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Introduction

Illicium merrillianum is a small tree or shrub which is endemic to southwestern China and Burma. Besides using the bark, root bark and fruit of this shrub in Traditional Chinese Medicine (TCM) for treating rheumatism,¹ it is also found to possess a vast plethora of structurally diverse and unique bioactive natural products.² Since the onset of the 21st century, Fukuyama and co-workers have been actively engaged in the isolation and bioactivity screening of several anisactone-type sesquiterpenes, *allo*-cedrane-type sesquiterpenes and seco-prizizaane type sesquiterpenoids from *I. merrillianum* and other *Illicium* species.² Indeed, their pioneering efforts in this arena led to the discovery of potent neurite outgrowth promoters such as merrilactone A,³ 11-*O*-debenzoyl tashironin⁴ and jiadifenolide⁵ which garnered significant world-wide attention from the scientific community^{6–8} with the scope of their application in treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's.

Further, in continuous pursuit for new bioactive compounds as potential leads for drug discovery, very recently Zhang *et al.* got interested in exploring the leaves and branches of *I. merrillianum* which ended up with the isolation of some unique abietane diterpenoids⁹ as well as some bioactive quinoid natural products.¹⁰ Perhaps, it was the bioactivity of the (+) antipode of merrilliaquinone (1), Fig. 1, reported by them and accessed *via* chiral HPLC separation from the racemic natural product that caught our attention. Interestingly, the (+) antipode of merrilliaquinone was found to be several fold more

Synthetic studies en route to the first total synthesis of a naturally occurring quinone from *Acorus gramineus*, iso-merrilliaquinone, iso-magnoshinin and 2-*epi*-3,4-dihydro magnoshinin†

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A unified synthetic strategy based on [4 + 2] cycloaddition of readily accessible coupling fragments was conceptualized for the racemic total synthesis of recently isolated bioactive merrilliaquinone and other closely related quinones such as gramineusquinone B as well as neolignan, magnoshinin. The present article discloses our efforts in this direction which culminated in the total syntheses of gramineusquinone B, iso-merrilliaquinone, iso-magnoshinin and 2-*epi*-3,4-dihydro magnoshinin.

potent and selective towards human hepatoma cells over normal hepatic cells in comparison to the (–) antipode or the racemic form of the natural product.¹⁰ Another, interesting fact related to 1 is, it was also reported in the racemic form by Lu *et al.* as acortatarinowin H from the rhizomes of *Acorus tatarinowii* Schott just after the report by Zhang *et al.*¹¹ Further, we were pleasantly surprised to learn that there exist structurally closely related quinones such as 2–4 and neolignans 5, 6 as captured in Fig. 1, all having their origins from herbs used in TCM. For instance, quinones 2 and 3 were of late isolated in optically pure form from the rhizomes of *Acorus gramineus*, and reported to exhibit decent anti-inflammatory as well as cytotoxicity against certain human cancer cell lines.¹² For convenience sake, we have preferred to refer them as gramineusquinone A and B respectively instead of the conventional

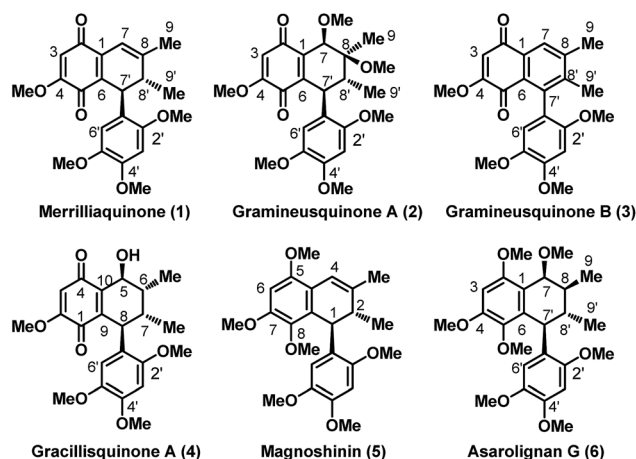


Fig. 1 Representative examples of bioactive quinones and neolignans isolated from herbal plants used in Traditional Chinese Medicine (TCM) [indicated numbering as per the isolation paper].

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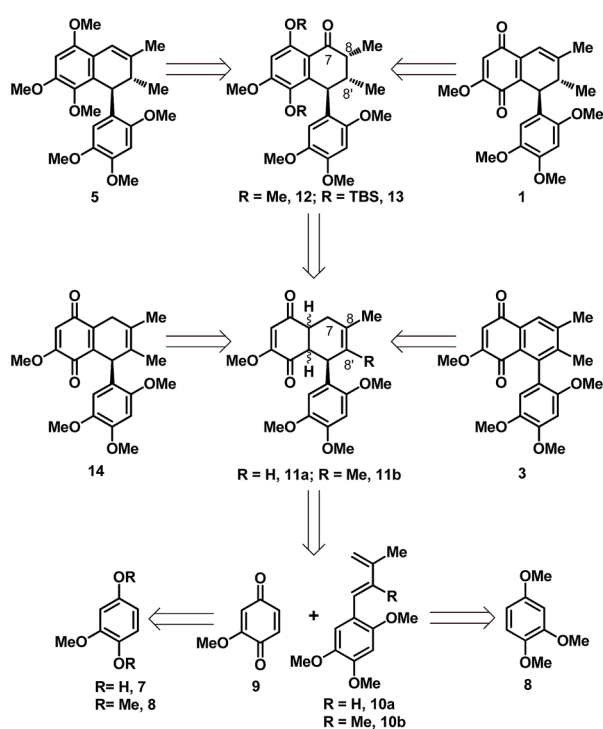


name assigned by Lee. *et al.*¹² On the other hand, with no bioactivity so far reported gracillisquinone (**4**) was isolated not long ago from *Spallerotheca gracilli*.¹³ While among the neolignan **5** and **6**, magnoshinin with prominent anti-inflammatory activity was reported in 1983 after its isolation from the flower buds of *Magnolia salicifolia*, more famous as “Shin-i” in TCM.¹⁴ Whereas, asarolignan G (**6**) with anti-neuroinflammatory activity is a very recently surfaced neolignan from the rhizomes of *Acorus tatarinowii*.¹⁵

The impressive bioactivity profile exhibited by **1** though in one of its enantiomeric pure form, as well as close structural resemblance with quinones **2–4**, together with a strong prospect to elaborate them to neolignans **5** and **6** engaged our interest towards these natural products. Further, the fact that except for **5** (ref. 16a–c) there exists no synthetic endeavors towards any of these natural products motivated us to embark on a synthetic journey directed towards the racemic total syntheses of these bioactive quinones and neolignans to access them in substantial quantities for thorough clinical assessment. Moreover, initially we aimed to develop a concise unified approach based on [4 + 2] cycloaddition strategy taking inspiration from our earlier success in application of similar approach in context of syntheses of quinoid natural products such as acremine G¹⁷ and allomicrophyllone.¹⁸

Results and discussion

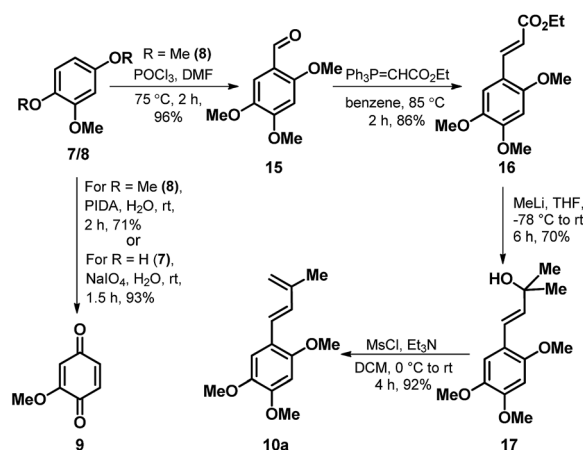
To test the viability of the approach we had in mind, we initially chose to focus on the development of a racemic synthesis for **1**, **3** and **5** before targeting other interested natural product depicted in Fig. 1. In this context, our retrosynthetic plan is as outlined in



Scheme 1 Retrosynthetic plan towards **1**, **3** and **5**.

Scheme 1, which hinges on a Diels–Alder coupling of quinone **9** with either of the arylated diene **10a/b** to arrive at the [4 + 2] cycloadduct **11a/b** in a highly regioselective fashion. While, the two coupling partner **9** and **10** were envisioned to be accessed through a common and readily available cheap starting material in the form of quinol **7** or its corresponding dimethyl ether **8**. A 4–6 step synthetic manipulation on **8** was expected to offer the dienes **10a/b** in contrast to a single step access of **9** from **7/8** through known protocol. We anticipated the cycloadduct **11a/b** to hold immense potential in context of its elaboration to the targeted natural product. As a simple oxidation of the dihydroquinone in **11b** to quinone would end up in the acquisition of **14** isomeric to **1**, having C₈=C_{8'} bond position instead of the C₇=C₈ bond position present in **1**, whereas a straightforward oxidative aromatization in the quinone fused cyclohexene ring of **11b** would lead to the natural quinone **3**. While, reductive methylation and then selective benzylic methylene oxidation at C-7 position of **11a** followed by stereoselective installation of the methyl group at C-8' position was the route we had in mind to arrive at an intermediate like **12** for accessing **5**. Similarly, reductive silylation and then selective benzylic methylene oxidation at C-7 position of **11b** followed by stereoselective C-8, C-8' double bond reduction was the route planned to access the functionally well placed intermediate like **13** which could be readily elaborated to either of the natural product **1** or **5** through some straightforward synthetic maneuvers.

Towards the realization of the retrosynthetic plan as outlined in Scheme 1, we commenced our foray with the synthesis of the two coupling partners **9** and **10a**. The known quinone **9** (ref. 19) was accessed both *via* hypervalent iodine mediated oxidation on **8** as well as through NaIO₄ mediated oxidation of **7**, with comparatively better yields observed in case of latter. While, the synthetic sequence towards the crafting of diene component **10a** as depicted in Scheme 2 emanates from the known aldehyde **15** (ref. 20) obtained through a Vilsmeier–Haack formylation on **8**. Wittig–Horner olefination of **15** with (carbethoxymethylene)triphenylphosphorane smoothly furnished the *trans*-cinnamate ester **16** exclusively, which on addition of excess methyl lithium resulted in the formation of



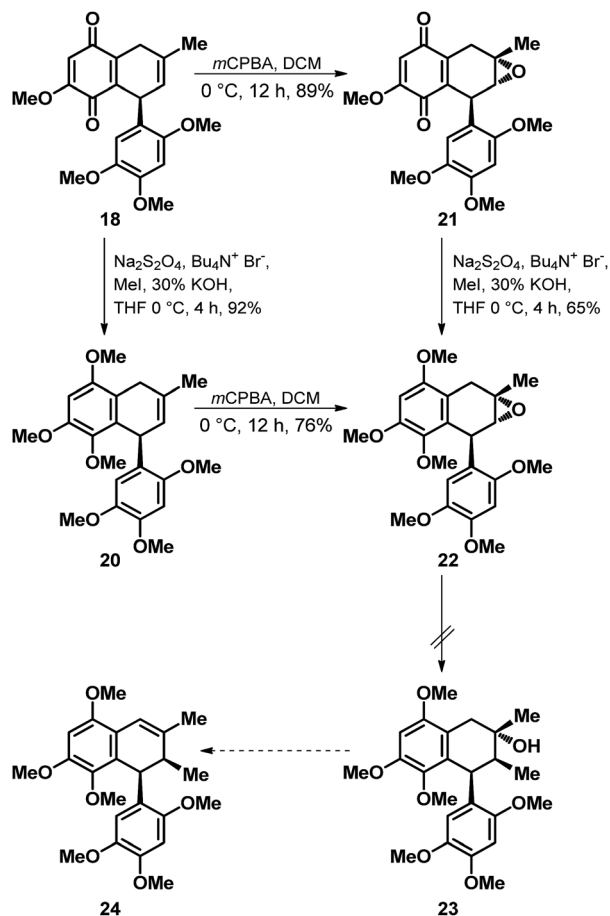
Scheme 2 Synthesis of the diene (**10a**) and dienophile (**9**).



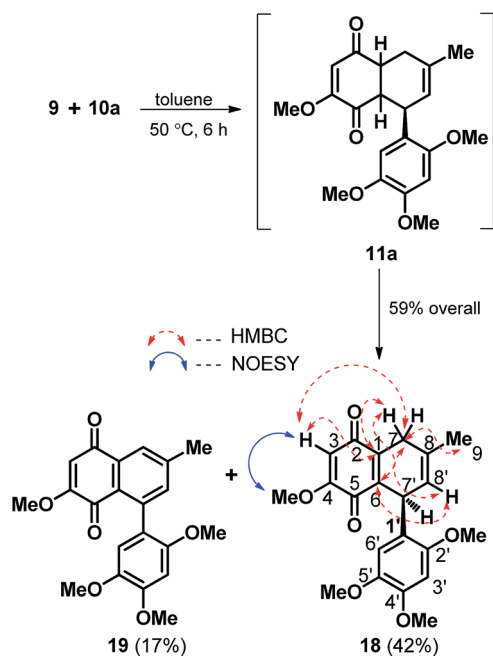
the cinnamyl alcohol **17**. Then, a careful dehydration on **17** in the presence of mesyl chloride and Et₃N as the base furnished the desired diene **10a** in excellent yield.

With both diene and dienophile in hand the next task was to execute the [4 + 2] coupling between the two. Indeed, to our delight as highlighted in Scheme 3, the Diels–Alder coupling between **9** and **10a** turned out to be quite eventful as the modest thermal activation of the diene and dienophilic component in dry toluene at 50 °C afforded a readily separable mixture of the bicyclic quinone **18** and naphthoquinone **19** in the ratio of ~2.5 : 1 and in 59% overall yield. The formation of **18** and **19** is clearly attributable to the spontaneous concomitant partial and complete oxidation in the quinone fused cyclohexene ring of the [4 + 2] cycloadduct **11a** respectively. While the structure of **18** was secured through 2D NMR analysis with the key HMBC and nOe correlations as indicated in red and blue arrows respectively (Scheme 3), the close spectral resemblance of naphthoquinone **19** with that of gramineusquinone B (**3**) hinted it to be the desmethyl derivative of the natural product **3**.

Encouraged by the outcome of the D–A reaction depicted in Scheme 3, we next turned our attention towards the functionalization of the quinone **18** for its elaboration to the natural products merrilliaquinone (**1**) and magnoshinin (**5**). In this regard, we thought of accessing **12/13** by first oxidizing the C-7 methylene position in **18** to arrive at an enone for executing the stereoselective installation of the methyl group at C-8' position *via* Gilman-type addition after masking the quinone in the form of methyl/silyl protected quinol. However, failure in our attempts to oxidize the C-7 methylene position both on **18** as well as **18** derived **20**, accessed *via* one-pot reductive methylation of **18** thwarted our plan of synthesizing **12/13**. Nevertheless, in our attempts to relocate the double bond from C-8, C-8' to C-



Scheme 4 Efforts towards the elaboration of **18** to racemic 2-*epi*-magnoshinin (**24**).

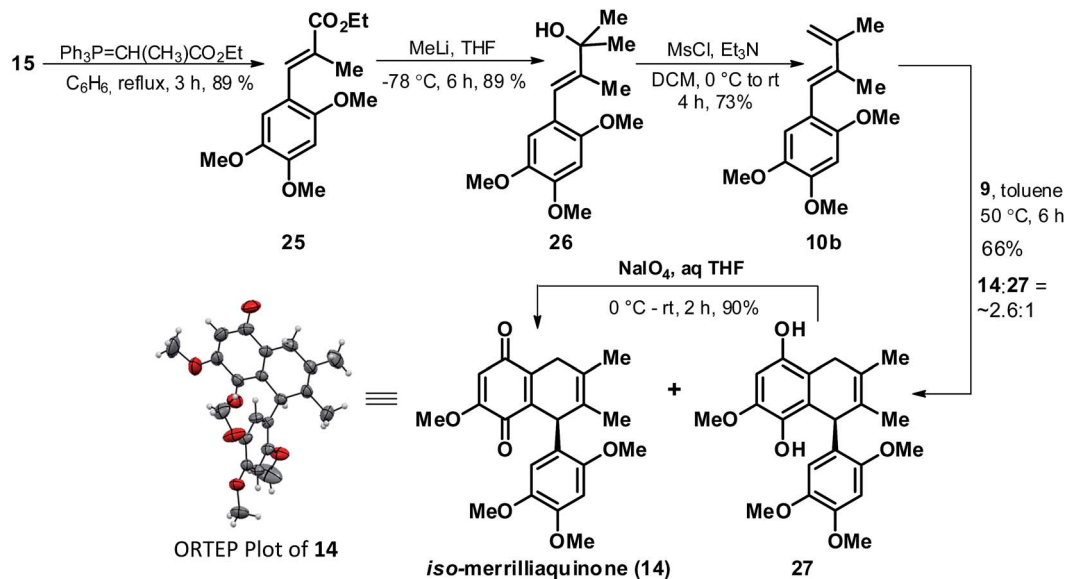


Scheme 3 Tandem [4 + 2] cycloaddition and oxidation leading to racemic **18** and desmethyl gramineusquinone B (**19**).

7, C-8 position we explored a modified strategy as depicted in Scheme 4. Indeed, subjection of **18** to the *m*-CPBA mediated epoxidation offered the epoxy quinone **21** in a diastereoselective manner and in decent yield. But then, the nucleophilic methyl mediated epoxide ring opening on **22** accessed from **21** *via* reductive methylation as well as *via* diastereoselective epoxidation of **20** turned out to be a difficult proposition as it failed to offer the desired ring opened product **23** for its further elaboration to 2-*epi*-magnoshinin (**24**).

Undeterred by our failures in elaborating the cycloadduct **18** to any of the targeted natural product, we next thought of revisiting the strategy in order to access cycloadduct **11b** with a pre-installed methyl group at C-8' position. In this context, through a similar synthetic sequence as earlier demonstrated for preparation of diene **10a** (Scheme 2), the diene **10b** was synthesized from **15** *via* the cinnamate ester **25** and tertiary alcohol **26** as depicted in Scheme 5. With access to diene **10b** in good yield we readily executed its [4 + 2] coupling with **9** under similar coupling condition as that used for **10a** in Scheme 3, but to our surprise with observation of a slight different outcome in terms of product profile. Contrary to the D–A reaction involving **10a**, the D–A reaction in case of **10b** afforded a mixture of quinone **14** and bicyclic quinol **27** in the ratio of ~2.6 : 1 respectively and in an overall yield of 66%. Though **14** could be carefully separated from

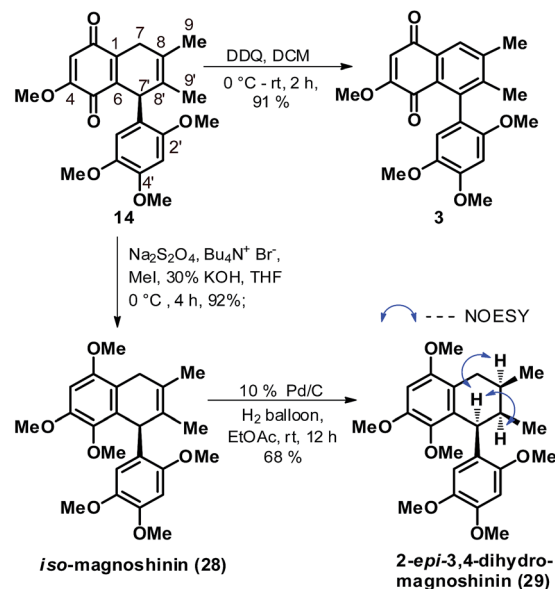




Scheme 5 [4 + 2] cycloaddition of 10b and 9 leading to racemic iso-merrilliaquinone.

27 but the tendency of the quinol 27 to readily undergo spontaneous partial conversion to the quinone form 14 made it difficult to isolate it in the purest form. However, it didn't turn out to be a serious concern as exposure of the mixture of 14 and 27 to NaIO_4 afforded a single product 14 which was better serviceable in context of further elaboration to the targeted natural products. Further, the structure of 14 was secured through comparison of its spectral data (^1H and ^{13}C NMR) with that of related quinone 18, however for sake of unambiguity we also confirmed the structure through X-ray crystallographic analysis.²¹ The ORTEP plot of 14 is as highlighted in Scheme 5. In view of the similar chemical constitution of the quinone 14 as that of targeted natural product (1), except for the position of the double bond in the quinone fused cyclohexene ring we presumed appropriate for quinone 14 to be referred as iso-merrilliaquinone.

Towards the end game, foremost keeping in mind the close proximity of 14 to natural product 3, the former was readily subjected to a DDQ mediated aromatization in the quinone fused cyclohexene ring to arrive at gramineusquinone B, 3 in good yields, Scheme 6. The synthetic sample of 3 was found to be spectroscopically (^1H and ^{13}C NMR) identical to the reported natural product.¹² Then, efforts were channelized towards elaboration of 14 as well as 14 derived 28 (isomeric to magnoshinin, 5) to an intermediate like 12/13 in context of its elaboration to natural product 1 and 5 as per the retrosynthetic plan envisioned in Scheme 1. But this time again, all our investigated conditions proved ineffective in oxidizing the C-7 methylene position in 14 as well as the 14 derived 28. Also, attempts to isomerise the double bond position in 14 as well as 28 proved unfruitful. After repeatedly failing in our attempts to unsymmetrically functionalize the $\text{C}_8=\text{C}_8'$ bond both in 14 and 28, we then executed a rather straightforward catalytic hydrogenation on iso-magnoshinin 28 with the hope of accessing the dihydro version of the natural product 5. Indeed the double bond reduction on 28 turned out to be stereoselective offering



Scheme 6 Synthesis of racemic gramineusquinone B (3), iso-magnoshinin (28) and 2-epi-3,4-dihydro-magnoshinin (29).

29 in decent yields but deviant from the desired stereochemistry at C-8' position in context of 5. 2D NMR analysis of 28 confirmed the delivery of the two H-atoms on the $\text{C}_8=\text{C}_8'$ bond from the side opposite to the phenyl ring at the C-7' position and hinted 29 to be 8'-epi-7,8-dihydro-magnoshinin or 2-epi-3,4-dihydro-magnoshinin as per the numbering given to the natural product in the isolation paper.¹⁴

Conclusions

In conclusion, we have successfully demonstrated the syntheses of gramineusquinone B, iso-merrilliaquinone and iso-



magnoshinin as well as 2-*epi*-3,4-dihydro-magnoshinin from readily accessible fragments through a straightforward Diels–Alder strategy. Efforts are currently underway to overcome the difficulties encountered in the present route for the total syntheses of merrilliaquinone and magnoshinin which may eventually pave the way for other interested bioactive quinones and neolignans.

Experimental

All the reagents were purchased from Sigma-Aldrich and other commercial suppliers and used without further purification. While most of the desired solvents supplied by commercial suppliers were dried using the standard drying procedures.²² All nonaqueous reactions were executed under nitrogen atmosphere. Melting points were determined on a Buchi M-560 apparatus and are uncorrected. The ¹H and ¹³C NMR spectra were recorded on 400 and 100 MHz Bruker spectrometer respectively using TMS as an internal standard. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = doublet of doublet, ddd = doublet of doublet of doublet and m = multiplet. The chemical shifts are reported as δ values (ppm) and the coupling constants (*J*) values are reported in Hz. High Resolution Mass Spectra (HRMS) were obtained using electron spray ionization (ESI) technique and as TOF mass analyzer. IR spectra were recorded on a Bruker FT/IR-460 Plus spectrometer. Reactions monitoring were done using precoated SiO₂-gel GF254 glass TLC plates while spot visualizations were done under UV light and spot developing stains like *p*-anisaldehyde or KMnO₄. Purifications were done using column chromatography with 100–200 mesh size SiO₂-gel as the stationary phase. Compound **9** (ref. 19) and **15** (ref. 20) were prepared according to the earlier reported procedures.

(*E*)-1,2,4-Trimethoxy-5-(3-methylbuta-1,3-dien-1-yl)benzene (10a)

To a solution of **17** (1 g, 3.968 mmol) in dry DCM (10 mL), 10 mL of triethylamine was added. The reaction mixture was then cooled to –5 °C before adding mesyl chloride (0.46 mL, 5.945 mmol) followed by DMAP (48.31 mg, 0.396 mmol). The reaction mixture was then allowed to warm to rt and stirred for another 1.5 h until complete consumption of starting material and formation of a new spot was indicated by the TLC analysis. The reaction was worked up by diluting it with water followed by extraction in DCM (4 × 40 mL). The organic layer after drying over Na₂SO₄ and then removal of the solvent under reduced pressure offered a crude oily residue which was purified by stirring the crude residue with 25–30% DCM for 30 min. followed by decantation of the solvent and evaporation under reduced pressure to get the diene **10a** (850 mg, 3.628 mmol, 91.5% yield) as an oil. IR (neat): ν_{\max} 2931, 1512, 1466, 1398, 1276, 1258, 1207, 1039, 757, 735 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.04 (s, 1H), 6.84 (d, *J* = 16.4 Hz, 1H), 6.75 (d, *J* = 16.4 Hz, 1H) 6.50 (s, 1H), 5.07 (d, *J* = 1.2 Hz, 1H), 5.01 (br s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 1.98 (s, 3H); ¹³C NMR (100

MHz, CDCl₃) δ 151.61, 149.48, 143.47, 142.76, 130.02, 122.87, 118.35, 115.96, 109.41, 97.82, 56.71, 56.52, 56.09, 18.73.

Procedure for the Diels–Alder reaction of **9** and **10a**

To a solution of dienophile **9** (294 mg, 2.130 mmol) in toluene (5 mL), diene **10a** (797 mg, 3.408 mmol) was added and allowed to stir at 50 °C for 6 h. On complete consumption of starting material by TLC analysis the reaction was worked up by evaporating out the entire toluene under reduced pressure and subjecting the resultant crude residue to SiO₂ gel column chromatographic purification using petroleum ether/ethyl acetate (7 : 3) as the eluent to first isolate the partially oxidised DA adduct **18** (332 mg, 0.896 mmol, 42% yield) followed by the aromatized naphthoquinone derivative **19** (135 mg, 0.366 mmol, 17%) with an overall yield of 59% for the D–A coupling.

2-Methoxy-6-methyl-8-(2,4,5-trimethoxyphenyl)naphthalene-1,4-(5*H*, 8*H*)-dione (18)

Brown-red solid, mp: 138.6–139.4 °C. IR (neat): ν_{\max} 2936, 1673, 1649, 1608, 1510, 1440, 1314, 1221, 1206, 1032 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.50 (s, 1H), 6.45 (s, 1H), 5.88 (s, 1H), 5.48 (d, *J* = 2.0 Hz, 1H), 4.89 (dd, *J*₁ = 5.6 Hz, *J*₂ = 10.4 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.75 (s, 3H), 3.73 (s, 3H), 3.08 (dd appearing as t, *J* = 7.0 Hz, 2H), 1.77 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 187.49, 180.85, 158.53, 151.31, 148.67, 143.39, 140.57, 139.91, 128.10, 123.18, 122.06, 113.25, 106.82, 98.81, 57.25, 56.92, 56.10 (2C), 35.25, 29.13, 22.70. HRMS (ESI) *m/z* calcd for C₂₁H₂₃O₆ (M + H)⁺: 371.1489; found: 371.1487.

2-Methoxy-6-methyl-8-(2,4,5-trimethoxyphenyl)naphthalene-1,4-dione (19)

Brown-red solid, mp: 167.3–168.4 °C. IR (neat): ν_{\max} 2937, 1683, 1649, 1615, 1595, 1516, 1465, 1215, 1033, 852 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.94 (d, *J* = 1.6 Hz, 1H), 7.31 (d, *J* = 1.5 Hz, 1H), 6.68 (s, 1H), 6.57 (s, 1H), 6.10 (s, 1H), 3.94 (s, 3H), 3.84 (s, 6H), 3.65 (s, 3H), 2.49 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 185.44, 179.56, 161.10, 150.64, 149.23, 144.42, 143.05, 139.78, 137.89, 133.07, 127.02, 126.47, 121.37, 113.07, 108.27, 97.37, 56.61, 56.36, 56.32, 56.20, 21.77. HRMS (ESI) *m/z* calcd for C₂₁H₂₁O₆ (M + H)⁺: 369.1333; found: 369.1366.

5,7,8-Trimethoxy-3-methyl-1-(2,4,5-trimethoxyphenyl)-1,4-dihydronaphthalene (20)

To a stirred solution of **18** (20 mg, 0.054 mmol) in THF (2 mL) containing *n*-Bu₄NBr (43.51 mg, 0.135 mmol) at 0 °C were added 30% aq. Na₂S₂O₄ (2.5 mL, 4.310 mmol), MeI (0.42 mL, 6.756 mmol) and aqueous KOH (1 mL) sequentially. After 5 min, the mixture was allowed to warm to rt, and stirring was continued for 1.5 h at the same temperature when complete consumption of starting material along with formation of a new spot was indicated by TLC analysis. The reaction was worked up by extracting it in ethyl acetate followed by drying of the separated organic phase over Na₂SO₄. Removal of the solvent under reduced pressure afforded a residue which was purified by SiO₂



gel column chromatography using hexane/ethyl acetate (7 : 3) as the eluent to get **20** (20 mg, 0.050 mmol, 92% yield) as an oil. IR (neat): ν_{\max} 2934, 2836, 1601, 1507, 1463, 1337, 1235, 1204, 1039, 829 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.54 (s, 1H), 6.44 (s, 1H), 6.28 (s, 1H), 5.61–5.59 (m, 1H), 5.17 (d, $J = 4.0$ Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.62 (s, 3H), 3.29 (s, 3H), 3.22–3.11 (m, 2H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.46, 150.92, 150.73, 147.71, 143.31, 140.45, 132.70, 129.34, 127.54, 122.90, 117.05, 113.30, 98.46, 95.56, 59.82, 57.21, 56.78, 56.28, 56.10, 55.67, 35.12, 28.89, 23.25. HRMS (ESI) m/z calcd for $\text{C}_{23}\text{H}_{29}\text{O}_6$ ($\text{M} + \text{H}$) $^+$: 401.1959; found: 401.1951.

5-Methoxy-1 α -methyl-7-(2,4,5-trimethoxyphenyl)-1 α ,2,7,7 α -tetrahydronaphtho[2,3-*b*]oxirene-3,6-dione (**21**)

To a cooled solution of **18** (15 mg, 0.040 mmol) in DCM (2 mL), *m*-CPBA (9.3 mg, 0.053 mmol) was added portion wise and allowed to stir for 12 h at 0 °C until complete consumption of starting material along with formation of a new spot was indicated by TLC analysis. The reaction was worked up by evaporating DCM and the resultant crude residue was purified by SiO_2 gel column chromatography using hexane/ethyl acetate (3 : 2) as the eluent to arrive at the epoxide **21** (14 mg, 0.036 mmol, 89% yield) as a pale yellow solid, mp: 139.7–140.8 °C. IR (neat): ν_{\max} 2936, 1674, 1655, 1611, 1511, 1461, 1314, 1221, 1032, 806 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.76 (s, 1H), 6.48 (s, 1H), 5.85 (s, 1H), 4.66 (d, $J = 1.6$ Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 3.22 (ddd, $J_1 = 1.2$ Hz, $J_2 = 2.4$ Hz, $J_3 = 20.0$ Hz, 1H), 3.16 (s, 1H), 2.68 (dd, $J_1 = 2.4$ Hz, $J_2 = 20.0$ Hz, 1H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 187.20, 181.05, 158.52, 152.13, 149.39, 143.12, 138.53, 137.20, 116.60, 115.04, 106.96, 97.67, 61.44, 57.40, 56.79, 56.38, 56.18, 56.13, 37.58, 29.08, 22.57. HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{23}\text{O}_7$ ($\text{M} + \text{H}$) $^+$: 387.1438; found: 387.1423.

3,5,6-Trimethoxy-1 α -methyl-7-(2,4,5-trimethoxyphenyl)-1 α ,2,7,7 α -tetrahydronaphtho[2,3-*b*]oxirene (**22**)

The compound **22** was obtained in 76% yield (11.9 mg, 0.028 mmol) *via* epoxidation of **20** (15 mg, 0.038 mmol) using *m*-CPBA (8.0 mg, 0.048 mmol) and employing similar epoxidation procedure as that described for **21**. Alternatively it was also obtained in 65% yield (7.0 mg, 0.017 mmol) by reductive methylation of **21** (10 mg, 0.026 mmol) using 30% aq. $\text{Na}_2\text{S}_2\text{O}_4$ (1.26 mL, 2.172 mmol), MeI (0.2 mL, 3.238 mmol) and aqueous KOH (1 mL) employing similar procedure as that described for **20**. IR (neat): ν_{\max} 2924, 2851, 1680, 1650, 1612, 1511, 1462, 1214, 1034, 850 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.56 (s, 1H), 6.42 (s, 1H), 6.31 (s, 1H), 5.19 (d, $J = 2.0$ Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.64 (s, 3H), 3.42 (d, $J = 19.0$ Hz, 1H), 3.41 (s, 3H), 3.25 (dd, $J = 2.0, 1.0$ Hz, 1H), 2.78 (d, $J = 18.0$ Hz, 1H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.07, 151.67, 151.32, 148.63, 143.13, 141.06, 130.12, 121.48, 114.06, 113.78, 98.10, 96.06, 62.08, 60.26, 57.02, 56.89, 56.76, 56.16, 56.09, 55.74, 35.55, 28.51, 22.93. HRMS (ESI) m/z calcd for $\text{C}_{23}\text{H}_{29}\text{O}_7$ ($\text{M} + \text{H}$) $^+$: 417.1908; found: 417.1941.

(*E*)-1-(2,3-Dimethylbuta-1,3-dien-1-yl)-2,4,5-trimethoxybenzene (**10b**)

To a solution of **26** (598 mg, 2.248 mmol) in dry DCM (10 mL), 10 mL of triethylamine was added. The reaction mixture was then cooled to –5 °C before adding mesyl chloride (0.26 mL, 3.372 mmol) followed by DMAP (27.4 mg, 0.224 mmol). The reaction mixture was then allowed to warm to rt and stirred for another 2 h until complete consumption of starting material and formation of a new spot was indicated by the TLC analysis. The reaction was worked up by diluting it with water and extracting in DCM (4 \times 40 mL) followed by drying of the separated organic phase over Na_2SO_4 . Removal of the solvent under reduced pressure afforded a residue which was purified by column chromatography using hexane/ethyl acetate (8 : 2) as the eluent to get **10b** (408 mg, 1.643 mmol, 73% yield) as an oil. IR (neat): ν_{\max} 2947, 2833, 1605, 1511, 1464, 1316, 1302, 1206, 1177, 1036, 875 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.79 (s, 1H), 6.66 (s, 1H), 6.53 (s, 1H), 5.15 (s, 1H), 5.03 (s, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 2.06 (d, $J = 0.4$ Hz, 3H), 1.99 (d, $J = 0.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.90, 148.68, 144.97, 142.47, 136.24, 122.65, 119.02, 114.72, 112.55, 97.50, 56.66, 56.53, 56.12, 21.08, 15.54. HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{21}\text{O}_3$ ($\text{M} + \text{H}$) $^+$: 249.1485; found: 249.1460.

2-Methoxy-6,7-dimethyl-8-(2,4,5-trimethoxyphenyl)naphthalene-1,4-(5*H*,8*H*)-dione (iso-merrilliaquinone, **14**)

To a solution of dienophile **9** (20 mg, 0.145 mmol) in toluene, diene **10b** (58 mg, 0.232 mmol) was added and allowed to stir at 50 °C for 6 h. On complete consumption of the dienophile and with formation of two new spots of **14** and **26** by TLC analysis, the reaction was worked up by evaporating out the entire toluene under reduced pressure. To the resultant crude residue was then added NaIO_4 (19.9 mg, 0.093 mmol) in aq. THF (1.5 mL) at 0 °C. The reaction was allowed to warm to rt over 2 h until the complete conversion of mixture of **14** and **26** to a single spot of **14** was indicated by TLC analysis. The reaction was worked by extracting it in EtOAc (4 \times 15 mL), washing the organic phase with brine and drying over Na_2SO_4 . Removal of the solvent under reduced pressure followed by purification of the crude residue by SiO_2 -gel column chromatography using petroleum ether/ethyl acetate (7 : 3) as the eluent afforded **14** (32.8 mg, 0.085 mmol, 59% overall yield) as an orange solid, mp: 197.8–198.3 °C. IR (neat): ν_{\max} 2935, 2851, 1674, 1652, 1636, 1609, 1512, 1351, 1227, 1033 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.49 (s, 1H), 6.47 (s, 1H), 5.84 (s, 1H), 4.76 (t, $J = 5.6$ Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.73 (s, 6H), 3.22–3.08 (m, 2H), 1.76 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 187.64, 180.95, 158.42, 151.95, 148.62, 143.30, 140.50, 139.96, 126.81, 122.85, 121.59, 113.36, 106.71, 98.65, 57.46, 56.73, 56.08, 56.01, 39.47, 31.07, 18.51, 16.20. HRMS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{25}\text{O}_6$ ($\text{M} + \text{H}$) $^+$: 385.1646; found: 385.1675.

Gramineusquinone B (**3**)

To stirred solution of **14** (10 mg, 0.026 mmol) in DCM (1 mL) at 0 °C, DDQ (5.9 mg, 0.026 mmol) was added. The reaction



mixture was then allowed to warm to rt and stirred for another 5 h until complete consumption of starting material and formation of a new spot was indicated by the TLC analysis. The reaction was worked up by removing the solvent under reduced pressure and then subjecting the resultant residue to SiO₂ gel column chromatographic purification using hexane/ethyl acetate (7 : 3) as the eluent to arrive at **3** (9 mg, 0.023 mmol, 91% yield) as a red solid, mp: 172.6–173.3 °C. IR (neat): ν_{\max} 2937, 2842, 1685, 1648, 1617, 1517, 1213, 1085, 1031, 856, cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.96 (s, 1H), 6.63 (s, 1H), 6.40 (s, 1H), 6.06 (s, 1H), 3.95 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H), 3.65 (s, 3H), 2.45 (s, 3H), 2.01 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 185.52, 179.83, 160.77, 150.39, 148.94, 143.80, 143.76, 143.63, 139.41, 130.74, 127.21, 127.04, 120.48, 112.72, 108.03, 97.91, 56.57, 56.43, 56.23, 56.16, 21.47, 16.92. HRMS (ESI) m/z calcd for C₂₂H₂₃O₆ (M + H)⁺: 383.1489; found: 383.1481.

5,7,8-Trimethoxy-2,3-dimethyl-1-(2,4,5-trimethoxyphenyl)-1,4-dihydronaphthalene (iso-magnoshinin, **28**)

Reductive methylation on **14** (20 mg, 0.052 mmol) using 30% aq. Na₂S₂O₄ (2.5 mL, 4.310 mmol), MeI (0.42 mL, 6.756 mmol) and aqueous KOH (1 mL) through similar procedure as described for preparation of **20**, afforded compound **28** (20 mg, 0.048 mmol, 92% yield) as pale yellow solid. IR (neat): ν_{\max} 2932, 1602, 1509, 1462, 1439, 1336, 1316, 1238, 1203, 1033 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.51 (s, 1H), 6.41 (s, 1H), 6.40 (s, 1H), 5.04 (br s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.64 (s, 3H), 3.32 (s, 3H), 3.30 (br s, 2H), 1.78 (s, 3H), 1.64 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 152.27, 151.23, 150.78, 147.61, 143.20, 140.03, 134.46, 127.73, 127.11, 122.74, 116.70, 113.73, 97.90, 95.21, 59.81, 56.96, 56.55, 56.22, 56.04, 55.68, 39.47, 30.98, 19.03, 16.66. HRMS (ESI) m/z calcd for C₂₄H₃₄NO₆ (M + NH₄)⁺: 432.2381; found: 432.2353.

5,7,8-Trimethoxy-2,3-dimethyl-1-(2,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (2-*epi*-3,4-dihydro-magnoshinin, **29**)

To stirred solution of **28** (16 mg, 0.0386 mmol) in MeOH (1 mL) was added 10% Pd/C (1.6 mg). The mixture was then allowed to stir at room temperature under hydrogen balloon pressure for 6 h until complete consumption of starting material was indicated by TLC analysis. The reaction mixture was then filtered through celite, washed with EtOAc (4 × 5 mL) and the filtrate was concentrated under reduced pressure. The resultant crude residue was purified by flash column chromatography (petroleum ether/EtOAc = 8 : 2) on silica gel to afford the desired 2-*epi*-3,4-dihydro-magnoshinin, **29** (11 mg, 0.026 mmol, 68% yield). IR (neat): ν_{\max} 2932, 2834, 1596, 1509, 1462, 1395, 1333, 1233, 1204, 1039 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.56 (s, 1H), 6.42 (s, 1H), 6.23 (s, 1H), 4.80 (d, J = 6.0 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 3.60 (s, 3H), 3.20 (s, 3H), 2.62 (dd, J_1 = 4.5 Hz, J_2 = 17.0 Hz, 1H), 2.29 (ddd, J_1 = 1.2 Hz, J_2 = 12.0 Hz, J_3 = 17.0 Hz, 1H), 2.14–2.08 (m, 1H), 1.97–1.92 (m, 1H), 1.06 (d, J = 7.0 Hz, 3H), 0.52 (d, J = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 152.56, 151.04, 150.84, 146.97, 142.35, 142.16, 133.84, 126.26, 120.45, 113.80, 98.11, 95.64, 59.59,

57.28, 56.57 (2C), 56.11, 55.64, 40.31, 35.91, 32.80, 26.60, 19.61, 10.00. HRMS (ESI) m/z calcd for C₂₄H₃₆NO₆ (M + NH₄)⁺: 434.2537; found: 434.2571.

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