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Graphical Abstract

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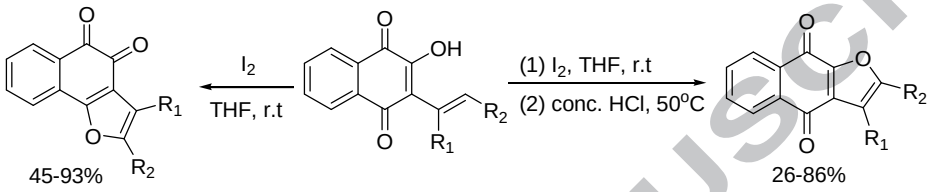

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The iodine-mediated highly regioselective synthesis of angular and linear naphthofuroquinones

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ABSTRACT

Naphthofuroquinones are of great value in medicinal chemistry. In this letter, a facile method for highly regioselective synthesis of both linear and angular naphthofuroquinones has been developed via iodine mediated cyclization of 2-hydroxy-3-substitutedvinyl-1, 4-naphthoquinones under very mild conditions.

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Both linear and angular naphthofuroquinones are of great interest to medicinal chemists mostly owing to the presence of a number of naturally occurring bioactive naphthofuroquinone derivatives. For instance, linear naphthofuroquinones **1-4** (Fig. 1), isolated from Bignoniaceae family, have shown promising anti-tumor activity against a variety types of cancer cell lines.[1] Especially, 2-acetylnaphthofuroquinone **3** has been successfully launched into a phase Ib clinical trial recently as a novel cancer stem cell inhibitor.[2] Naphtho[1,2-*b*]furan-4,5-dione (**5**, Fig. 1), an angular naphthofuroquinone from *Avicennia marina*, also exhibited very potent antitumor activities through inactivating EGFR and PI3K/Akt signaling pathways.[3] Tanshinone IIA (**6**, Fig. 1), a major bioactive constituent from *Salvia miltiorrhiza* Bunge is used in China and other neighboring countries for the treatment of cardiac and vascular disorders.[4] Tanshinone IIA and its derivatives also displayed some other intriguing activities, such as neuroprotection and anti-tumor.[5]

The synthesis of naphthofuroquinones has been extensively studied and a variety of protocols have been developed, including three-component condensation of 2-hydroxy-1,4-naphthoquinone, isocyanide and aldehyde,[6] cycloaddition of 2-hydroxy-1,4-naphthoquinone with 3,4-dibromo-2-butanone followed by oxidation with MnO_2,[7] CAN-mediated oxidative cycloaddition of 2-hydroxy-1,4-naphthoquinone with vinyl sulfide followed by oxidative elimination of a thiol,[8] CAN-mediated oxidative cycloaddition of 2-hydroxy-1,4-naphthoquinone with enol ether followed by elimination of an alcohol,[8a,9] oxidative cyclization of the 2-hydroxy-3-butenyl-1,4-naphthoquinone with mercuric acetate[10] or DDQ[11], Sonogashira coupling of 2-hydroxy-3-iodo-1,4-naphthoquinone with terminal alkyne followed by intramolecular cyclization,[12] addition of thio-substituted 1,4-naphthoquinone with lithium enolate or pyridinium ylide followed by bromine mediated intramolecular cyclization,[13] the reaction of 2,3-Dichloronaphthoquinone with 1,3-dicarbonyl compounds,[14] Diels-Alder addition of furoquinones with diene followed by aromatization at high temperature,[15] and [3+2] photoaddition of 2-hydroxy-1,4-naphthoquinone with alkene or alkyne.[16] However, many of the above mentioned protocols suffer from disadvantages such as low regioselectivities, multi-step reactions, low yields and involvement of toxic heavy metals or rare metals. It prompted us to develop a benign and regioselective method for the synthesis of both angular and linear naphthofuroquinone derivatives.

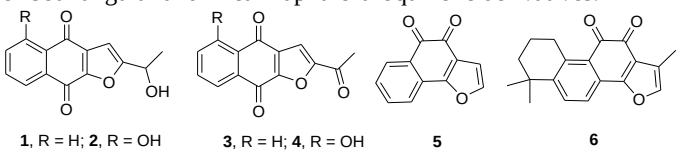

Figure 1. Natural bioactive naphthofuroquinones

Dudley and his coworkers reported in 1966 a regioselective preparation of naphthofuroquinones, that the mercuric acetate oxidation of isolapachol afforded corresponding angular or linear naphthofuroquinones selectively depending on the time of heating and the amount of mineral acid used.[10] However, this

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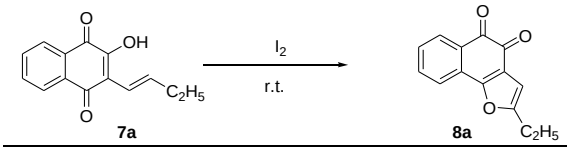
conversion is highly restricted in practical application because two equivalents of highly toxic mercuric acetate were required. In the proposed mechanism, the reaction is initiated by the nucleophilic attack of the olefinic double bond to mercuric acetate to form the mercurinium ion. The following decomposition of the mercurinium ion produces the angular naphthofuroquinones which isomerizes to the linear naphthofuroquinones under acidic condition. In light of the similar ability of iodine to form the unstable iodonium ion with olefins, we envisage that iodine, a much more environmentally benign reagent, might be used in this reaction instead of mercuric acetate. To our pleasure, as shown in table 1, using iodine as oxidative reagent, we did obtain angular naphthofuroquinone **8a** from 2-hydroxy-3-butenyl-1,4-naphthoquinone **7a**. This reaction worked ideally in THF, while not as effective in other solvents such as acetonitrile, dichloromethane and ethanol (entry 1-4, table 1). By simply stirring **7a** with one equivalent iodine in THF at room temperature for 1h, 89% of **8a** was obtained (entry 4, table 1). One equivalent of iodine is necessary for the full conversion of the **7a**. When 0.5 equivalent iodine was used, only 37% angular product **8a** was obtained even after 12 h (52% **7a** recovered), while excess amount of iodine led to lower yield of **8a** due to formation of more impurities (entry 4-6, table 1).

Table1

Optimization of reaction conditions



Entry	Solvent	I_2 (eq)	Time	Yield[a] (%)
1	CH_3CN	1	5 d	73
2	CH_2Cl_2	1	7 d	60
3	Ethanol	1	6 h	40
4	THF	1	1 h	89
5	THF	0.5	12 h	37[b]
6	THF	1.5	1 h	53

[a] isolated yield; [b] 52% **7a** was recovered.

Table 2

Preparation of angular naphthofuroquinones **8**[18]

Entry	**7** (R_1, R_2)	Time	Product (yield,%)[a]
1	**7a** (R_1 =H, R_2 = Et)	1h	**8a** (89)
2	**7b** (R_1 =H, R_2 = Me)	1h	**8b** (93)
3	**7c** (R_1 =H, R_2 = $CH(CH_3)_2$)	2h	**8c** (64)
4	**7d** (R_1, R_2 = $(CH_2)_4$)	6h	**8d** (45)
5	**7e** (R_1 =H, R_2 = C_6H_5)	2h	**8e** (63)
6	**7f** (R_1 =H, R_2 = 4-$MeOC_6H_4$)	1h	**8f** (91)
7	**7g** (R_1 =H, R_2 =3,4-$(MeO)_2C_6H_3$)	1h	**8g** (57)
8	**7h** (R_1 =H, R_2 = 2-MeC_6H_4)	1h	**8h** (91)
9	**7i** (R_1 =H, R_2 = 4-MeC_6H_4)	1h	**8i** (90)
10	**7j** (R_1 =H, R_2 = 2-BrC_6H_4)	5d	**8j** (86)
11	**7k** (R_1 =H, R_2 = 2-ClC_6H_4)	5d	**8k** (--)[b]
12	**7l** (R_1 =H, R_2 = 4-ClC_6H_4)	5d	**8l** (--)[b]

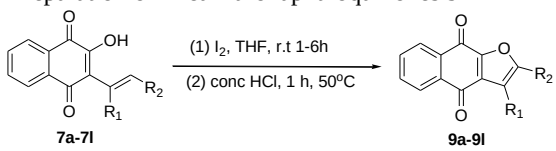
[a] isolated yield; [b] starting material decomposed to complicated mixtures.

The reaction scope was further explored. 2-Hydroxy-3-substitutedvinyl-1,4-naphthoquinones **7a-7l** were prepared from 2-hydroxy-1,4-naphthoquinone and aldehydes or ketones according to Bock's procedure.[17] As shown in table 2, the cyclization of 2-hydroxy-3-substitutedvinyl-1,4-naphthoquinones **7** worked generally well with alkyl and phenyl substituent on the double bond, affording the angular naphthofuroquinones **8** in 45-93% yields.[18] The steric effect of the substituted group on both the reaction time and yield was observed. The conversion of the most sterically hindered substrate **7d** took 6 h and gave only 45% yield to **8d** (entry 4, table 2). The electronic property of R_2 group had a great influence on the cyclization activity of **7**. Compound **7f**, **7h**, **7i** with electron donating methoxy phenyl or methyl phenyl R_2 group cyclized generally faster than compound **7e** with phenyl R_2 group (entry 5-9, table 2). With electron withdrawing 2-bromophenyl R_2 group, compound **7j** cyclized very slowly to **8j** (entry 10, table 2). When 2-bromophenyl group was replaced with more electron withdrawing 2- or 4-chlorophenyl group, compound **7k-7l** failed to give the desired angular naphthofuroquinones **8k-8l** (entry 11-12, table 2).

With the angular naphthofuroquinones in hand, we were then intending to prepare the linear naphthofuroquinones. Following Dudley's procedure,[10a] angular naphthofuroquinone **8a** was successfully transformed to the linear **9a** in 85% yield when heated in a 1:1 mixture of concentrated HCl and EtOH. We were then pleased to find that the linear naphthofuroquinone **9a** can be obtained *in situ* in good yield simply by adding concentrated HCl to the reaction mixture of **8a.** Following this one-pot mode, linear naphthofuroquinones **9a-9i** were readily prepared in 26-86% yields directly from corresponding 2-hydroxy-3-substitutedvinyl-1,4-naphthoquinones **7a-7i** (entry 1-9, table 3). Similar to the production of angular naphthofuroquinones **8**, both steric and electronic effects of the substituents on the reactivity of compound **7** were observed. As shown in table 3, compound **7j-7l** with electron withdrawing R_2 group failed to give the desired linear naphthofuroquinones **9j-9l**. The reaction of compound **7j** with 2-bromophenyl R_2 group stopped at the stage of the angular product **8j** and the reaction of compound **7k**/**7l** with 2-chlorophenyl/4-chlorophenyl R_2 group gave complicated mixtures (entry 10-12, table 3).

Table 3

Preparation of linear furonaphthoquinones **9**[19]



Entry	**7** (R_1, R_2)	Product (yield[a], %)
1	**7a** (R_1 =H, R_2 = Et)	**9a** (73)
2	**7b** (R_1 =H, R_2 = Me)	**9b** (75)
3	**7c** (R_1 =H, R_2 = $CH(CH_3)_2$)	**9c** (56)
4	**7d** (R_1, R_2 = $(CH_2)_4$)	**9d** (26)
5	**7e** (R_1 =H, R_2 = C_6H_5)	**9e** (47)
6	**7f** (R_1 =H, R_2 = 4-$MeOC_6H_4$)	**9f** (86)
7	**7g** (R_1 =H, R_2 =3,4-$(MeO)_2C_6H_3$)	**9g** (50)
8	**7h** (R_1 =H, R_2 = 2-MeC_6H_4)	**9h** (75)
9	**7i** (R_1 =H, R_2 = 4-MeC_6H_4)	**9i** (78)
10	**7j** (R_1 =H, R_2 = 2-BrC_6H_4)	**9j** (--)[b]
11	**7k** (R_1 =H, R_2 = 2-ClC_6H_4)	**9k** (--)[c]
12	**7l** (R_1 =H, R_2 = 4-ClC_6H_4)	**9l** (--)[c]

[a] isolated yield; [b] 85% angular product **8j** was obtained after 5days; [a] starting material decomposed to complicated mixtures.

Thus, through simple manipulation of reaction conditions, both angular and linear naphthofuroquinones can be selectively prepared from 2-hydroxy-3-substitutedvinyl-1,4-

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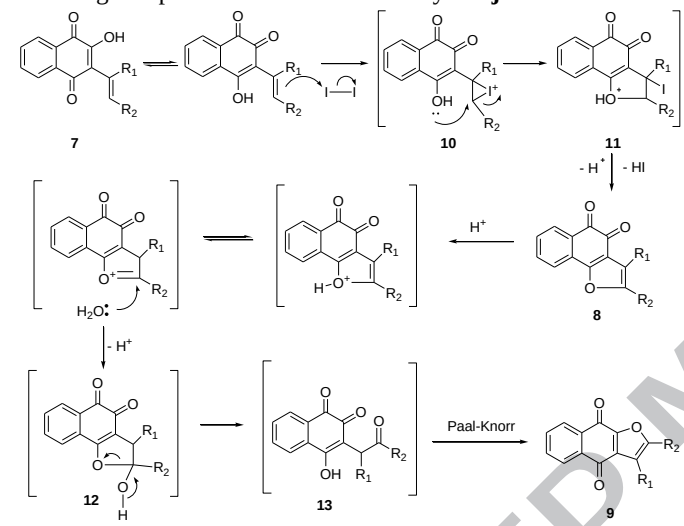
naphthoquinones using iodine as oxidative reagent. Besides the environmentally benign feature of iodine, the operation of this iodine mediated conversion is also much simpler than Dudley's method which involves additional operations to remove the mercurous acetate in between the reaction.

The possible reaction mechanism was proposed as shown in Scheme 1. The reaction was supposed to be initiated by the nucleophilic attack of the olefinic double bond to iodine to form the iodonium ion **10**. The following decomposition of the iodonium ion **10** might involve the attack from the neighboring hydroxyl group to form the unstable iodide intermediate **11** which would automatically eliminate one molecular of HI to give the angular naphthofuroquinone **8**. In this process, one equivalent of iodine will be consumed. An electron withdrawing R_2 group will decrease the nucleophilic ability of the olefinic double bond, which might explain the inhibited reactivity of **7j-7l**.



Scheme 1. Proposed mechanism for the formation of **8** and **9**.

Under acidic condition, hemiketal **12** could be formed through the nucleophilic attack of H_2O to the C-2 position of the protonated angular naphthofuroquinone **8**. The following decomposition of hemiketal **12** would give the 1,4 diketone intermediate **13**, which would finally afford the linear naphthofuroquinone **9** through a classic Paal-Knorr process.[20] The angular naphthofuroquinone **8j** with an electron withdrawing 2-bromophenyl R_2 group failed to give the corresponding linear isomer probably due to its reduced protonation ability.

In summary, a new method for highly regioselective synthesis of both angular and linear naphthofuroquinones has been developed via iodine-mediated hetero-annulation. Considering the very mild reaction condition, high yields, high angular/linear selectivity and noninvolvement of transitional metals, this method might find great application in the synthesis of naphthofuroquinones.

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Supplementary data

Supplementary data associated with this article can be found in the online version.

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18. General method for the synthesis of 2-substitutednaphtho[1,2-b]furan-4,5-dione **8**: to a solution of 2-hydroxy-3-alkenyl-1,4-naphthoquinone (0.5 mmol) in 5 mL THF was added iodine (0.5 mmol, 127 mg). The mixture was stirred for 1-6 hours at room temperature until the full conversion of the starting material and then diluted with 30 mL of H_2O, extracted with ethyl acetate (15 mL X 3). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residual was applied on a silica column chromatography, eluting with a mixture of petroleum ether and ethyl acetate (15:1) to afford the angular naphthofuroquinones **8**. 2-ethylnaphtho[1,2-b]furan-4,5-dione **8a**: red solid, yield 89%, mp 136-138ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.65 (t, J = 7.2 Hz, 1H), 7.45 (td, J = 7.2, 1.2 Hz, 1H), 6.48 (s), 2.78 (q, J = 7.6 Hz, 2H), 1.34 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100

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MHz, $CDCl_3$) δ 180.8, 174.5, 161.5, 159.6, 135.3, 130.4, 129.8, 128.8, 128.7, 122.5, 122.0, 103.0, 21.3, 11.7; HRMS (ESI) m/z $[M+H]^+$ calcd. for $C_{14}H_{11}O_3$, 227.0708; found 227.0699.

19. General method for the one-pot preparation of 2-substituted naphtho[2,3-b]furan-4,9-dione **9**: to a solution of 2-hydroxy-3-alkenyl-1,4-naphthoquinone (0.5 mmol) in 5 mL THF was added iodine (0.5 mmol, 127 mg). The mixture was stirred for 1-6 hours at room temperature until the full conversion of the starting material. To the mixture was added 5 mL concentrated HCl and the resulting mixture was stirred at 50°C for 1 hour then diluted with 30 mL H_2O, extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residual was applied on a silica column chromatography, eluting with a mixture of petroleum ether and ethyl acetate (15:1) to afford the linear naphthofuroquinones **9**. 2-ethylnaphtho[2,3-b]furan-4,9-dione **9a**: yellow solid, yield 73%, mp 145-146°C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25-8.22 (m, 1H), 8.18-8.20 (m, 1H), 7.79-7.73 (m, 2H), 6.65 (s), 2.87 (q, J = 7.6 Hz, 2H), 1.39 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.9, 173.1, 165.8, 151.6, 133.8, 133.5, 133.1, 132.6, 131.8, 126.84, 126.77, 103.5, 21.8, 11.6; HRMS (ESI) m/z $[M+H]^+$ calcd. for $C_{14}H_{11}O_3$, 227.0708; found 227.0699.

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