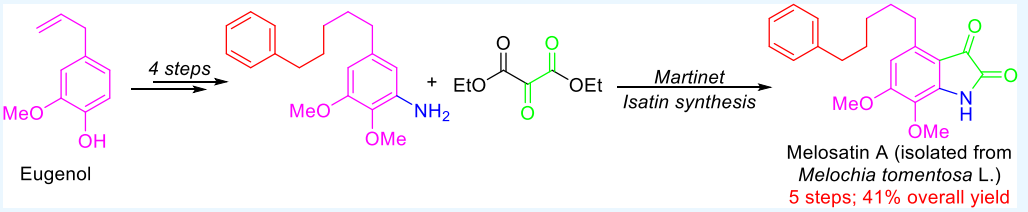

ABSTRACT: An efficient and straightforward route toward the isatin-type natural product melosatin A is reported, employing a trisubstituted aniline as a key intermediate. The latter was synthesized in 4 steps and 60% overall yield from eugenol, through its regioselective nitration, sequentially followed by a Williamson methylation, an olefin cross-metathesis with 4-phenyl-1-butene and the simultaneous reduction of olefin and nitro groups. The final step, a Martinet cyclocondensation of the key aniline with diethyl 2-ketomalonate, provided the natural product with 68% yield.

INTRODUCTION

Isatin (1*H*-indole-2,3-dione) is a privileged structural motif. Its derivatives are valuable synthetic intermediates in the areas of heterocyclic and pharmaceutical chemistry[1] because they are embodied with diverse and interesting biological activities; these include cytotoxic, antimicrobial, and enzyme (carbonic anhydrase) inhibition, among others. The syntheses, reactions, and applications of isatins have been recently summarized in a number of reviews.[2]

During their studies on tumorigenic Caribbean plants, Kapadia et al. examined the roots of the Colombian shrub *Melochia tomentosa* L. (Sterculiaceae, currently Malvaceae), isolating several isatins and 3-methoxy-4-quinolones, along with pyridines and cyclopeptides.[3] The isatins obtained from this plant (Figure 1) were named melosatins A−D (**1**−**4**) and presented a distinctive and unique 5-phenyl-1-pentyl motif attached at C4, typically accompanied by oxygen functionalities at positions C5−C7.[3a,4] These authors also performed the first total synthesis of Melosatin A (**1**) to verify its proposed structure.[3a] However, their sequence was rather long (7 steps), proceeded in low overall yield (ca. 2%) and, surprisingly, the performance of its last step (Stollé reaction) was not reported.

To date, *M. tomentosa* is the only source of this reduced and quite rare group of 3-keto-indolinones. Contrastingly, isatins are rather widespread in nature; they occur mainly in plants belonging to the genus *Isatis*,[5] but the floral parts of the Guyanan evergreen tree *Couroupita guianensis* Aublet (Lecythidaceae) and the Japanese orchid *Calanthe discolor* Lindl are other natural sources.[6] Isatins have also been isolated from fungi (*Chaetomium globosum* and *Streptomyces albus*), from the parotid glands of toads of genus *Bufo*, and even from some marine mollusks.[7]

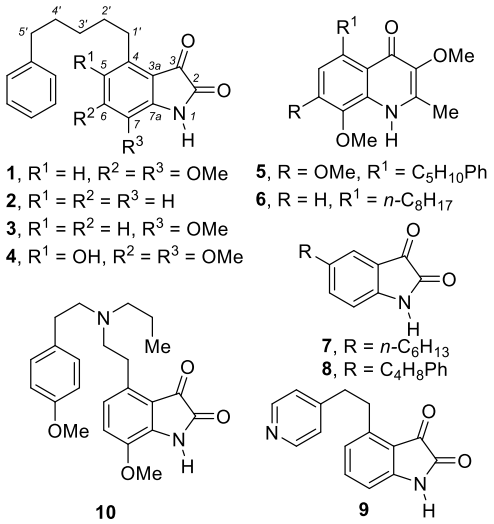

Figure 1. Naturally occurring isatin and quinolone alkaloids isolated from *M. tomentosa* (**1**−**5**) and *Waltheria indica* (**6**) along with other relevant synthetic isatins (**7**−**10**).

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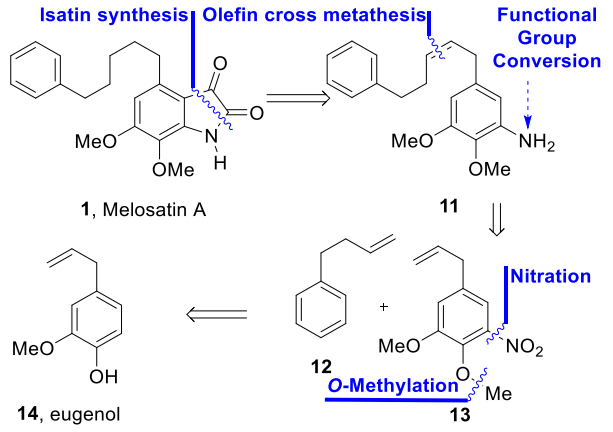
In the course of our program on the synthesis of heterocyclic natural products with intriguing structures and unique biological activities,[8] we focused our attention on nonrutaceous quinoline alkaloids isolated from plants belonging to the genera *Melochia* and *Waltheria*. Our efforts were crowned with the first total syntheses of melovinone (**5**) and waltherione-F (**6**).[9] During these studies, we also noticed that compounds like **7** are synthetic intermediates to new materials of importance in optoelectronics[10] and that **8** is a potent and selective inhibitor of the enzyme monoamino-oxidase B (MAO B, IC_{50} = 0.66 nM).[11]

We also realized that certain 4-substituted isatins like **9** induce dopaminergic or D2-agonist activity useful for treating hypertension[12a] and others such as **10** proved to be relevant inhibitors of enzyme CDK2.[12b] As a result, we became interested in melosatin A (**1**), which is reminiscent of **7**−**10** and shares structural similarity with the substitution pattern of the carbocyclic ring of melovinone (**5**). Remarkably, being co-occurring metabolites, Kapadia et al. suggested a plausible common biogenetic origin for **1** and **5**.[3a]

Therefore, considering the relevance of isatin natural products and the contrastingly scarce current knowledge on the melosatins, we decided to develop a new and efficient synthetic approach to melosatin A (**1**), based on premises of atom and step-economy, avoidance of protective groups and the use of a naturally abundant and affordable starting material, as outlined in the corresponding retrosynthetic analysis (Scheme 1).

Scheme 1. Retrosynthetic Analysis of Melosatin A (1)



RESULTS AND DISCUSSION

The analysis commenced with the retrosynthetic disconnections of the N−C2 and C3−C3a bonds, which unmasked the polysubstituted aniline **11** and an oxalyl derivative as logic precursors. Synthetically, it was conjectured that an isatin synthesis involving **11** and an appropriate two-carbon atoms unit like $(COCl)_2$,[13] reacting as in the long known Stollé reaction, could provide the required connectivity.

On continuing with the analysis, the characteristic 5-phenyl-1-pentyl pendant side chain of aniline **11** was dissected at the C2′−C3′ bond level, unveiling two fragments. These included the commercially available 4-phenyl-1-butene (**12**) and the allylbenzenoid **13**, resulting from functional group conversion on the nitrogen atom, on the basis that olefin cross metathesis between the fragments along with nitro and alkene reduction should constructively provide the intermediate **11**. Further C−O and C−N disconnections uncovered the economic and readily available eugenol (**14**) as a suitable starting material. Interestingly, the allylbenzene **13** was previously prepared by a two-step reactions sequence (regioselective nitration → *O*-methylation) from eugenol (**14**),[14] and we developed a similar protocol toward **13** during our synthesis of 5-methylaaptamine.[15]

As shown in Scheme 2, the synthesis commenced with the regioselective *ortho*-nitration of eugenol (**14**). This was performed by heating a mixture of the commercial product with solid NH_4NO_3 and $KHSO_4$ in MeCN at 80 °C for 24 h, which efficiently provided **15** in 96% yield after filtration of the reaction mixture through a short pad of silica gel. In line with previous reports,[15] it was observed that longer reaction times strongly affected the reaction outcome, diminishing yields and giving rise to highly impure samples. Presumably, this could be a result of polynitration and product polymerization. Under certain circumstances, it was also observed that column chromatography enabled the isolation of minor amounts of the catechol **16**, possibly resulting from acid-promoted demethylation of **15**. Next, the projected Williamson *O*-methylation reaction of **15** was accomplished with MeI in refluxing absolute EtOH using K_2CO_3 as the base, to give **13** in 98% yield after 24 h. With the required compound in hand, the olefin cross-metathesis step was undertaken. The latter is a powerful synthetic tool that enables the facile preparation of otherwise hardly accessible compounds.[16] After reacting olefin **13** with 4-phenyl-1-butene (**12**) under Grubbs I catalyst in refluxing anhydrous CH_2Cl_2,[16b] the expected product **17** was consistently obtained in 73% yield as a mixture of olefins (*E*/*Z* ∼ 2.2).[16c]

The seemingly easy concomitant NO_2 group reduction and olefin hydrogenation proved to be hard to perform. Several conventional hydrogenation conditions were assayed [H_2 (1−5 atm), 10% Pd/C EtOH; H_2 (3 → 7 atm), 20% $Pd(OH)_2$/C, EtOH], affording mixtures of products resulting from the partial reduction of the nitro group and incomplete reduction of the double bond. Disappointingly, the best alternative [20% $Pd(OH)_2$/C, H_2 3−7 atm] afforded only 49% yield of the desired product **11**.[17] However, the use of the approach of McMurray, dealing with a catalytic transfer of hydrogen, proved to be a promising solution.[18] In this reaction, molecular H_2 is generated in situ from triethylsilane in MeOH, in the presence of chloroform and 10% Pd/C as a catalyst. Under these conditions, the desired aniline **11** was obtained in 88% yield.

Having secured a satisfactory route toward **11**, the Stollé reaction, as reported by Kapadia et al. and by other research groups was tested.[3,19] Therefore, a solution of **11** in neat oxalyl chloride was sealed in an ampoule and heated at 165 °C for 2 h. However, this resulted in extensive decomposition of the starting material and, except for the related bis-oxalamide **19** (obtained in very low yield), no other products could be identified. Testing the reaction at a lower temperature (65−70 °C) also gave **19** as the only identifiable reaction by-product in approximately 10% yield, whereas attempts at thermal cyclization of this compound met with failure.

Aiming to circumvent this obstacle, modifications and alternatives to the synthesis of Stollé were sought and selected,[20] and models such as *meta*-anisidine (**20**) and the simplified analog **22** were used for testing. The most relevant results are summarized in Table 1. The Stollé reaction was re-

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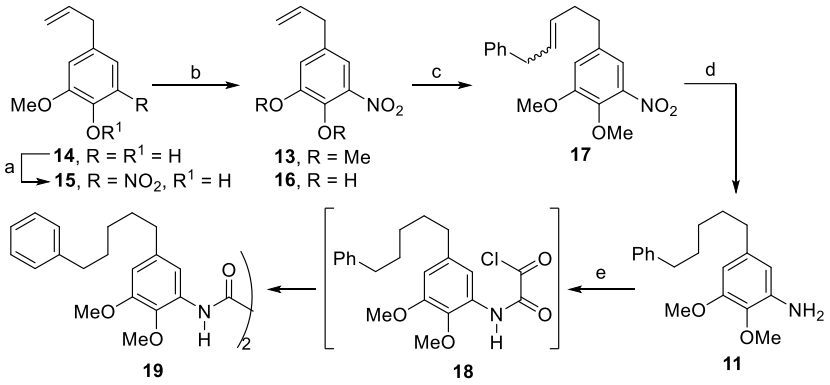
Scheme 2. Reagents and Conditions[a]



[a](a) $KHSO_4$, NH_4NO_3, MeCN, reflux, 24 h (96%); (b) MeI, K_2CO_3, $EtOH_{(abs.)}$, reflux, 24 h (98%); (c) **12**, Grubbs I, CH_2Cl_2, reflux, 4 h (73%); (d) 10% Pd/C, Et_3SiH, MeOH/$CHCl_3$ (10:1, v/v), r.t., 24 h (88%); (e) $(COCl)_2$ (neat), 165 °C, 2 h or neat $(COCl)_2$, 65−70 °C, 6 h (**19**, 10%).

Table 1. Optimization of the Cyclization Conditions toward the Isatin Framework

entry	aniline	reaction conditions	product	yield (%)
1	**20**	$(COCl)_2$, 165 °C, 2 h[a]	**21**	[b]
2	**20·HCl**	$(COCl)_2$, 165 °C, 2 h[a]	**21**	[b]
3	**20**	(1) neat $(COCl)_2$, r.t. → 60 °C, 2 h	**21**	32
4	**22**	(2) solvent distillation to dryness	**23**	40
5	**11**	(3) heat residue at 130 °C	**1**	3[c]
6	**20**	(1) O═C$(CO_2Et)_2$ (**24**), $AcOH_{(gl.)}$, 120 °C, 4 h	**21**	20
7	**22**	(2) 1 M KOH, air bubbling, r.t., 17 h	**23**	40
8	**11**	(3) 6 M HCl, r.t., pH ∼ 2−3, 30 min	**1**	68

[a]Sealed ampoule. [b]No reaction. [c]Along with bis-oxalamide **19** (44%).

evaluated with model **20** and no product was detected under the tested conditions (entry 1); therefore, a protocol where its hydrochloride (**20·HCl**) was heated at the same temperature was tested. Unfortunately, however, in our hands, this procedure proved to be fruitless, resulting in no reaction (entry 2).[20a,b]

Therefore, the alternative technique reported by Piggott and Wege[20c] was put in place. The latter involved the sequential addition of the aniline over $(COCl)_2$ at room temperature, in order to maximize the formation of the oxalamidoacyl chloride intermediate **18**, followed by a cyclization reaction under solventless conditions. Gratifyingly, under these reaction conditions, the expected isatins **21** and **23** were consistently obtained at 32 and 40% of the yield, respectively (entries 3 and 4). However, when aniline **11** was subjected to identical reaction conditions, the related bis-oxalamide **19** was isolated at 43% of the yield (entry 5), accompanied by melosatin A in a disappointing 3% yield. The ^1H NMR spectrum of the latter showed all the resonances compatible with the natural product, confirming its structure.

Klein and Tufano suggested that most of the common methods for the production of isatins become less than adequate when the number and lipophilicity of substituents on the targeted isatin are increased.[21] Therefore, it was conjectured that the failure of aniline **11** to afford melosatin A in satisfactory yields was a consequence of the nature of the substituents and steric effects resulting from polyfunctionalization of the starting material.

Based on these results, this procedure was considered unsatisfactory, and the need to follow an alternative strategy was put forward. Although several methodologies have been developed for the construction of isatins, most of them usually involve multi-step reactions, require proper substrate pre-functionalization, or demand harsh reaction conditions, or complex operations which must be adapted to milligram-scale reactions.[22]

Taking into account literature precedents,[23] we considered that due to its mild and essentially neutral conditions, the Martinet isatin synthesis which employs diethyl 2-ketomalonate (**24**) as the two-carbon synthon, would fulfill our synthetic requirements. This is a century-old reaction, which has been used sporadically in the past; however, in recent times, it experienced a revival, finding frequent use in the synthesis of natural product and their analogs,[24] medicinal chemistry,[25] materials science,[26] and structural studies,[27] among others,[28] which also resulted in being mentioned in patent literature.[29] However, one of the major drawbacks of this approach is the poor predictability of its performance.[11]

In order to evaluate the reported protocols, attempts were made to prepare the reagent **24** from diethyl malonate, following known procedures.[30] Sadly, however, these methods did not provide the expected results. After searching for suitable alternatives, it was found that the aerobic (air bubbling) oxidation of the malonate ester with stoichiometric amounts of ceric ammonium nitrate (CAN) in MeCN[31] provided the expected product, albeit in 20% yield after 60 h of stirring and a troublesome column chromatographic separation.

Therefore, aiming to improve the reaction performance, the procedure was modified to run the reaction under pure oxygen (from a balloon). Luckily, after stirring a mixture of diethyl malonate and CAN in MeCN, under this static O_2 atmosphere for 4 days at room temperature, complete consumption of the starting material was observed, with the concomitant formation of the oxidized derivative as the sole product in 67% of the yield. Despite the product being obtained in the hydrate form, the latter was easily converted into the corresponding anhydrous 2-keto form (**24**) after azeotropic drying with toluene in the rotary evaporator, followed by the removal of traces of the solvent under high vacuum.

The Martinet reaction, which entails a series of successive operations, was tested with **20** under the conditions reported by Trost et al.[23b] The aniline was firstly condensed with **24** in

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glacial AcOH at 120 °C, and after stirring for 4 h, the reaction solvent was removed under reduced pressure and the oily residue was quenched with 1 M KOH. Immediately, air was bubbled overnight followed by an adjustment of the acidity of the medium to pH ∼ 2−3 by the cautious addition of 6 M HCl. This provided the expected isatin **21** in 20% yield (entry 6), whereas replication of the reaction with aniline **22** provided the related isatin **23** in 40% yield (entry 7).

Encouraged by these results, the aniline **11** was subjected to the same reaction conditions, giving a 68% of the yield of a product whose R_f was consistent with that of the previously obtained melosatin A (entry 8). Delightfully, its ^{1}H NMR spectrum in $CDCl_3$ was in complete agreement with that of the natural product.[3a] The heterocycle was fully characterized by employing additional NMR experiments.

Since crystalline samples were obtained, the molecular structure was also confirmed by single-crystal X-ray diffraction. It was observed that compound **1** crystallizes in the triclinic space group *P*-1, without the presence of solvent molecules in the unit cell (Figure 2).[32]

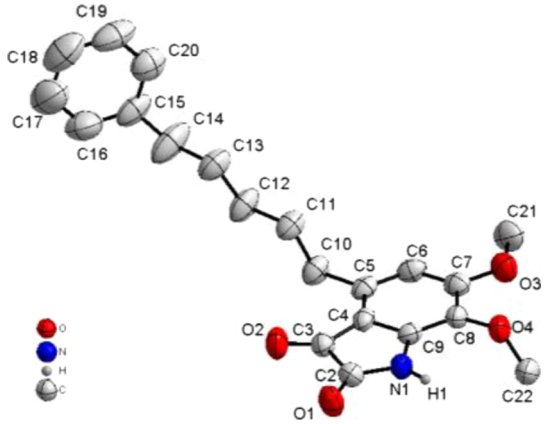


Figure 2. Molecular structure of **1** including the atom-numbering scheme. The displacement ellipsoids were drawn at the 50% probability level, and the hydrogen atoms were omitted for the sake of clarity.

Although the complete details of the mechanism of the Martinet reaction remain unknown, a mechanistic picture can be drawn (Scheme 3) based on data from the literature and analogous transformations.[23a] It can be conjectured that the reaction could proceed through an initial nucleophilic attack of the aniline (**25**) to one of the ester moieties of an alkyl-2-ketomalonate (mesoxalic ester **26**) in AcOH to provide the amide ***i***. In turn, this intermediate could cyclize under the promotion of the electron pair of the nitrogen atom, to afford species ***ii***, resulting from isomerization or a [1,3]-hydrogen shift that regenerates the aromatic ring. Subsequent treatment with aqueous 1 M KOH, would cause hydrolysis of the ester and triggers the decarboxylation of the 1,3-dicarbonyl intermediate ***iii*** to deliver the 3-hydroxyindolinone (***iv***). Final oxidation of the latter by air bubbling would provide the related isatin **27**, after acidification with aqueous 6 M HCl.

CONCLUSIONS

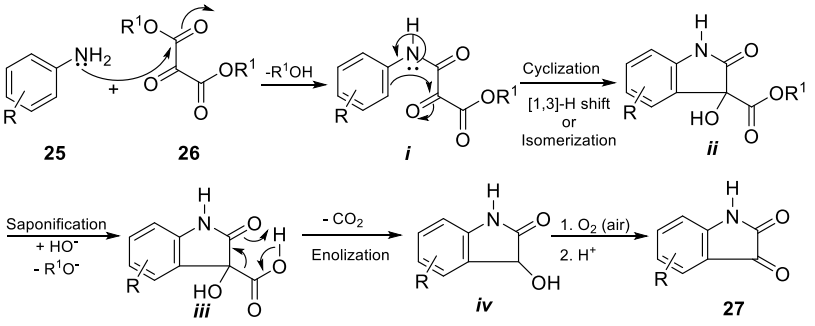
In conclusion, an alternative, reliable, and efficient total synthesis of melosatin A was accomplished in five steps and 41% global yield from commercial eugenol, ethyl malonate, and 4-phenyl-1-butene. The sequence involved a greatly improved preparation of the 2,3-dimethoxy-5-phenyl-1-propyl-aniline intermediate and its cyclization to the natural product under the mild and essentially neutral Martinet isatin synthesis conditions. The procedure was designed under a modular concept and would allow one to obtain other natural isatins and related substances as well.

EXPERIMENTAL SECTION

General Information. The reactions were performed under dry argon atmospheres, using oven-dried glassware. Anhydrous MeOH and EtOH were obtained by treatment of the analytical grade solvents with magnesium turnings and iodine, followed by distillation from the resulting alkoxides. Anhydrous 1,2-dichloroethane and CH_2Cl_2 were prepared by refluxing the corresponding analytical grade solvent over P_2O_5 for 4 h, followed by distillation. Anhydrous toluene was prepared by distillation from Na-benzophenone ketyl, whereas anhydrous MeCN was obtained by refluxing the AR grade solvent for 3 h over CaH_2 and distillation of the product. For storage, the anhydrous solvents were transferred to dry Young ampoules containing activated molecular sieves. All other reagents were used as received.

The reactions were monitored by TLC run in hexanes/EtOAc mixtures. The chromatographic spots were revealed by exposure to UV light (254 and 365 nm) and spraying with appropriate reagents, including Godin, ninhydrin, etc., followed by careful heating to improve selectivity. In the general workup procedure, the reaction mixtures were diluted with brine, and the products were extracted three times with EtOAc. The combined organic extracts were then washed once with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel 60 H, particle size <55 μm),

Scheme 3. Proposed Mechanism of the Martinet Isatin Synthesis



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employing a gradient of solvent (hexanes/EtOAc) polarity techniques, under positive pressure.

Equipment. The melting points (uncorrected) were determined on an Ernst Leitz Wetzlar model 350 hot-stage microscope. The FT-IR spectra were recorded on a Shimadzu Prestige 21 spectrophotometer, as thin films held between NaCl cells (for oily substances) or as solid dispersions in KBr (for solid compounds). The NMR spectra were recorded on a Bruker Avance 300 FT-NMR spectrometer (300.13 MHz for ^{1}H NMR and 75.48 MHz for ^{13}C{^{1}H} NMR) in $CDCl_3$ or acetone-d_6, as required. Chemical shifts are reported in ppm in the δ scale, using TMS as the internal standard, scalar coupling constants (J), and half-band width ($w_{1/2}$) are informed in hertz (Hz), and the residual solvent peaks of $CDCl_3$ (δ_H = 7.26 ppm, δ_C = 77.16 ppm) were used as an internal reference. In special cases, 2D NMR experiments (COSY, HSQC, and HMBC) were also employed. HRMS were obtained with a Bruker MicroTOF-Q II instrument (Bruker Daltonics, Billerica, MA, USA) from UMyMFOR (Buenos Aires, Argentina). Detection of the ions was performed by electrospray ionization in positive ion mode.

For single-crystal structure determination, the data were collected on a Bruker D8 Quest ECO diffractometer (Bruker AXS) with a Photon II detector. The equipment was operated using Mo-Kα radiation (λ = 0.71073 Å) at 297 K. Absorption corrections were performed by the multiscan method.[33] The structure was solved using SHELXT 2018/2 (Sheldrick, 2018) and refined with SHELXT 2018/2 (Sheldrick, 2018) on F^2 using anisotropic temperature parameters for all nonhydrogen atoms.[33] The positions of the hydrogen atoms were calculated starting from the idealized positions.

*Diethyl 2-Oxomalonate Hydrate (**24**·H_2O).* Under an oxygen atmosphere (balloon), CAN (1.027 g, 1.87 mmol) was added to a stirred solution of diethyl malonate (2.00 g, 12.49 mmol) in anhydrous MeCN (6 mL). The resulting mixture was further stirred at room temperature for 4 days. The solution was concentrated under reduced pressure, the residue was dissolved with EtOAc (80 mL), and the organic phase was washed with brine (2 × 40 mL) and dried over $MgSO_4$ to furnish the hydrate form of **24** (1.456 g, 67%), as a colorless solid:[34] m.p. = 58−60 °C (hexanes/AcOEt: 70/30), lit. = 54.6−56.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (s_b, $w_{1/2}$ ∼ 10.5, 2H), 4.23 (q, J = 7.3, 4H), 1.24 (t, J = 7.3, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 169.3 (C═O, ester), 92.3 [$C(OH)_2$], 62.6 (2C, OCH_2CH_3), 14.2 (2C, OCH_2CH_3).

*4-Allyl-2-methoxy-6-nitrophenol (**15**).* Eugenol (**14**, 335 mg, 2.04 mmol) was added dropwise under stirring to a finely milled solid mixture of NH_4NO_3 (371 mg, 4.63 mmol) and $NaHSO_4$ (2.13 g, 24.9 mmol) suspended with dry MeCN (5 mL). The mixture was refluxed for 24 h when it was filtered under reduced pressure. The resulting colored organic solution was concentrated under vacuum to afford a reddish oil, containing essentially pure 4-allyl-2-methoxy-6-nitrophenol (410 mg, ca. 96%), which was used in the next step without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.67 (s, 1H, −OH), 7.52 (s, 1H, H-2), 6.96 (s, 1H, H-3), 5.92 (ddt, J = 17.1, 10.5 and 6.7, 1H, H-2′), 5.17−5.09 (m, 2H, H-3′), 3.94 (s, 3H, OMe), 3.36 (d, J = 6.7, 2H, H-1′); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 150.0 (C-2), 145.1 (C-1), 136.1 (C-2′), 133.8 (C-6), 131.4 (C-4), 118.8 (C-3), 117.3 (C-3′), 115.3 (C-5), 56.9 (C-OMe), 39.6 (C-1′).[15]

*5-Allyl-1,2-dimethoxy-3-nitrobenzene (**13**).* Anhydrous K_2CO_3 (1361 mg, 14.0 mmol) was added to a stirred solution of **15** (559 mg, 2.67 mmol) in absolute EtOH (10 mL) and the resulting suspension was treated with MeI (0.8 mL, 14.0 mmol). The reaction was refluxed until complete consumption of starting material (24 h), when the crude was filtered through a cotton pad, which was washed with EtOAc (5 mL). The combined filtrates were concentrated under reduced pressure, taken in EtOAc (10 mL) and sequentially washed with water (10 mL) and brine (2 × 10 mL), then dried over $MgSO_4$ and finally filtered and concentrated under vacuum. Chromatographic purification of the resulting brown oil furnished **15** (585 mg, 98%), as a yellowish oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, J = 1.3, 1H, H-4), 6.92 (d, J = 1.3, 1H, H-6), 5.99−5.85 (m, 1H, H-2′), 5.17−5.09 (m, 2H, H-3′), 3.95 (s, 3H, 2-OMe), 3.90 (s, 3H, 1-OMe), 3.38 (d, J = 6.7, 2H, H-1′); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 154.0 (C-1), 144.8 (C-3), 141.2 (C-2), 136.4 (C-5), 135.9 (C-2′), 117.3 (C-3′), 116.5 (C-6), 115.7 (C-4), 62.0 (2-OMe), 56.5 (1-OMe), 39.7 (C-1′).[15]

*(E)-1,2-Dimethoxy-3-nitro-5-(5-phenylpent-2-en-1-yl)-benzene (**17**).* Grubbs I catalyst (18 mg, 1.84 mmol) was added to a stirred solution of 4-phenyl-1-butene (**12**, 311 μL, 1.84 mmol) in CH_2Cl_2 (5 mL). The system was treated dropwise with **13** (137 mg, 0.614 mmol) and heated to reflux for 12 h. Additional amounts of **12** (192 μL, 1.84 mmol) and Grubbs I catalyst (10 mg, 1.84 mmol) were added and the reaction was refluxed for another 12 h period. Then, the mixture was filtered through a short Florisil pad, which was washed with CH_2Cl_2 (5 mL) and the combined filtrates were concentrated under vacuum. Chromatographic purification of the oily residue afforded **17** (141 mg, 70%) as a yellowish oil (E:Z ≈ 2.1): ^{1}H NMR (300 MHz, $CDCl_3$, E-isomer) δ 7.18 (m, 5H, Ph), 7.08 (s, 1H, H-4), 6.86 (s, 1H, H-6), 5.65−5.47 (m, 2H, H-3′ and H-4′), 3.95 (s, 3H, 2-OMe), 3.88 (s, 3H, 1-OMe), 3.30 (d, J = 5.0, 2H, H-1′), 2.71 (t, J = 7.7, 2H, H-5′) and 2.42−2.34 (m, 2H, H-2′); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, E-isomer) δ 153.9 (C-1), 144.7 (C_{ipso}), 141.7 (C-2), 137.3 (C-3), 132.7 (C-4′),* 131.3 (C-5), 128.6 (C-3′),* 128.5 (2C, C_{meta}), 128.4 (2C, C_{ortho}), 126.0 (C_{para}), 116.4 (C-6), 116.2 (C-4), 62.0 (1-OMe), 56.5 (2-OMe), 38.6 (C-5′), 35.8 (C-1′), 34.2 (C-2′); HRMS (ESI$^+$-TOF) found m/z = 350.1367; $C_{19}H_{21}NNaO_4$ $[M + Na]^+$ requires m/z = 350.1363.

*2,3-Dimethoxy-5-(5-phenyl-1-pentyl)aniline (**11**).* A stirred solution of **17** (55 mg, 0.168 mmol) in a mixed MeOH/$CHCl_3$ (10:1, v/v) solvent (1 mL) was treated with 10% Pd/C (8 mg). Then, Et_3SiH (0.27 mL, 2.52 mmol) was added dropwise for 5 min under argon atmosphere. The suspension was further stirred for 24 h at room temperature when it was filtered through Florisil and washed with MeOH/$CHCl_3$ (10:1, v/v). The combined organic solutions were concentrated under vacuum and the oily residue was chromatographed giving **11** (35 mg, 70%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.15 (m, 5H, Ph), 6.21 (d, J = 1.8, 1H, H-4), 6.15 (d, J = 1.8, 1H, H-6), 3.82 (s, 3H, 2-OMe), 3.80 (s, 3H, 3-OMe), 3.49 (s_b, 2H, NH_2), 2.60 (t, J = 7.8, 2H, H-5′), 2.46 (t, J = 7.5, 2H, H-1′), 1.70−1.55 (m, 4H, H-2′ and H-4′), 1.43−1.38 (m, 2H, H-3′). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 152.8 (C-3), 142.9 (C_{ipso}), 139.9 (C-1), 139.2 (C-2), 134.3 (C-5), 128.5 (2C, C_{meta}), 128.4 (2C, C_{ortho}), 125.7 (C_{para}), 108.9 (C-6), 103.0 (C-4), 60.0 (2-OMe), 55.8 (3-OMe), 36.1 (C-1′)*, 36.0 (C-5′)*, 31.5 (C-3′), 31.4 (C-4′), 29.1 (C-2′); HRMS (ESI$^+$-

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TOF) found m/z = 300.1959; $C_{19}H_{26}NO_2$ $[M + H]^+$ requires m/z = 300.1958.

*N^1,N^2-Bis[2,3-dimethoxy-5-(5-phenylpentyl)phenyl]-oxalamide (**19**).* Oxalyl chloride (780 mg, 6.14 mmol) was added to a stirred solution of **11** (53 mg, 0.177 mmol) in anhydrous toluene (30 μL). The mixture was stirred at room temperature for 15 min, and then heated to 60 °C for 2 h. After this period, the volatiles were removed with a stream of dry nitrogen, rendering an oily material which was further dried under high vacuum. The resulting waxy solid was heated at 130 °C for 2 h, then the system was cooled to room temperature and the remaining was purified chromatographically, to give oxalamide **19** (51 mg, 44%), as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.97 (s_b, $w^1/_2$ ∼ 3.7, 2H, N−*H*), 7.89 (d, J = 2, 2H, H-6), 7.30−7.17 (m, 10H, Ph), 6.56 (d, J = 2, 2H, H-4), 3.92 (s, 6H, 3-OMe), 3.87 (s, 6H, 2-OMe), 2.64−2.56 (m, 8H, H-5′ and H-1′), 1.69−1.35 (m, 12H, H-2′, H-3′ and H-4′); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.6 (ArNHCO), 151.9 (C-2), 142.9 (C_{ipso}), 139.5 (C-5), 136.5 (C-3), 130.3 (C-1), 128.5 (2C, C_{meta}), 128.4 (2C, C_{ortho}), 125.8 (C_{para}), 111.9 (C-6), 109.3 (C-4), 61.2 (3-OMe), 56.0 (2-OMe), 36.4 (C-5′),# 36.0 (C-1′),# 31.7 (C-2′),* 31.5 (C-4′),* 29.2 (C-3′); HRMS (ESI$^+$-TOF) found m/z = 653.3585; $C_{40}H_{49}N_2O_6$ $[M + H]^+$ requires m/z = 653.3591.

*6-Methoxy-1H-indole-2,3-dione (**21**).* Diethyl 2-ketomalonate (**24**, 62 mg, 0.356 mmol) was added to a stirred solution of *m*-anisidine (40 mg, 0.325 mmol) in glacial AcOH (2 mL). The mixture was heated to 120 °C for 4 h, after this the solvent was removed under vacuum, then a 1 M solution of KOH (4 mL) was added and the solution was stirred under air bubbling. The aerobic conditions were kept overnight; then, the solution was acidified to pH 2−3. The organic products were extracted with EtOAc (2 × 10 mL), and the combined organic phases were washed with brine (2 × 10 mL), dried over $MgSO_4$ and finally filtered and concentrated under vacuum. Chromatographic purification of the yellow oily residue gave **21** (11.5 mg, 20%) as a yellowish solid: m.p. = 220−222 °C (PhH/Me_2CO, 3:1, v/v), lit. = 228−230 °C.[35] ^{1}H NMR (300 MHz, acetone-d_6) δ 9.86 (s_b, $w^1/_2$ ∼ 24.3, 1H, N−*H*), 7.50 (d, J = 8.5, 1H, H-4), 6.64 (dd, J = 8.5, 2.2, 1H, H-5), 6.55 (d, J = 2.2, 1H, H-7), 3.94 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, acetone-d_6) δ 181.9 (C-3), 169.2 (C-6), 161.3 (C-2), 154.2 (C-7a), 127.4 (C-4), 112.6 (C-3a), 109.7 (C-5), 98.8 (C-7), 56.6 (6-OMe).

*3-Amino-1,2-dimethoxy-5-propylbenzene (**22**).* A stirred solution (2 mL) of **13** (84 mg, 0.376 mmol) in a mixture of MeOH/$CHCl_3$ (10:1, v/v) was treated with 10% Pd/C (7.5 mg) and the resulting suspension was treated dropwise over 10 min with Et_3SiH (600 μL, 3.76 mmol). The reaction mixture was further stirred at room temperature for 30 min until the bubbling of hydrogen generated during the reaction ceased. Then, the mixture was filtered through a pad of Celite, the filter was washed with CH_2Cl_2 (5 mL) and the combined filtrates were successively washed with 3 M NaOH (3 × 20 mL) and brine (2 × 20 mL), dried over Na_2SO_4, filtered and concentrated in a rotary evaporator. The crude material was purified chromatographically to afford **22** (62 mg, 84%), as an orange oil:[36] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (d, J = 1.7, 1H, H-4), 6.16 (d, J = 1.7, 1H, H-6), 3.83 (s, 3H, 2-OMe), 3.80 (s, 3H, 3-OMe), 2.44 (t, J = 7.2, 2H, H-1′), 1.59 (dd, J = 7.2, 2H, H-2′), 0.94 (t, J = 7.2, 3H, H-3′); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 152.8 (C-3), 140.2 (C-2), 139.1 (C-1), 134.1 (C-5), 108.8 (C-4), 102.8 (C-6), 60.0 (2-OMe), 55.8 (3-OMe), 38.3 (C-1′), 24.7 (C-2′), 14.1 (C-3′).

*6,7-Dimethoxy-4-propyl-1H-indole-2,3-dione (**23**).* Diethyl 2-ketomalonate (**24**, 62 mg, 0.356 mmol) was added to a stirred solution of **22** (40 mg, 0.223 mmol) in glacial AcOH (2 mL), and the mixture was heated to 120 °C for 4 h, after this the solvent was removed under vacuum, then a 1 M solution of KOH (4 mL) was added and the solution was stirred under air bubbling. The aerobic conditions were kept overnight; then, the solution was acidified to pH 2−3 and extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to obtain a yellow oil. Chromatographic purification of the residue afforded **23** (22 mg, 40%), as a solid: m.p. = 177−179 °C (hexanes/PhH, 1:4, v/v): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (s_b, $w^1/_2$ ∼ 9.7, 1H, N−*H*), 6.34 (s, 1H, H-5), 3.96 (s, 3H, OMe-7), 3.86 (s, 3H, OMe-6), 2.87 (d, J = 7.7, 2H, H-1′), 1.66 (dd, J = 7.7, 2H, H-2′), 0.97 (t, J = 7.7, 3H, H-3′); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 180.8 (C-3), 160.6 (C-2), 159.8 (C-6), 144.6 (C-7), 142.1 (C-4), 131.4 (C-7a), 110.7 (C-3a), 107.4 (C-5), 61.4 (7-OMe), 56.4 (6-OMe), 34.0 (C-1′), 23.6 (C-2′),14.0 (C-3′); HRMS (ESI$^+$-TOF) found m/z = 250.1068; $C_{13}H_{16}NO_4$ $[M + H]^+$ requires m/z = 250.1079.

*6,7-Dimethoxy-4-(5-phenylpentyl)-1H-indole-2,3-dione (**1**).* Diethyl 2-ketomalonate (**24**, 62 mg, 0.356 mmol) was added to a stirred solution of **11** (50 mg, 0.167 mmol) in glacial AcOH (2 mL), and the mixture was heated to 120 °C for 4 h, after this the solvent was removed under vacuum, then a 1 M solution of KOH (4 mL) was added and the solution was stirred under air bubbling. The aerobic conditions were kept overnight; then, the solution was acidified to pH 2−3. and the products were extracted with EtOAc (2 × 10 mL). The organic extracts were washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Chromatographic purification of the resulting yellow oil afforded melosatin A (**1**, 40 mg, 68%), as a solid: m.p. = 95−97 °C (*n*-hexane/PhH, 2:3, v/v), lit. = 119−121 °C (petroleum ether/PhH)].[3] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s_b, $w^1/_2$ ∼ 5.8, 1H, N−*H*), 7.29−7.15 (m, 5H, Ph), 6.31 (s, 1H, H-5), 3.94 (s, 3H, OMe-6), 3.86 (s, 3H, OMe-7), 2.87 (t, J = 7.7, 2H, H-1′), 2.61 (t, J = 7.7, 2H, H-5′), 1.71−1.39 (m, 6H, H-2′, H-3′, H-4′);[6b] ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 180.9 (C-3), 160.7 (C-6), 160.4 (C-2), 144.7 (C_{ipso}), 142.8 (C-7a), 142.2 (C-4), 131.5 (C-7), 128.5 (2C, C_{meta}), 128.4 (2C, C_{ortho}), 125.7 (C_{para}), 110.5 (C-3a), 107.3 (C-5), 61.4 (7-OMe), 56.4 (6-OMe), 35.9 (C-5′), 32.1 (C-1′), 31.3 (C-2′), 30.2 (C-4′), 29.1 (C-3′); HRMS (ESI$^+$-TOF) found m/z = 354.1705; $C_{21}H_{24}NO_4$ $[M + H]^+$ requires m/z = 354.1705.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c02722.

Detailed experimental procedures and characterization data of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Shvekhgeimer, M.-G. A. Synthesis of heterocyclic compounds by the cyclization of isatin and its derivatives (review). *Chem. Heterocycl. Compd.* **1996**, *32*, 249−276.

(2) (a) Chauhan, G.; Pathak, D. P.; Ali, F.; Dubey, P.; Khasimbi, S. In-vitro evaluation of isatin derivatives as potent anti-breast cancer agents against MCF-7, MDA MB 231, MDA-MB 435 and MDA-MB 468 breast cancers cell lines: a review. *Anti-Cancer Agents Med. Chem.* **2022**, *22*, 1883−1896. (b) Varum; Sonam; Kakkar, R. Isatin and its derivatives: A survey of recent syntheses, reactions, and applications. *Med. Chem. Commun.* **2019**, *10*, 351−368. (c) Bogdanov, A. V.; Mironov, V. F. Advances in the synthesis of isatins: a survey of the last decade. *Synthesis* **2018**, *50*, 1601−1609. (d) Vine, K. L.; Matesic, L.; Locke, J. M.; Ranson, M.; Skropeta, D. Cytotoxic and anticancer activities of isatin and its derivatives: a comprehensive review from 2000−2008. *Anti-Cancer Agents Med. Chem.* **2009**, *9*, 397−414. (e) Nath, P.; Mukherjee, A.; Mukherjee, S.; Banerjee, S.; Das, S.; Banerjee, S. Isatin: a scaffold with immense biodiversity. *Mini Rev. Med. Chem.* **2021**, *21*, 1096−1112.

(3) (a) Kapadia, G. J.; Shukla, Y. N.; Basak, S. P.; Sokoloski, E. A.; Fales, H. M. The melosatins- a novel class of alkaloids from *Melochia tomentosa*. *Tetrahedron* **1980**, *36*, 2441−2441. (b) Kapadia, G. J.; Shukla, Y. N.; Chowdhury, B. K.; Basak, S. P.; Fates, H. M.; Sokoloski, E. A. Phenylpentylisatins: a novel class of alkaloids from *Melochia tomentosa*. *J. Chem. Soc., Chem. Commun.* **1977**, 535−536.

(4) Kapadia, G. J.; Shukla, Y. N. Melosatin D: A new isatin alkaloid from *Melochia tomentosa* roots. *Planta Med.* **1993**, *59*, 568−569.

(5) Medvedev, A.; Buneeva, O.; Glover, V. Biological targets for isatin and its analogues: implications for therapy. *Biol. Targets Ther.* **2007**, *1*, 151−162.

(6) Premanathan, M.; Radhakrishnan, S.; Kulangiappar, K.; Singaravelu, G.; Thirumalaiarasu, V.; Sivakumar, T.; Kathiresan, K. Antioxidant & anticancer activities of isatin (*1H*-indole-2,3-dione), isolated from the flowers of *Couroupita guianensis* Aubl. *Ind. J. Med. Res.* **2012**, *136*, 822−826.

(7) (a) Gräfe, U.; Radics, L. Isolation and structure elucidation of 6-(3′-methylbuten-2′-yl) isatin, an unusual metabolite from *Streptomyces albus*. *J. Antibiot.* **1986**, *39*, 162−163. (b) Breinholt, J.; Demuth, H.; Heide, M.; Jensen, G. W.; Møller, I. L.; Nielsen, R. I.; Olsen, C. E.; Rosendahl, C. N. Prenisatin (5-(3-Methyl-2-butenyl)-indole-2,3-dione): an antifungal isatin derivative from *Chaetomium globosum*. *Acta Chem. Scand.* **1996**, *50*, 443−445. (c) Wei, L.; Wang, Q.; Liu, X Application of thin-layer chromatography in quality control of Chinese medicinal preparations. II. Qualitative analysis of some Chinese medicinal preparations of Chansu. *Yaowu Fenxi Zazhi* **1982**, *2*, 288. (CA 98:95726b). (d) Esmaeelian, B.; Abbott, C. A.; Le Leu, R. K.; Benkendorff, K. 6-Bromoisatin found in muricid mollusc extracts inhibits colon cancer cell proliferation and induces apoptosis, preventing early stage tumor formation in a colorectal cancer rodent model. *Mar. Drugs* **2014**, *12*, 17−35.

(8) (a) Vargas, D. F.; Kaufman, T. S.; Larghi, E. L. Total synthesis of aqabamycin G, a nitrophenyl indolylmaleimide marine alkaloid from *Vibrio sp. WMBA*. *J. Org. Chem.* **2022**, *87*, 13494−13500. (b) Vargas, D. F. V.; Romero, B. S.; Larghi, E. L.; Kaufman, T. S. Rh(III)-Catalyzed C−H activation-based first total synthesis of 6-*O*-methyl anciscochine, an alkaloid isolated from *Ancistrocladus tectorius*. *Synthesis* **2019**, *51*, 4253−4263. (c) Vargas, D. F. V.; Larghi, E. L.; Kaufman, T. S. First total synthesis of ampullosine, a unique isoquinoline alkaloid isolated from *Sepedonium ampullosporum*, and of the related permethylampullosine. *RSC Adv.* **2019**, *9*, 33096−33106.

(9) (a) Arroyo Aguilar, A. A.; Ledesma, G. N.; Tirloni, B.; Kaufman, T. S.; Larghi, E. L. Convergent first total synthesis of melovinone, a densely substituted 3-methoxy-4-quinolone isolated from *Melochia tomentosa* L. *Synthesis* **2019**, *51*, 4253−4263. (b) Arroyo Aguilar, A. A.; Bolívar Avila, S. J.; Kaufman, T. S.; Larghi, E. L. Total synthesis of waltherione F, a nonrutaceous 3-methoxy-4-quinolone, isolated from *Waltheria indica* LF. *Org. Lett.* **2018**, *20*, 5058−5061.

(10) Purdy, M.; Fallon, K.; Congrave, D. G.; Toolan, D. T. W.; Zeng, W.; Bronstein, H. Synthesis of asymmetric indolonaphthyridines with enhanced excited state charge-transfer character. *J. Mater. Chem. C* **2022**, *10*, 10742−10747.

(11) Manley-King, C. I.; Bergh, J. J.; Petzer, J. P. Inhibition of monoamine oxidase by selected C5-and C6-substituted isatin analogues. *Bioorg. Med. Chem.* **2011**, *19*, 261−274.

(12) (a) Stringer, O. D.; Weinstock, J.; Wilson, J. W. 4-[2-(Dialkylamino)ethyl]isatins useful as antihypertensives and antianginal agents. Patent EP 167288, 1986; *Chem. Abstr. 107*, 236508. (b) Bramson, H. N.; Corona, J.; Davis, S. T.; Dickerson, S. H.; Edelstein, M.; Frye, S. V.; Gampe, R. T., Jr.; Harris, P. A.; Hassell, A.; Holmes, W. D.; Hunter, R. N.; Lackey, K. E.; Lovejoy, B.; Luzzio, M. J.; Montana, V.; Rocque, W. J.; Rusnak, D.; Shewchuk, L.; Veal, J. M.; Walker, D. H.; Kuyper, L. F. Oxindole-based inhibitors of cyclin-dependent kinase 2 (CDK2): design, synthesis, enzymatic activities, and X-ray crystallographic analysis. *J. Med. Chem.* **2001**, *44*, 4339−4358.

(13) (a) Liu, Y.-C.; Zhang, R.; Wu, Q.-Y.; Chen, Q.; Yang, G.-F. Recent developments in the synthesis and applications of isatins. *Org. Prep. Proc. Int.* **2014**, *46*, 317−362. (b) da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. The chemistry of isatins: a review from 1975 to 1999. *J. Braz. Chem. Soc.* **2001**, *12*, 273−324.

(14) Sudarma, I. M.; Wazni, N.; Wildawaty, N.; Yuanita, E.; Suana, I. W. An efficient method on nitration of eugenol using NH_4NO_3 and $KHSO_4$. *Asian J. Chem.* **2013**, *26*, 173−175.

(15) Heredia, D. A.; Larghi, E. L.; Kaufman, T. S. A straightforward synthesis of 5-methylaaptamine from eugenol, employing a 6π-

electrocyclization reaction of a 1-azatriene. *Eur. J. Org. Chem.* **2016**, 1397−1404.
(16) (a) Montgomery, T. P.; Johns, A. M.; Grubbs, R. H. Recent advancements in stereoselective olefin metathesis using ruthenium catalysts. *Catalysts* **2017**, *7*, 87. (b) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. A general model for selectivity in olefin cross metathesis. *J. Am. Chem. Soc.* **2003**, *125*, 11360−11370. (c) Lower yields (39%) resulted from use of Grubbs II catalyst.
(17) Nakpathom, M.; Hinks, D.; Freeman, H. S. Synthesis and evaluation of organic pigments. 4. New monoarylide and diarylide pigments. *Dyes Pigm.* **2001**, *48*, 93−106.
(18) Mandal, P. K.; McMurray, J. S. Pd−C-induced catalytic transfer hydrogenation with triethylsilane. *J. Org. Chem.* **2007**, *72*, 6599−6601.
(19) Rashad, A. A.; Neyts, J.; Leyssen, P.; Keller, P. A. A reassessment of mycophenolic acid as a lead compound for the development of inhibitors of Chikungunya virus replication. *Tetrahedron* **2018**, *74*, 1294−1306.
(20) (a) Duan, H.; Zheng, J.; Lai, Q.; Liu, Z.; Tian, G.; Wang, Z.; Li, J.; Shen, J. 2-Phenylquinazolin-4(3*H*)-one, a class of potent PDE5 inhibitors with high selectivity versus PDE6. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2777−2779. (b) Kallander, L. S.; Lawhorn, B. G.; Philp, J. Quinazoline compounds. Preparation of quinazoline derivatives as TNNI3K inhibitors useful for treating congestive heart failure. WO2011056740. *Chem. Abstr.* **2011**, *2011*, 565274. (c) Piggott, M. J.; Wege, D. The synthesis of ventilone A. *Aust. J. Chem.* **2000**, *53*, 749−754.
(21) Klein, L. L.; Tufano, M. D. Synthesis of substituted isatins. *Tetrahedron Lett.* **2013**, *54*, 1008−1011.
(22) (a) Li, W.; Duan, Z.; Zhang, X.; Zhang, H.; Wang, M.; Jiang, R.; Zeng, H.; Liu, C.; Lei, A. From Anilines to isatins: oxidative palladium-catalyzed double carbonylation of CH Bonds. *Angew. Chem., Int. Ed.* **2015**, *127*, 1913−1916. and references therein. (b) Kumar, G.; Singh, N. P.; Kumar, K. Recent advancement of synthesis of isatins as a versatile pharmacophore: A review. *Drug Res.* **2021**, *71*, 115−121.
(23) (a) Wang, Z. *Comprehensive Organic Name Reactions and Reagents*, 1st edition; John Wiley and Sons, Inc.: Hoboken, NJ, 2010, pp 1838−1840. (b) Trost, B. M.; Kalnmals, C. A.; Ramakrishnan, D.; Ryan, M. C.; Smaha, R. W.; Parkin, S. Ruthenium-catalyzed asymmetric allylic alkylation of isatins. *Org. Lett.* **2020**, *22*, 2584−2589.
(24) Hong, J.; Zhang, M.; Shi, L.; Liu, P.; Guo, Y.; Zhao, T.; Li, Q. X.; Yang, L. Copper(I)-catalyzed synthesis of natural alkaloid tryptanthrin and its derivatives. *New J. Chem.* **2022**, *46*, 13540−13545.
(25) (a) Benington, F.; Morin, R. D.; Clark, L. C. Mescaline analogs. IV. Substituted 4,5,6-trimethoxyindoles. *J. Org. Chem.* **1955**, *20*, 1454−1457. (b) Kawai, M.; BaMaung, N. Y.; Fidanze, S. D.; Erickson, S. A.; Tedrow, J. S.; Sanders, W. J.; Vasudevan, A.; Park, C.; Hutchins, C.; Comess, K. M.; Kalvin, D.; Wang, J.; Zhang, Q.; Lou, P.; Tucker-Garcia, L.; Bouska, J.; Bell, R. L.; Lesniewski, R.; Henkin, J.; Sheppard, G. S. Development of sulfonamide compounds as potent methionine aminopeptidase type II inhibitors with antiproliferative properties. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3574−3577. (c) Pirrung, M. C.; Pansare, S. V.; Das Sarma, K.; Keith, K. A.; Kern, E. R. Combinatorial optimization of isatin-β-thiosemicarbazones as anti-poxvirus agents. *J. Med. Chem.* **2005**, *48*, 3045−3050. (d) Uddin, M. K.; Reignier, S. G.; Coulter, T.; Montalbetti, C.; Granaes, C.; Butcher, S.; Krog-Jensen, C.; Felding, J. Syntheses and antiproliferative evaluation of oxyphenisatin derivatives. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2854−2857.
(26) (a) Alsufyani, M.; Stoeckel, M.-A.; Chen, X.; Thorley, K.; Hallani, R. K.; Puttisong, Y.; Ji, X.; Meli, D.; Paulsen, B. D.; Strzalka, J.; Regeta, K.; Combe, C.; Chen, H.; Tian, J.; Rivnay, J.; Fabiano, S.; McCulloch, I. Lactone backbone density in rigid electron-deficient semiconducting polymers enabling high n-type organic thermoelectric performance. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202113078. (b) Huang, Y.-W.; Lin, Y.-C.; Li, J.-S.; Chen, W.-C.; Chueh, C.-C. Investigating the backbone conformation and configuration effects for donor−acceptor conjugated polymers with ladder-type structures synthesized through aldol polycondensation. *J. Mater. Chem. C* **2021**, *9*, 9473−9483.
(27) Tisovský, P.; Šandrik, R.; Horváth, M.; Donovalová, J.; Filo, J.; Gáplovský, M.; Jakusová, K.; Cigáň, M.; Sokolík, R.; Gáplovský, A. Effect of structure on charge distribution in the isatin anions in aprotic environment: spectral study. *Molecules* **2017**, *22*, 1961.
(28) (a) Randell, N. M.; Boutin, P. C.; Kelly, T. L. Bisisoindigo: using a ring-fusion approach to extend the conjugation length of isoindigo. *J. Mater. Chem. A* **2016**, *4*, 6940−6945. (b) Dhondge, A. P.; Tsai, P.-C.; Nien, C.-Y.; Xu, W.-Y.; Chen, P.-M.; Hsu, Y.-H.; Li, K.-W.; Yen, F.-M.; Tseng, S.-L.; Chang, Y.-C.; Chen, H. J. H.; Kuo, M.-Y. Angular-shaped naphthalene bis(1,5-diamide-2,6-diylidene)-malononitrile for high-performance, air-stable n-type organic field-effect transistors. *Org. Lett.* **2018**, *20*, 2538−2542. (c) Chen, H.; Moser, M.; Wang, S.; Jellett, C.; Thorley, K.; Harrison, G. T.; Jiao, X.; Xiao, M.; Purushothaman, B.; Alsufyani, M.; Bristow, H.; De Wolf, S.; Gasparini, N.; Wadsworth, A.; McNeill, C. R.; Sirringhaus, H.; Fabiano, S.; McCulloch, I. Acene ring size optimization in fused lactam polymers enabling high n-type organic thermoelectric performance. *J. Am. Chem. Soc.* **2021**, *143*, 260−268.
(29) (a) Waetjen, F.; Dahl, B. H.; Drejer, J.; Jensen, L. H. Isatin oxime derivatives, their preparation and use as antagonists of excitatory amino acids at the AMPA receptor. US 5436250, 1995; *Chem. Abstr.*, *123*, 340088. (b) Comess, K. M.; Erickson, S. A.; Henkin, J.; Kalvin, D. M.; Kawai, M.; Kim, K. H.; Ba-Maung, N. Y.; Park, C. H.; Sheppard, G. S.; Vasudevan, A.; Wang, J.; Barnes, D. M.; Fidanze, S. D.; Kolaczkowski, L.; Mantei, R. A.; Park, D. C.; Sanders, W. J.; Tedrow, J. S.; Wang, G. T.Preparation of sulfonamides having antiangiogenic and anticancer activity. Patent US 20040167128, 2004; *Chem. Abstr. 141*, 173972. (c) Waetjen, F.; Dahl, B. H.; Drejer, J.; Jensen, L. H. Preparation of benzodipyrrolediones and analogs as excitatory amino acid antagonists. Patent EP 529636, 1993; *Chem. Abstr.*, *118*, 254913.
(30) (a) Sivan, A.; Deepthi, A. Facile synthesis of 1, 2, 3-tricarbonyls from 1, 3-dicarbonyls mediated by cerium (IV) ammonium nitrate. *Tetrahedron Lett.* **2014**, *55*, 1890−1893. (b) Tani, S. Process for production of ketomalonic acid compounds or hydrates thereof. Patent WO 2010150548, 2010; *Chem. Abstr.* 154, 64332.
(31) Kattamuri, P. V.; Yin, J.; Siriwongsup, S.; Kwon, D.-H.; Ess, D. H.; Li, Q.; Li, G.; Yousufuddin, M.; Richardson, P. F.; Sutton, S.; Kürti, C. L. Practical singly and doubly electrophilic aminating agents: a new, more sustainable platform for carbon−nitrogen bond formation. *J. Am. Chem. Soc.* **2017**, *139*, 11184−11196.
(32) CCDC 2240753 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures. In addition, a brief molecular structure discussion is provided in Supplementary Information.
(33) Sheldrick, G. M. *SADABS*; University of Göttingen: Göttingen, Germany, 1996.
(34) Shinki, T. Process for production of ketomalonic acid compounds or hydrates thereof. US 8859803 B2, 2014.
(35) Lollar, C. T.; Krenek, K. M.; Bruemmer, K. J.; Lippert, A. R. Ylide mediated carbonyl homologations for the preparation of isatin derivatives. *Org. Biomol. Chem.* **2014**, *12*, 406−409.
(36) Clemo, G. R.; Turnbull, J. H. The sulphonation of some derivatives of eugenol. *J. Chem. Soc.* **1947**, 124−127.

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