Tetrahedron 64 (2008) 4985–4992

Contents lists available at ScienceDirect

Tetrahedron

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

Synthesis of *N*-substituted 1,2-dihydrobenz[*g*]isoquinoline-5,10-diones

Jan Jacobs, Bart Kesteleyn, Norbert De Kimpe *

Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure links 653, B-9000 Ghent, Belgium

ARTICLE INFO

Article history:
Received 16 November 2007
Received in revised form 20 March 2008
Accepted 26 March 2008
Available online 29 March 2008

Keywords:
1,2-Dihydrobenz[*g*]isoquinoline-5,10-diones
2-Azaanthraquinones
Pyranonaphthoquinones
Pentalongin
Friedel–Crafts cyclization

ABSTRACT

The synthesis of *N*-substituted 1,2-dihydrobenz[*g*]isoquinoline-5,10-diones was envisaged as part of our research on structural modifications of pentalongin, the active principle of *Pentas longiflora* Oliv. Therefore, a synthesis of the 2-aza analogues of this natural pyranonaphthoquinone with an acid-mediated intramolecular cyclization of different *N*-protected 2-(((2,2-dimethoxyethyl)amino)methyl)-1,4-naphthoquinones in the key step was conducted. The synthesized 1,2-dihydrobenz[*g*]isoquinoline-5,10-diones represent a new class of compounds, which has been undescribed in organic chemistry.

1. Introduction

Although pyranonaphthoquinones represent a large class of natural products, their naturally occurring 2-aza analogues, all of which have been isolated as the aromatic 2-azaanthraquinones, have rarely been found in nature. So far, only a few naturally occurring 2-azaanthraquinones have been reported: bostrycoidin (**1**),[1] 9-*O*-methylbostrycoidin (**2**),[2] tolypocladin (**3**),[3] 6-deoxy-8-methylbostrycoidin (**4**),[4,5] 6-deoxybostrycoidin (**5**),[6] scorpinone (**6**),[4] and benz[*g*]isoquinoline-5,10-dione (**7**).[7] Nevertheless, also these compounds have been found to possess interesting physiological activities. For instance, bostrycoidin (**1**), a 2-azaanthraquinone isolated from several fungi of the *Fusarium* species,[1] has been shown to possess significant in vitro antibiotic activity against *Mycobacterium tuberculosis*.[8] 9-*O*-Methylbostrycoidin (**2**) revealed antibiotic activity against Gram-positive bacteria[2,9] and benz[*g*]isoquinoline-5,10-dione (**7**), isolated form *Psychotria camponutans*, has been found active against the multi-drug resistant *Plasmodium falciparum*.[7]

In view of interesting physiological properties of pentalongin (**8**),[10] the active principle of the medicinal plant *Pentas longiflora*, and naturally occurring 2-azaanthraquinones **1**–**7**, and as a part of our research on the structural modifications of pentalongin (**8**),[11] the synthesis of *N*-substituted 1,2-dihydrobenz[*g*]isoquinoline-5,10-diones **9** as direct 2-aza analogues of this natural pyranonaphthoquinone was envisaged. Remarkably, 1,2-dihydrobenz[*g*]isoquinoline-5,10-diones **9** have never been reported in literature and as this structure was totally new, an extra impetus was given to the synthesis of such novel compounds. As part of an explanation for the lack of occurrence of 1,2-dihydrobenz[*g*]isoquinoline-5,10-diones **9** in nature, this might be due to their tendency to spontaneously aromatize to the corresponding 2-azaanthraquinones. Since there is no doubt that the *N*-unsubstituted compound **9** (R=H) cannot be synthesized as it would oxidatively aromatize to benz[*g*]isoquinoline-5,10-dione **7**, the inclusion of N-protection for the synthesis of the targeted 1,2-dihydrobenz[*g*]isoquinoline-5,10-diones **9** will be necessary.

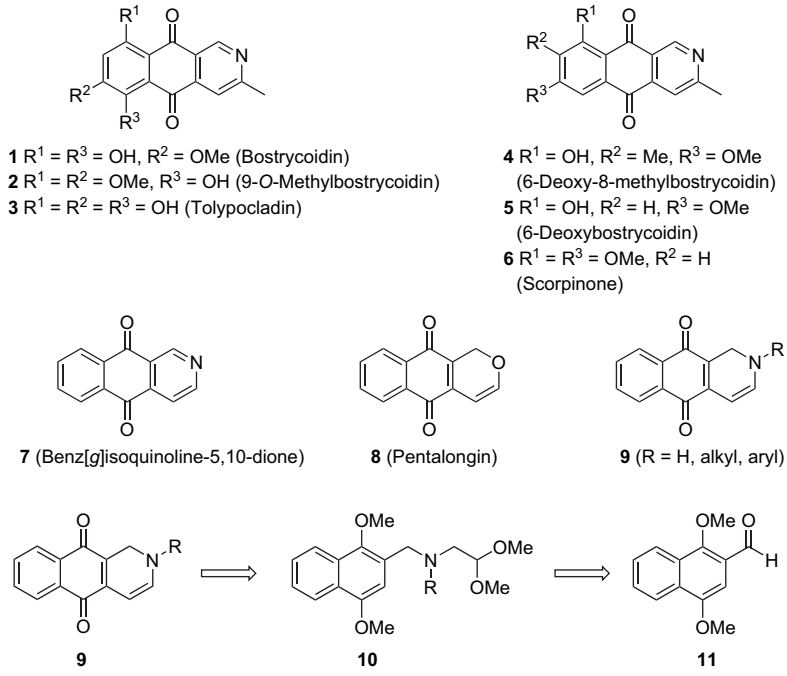
Retrosynthetic analysis suggested that the target compounds **9** could be prepared starting from 1,4-dimethoxy-2-formylnaphthalene (**11**). Condensation with aminoacetaldehyde dimethyl acetal, followed by reduction of the imine and N-protection should give tertiary amines **10**. Oxidative demethylation of compounds **10** to the corresponding 1,4-naphthoquinones and acid-mediated intramolecular ring closure should give the target 1,2-dihydrobenz[*g*]isoquinoline-5,10-diones **9**.

2. Results and discussion

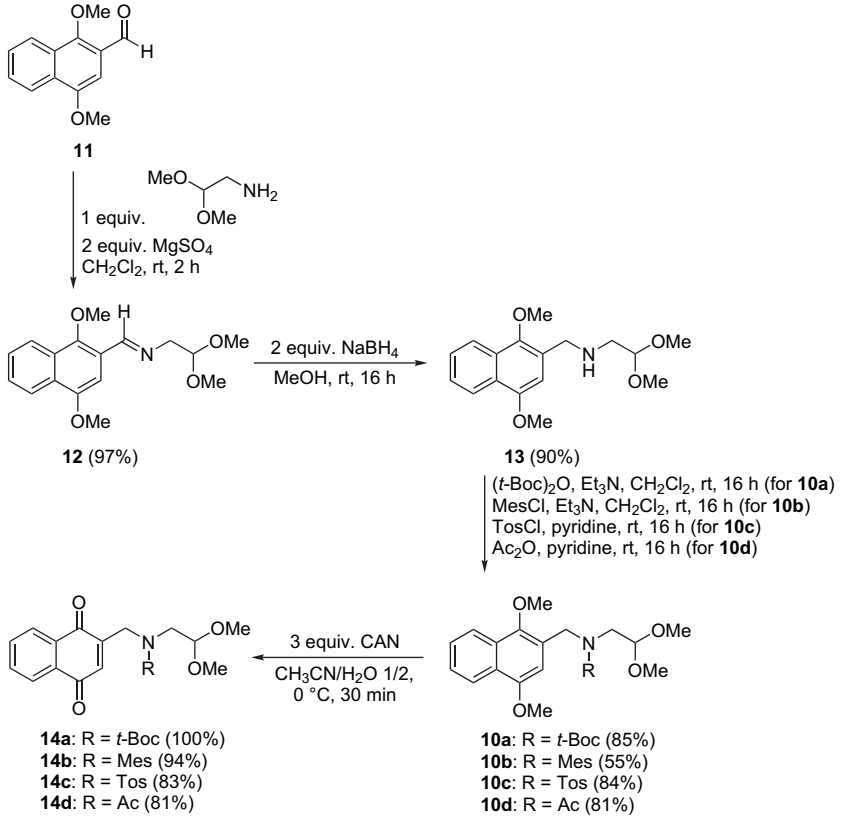
N-((1,4-Dimethoxynaphth-2-yl)methylene)-*N*-(2,2-dimethoxyethyl)amine (**12**) was prepared in 97% yield by condensation of 1,4-dimethoxy-2-formylnaphthalene (**11**)[12] with aminoacetaldehyde dimethyl acetal in dichloromethane in the presence of magnesium(II) sulfate (Scheme 1). Reduction of this aldimine **12** with sodium borohydride in methanol at room temperature gave *N*-(2,2-dimethoxyethyl)-*N*-((1,4-dimethoxynaphth-2-yl)-methyl)amine (**13**) in 90% yield. At this stage of the reaction sequence,

* 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.2008.03.084



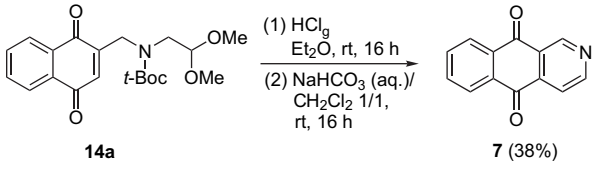
several different types of *N*-protecting groups were then introduced in order to (1) avoid the oxidation of the nitrogen atom during the next oxidative demethylation step with cerium(IV) ammonium nitrate and (2) to test the stability of the different *N*-protecting groups during the final acid-catalyzed cyclization step. In this way, secondary amine **13** was converted into its *N*-*t*-Boc, *N*-methanesulfonyl, *N*-*p*-toluenesulfonyl, and *N*-acetyl derivatives **10a**–**d** in 55–85% yield by reaction with di-*tert*-butyl dicarbonate, methanesulfonyl chloride, *p*-toluenesulfonyl chloride, and acetic anhydride, respectively (Scheme 1). However, it was not possible to introduce more electron-rich *N*-substituents on secondary amine **13**, since reaction with iodomethane in dichloromethane in the presence of silver(I) oxide or potassium carbonate resulted in unaltered starting material. All attempts to cyclize amino acetal **13** and *N*-protected analogues **10** directly under Friedel–Crafts conditions failed completely. Therefore, cerium(IV) ammonium nitrate mediated oxidative demethylation afforded the corresponding 1,4-naphthoquinone



Scheme 1.

acetals **14a**–**d**, which were then also evaluated in the cyclization protocol.

The acid-catalyzed intramolecular cyclization of the *N*-*t*-Boc protected 1,4-napthoquinone acetal **14a** was found only to proceed upon treatment with a saturated solution of dry hydrogen chloride in diethyl ether at room temperature for 16 h (Scheme 2). In a first step, the acetal function of compound **14a** was protonated and after elimination of methanol, the corresponding stabilized carbenium ion was formed, which gave rise to an intramolecular 6-*endo*-*trig* ring closure. It seems that the electron-poor double bond of the quinone system is reactive enough to bring about this cyclization. Then, elimination of methanol and deprotection of the *N*-*t*-Boc group, followed by spontaneous oxidation in air gave rise to the formation of benz[*g*]isoquinoline-5,10-dione (**7**), which was obtained in 38% yield after isolation by flash chromatography. Although the deprotection of the *N*-*t*-Boc group was not targeted, it could not be prevented using the above-mentioned severe reaction conditions. However, treatment of **14a** with diluted aqueous solutions of hydrochloric acid or oxalic acid resulted only in the hydrolysis of the acetal function and no cyclization was observed in these cases. Thus, the conversion of **14a** to the corresponding 1,2-dihydrobenz[*g*]isoquinoline-5,10-dione **9** (R=*t*-Boc) failed due to removal of the *N*-protecting group, which was followed by spontaneous oxidation to the aromatic compound **7**. This conversion was best performed by treatment of the reaction mixture with aqueous sodium hydrogen carbonate at room temperature after the acid-mediated intramolecular cyclization.



14a **7** (38%)

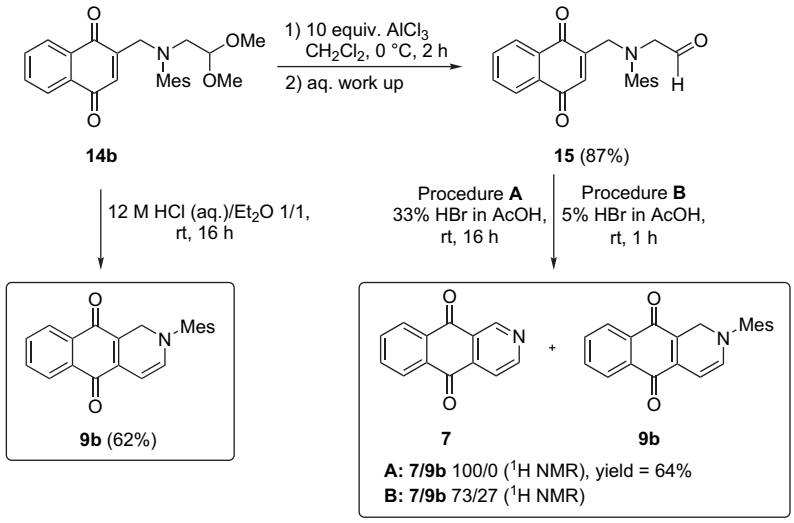
Scheme 2.

Using *N*-methanesulfonyl protected 1,4-naphthoquinone acetal **14b** as a substrate for the Lewis acid-catalyzed intramolecular cyclization, treatment with excess aluminum(III) chloride in dichloromethane afforded aldehyde **15** in 87% yield (Scheme 3). The intramolecular cyclization of this aldehyde **15** was first attempted using different concentrations of hydrobromic acid. The outcome of the cyclization reaction was observed to be dependent upon the applied concentration of hydrobromic acid. Treatment of aldehyde **15** with 33% HBr in acetic acid for 16 h at room temperature gave complete conversion to benz[*g*]isoquinoline-5,10-dione (**7**). However, the hydrolysis of the *N*-methanesulfonyl group could be diminished using less concentrated solutions of hydrobromic acid and a shorter reaction time. Even upon reaction of aldehyde **15** in 5% HBr in acetic acid at room temperature for 1 h, the desired 2-methanesulfonyl-1,2-dihydrobenz[*g*]isoquinoline-5,10-dione (**9b**) was still obtained in a mixture together with 2-azaanthraquinone **7** in a ratio of 73:27 (^{1}H NMR). It was found, however, that the intramolecular cyclization of 1,4-naphthoquinone acetal **14b** could be accomplished using a mixture of 12 M aqueous hydrochloric acid in diethyl ether to afford 2-methanesulfonyl-1,2-dihydrobenz[*g*]isoquinoline-5,10-dione (**9b**) in 62% yield as the sole reaction product without any hydrolysis of the *N*-methanesulfonyl group. Mechanistically, the acetal function of compound **14b** was hydrolyzed by 12 M aqueous hydrochloric acid to the corresponding aldehyde. The protonated aldehyde function then gave rise to an intramolecular 6-*endo*-*trig* ring closure, which was followed by elimination of water and tautomerization to give the target compound **9b**.

Curiously, similar treatment of the *N*-*p*-toluenesulfonyl protected 1,4-naphthoquine acetal **14c** with 12 M aqueous hydrochloric acid for 16 h at room temperature afforded the desired 2-(*p*-toluenesulfonyl)-1,2-dihydrobenz[*g*]isoquinoline-5,10-dione (**9c**) in only 8% yield, together with the 4-hydroxy-2-(*p*-toluenesulfonyl)-1,2,3,4-tetrahydro-benz[*g*]isoquinoline-5,10-dione (**16**), which was isolated in 38% after purification by flash chromatography. It has been reported that *N*-*p*-toluenesulfonyl protected (benzylamino)acetaldehyde acetals selectively afford 4-hydroxy-1,2,3,4-tetrahydroisoquinolines upon treatment with concentrated hydrochloric acid.[13] The complete conversion of 1,4-naphthoquinone acetal **14c** to 3,4-dehydro derivative **9c** could be accomplished after a reaction time of 5 days in a mixture of 12 M aqueous hydrochloric acid and diethyl ether and afforded the pure compound **9c** in 84% yield after recrystallization from ethanol (Scheme 4).

Finally, also the *N*-acetyl protected 1,4-naphthoquinone **14d** was treated with 12 M aqueous hydrochloric acid (Scheme 5). In this case, the reaction conditions seemed to be too strong for the acetyl group to survive and only complex reaction mixtures were obtained.

As it is clear from the above presented results, the synthesis of the targeted *N*-protected benz[*g*]isoquinoline-5,10-diones **9** as direct 2-aza analogues of the natural product pentalongin (**8**) is subject to some severe limitations. First of all, only electron-withdrawing protecting groups could be introduced at nitrogen of



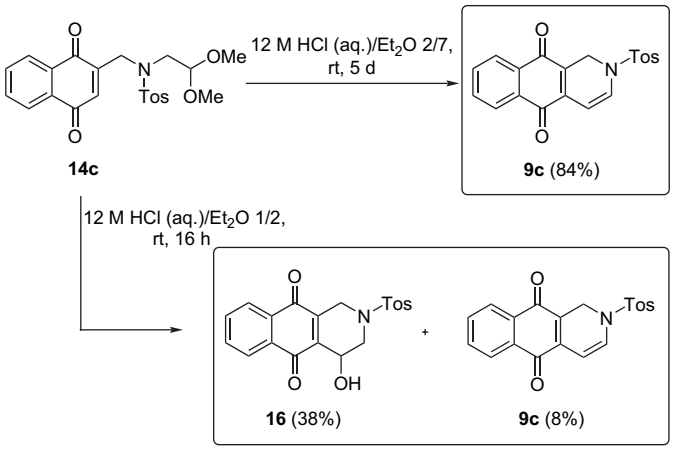
14b **15** (87%)

9b (62%)

7 **9b**

A: 7/9b 100/0 (^{1}H NMR), yield = 64%
B: 7/9b 73/27 (^{1}H NMR)

Scheme 3.



Scheme 4.

N-(2,2-dimethoxyethyl)-*N*-((1,4-dimethoxynaphth-2-yl)methyl)-amine (**13**). Eventually, two derivatives **9b** and **9c** could be synthesized bearing the desired enamine functionality, which is not as straightforward as it seems since in other cases cleavage caused by oxidative aromatization with this type of protecting groups has been established.[14]

3. Conclusion

A synthetic program was directed toward the synthesis of *N*-protected benz[*g*]isoquinoline-5,10-diones **9**, which represent a new class of compounds in organic chemistry. The synthesis toward these 2-aza analogues of pentalongin (**8**) was achieved by the synthesis of different 1,4-naphthoquinone aminoacetals **14**, which could be converted into the target compounds with an acid-mediated intramolecular cyclization.

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 *N*-((1,4-dimethoxynaphth-2-yl)methylene)-(2,2-dimethoxyethyl)amine (12)

1,4-Dimethoxy-2-formylnaphthalene (**11**)[12] (0.016 mol, 3.5 g), aminoacetaldehyde dimethyl acetal (0.016 mol, 1.68 g), and magnesium(II) sulfate (0.032 mol, 3.84 g) were dissolved in dichloromethane in a flask, which was fitted with a calcium chloride tube, and the mixture was stirred for 2 h. Filtration and evaporation of the solvent in vacuo gave the crude imine **12** (4.7 g, 97% yield), which was used without purification in the next step (purity by ^{1}H NMR>95%). An analytical sample was obtained by recrystallization from methanol to give *N*-((1,4-dimethoxynaphth-2-yl)methylene)-*N*-(2,2-dimethoxyethyl)amine (**12**) as yellow flakes, mp 68 °C.

*4.2.1. N-((1,4-Dimethoxynaphth-2-yl)methylene)-N-(2,2-dimethoxyethyl)amine (**12**)*

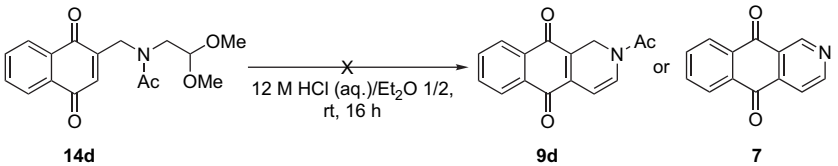
^{1}H NMR ($CDCl_3$): δ 3.42 (6H, s, CH(OCH_3)$_2$), 3.88 (2H, d, J=5.3 Hz, NCH_2), 3.92 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 4.73 (1H, t, J=5.3 Hz, $CH(OCH_3)_2$), 7.48–7.52 (2H, m, H-6 and H-7), 7.35 (1H, s, H-3), 8.06–8.25 (2H, m, H-5 and H-8). ^{13}C NMR ($CDCl_3$): δ 53.9 (CH(OCH_3)$_2$), 55.7 (OCH_3), 63.9 (OCH_3), 64.1 (NCH_2), 100.0 (C-3), 103.8 ($CH(OCH_3)_2$), 122.3 and 122.6 (C-5 and C-8), 124.3 (=C_{quat}), 126.8 and 126.9 (C-6 and C-7), 128.4 (=C_{quat}), 128.5 (=C_{quat}), 151.6 (=C–O), 152.0 (=C–O), 159.6 (C=N). IR (KBr): ν_{max} 1624, 1592, 1449, 1365, 1265 cm^{-1}. MS (ES) m/z (%): 303 (M^+, 11), 216 (6), 199 (6), 75 (100). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.48; H, 6.96; N, 4.52.

4.3. Synthesis of *N*-(2,2-dimethoxyethyl)-*N*-((1,4-dimethoxynaphth-2-yl)methyl)amine (13)

To a cooled (0 °C) solution of *N*-((1,4-dimethoxynaphth-2-yl)methylene)-*N*-(2,2-dimethoxyethyl)amine (**12**) (3 mmol, 0.91 g) in methanol (20 ml) was added sodium borohydride (6 mmol, 0.20 g) and the reaction mixture was stirred for 16 h at room temperature in a flask fitted with a calcium chloride tube. The reaction was quenched by careful addition of water (1 ml) and the solution was concentrated in vacuo to 5 ml. After the addition of water, 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. Flash chromatography on silica gel using a solution of 2% methanol in chloroform as eluent gave *N*-(2,2-dimethoxyethyl)-*N*-((1,4-dimethoxynaphth-2-yl)methyl)amine (**13**) (0.82 g, 90% yield) as an oil.

*4.3.1. N-(2,2-Dimethoxyethyl)-N-((1,4-dimethoxynaphth-2-yl)methyl)amine (**13**)*

^{1}H NMR ($CDCl_3$): δ 2.80 (2H, d, J=5.6 Hz, NCH_2CH), 3.36 (6H, s, CH(OCH_3)$_2$), 3.90 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 4.00 (2H, s, $ArCH_2$), 4.52 (1H, t, J=5.6 Hz, $CH(OCH_3)_2$), 6.81 (1H, s, H-3), 7.43–7.56 (2H, m, H-6 and H-7), 8.02–8.05 (1H, m, H-5 or H-8), 8.20–8.23 (1H, m, H-5 or H-8). ^{13}C NMR ($CDCl_3$): δ 48.3 ($ArCH_2$), 50.5 (NCH_2CH), 53.8 (CH(OCH_3)$_2$), 55.6 (OCH_3), 62.3 (OCH_3), 103.8 ($CH(OCH_3)_2$), 104.8 (C-3), 121.8 and 122.4 (C-5 and C-8), 125.2 and 126.5 (C-6 and C-7), 126.0 (=C_{quat}), 127.7 (=C_{quat}), 128.5 (=C_{quat}),



Scheme 5.

147.5 (=C–O), 152.0 (=C–O). IR (NaCl): ν_{max} 3337, 1629, 1596, 1455, 1372, 1266 cm^{-1}. MS (ES) *m*/*z* (%): 305 (M^+, 11), 216 (32), 201 (100), 75 (93). Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.70; H, 7.44, N, 4.31.

4.4. Synthesis of *N*-(*tert*-butoxycarbonyl)-*N*-(2,2-dimethoxyethyl)-*N*-((1,4-dimethoxy-naphth-2-yl)methyl)amine (10a)

A solution of *N*-(2,2-dimethoxyethyl)-*N*-((1,4-dimethoxynaphth-2-yl)methyl)amine (**13**) (3 mmol, 0.92 g), di-*tert*-butyldicarbonate (3 mmol, 0.65 g), and triethylamine (3 mmol, 0.30 g) in dichloromethane (20 ml) was stirred for 16 h at room temperature under nitrogen atmosphere. The solution was poured in 2 M HCl and the aqueous solution was extracted with dichloromethane, dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel using ethyl acetate/hexane (1:4) as eluent gave *N*-(*tert*-butoxycarbonyl)-*N*-(2,2-dimethoxyethyl)-*N*-((1,4-dimethoxynaphth-2-yl)methyl)amine (**10a**) (1.03 g, 85% yield) as an oil. Product **10a** occurred as a 1:1 mixture of rotamers ($CDCl_3$).

4.4.1. *N-(tert-Butoxycarbonyl)-N-(2,2-dimethoxyethyl)-N-((1,4-dimethoxynaphth-2-yl)methyl)amine (**10a**)*

^1H NMR ($CDCl_3$): δ 1.47 and 1.54 (9H, each s, $C(CH_3)_3$), 3.26 and 3.36 (2H, each d, *J*=4.7 Hz, NCH_2CH), 3.87 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.50 and 4.61 (1H, each t, *J*=4.7 Hz, $CH(OCH_3)_2$), 4.76 and 4.79 (2H, each s, $ArCH_2$), 5.35 and 5.38 (6H, each s, $CH(OCH_3)_2$), 6.67 and 6.75 (1H, each s, H-3), 7.42–7.55 (2H, m, H-6 and H-7), 8.01–8.04 (1H, m, H-5 or H-8), 8.20–8.23 (1H, m, H-5 or H-8). ^{13}C NMR ($CDCl_3$): δ 28.5 ($C(CH_3)_3$), 45.1 and 46.3 ($ArCH_2$), 48.1 and 48.3 (NCH_2CH), 54.2 ($CH(OCH_3)_2$), 55.5 (OCH_3), 62.0 (OCH_3), 62.4 (OCH_3), 80.0 ($C(CH_3)_3$), 102.9 and 103.1 ($CH(OCH_3)_2$), 103.5 and 103.9 (C-3), 121.81 and 122.83 (C-5 and C-8), 125.3 and 126.6 (C-6 and C-7), 126.2 (=C_{quat}), 128.5 (=C_{quat}), 147.0 and 147.5 (N–C=O), 152.1 (=C–O), 156.2 (=C–O). IR (NaCl): ν_{max} 1693, 1629, 1597, 1460, 1369 cm^{-1}. MS (ES) *m*/*z* (%): 405 (M^+, 1), 152 (35), 121 (17), 86 (63), 84 (100). Anal. Calcd for $C_{22}H_{31}NO_6$: C, 65.17; H, 7.71; N, 3.45. Found: C, 64.84; H, 7.46; N, 3.25.

4.5. Synthesis of *N*-methanesulfonyl-*N*-(2,2-dimethoxyethyl)-*N*-((1,4-dimethoxynaphth-2-yl)methyl)amine (10b)

A solution of methanesulfonyl chloride (2 mmol, 0.23 g) in anhydrous dichloromethane (2 ml) was added dropwise to a solution of *N*-(2,2-dimethoxyethyl)-*N*-((1,4-dimethoxynaphth-2-yl)methyl)amine (**13**) (2 mmol, 0.61 g) and triethylamine (2 mmol, 0.20 g) in anhydrous dichloromethane (20 ml) and the reaction mixture was stirred for 16 h at room temperature. The solution was concentrated in vacuo to 5 ml and was poured in 2 M HCl. The aqueous solution was extracted with small portions of dichloromethane and the combined organic extracts were washed with a saturated aqueous solution of sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel using ethyl acetate/hexane (1:1) as eluent gave *N*-methanesulfonyl-*N*-(2,2-dimethoxyethyl)-*N*-((1,4-dimethoxynaphth-2-yl)methyl)amine (**10b**) (0.41 g, 55% yield) as a colorless oil.

4.5.1. *N-Methanesulfonyl-N-(2,2-dimethoxyethyl)-N-((1,4-dimethoxynaphth-2-yl)methyl)amine (**10b**)*

^1H NMR ($CDCl_3$): δ 3.00 (3H, s, SO_2CH_3), 3.31 (2H, d, *J*=5.3 Hz, NCH_2CH), 3.35 (6H, s, $CH(OCH_3)_2$), 3.89 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 4.54 (1H, t, *J*=5.3 Hz, $CH(OCH_3)_2$), 4.70 (2H, s, $ArCH_2$), 6.92 (1H, s, H-3), 7.46–7.58 (2H, m, H-6 and H-7), 8.01–8.04 (1H, m, H-5 or H-8), 8.22–8.25 (1H, m, H-5 or H-8). ^{13}C NMR ($CDCl_3$): δ 39.7 (SO_2CH_3), 45.9 ($ArCH_2$), 47.8 (NCH_2CH), 54.4 ($CH(OCH_3)_2$), 55.8 (OCH_3), 62.6 (OCH_3), 103.0 ($CH(OCH_3)_2$), 104.4 (C-3), 121.9 and 122.5 (C-5 and C-8), 123.8 (=C_{quat}), 125.8 and 126.8 (C-6 and C-7), 126.6 (=C_{quat}), 128.3 (=C_{quat}), 148.0 (=C–O), 152.3 (=C–O). IR (NaCl): ν_{max} 1625, 1595, 1458, 1332, 1146 cm^{-1}. MS (ES) *m*/*z* (%): 383 (M^+, 9), 201 (28), 75 (100). Anal. Calcd for $C_{18}H_{22}NO_6S$: C, 56.38; H, 6.57; N, 3.65. Found: C, 56.06; H, 6.29; N, 3.82.

4.6. Synthesis of *N*-(*p*-toluenesulfonyl)-*N*-(2,2-dimethoxyethyl)-*N*-((1,4-dimethoxynaphth-2-yl)methyl)amine (10c)

p-Toluenesulfonyl chloride (0.01 mol, 2.00 g) was added portionwise over a period of 30 min to a solution of *N*-(2,2-dimethoxyethyl)-*N*-((1,4-dimethoxynaphth-2-yl)methyl)amine (**13**) (0.01 mol, 3.05 g) in pyridine (10 ml) and the reaction mixture was stirred for 16 h at room temperature in a flask, which was fitted with a calcium chloride tube. Water was added and the aqueous solution was extracted with small portions of diethyl ether. The combined organic extracts were washed with 2 M HCl and subsequently with a saturated aqueous solution of sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel with ethyl acetate/hexane (1:4) as eluent gave *N*-(*p*-toluenesulfonyl)-*N*-(2,2-dimethoxyethyl)-*N*-((1,4-dimethoxynaphth-2-yl)methyl)amine (**10c**) (3.87 g, 84% yield) as yellow crystals.

4.6.1. *N-(p-Toluenesulfonyl)-N-(2,2-dimethoxyethyl)-N-((1,4-dimethoxynaphth-2-yl)methyl)amine (**10c**)*

An analytical sample was obtained by recrystallization from ethanol and afforded **10c** as fine yellow needles, mp 80 °C. ^1H NMR ($CDCl_3$): δ 2.42 (3H, s, CH_3), 3.18 (6H, s, $CH(OCH_3)_2$), 3.28 (2H, d, *J*=5.6 Hz, NCH_2CH), 3.83 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.40 (1H, t, *J*=5.6 Hz, $CH(OCH_3)_2$), 4.69 (2H, s, $ArCH_2$), 6.72 (1H, s, H-3), 7.30 (2H, d, *J*=8.3 Hz, 2×CH_{ar}), 7.73–7.55 (2H, m, H-6 and H-7), 7.78 (2H, d, *J*=8.3 Hz, 2×CH_{ar}), 7.87–8.01 (1H, m, H-5 or H-8), 8.18–8.21 (1H, m, H-5 or H-8). ^{13}C NMR ($CDCl_3$): δ 21.5 (CH_3), 47.1 ($ArCH_2$), 49.4 (NCH_2CH), 54.3 ($CH(OCH_3)_2$), 55.6 (OCH_3), 62.4 (OCH_3), 103.3 ($CH(OCH_3)_2$), 103.9 (C-3), 121.9 and 122.4 (C-5 and C-8), 124.2 (=C_{quat}), 125.6 and 126.7 (C-6 and C-7), 126.3 (=C_{quat}), 127.3 (2×CH_{ar}), 128.3 (=C_{quat}), 129.7 (2×CH_{ar}), 137.6 (=C_{quat}), 143.3 (=C_{quat}), 147.6 (=C–O), 152.1 (=C–O). IR (KBr): ν_{max} 1613, 1156 cm^{-1}. MS (ES) *m*/*z* (%): 459 (M^+, 1), 216 (12), 187 (10), 75 (100). Anal. Calcd for $C_{24}H_{29}NO_6S$: C, 62.73; H, 6.36; N, 3.05. Found: C, 62.58; H, 6.41; N, 2.96.

4.7. Synthesis of *N*-acetyl-*N*-(2,2-dimethoxyethyl)-*N*-((1,4-dimethoxynaphth-2-yl)-methyl)amine (10d)

A solution of *N*-(2,2-dimethoxyethyl)-*N*-((1,4-dimethoxynaphth-2-yl)methyl)amine (**13**) (3 mmol, 0.92 g) in pyridine (10 ml) and acetic anhydride (30 mmol, 3.06 g) was stirred for 16 h at room temperature in a flask, fitted with a calcium chloride tube. The reaction mixture was poured in water and the aqueous solution was extracted with small portions of diethyl ether. The combined organic extracts were washed with 2 M HCl and then with a saturated aqueous solution of sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel with ethyl acetate/hexane (4:1) as eluent gave *N*-acetyl-*N*-(2,2-dimethoxyethyl)-*N*-((1,4-dimethoxynaphth-2-yl)-methyl)amine (**10d**) (0.95 g, 87%) as an oil. Product **10d** occurred as a 1:1 mixture of rotamers ($CDCl_3$).

4.7.1. *N-Acetyl-N-(2,2-dimethoxyethyl)-N-((1,4-dimethoxynaphth-2-yl)-methyl)amine (**10d**)*

^1H NMR ($CDCl_3$): δ 2.19 and 2.24 (3H, each s, CH_3), 3.32 and 3.41 (6H, each s, $CH(OCH_3)_2$), 3.35 and 3.54 (2H, each d, *J*=5.3 Hz, NCH_2CH), 3.88 and 3.89 (3H, each s, OCH_3), 3.94 and 3.95 (3H, each s, OCH_3), 4.33 and 4.64 (1H, each t, *J*=5.3 Hz, $CH(OCH_3)_2$), 4.85 and 4.90 (2H, each s, $ArCH_2$), 6.50 and 6.72 (1H, each s, H-3), 7.45–7.59

(2H, m, H-6 and H-7), 8.00–8.05 (1H, m, H-5 or H-8), 8.20–8.25 (1H, m, H-5 or H-8). ^{13}C NMR ($CDCl_3$): δ 21.8 and 21.9 (CH_3), 43.0 and 48.5 (ArCH_2), 48.0 and 50.2 (NCH_2CH), 54.6 and 55.2 (CH(OCH_3)$_2$), 55.7 (OCH_3), 61.9 (OCH_3), 62.6 (OCH_3), 101.8 and 104.4 (C-3), 103.1 and 103.5 (*C*H(OCH_3)$_2$), 121.7 and 121.8 and 122.4 and 122.5 (C-5 and C-8), 124.7 and 125.7 (=C_{quat}), 125.5 and 125.6 and 126.7 and 126.9 (C-6 and C-7), 126.1 and 126.3 (=C_{quat}), 128.3 and 128.5 (=C_{quat}), 147.0 and 147.8 (=C–O), 152.3 and 152.5 (=C–O), 171.7 and 172.1 (C=O). IR (NaCl): ν_{max} 1637, 1594 cm^{-1}. MS (ES) *m*/*z* (%): 347 (M$^+$, 36), 284 (8), 257 (7), 201 (30), 75 (100). Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.50; H, 7.10; N, 4.25.

4.8. Cerium(IV) ammonium nitrate mediated oxidative demethylation of *N*-protected amines 10

General procedure. A solution of cerium(IV) ammonium nitrate (3 mmol) in water (10 ml) was added dropwise to a cooled (0 °C) solution of an *N*-protected amine **10** (1 mmol) in acetonitrile (5 ml) and the resulting mixture was stirred for 30 min at room temperature. The reaction mixture was poured in water and the aqueous solution was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated in vacuo to afford the crude 1,4-naphthoquinones **14**.

*4.8.1. N-(tert-Butoxycarbonyl)-2-(((2,2-dimethoxyethyl)amino)-methyl)-1,4-naphthoquinone (**14a**)*

Oil, crude yield: 100%. The product decomposed upon flash chromatography on silica gel with ethyl acetate/hexane (1:4) as eluent. The product occurred as a 1:1 mixture of rotamers ($CDCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.41 and 1.51 (9H, each s, C(CH_3)$_3$), 3.35 and 3.42 (2H, each d, *J*=5.3 Hz, NC*H*$_2$CH), 3.38 and 3.39 (6H, each s, CH(OC*H*$_3$)$_2$), 4.43–4.54 (3H, m, ArC*H*$_2$ and C*H*(OCH_3)$_2$), 6.66 and 6.72 (1H, each s, H-3), 7.72–7.77 (2H, m, H-6 and H-7), 8.04–8.11 (2H, m, H-5 and H-8). ^{13}C NMR ($CDCl_3$): δ 27.4 and 28.3 (C(*C*H$_3$)$_3$), 47.0 and 47.4 (ArCH_2), 49.7 and 50.0 (NCH_2CH), 54.6 (CH(OCH_3)$_2$), 80.6 and 80.7 (*C*(CH$_3$)$_3$), 103.4 and 104.0 (*C*H(OCH_3)$_2$), 126.09 and 126.16 and 126.27 and 126.32 (C-5 and C-8), 132.0 (=C_{quat}), 132.1 and 132.2 (=C_{quat}), 133.2 and 133.3 and 133.7 and 133.8 and 133.9 (C-3, C-6 and C-7), 146.8 and 147.3 (N–C=O), 155.25 and 155.34 (=C_{quat}), 184.7 and 184.8 (C=O), 185.0 (C=O). IR (NaCl): ν_{max} 1695, 1662, 1593 cm^{-1}. MS (ES) *m*/*z* (%): 375 (M$^+$, 1), 75 (100).

*4.8.2. N-Methanesulfonyl-2-(((2,2-dimethoxyethyl)amino)methyl)-1,4-naphthoquinone (**14b**)*

Oil, yield: 94%. The product was used without purification in the next step (purity by ^{1}H NMR>95%). An analytical sample was obtained by recrystallization from ethanol to give **14b** as brown crystals, mp 118–119 °C. ^{1}H NMR ($CDCl_3$): δ 3.02 (3H, s, SO_2CH_3), 3.37 (6H, s, CH(OC*H*$_3$)$_2$), 3.40 (2H, d, *J*=5.0 Hz, NC*H*$_2$CH), 4.47–4.51 (3H, m, ArC*H*$_2$ and C*H*(OCH_3)$_2$), 7.06 (1H, t, *J*=1.7 Hz, H-3), 7.74–7.77 (2H, m, H-6 and H-7), 8.08–8.11 (2H, m, H-5 and H-8). ^{13}C NMR ($CDCl_3$): δ 39.03 (SO_2CH_3), 47.42 (ArCH_2), 49.77 (NCH_2CH), 54.81 (CH(OCH_3)$_2$), 103.66 (*C*H(OCH_3)$_2$), 126.34 and 126.38 (C-5 and C-8), 132.02 (=C_{quat}), 132.07 (=C_{quat}), 133.83 and 134.10 (C-6 and C-7), 135.34 (C-3), 145.77 (=C_{quat}), 184.62 (C=O), 185.03 (C=O). IR (NaCl): ν_{max} 1651, 1613, 1590, 1143 cm^{-1}. MS (ES) *m*/*z* (%): no M$^+$, 75 (100). Anal. Calcd for $C_{16}H_{19}NO_6S$: C, 54.38; H, 5.42; N, 3.96. Found: C, 54.71; H, 5.44; N, 3.81.

*4.8.3. N-(p-Toluenesulfonyl)-2-(((2,2-dimethoxyethyl)amino)-methyl)-1,4-naphthoquinone (**14c**)*

Recrystallization from ethanol gave **14c** (83% yield) as yellow crystals, mp 98–100 °C. ^{1}H NMR ($CDCl_3$): δ 2.41 (3H, s, CH_3), 3.30 (6H, s, CH(OC*H*$_3$)$_2$), 3.32 (2H, d, *J*=5.3 Hz, NC*H*$_2$CH), 4.39 (2H, d, *J*=1.7 Hz, ArC*H*$_2$), 4.45 (1H, t, *J*=5.3 Hz, C*H*(OCH_3)$_2$), 7.04 (1H, t, *J*=1.7 Hz, H-3), 7.24–7.31 (2H, m, 2×CH_{ar}), 7.69–7.76 (4H, m, 2×CH_{ar}, H-6 and H-7), 8.04–8.09 (2H, m, H-5 and H-8). ^{13}C NMR ($CDCl_3$): δ 21.51 (CH_3), 48.45 (ArCH_2), 51.59 (NCH_2CH), 54.70 (CH(OCH_3)$_2$), 103.95 (*C*H(OCH_3)$_2$), 126.23 and 126.32 (H-5 and H-8), 127.28 (2×CH_{ar}), 129.92 (2×CH_{ar}), 132.04 (=C_{quat}), 133.71 and 133.96 and 135.24 (C-3, C-6 and C-7), 136.15 (=C_{quat}), 143.93 (=C_{quat}), 146.22 (=C_{quat}), 184.69 (C=O), 184.90 (C=O). IR (KBr): ν_{max} 1652, 1628, 1590, 1157 cm^{-1}. MS (ES) *m*/*z* (%): 429 (M$^+$, 2), 274 (100), 242 (47), 227 (65). Anal. Calcd for $C_{22}H_{23}NO_6S$: C, 61.52; H, 5.40; N, 3.26. Found: C, 61.32; H, 5.22; N, 3.22.

*4.8.4. N-Acetyl-2-(((2,2-dimethoxyethyl)amino)methyl)-1,4-naphthoquinone (**14d**)*

Flash chromatography on silica gel with ethyl acetate/hexane (4:1) gave **14d** (81% yield) as a yellow oil. Product **14d** occurred as a 1:1 mixture of rotamers. ^{1}H NMR ($CDCl_3$): δ 2.11 and 2.24 (3H, each s, CH_3), 3.39 and 3.42 (6H, each s, CH(OC*H*$_3$)$_2$), 3.46 and 3.48 (2H, d, *J*=5.6 Hz, NC*H*$_2$CH), 4.44 and 4.54 (1H, t, *J*=5.6 Hz, C*H*(OCH_3)$_2$), 4.58–4.61 (2H, d, *J*=1.7 Hz, ArC*H*$_2$), 6.65–6.72 (1H, t, *J*=1.7 Hz, H-3), 7.73–7.79 (2H, m, H-6 and H-7), 8.04–8.12 (2H, m, H-5 and H-8). ^{13}C NMR ($CDCl_3$): δ 20.83 and 21.10 (CH_3), 45.19 and 48.34 (ArCH_2), 48.07 and 51.34 (NCH_2CH), 54.38 and 54.59 (CH(OCH_3)$_2$), 102.61 and 102.97 (*C*H(OCH_3)$_2$), 125.54 and 125.75 and 125.84 (C-5 and C-8), 131.38 and 131.48 (=C_{quat}), 131.54 (=C_{quat}), 132.97 and 133.10 (C-3), 133.24 and 133.41 and 133.48 and 133.68 (C-6 and C-7), 145.36 and 145.55 (=C_{quat}), 171.07 and 171.23 (N–C=O), 183.77 (C=O), 184.20 and 184.46 (C=O). IR (NaCl): ν_{max} 1661, 1628, 1595 cm^{-1}. MS (ES) *m*/*z* (%): 317 (M$^+$, 1), 201 (15), 75 (100). Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.02; H, 5.88; N, 4.39.

4.9. Reaction of *N*-(*tert*-butoxycarbonyl)-2-(((2,2-dimethoxyethyl)amino)methyl)-1,4-naphthoquinone (14a) with HCl(g)

N-(*tert*-Butoxycarbonyl)-2-(((2,2-dimethoxyethyl)amino)-methyl)-1,4-naphthoquinone (**14a**) (2.5 mmol, 1 g) was added to a saturated solution of dry HCl gas in dry diethyl ether (50 ml) and the mixture was stirred for 16 h in a stoppered flask. A precipitate was gradually formed during the course of the reaction and was dissolved in dichloromethane (50 ml) after isolation by filtration. The solution was stirred vigorously for 16 h at room temperature with a saturated aqueous solution of sodium hydrogen carbonate (50 ml) in an open flask. The organic phase was separated, dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel using ethyl acetate/hexane (1:4) as eluent gave benz[g]isoquinoline-5,10-dione (**7**) (200 mg, 38% yield) as white crystals. Spectral data were in accordance with the literature data.[15]

4.10. Synthesis of *N*-methanesulfonyl-(((1,4-dioxonaphth-2-yl)methyl)amino)acetaldehyde (15)

Aluminum(III) chloride (6 mmol, 0.80 g) was added portionwise to a cooled (0 °C) solution of *N*-methanesulfonyl-2-(((2,2-dimethoxyethyl)amino)methyl)-1,4-naphthoquinone (**14b**) (0.6 mmol, 212 mg) in dichloromethane (20 ml) and the resulting mixture was stirred for 2 h at 0 °C. The reaction was quenched by careful addition of water (5 ml) and then 2 M HCl was added. The mixture was extracted with dichloromethane and the combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel using ethyl acetate/hexane (1:1) as eluent gave *N*-methanesulfonyl-(((1,4-dioxonaphth-2-yl)methyl)amino)acetaldehyde (**15**) (160 mg, 87%) as a brown oil, which was found to decompose rapidly.

*4.10.1. N-Methanesulfonyl-(((1,4-dioxonaphth-2-yl)methyl)-amino)acetaldehyde (**15**)*

^{1}H NMR ($CDCl_3$): δ 3.08 (3H, s, SO_2CH_3), 4.37 (2H, s, CH_2CHO), 4.40 (2H, d, J=1.7 Hz, $ArCH_2$), 7.06 (1H, t, J=1.7 Hz, H-3), 7.75–7.81 (2H, m, H-6 and H-7), 8.07–8.11 (2H, m, H-5 and H-8), 9.60 (1H, s, CHO). ^{13}C NMR ($CDCl_3$): δ 40.0 (SO_2CH_3), 47.0 ($ArCH_2$), 57.8 (CH_2CHO), 126.4 and 126.5 (C-5 and C-8), 131.9 (=C_{quat}), 132.0 (=C_{quat}), 134.0 and 134.3 (C-6 and C-7), 135.8 (C-3), 144.9 (=C_{quat}), 185.5 (C=O), 185.1 (C=O), 196.7 (CHO).

4.11. Reaction of *N*-methanesulfonyl-(((1,4-dioxonaphth-2-yl)-methyl)amino)acetaldehyde (15) with 33% HBr in acetic acid

N-Methanesulfonyl-(((1,4-dioxonaphth-2-yl)methyl)amino)-acetaldehyde (**15**) (0.3 mmol, 100 mg) was mixed with 33% HBr in acetic acid and stirred for 16 h at room temperature in a stoppered flask. Water was added and the aqueous solution was extracted with dichloromethane. The combined organic extracts were washed with a saturated aqueous solution of sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel with ethyl acetate/hexane (1:4) as eluent gave benz[*g*]isoquinoline-5,10-dione (**7**) (40 mg, 64% yield) as white crystals. Spectral data were in accordance with the literature data.[15]

4.12. Reaction of *N*-methanesulfonyl-(((1,4-dioxonaphth-2-yl)methyl)amino)acetaldehyde (15) with 5% HBr in acetic acid

To a cooled (0 °C) solution of *N*-methanesulfonyl-(((1,4-dioxonaphth-2-yl)methyl)amino)acetaldehyde (**15**) (0.6 mmol, 200 mg) in glacial acetic acid (5 ml) was added dropwise a solution of 33% HBr in acetic acid (1 ml) and the reaction mixture was stirred for 1 h at room temperature. The mixture was poured in water and extracted with dichloromethane. The combined organic extracts were washed with a saturated aqueous solution of sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated in vacuo to give a mixture of benz[*g*]isoquinoline-5,10-dione (**7**) and 2-methanesulfonyl-1,2-dihydrobenz[*g*]isoquinoline-5,10-dione (**9b**) in a ratio of 73:27 (^{1}H NMR). Spectral data of benz[*g*]isoquinoline-5,10-dione (**7**) were in accordance with the literature data.[15]

*4.12.1. 2-Methanesulfonyl-1,2-dihydrobenz[g]isoquinoline-5,10-dione (**9b**)*

An analytical sample was prepared by recrystallization from ethanol and afforded **9b** as fine red needles, mp 161–163 °C. ^{1}H NMR ($CDCl_3$): δ 3.04 (3H, s, SO_2CH_3), 4.84 (2H, s, CH_2), 6.17 (1H, d, J=7.4 Hz, H-4), 7.12 (1H, d, J=7.4 Hz, H-4), 7.74–7.77 (2H, m, H-7 and H-8), 8.08–8.13 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$): δ 39.0 (SO_2CH_3), 41.3 (CH_2), 100.6 (C-4), 126.2 and 126.7 (C-6 and C-9), 126.3 (=C_{quat}), 131.4 (=C_{quat}), 132.3 (=C_{quat}), 133.7 and 134.2 (C-7 and C-8), 134.4 (C-3), 137.1 (=C_{quat}), 181.7 (C=O), 181.9 (C=O). IR (KBr): ν_{max} 1661, 1646, 1634, 1613, 1583, 1563, 1157 cm^{-1}. MS (ES) m/z (%): 289 (M^+, 9), 210 (100), 182 (8), 154 (7), 127 (19). Anal. Calcd for $C_{14}H_{11}NO_4S$: C, 58.12; H, 3.83; N, 4.84. Found: C, 57.89; H, 3.79; N, 4.72.

4.13. Synthesis of 2-methanesulfonyl-1,2-dihydrobenz[g]-isoquinoline-5,10-dione (9b) from *N*-methanesulfonyl-2-(((2,2-dimethoxyethyl)amino)methyl)-1,4-naphthoquinone (14b)

To a cooled (0 °C) solution of *N*-methanesulfonyl-2-(((2,2-dimethoxyethyl)amino)methyl)-1,4-naphthoquinone (**14b**) (1.4 mmol, 0.49 g) in diethyl ether (20 ml) was added portionwise 12 M HCl (20 ml) and the mixture was stirred vigorously for 16 h at room temperature in a stoppered flask, which was protected from light with aluminum foil. The suspension was poured in water, extracted with dichloromethane, dried ($MgSO_4$), and evaporated in vacuo. Recrysallization form ethanol gave 2-methanesulfonyl-1,2-dihydrobenz[*g*]isoquinoline-5,10-dione (**9b**) (250 mg, 62% yield) as fine red needles, mp 161–163 °C. For spectral data of 2-methanesulfonyl-1,2-dihydrobenz[*g*]isoquinoline-5,10-dione (**9b**) vide supra.

4.14. Synthesis of 2-(*p*-toluenesulfonyl)-1,2-dihydrobenz[*g*]-isoquinoline-5,10-dione (9c) and 4-hydroxy-2-(*p*-toluenesulfonyl)-1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-dione (16)

Procedure 1. To a cooled (0 °C) solution of *N*-(*p*-toluenesulfonyl)-2-(((2,2-dimethoxyethyl)amino)methyl)-1,4-naphthoquinone (**14c**) (2 mmol, 0.86 g) in diethyl ether (40 ml) was added dropwise 12 M HCl (20 ml) and the reaction mixture was stirred vigorously for 16 h at room temperature in a stoppered flask, which was protected from light with aluminum foil. The mixture was poured in water, extracted with dichloromethane, dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel using ethyl acetate/hexane (1:4) as eluent gave 2-(*p*-toluenesulfonyl)-1,2-dihydrobenz[*g*]-isoquinoline-5,10-dione (**9c**) (60 mg, 8% yield) as red crystals. A second fraction was collected by elution with ethyl acetate/hexane (1:1) as eluent to give 4-hydroxy-2-(*p*-toluenesulfonyl)-1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-dione (**16**) (290 mg, 38% yield) as yellow crystals, mp 178 °C.

Procedure 2. To a cooled (0 °C) solution of *N*-(*p*-toluenesulfonyl)-2-(((2,2-dimethoxyethyl)amino)methyl)-1,4-naphthoquinone (**14c**) (2.8 mmol, 1.20 g) in diethyl ether (70 ml) was added dropwise 12 M HCl (20 ml) and the reaction mixture was stirred vigorously for 5 days at room temperature in a stoppered flask, which was protected from light with aluminum foil. Water was added and the suspension was extracted with dichloromethane, dried ($MgSO_4$), and evaporated in vacuo. Recrystallization from ethanol gave 2-(*p*-toluenesulfonyl)-1,2-dihydrobenz[*g*]isoquinoline-5,10-dione (**9c**) (0.86 g, 84% yield) as red needles, 154 °C.

*4.14.1. 2-(p-Toluenesulfonyl)-1,2-dihydrobenz[g]isoquinoline-5,10-dione (**9c**)*

^{1}H NMR ($CDCl_3$): δ 2.41 (3H, s, CH_3), 4.61 (2H, s, CH_2), 6.07 (1H, d, J=7.6 Hz, H-4), 7.26 (1H, d, J=7.6 Hz, H-3), 7.35 (2H, d, J=8.3 Hz, 2×CH_{ar}), 7.68–7.72 (2H, m, H-7 and H-8), 7.75 (2H, d, J=8.3 Hz, 2×CH_{ar}), 8.02–8.07 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$): δ 21.6 (CH_3), 41.1 (CH_2), 100.0 (C-4), 126.1 and 126.6 (C-6 and C-9), 126.4 (=C_{quat}), 127.5 (2×CH_{ar}), 130.2 (2×CH_{ar}), 131.4 (=C_{quat}), 132.3 (=C_{quat}), 133.5 and 134.1 (C-7 and C-8), 133.6 (=C_{quat}), 134.8 (C-3), 136.9 (=C_{quat}), 145.1 (=C_{quat}), 181.7 (C=O), 181.8 (C=O). IR (KBr): ν_{max} 1670, 1646, 1616, 1594, 1564, 1163 cm^{-1}. MS (ES) m/z (%): 365 (M^+, 12), 210 (100). Anal. Calcd for $C_{20}H_{15}NO_4S$: C, 65.74; H, 4.14; N, 3.83. Found: C, 65.50; H, 4.27; N, 3.68.

*4.14.2. 4-Hydroxy-2-(p-toluenesulfonyl)-1,2,3,4-tetrahydrobenz[g]-isoquinoline-5,10-dione (**16**)*

^{1}H NMR ($CDCl_3$): δ 2.43 (3H, s, CH_3), 3.04 (1H, d×d, J=2.6, 13.2 Hz, C*H*H-3), 3.72 (1H, d×d, J=1.3, 19.8 Hz, C*H*H-1), 4.24 (1H, m, CH*H*-3), 4.69 (1H, d, J=19.8 Hz, CH*H*-1), 5.26 (1H, d, J=1.3 Hz, H-4), 7.36 (2H, d, J=7.9 Hz, 2×CH_{ar}), 7.68–7.81 (4H, m, H-7 and H-8, 2×CH_{ar}), 8.06–8.13 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$): δ 21.6 (CH_3), 42.5 (C-1), 46.6 (C-4), 49.3 (C-3), 126.6 and 126.9 (C-6 and C-9), 127.9 (2×CH_{ar}), 128.1 (=C_{quat}), 130.0 (2×CH_{ar}), 130.2 (=C_{quat}), 131.5 (=C_{quat}), 133.3 (=C_{quat}), 134.3 and 134.5 (C-7 and C-8), 139.9 (=C_{quat}), 140.8 (=C_{quat}), 144.4 (=C_{quat}), 181.0 (C=O), 182.9 (C=O). IR (KBr): ν_{max} 1667, 1638, 1593, 1162 cm^{-1}. MS (ES) m/z (%): 365

(M^+-H_2O, 1), 210 (18), 209 (100), 181 (35). Anal. Calcd for $C_{20}H_{17}NO_5S$: C, 62.65; H, 4.47; N, 4.47. Found: C, 62.43; H, 4.27; N, 3.62.

Acknowledgements

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

References and notes

1. Arsenault, G. P. *Tetrahedron Lett.* **1965**, *45*, 4033–4037 and references therein.
2. Steyn, P. S.; Wessels, P. L.; Marasas, W. F. O. *Tetrahedron* **1979**, *35*, 1551–1555.
3. 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.
4. (a) Miljkovic, A.; Mantle, P. G.; Williams, D. J.; Rassing, B. *J. Nat. Prod.* **2001**, *64*, 1251–1253; (b) Moriyasu, Y.; Miyagawa, H.; Hamada, N.; Miyakawi, H.; Ueno, T. *Phytochemistry* **2001**, *58*, 239–241.
5. Nguyen Van, T.; Verniest, G.; Claessens, S.; De Kimpe, N. *Tetrahedron* **2005**, *61*, 2295–2300.
6. Parisot, D.; Devys, M.; Barbier, M. *Z. Naturforsch.* **1989**, *44*, 1473–1474.
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. Parisot, D.; Devys, M.; Barbier, M. *J. Antibiot.* **1989**, *42*, 1189–1190.
9. Visconti, A.; Surico, G.; Iacobellis, N. S.; Bottalico, A. *Phytopath. Medit.* **1983**, *22*, 122–156.
10. 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.
11. (a) Kesteleyn, B.; De Kimpe, N.; Van Puyvelde, L. *J. Org. Chem.* **1999**, *64*, 1173–1179; (b) Kesteleyn, B.; De Kimpe, N. *Tetrahedron Lett.* **2000**, *41*, 755–758.
12. Syper, L.; Mchlochowski, J.; Kloc, K. *Tetrahedron* **1983**, *39*, 781–792.
13. Bates, H. A.; Garelick, J. S. *J. Org. Chem.* **1984**, *49*, 4552–4555.
14. Claessens, S.; Jacobs, J.; De Kimpe, N. *Synlett* **2007**, 741–744.
15. (a) Potts, K. T.; Bhattacharjee, D.; Walsh, E. B. *J. Org. Chem.* **1986**, *51*, 2011–2021; (b) Ohgaki, E.; Motoyoshiya, J.; Narita, S.; Kakurai, T.; Hayashi, S.; Hirakawa, K.-I. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3109–3112.