Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2021, **19**, 3434

Synthesis of fused 1,2-naphthoquinones with cytotoxic activity using a one-pot three-step reaction†

Anton A. Nechaev,[a] Pratap R. Jagtap,[a] Ema Bažíková,[a] Johana Neumannová,[a] Ivana Císařová[b] and Eliška Matoušová *[a]

Received 2nd February 2021,
Accepted 18th March 2021

DOI: 10.1039/d1ob00205h

rsc.li/obc

A method for the synthesis of fused 1,2-naphthoquinones, as analogues of biologically active natural terpene quinones, is described. The intermediate polycyclic naphthalenes were prepared by a one-pot palladium-catalysed process from simple alkynes, one of which was made from an optically pure biomass-derived levoglucosenone. The prepared methoxy-substituted naphthalenes were subsequently transformed in one step to 1,2-naphthoquinones by a trivalent-iodine-mediated oxidation. The naphthoquinone products were found to have cytotoxic properties.

Naphthalene and naphthoquinone moieties are present in many biologically active compounds occurring in nature.[1] Their properties include cytotoxic,[2–6] antibacterial,[7,8] and other activities.[9–19] More specifically, a 1,3-dihydronaphtho[2,3-*c*]furan skeleton can be found among naturally occurring lignans,[11,16,20] of which justicidin B (Fig. 1) displays a remarkably wide range of biological properties.[21] The previously published syntheses of compounds with this structural motif are usually based on the formation of the middle ring, either by cycloaddition,[22–30] electrocyclisation,[31,32] photocyclisation,[33] or base-mediated[34,35] and metal-catalysed[36–41] cyclisations.

The related 1,2-naphthoquinones are less abundant in nature than 1,4-naphthoquinones, and the same applies to the reports of their syntheses. The preparation of *o*-naphthoquinones fused with aliphatic ring or rings, as *e.g.* in mansonone D or miltirone, has been rather scarce in the literature.[17,42–46] For this reason, and also to achieve higher structural diversity for future bioactivity screening, we aimed to develop a new method for the synthesis of such compounds, preferably performing several metal-catalysed steps in one pot to achieve better efficiency and atom economy.[47–49] Fused benzene rings were synthesised by a related one-pot process previously.[50–52]

To this end, we proposed a palladium-catalysed tandem reaction which would combine three catalytic steps: cyclic carbopalladation, Suzuki cross-coupling and the Heck reaction, transforming alkynes **1** directly to fused naphthalenes **3** (Scheme 1). To achieve a good selectivity in the tandem reaction, we planned to use 2-bromo-substituted arylboronic acids, which should ensure that the rate of the first carbopalladation step (*via* oxidative addition to the C–I bond) is higher than

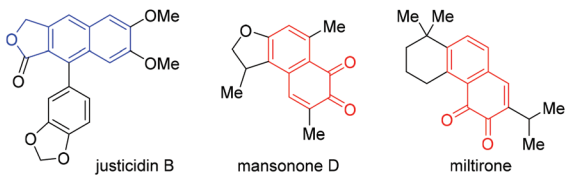
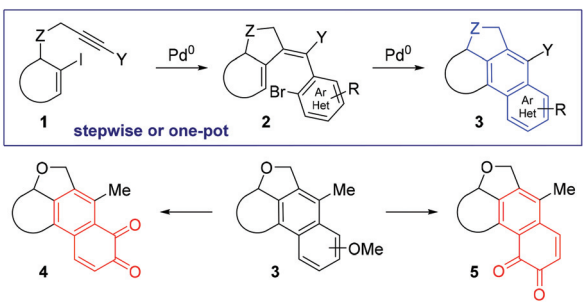


Fig. 1 Natural products with naphthalene and *o*-naphthoquinone cores.



Scheme 1 Proposed one-pot synthesis of naphthalenes **3** and their oxidation to 1,2-naphthoquinones **4** or **5**.

[a]*Department of Organic Chemistry, Faculty of Science, Charles University, Hlavova 8, 128 00 Praha 2, Czech Republic. E-mail: eliska.matousova@natur.cuni.cz*
[b]*Department of Inorganic Chemistry, Faculty of Science, Charles University, Hlavova 8, 128 00 Praha 2, Czech Republic*

†Electronic supplementary information (ESI) available: Additional experiments and characterisation data; copies of ^{1}H and ^{13}C NMR spectra for all new compounds; cytotoxicity data for **3ba**, **4a**, **4b** and **5a**; and X-ray data for **5a**. CCDC 1985309. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ob00205h

that of the Heck reaction (*i.e.* the third step). Because of the rigidity of the benzylic double bond in dienes **2**, a 6-*endo* mode should be preferred in the Heck reaction over a 5-*exo* cyclisation. In addition, we planned to develop an oxidation method to convert the methoxy-substituted products **3** to *o*-naphthoquinones **4** or **5**, structurally similar to natural terpene quinones (such as those in Fig. 1), and evaluate their cytotoxic properties.

As a starting material we chose a simple alkyne **1a** (Fig. 2), which was prepared from cyclohexenone in three steps, two of which do not require purification. An optically pure starting compound **1b** was obtained by a similar three-step procedure from a biomass-derived levoglucosenone, which is a versatile chiral building block[53–55] that provides a greener alternative to conventional chemicals. Besides, we prepared two nitrogen-containing alkynes **1c** and **1d** (see the ESI† for details).

We began our study by exploration of the stepwise procedure for the synthesis of naphthalenes **3**. Regarding the conditions, after several attempts we found that our previously reported conditions[56] for Suzuki cross-coupling (5 mol% of Pd$(PPh_3)_4$, 2 equiv. of Cs_2CO_3, THF/H_2O, 70 °C) can be used for the first part of the synthesis, providing good yields of bromides **2** despite the presence of the aromatic C–Br bond. The following Heck reaction was initially performed with a methoxy-substituted product **2aa** using $Pd_2(dba)_3$ as a catalyst and XPhos as a ligand in DMF/H_2O at 110 °C, providing the product of 6-*endo* cyclisation **3aa** in 60% isolated yield. Notably, the corresponding 5-*exo* product was not observed in the reaction mixture. Screening of palladium sources and ligands showed that the best combination was either $Pd(OAc)_2$ with XPhos or dppf ligands, or XPhosPd G2 with an additional XPhos ligand (see the ESI† for the optimisation details). The latter catalytic system gave the best ^{1}H NMR yield (70%) and was therefore used in the following investigation of the scope.

First, we explored the scope for reactions of alkyne **1a** with a series of 2-bromo-substituted (hetero)arylboronic acids (Table 1). The results showed that the substituent in position 5 of the boronic acid had almost no influence on the outcome, the yields being similarly good for both methoxy (**2aa**, **3aa**) and fluoro substituents (**2af**, **3af**), as for an unsubstituted aromatic ring (**2ad**, **3ad**). Methoxy substituents were generally well tolerated in the cyclisation/Suzuki reaction – compounds **2ab**, **2ac** and **2ae** were isolated in good yields of 81, 93, and 67%, respectively. Unfortunately, out of the three, only **2ab** reacted in the following Heck reaction step, yielding the naphthalene product **3ab** in 55% isolated yield. The 6-fluoro-substituted arylboronic acids did not participate in the reaction sequence

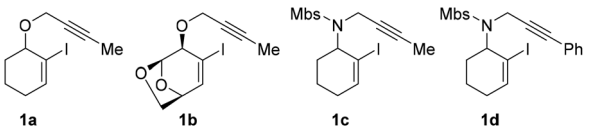
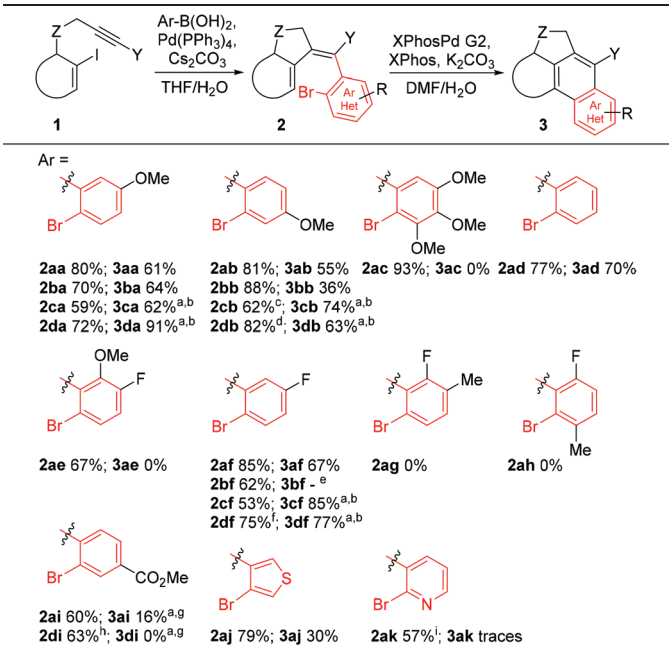


Fig. 2 Substrates used in this work (Mbs = 4-methoxybenzenesulfonamide).

Table 1 Substrate scope of the cyclisation/Suzuki and Heck reactions



All yields in Table 1 are isolated yields. Conditions for the tandem reaction: Pd$(PPh_3)_4$ (4 mol%), Cs_2CO_3 (2 equiv.), boronic acid (1.6 eq.), 70 °C, THF/H_2O (4 : 1). Conditions for the Heck reaction: XphosPd G2 (10 mol%), XPhos (20 mol%), K_2CO_3 (2 equiv.), 110 °C, DMF/H_2O (4 : 1). [a] Conditions: $Pd_2(dba)_3$ (10 mol%), P(*o*-tol)$_3$ (20 mol%), Cs_2CO_3 (2 equiv.), DMF/H_2O (10 : 1). [b] At 130 °C. [c] At 80 °C, mixture of *E*/*Z* isomers (9.7 : 1). [d] At 80 °C, mixture of *E*/*Z* isomers (2.4 : 1). [e] Inseparable mixture. [f] Mixture of *E*/*Z* isomers (2.5 : 1). [g] Partial hydrolysis of the ester group was observed. [h] Mixture of *E*/*Z* isomers (3.2 : 1). [i] In DMF/H_2O.

at all (products **2ag** and **2ah** were not observed). On the other hand, the ester-substituted and heteroaromatic boronic acids were well tolerated in the first step, but the corresponding Suzuki products **2ai**, **2aj** and **2ak** showed only poor reactivity in the Heck reaction. In the case of naphthalene **3ai**, only 16% of the desired ester product was isolated, and the formation of a small amount of the corresponding carboxylic acid was observed. Its mass was determined by MS and product-specific signals appeared in the ^{1}H NMR spectra but we were unable to obtain a pure compound.

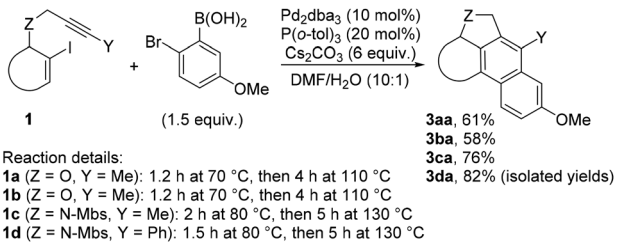
Other alkynes **1b**, **1c** and **1d** were tested in the reactions with both 5- and 4-methoxy- and with 5-fluoro-substituted phenylboronic acids. Alkyne **1b** gave good yields of methoxy-substituted products **2ba** and **2bb** (70 and 88%), the first of which underwent the following Heck reaction smoothly (64% yield of **3ba**), and the latter yielded only 36% of **3bb**. The fluoro-substituted boronic acid behaved well in the first reaction, producing 62% of **2bf**, but the next step resulted in an inseparable mixture of compounds. In the case of the nitrogen-containing alkynes **1c** and **1d**, the yields of both reactions were good with all the three above-mentioned boronic acids, with generally better overall yields for **1d**, including a noticeable excellent 91% yield of naphthalene **3da**. However, both

steps required longer reaction times and/or higher temperatures compared to the reactions with oxygen-containing substrates **1a** and **1b**. In a few cases, especially with alkyne **1d**, the formation of the undesired *Z*-isomer of **2** was observed in the Suzuki reaction. In particular, **2cb**, **2db**, **2df** and **2di** were produced as inseparable mixtures of *E* and *Z* isomers, in *E*/*Z* ratios ranging from 9.7 : 1 for **2cb** to 2.4 : 1 for **2db**. In the reaction of **1d** with the methoxycarbonyl-substituted boronic acid, the corresponding product **2di** was formed in 63% yield, but, similarly as with **2ai**, the following Heck reaction conditions caused hydrolysis of the ester group and no naphthalene product **3di** was isolated.

After having studied both reactions individually, we began our investigation of the conditions suitable for a one-pot reaction which would comprise all the three catalytic steps (Table 2). Firstly, we subjected starting material **1a** directly to the optimised Heck reaction conditions, in an attempt at a one-pot synthesis of **3aa**, but only a mixture of products was obtained, with approximately 15% yield of the intermediate **2aa** and 7% yield of the final product **3aa** (entry 1). Changing the catalyst to $Pd(PPh_3)_4$ used in the Suzuki reaction, but with 6 equiv. of the base and in a higher boiling DMF/H_2O solvent system, increased the yield of naphthalene **3aa** to 20% (entry 2). We found that higher temperature was necessary for the Heck reaction to occur, while the first two steps proceeded easily at 70 °C with full consumption of starting alkyne **1a** in less than two hours. Therefore, in all the following experiments, we set up the reaction at 70 °C, later increasing the temperature to 110 °C, without monitoring the reaction between the steps. It was also found during optimisation that the Heck reaction required much more thorough solvent degassing than the Suzuki step. Regarding the base and solvent, replacing K_2CO_3 with Cs_2CO_3 improved the outcome slightly, but using different solvents slowed down the Heck reaction and it never proceeded to completion (entries 4–6, and Table S2 in the ESI†).

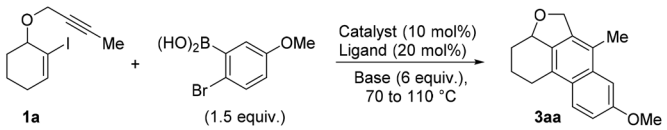
Screening experiments in deuterated solvents (entries 7–16) enabled us to rapidly identify the best catalytic system for the one-pot reaction. It was the combination of $Pd_2(dba)_3$ with tri(*o*-tolyl)phosphine that improved the ^{1}H NMR yield of the final product **3aa** to 72% with no remaining intermediate **2aa** detected (entry 12). Out of the other electron-rich ligands, tricyclohexylphosphine provided the second best yield of 50% (entry 10), but the bulky trimesityl- and tributylphosphine gave only low yields of the naphthalene product (entries 14 and 15).

The optimised conditions for the one-pot process were then applied to the other substrates **1** with 2-bromo-5-methoxyphenylboronic acid (Scheme 2). To our delight, we obtained the



Scheme 2 One-pot three-step tandem reaction of alkynes **1** providing naphthalenes **3**.

Table 2 Optimisation of the one-pot cyclisation/Suzuki/Heck reaction



Entry	Catalyst	Ligand	Base	Solvent	Time at 70 °C [h]	Time at 110 °C [h]	Yield[a] of **2aa** [%]	Yield[a] of **3aa** [%]
1	$Pd(OAc)_2$	XPhos	K_2CO_3[b]	DMF/H_2O (4 : 1)	—	20	15	7
2	$Pd(PPh_3)_4$	—	K_2CO_3	DMF/H_2O (10 : 1)	3	2	11	20
3	$Pd(PPh_3)_4$	XPhos	K_2CO_3	DMF/H_2O (10 : 1)	3	2	5	26
4	$Pd(PPh_3)_4$	—	Cs_2CO_3	DMF/H_2O (10 : 1)	2	3	0	26
5	$Pd(PPh_3)_4$	—	Cs_2CO_3	Dioxane/H_2O (15 : 1)	2	16[c]	6	26
6	$Pd(PPh_3)_4$	—	Cs_2CO_3	Toluene/H_2O (10 : 1)	2	3	15	30
7	$Pd(PPh_3)_4$	—	K_2CO_3[d]	DMF-d_7/D_2O (10 : 1)	1.5	3	8	34
8	$Pd_2(dba)_3$	PPh_3	Cs_2CO_3	DMF-d_7/D_2O (10 : 1)	1.5	3	47	30
9	$Pd_2(dba)_3$	dppf	Cs_2CO_3	DMF-d_7/D_2O (10 : 1)	1.5	3	Traces	Traces
10	$Pd_2(dba)_3$	PCy_3	Cs_2CO_3	DMF-d_7/D_2O (10 : 1)	1.5	3	14	50
11	$Pd_2(dba)_3$	P(*o*-tol)$_3$	Cs_2CO_3	DMF-d_7/D_2O (10 : 1)	1.5	3	16	60
12	$Pd_2(dba)_3$	P(*o*-tol)$_3$	Cs_2CO_3	DMF-d_7/D_2O (10 : 1)	1.5	4	0	72
13	$Pd(OAc)_2$	P(*o*-tol)$_3$	Cs_2CO_3	DMF-d_7/D_2O (10 : 1)	1.5	4	0	60
14	$Pd_2(dba)_3$	P(mes)$_3$	Cs_2CO_3	DMF-d_7/D_2O (10 : 1)	1.5	4	20	4
15	$Pd_2(dba)_3$	TTBP·HBF_4	Cs_2CO_3	DMF-d_7/D_2O (10 : 1)	1.5	4	0	14
16	Herrmann[e]	—	Cs_2CO_3	DMF-d_7/D_2O (10 : 1)	1.5	4	0	28

[a] ^{1}H NMR yield; 3,4,5-trichloropyridine was used as the internal standard. [b] 2 equiv. of the base used. [c] At 100 °C. [d] 0.5 equiv. of CsOPiv was added. [e] *trans*-Di(μ-acetato)bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II).

oxygen-containing products **3aa** and **3ba** in 61 and 58% isolated yields, respectively. In both cases, it meant an increase in the yield in comparison with the results for the stepwise process, where the overall yields were 49% of **3aa** and 45% of **3ba** (compare Scheme 2 with Table 1). Even better results were observed for the nitrogen-containing starting materials **1c** and **1d**, providing naphthalenes **3ca** in 76% yield and **3da** in 82% yield, which was a great improvement in overall yields (previously 37 and 66%).

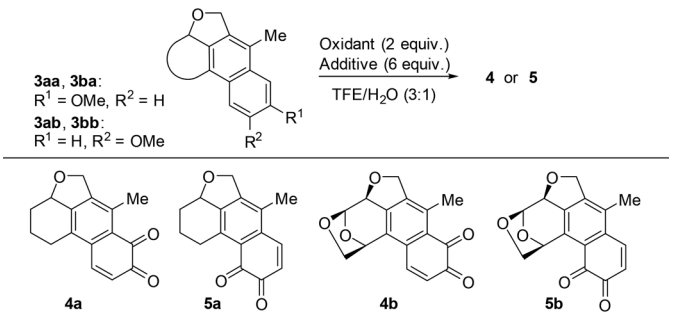
Both the one-pot reaction and the cyclisation/Suzuki reaction were also attempted using the corresponding pinacol boronates and BF_3K salts instead of boronic acids. We found that the reactivity of pinacol esters was very similar to that of free boronic acids in both steps; the reactions with esters were cleaner but with slightly lower yields. BF_3K salts, on the other hand, reacted only sluggishly under the same conditions (see the ESI† for the detailed experimentation).

As the next step in the synthesis of *o*-naphthoquinones with a natural-product-like skeleton, we studied the oxidation of the two methoxy-substituted naphthalene products **3aa** and **3ab** to the corresponding quinones. A two-step approach consisting of methyl cleavage followed by oxidation, which is the most common approach,[42–45,57–59] was not successful in our case as **3aa** failed to produce the corresponding naphthol when treated with BBr_3. Therefore, we focused on a direct oxidative demethylation. There have been only a few examples of such direct oxidations in the literature, mostly to prepare 1,4-naphthoquinones using either ceric ammonium nitrate (CAN),[60] Dess–Martin periodinane,[61] or [bis(trifluoroacetoxy) iodo]benzene (PIFA)[62,63] as an oxidant.

In the case of substrate **3aa**, however, oxidation with CAN gave only 9% yield of the desired quinone **4a** (Table 3, entry 1), and a pentavalent IBX reagent did not bring about the oxidation at all. A more thorough screening revealed that the trivalent iodine reagents (PIFA, PIDA and $PhI(OPiv)_2$) under acidic conditions were the oxidants of choice for this transformation. Under basic conditions, on the other hand, we observed only low yields of the naphthoquinone product (see entry 7 and additional optimisation experiments in the ESI†). The best results were obtained with sulphuric acid as an additive (compare entries 3–6), which in combination with PIDA provided the highest isolated yield of quinone **4a** (84%, entry 9). These conditions were also suitable for the regioisomeric naphthalene **3ab**, which was transformed into product **5a** in 71% isolated yield (entry 14). The structure of compound **5a** was unequivocally confirmed by single-crystal X-ray analysis (Fig. 3).

The optimised conditions were then used for the oxidation of levoglucosenone-derived compounds **3ba** and **3bb**. Despite the presence of an acid-labile acetal group in their structure,

Table 3 Oxidation of naphthalenes **3** to naphthoquinones **4** and **5**



Entry, substrate	Oxidant	Additive	Temp. [°C]	Time [min]	Product, yield[a] [%]
1, **3aa**	CAN[b]	—	0 to r.t.	60	**4a**, 9
2, **3aa**	$PhI(OPiv)_2$	$BF_3{\cdot}Et_2O$[c]	0	5	**4a**, 32 (31)
3, **3aa**	$PhI(OPiv)_2$	$BF_3{\cdot}Et_2O$	−15	5	**4a**, 41
4, **3aa**	$PhI(OPiv)_2$	TMSOTf	−15 to 0	35	**4a**, 40
5, **3aa**	$PhI(OPiv)_2$	TfOH	−15	5	**4a**, 49
6, **3aa**	$PhI(OPiv)_2$	H_2SO_4	−15	5	**4a**, 84
7, **3aa**	PIFA[d]	$NaHCO_3$[e]	−12 to r.t.	30	**4a**, 20
8, **3aa**	PIFA	H_2SO_4	−15	30	**4a**, 54
9, **3aa**	PIDA[f]	H_2SO_4	−15	5	**4a**, 85 (84)
10, **3ab**	PIDA	H_2SO_4	−15	5	**5a**, 42
11, **3ab**	PIFA	H_2SO_4	−15 to r.t.	30	**5a**, 35
12, **3ab**	PIDA	$BF_3{\cdot}Et_2O$	−15	5	**5a**, 17
13, **3ab**	PIDA[g]	H_2SO_4	−35 to 10	60	**5a**, 62
14, **3ab**	PIDA[g]	H_2SO_4	−35 to r.t.	40	**5a**, (71)
15, **3ba**	PIFA	H_2SO_4	−15 to r.t.	20	**4b**, (52)
16, **3bb**	PIFA	H_2SO_4	−15 to 5	40	**5b**, (24)

[a] ^{1}H NMR yield; 3,4,5-trimethoxybenzaldehyde was used as the internal standard. Isolated yield in brackets. [b] 5 equiv. of the oxidant used, MeCN/H_2O (4 : 1) as a solvent. CAN = ammonium cerium(IV) nitrate. [c] 3 equiv. of the additive used. [d] PIFA = [bis(trifluoroacetoxy)iodo]benzene. [e] 2 equiv. of the base used. [f] PIDA = (diacetoxyiodo)benzene. [g] MeCN/H_2O (3 : 1) used as a solvent.

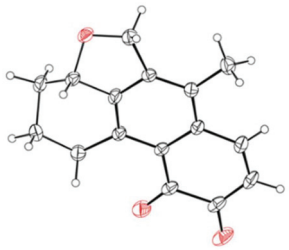


Fig. 3 PLATON plot of naphthoquinone **5a** showing displacement ellipsoids drawn at the 30% probability level.

the corresponding regioisomeric *o*-naphthoquinone products **4b** and **5b** were formed in both cases, albeit in lower isolated yields: 52 and 24%, respectively (Table 3, entries 15 and 16). Nitrogen-containing compounds **3ca** and **3da** were subjected to the same conditions too, but the starting naphthalenes mostly decomposed during the reaction and only traces of the corresponding quinone products were observed.

Regarding the mechanism of the oxidation, since the usual nucleophilic attack of a free phenolic hydroxyl group on iodine is not possible in this case, we suppose that the activation of the *ortho* position next to the methoxy substituent occurs as an attack of the electron-rich aromatic ring on the electrophilic iodine atom of the reagent. This step would be later followed by elimination of methanol, similarly as described in the work of Kita.[64] Such a mechanism would rationalise the necessity of using acidic conditions in this reaction because the methoxy group would become a better leaving group by protonation.

The cytotoxic activity of product **3ba** and three of the prepared 1,2-naphthoquinones was evaluated on five cell lines, including four human cancer cell lines and normal dermal fibroblasts. Naphthalene **3ba** did not show any cytotoxic properties, but all the tested naphthoquinones **4a**, **4b** and **5a** displayed activities against the two tested leukemic cell lines and cervical carcinoma cells with IC_{50} values in the range of 1.5 to 6.3 μmol L^{-1}. However, the mentioned quinones were also toxic for normal human fibroblasts at concentrations of the same order of magnitude (see the ESI† for details of cytotoxicity screening and description of the used method).

Conclusions

In summary, biologically active fused 1,2-naphthoquinones were synthesised using a palladium-catalysed one-pot reaction (with up to 82% isolated yield) and a one-step oxidation of the resulting naphthalenes with trivalent iodine reagents in up to 84% isolated yield. Two of the naphthoquinone products were prepared in optically pure forms starting from levoglucosenone, which is available from renewable sources. The prepared compounds were subjected to cytotoxicity screening, showing that the studied 1,2-naphthoquinones were active against three human cancer cell lines in μM concentrations. Thus, the results can serve as a background for further studies of this interesting class of compounds.

Experimental

General procedure for the cyclisation/Suzuki reaction

Iodide **1** (1 mmol) was dissolved in 9.1 mL of THF or DMF followed by addition of (hetero)arylboronic acid (1.5 mmol), Cs_2CO_3 (2.0 mmol) and water (0.9 mL). The reaction mixture was degassed and backfilled with argon (2×); then $Pd(PPh_3)_4$ (4 mol%) was added and the degassing procedure was repeated twice more. The reaction mixture was stirred at 70 °C (or 80 °C for DMF) until the full conversion of the starting material was observed by TLC, and then cooled down and extracted with water (25 mL) and EtOAc (2 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was subjected to column chromatography delivering the desired Heck/Suzuki product **2**.

General procedure for the Heck reaction

Compound **2** (1.0 mmol), K_2CO_3 (2.0 mmol), XPhos (20 mol%) and XPhosPd G2 (10 mol%) were dissolved in DMF (8 mL) and stirred for 5 minutes before water (2 mL) was added. The reaction mixture was degassed and backfilled with argon (3×) and stirred at 110 °C for an indicated time. Upon completion, it was cooled down, filtered through a sand/cotton layer and extracted between brine (2 × 20 mL) and EtOAc (20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was subjected to column chromatography providing the desired product **3**.

General procedure for the one-pot tandem reaction

Compound **1** (0.2 mmol), arylboronic acid (0.3 mmol) and Cs_2CO_3 (1.2 mmol) were dissolved in DMF (1.8 mL) and water (0.18 mL). The reaction mixture was degassed and backfilled with argon (3×), or degassed by bubbling Ar through the mixture for 5 minutes. Then $Pd_2(dba)_3$ (0.02 mmol) and P(*o*-tol)$_3$ (0.04 mmol) were added; the mixture was degassed again and stirred for an indicated time at 70 or 80 °C, and then at 110 or 130 °C. Upon completion, the reaction mixture was cooled down, diluted with toluene and concentrated under reduced pressure. The crude mixture was subjected to column chromatography on silica gel providing the desired naphthalene product **3**.

General procedure for the oxidation

Naphthalene **3** (0.3 mmol) was suspended in 2,2,2-trifluoroethanol (TFE) or MeCN (1.8 mL) under an argon atmosphere and cooled down to an indicated temperature. Sulphuric acid (1.8 mmol), preliminarily mixed with water (0.6 mL), followed by PIDA or PIFA (0.6 mmol), were added to the mixture and stirred vigorously for an indicated time and temperature. Upon completion, the reaction was quenched at 0 °C by a slow addition of saturated aqueous $NaHCO_3$ and the mixture was extracted between water (15 mL) and EtOAc (2 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was

purified by column chromatography on silica gel yielding the desired 1,2-naphthoquinone **4** or **5**.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the Czech Science Foundation (project no. 16-22419Y), funding of Charles University (project PRIMUS/17/SCI/14), and Charles University Research Centre (programme UNCE/SCI/014). We are grateful to Dr Helena Mertlíková-Kaiserová and her group for cytotoxicity testing. We also thank Circa Group Pty Ltd for kindly supplying a sample of levoglucosenone.

Notes and references

1 R. H. Thomson, *Naturally Occurring Quinones IV. Recent Advances*, Chapman & Hall, London, 4th edn, 1997.
2 M. A. El Had, J. J. Guardia, J. M. Ramos, M. Taourirte, R. Chahboun and E. Alvarez-Manzaneda, *Org. Lett.*, 2018, **20**, 5666–5670.
3 Z. Zhu, *Oncol. Lett.*, 2018, **15**, 8841–8846.
4 C.-F. Wu, S. M. Klauck and T. Efferth, *Arch. Toxicol.*, 2016, **90**, 2275–2286.
5 R. Inagaki, M. Ninomiya, K. Tanaka and M. Koketsu, *ChemMedChem*, 2015, **10**, 1413–1423.
6 S. Boonsri, C. Karalai, C. Ponglimanont, S. Chantrapromma and A. Kanjana-opas, *J. Nat. Prod.*, 2008, **71**, 1173–1177.
7 Z. Shang, A. A. Salim, Z. Khalil, M. Quezada, P. V. Bernhardt and R. J. Capon, *J. Org. Chem.*, 2015, **80**, 12501–12508.
8 J.-D. Cha, J.-H. Lee, K. M. Choi, S.-M. Choi and J. H. Park, *Evidence-Based Complementary Altern. Med.*, 2014, 450572.
9 C. Salas, R. A. Tapia, K. Ciudad, V. Armstrong, M. Orellana, U. Kemmerling, J. Ferreira, J. D. Maya and A. Morello, *Bioorg. Med. Chem.*, 2008, **16**, 668–674.
10 C. Panethymitaki, P. W. Bowyer, H. P. Price, R. J. Leatherbarrow, K. A. Brown and D. F. Smith, *Biochem. J.*, 2006, **396**, 277–285.
11 J. L. Charlton, *J. Nat. Prod.*, 1998, **61**, 1447–1451.
12 H.-N. Sun, Y.-H. Luo, L.-Q. Meng, X.-J. Piao, Y. Wang, J.-R. Wang, H. Wang, Y. Zhang, J.-Q. Li, W.-T. Xu, Y. Liu, Y. Zhang, T. Zhang, Y.-H. Han, M.-H. Jin, G.-N. Shen, Y.-Q. Zang, L.-K. Cao, D.-J. Zhang and C.-H. Jin, *Int. J. Mol. Med.*, 2019, **43**, 1067–1075.
13 X. Liu, O. Kunert, M. Blunder, N. Fakhrudin, S. M. Noha, C. Malainer, A. Schinkovitz, E. H. Heiss, A. G. Atanasov, M. Kollroser, D. Schuster, V. M. Dirsch and R. Bauer, *J. Nat. Prod.*, 2014, **77**, 2513–2521.
14 D. Delorme, Y. Ducharme, C. Brideau, C.-C. Chan, N. Chauret, S. Desmarais, D. Daniel, J.-P. Falgueyret, R. Fortin, J. Guay, P. Hamel, T. R. Jones, C. Lépine, C. Li, M. McAuliffe, C. S. McFarlane, D. A. Nicoll-Griffith, D. Riendeau, J. A. Yergey and Y. Girard, *J. Med. Chem.*, 1996, **39**, 3951–3970.
15 F. Maione, V. De Feo, E. Caiazzo, L. De Martino, C. Cicala and N. Mascolo, *J. Ethnopharmacol.*, 2014, **155**, 1236–1242.
16 C.-C. Chen, W.-C. Hsin, F.-N. Ko, Y.-L. Huang, J.-C. Ou and C.-M. Teng, *J. Nat. Prod.*, 1996, **59**, 1149–1150.
17 H. M. Chang, K. Y. Chui, F. W. L. Tan, Y. Yang, Z. P. Zhong, C. M. Lee, H. L. Sham and H. N. C. Wong, *J. Med. Chem.*, 1991, **34**, 1675–1692.
18 H. Tang, P. Song, J. Li and D. Zhao, *Int. J. Biol. Macromol.*, 2019, **135**, 303–313.
19 S. Makar, T. Saha and S. K. Singh, *Eur. J. Med. Chem.*, 2019, **161**, 252–276.
20 A. Mohagheghzadeh, T. J. Schmidt and A. W. Alfermann, *J. Nat. Prod.*, 2002, **65**, 69–71.
21 S. Hemmati and H. Seradj, *Molecules*, 2016, **21**, 820.
22 J. L. Woodard, A. C. Huntsman, P. A. Patel, H.-B. Chai, R. Kanagasabai, S. Karmahapatra, A. N. Young, Y. Ren, M. S. Cole, D. Herrera, J. C. Yalowich, A. D. Kinghorn, J. E. Burdette and J. R. Fuchs, *Bioorg. Med. Chem.*, 2018, **26**, 2354–2364.
23 T. B. Grimaldi, D. F. Back and G. Zeni, *Eur. J. Org. Chem.*, 2015, 6924–6931.
24 L. S. Kocsis, E. Benedetti and K. M. Brummond, *Org. Lett.*, 2012, **14**, 4430–4433.
25 T. Ozawa, T. Kurahashi and S. Matsubara, *Org. Lett.*, 2011, **13**, 5390–5393.
26 T. Kudoh, T. Mori, M. Shirahama, M. Yamada, T. Ishikawa, S. Saito and H. Kobayashi, *J. Am. Chem. Soc.*, 2007, **129**, 4939–4947.
27 B. S. Chinta and B. Baire, *Eur. J. Org. Chem.*, 2017, 3381–3385.
28 T. Kudoh, S. Fujisawa, M. Kitamura and A. Sakakura, *Synlett*, 2017, **28**, 2189–2193.
29 T. Shibata, R. Fujiwara and D. Takano, *Synlett*, 2005, 2062–2066.
30 J. L. Charlton, C. J. Oleschuk and G.-L. Chee, *J. Org. Chem.*, 1996, **61**, 3452–3457.
31 L. Liu, J. Wang and H. Zhou, *J. Org. Chem.*, 2015, **80**, 4749–4753.
32 F. Wang, X. Tong, J. Cheng and Z. Zhang, *Chem. – Eur. J.*, 2004, **10**, 5338–5344.
33 Y. Yamamoto, S. Mori and M. Shibuya, *Chem. – Eur. J.*, 2015, **21**, 9093–9100.
34 J. Das, R. Mukherjee and A. Basak, *J. Org. Chem.*, 2014, **79**, 3789–3798.
35 S. Mondal, M. Maji and A. Basak, *Tetrahedron Lett.*, 2011, **52**, 1183–1186.
36 H. J. Mun, E. Y. Seong, K.-H. Ahn and E. J. Kang, *J. Org. Chem.*, 2018, **83**, 1196–1203.
37 J. Joussot, A. Schoenfelder, J. Suffert and G. Blond, *C. R. Chim.*, 2017, **20**, 665–681.

38 G. Naresh, R. Kant and T. Narender, *Org. Lett.*, 2015, **17**, 3446–3449.
39 R. M. Patel and N. P. Argade, *Org. Lett.*, 2013, **15**, 14–17.
40 V. Gudla and R. Balamurugan, *J. Org. Chem.*, 2011, **76**, 9919–9933.
41 J.-C. Hsieh and C.-H. Cheng, *Chem. Commun.*, 2005, 2459–2461.
42 R. J. Binder, M. J. Hatfield, L. Chi and P. M. Potter, *Eur. J. Med. Chem.*, 2018, **149**, 79–89.
43 T. Matsumoto, Y. Takeda, K. Soh, H. Gotoh and S. Imai, *Chem. Pharm. Bull.*, 1996, **44**, 1318–1325.
44 K. Ghosh and U. R. Ghatak, *Tetrahedron Lett.*, 1994, **35**, 5943–5944.
45 R. L. Danheiser, D. S. Casebier and A. H. Huboux, *J. Org. Chem.*, 1994, **59**, 4844–4848.
46 J. Lee and J. K. Snyder, *J. Am. Chem. Soc.*, 1989, **111**, 1522–1524.
47 G. K. Zieliński and K. Grela, *Chem. – Eur. J.*, 2016, **22**, 9440–9454.
48 J. Biemolt and E. Ruijter, *Adv. Synth. Catal.*, 2018, **360**, 3821–3871.
49 Y. Ping, Y. Li, J. Zhu and W. Kong, *Angew. Chem., Int. Ed.*, 2019, **58**, 1562–1573.
50 F. E. Meyer and A. de Meijere, *Synlett*, 1991, 777–778.
51 M. Leibeling, D. C. Koester, M. Pawliczek, S. C. Schild and D. B. Werz, *Nat. Chem. Biol.*, 2010, **6**, 199–201.
52 S. S. Goh, G. Chaubet, B. Gockel, M.-C. A. Cordonnier, H. Baars, A. W. Phillips and E. A. Anderson, *Angew. Chem., Int. Ed.*, 2015, **54**, 12618–12621.
53 F. W. Lichtenthaler, *Acc. Chem. Res.*, 2002, **35**, 728–737.
54 A. M. Sarotti, M. M. Zanardi, R. A. Spanevello and A. G. Suarez, *Curr. Org. Synth.*, 2012, **9**, 439–459.
55 Y. Halpern, R. Riffer and A. Broido, *J. Org. Chem.*, 1973, **38**, 204–209.
56 J. Mikušek, P. Jansa, P. R. Jagtap, T. Vašíček, I. Císařová and E. Matoušová, *Chem. – Eur. J.*, 2018, **24**, 10069–10072.
57 M. Uyanik, T. Mutsuga and K. Ishihara, *Angew. Chem., Int. Ed.*, 2017, **56**, 3956–3960.
58 M. Uyanik, T. Mutsuga and K. Ishihara, *Molecules*, 2012, **17**, 8604–8616.
59 A. Wu, Y. Duan, D. Xu, T. M. Penning and R. G. Harvey, *Tetrahedron*, 2010, **66**, 2111–2118.
60 R. G. F. Giles, I. R. Green and N. van Eeden, *Eur. J. Org. Chem.*, 2004, 4416–4423.
61 S. Rasapalli, G. Jarugumilli, G. R. Yarrapothu, J. A. Golen and A. L. Rheingold, *Tetrahedron Lett.*, 2013, **54**, 2615–2618.
62 J. Sperry, J. J. P. Sejberg, F. M. Stiemke and M. A. Brimble, *Org. Biomol. Chem.*, 2009, **7**, 2599–2603.
63 R. A. Fernandes, A. B. Ingle and V. P. Chavan, *Org. Biomol. Chem.*, 2012, **10**, 4462–4466.
64 H. Tohma, H. Morioka, Y. Harayama, M. Hashizume and Y. Kita, *Tetrahedron Lett.*, 2001, **42**, 6899–6902.