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Synthesis and structural elucidation of 2,3-dimethylnaphthazarin ester derivatives

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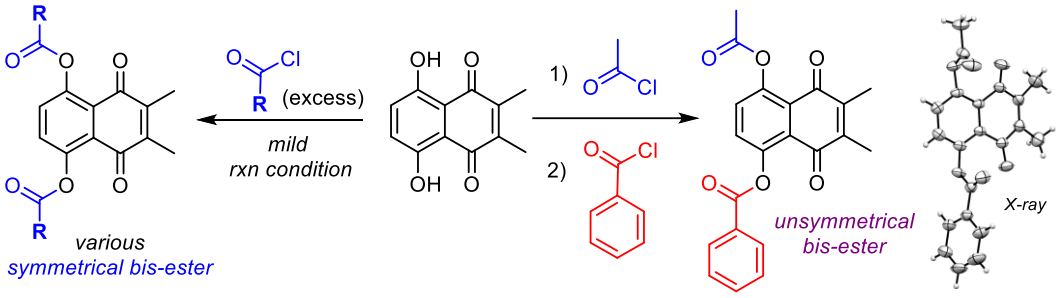
Abstract

A simple and efficient synthesis of bis-ester substituted 2,3-dimethylnaphthazarins is described. The preparation of 5-*O*,8-*O*-bis-ester derivatives of 2,3-dimethylnaphthazarin was achieved via double esterification reaction of 5,8-dihydroxy-2,3-dimethylnaphthazarin with a range of acyl chlorides under mild reaction conditions. Additionally, 5-*O*- mono ester and unsymmetrical 5-*O*,8-*O*-bis-ester derivatives of 2,3-dimethylnaphthazarins were successfully synthesized. The identities of new compounds were confirmed by ^{1}H NMR, ^{13}C NMR, FTIR, HRMS and X-ray single-crystal diffraction techniques.



Keywords: Naphthazarins, synthesis, esterification, structure elucidation

Introduction

Naphthazarin (5,8-dihydroxy-1,4-naphthoquinone) and congeners constitute an important class of compounds which have been isolated from natural sources and display a wide range of pharmacological activities.[1-3] Synthetic analogues of the naphthazarins also possess potent and often valuable biological activities such as antimicrobial, antibacterial, antiviral, anticancer, anti-inflammatory, analgesic and antithrombotic effects.[4-6] Well known naphthazarin-based compounds, such as Shikonin and its enantiomer Alkannin (Figure 1) have been isolated from in the roots of *Lithospermum erythrorhizon* and *Arnebia euchroma*.[5,7] Among the naphthazarin derivatives, 2,3-dimethylnaphthazarin (DMN) is of significant synthetic interest due to its biological activity.[8] In particular, bis-benzoyl ester dimethylnapthazarin derivatives have been reported to possess borderline inhibitory activity against leukemia P388 cells.[8] Apart from the pharmaceutical importance, DMN-based compounds have been employed as charge-transfer complexes.[9] Consequently, naphthazarin-containing analogues have been recognized as being of value and their synthesis has thus been targeted by organic chemists.

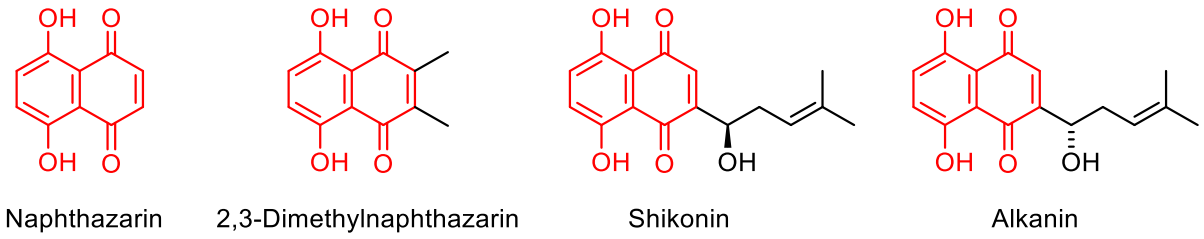


Figure 1. Naphthazarin and its biologically important derivatives.

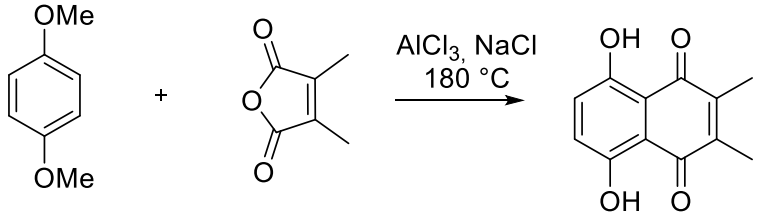
Limited synthetic approaches have been reported for the synthesis of DMN and its derivatives. One of the oldest methods was reported by Rodriguez in 1984 which involved a multi-step procedure including an initial cycloaddition between 2,3-dimethyl-1,3-butadiene and *p*-benzoquinone. This step was followed by acetylation and chromium trioxide oxidation of the resulting adducts and subsequent hydrolysis of the resultant naphthazarin diacetate.[9] In a similar manner, DMN has also been prepared from 1,3-butadiene and 2,3-dimethylquinone.[9] The most efficient, and more recent synthesis of DMN has been achieved in a one-pot process by the direct reaction of 2,3-dimethylmaleic anhydride and 1,4-dimethoxybenzene, in the presence of aluminum chloride and sodium chloride.[10] The main advantage of this latter method is that the DMN could be synthesized in relatively high yield from inexpensive commercial chemicals.

In conjunction with the synthetic efforts focused on naphthazarin, the presence of the hydroxyl groups, located at the C5 and C8 positions on the naphthazarin aromatic ring, should allow the synthesis of a range of targeted mono- and bis- ester compounds. It is known that a range of ester derivatives have been prepared from Shikonin and Alkannin, wherein the secondary alcohol functionality located on the side chain were converted to the corresponding *O*-ester.[11-12] However, (selective) derivatization of the parent DMN has rarely been studied in the literature,[10] presumably due to the harsh reaction conditions and multi-step processes involved in the previously reported synthetic routes. The current study presents the development of a general method for the synthesis of bis-ester 2,3-dimethylnaphthazarin derivatives from reaction of DMN with acyl chlorides under mild reaction conditions. The reaction is facilitated by the phenoxy groups located at the C5 and C8 positions and yields both mono-ester and unsymmetrical bis-ester derivatives of the parent 2,3-dimethylnaphthazarin.

Results and Discussion

In earlier studies, the synthesis of bis-acetyl and bis-benzoyl ester derivatives of 2,3-dimethylnapthazarin **5** and **12** were prepared via multi-step reactions, requiring harsh reaction conditions and long reaction times. For example, Cheng and coworkers reported the synthesis of bis-acetyl-2,3-dimethylnaphthazarin **5** in three steps starting from building the naphthoquinone platform *via* a Diels-Alder reaction of 2,3-dimethyl-1,3-butadiene and *p*-benzoquinone, followed by acetylation and oxidation with chromium trioxide.[8] The yield of the reaction was mentioned as extremely low and no characterization data was reported for the bis-acetate product **5**. Using the same synthetic route, the group also reported the synthesis of bis-benzoyl derivative **12** in three steps using benzoyl chloride as an acylation reagent. The overall yield for this reaction sequence was likewise very low, as the yield from the final oxidation was only 14%. In addition, the total reaction time was reported to be 32 hours. The detailed characterization data for derivative **12** was also not reported. In 1986, Rodriguez and coworkers reported the synthesis of the bis-acetyl ester of 2,3-dimethylnaphthazarin **5** following the same reaction sequence.[13] After building the naphthoquinone structure using a Diels-Alder reaction, treatment of the resulting adduct with acetic anhydride in acetic acid under reflux for 3 hours and subsequent oxidation with chromium trioxide generated product **5**. The final oxidation step provided bis-acetyl-2,3-dimethylnaphthazarin **5** in 35% yield and ^{1}H NMR characterization data of product **5** was provided. To best of our knowledge, there is no other study in the literature for the synthesis of symmetrical bis-ester derivatives of the parent 2,3-dimethylnapthazarin. In addition to this, the preparation of mono-ester or unsymmetrical bis-ester derivatives of DMN have not been reported thus far.

In order to bridge this gap, DMN **3** was synthesized by following a literature procedure[10] involving a double Friedel-Craft acylation reaction between 1,4-dimethoxybenzene **1** and 2,3-dimethylmaleic anhydride **2** in the presence of molten form of aluminum chloride-sodium chloride, providing DMN **3** in an isolated yield of 37% (Scheme 1).

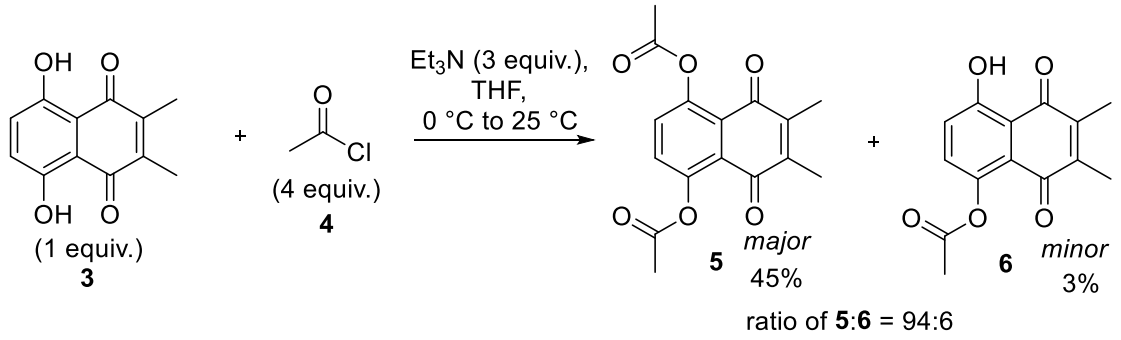


1 **2** **3**

Scheme 1. Synthesis of 2,3-dimethylnaphthazarin.

With DMN **3** in hand, reaction conditions for its double esterification were investigated using acetyl chloride **4** as an acylation reagent. Initially, one equivalent of naphthazarin **3** was treated with three equivalents of base at room temperature, followed by four equivalents of acetyl chloride and the reaction progress was monitored by TLC analysis. When potassium carbonate or pyridine was used as the base, only a trace amount of the target product **5** was isolated. When the base was changed to triethylamine, the reaction gave the targeted bis-ester **5** in 28% yield along with its mono-ester, 5-*O*-acetyl-2,3-dimethylnaphthazarin **6**, in 4% yield. Following optimization, it was found that the treatment of naphthazarin **3** with three equivalents of triethylamine at room temperature for 30 minutes, followed by the addition of acetyl chloride **4** at 0 °C and subsequent warming to room temperature provided the highest yield of the target product **5** in 45% yield, along

with the 5-*O*-acetyl-mono-ester **6** in 3% yield (Scheme 2). The structures of products **5** and **6** were elucidated by a detailed one- and two-dimensional NMR spectroscopy investigation, as well as being fully characterized using FTIR, HRMS and finally confirmed by single crystal X-ray analysis (Figure 2).



Scheme 2. Optimized reaction conditions for the double esterification of 2,3-dimethylnaphthazarin **3**.

The ^{1}H NMR spectrum of the bis-ester **5** at room temperature in $CDCl_3$ is consistent with that reported in the literature.[13] The most important evidence for successful double esterification of **3** is the disappearance of both of the phenolic O***H*** signals which initially appear as a singlet at δ12.63 ppm due to intramolecular hydrogen-bonding interaction between the carbonyl oxygen of quinonoid ring and the proton of phenolic hydroxyl group proton in the aromatic ring of **3**. The appearance of a new singlet signal at δ2.44 ppm in the proton NMR spectrum of **5** was associated with the protons of the two acetyl ester C***H₃*** group. In the ^{13}C NMR spectrum of the bis-product **5**, the appearance of new signals in the high field region was associated with acetyl methyl ***C***H_3 carbons (δ21.2 ppm), while additional signals in the low field region were associated with the acetyl ester carbonyl ***C***=O carbons (δ 169.5 ppm), proving that the double esterification of **3** has taken place. High-resolution mass spectrometry indicated that the molecular ion of product **5** has a mass to charge ratio of 325.0676, consistent with the molecular formula $C_{16}H_{14}O_6$ $[M+Na]^+$. The structure of bis-ester **5** was further confirmed by single crystal X-ray crystallography analysis (Figure 2).

The new minor mono-ester **6** was also fully characterized. HRMS showed that the molecular ion of product **6** has a mass to charge ratio of 260.0686, consistent with the molecular formula $C_{14}H_{12}O_5$ $[M]^+$. Finally, an analytical sample of mono-ester **6** was successfully recrystallized and its structure was also confirmed by single crystal X-ray (Figure 2).

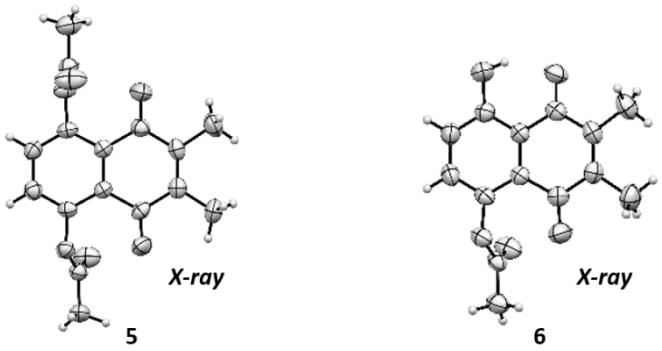
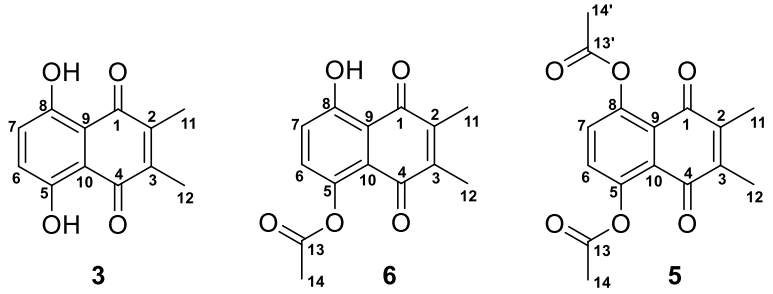


Figure 2. X-ray structures of 5-*O*,8-*O*-diacetyl-bis-ester **5** and 5-*O*-acetyl-mono-ester **6** derivatives of 2,3-dimethylnaphthazarin.

The structure of mono-ester **6** was elucidated with further NMR experiments, namely APT NMR, 2-dimensional ^{1}H -^{1}H (COSY), and ^{1}H-^{13}C (HMQC, HMBC) correlation experiments in $CDCl_3$ at room temperature. In the ^{1}H NMR spectrum of **6**, only one phenolic O***H*** signal was observed at δ12.62 ppm as a singlet. This signal proved that the single esterification took place. As mono-ester **6** is not symmetrical, unlike the starting material DMN **3** and bis-ester **5**, both of the methyl group C***H₃*** protons on the quinonoid ring give different proton resonances as singlets at δ2.15 and 2.12 ppm. The ^{13}C NMR spectrum of mono-ester **6** showed the methyl ***C***H_3 carbons on quinonoid ring at different chemical shifts of δ13.2 and 12.3 ppm. The signals appearing at δ21.2 ppm and 169.8 ppm associated with the acetyl ester methyl carbon ***C***H_3 and carbonyl carbon ***C***=O, respectively. It is worth to note that while the carbonyl carbon signal (C1) on the quinonoid ring shifted to downfield region and appears at δ189.9 ppm, the other carbonyl carbon signal (C4) resonates at δ182.9 ppm, which is further upfield when compared to the starting material **3** (δ186.5 ppm) (Table 1). It shows that the carbonyl oxygen C=**O** at C1 is intramolecularly hydrogen bonded with the phenolic O***H*** proton of the aromatic ring, whereas the C4 carbonyl oxygen is not. Additionally, carbon atoms attached to the phenolic hydroxyl group showed significant chemical shift differences. For example, the phenoxy group attached to carbon C8 of mono-ester **6** resonated at δ159.9 ppm, similar to DMN **3** (Table 1). However, once the phenolic hydroxyl group was converted into the corresponding ester derivative **5**, the carbon atom (C5) signal at the aromatic ring appeared in the far upfield region at δ142.6 ppm, as compared to DMN **3** (δ158.6) (Table 1). Another important chemical shift difference was observed at the fused carbon atoms such as C10, which is next to the acetyl substituted carbon (C5) on the aromatic ring, which resonated downfield at δ122.1 ppm, whereas carbon C9, neighboring to phenolic hydroxyl substituted carbon (C8), resonated at δ114.8 ppm. On the contrary, the fused carbon signals of bis-ester **5** appeared in the far downfield region at δ124.7 ppm (Table 1).

In order to extend this study to generate a variety of new 2,3-dimethylnaphthazarin bis-ester derivatives, various commercially available aromatic acyl , such as benzoyl, *p*-methyl-, *p*-bromo-, *p*-methoxy-, and *p*-nitrobenzoyl chlorides (**7-11**), were also used (Table 2). The esterification reaction was performed using the optimum reaction conditions as described earlier. The reaction progress was monitored by TLC analysis and the reaction was worked up once no further change was observed on the TLC. It was found that the reaction with *p*-bromobenzoyl chloride **9** was completed in 1.5 hours, whereas the reaction with benzoyl chloride **7** took 22 hours; both of them gave bis-ester **14** and **12** in 30% and 23% yield, respectively, as sole products (Table 2). The reaction with *p*-methylbenzoyl chloride **8** resulted in bis-adduct **13** as major product in 30% yield, along with mono-ester **17** in 5% yield, while the reaction with *p*-nitrobenzoyl chloride **11** gave bis-ester **16** and mono-ester **19** products, 21% and 27%, respectively. In contrast, the reaction between 2,3-dimethylnapthazarin **3** and *p*-methoxybenzoyl chloride **10** resulted in mono-ester **18** in 73% yield as a major product along with bis-ester **15** in 13% yield as the minor product.

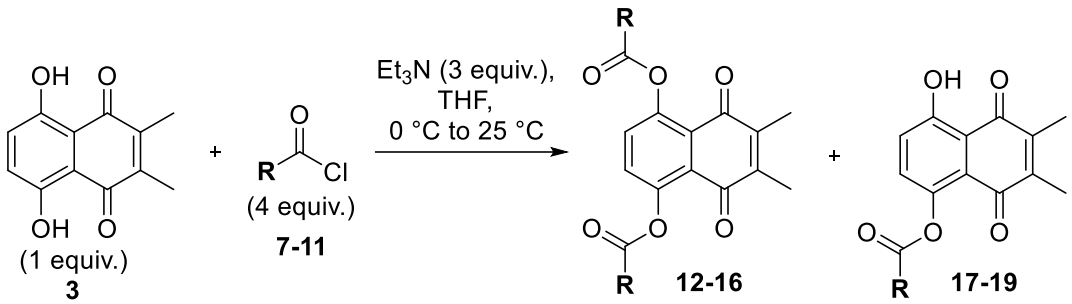
Table 1. ^{1}H and ^{13}C NMR chemical shifts of DMN **3**, 5-*O*-acetyl mono-ester **6**, and 5-*O*,8-*O*-diacetyl bis-ester **5**

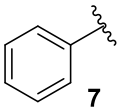
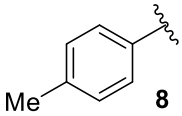
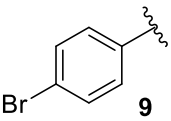
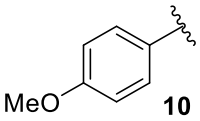
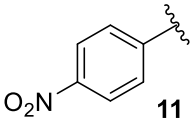


Position	DMN **3**		Mono-ester **6**		Bis-ester **5**	
	δ_H / ppm	δ_C / ppm	δ_H / ppm	δ_C / ppm	δ_H / ppm	δ_C / ppm
1	-	186.5	-	189.9	-	183.2
2	-	144.5	-	142.3	-	143.5
3	-	144.5	-	145.8	-	143.5
4	-	186.5	-	182.9	-	183.2
5	12.63 (O*H*)	158.6	-	142.6	-	147.3
6	7.20	129.4	7.24	132.6	7.32	130.3
7	7.20	129.4	7.23	125.5	7.32	130.3
8	12.63 (O*H*)	158.6	12.62 (O*H*)	159.9	-	147.3
9	-	111.7	-	114.8	-	124.7
10	-	111.7	-	122.1	-	124.7
11	2.20	12.6	2.15	12.3	2.08	13.0
12	2.20	12.6	2.12	13.2	2.08	13.0
13	NA	-	-	169.8	-	169.5
14	NA	-	2.42	21.2	2.44	21.2
13´	NA	-	NA	-	-	169.5
14´	NA	-	NA	-	2.44	21.2

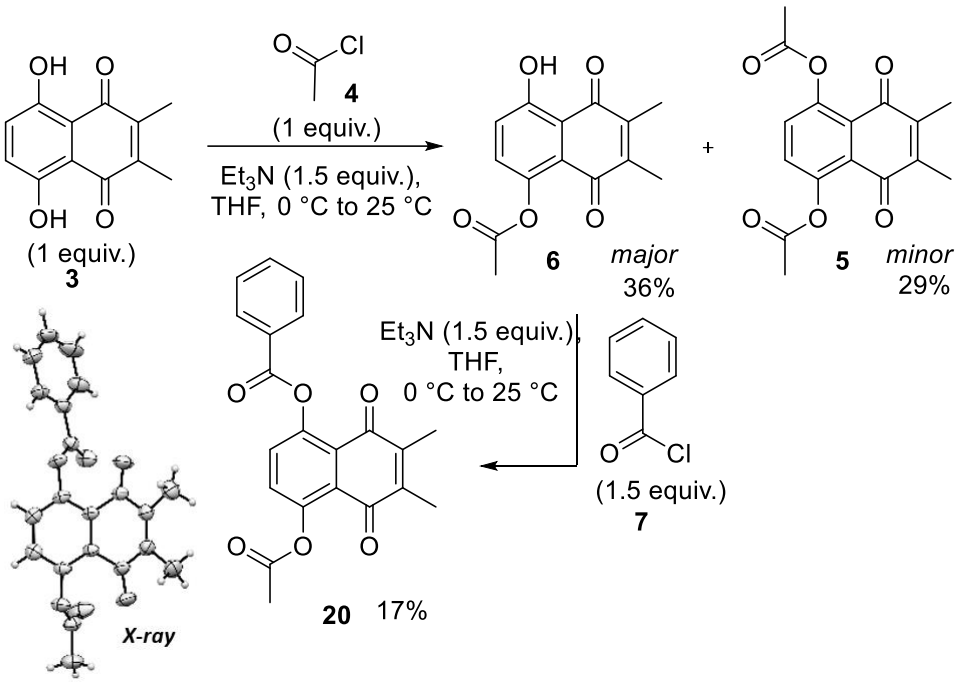
^{1}H NMR (in $CDCl_3$, 500 MHz), ^{13}C NMR (in $CDCl_3$, 125 MHz).

Table 2. Synthesis of *symmetrical* bis-ester derivatives of 2,3-dimethylnaphthazarin



Acyl chloride (4 equiv.)	Time (hours, h)	Bis-ester (isolated yield, %)	Mono-ester (isolated yield, %)
 **7**	22 h	**12** (23%)	-
 Me **8**	1.5 h	**13** (30%)	**17** (5%)
 Br **9**	1.5 h	**14** (30%)	-
 MeO **10**	2.5 h	**15** (13%)	**18** (73%)
 O_2N **11**	22 h	**16** (21%)	**19** (27%)

Following the successful synthesis of symmetrical bis-ester derivatives of DMN (**5**,**12-16**), the synthesis of an *unsymmetrical* bis-ester of DMN was examined. By using similar reaction conditions, that is treating one equivalent of DMN **3** with one equivalent of acetyl chloride **4** in THF, 5-*O*-acetyl-mono-ester **6** was generated in 36% yield, bis-ester **5** in 29% yield, while 3% of unreacted DMN **3** was recovered (Scheme 3). One equivalent of mono-ester **6** was then treated with one and a half equivalents of benzoyl chloride **7** at room temperature, in the presence of one and a half equivalents of triethylamine and THF, to result in the *unsymmetrical* bis-ester **20** in 17% yield (Scheme 3). This product **20** was fully characterized using spectroscopic methods and its structure was also confirmed by single crystal x-ray crystallography.



Scheme 3. Synthesis of *unsymmetrical* 2,3-dimethylnaphthazarin bis-ester **20**.

Conclusions

In summary, a variety of new ester derivatives of 2,3-dimethylnaphthazarin was achieved under mild reaction conditions in one step. These new dimethylnaphthazarin structures have considerable potential for development in areas including medicinal chemistry. Additionally, mono-ester derivatives create an opportunity to generate a library of *unsymmetrical* bis-substituted naphthazarins, and this work is currently in progress.

Experimental Section

General Information. Reactions were performed under a positive pressure of nitrogen or argon in oven or flame dried glassware, unless otherwise specified. All reagents and solvents were obtained from commercial sources and appropriately purified, if necessary. Anhydrous THF was dried over sodium wire and distilled from sodium benzophenone ketyl. ^{1}H and ^{13}C NMR spectra were recorded at 298 K on a Varian 500 MHz NMR spectrometer. The deuterated solvent (deutero chloroform ($CDCl_3$) for NMR spectroscopy was obtained from Merck. The central line of the residual chloroform ($CHCl_3$ in $CDCl_3$) (δ = 7.26 ppm) and triplet (δ = 77.10 ppm) was used for ^{1}H NMR and ^{13}C NMR spectra as an internal reference, respectively. The following abbreviations and combinations thereof are used to describe ^{1}H NMR spectra multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad. Assignment of proton signals was assisted by COSY experiment where necessary. Assignment of carbon signals was assisted by APT, HMBC, and HSQC experiment where necessary. IR spectra were recorded on between 4000 and 650 cm^{-1} using a Perkin Elmer Spectrum 100 FT-IR spectrometer with an attenuated total reflection (ATR) accessory. Mass spectra were recorded on a Thermo ORBITRAP Q-EXACTIVE mass spectrometer (Bremen, Germany) equipped with a Troyasil (Istanbul Turkiye) C18 column (150 x 3 mm i.e., 3 µm particle size) for measurements of HRMS. Melting points were measured using a Stuart SMP10

melting point apparatus. Analytical TLC was performed with Merck silica gel plates, precoated with silica gel 60 F254 (0.2 mm) on aluminium sheets and visualized using UV fluorescence (λmax = 254 nm). Flash column chromatography employed Merck Kieselgel 60 (230–400 mesh) silica gel.

Experimental procedures and characterization data

5,8-Dihydroxy-2,3-dimethylnaphthalene-1,4-dione (DMN) (3). This compound **3** was prepared following the literature procedure.[10] A two necked 100 mL reaction flask was charged with dry $AlCl_3$ (6.0 g, 45 mmol) and NaCl (1.35 g, 23 mmol) under nitrogen gas atmosphere. The mixture stirred and heated to 180 °C to provide a melt. To this was carefully added 1,4-dimethoxybenzene **1** (0.69 g, 5.0 mmol) and 2,3-dimethylmaleic anhydride **2** (1.9 g, 15 mmol) portion-wise (4 portions) which resulted in a dark red mixture. The reaction mixture was heated to 200 °C and maintained at this temperature for 5 minutes. After gas evolution ceased the reaction mixture was cooled to 100 °C, after which a ice-cold solution of 10% HCl (60 mL) was carefully added portion-wise (10 mL/each portion) to afford a maroon-coloured suspension. The reaction mixture was then allowed to cool to room temperature and stirred for overnight. The resulting mixture was extracted with DCM (5 x 20 mL) and the organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product as a red solid (1.84 g). Purification by flash column chromatography (SiO_2, acetone:hexane (15:85)) gave the title compound **3** (0.41 g, 1.87 mmol, 37% yield) as a red shiny solid, as well as recovered 2,3-dimethylmaleic anhydride **2** (0.71 g). R_f 0.43 (acetone:hexane (10:90)); mp 166-168 °C.[13] The ^{1}H NMR spectroscopy data for 2,3-dimethylnaphthazarin (DMN) **3** was in agreement with that reported in the literature.[10] ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.63 (s, 2H), 7.20 (s, 2H), 2.20 (s, 6H) ppm.

General Procedure-1. Double esterification reactions of 2,3-dimethylnaphthazarin (DMN). To a stirred solution of 2,3-dimethylnaphthazarin (DMN) **3** in dry THF under argon atmosphere at room temperature, dry three equivalents of Et_3N was added dropwise and the dark red colour reaction mixture was stirred for 30 minutes at 25 °C in the dark. The reaction mixture was then cooled to 0 °C and stirred for 10 minutes before four equivalents of an acyl chloride was added. The resulting reaction mixture was then warmed to room temperature and stirred for **1.5-22** hours. The reaction solvent was then removed by rotary evaporator and the resulted residue subjected to quick filtration using SiO_2. The solvent of the collected fractions were then concentrated and subjected to column chromatography to give the target product.

6,7-Dimethyl-5,8-dioxo-5,8-dihydronaphthalene-1,4-diyl diacetate (5). The bis-acetylester DMN **5** was synthesized following general procedure-1 using DMN **3** (50 mg, 0.23 mmol) and acetyl chloride **4** (65 µL, 0.92 mmol) in dry THF (5.0 mL) and dry Et_3N (96 µl, 0.69 mmol). The reaction mixture was stirred at 25 °C for 3 hours. The resulting reaction solvent was then removed by rotary evaporator and the crude material was subjected to column chromatography (EtOAc:Hexane (20:80)) to give the target bis-ester compound **5** (31 mg, 45%) as orange colour solid, along with the mono-ester by-product **6** (2 mg, 3%) as yellow coloured solid. The ^{1}H NMR data for bis-acetyl-2,3-dimethylnaphthazarin **5** was in agreement with that reported in the literature.[13] An analytical sample of **5** was obtained by recrystallization from dichloromethane/hexane to give yellow color needles. R_f 0.24 (in ethyl acetate:hexane (20:80)); mp 185-187 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (s, 2H), 2.44 (s, 6H), 2.08 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 183.2, 169.5, 147.3, 143.5, 130.3, 124.7, 21.2, 13.0 ppm; FT-IR: $\bar{\nu}_{max}$ 3081, 3007, 1753, 1647, 1589, 1466, 1369, 1263, 1182, 937, 764 cm^{-1}; HRMS: calc for $C_{16}H_{14}O_6$ $[M+Na]^+$: 325.0688; found 325.0676.

4-Hydroxy-6,7-dimethyl-5,8-dioxo-5,8-dihydronaphthalen-1-yl acetate (6). R_f 0.37 (in ethyl acetate:hexane (20:80)); mp 143-145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.62 (s, 1H), 7.24 (s, 1H), 7.23 (s, 1H), 2.42 (s, 3H), 2.15 (s, 3H), 2.12 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.9, 182.9, 169.8, 159.9, 145.8, 142.6, 142.3, 132.6, 125.5,

122.1, 114.8, 21.2, 13.2, 12.3 ppm; FT-IR: $\bar{\nu}_{max}$ 2920, 2850, 1757, 1652, 1634, 1618, 1461, 1435, 1359, 1280, 1186, 1011, 786 cm^{-1}; HRMS: calc for $C_{14}H_{12}O_5$ $[M]^+$: 260.0685; found 260.0686.

6,7-Dimethyl-5,8-dioxo-5,8-dihydronaphthalene-1,4-diyl dibenzoate (12). The bis-benzoylester DMN **12** was synthesized following general procedure-1 using DMN **3** (50 mg, 0.23 mmol) and benzoyl chloride **7** (0.27 mL, 2.3 mmol) in dry THF (5.0 mL) and dry Et_3N (96 µl, 0.69 mmol). The reaction mixture was stirred at 25 °C for 22 hours. The resulting reaction solvent was then removed by rotary evaporator and the crude material was subjected to column chromatography (EtOAc:Hexane (20:80)) to give the compound **12** (22 mg, 23%) as an orange coloured solid. An analytical sample of **12** was obtained by recrystallization from dichloromethane/hexane to give orange color needles. R_f 0.67 (in dichloromethane); mp 274-276 °C;[8] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (dd, *J* 11.3, 10.0 Hz, 4H), 7.71 – 7.65 (m, 2H), 7.60 – 7.53 (m, 4H), 7.51 (s, 2H), 2.04 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.2, 165.2, 147.7, 143.5, 133.8, 130.6, 130.5, 129.4, 128.8, 125.1, 13.0 ppm; FT-IR: $\bar{\nu}_{max}$ 2919, 1733, 1650, 1636, 1584, 1491, 1466, 1450, 1418, 1262, 1219, 1064, 702 cm^{-1}; HRMS: calc for $C_{26}H_{18}O_6Na$ $[M+Na]^+$: 449.1001; found 449.0988.

6,7-Dimethyl-5,8-dioxo-5,8-dihydronaphthalene-1,4-diyl bis(4-methylbenzoate) (13). The bis-*p*-methylbenzoylester DMN **13** was synthesized following general procedure-1 using DMN **3** (50 mg, 0.23 mmol) and *p*-methylbenzoyl chloride **8** (0.12 mL, 0.92 mmol) in dry THF (2.0 mL) and dry Et_3N (96 µl, 0.69 mmol). The reaction mixture was stirred at 25 °C for 1.5 hours. The resulting reaction solvent was then removed by rotary evaporator and the crude material was subjected to column chromatography (EtOAc:Hexane (20:80)) to give the compound **13** (31 mg, 30%) as yellow coloured solid along with by product mono-ester **17** (4 mg, 5%) as an orange-coloured solid. R_f 0.64 ((in dichloromethane:ethanol (99:1)); mp 265-267 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm; NMR (500 MHz,) δ 8.15 (d, *J* 8.0 Hz, 4H), 7.49 (s, 2H), 7.36 (d, *J* 8.0 Hz, 4H), 2.48 (s, 6H), 2.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.15, 165.21, 147.67, 144.68, 143.48, 130.61, 130.49, 129.48, 126.69, 125.10, 21.91, 12.99; FT-IR: $\bar{\nu}_{max}$ 2916, 1752, 1743, 1658, 1578, 1271, 1223, 1178, 1077, 734 cm^{-1}; HRMS: calc for $C_{28}H_{22}O_4Na$ $[M+Na]^+$: 477.1314; found 477.1303.

4-Hydroxy-6,7-dimethyl-5,8-dioxo-5,8-dihydronaphthalen-1-yl 4-methylbenzoate (17). R_f 0.37 (in ethylacetate:hexane (20:80)); mp 249-251 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.68 (s, 1H), 8.13 (d, *J* 8.0 Hz, 2H), 7.37 – 7.31 (m, 3H), 7.31 – 7.27 (m, 1H), 2.47 (s, 3H), 2.14 (s, 3H), 2.07 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.0, 182.7, 165.4, 159.9, 146.0, 144.6, 142.8, 142.2, 132.9, 130.5, 129.5, 126.8, 125.4, 122.5, 114.9, 21.9, 13.3, 12.3 ppm; FT-IR: $\bar{\nu}_{max}$ 2919, 2850, 1727, 1687, 1614, 1469, 1225, 1086, 1059, 737 cm^{-1}; HRMS: calc for $C_{20}H_{16}O_5Na$ $[M+Na]^+$: 359.0895; found 359.0884.

6,7-Dimethyl-5,8-dioxo-5,8-dihydronaphthalene-1,4-diyl bis(4-bromobenzoate) (14). The bis-*p*-bromobenzoylester DMN **14** was synthesized following general procedure-1 using DMN **3** (50 mg, 0.23 mmol) and *p*-bromobenzoyl chloride **9** (0.20 g, 0.92 mmol) in dry THF (2.0 mL) and dry Et_3N (96 µl, 0.69 mmol). The reaction mixture was stirred at 25 °C for 1.5 hours. The resulting reaction mixture subjected a quick filtration with silica gel and combined fraction solvent was then removed by rotary evaporator. The crude material was subjected to column chromatography eluting with dichloromethane to give the compound **14** (40 mg, 30%) as orange-coloured solid. R_f 0.59 (in dichloromethane); mp 293-295 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* 8.3 Hz, 4H), 7.71 (d, *J* 8.4 Hz, 4H), 7.50 (s, 2H), 2.03 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.1, 164.5, 147.5, 143.6, 132.2, 132.1, 130.4, 129.2, 128.3, 125.0, 13.0 ppm; FT-IR: $\bar{\nu}_{max}$ 1743, 1657, 1584, 1465, 1377, 1222, 1078, 1010, 843, 741 cm^{-1}; HRMS: calc for $C_{26}H_{16}{}^{81}Br_2O_6$ $[M]^+$: 608.9191; found 608.9166, calc for $C_{26}H_{16}{}^{81}Br^{79}BrO_6$ $[M]^+$: 606.9191; found 606.9176; calc for $C_{26}H_{16}{}^{79}BrO_6$ $[M]^+$: 604.9211; found 604.9207.

6,7-Dimethyl-5,8-dioxo-5,8-dihydronaphthalene-1,4-diyl bis(4-methoxybenzoate) (15). The bis-*p*-methoxybenzoylester DMN **15** was synthesized following general procedure-1 using DMN **3** (50 mg, 0.23 mmol) and *p*-methoxybenzoyl chloride **10** (0.15 g, 0.92 mmol) in dry THF (2.0 mL) and dry Et_3N (96 µl, 0.69 mmol). The

reaction mixture was stirred at 25 °C for 2.5 hours. The resulting reaction mixture subjected a quick filtration with silica gel and combined fraction solvent was then removed by rotary evaporator. The crude material was subjected to column chromatography (dichloromethane:hexane (90:10)) to give the target bis-product **15** (15 mg, 13%) as yellow-coloured solid, along with mono-product **18** (59 mg, 73%) as by-product as an orange-coloured solid. R_f 0.30 (in dichloromethane:hexane (90:10)); mp 240-242 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* 8.7 Hz, 4H), 7.48 (s, 2H), 7.03 (d, *J* 8.7 Hz, 4H), 3.91 (s, 6H), 2.03 (s, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.2, 164.8, 164.1, 147.7, 143.5, 132.7, 130.5, 125.1, 121.8, 114.1, 55.6, 13.0 ppm; FT-IR: $\bar{\nu}_{max}$ 1752, 1660, 1608, 1578, 1511, 1224, 1167, 1080, 840, 682 cm^{-1}; HRMS: calc for $C_{28}H_{22}O_8$ $[M+Na]^+$: 509.1212; found 509.1203.

4-Hydroxy-6,7-dimethyl-5,8-dioxo-5,8-dihydronaphthalen-1-yl 4-methoxybenzoate (18): R_f 0.49 (in dichloromethane:hexane (90:10)); mp 167-169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.67 (s, 1H), 8.19 (d, *J* 8.7 Hz, 2H), 7.34 (d, *J* 9.1 Hz, 1H), 7.28 (d, *J* 9.1 Hz, 1H), 7.01 (d, *J* 8.8 Hz, 2H), 3.90 (s, 3H), 2.14 (s, 3H), 2.07 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.0, 182.7, 165.0, 164.1, 159.9, 146.0, 142.9, 142.1, 133.0, 132.6, 125.3, 122.5, 121.9, 114.8, 114.0, 55.6, 13.28, 12.3 ppm; FT-IR: $\bar{\nu}_{max}$ 2928, 2845, 1788, 1721, 1638, 1610, 1582, 1470, 1263, 1243, 1219, 1058, 1028 cm^{-1}; HRMS: calc for $C_{20}H_{16}O_6$ $[M-H]^+$: 351.0869; found 351.0875.

6,7-Dimethyl-5,8-dioxo-5,8-dihydronaphthalene-1,4-diyl bis(4-nitrobenzoate) (16). The bis-*p*-nitrobenzoylester DMN **16** was synthesized following the general procedure-1 using DMN **3** (50 mg, 0.23 mmol) and *p*-nitrobenzoyl chloride **11** (0.17 g, 0.92 mmol) in dry THF (5.0 mL) and dry Et_3N (96 µl, 0.69 mmol). The reaction mixture was stirred at 25 °C for 22 hours. The resulting reaction solvent was then removed by rotary evaporator and the crude material was subjected to column chromatography eluting with (EtOAc:Hexane (20:80)) to give the compound **16** (19 mg, 21%) as yellow colour solid along with mono-ester **19** (23 mg, 27%) as orange-coloured solid. An analytical sample of **16** was obtained by recrystallization from dichloromethane/hexane to give orange-colored needles. R_f 0.42 (in dichloromethane); mp 259-261 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, *J* 8.3 Hz, 4H), 8.41 (d, *J* 8.2 Hz, 4H), 7.56 (s, 2H), 2.04 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.9, 163.4, 151.1, 147.4, 143.8, 134.8, 131.7, 130.4, 124.8, 123.9, 13.0 ppm; FT-IR: $\bar{\nu}_{max}$ 3113, 1742, 1657, 1526, 1348, 1323, 1267, 1221, 1084, 842, 707 cm^{-1}; HRMS: calc for $C_{26}H_{16}N_2O_{10}$ $[M]^+$: 516.0805; found 516.0811.

4-Hydroxy-6,7-dimethyl-5,8-dioxo-5,8-dihydronaphthalen-1-yl 4-nitrobenzoate (19). R_f 0.53 (in dichloromethane); mp 198-200 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.65 (s, 1H), 8.44 – 8.40 (m, 2H), 8.40 – 8.36 (m, 2H), 7.37 (d, *J* 9.1 Hz, 1H), 7.32 (d, *J* 9.1 Hz, 1H), 2.16 (s, 3H), 2.06 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.8, 182.8, 163.6, 160.2, 151.0, 145.82, 142.6, 142.0, 135.0, 132.3, 131.6, 125.6, 123.8, 122.1, 114.9, 13.2, 12.4 ppm; FT-IR: $\bar{\nu}_{max}$ 3118, 2922, 2853, 1731, 1664, 1638, 1617, 1520, 1470, 1349, 1262, 1243, 1225, 1095, 1064, 850, 709 cm^{-1}; HRMS: calc for $C_{19}H_{12}NO_7$ $[M-H]^+$: 366.0614; found 366.0619.

4-Hydroxy-6,7-dimethyl-5,8-dioxo-5,8-dihydronaphthalen-1-yl acetate (6). DMN **3** (0.10 g, 0.46 mmol) was dissolved in dry THF (10 mL) and one and a half equivalents of dry Et_3N (96 µl, 0.69 mmol) was added slowly. The reaction mixture was stirred for 30 minutes at room temperature and then one equivalent of acetyl chloride **4** (33 µL, 0.46 mmol) was added slowly. The resulting reaction mixture was stirred at 25 °C for 20 hours. The resulting reaction solvent was then removed by rotary evaporator and the crude material was subjected to column chromatography (EtOAc:Hexane (20:80)) to give the target mono-ester compound **6** (43 mg, 36%) as an orange-coloured solid, along with the bis-ester **5** by-product (20 mg, 29%) as yellow-coloured solid. An analytical sample of **6** was obtained by recrystallization from dichloromethane/hexane to give orange color needles. R_f 0.37 (in ethylacetate:hexane (20:80)); mp 143-145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.62 (s, 1H), 7.24 (s, 1H), 7.23 (s, 1H), 2.42 (s, 3H), 2.15 (s, 3H), 2.12 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.9, 182.9, 169.8, 159.9, 145.8, 142.6, 142.3, 132.6, 125.5, 122.1, 114.8, 21.2, 13.2, 12.3 ppm; FT-IR: $\bar{\nu}_{max}$ 2920, 2850, 1757, 1652, 1634, 1618, 1461, 1435, 1359, 1280, 1186, 1011, 786 cm^{-1}; HRMS: calc for $C_{14}H_{12}O_5$ $[M]^+$: 260.0685; found 260.0686.

4-Acetoxy-6,7-dimethyl-5,8-dioxo-5,8-dihydronaphthalen-1-yl benzoate (20). To a stirred mixture of mono-asetil-DMN **6** (40 mg, 0.15 mmol) in dry THF (3.0 mL) was added one and a half equivalents of dry Et_3N (32 µl, 0.23 mmol) dropwise at 25 °C and stirred for 30 minutes. The reaction mixture was cooled to 0 °C and one and a half equivalents of benzoyl chloride **7** (27 µl, 0.23 mmol) was slowly added. The reaction mixture was warmed to 25 °C and stirred for 2 days. The resulting reaction solvent was then removed by rotary evaporator and the crude material was subjected to column chromatography eluting with dichloromethane to give the compound **20** (9.5 mg, 17%) as yellow-coloured solid. An analytical sample of **20** was obtained by recrystallization from dichloromethane/hexane to give yellow color needles. R_f 0.28 ((in ethylacetate:hexane (20:80)); mp 190-192 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 – 8.23 (m, 2H), 7.70 – 7.64 (m, 1H), 7.55 (t, *J* 7.8 Hz, 2H), 7.45 (d, *J* 8.8 Hz, 1H), 7.37 (d, *J* 8.8 Hz, 1H), 2.46 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.3, 183.1, 169.6, 165.1, 147.6, 147.4, 143.6, 143.4, 133.8, 130.6, 130.5, 130.3, 129.4, 128.8, 125.0, 124.8, 21.2, 13.0, 13.0 ppm; FT-IR: $\bar{\nu}_{max}$ 2919, 1758, 1729, 1658, 1630, 1587, 1449, 1324, 1253, 1220, 1185, 1023, 992, 705 cm^{-1}; HRMS: calc for $C_{21}H_{16}O_6$ $[M+H]^+$: 365.1025; found 365.1014.

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Supplementary Material

NMR spectra are provided in the supplementary material file. Additional crystallographic data with CCDC reference numbers 1948087 (**5**), 1946392 (**6**), 2048115 (**12**), 2184617 (**19**), and 2184607 (**20**) have been deposited within the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/deposit

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