Tetrahedron 64 (2008) 6364–6371

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Straightforward palladium-mediated synthesis of *N*-substituted 1,2-dihydrobenz[*g*]isoquinoline-5,10-diones

Jan Jacobs [a], Blaise Mavinga Mbala [a], Bart Kesteleyn [a], Gaston Diels [b], Norbert De Kimpe [a,*]

[a] *Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure links 653, B-9000 Ghent, Belgium*
[b] *Johnson & Johnson Pharmaceutical Research & Development, Synthesis Enabling Technologies, Turnhoutseweg 30, B-2340 Beerse, Belgium*

ARTICLE INFO

Article history:
Received 20 March 2008
Received in revised form 9 April 2008
Accepted 22 April 2008
Available online 25 April 2008

Keywords:
1,2-Dihydrobenz[g]isoquinoline-5,10-diones
2-Azaanthraquinones
Pyranonaphthoquinones
Pentalongin
Heck reaction

ABSTRACT

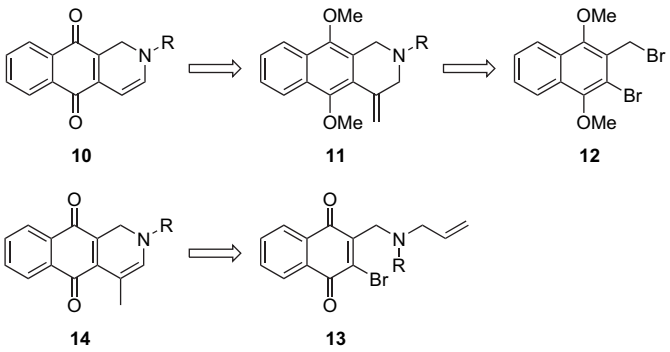
Related to our research on structural modifications of pentalongin, the active principle of the medicinal plant *Pentas longiflora* Oliv., a new synthesis of *N*-protected 1,2-dihydrobenz[*g*]isoquinoline-5,10-diones and their 4-methyl derivatives, which represent a new class of compounds, is reported. In both cases, the benz[*g*]isoquinoline skeleton was constructed by an intramolecular Heck reaction of *N*-protected 2-((allylamino)methyl)-3-bromo-1,4-dimethoxynaphthalenes and *N*-protected 2-((allylamino)methyl)-3-bromo-1,4-naphthoquinones, respectively.

1. Introduction

Pyranonaphthoquinones **1**, which are prevalent in nature, constitute an important research area in organic synthesis due to the pronounced biological activities of these heterocyclic compounds.[1,2] Their applicability for medicinal use explains the synthetic efforts made by different chemists over the years.[2,3] Although their 2-aza analogues (Fig. 1), all of which have been isolated as 2-azaanthraquinones **2**–**8**, have rarely been found in nature, they nevertheless possess promising antifungal and antibiotic properties.[4–7] Moreover, an important anti-tumour activity has been identified for several synthetic 2-azaanthraquinones.[8]

Within this scientific framework, structural modifications of the natural pyranonaphthoquinone pentalongin (**9**) were envisaged, the active principle of *Pentas longiflora* Oliv.[1] In the past, we have reported on a new synthesis of *N*-substituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones,[9] and recently we have described the use of an acid-mediated intramolecular cyclization for the synthesis of 1,2-dihydrobenz[*g*]isoquinoline-5,10-diones.[10] However, the severe reaction conditions, which were required to synthesize the targeted 1,2-dihydrobenz[*g*]isoquinoline-5,10-diones **10** were often incompatible with the use of *N*-protecting groups and as a consequence benz[*g*]isoquinoline-5,10-dione (**8**) and complex reaction mixtures were obtained. Therefore, we now wish to report on the use of an intramolecular Heck reaction for the construction of the benz[*g*]isoquinoline skeleton. The Heck reaction, which is not disturbed by heteroatoms such as nitrogen and oxygen,[11] allowed a simple and straightforward synthesis of 1,2-dihydrobenz[*g*]isoquinoline-5,10-diones and their 4-methyl substituted derivatives.

In order to avoid full aromatization of the targeted 1,2-dihydrobenz[*g*]isoquinoline-5,10-diones **10** and their 4-methyl substituted derivatives **14** to the corresponding 2-azaanthraquinones, N-protection was included for the synthesis of the target compounds.[10]



Retrosynthetic analysis suggested that target compounds **10** could be prepared starting from 2-bromo-3-bromomethyl-1,4-dimethoxynaphthalene (**12**). Reaction with allylamine, followed by

* Corresponding author. Tel.: +32 9 264 59 51; fax: +32 9 264 62 43.
E-mail address: norbert.dekimpe@ugent.be (N. De Kimpe).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.04.083

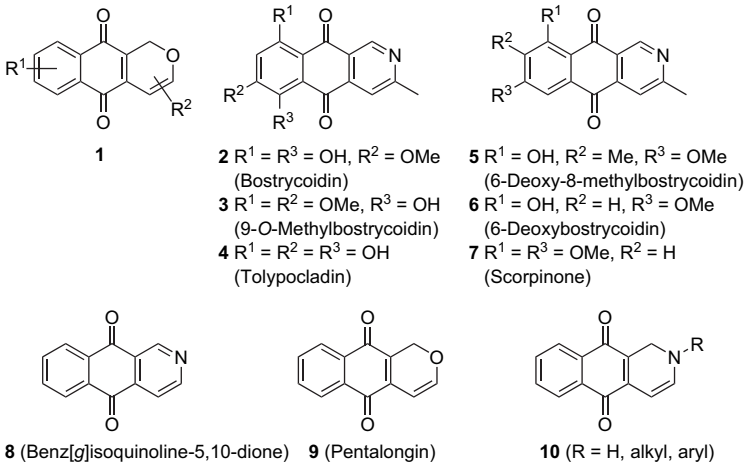


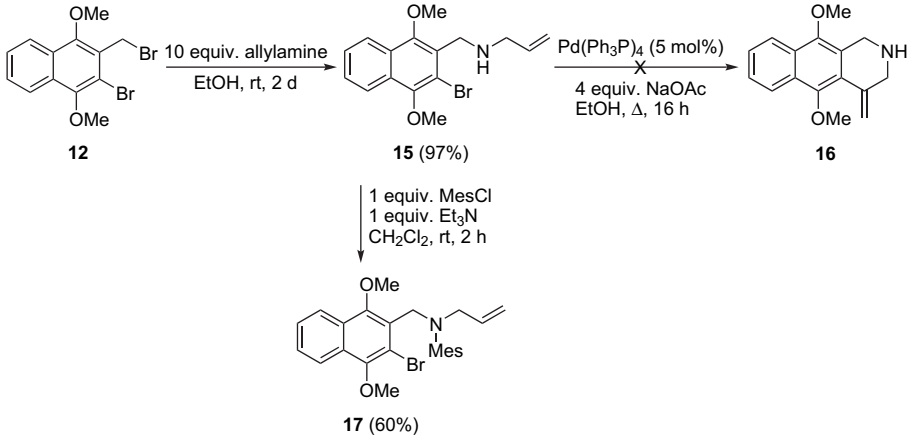
Figure 1.

N-protection and palladium-catalyzed intramolecular cyclization should give *N*-protected 5,10-dimethoxy-4-methylene-1,2,3,4-tetrahydrobenz[*g*]isoquinoline (**11**) as the desired Heck-reaction product. Oxidative cleavage of the 4-methylene group of compound **11** should give the corresponding ketone, which could be converted to the target compounds **10** after reduction and subsequent dehydration. In addition, oxidation of the synthesized *N*-protected 2-((allylamino)methyl)-3-bromo-1,4-dimethoxynaphthalene should give the corresponding 1,4-naphthoquinone **13**, which could then be converted to the target *N*-protected 4-methyl-1,2-dihydrobenz[*g*]isoquinoline-5,10-dione **14** by an intramolecular Heck reaction.

2. Results and discussion

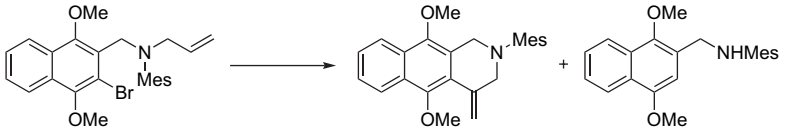
Reaction of 2-bromo-3-bromomethyl-1,4-dimethoxynaphthalene (**12**)[12] with an excess of allylamine in absolute ethanol afforded 2-((allylamino)methyl)-3-bromo-1,4-dimethoxynaphthalene (**15**) in 97% yield (Scheme 1). Reaction of compound **15** with a catalytic amount of tetrakis(triphenylphosphine)palladium(0) and 4 equiv of sodium acetate in boiling ethanol failed to give intramolecular ring closure and the starting material was recovered. Therefore, 2-((allylamino)methyl)-3-bromo-1,4-dimethoxynaphthalene (**15**) was converted into its *N*-methanesulfonyl analogue **17** in 60% yield by reaction with methanesulfonyl chloride in dichloromethane in the presence of triethylamine.

Having a suitable substrate for an intramolecular palladium-mediated cyclization under Heck conditions in hand, different catalytic systems were tested in order to obtain 2-methanesulfonyl-5,10-dimethoxy-4-methylene-1,2,3,4-tetrahydrobenz[*g*]-isoquinoline (**18**) in an efficient way (Table 1). At first, palladium(II) acetate was used in the presence of 1,3-bis(diphenylphosphino)-propane (dppp) as a ligand. Although the first results were not convincing, changing the solvent from ethanol to *N*,*N*-dimethylacetamide (DMA) brought about a remarkable improvement in the formation of the desired Heck-cyclization product **18** along with the deallylated and debrominated naphthalene **19**. Since a series of bulky electron-rich phosphines, which have been developed by the Buchwald group over the past several years, have attracted much attention for their ability to effect various C–C, C–N and C–O bond formations,[13–15] several Buchwald phosphine ligands were evaluated in the Heck reaction. In this way, palladium(II) acetate was used in the presence of several of these phosphine ligands: 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (x-phos), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xanth-phos), 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (*t*-Bu x-phos), 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (S-phos) and 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (Dave-phos). In the course of these test reactions, the most promising results were obtained upon the use of palladium(II) acetate in the presence of x-phos and potassium acetate in DMA at 80 °C for 3 days. However, when this reaction was scaled-up for preparative purposes, the ratio of the desired Heck-cyclization product **18** and the deallylated and debrominated naphthalene **19** shifted towards the disturbing side-product **19**. This effect could be partially countered by the use of bis(2-methoxyethyl)ether as



Scheme 1.

Table 1
Optimization of the Heck reaction starting from *N*-methanesulfonyl-2-((allylamino)methyl)-3-bromo-1,4-dimethoxynaphthalene (**17**)



17 **18** **19**

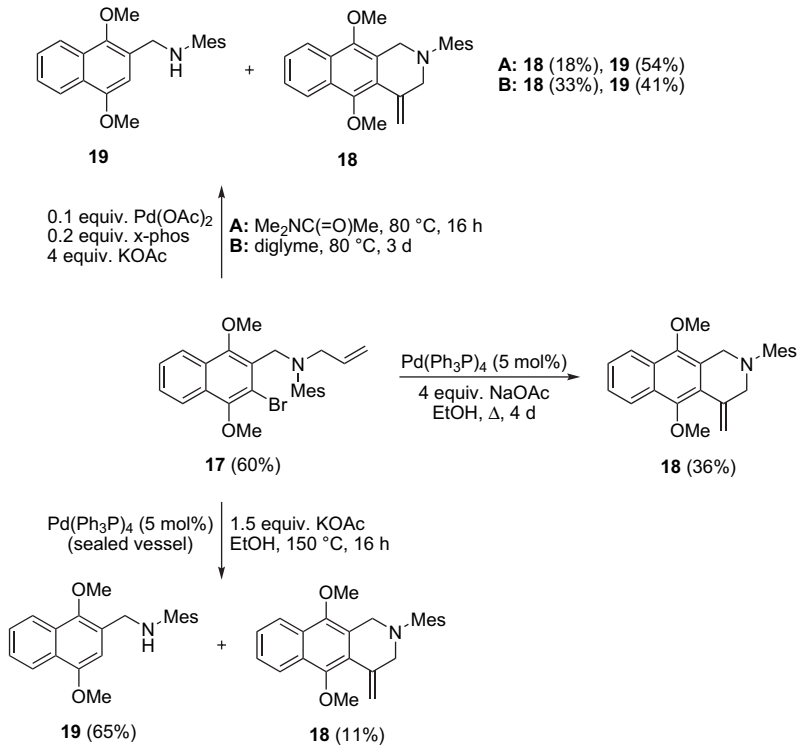
Entry	Reagents	Reaction conditions	Scale (mmol)	LC–MS (%)[c]	
				18	**19**
1	$Pd(OAc)_2$ (0.10 equiv) dppp (0.20 equiv) KOAc (4 equiv)	EtOH, 80 °C, 3 days[a]	0.2	2	13
2	$Pd(OAc)_2$ (0.10 equiv) dppp (0.20 equiv) KOAc (4 equiv)	DMA, 80 °C, 3 days[a]	0.2	28	49
3	$Pd(OAc)_2$ (0.10 equiv) Bu_4NBr (0.20 equiv) KOAc (4 equiv)	DMA, 80 °C, 3 days[a]	0.2	8	83
4	$Pd(OAc)_2$ (0.10 equiv) x-phos (0.20 equiv) KOAc (4 equiv)	DMA, 80 °C, 3 days[a]	0.2	51	39
5	$Pd(OAc)_2$ (0.10 equiv) x-phos (0.20 equiv) KOAc (4 equiv)	DMA, 80 °C, 16 h[b]	1.0	20	66
6	$Pd(OAc)_2$ (0.10 equiv) x-phos (0.20 equiv) KOAc (4 equiv)	Diglyme, 80 °C, 3 days[b]	1.0	36	52
7	$Pd(OAc)_2$ (0.10 equiv) xanth-phos (0.20 equiv) KOAc (4 equiv)	DMA, 80 °C, 3 days[a]	0.2	19	52
8	$Pd(OAc)_2$ (0.10 equiv) *t*-Bu X-phos (0.20 equiv) KOAc (4 equiv)	DMA, 80 °C, 3 days[a]	0.2	6	41
9	$Pd(OAc)_2$ (0.10 equiv) S-phos (0.20 equiv) KOAc (4 equiv)	DMA, 80 °C, 3 days[a]	0.2	16	31
10	$Pd(OAc)_2$ (0.10 equiv) Dave-phos (0.20 equiv) KOAc (4 equiv)	DMA, 80 °C, 3 days[a]	0.2	21	31
11	$Pd(PPh_3)_4$ (0.05 equiv) KOAc (1.5 equiv)	EtOH, 150 °C, 16 h[a]	4.8	14	86
12	$Pd(PPh_3)_4$ (0.05 equiv) NaOAc (4 equiv)	EtOH, Δ, 4 days[b]	1.0	34	15

Abbrevations: dppp, 1,3-bis(diphenylphosphino)propane; DMA, *N*,*N*-dimethylacetamide; x-phos, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; xanth-phos, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; *t*-Bu x-phos, 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl; S-phos, 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl; Dave-phos, 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl; diglyme, bis(2-methoxyethyl)ether.
[a] The reaction was performed in a sealed vessel.
[b] The reaction was performed under atmospheric pressure.
[c] The remaining fraction represents unidentified reaction products.

a solvent. Finally, the use of tetrakis(triphenylphosphine)palladium(0) as Heck-catalyst in the presence of sodium acetate in boiling ethanol resulted in the most efficient synthesis of the target compound **18** in comparison with previous reactions.

Since none of the test reactions are preferential in the synthesis of the desired Heck-cyclization product **18**, four reactions were selected for purification by column chromatography (Scheme 2). Comparing the isolated yields of the target compound **18**, two reactions were found to be of further interest. In a first reaction, *N*-methanesulfonyl-2-((allylamino)methyl)-3-bromo-1,4-dimethoxynaphthalene (**17**) was treated with a catalytic amount of palladium(II) acetate in the presence of 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (x-phos) and potassium acetate in bis(2-methoxyethyl)ether at 80 °C for 3 days, after which the desired Heck-cyclization product **18** was isolated in 33% yield together with 41% of the deallylated and debrominated naphthalene **19**. In the second reaction, *N*-methanesulfonyl-2-((allylamino)methyl)-3-bromo-1,4-dimethoxynaphthalene (**17**) was treated with a catalytic amount of tetrakis(triphenylphosphine)palladium(0) and 4 equiv of sodium acetate in boiling ethanol. After a reaction time of 4 days the desired Heck-reaction product **18** was isolated in 36% yield. Although these two reactions give similar results, the latter reaction conditions were selected to perform the Heck-cyclization of naphthalene **17** since the desired Heck-cyclization product was formed predominantly under these conditions (Table 1) and could easily be purified by column chromatography.

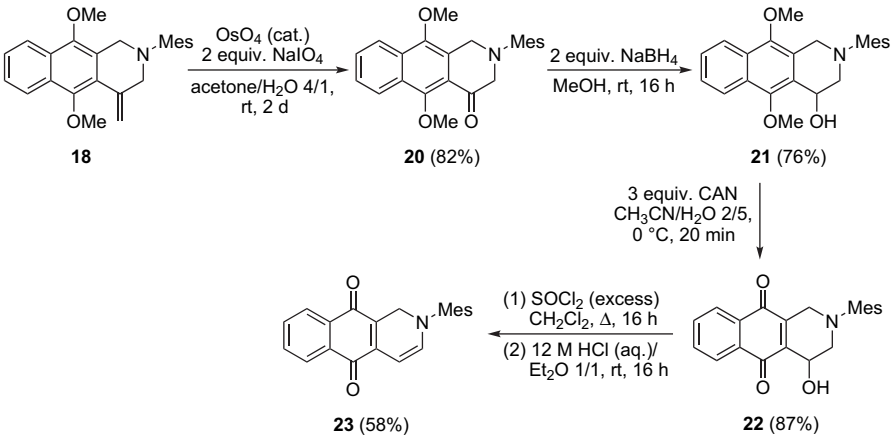
After the Heck reaction, 2-methanesulfonyl-5,10-dimethoxy-4-methylene-1,2,3,4-tetrahydrobenz[*g*]isoquinoline (**18**) was reacted with a catalytic amount of osmium(VIII) oxide and an excess of sodium periodate in aqueous acetone for 2 days at room temperature (Scheme 3). Oxidative cleavage of the 4-methylene group of compound **18** resulted in the formation of 2-methanesulfonyl-5,10-dimethoxy-2,3-dihydrobenz[*g*]isoquinoline-4(1*H*)-one (**20**) in 82% yield. Reduction of the ketone function with sodium borohydride in methanol and subsequent cerium(IV) ammonium nitrate (CAN) mediated oxidative demethylation afforded 2-methanesulfonyl-4-hydroxy-1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-dione (**22**) in 87% yield. Surprisingly, this compound resisted acid-catalyzed dehydration and even treatment with concentrated hydrochloric acid (12 M) did not give the desired 1,2-dihydrobenz[*g*]isoquinoline-



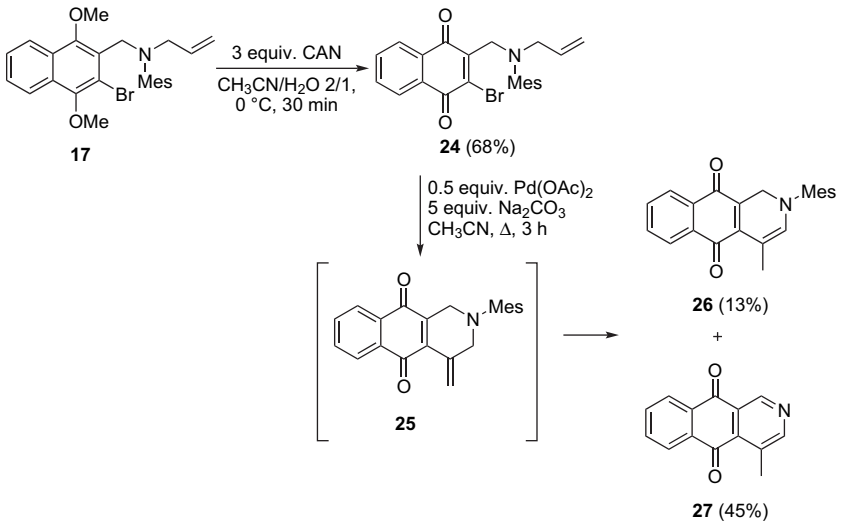
Scheme 2.

5,10-dione **23**. However, dehydration could be accomplished by reaction of **22** with an excess of thionyl chloride and subsequent treatment of the intermediate 4-chloro derivative with concentrated aqueous hydrochloric acid in diethyl ether to afford 2-methanesulfonyl-1,2-dihydrobenz[*g*]isoquinoline-5,10-dione (**23**) in 58% yield.

In connection with our interest in palladium-mediated coupling reactions of halogenated quinones with alkenes, the intramolecular palladium-catalyzed cyclization of *N*-methanesulfonyl-2-((allylamino)methyl)-3-bromo-1,4-naphthoquinone (**24**) was also investigated (Scheme 4). The *N*-methanesulfonyl protected 1,4-naphthoquinone **24** was prepared in 68% yield by oxidative demethylation of *N*-methanesulfonyl-2-((allylamino)methyl)-3-bromo-1,4-dimethoxynaphthalene (**17**) with cerium(IV) ammonium nitrate. The palladium-mediated intramolecular cyclization of *N*-methanesulfonyl-2-((allylamino)methyl)-3-bromo-1,4-naphthoquinone (**24**) was believed to give rise to the formation of 4-methylene intermediate **25**, which is formed as the Heck-cyclization product and is likely to isomerize to the more conjugated and thus, more stable isomer **26**. Indeed, after treatment of the *N*-protected 1,4-naphthoquinone **24** with palladium(II) acetate and an excess of sodium carbonate in boiling acetonitrile for 3 h, none of the 4-methylene intermediate **25** was detected in the reaction mixture. Instead, 4-methylbenz[*g*]isoquinoline-5,10-dione (**27**) was obtained as the major reaction product and it was isolated in 45% yield together with 13% of the desired 2-methanesulfonyl-4-methyl-1,2-dihydrobenz[g]isoquinoline-5,10-dione (**26**). Probably, 2-methanesulfonyl-4-methyl-1,2-dihydrobenz[g]isoquinoline-5,10-dione (**26**) oxidizes spontaneously to the more stable 4-methylbenz[g]isoquinoline-5,10-dione (**27**), which has been recently established as an antimicrobial compound.[16] In vitro testing revealed compound **27** to have a good bioactivity against representative strains of Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*), Gram-negative bacteria (*Proteus vulgaris*, *Pseudomonas aeruginosa*), yeasts (*Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Candida utilis*, *Rhodotorula rubra*), and



Scheme 3.



Scheme 4.

filamentous fungi (*Aspergillus niger*, *Penicillium chrysogenum*, *Mucor mucedo*).[16]

3. Conclusion

Synthetic efforts were directed to 2-methanesulfonyl-1,2-dihydrobenz[*g*]isoquinoline-5,10-dione with an intramolecular Heck reaction of *N*-methanesulfonyl-2-((allylamino)methyl)-3-bromo-1,4-dimethoxynaphthalene in the key step. In addition, a first synthesis of 2-methanesulfonyl-4-methyl-1,2-dihydrobenz[*g*]isoquinoline-5,10-dione and 4-methylbenz[*g*]isoquinoline-5,10-dione was achieved using *N*-methanesulfonyl-2-((allylamino)methyl)-3-bromo-1,4-naphthoquinone as substrate for the intramolecular Heck reaction.

4. Experimental section

4.1. General experimental methods

Spectroscopic data were recorded as follows: ^{1}H NMR spectra were recorded at 270 MHz and ^{13}C NMR spectra were recorded at 68 MHz. Peak assignments were performed with the aid of the DEPT technique, 2D-COSY and HETCOR spectra. Mass spectra were recorded using a direct inlet system (70 eV) with a VL detector (ES, 4000 V). Elemental analyses were executed with a Perkin Elmer Series II CHNS/O Analyzer 2400. The reported melting points are not corrected. Flash chromatography was carried out using a glass column with silica gel (particle size 0.035–0.07 mm, pore diameter ca. 6 nm). Solvent systems were determined via initial TLC analysis (Merck, silica gel 60F_{254}). Diethyl ether was freshly distilled over sodium benzophenone ketyl and dichloromethane was distilled over calcium hydride.

4.2. Synthesis of 2-((allylamino)methyl)-3-bromo-1,4-dimethoxynaphthalene (15)

To a stirred solution of allylamine (0.175 mol, 10 g) in ethanol (20 ml) was added dropwise a solution of 2-bromo-3-bromomethyl-1,4-dimethoxynaphthalene (**12**)[12] (0.0175 mol, 6.3 g) in ethanol (100 ml) and the reaction mixture was stirred in a stoppered flask at room temperature for 2 days. Most of the solvent was evaporated in vacuo and the residue was dissolved in dichloromethane (100 ml), washed twice with water and dried ($MgSO_4$). Flash chromatography on silica gel using 2% methanol in chloroform as eluent gave **15** (5.7 g, 97% yield) as a brown oil, which was found to decompose rapidly. Therefore, this compound was used as such in the next step.

*4.2.1. 2-((Allylamino)methyl)-3-bromo-1,4-dimethoxynaphthalene (**15**)*

^{1}H NMR ($CDCl_3$): δ 3.30–3.33 (2H, m, NCH_2CH=CH_2), 3.97 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.12 (2H, s, ArCH_2), 5.08–5.30 (2H, m, CH=CH_2), 5.88–6.01 (1H, m, C*H*=CH_2), 7.51–7.58 (2H, m, H-6 and H-7), 8.06–8.11 (2H, m, H-5 and H-8). ^{13}C NMR ($CDCl_3$): δ 47.1 (ArCH_2), 51.4 (NCH_2), 61.4 (OCH_3), 63.1 (OCH_3), 115.8 (=C_{quat}), 116.8 (CH=CH_2), 122.5 and 122.9 (C-5 and C-8), 126.8 and 127.1 (C-6 and C-7), 127.8 (=C_{quat}), 128.4 (=C_{quat}), 128.7 (=C_{quat}), 135.9 (C*H*=CH$_2$), 150.2 (=C–O), 151.8 (=C–O). IR (NaCl): ν_{max} 3378, 1643, 1605, 1574 cm^{-1}. MS (ES) *m*/*z* (%): 335/337 (M^+, 3), 279 (5), 201 (12), 50 (100).

4.3. Synthesis of *N*-methanesulfonyl-2-((allylamino)methyl)-3-bromo-1,4-dimethoxynaphthalene (17)

A solution of methanesulfonyl chloride (0.012 mol, 1.37 g) in dichloromethane (10 ml) was added dropwise to a stirred solution of 2-((allylamino)methyl)-3-bromo-1,4-dimethoxynaphthalene (**15**) (0.012 mol, 4.12 g) and triethylamine (0.012 mol, 1.21 g) in dichloromethane (50 ml) under nitrogen atmosphere. After 2 h, the solution was washed with 2 M HCl and then with a saturated aqueous solution of sodium hydrogen carbonate. The organic phase was dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography on silica gel with ethyl acetate/hexane (1:4) as eluent gave **17** (3 g, 60% yield) as white crystals.

*4.3.1. N-Methanesulfonyl-2-((allylamino)methyl)-3-bromo-1,4-dimethoxynaphthalene (**17**)*

An analytical sample was prepared by recrystallization from ethanol, which afforded **17** as white crystals, mp 120.0–120.9 °C. ^{1}H NMR ($CDCl_3$): δ 3.01 (3H, s, SO_2CH_3), 3.78 (2H, d×t, *J*=1.3, 6.3 Hz, NCH_2CH=CH_2), 3.97 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.85 (2H, s, ArCH_2), 4.95–5.13 (2H, m, CH=CH_2), 5.70 (1H, d×d×t, *J*=6.3, 10.2, 17.2 Hz, C*H*=CH$_2$), 7.56–7.62 (2H, m, H-6 and H-7), 8.06–8.15 (2H, m, H-5 and H-8). ^{13}C NMR ($CDCl_3$): δ 39.5 (SO_2CH_3), 46.2 (ArCH_2), 49.3 (NCH_2), 61.4 (OCH_3), 63.1 (OCH_3), 116.2 (=C_{quat}), 117.8 (CH=CH_2), 122.7 and 123.0 (C-5 and C-8), 124.5 (=C_{quat}), 127.0 and 127.69 (C-6 and C-7), 127.74 (=C_{quat}), 129.3 (=C_{quat}), 133.4 (C*H*=CH$_2$), 150.4 (=C–O), 153.2 (=C–O). IR (KBr): ν_{max} 1634, 1612,

1566, 1138 cm^{-1}. MS (ES) *m*/*z* (%): 413/415 (M^+, 27), 334/336 (19), 281 (28), 201 (100). Anal. Calcd for $C_{17}H_{20}BrNO_4S$: C, 49.26; H, 4.87; N, 3.38. Found: C, 49.44; H, 4.88; N, 3.20.

4.4. Reaction of *N*-methanesulfonyl-2-((allylamino)methyl)-3-bromo-1,4-dimethoxy-naphthalene (17) with tetrakis-(triphenylphosphine)palladium(0)

Procedure 1. A mixture of *N*-methanesulfonyl-2-((allylamino)-methyl)-3-bromo-1,4-dimethoxynaphthalene (**17**) (4.8 mmol, 2.0 g), anhydrous potassium acetate (7.7 mmol, 0.75 g) and tetrakis(triphenylphosphine)palladium(0) (0.24 mmol, 300 mg) in anhydrous ethanol (100 ml) was heated in an autoclave at 150 °C for 16 h. The reaction mixture was allowed to cool to room temperature, filtered and evaporated in vacuo. The residue was dissolved in dichloromethane, washed with water, dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography on silica gel using ethyl acetate/petroleum ether (1:4) gave 2-methanesulfonyl-5,10-dimethoxy-4-methylene-1,2,3,4-tetrahydrobenz[*g*]isoquinoline (**18**) (180 mg, 11% yield) as fine white needles, mp 115.1–115.5 °C. A second fraction was collected by elution with ethyl acetate/petroleum ether (1:1) to give *N*-methanesulfonyl-2-(aminomethyl)-1,4-dimethoxynaphthalene (**19**) (0.91 g, 64%) as yellow-brown crystals.

Procedure 2. A mixture of *N*-methanesulfonyl-2-((allylamino)-methyl)-3-bromo-1,4-dimethoxynaphthalene (**17**) (1 mmol, 0.41 g), anhydrous sodium acetate (4 mmol, 0.33 g) and tetrakis-(triphenylphosphine)palladium(0) (0.05 mmol, 58 mg) in anhydrous ethanol (20 ml) was heated under reflux for 4 days under nitrogen atmosphere. The solvent was evaporated in vacuo and the residue was dissolved in dichloromethane (50 ml), washed with water, dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography on silica gel with ethyl acetate/hexane (1:4) as eluent afforded 2-methanesulfonyl-5,10-dimethoxy-4-methylene-1,2,3,4-tetrahydrobenz[*g*]isoquinoline (**18**) (120 mg, 36% yield) as white crystals.

Procedure 3. A mixture of *N*-methanesulfonyl-2-((allylamino)-methyl)-3-bromo-1,4-dimethoxynaphthalene (**17**) (1.0 mmol, 414 mg), anhydrous potassium acetate (4.0 mmol, 393 g) and palladium(II) acetate (0.10 mmol, 23 mg) in anhydrous *N*,*N*-dimethylacetamide or bis(2-methoxyethyl)ether (15 ml) was heated at 80 °C for 16 h and 3 days, respectively. The reaction mixture was allowed to cool to room temperature, filtered and poured in water. The aqueous phase was extracted with small portions of ethyl acetate (3×). The organic extracts were washed with water, dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography on silica gel using ethyl acetate/petroleum ether (1:4) gave 2-methanesulfonyl-5,10-dimethoxy-4-methylene-1,2,3,4-tetrahydrobenz-[*g*]isoquinoline (**18**) in 18–33% yield (Scheme 2). A second fraction was collected by elution with ethyl acetate/petroleum ether (1:1) to give *N*-methanesulfonyl-2-(aminomethyl)-1,4-dimethoxynaphthalene (**19**) in 41–54% yield (Scheme 2).

*4.4.1. 2-Methanesulfonyl-5,10-dimethoxy-4-methylene-1,2,3,4-tetrahydrobenz[g]isoquinoline (**18**)*

An analytical sample was prepared by recrystallization from ethanol to give **18** as fine white needles, mp 115.1–115.5 °C. ^{1}H NMR ($CDCl_3$): δ 2.69 (3H, s, SO_2CH_3), 3.83 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 4.27 (2H, s, H-3), 4.81 (2H, s, H-1), 5.61 (1H, m, $=CH_aH_b$), 6.44 (1H, m, $=CH_aH_b$), 7.54–7.57 (2H, m, H-7 and H-8), 8.03–8.18 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$): δ 37.8 (SO_2CH_3), 44.0 (C-1), 53.1 (C-3), 60.3 (OCH_3), 61.6 (OCH_3), 118.0 ($=CH_2$), 121.5 ($=C_{quat}$), 122.0 and 123.2 (C-6 and C-9), 126.6 and 127.1 (C-7 and C-8), 128.0 ($=C_{quat}$), 128.7 ($=C_{quat}$), 133.4 ($=C_{quat}$), 148.3 (=C–O), 151.5 (=C–O). IR (KBr): ν_{max} 1634, 1613, 1152 cm^{-1}. MS (ES) *m*/*z* (%): 333 (M^+, 100), 302 (19), 254 (32), 238 (51). Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20. Found: C, 61.16; H, 5.80; N, 4.06.

*4.4.2. N-Methanesulfonyl-2-(aminomethyl)-1,4-dimethoxynaphthalene (**19**)*

An analytical sample was prepared by recrystallization from methanol to afford **19** as yellow-brown crystals, mp 99.4–100.9 °C. ^{1}H NMR ($CDCl_3$): δ 2.84 (3H, s, SO_2CH_3), 3.91 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.48 (2H, d, J=5.9 Hz, NCH_2), 5.15 (1H, t, J=5.9 Hz, NH), 6.73 (1H, s, H-3), 7.46–7.58 (2H, m, H-6 and H-7), 7.98–8.02 (1H, m, H-5 or H-8), 8.21–8.24 (1H, m, H-5 or H-8). ^{13}C NMR ($CDCl_3$): δ 40.8 (SO_2CH_3), 43.0 (NCH_2), 55.8 (OCH_3), 62.4 (OCH_3), 104.1 (C-3), 121.8 and 122.6 (C-5 and C-8), 124.6 ($=C_{quat}$), 125.9 and 127.0 (C-6 and C-7), 126.5 ($=C_{quat}$), 128.4 ($=C_{quat}$), 147.5 (=C–O), 152.4 (=C–O). IR (KBr): ν_{max} 3287, 1630, 1598, 1143 cm^{-1}. MS (ES) *m*/*z* (%): 295 (M^+, 2), 212 (13), 91 (100). Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74. Found: C, 56.74; H, 5.73; N, 4.52.

4.5. Synthesis of 2-methanesulfonyl-5,10-dimethoxy-2,3-dihydrobenz[*g*]isoquinoline-4(1*H*)-one (20)

To a stirred solution of 2-methanesulfonyl-5,10-dimethoxy-4-methylene-1,2,3,4-tetrahydrobenz[*g*]isoquinoline (**19**) (1.6 mmol, 0.52 g) in acetone (40 ml) and water (10 ml) was added first a catalytic amount of osmium(VIII) oxide. Sodium periodate (3.2 mmol, 0.68 g) was added in small potions over a period of 1 h and the mixture was stirred for 2 days, after which it was poured in 1 M HCl. The aqueous solution was extracted with dichloromethane, dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography on silica gel with ethyl acetate/hexane (1:1) as eluent gave 2-methanesulfonyl-5,10-dimethoxy-2,3-dihydrobenz[*g*]isoquinoline-4(1*H*)-one (**20**) as a grey powder.

*4.5.1. 2-Methanesulfonyl-5,10-dimethoxy-2,3-dihydrobenz[g]-isoquinoline-4(1H)-one (**20**)*

An analytical sample was prepared by recrystallization from ethanol to afford **20** as grey crystals, mp 170.5–170.9 °C. ^{1}H NMR ($CDCl_3$): δ 2.80 (3H, s, SO_2CH_3), 3.85 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 4.22 (2H, s, H-3), 4.81 (2H, s, H-1), 7.56–7.73 (2H, m, H-7 and H-8), 8.07–8.10 (1H, m, H-6 or H-9), 8.33–8.36 (2H, m, H-6 or H-9). ^{13}C NMR ($CDCl_3$): δ 37.5 (SO_2CH_3), 43.2 (C-1), 55.1 (C-3), 62.1 (OCH_3), 63.3 (OCH_3), 118.6 ($=C_{quat}$), 122.2 and 125.0 (C-6 and C-9), 124.9 ($=C_{quat}$), 127.2 and 130.1 (C-7 and C-8), 129.2 ($=C_{quat}$), 131.6 ($=C_{quat}$), 147.7 (=C–O), 156.5 (=C–O). IR (KBr): ν_{max} 1685, 1634, 1613, 1562, 1157 cm^{-1}. MS (ES) *m*/*z* (%): 335 (M^+, 43), 256 (100), 241 (11). Anal. Calcd for $C_{16}H_{17}NO_5S$: C, 57.30; H, 5.11; N, 4.18. Found: C, 56.91; H, 5.06; N, 4.05.

4.6. Synthesis of 2-methanesulfonyl-5,10-dimethoxy-2,3-dihydrobenz[*g*]isoquinoline-4(1*H*)-ol (21)

To a cooled (0 °C) solution of 2-methanesulfonyl-5,10-dimethoxy-2,3-dihydrobenz[*g*]isoquinoline-4(1*H*)-one (**20**) (3.3 mmol, 1.11 g) in methanol (20 ml) was added sodium borohydride (6.6 mmol, 0.25 g) and the mixture was stirred for 16 h at room temperature in a flask, which was fitted with a calcium chloride tube. The reaction was quenched by the careful addition of water (1 ml) and the solution was concentrated in vacuo to 5 ml. After the addition of 2 M HCl, the aqueous solution was extracted with small portions of dichloromethane. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated in vacuo. Recrystallization from ethyl acetate/hexane (1:1) gave 2-methanesulfonyl-5,10-dimethoxy-2,3-dihydrobenz[*g*]isoquinoline-4(1*H*)-ol (**21**) (0.85 g, 76% yield) as colourless needles.

*4.6.1. 2-Methanesulfonyl-5,10-dimethoxy-2,3-dihydrobenz[g]-isoquinoline-4(1H)-ol (**21**)*

^{1}H NMR ($CDCl_3$): δ 2.96 (3H, s, SO_2CH_3), 3.05 (1H, d, J=5.3 Hz, OH), 3.48 (1H, d×d, J=3.3, 13.5 Hz, C*H*H-3), 3.94 (3H, s, OCH_3), 4.00

(1H, d×d×d, J=1.3, 3.6, 13.5 Hz, CH*H*-3), 4.07 (3H, s, OCH_3), 4.45 (1H, d, J=16.5 Hz, CH_aH$_b$-1), 4.93 (1H, dd, J=1.3, 16.5 Hz, CH$_a$*H*$_b$-1), 5.26–5.31 (1H, m, H-4), 7.52–7.59 (2H, m, H-7 and H-8), 8.05–8.11 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$): δ 36.9 (SO_2CH_3), 43.5 (C-1), 50.0 (C-3), 61.6 (OCH_3), 62.2 (C-4), 63.2 (OCH_3), 121.4 (=C_{quat}), 122.34 and 122.6 (C-6 and C-9), 125.7 (=C_{quat}), 126.4 and 126.9 (C-7 and C-8), 127.8 (=C_{quat}), 128.3 (=C_{quat}), 148.4 (=C–O), 151.5 (=C–O). IR (KBr): ν_{max} 3460, 1646, 1616, 1172 cm^{-1}. MS (ES) m/z (%): 337 (M^+, 6), 150 (11), 149 (10), 135 (19), 43 (100). Anal. Calcd for $C_{16}H_{19}NO_5S$: C, 56.96; H, 5.68; N, 4.15. Found: C, 56.73; H, 5.61; N, 4.03.

4.7. Synthesis of 2-methanesulfonyl-4-hydroxy-1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-dione (22)

A solution of cerium(IV) ammonium nitrate in water (5 ml) was added dropwise to a cooled (0 °C) solution of 2-methanesulfonyl-5,10-dimethoxy-2,3-dihydrobenz[*g*]isoquinoline-4(1*H*)-ol (**21**) (0.15 mmol, 50 mg) in acetonitrile (2 ml) and the mixture was stirred for 20 min at 0 °C. The mixture was poured in water and extracted with small portions of ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated in vacuo. Recrystallization from ethyl acetate/hexane (1:1) gave 2-methanesulfonyl-4-hydroxy-1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-dione (**22**) (40 mg, 87%) as yellow crystals, mp 178.5–178.8 °C.

*4.7.1. 2-Methanesulfonyl-4-hydroxy-1,2,3,4-tetrahydrobenz[g]-isoquinoline-5,10-dione (**22**)*

^{1}H NMR (DMSO-d_6): δ 3.04 (3H, s, SO_2CH_3), 3.03–3.10 (1H, m, C*H*H-3), 3.73 (1H, d×d, J=1.7, 13.2 Hz, CH*H*-3), 4.03 (1H, d, J=19.5 Hz, CH_aH$_b$-1), 4.45 (1H, d, J=19.5 Hz, CH$_a$*H*$_b$-1), 4.81 (1H, m, H-4), 5.66 (1H, d, J=5.9 Hz, OH), 7.88–7.93 (2H, m, H-7 and H-8), 8.02–8.07 (2H, m, H-6 and H-9). ^{13}C NMR (DMSO-d_6): δ 36.0 (SO_2CH_3), 41.9 (C-1), 49.1 (C-3), 58.5 (C-4), 125.8 and 126.0 (C-6 and C-9), 131.3 (=C_{quat}), 131.4 (=C_{quat}), 134.1 and 134.4 (C-7 and C-8), 140.5 (=C_{quat}), 140.6 (=C_{quat}), 182.4 (C=O), 183.4 (C=O). IR (KBr): ν_{max} 3420, 1654, 1589 cm^{-1}. MS (ES) m/z (%): 307 (M^+, 11), 289 (14), 288 (13), 210 (54), 209 (50), 200 (100). Anal. Calcd for $C_{14}H_{13}NO_5S$: C, 54.72; H, 4.26; N, 4.56. Found: C, 54.60; H, 4.11; N, 4.30.

4.8. Synthesis of 2-methanesulfonyl-1,2-dihydrobenz[g]-isoquinoline-5,10-dione (23)

To a solution of 2-methanesulfonyl-4-hydroxy-1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-dione (**22**) (0.03 mmol, 9 mg) in dichloromethane (5 ml) was added thionyl chloride (0.15 mmol, 18 mg) and the mixture was heated under reflux for 16 h. The solvent was evaporated in vacuo and the residue was mixed with diethyl ether (2 ml) and 12 M HCl (2 ml). The mixture was stirred vigorously for 1 day in a stoppered flask, which was protected from light with aluminium foil. Water was added and the solution was extracted with diethyl ether, dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography on silica gel using ethyl acetate/hexane (2:3) as eluent gave 2-methanesulfonyl-1,2-dihydrobenz[*g*]isoquinoline-5,10-dione (**23**) (5 mg, 58%) as red crystals. Spectral data were in accordance with literature data.[10]

4.9. Synthesis of *N*-methanesulfonyl-2-((allylamino)methyl)-3-bromo-1,4-naphthoquinone (24)

A solution of cerium(IV) ammonium nitrate (3 mmol, 1.63 g) in water (10 ml) was added dropwise to a cooled (0 °C) solution of *N*-methanesulfonyl-2-((allylamino)methyl)-3-bromo-1,4-dimethoxynaphthalene (**17**) (1 mmol, 0.41 g) in acetonitrile (20 ml) and the reaction mixture was stirred for an additional 30 min at the same temperature. After the addition of water, the aqueous solution was extracted with small portions of ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated in vacuo. Recrystallization from ethyl acetate afforded *N*-methanesulfonyl-2-((allylamino)methyl)-3-bromo-1,4-naphthoquinone (**24**) (0.26 g, 68% yield) as fine yellow needles, mp 162.6–163.5 °C.

*4.9.1. N-Methanesulfonyl-2-((allylamino)methyl)-3-bromo-1,4-naphthoquinone (**24**)*

^{1}H NMR ($CDCl_3$): δ 3.02 (3H, s, SO_2CH_3), 3.96 (2H, br d, J=6.3 Hz, CH_2CH=CH$_2$), 4.58 (2H, s, ArCH_2), 5.17–5.31 (2H, m, CH=CH_2), 5.88 (1H, d×d×t, J=6.3, 10.2, 17.2 Hz, C*H*=CH$_2$), 7.74–7.84 (2H, m, H-7 and H-8), 8.11–8.19 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$): δ 38.8 (SO_2CH_3), 46.9 (Ar*C*H$_2$), 51.9 (*C*H$_2$CH=CH$_2$), 119.5 (CH=*C*H$_2$), 127.3 and 127.8 (C-6 and C-9), 130.9 (=C_{quat}), 131.3 (=C_{quat}), 132.9 (*C*H=CH$_2$), 134.3 and 134.6 (C-6 and C-7), 141.9 (=C_{quat}), 145.3 (=C_{quat}), 177.4 (C=O), 181.5 (C=O). IR (KBr): ν_{max} 1673, 1591, 1147 cm^{-1}. MS (ES) m/z 304/306 (M^+–SO_2CH_3, 6), 149 (12), 84 (79), 49 (100). Anal. Calcd for $C_{15}H_{14}BrNO_4S$: C, 46.89; H, 3.67; N, 3.65. Found: C, 46.81; H, 3.60; N, 3.68.

4.10. Reaction of *N*-methanesulfonyl-2-((allylamino)methyl)-3-bromo-1,4-naphthoquinone (24) with palladium(II) acetate

A mixture of *N*-methanesulfonyl-2-((allylamino)methyl)-3-bromo-1,4-naphthoquinone (**24**) (0.5 mmol, 192 mg), sodium carbonate (2.5 mmol, 265 mg) and palladium(II) acetate (0.25 mmol, 56 mg) in acetonitrile (20 ml) was heated under reflux for 3 h. Water was added and the aqueous solution was extracted with small portions of ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography on silica gel using ethyl acetate/petroleum ether (1:4) as eluent gave first 4-methylbenz[*g*]isoquinoline-5,10-dione (**27**) (R_f=0.20, 50 mg, 45% yield), mp 126.5 °C. Using the same solvent mixture, 2-methanesulfonyl-4-methyl-1,2-dihydrobenz[*g*]isoquinoline-5,10-dione (**26**) (R_f=0.12, 20 mg, 13% yield) eluted as a second fraction from the column. Recrystallization from acetone afforded **26** as dark red crystals, mp 185.0–185.4 °C.

*4.10.1. 2-Methanesulfonyl-4-methyl-1,2-dihydrobenz[g]-isoquinoline-5,10-dione (**26**)*

^{1}H NMR ($CDCl_3$): δ 2.28 (3H, d, J=1.5 Hz, CH_3), 2.98 (3H, s, SO_2CH_3), 4.73 (2H,s, H-1), 6.86 (1H, d, J=1.5 Hz, H-3), 7.73–7.76 (2H, m, H-7 and H-8), 8.07–8.10 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$): δ 18.0 (CH_3), 39.1 (SO_2CH_3), 41.2 (C-1), 115.9 (=C_{quat}), 125.9 and 126.7 (C-6 and C-9), 129.2 (=C_{quat}), 131.5 (=C_{quat}), 131.8 (C-3), 132.3 (=C_{quat}), 133.8 (C-7 and C-8), 137.9 (=C_{quat}), 182.1 (C=O), 183.6 (C=O). IR (KBr): ν_{max} 1668, 1639, 1618, 1588, 1549, 1145 cm^{-1}. MS (ES) m/z 223 (M^+–SO_2CH_3, 30), 195 (9), 149 (22), 57 (100). Anal. Calcd for $C_{15}H_{13}NO_4S$: C, 59.39; H, 4.32; N, 4.62. Found: C, 59.61; H, 4.66; N, 4.58.

*4.10.2. 4-Methylbenz[g]isoquinoline-5,10-dione (**27**)*

^{1}H NMR ($CDCl_3$): δ 2.84 (3H, s, CH_3), 7.82–7.86 (2H, m, H-7 and H-8), 8.25–8.30 (2H, m, H-6 and H-9), 8.89 (1H, s, H-3), 9.45 (H-1). ^{13}C NMR ($CDCl_3$): δ 19.4 (CH_3), 126.6 (=C_{quat}), 126.8 and 127.3 (C-6 and C-9), 132.5 (=C_{quat}), 133.4 (=C_{quat}), 134.1 (=C_{quat}), 134.5 and 134.6 (C-7 and C-8), 135.5 (=C_{quat}), 148.2 (C-1), 158.5 (C-3), 183.1 (C=O), 184.8 (C=O). IR (KBr): ν_{max} 1678, 1638, 1617 cm^{-1}. MS (ES) m/z 223 (M^+, 13), 84 (13), 58 (31), 43 (100). Anal. Calcd for

$C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27. Found: C, 75.71; H, 4.22; N, 6.30.

Acknowledgements

The authors are indebted to the 'Research Foundation—Flanders (FWO-Vlaanderen)' for financial support of this research.

References and notes

1. (a) Thomson, R. H. *Naturally Occurring Quinones III, Recent Advances*; Chapman and Hall: London, 1987, pp 609–633; (b) Brimble, M. A.; Nairn, M. R.; Prabaharan, H. *Tetrahedron* **2000**, *56*, 1937–1992.
2. For a recent review on the isolation and the synthesis of pentalongin and related pyranonaphthoquinones, see: Claessens, S.; Verniest, G.; Jacobs, J.; Van Hende, E.; Habonimana, P.; Nguyen Van, T.; Van Puyvelde, L.; De Kimpe, N. *Synlett* **2007**, 829–850.
3. For leading recent references, see: (a) Mmutlane, E. M.; Michael, J. P.; Green, I. R.; De Koning, C. B. *Org. Biomol. Chem.* **2004**, *2*, 2461–2470; (b) Nguyen Van, T.; De Kimpe, N. *Tetrahedron Lett.* **2004**, *45*, 3443–3446; (c) Lee, Y. R.; Choi, J. H.; Trinh, D. T. L.; Kim, N. W. *Synthesis* **2005**, 3026–3034; (d) Gibson, J. S.; Andrey, O.; Brimble, M. A. *Synthesis* **2007**, 2611–2613; (e) Brimble, M. A.; Bachu, P.; Sperry, J. *Synthesis* **2007**, 2887–2893.
4. (a) Arsenault, G. P. *Tetrahedron Lett.* **1965**, *45*, 4033–4037 and references therein; (b) Parisot, D.; Devys, M.; Barbier, M. *J. Antibiot.* **1989**, *42*, 1189–1190.
5. (a) Steyn, P. S.; Wessels, P. L.; Marasas, W. F. O. *Tetrahedron* **1979**, *35*, 1551–1555; (b) Visconti, A.; Surico, G.; Iacobellis, N. S.; Bottalico, A. *Phytopath. Mediterr.* **1983**, *22*, 122–156.
6. Gräfe, U.; Ihn, W.; Tresselt, D.; Miosga, N.; Kaden, U.; Schlegel, B.; Bormann, E.-J.; Sedmera, P.; Novak, J. *Biol. Met.* **1990**, *3*, 39–44.
7. (a) Solis, P. N.; Lang'at, C.; Gupta, M. P.; Kirby, G. C.; Warhurst, D. S.; Phillipson, J. D. *Planta Med.* **1995**, *61*, 62–65; (b) Phillipson, J. D. *Phytochemistry* **1995**, *38*, 1319–1343.
8. Croisy-Delsey, M.; Carrez, D.; Bisagni, E. *Eur. J. Med. Chem.* **1988**, *23*, 101–106.
9. Jacobs, J.; Claessens, S.; Kesteleyn, B.; Huygen, K.; De Kimpe, N. *Tetrahedron* **2007**, *63*, 2503–2510.
10. Jacobs, J.; Kesteleyn, B.; De Kimpe, N. *Tetrahedron* **2008**, *64*, 4985–4992.
11. For reviews on the Heck reaction, see: (a) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379–2411; (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963.
12. Nguyen Van, T.; Kesteleyn, B.; De Kimpe, N. *Tetrahedron* **2002**, *58*, 121–127.
13. For a review on Buchwald phosphine ligands, see: Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599–1626.
14. (a) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334–5341; (b) Kaye, S.; Fox, J. M.; Hicks, F. A.; Buchwald, S. L. *Adv. Synth. Catal.* **2001**, *343*, 789–794; (c) Buchwald, S. L.; Huang, X.; Zim, D. World Patent WO 2004/052939, June 24, 2004.
15. (a) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051–12052; (b) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162–1163; (c) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818–11819.
16. Koyama, J.; Morita, I.; Kobayashi, N.; Osakai, T.; Usuki, Y.; Taniguchi, M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1079–1082.