Vicinal acetylenic derivatives of 2-amino-1,4-naphthoquinone as key precursors of heterocyclic quinones

M. S. Shvartsberg, E. A. Kolodina, N. I. Lebedeva, and L. G. Fedenok*

Institute of Chemical Kinetics and Combustion, Siberian Branch of the Russian Academy of Sciences, 3 ul. Institutskaya, 630090 Novosibirsk, Russian Federation. Fax: +7 (383) 330 7350. E-mail: shvarts@kinetics.nsc.ru

The Pd-catalyzed reaction between 3-acetylamino-2-bromo-1,4-naphthoquinones and Cu^I acetylides prepared *in situ* gave 3-acetylamino-2-alkynyl-1,4-naphthoquinones, which were transformed into benz[*f*]indole-4,9-dione and benzo[*g*]quinoline-5,10-dione derivatives.

Key words: 1,4-naphthoquinones, bromoarenes, alkynes, organocopper compounds, heterocyclization, benz[*f*]indole-4,9-diones, benzo[*g*]quinoline-5,10-diones.

Many biologically active compounds of the natural and synthetic origin, for example, serotonin,[1] physostigmine,[2] arbidol,[3] indometacine,[4] quinine,[5] 20(*S*)-camptothecin,[6] and arylquinolines[7] contain the indole or quinoline moiety. Due to the high efficiency of the search for new biologically active indole and quinoline derivatives, the parent heterocycles, in the first turn indole, can be considered as privileged structures.[8,9] In 1970s, catalytic methods were developed for the replacement of halogen atoms in aromatic compounds by acetylenic groups.[10—13] Later on, a general methodology was elaborated for the design of various multinuclear fused heterocycles starting from functionalized *ortho*- and *peri*-substituted arylacetylenes. In terms of this methodology, methods for the synthesis of indoles and quinolines by the heterocyclization of *ortho*-acetylenic derivatives of arylamines or -amides were developed and are widely used.[14—17] However, the application of this method to the synthesis of indole- and quinoline quinones, *i.e.*, compounds in which the quinone ring is fused directly to the heterocycle, is virtually unstudied since the methods for the introduction of acetylenic substituents into the quinone ring are poorly developed. Meanwhile, a number of compounds exhibiting pronounced biological activity, *e.g.* mitomycin,[18] EO 9,[19] streptonigrin,[20] and marcanines[21] contain the indole quinone or quinoline quinone moiety.

In the present study, we developed a general method for the synthesis of *vic*-acetylenic derivatives of 2-aminonaphthoquinone and showed that they can undergo heterocyclization to form benz[*f*]indole-4,9-diones and benzo[*g*]quinoline-5,10-diones. The first results of the present study have been published in the preliminary communication.[22]

In fact, 2-bromo-1,4-naphthoquinone (**1**) containing the halogen atom in the quinone ring does not give cross-coupling products with terminal acetylenes in the conventional Sonogashira reaction,[23] but reacts with Cu^I acetylides in the presence of the Pd complex as the catalyst.[24] Unlike compound **1**, neither 3-amino-2-bromo- (**2**) nor 3-amino-2-iodo-1,4-naphthoquinone (**3**) react with Cu^I acetylides under the same conditions. We suggested that a decrease in the reactivity of compounds **2** and **3** is associated with the formation of the push-pull conjugated system $H_2N\overset{\curvearrowright}{-}C=\overset{\curvearrowright}{C}-C=\overset{\curvearrowright}{O}$ and the resulting increase in the electron density on the C(2) atom. Obviously, *N*-acetylated analogs should be more active because the +M effect of the amido group is much weaker. The difference in the electron density on the C(2) atom of compound **2** and its *N*-acetyl derivative **4** is confirmed by their ^{13}C NMR spectra. The signal of the C(2) atom in the spectrum of amide **4** is shifted downfield by 29 ppm with respect to this signal in the spectrum of amine **2**. The experiment showed that 3-acetylamino-2-bromo-1,4-naphthoquinone (**4**) and its iodine-containing analog **5** exothermically react with Cu^I acetylides in the presence of $Pd(PPh_3)_2Cl_2$ in a DMSO—$CHCl_3$ mixture even at 20 °C. 3,5-Bis(acetylamino)-2-bromo-1,4-naphthoquinone (**6**), in which the benzene ring is potentially activated toward the electrophilic substitution, also readily reacts with Cu^I acetylides. To develop a facile and versatile method for the synthesis of 3-acetylamino-2-alkynyl-1,4-naphthoquinones **7** and **8**, we combined the preparation of copper acetylides from terminal acetylenes **9** and the subsequent cross-coupling in a one-pot process (Scheme 1, Table 1).

Acetylides, including those unstable in the solid state, were synthesized by the reaction of acetylenes **9** with equivalent amounts of CuI and Et_3N in DMSO. Then bromo derivatives **4** or **6** and the catalyst were added, and the cross-coupling was performed, which took 15—40 min. In

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 580—586, March, 2012.

1066-5285/12/6103-582

Scheme 1

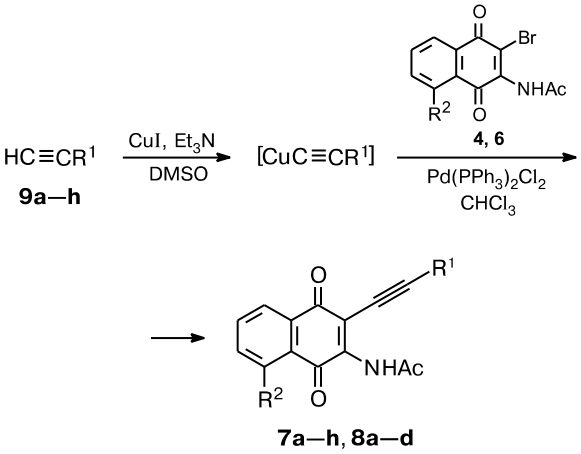
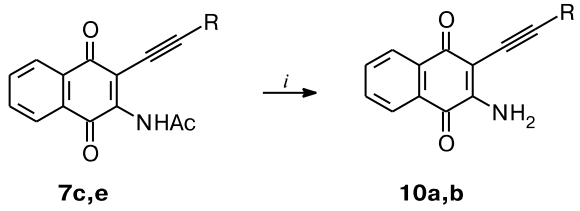


Table 1. Cross-coupling of bromine-containing naphthoquinones **4** and **6** with terminal acetylenes **9**

Compound	R^1	R^2	Yield (%)
7a	Ph	H	73
7b	4-$O_2NC_6H_4$	H	81
7c	CH_2OTHP*	H	65
7d	CH_2CH_2OH	H	82
7e	$CH(OH)Pr^i$	H	83
7f	$C(OH)Me_2$	H	73
7g	C(*cyclo*-Pr)(Me)OH	H	73
7h	1-Hydroxycyclohexyl	H	77
8a	Ph	NHAc	85
8b	CH_2OTHP*	NHAc	90
8c	$C(OH)Me_2$	NHAc	92
8d	1-Hydroxycyclohexyl	NHAc	93

* THP is tetrahydropyran-2-yl.

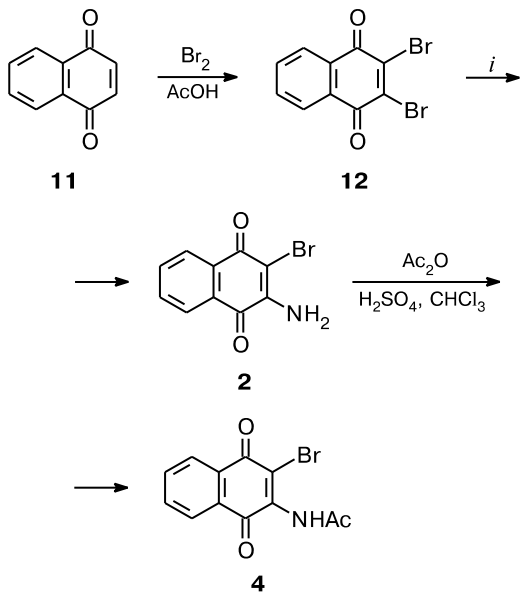
Scheme 2



i. NaOH, dioxane, aqueous solution of EtOH.

10: R = CH_2OTHP (**a**), $CH(OH)Pr^i$ (**b**)

Scheme 3



i. NH_3, aqueous solution of dioxane.

the absence of the Pd catalyst, the reaction proceeded much more slowly and was accompanied by the formation of by-products. This synthesis is actually the one-pot two-step cross-coupling of amidoquinonyl bromides with terminal acetylenes.

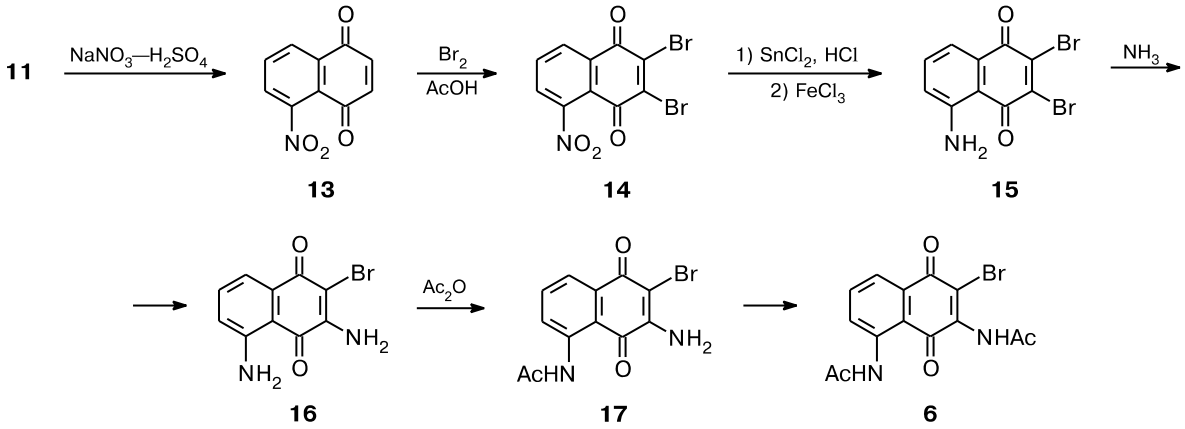
Acetamidonaphthoquinonyl acetylenes **7** are easily *N*-deacetylated in dioxane at 5—12 °C when treated with a ~1% aqueous ethanol solution of NaOH (Scheme 2).

The precursor of acetylenes **7**, *viz.*, bromo derivative **4**, was synthesized from 1,4-naphthoquinone **11** (Scheme 3). The treatment of quinone **11** with bromine in AcOH in the presence of I_2 at 118 °C afforded 2,3-dibromo derivative **12**.[25] One of the halogen atoms in dibromide **12** was replaced by the amino group using aqueous NH_3 in dioxane. Then product **2** was treated with Ac_2O in the presence of a catalytic amount of H_2SO_4 in $CHCl_3$ at 50 °C to prepare compound **4**.

3,5-Diacetylamino-2-bromo-1,4-naphthoquinone (**6**) was synthesized in a similar way (Scheme 4). Naphthoquinone **11** was nitrated with a mixture of $NaNO_3$ and H_2SO_4 at 0—40 °C.[26] The bromination of nitro quinone **13** afforded nitro dibromide **14**, and the nitro group in the latter was reduced with $SnCl_2$ in a AcOH—HCl mixture at 70 °C. The amino group at position 5 of compound **15** promotes the nucleophilic attack predominantly on position 3.[16] In accordance with this fact, the reaction of **15** with aqueous NH_3 produced almost exclusively individual 3,5-diamino-2-bromo-1,4-naphthoquinone (**16**). The acetylation of diamine **16** was performed in two steps. In the first step (Ac_2O, H_2SO_4, dioxane, 50 °C), 5-acetylamino-3-amino-2-bromo-1,4-naphthoquinone (**17**) was obtained. The latter was transformed into diacetyl derivative **6** under the conditions of the acetylation of amine **2**.

The proposed methods for the synthesis of bromo derivatives **4** and **6** and their cross-coupling with terminal acetylenes **9**, as a whole, provide a preparatively simple and versatile route from naphthoquinone **11** to *vic*-acety-

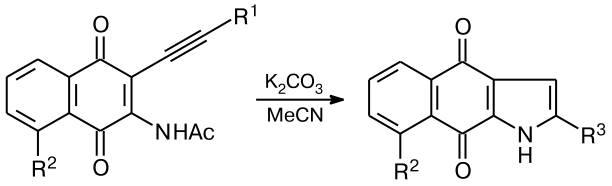
Scheme 4



lenic derivatives of 2-acetylamino- and 2-aminonaphthoquinones **7**, **8**, and **10**. We demonstrated the key role of these acetylenes as precursors of nitrogen-containing heterocyclic quinones by performing the synthesis of benz[*f*]indole-4,9-diones and benzo[*g*]quinoline-5,10-diones.

It is known that the cyclization of *o*-alkynylarylamines or -amides to indoles is catalyzed by transition metal salts and complexes and strong bases.[27] Under drastic conditions of cyclization, naphthoquinone derivatives are unstable. Hence, it was important to find out whether these compounds are, in principle, able to undergo cyclization under relatively mild conditions. We succeeded in performing the cyclization of a number of the synthesized amido acetylenes **7a**,**c**,**f**—**h** and **8c**,**d** to the corresponding indole quinones **18a**—**e** and **19a**,**b** in the presence of an equimolar amount of anhydrous K_2CO_3 powder in MeCN at 80 °C (Scheme 5, Table 2).

Scheme 5



7a,c,f—h, **8f,h** **18a,c,f—h**, **19f,h**

The reaction is completed within 15—40 min. The heterocyclization is accompanied by the deacylation to give 2-substituted benz[*f*]indole-4,9-diones **18** and **19**. In the case of substrates containing the tertiary alcohol group **7f**—**h** and **8c**,**d**, the reaction involves the dehydration to form alkenyl-substituted derivatives **18** and **19**. Under the reaction conditions used, 2-alkynyl-3-aminonaphthoquinones do not undergo cyclization. The fact that the cyclization of these compounds does not proceed under mild conditions is apparently attributed to the characteristic features of their conjugation system. The possibility of cyclization depends on the delocalization of the negative charge, which appears on the α-C atom of the acetylenic substituent in the course of the nucleophilic addition of the amino group. The polarization of the C(2)=C(3) double bond and an increase in the electron density on the C(2) atom hinder delocalization and, consequently, interfere with the reaction. In addition, it cannot be ruled out that the nucleophilic attack on the triple bond is preceded by its deprotonation, which is more probable in the case of amide substrates.

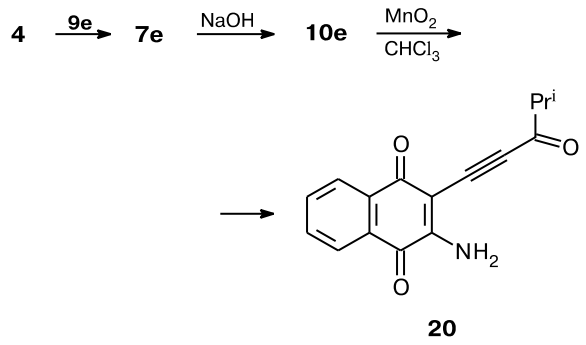
Table 2. Cyclization of amido acetylenes **7** and **8** to indole quinones **18** and **19**

Starting compound	Product	R^1	R^2	R^3	Yield (%)
7a	**18a**	Ph	H	Ph	73
7c	**18b**	CH_2OTHP	H	CH_2OTHP	43
7f	**18c**	$C(OH)Me_2$	H	$C(Me)=CH_2$	65
7g	**18d**	C(OH)Me(*cyclo*-Pr)	H	C(*cyclo*-Pr)=CH_2	53
7h	**18e**	1-Hydroxycyclohexyl	H	Cyclohex-1-enyl	70
8c	**19a**	$C(OH)Me_2$	NHAc	$C(Me)=CH_2$	75
8d	**19b**	1-Hydroxycyclohexyl	NHAc	Cyclohex-1-enyl	40

It should be noted that the method used for the cyclization of amido acetylenes **7** and **8** is not versatile. The cyclization of certain amido acetylenes, for example, of **7d**,**e** and **8b**, was accompanied by side reactions and resinification and gives indole quinones in low yields.

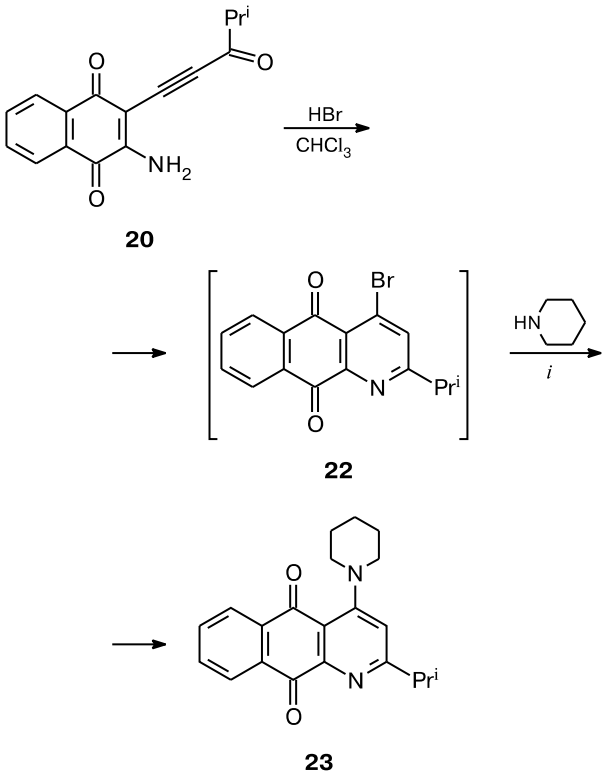
The proposed method for the cross-coupling of bromoquinonylamides with terminal acetylenes is a key to the annulation of naphthoquinone not only to the pyrrole ring but also to the six-membered pyridine ring. Previously, we have performed the cyclization of 3-amino-2-(4-methyl-3-oxopentenyl)-1,4-naphthoquinone (**20**) using HCl in an organic solvent and prepared 4-chloro-2-isopropylbenzo[*g*]quinoline-5,10-dione (**21**).[28] The most facile and efficient method for the synthesis of such acetylenic precursors of quinoline quinones involves the condensation of bromo amide **4** with secondary acetylenic alcohols **9** followed by the deacylation and selective oxidation of the resulting amino alcohol with active MnO_2. Ketone **20** was synthesized from bromo derivative **4** in a total yield of 62% (Scheme 6).

Scheme 6



The nature of the halogen atom in quinoline quinones **21** can have a considerable effect on their reactivity toward nucleophiles. The chlorine atom is easily replaced in the reactions with such nucleophiles as amines and phenols.[28] In the catalytic cross-coupling, bromides and iodides are active, whereas chlorides are inactive.[23] Since we showed that it is, in principle, possible to construct the pyridine ring based on acylethynylamines, which were prepared from bromo derivatives **4**, it was of interest to study the prospects of the functionalization of the resulting 4-halo-1-azaanthraquinones. For this purpose, we performed the synthesis of 4-bromo-2-isopropylbenzo[*g*]-quinoline-5,10-dione (**22**). As expected, the reaction of ketone **20** with HBr under the same conditions as those used in the reaction with HCl affords bromoazaanthraquinone **22** (Scheme 7). However, we failed to isolate compound **22** in the analytically pure form due apparently to its insufficient stability. Nevertheless, according to the TLC data, compound **22** is the major reaction product, and its structure was confirmed by ^{1}H NMR spectroscopy. The replacement of the bromine atom in compound **22** without its isolation can be performed by the one-pot procedure. This method was used to synthesize piperidine derivative **23** from ketone **20** (see Scheme 7).

Scheme 7



i. Dioxane.

Therefore, amido acetylenes of type **7**, which are produced by the cross-coupling of amido bromide **4** with secondary acetylenic alcohols, can be used as precursors of 4-halo-1-azaanthraquinones. The presence of a labile halogen atom in the latter compounds provides the ability to introduce various functional groups into these heterocyclic quinones.

Experimental

The ^{1}H NMR spectra were recorded on a Bruker DPX-200 spectrometer (200 MHz) in $CDCl_3$. The ^{13}C NMR spectra were measured on a Bruker AV-300 spectrometer (75 MHz) in DMSO-d_6. The IR spectra were recorded on a Bruker Vector 22 instrument in $CHCl_3$. The course of the reactions was monitored and the purity of the compounds was checked by TLC on Silufol UV 254 plates.

5-Nitro-1,4-naphthoquinone (13) was synthesized according to a known procedure[26] in 78% yield, m.p. 167—168 °C (MeOH).

2,3-Dibromo-1,4-naphthoquinone (12) was synthesized by the bromination of 1,4-naphthoquinone (**11**) according to a known procedure[29] in 93% yield, m.p. 216—217 °C (toluene).

2,3-Dibromo-5-nitro-1,4-naphthoquinone (14) was synthesized as described for dibromide **12** starting from nitroquinone **13** in 78% yield, m.p. 209—210 °C (1,2-dichloroethane—hexane).[29]

5-Amino-2,3-dibromo-1,4-naphthoquinone (15). A solution of $SnCl_2 \cdot 2H_2O$ (22.4 g, 99.0 mmol) in concentrated HCl (26 mL) was added dropwise to a suspension of compound **14** (6.7 g, 18.0 mmol) in AcOH (130 mL) under Ar at 50 °C. The reaction mixture was stirred at 70 °C for 15 min and then cooled. Water (0.5 L) and a solution of $FeCl_3 \cdot 6H_2O$ (31.3 g, 116.0 mmol) in water (0.4 L) were successively added, and the reaction mixture was stirred for 30 min. The precipitate was filtered off, washed with water, and dried. The yield of amine **15** was 5.7 g (93%), m.p. ~225 °C (decomp., toluene—hexane). Found (%): C, 36.00; H, 1.83; Br, 48.08. $C_{10}H_5Br_2NO_2$. Calculated (%): C, 36.29; H, 1.52; Br, 48.28. ^{1}H NMR, δ: 6.76 (br.s, 2 H, NH_2); 6.97 (dd, 1 H, H(6), J_1 = 8.3 Hz, J_2 = 1.1 Hz); 7.35—7.50 (m, 1 H, H(7)); 7.55 (dd, 1 H, H(8), J_1 = 7.3 Hz, J_2 = 1.1 Hz). IR, ν/cm^{-1}: 1610, 1670 (C=O); 3360, 3500 (NH_2).

3-Amino-2-bromo-1,4-naphthoquinone (2). A mixture of dibromide **12** (8.0 g, 20.0 mmol), dioxane (130 mL), and 25% aqueous NH_3 (110 mL) was stirred at 25—30 °C for 2.5 h and then poured into water (1.5 L). The precipitate was filtered off, washed with water, and dried in air. The yield of product **2** was 5.8 g (91%), m.p. 204—205 °C (toluene, *cf.* lit. data[25]). ^{13}C NMR, δ: 101.4 (C(2)); 126.1, 126.4, 132.6, 132.8 (C(5), C(6), C(7), C(8)); 129.6, 132.2 (C(4a), C(8a)); 148.8 (C(3)); 175.1, 178.7 (C(1), C(4)).

3,5-Diamino-2-bromo-1,4-naphthoquinone (16). The amination of compound **15** (4.0 g, 12.0 mmol) was performed as described for amine **2**. The yield of product **16** was 3.0 g (93%), m.p. ~260 °C (decomp., toluene). Found (%): C, 44.83; H, 2.60; Br, 29.59. $C_{10}H_7BrN_2O_2$. Calculated (%): C, 44.97; H, 2.64; Br, 29.92. ^{1}H NMR, δ: 5.68 (br.s, 2 H, NH_2); 6.64 (br.s, 2 H, NH_2); 6.84 (dd, 1 H, H(6), J_1 = 8.4 Hz, J_2 = 1.1 Hz); 7.35—7.50 (m, 1 H, H(7)); 7.55 (dd, 1 H, H(8), J_1 = 7.3 Hz, J_2 = 1.1 Hz). IR, ν/cm^{-1}: 1610 (C=O); 3340, 3450 (NH_2); 3315, 3430 (NH_2).

3-Acetylamino-2-bromo-1,4-naphthoquinone (4). The acetylating reagent, which was prepared by shacking Ac_2O (2.4 g, 2.3 mL, 24.3 mmol), concentrated H_2SO_4 (0.10—0.15 mL), and $CHCl_3$ (2 mL), was added with stirring to a solution of amine **2** (1.5 g, 5.9 mmol) in anhydrous $CHCl_3$ (75 mL). The reaction mixture was heated at 50 °C for 45 min, cooled, and poured into water (0.5 L). The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$. The combined extracts were washed with water and dried with $MgSO_4$. The solvent was removed *in vacuo*. Toluene was added to the residue, and the solvent was again removed *in vacuo*. This operation was repeated several times. After recrystallization of the solid residue from a mixture of $CHCl_3$ and toluene, amide **4** was isolated in a yield of 1.0 g (62%), m.p. 226—227 °C (*cf.* lit. data[25]). ^{13}C NMR, δ: 23.0 (Me); 126.7, 126.9, 134.5 (C(5), C(6), C(7), C(8)); 130.3 (C(2)); 130.7, 130.9 (C(4a), C(8a)); 144.6 (C(3)); 168.1 (CO (Ac)); 177.8, 178.1 (C(1), C(4)).

3,5-Bis(acetylamino)-2-bromo-1,4-naphthoquinone (6). Step 1. 5-Acetylamino-3-amino-2-bromo-1,4-naphthoquinone (**17**). A solution of diamine **16** (1.1 g, 4.0 mmol) and Ac_2O (4.3 g, 4.0 mL, 42.0 mmol) in anhydrous dioxane (75 mL) acidified with concentrated H_2SO_4 (0.05 mL) was stirred at 60 °C for 15 min, cooled, diluted with water, and extracted with $CHCl_3$. The extract was washed with water and dried with $MgSO_4$. The solvent was removed *in vacuo*. The yield of compound **17** containing a small amount of diamide **6** was obtained in a yield of 1.2 g (97%). M.p. compound **17** ~260 °C (decomp., toluene). Found (%): C, 47.00; H, 2.95; Br, 25.30. $C_{12}H_9BrN_2O_3$. Calculated (%): C, 46.63; H, 2.93; Br, 25.85. ^{1}H NMR, δ: 2.29 (s, 3 H, Me); 5.73 (br.s, 2 H, NH_2); 7.55—7.95 (m, 2 H, H(7), H(8)); 8.90—9.00 (m, 1 H, H(6)); 11.50 (br.s, 1 H, NH).

Step 2. The acetylation of monoamide **17** (1.0 g, 3.0 mmol) with Ac_2O (2.2 g, 2.0 mL, 21.5 mmol) in $CHCl_3$ (40 mL), which was performed as described for compound **2**, afforded 3,5-bis-(acetylamino)-2-bromo-1,4-naphthoquinone in a yield of 1.1 g (97%) (**6**), m.p. ~275 °C (decomp., toluene). Found (%): C, 47.78; H, 3.25; Br, 25.65. $C_{14}H_{11}BrN_2O_4$. Calculated (%): C, 47.88; H, 3.16; Br, 22.75. ^{1}H NMR, δ: 2.29 (s, 6 H, Ac); 7.55 (br.s, 1 H, 3-NH); 7.65—7.80 (m, 1 H, H(7)); 7.94 (dd, 1 H, H(8), J_1 = 7.6 Hz, J_2 = 1.2 Hz); 9.08 (dd, 1 H, H(6), J_1 = 8.6 Hz, J_2 = 1.2 Hz); 11.45 (br.s, 1 H, 5-NH). IR, ν/cm^{-1}: 1620,1645, 1675, 1710 (C=O); 3310, 3375 (NH).

Cross-coupling of 3-acetylamino-2-bromo-1,4-naphthoquinones 4 and 6 with terminal acetylenes 9 (general procedure). Copper iodide (0.35 g, 1.8 mmol) was added to DMSO (10 mL), and this was stirred under argon at 20 °C for 10 min. Then Et_3N (0.18 g, 0.25 mL, 1.8 mmol) and terminal acetylene **9** (2.0 mmol) were added. After 10 min, a solution of bromide **4** or **6** (1.5 mmol) and $Pd(PPh_3)_2Cl_2$ (10 mg) in anhydrous $CHCl_3$ (5 mL) were added. The reaction mixture was stirred at ~20 °C for 15—40 min (until the completion of the reaction), diluted with $CHCl_3$ (100 mL) containing AcOH (0.5 mL), and poured into water (0.4 L) acidified with AcOH (1 mL). The precipitate was filtered off and washed with $CHCl_3$. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$. The combined chloroform extracts were washed with water and dried with $MgSO_4$. The solvent was removed *in vacuo*. Product **7** or **8** was recrystallized from hexane, cooled, filtered off, and washed with a small amount of diethyl ether (see Table 1).

3-Acetylamino-2-phenylethynyl-1,4-naphthoquinone (7a). M.p. 186—187 °C (decomp., EtOH).[24]

3-Acetylamino-2-(4-nitrophenylethynyl)-1,4-naphthoquinone (7b). M.p. 222—223 °C (decomp., EtOAc). Found (%): C, 66.59; H, 3.09. $C_{20}H_{12}N_2O_5$. Calculated (%): C, 66.67; H, 3.36. ^{1}H NMR, δ: 2.35 (s, 3 H, Ac); 7.65—7.85 (m, 4 H, H(6), H(7), $PhNO_2$); 8.05—8.30 (m, 5 H, H(5), H(8), $PhNO_2$, NH). IR, ν/cm^{-1}: 1668, 1730 (C=O); 2203 (C≡C); 3358 (NH).

3-Acetylamino-2-[3-(tetrahydropyran-2-yloxy)prop-1-yn-1-yl]-1,4-naphthoquinone (7c). M.p. 139—140 °C (toluene). Found (%): C, 67.92; H, 5.68; N, 4.30. $C_{20}H_{19}NO_5$. Calculated (%): C, 67.98; H, 5.42; N, 3.96. ^{1}H NMR, δ: 1.50—1.90 (m, 6 H, $(CH_2)_3$); 2.27 (s, 3 H, Ac); 3.50—3.65 and 3.80—3.95 (both m, 2 H, OCH_2); 4.60 (d, 2 H, C≡CCH_2, J = 0.8 Hz); 4.95 (br.s, 1 H, OCHO); 7.70—7.80 (m, 2 H, H(6), H(7)); 7.94 (br.s, 1 H, NH); 8.00—8.20 (m, 2 H, H(5), H(8)). IR, ν/cm^{-1}: 1666, 1730 (C=O); 2223 (C≡C); 3365 (NH).

3-Acetylamino-2-(4-hydroxybut-1-yn-1-yl)-1,4-naphthoquinone (7d). M.p. 163—164 °C (toluene). Found (%): C, 68.07; H, 4.59; N, 5.02. $C_{16}H_{13}NO_4$. Calculated (%): C, 67.84; H, 4.63; N, 4.94. ^{1}H NMR, δ: 2.30 (s, 3 H, Ac); 2.79 (т, 2 H, C≡CCH_2, J = = 5.3 Hz); 3.60—3.90 (m, 3 H, CH_2, OH); 7.65—7.85 (m, 2 H, H(6), H(7)); 8.00—8.20 (m, 3 H, H(5), H(8), NH). IR, ν/cm^{-1}: 1699, 1705, 1717 sh (C=O); 2222 (C≡C); 3362 (NH); 3486 w (OH).

3-Acetylamino-2-(3-hydroxy-4-methylpent-1-yn-1-yl)-1,4-naphthoquinone (7e). M.p. 148—149 °C (toluene).[28]

3-Acetylamino-2-(3-hydroxy-3-methylbut-1-yn-1-yl)-1,4-naphthoquinone (7f). M.p. 160—161 °C (toluene). Found (%): C, 68.44; H, 5.11; N, 4.94. $C_{17}H_{15}NO_4$. Calculated (%): C, 68.68; H, 5.09; N, 4.71. ^{1}H NMR, δ: 1.61 (s, 6 H, Me); 2.28 (s, 3 H, Ac); 2.47 (br.s, 1 H, OH); 7.70—7.80 (m, 2 H, H(6), H(7)); 7.97

(br.s, 1 H, NH); 8.05—8.20 (m, 2 H, H(5), H(8)). IR, ν/cm^{-1}: 1669, 1727 (C=O); 2219 (C≡C); 3365 (NH); 3498 br (OH).

3-Acetylamino-2-(3-hydroxy-3-cyclopropylbut-1-yn-1-yl)-1,4-naphthoquinone (7g). M.p. 134—135 °C (toluene). Found (%): C, 70.80; H, 5.46; N, 4.46. $C_{19}H_{17}NO_4$. Calculated (%): C, 70.58; H, 5.30; N, 4.33. ^{1}H NMR, δ: 0.40—0.80 (m, 4 H, $(CH_2)_2$); 1.15—1.30 (m, 1 H, CH); 1.66 (s, 3 H, Me); 2.28 (s, 3 H, Ac); 2.60 (br.s, 1 H, OH); 7.65—7.80 (m, 2 H, H(6), H(7)); 7.97 (br.s, 1 H, NH); 8.00—8.15 (m, 2 H, H(5), H(8)). IR, ν/cm^{-1}: 1667, 1723 (C=O); 2218 (C≡C); 3366 (NH); 3585 br (OH).

3-Acetylamino-2-(1-hydroxycyclohexylethynyl)-1,4-naphthoquinone (7h). M.p. 164—165 °C (toluene). Found (%): C, 71.13; H, 5.87; N, 4.33. $C_{20}H_{19}NO_4$. Calculated (%): C, 71.20; H, 5.68; N, 4.15. ^{1}H NMR, δ: 1.50—1.80 and 1.95—2.10 (both m, 10 H, $(CH_2)_5$); 2.28 (s, 3 H, Ac); 2.67 (br.s, 1 H, OH); 7.65—7.80 (m, 2 H, H(6), H(7)); 7.97 (br.s, 1 H, NH); 8.00—8.15 (m, 2 H, H(5), H(8)). IR, ν/cm^{-1}: 1667, 1727 (C=O); 2215 (C≡C); 3366 (NH); 3492 s (OH).

3,5-Bis(acetylamino)-2-phenylethynyl-1,4-naphthoquinone (8a). M.p. 148—149.5 °C (decomp., toluene). Found (%): C, 70.96; H, 4.63; N, 7.29. $C_{22}H_{16}N_2O_4$. Calculated (%): C, 70.96; H, 4.33; N, 7.52. ^{1}H NMR, δ: 2.24 and 2.33 (both s, 6 H, Ac); 7.30—7.45 (m, 3 H, Ph); 7.50—7.65 (m, 2 H, Ph); 7.65—7.80 (m, 1 H, H(7)); 7.80—7.95 (m, 1 H, H(8)); 7.98 (br.s, 1 H, 3-NH); 8.95—9.10 (m, 1 H, H(6)); 11.63 (br.s, 1 H, 5-NH). IR, ν/cm^{-1}: 1635, 1670, 1710 (C=O); 2207 (C≡C); 3310, 3380 (NH).

3,5-Bis(acetylamino)-2-[3-(tetrahydropyran-2-yloxy)prop-1-yn-1-yl]-1,4-naphthoquinone (8b). M.p. ~118 °C (decomp., toluene). Found (%): C, 64.09; H, 5.19; N, 7.03. $C_{22}H_{22}N_2O_6$. Calculated (%): C, 64.38; H, 5.40; N, 6.83. ^{1}H NMR, δ: 1.60—1.90 (m, 6 H, $(CH_2)_3$); 2.27 and 2.28 (both s, 6 H, Ac); 3.45—3.60 and 3.75—3.95 (both m, 2 H, OCH_2); 4.59 (s, 2 H, C≡CCH_2); 4.93 (br.s, 1 H, OCHO); 7.60—7.80 (m, 1 H, H(7)); 7.86 (dd, 1 H, H(8), J_1 = 7.5 Hz, J_2 = 1.2 Hz); 7.95 (br.s, 1 H, 3-NH); 9.03 (dd, 1 H, H(6), J_1 = 8.5 Hz, J_2 = 1.2 Hz); 11.57 (br.s, 1 H, 5-NH). IR, ν/cm^{-1}: 1634, 1668, 1707 (C=O); 2227 (C≡C); 3302, 3370 (NH).

3,5-Bis(acetylamino)-2-(3-hydroxy-3-methylbut-1-yn-1-yl)-1,4-naphthoquinone (8c). M.p. ~170 °C (decomp., toluene—diethyl ether). Found (%): C, 64.19; H, 5.18; N, 8.02. $C_{19}H_{18}N_2O_5$. Calculated (%): C, 64.40; H, 5.12; N, 7.90. ^{1}H NMR, δ): 1.61 (s, 6 H, Me); 2.28 and 2.29 (both s, 6 H, Ac); 2.72 (br.s, 1 H, OH); 7.65—7.80 (m, 1 H, H(7)); 7.84 (dd, 1 H, H(8), J = 7.6 Hz, J = 1.3 Hz); 7.99 (br.s, 1 H, 3-NH); 9.03 (dd, 1 H, H(6) J = 8.5 Hz, J = 1.3 Hz); 11.59 (br.s, 1 H, 5-NH). IR, ν/cm^{-1}: 1634, 1666, 1707 (C=O); 2217 (C≡C); 3303, 3369 (NH); 3496 w (OH).

3,5-Bis(acetylamino)-2-(1-hydroxycyclohexylethynyl)-1,4-naphthoquinone (8d). M.p. 172—173 °C (toluene—diethyl ether). Found (%): C, 67.11; H, 5.41; N, 7.24. $C_{22}H_{22}N_2O_5$. Calculated (%): C, 66.99; H, 5.62; N, 7.10. ^{1}H NMR, δ: 1.50—1.80 and 1.95—2.10 (both m, 10 H, $(CH_2)_5$); 2.29 (s, 6 H, Ac); 2.75 (br.s, 1 H, OH); 7.65—7.90 (m, 2 H, H(7), H(8)); 7.97 (br.s, 1 H, 3-NH); 9.03 (dd, 1 H, H(6), J = 8.5 Hz, J = 1.2 Hz); 11.61 (br.s, 1 H, 5-NH). IR, ν/cm^{-1}: 1633, 1666, 1712 (C=O); 2213 (C≡C); 3299, 3370 (NH), 3496 w (OH).

3-Amino-2-[3-(tetrahydropyran-2-yloxy)prop-1-yn-1-yl]-1,4-naphthoquinone (10a). A solution of NaOH (0.06 g, 1.5 mmol) in aqueous EtOH (1 : 1, v/v, 10 mL) was gradually added with stirring to a solution of amide **7c** (0.34 g, 0.9 mmol) in dioxane (20 mL) at 5—12 °C for 1.5 h until the starting compound was consumed. The reaction mixture was diluted with water (0.3 L) and extracted with CH_2Cl_2. The organic extract was washed with water and dried with $MgSO_4$, and the solvent was removed *in vacuo*. The product was crystallized in hexane and filtered off. The yield of compound **10c** was 0.24 g (80.0%), m.p. 129—130 °C (diethyl ether). Found (%): C, 69.28; H, 5.53; N, 4.48. $C_{18}H_{17}NO_4$. Calculated (%): C, 69.44; H, 5.50; N, 4.50. ^{1}H NMR, δ: 1.60—1.90 (m, 6 H, $(CH_2)_3$); 3.45—3.60 and 3.80—3.95 (both m, 2 H, OCH_2); 4.60 (s, 2 H, C≡CCH_2); 4.85—4.95 (m, 1 H, OCHO); 5.95 (br.s, 2 H, NH_2); 7.55—7.80 (m, 2 H, H(6), H(7)); 8.00—8.15 (m, 2 H, H(5), H(8)). IR, ν/cm^{-1}: 1645, 1677 (C=O); 2217 (C≡C); 3384, 3502 (NH_2).

3-Amino-2-(3-hydroxy-4-methylpent-1-yn-1-yl)-1,4-naphthoquinone (10b). Amino alcohol **10b** was synthesized as described for amine **10a**, m.p. 143—144 °C.[28]

3-Amino-2-(4-methyl-3-oxopent-1-yn-1-yl)-1,4-naphthoquinone (20). A mixture of amino alcohol **10b** (0.7 g, 2.6 mmol) and activated MnO_2 (7.0 g) in anhydrous $CHCl_3$ (90 mL) was stirred at 20 °C for 30—40 min (until the competion of the reaction). The precipitate was filtered off and thoroughly washed with $CHCl_3$. The solvent was removed *in vacuo*, and the residue was crystallized in hexane. The yield was 0.6 g (85.7%), m.p. 145—146 °C (toluene—hexane).[28]

Indoles 18 and 19 (general procedure). A mixture of amide **7a—h** or **8c,d** (0.8 mmol), freshly calcined K_2CO_3 powder (0.8 mmol), and MeCN (30 mL) was stirred at 80 °C until the competion of the reaction. Then the reaction mixture was cooled and filtered. The filtrate was diluted with water (0.2 L) acidified with AcOH (1 mL) and extracted with $CHCl_3$. The extract was washed with water and dried with $MgSO_4$. The solvent was removed *in vacuo*. Product **18** or **19** was isolated by chromatography on SiO_2 using CH_2Cl_2, a toluene—$CHCl_3$ mixture, or a toluene—AcOEt mixture as the eluent (see Table 2).

2-Phenylbenz[*f*]indole-4,9-dione (18a). M.p. 305—306 °C (toluene—diethyl ether). Found (%): C, 79.07; H, 4.05; N, 4.94. $C_{18}H_{11}NO_2$. Calculated (%): C, 79.11; H, 4.06; N, 5.12. ^{1}H NMR, δ: 7.09 (s, 1 H, H(3)); 7.30—7.55 (m, 3 H, Ph); 7.65—7.75 (m, 4 H, H(6), H(7), Ph); 8.10—8.25 (m, 2 H, H(5), H(8)); 10.25 (br.s, 1 H, NH). IR, ν/cm^{-1}: 1654 (C=O); 3428 (NH).

2-(Tetrahydropyran-2-yloxy)benz[*f*]indole-4,9-dione (18b). M.p. 166—167 °C (toluene—diethyl ether). Found (%): C, 69.52; H, 5.65; N, 4.69. $C_{18}H_{17}NO_4$. Calculated (%): C, 69.44; H, 5.50; N, 4.50. ^{1}H NMR, δ: 1.50—2.00 (m, 6 H, $(CH_2)_3$); 3.50—3.70 and 3.90—4.05 (both m, 2 H, CH_2O); 4.65—4.80 (m, 1 H, OCHO); 4.75 (d, 2 H, CH_2O, J = 3.4 Hz); 6.65 (s, 1 H, H(3)); 7.60—7.75 (m, 2 H, H(6), H(7)); 8.05—8.20 (m, 2 H, H(5), H(8)); 9.95 (br.s, 1 H, NH). IR, ν/cm^{-1}: 1693 (C=O); 3420 (NH).

2-Isopropenylbenz[*f*]indole-4,9-dione (18c). M.p. 168—169 °C (toluene—hexane). Found (%): C, 75.69; H, 4.92; N, 5.97. $C_{15}H_{11}NO_2$. Calculated (%): C, 75.93; H, 4.67; N, 5.90. ^{1}H NMR, δ: 2.15 (s, 3 H, Me); 5.21 (d, 1 H, =CH_a, J = 1.4 Hz); 5.48 (s, 1 H, =CH_b); 6.82 (d, 1 H, H(3), J = 2.4 Hz); 7.60—7.75 (m, 2 H, H(6), H(7)); 8.05—8.20 (m, 2 H, H(5), H(8)); 9.55 (br.s, 1 H, NH). IR, ν/cm^{-1}: 1653 (C=O); 3432 (NH).

2-(1-Cyclopropylvinyl)benz[*f*]indole-4,9-dione (18d). M.p. 177—178 °C (toluene). Found (%): C, 77.72; H, 5.13; N, 5.21. $C_{17}H_{13}NO_2$. Calculated (%): C, 77.55; H, 4.98; N, 5.32. ^{1}H NMR, δ: 0.55—0.70 and 0.80—0.95 (both m, 4 H, $(CH_2)_2$); 1.60—1.80 (m, 1 H, CH); 5.13 (d, 1 H, C=CH_a, J = 2.3 Hz); 5.51 (s, 1 H, C=CH_b); 6.99 (d, 1 H, H(3), J = 2.4 Hz); 7.60—7.75 (m, 2 H, H(6), H(7)); 8.05—8.20 (m, 2 H, H(5), H(8)); 9.75 (br.s, 1 H, NH). IR, ν/cm^{-1}: 1655 (C=O); 3434 (NH).

2-(Cyclohex-1-enyl)benz[*f*]indole-4,9-dione (18e). M.p. 245—246 °C (toluene—diethyl ether). Found (%): C, 77.73; H, 5.56; N, 5.14. $C_{18}H_{15}NO_2$. Calculated (%): C, 77.96; H, 5.45; N, 5.05. ^{1}H NMR, δ: 1.55—1.85 (m, 4 H, $(CH_2)_2$, cyclohexenyl); 2.15—2.45 (m, 4 H, CH_2—C=C—CH_2); 6.35—6.45 (m, 1 H, HC=C); 6.73 (d, 1 H, H(3), J = 2.3 Hz); 7.55—7.75 (m, 2 H, H(6), H(7)); 8.05—8.20 (m, 2 H, H(5), H(8)); 9.90 (br.s, 1 H, NH). IR, ν/cm^{-1}: 1647 (C=O); 3432 (NH).

8-Acetylamino-2-isopropenylbenz[*f*]indole-4,9-dione (19a). M.p. 191—192 °C (toluene). Found (%): C, 69.30; H, 5.08; N, 9.74. $C_{17}H_{14}N_2O_3$. Calculated (%): C, 69.38; H, 4.80; N, 9.52. ^{1}H NMR, δ: 2.14 (s, 3 H, Me); 2.29 (s, 3 H, Ac); 5.23 (d, 1 H, $=CH_a$, J = 1.5 Hz); 5.46 (s, 1 H, $=CH_b$); 6.78 (d, 1 H, H(3), J = 2.4 Hz); 7.55—7.70 (m, 1 H, H(6)); 7.93 (dd, 1 H, H(5), J_1 = 7.6 Hz, J_2 = 1.2 Hz); 8.97 (dd, 1 H, H(7), J_1 = 8.5 Hz, J_2 = 1.2 Hz); 9.33 (br.s, 1 H, H(1)); 12.18 (br.s, 1 H, 8 NH). IR, ν/cm^{-1}: 1628, 1669, 1695 (C=O); 3432 (NH).

8-Acetylamino-2-(cyclohex-1-enyl)benz[*f*]indole-4,9-dione (19b). M.p. 149—150 °C (toluene—hexane). Found (%): C, 71.95; H, 5.50; N, 8.26. $C_{20}H_{18}N_2O_3$. Calculated (%): C, 71.84; H, 5.43; N, 8.38. ^{1}H NMR, δ: 1.60—1.85 (m, 4 H, $(CH_2)_2$, cyclohexenyl); 2.15—2.40 (m, 7 H, Ac, CH_2—C=C—CH_2); 6.25—6.35 (m, 1 H, C=CH); 6.69 (d, 1 H, H(3), J = 2.3 Hz); 7.55—7.70 (m, 1 H, H(6)); 7.92 (dd, 1 H, H(5), J_1 = 7.6 Hz, J_2=1.2 Hz); 8.97 (dd, 1 H, H(7), J_1 = 8.6 Hz, J_2 = 1.2 Hz); 9.25 (br.s, 1 H, H(1)); 12.23 (br.s, 1 H, 8 NH). IR, ν/cm^{-1}: 1623, 1668, 1696 (C=O); 3435 (NH).

2-Isopropyl-4-piperidinobenzo[*g*]quinoline-5,10-dione (23). A HBr solution (9—10 mL, 1.5—1.7 mmol of HBr), which was prepared by saturation of $CHCl_3$ with gaseous HBr, was added to a solution of compound **20** (0.2 g, 0.75 mmol) in anhydrous $CHCl_3$ (7 mL) under Ar for 2—3 min. The reaction mixture was stirred at 20 °C for 7—10 h. During this period of time, the same HBr solution (8 mL, 1.4—1.5 mmol of HBr) was additionally added in three portions. Then the solvent and an excess of HBr were removed under an argon flow, the residue was dissolved in dioxane (10 mL), and piperidine (3.4 h, 4.0 mL, 40.0 mmol) was added. The reaction mixture was stirred at 20 °C for 30 min and diluted with water (0.3 L). The product was extracted with $CHCl_3$. The organic extract was washed with water and dried with $MgSO_4$. The solvent was removed *in vacuo*, and the residue was chromatographed on SiO_2 (a toluene—ethylacetate mixture, 5 : 1, as the eluent). The yield of product **23** was 0.10 g (40%), m.p. 123—124 °C (diethyl ether—hexane).[30]

References

1. D. E. Metzles, *Biochemistry, The Chemical Reactions of Living Cells*, Iowa State University, Academic Press, Inc., New York—San Francisco—London, 1977.
2. A. Huang, J. J. Kodanko, L. E. Overman, *J. Am. Chem. Soc.*, 2004, **126**, 14043.
3. R. G. Glushkov, N. I. Fadeeva, I. A. Leneva, S. F. Gerasina, L. I. Budanova, N. D. Sokolova, L. F. Stebaeva, V. A. Kuzovkin, E. V. Dektyarev, T. M. Sokolova, I. T. Fedyakina, *Khim.-farm. Zh.*, 1992, **26**, No. 2, 8 [*Pharm. Chem. J.* (*Engl. Transl.*), 1992, **26**, No. 2].
4. P. A. Insel, in *Goodman and Gilman's. The Pharmacological Basis of Therapeutics,* 9th ed., Ed. R. W. Ruddon, McCrow-Hill, New York, 1996, 617.
5. V. V. Kouznetsov, L. Y. Vargas Mendez, C. M. Melendez Gomez, *Curr. Org. Chem.*, 2005, **9**, 141.
6. W. Du, *Tetrahedron*, 2003, **59**, 8649.
7. A. Capelli, G. Pericot Mohr, A. Gallelli, G. Cuiliani, M. Anzini, S. Vonuro, M. Fresta, P. Porcu, E. Macaiocco, A. Concas, G. Biggio, A. Donati, *J. Med. Chem.*, 2003, **46**, 3668.
8. B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinder, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer, J. Hirshfield, *J. Med. Chem.*, 1988, **31**, 2235.
9. G. R. Humphrey, J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875.
10. M. S. Shvartsberg, A. A. Moroz, I. L. Kotlyarevskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1972, 981 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.* (*Engl. Transl.*), 1972, **21**, 946].
11. H. A. Dieck, F. R. Heck, *J. Organomet. Chem.*, 1975, **93**, 259.
12. L. Cassar, *J. Organomet. Chem.*, 1975, **93**, 253.
13. K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.*, 1975, 4467.
14. S. Cacchi, G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873.
15. M. S. Shvartsberg, A. V. Piskunov, M. A. Mzhel´skaya, A. A. Moroz, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1423 [*Russ. Chem. Bull.* (*Engl. Transl.*), 1993, **42**, 1357].
16. E. A. Yakovleva, I. D. Ivanchikova, M. S. Shvartsberg, *Izv. Akad. Nauk, Ser. Khim.*, 2005, 412 [*Russ. Chem. Bull., Int. Ed.*, 2005, **54**, 421].
17. G. Abbiati, A. Arcadi, F. Marinelli, E. Rossi, M. Verdecchia, *Synlett*, 2006, 3218.
18. E. R. Ashley, E. G. Cruz, B. M. Stoltz, *J. Am. Chem. Soc.*, 2003, **125**, 15000.
19. M. Kinugawa, H. Arai, H. Nishikawa, A. Sakaguchi, S. Agasa, Sh. Tomioka, M. Kasai, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2677.
20. K. V. Rao, K. Biemann, R. B. Woodward, *J. Am. Chem. Soc.*, 1963, **85**, 2532.
21. N. Soonthornchareonnon, K. Suwanborirux, R. Bavovada, C. Patarapanich, J. Cassady, *J. Nat. Prod.*, 1999, **62**, 1390.
22. M. S. Shvartsberg, E. A. Kolodina, N. I. Lebedeva, L. G. Fedenok, *Tetrahedron Lett.*, 2009, **50**, 6769.
23. R. Chinchilla, C. Najera, *Chem. Rev.*, 2007, **107**, 874.
24. V. S. Romanov, I. D. Ivanchikova, A. A. Moroz, M. S. Shvartsberg, *Izv. Akad. Nauk, Ser. Khim.*, 2005, 1636 [*Russ. Chem. Bull., Int. Ed.*, 2005, **54**, 1686].
25. N. J. Ikeda, *Pharm. Soc. (Japan)*, 1955, **75**, 649.
26. N. V. Ivashkina, V. S. Romanov, A. A. Moroz, M. S. Shvartsberg, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1984, 2561 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.* (*Engl. Transl.*), 1984, **33**, 2345].
27. Y. Yasuhara, Y. Kanamori, M. Kaneko, A. Numata, Y. Kondo, T. Sakamoto, *J. Chem. Soc., Perkin Trans. 1*, 1999, 529.
28. E. A. Kolodina, N. I. Lebedeva, M. S. Shvartsberg, *Izv. Akad. Nauk, Ser. Khim.*, 2007, 2381 [*Russ. Chem. Bull., Int. Ed.*, 2007, **56**, 2466].
29. A. Inoue, N. Kuroki, K. Konishi, *Soc. Org. Synth. Chem. (Jpn)*, 1958, **16**, 603; *Chem. Abstr.*, 1959, **53**, 3233.
30. M. S. Shvartsberg, E. A. Kolodina, *Mendeleev Commun.*, 2008, **18**, 109.

Received April 14, 2011;
in revised form January 23, 2012