Pergamon

TETRAHEDRON

Tetrahedron 56 (2000) 5147–5155

Regioselective Synthesis of Benzo[*g*]isoquinoline-5,10-dione Derivatives as DNA Intercalators

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Received 11 October 1999; revised 18 February 2000; accepted 28 February 2000

Abstract—We describe a new total synthesis for 9-(2-dimethylaminoethylamino)-6-hydroxy-7-methoxybenzo-[*g*]isoquinoline-5,10-dione (**1**) via cyclization and amination. Compound **1** acts as a DNA intercalator and inhibitor of gyrase and mammalian topoisomerase I and II. Preparation of the precursor heterocycle **2a** can be accompanied by the Hayashi rearrangement, which is studied by semiempirical methods (AM1, PM3). Moreover, a new regio-selective route to substituted benzo[*g*]isoquinolines (e.g. tolypocladin (**3**)) is established via hetero-Diels–Alder methodology. The regioselectivity of these Diels–Alder reactions is predicted with semiempirical calculations (AM1) of the transition states. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Amino substituted anthraquinones such as mitoxanthrone belong to the most active anticancer compounds. Mitoxanthrone is used in the treatment of mammary carcinoma, non-Hodgkins lymphoma, and acute leukemia of adults.[1] In the search for improved anti-cancer[2] compounds, the amino substituted azaanthraquinones of natural or even synthetic origin (tolypocladin,[3] bostrycoidin[4–6] and synthetic 1- and 2-azaanthraquinones) have attracted much interest due to their possible role as DNA intercalators.[7] In this paper we report on the regioselective synthesis of compound **1** (Fig. 1) via coupling of the magnesium compound, and cyclization. As we have shown, this compound intercalates into poly (dA-dT) poly (dA-dT), and poly (dA) poly (dT)-sequences inhibiting the DNA gyrase and the activity of mammalian topoisomerases I and II.[7] Until now tolypocladin (**3**) was not available in large scale, neither from natural sources nor via synthesis.[3,8,9] We therefore synthesized compound **1** from nor-bostrycoidin (**2a**).

Our further synthetic aim was a new regioselective route to naturally and non-naturally occurring azaanthraquinones via hetero-Diels–Alder reactions by using a nitrogen atom containing diene.

Results and Discussion

Synthesis of nor-bostrycoidin derivatives

The first step of our synthesis of **1** (Scheme 1) was the coupling of 1-bromomagnesium-2,3,5-trimethoxybenzene (**5**) with pyridine-3,4-dicarboxylic acid anhydride (**6**), using tetramethylethylenediamine (TMEDA) as cosolvent. Hydrolysis with diluted HCl yielded the keto carboxylic

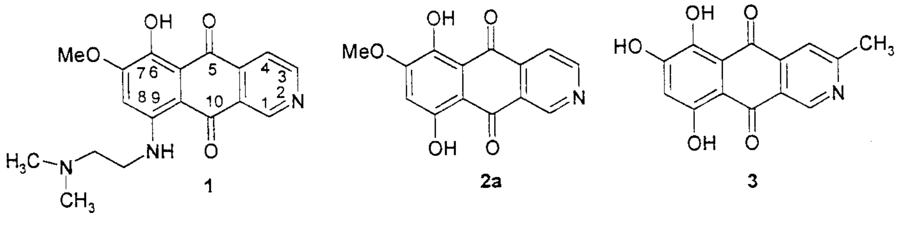

Figure 1.

Keywords: DNA; Hayashi rearrangement; anthraquinones.

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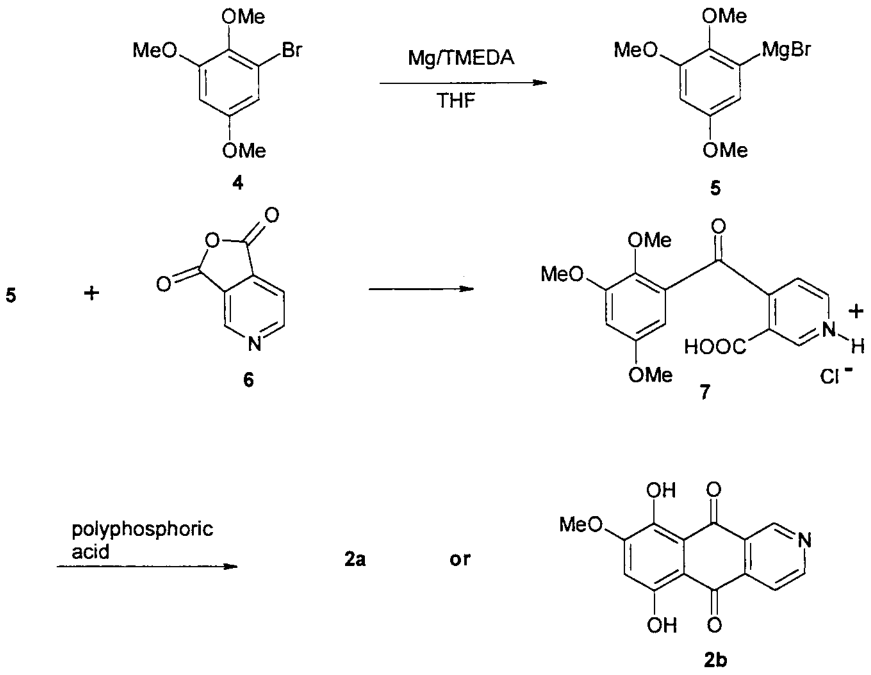
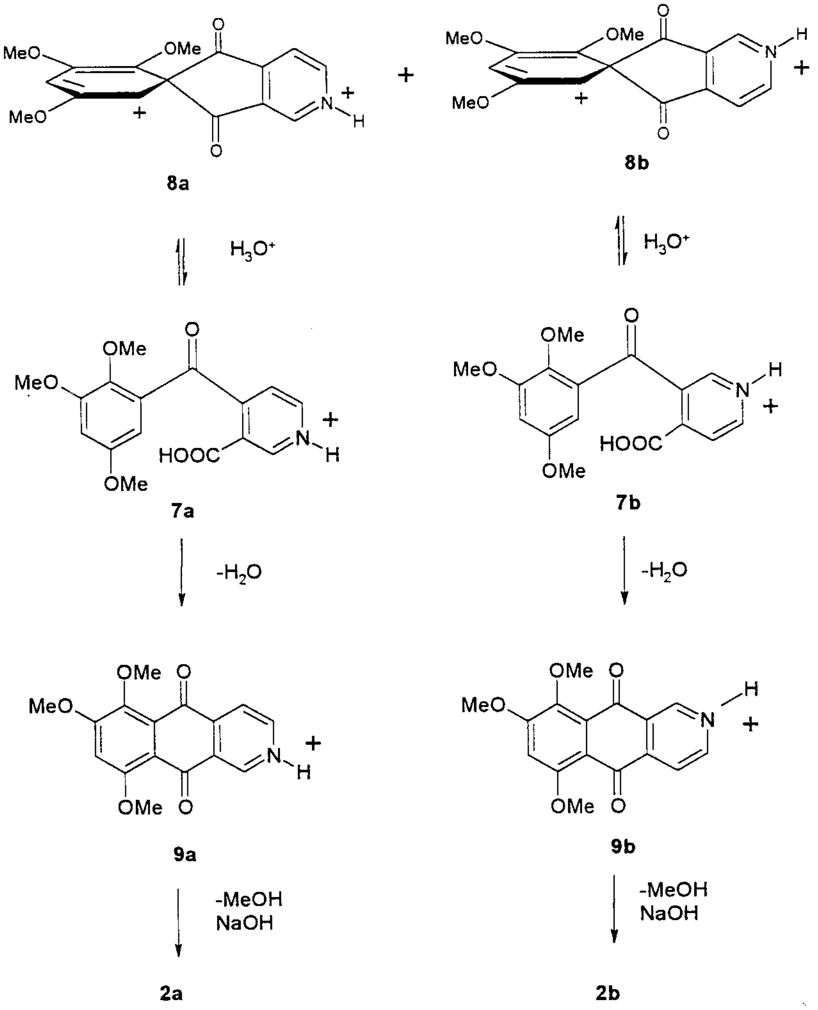
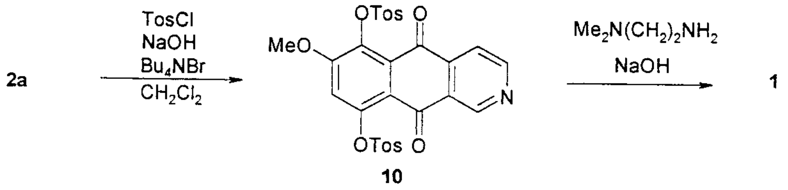
PII: S0040-4020(00)00186-1



Scheme 1.



Scheme 2.



Scheme 3.

acid **7**. Performing the synthesis in the absence of TMEDA yielded little of the desired product. Employment of lithium instead of magnesium did not result in higher yields. The cyclization of **7** with polyphosphoric acid at temperatures higher than 90°C gives a mixture of the regioisomers nor-bostrycoidin (**2a**) (main compound) and isonor-bostrycoidin (**2b**) due to the Hayashi-rearrangement[10–12] which has to be suppressed, because chromatographic separation of **2a** and **2b**, even by TLC, is not possible.

This reaction (discovered in 1927[10]) explains the formation of isomeric quinones from the keto carboxylic acid under acidic conditions. The rearrangement was proposed to proceed via dicationic spirocyclic intermediates (Scheme 2) such as **8a** and **8b** that reacts to **7a** and **7b** then proceeds to **9a** and **9b**, which are demethylated under reaction conditions to yield **2a** and **2b**. Semiempirical calculations indicate that **7a** is thermodynamically more stable than **7b**. For a detailed discussion see the theoretical part of this work.

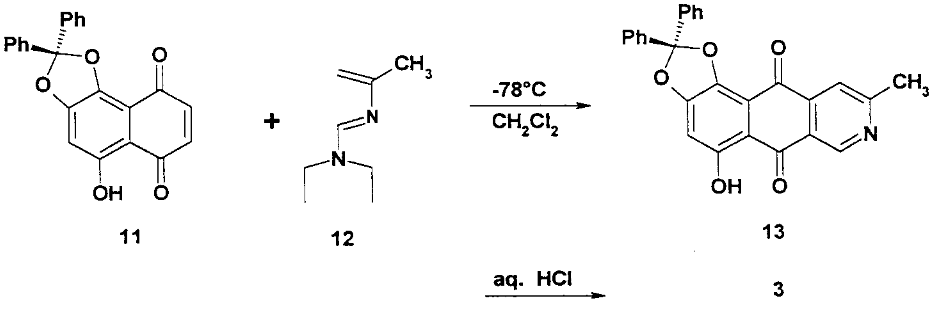
In order to avoid the Hayashi rearrangement, various reaction conditions have been investigated and described in the literature.[11] Whereas the rearrangement was observed in the presence of H_2SO_4, even at low temperatures, TFA and polyphosphoric acid at temperatures up to 100°C showed no isomeric product. We therefore performed the cyclization sequence of **7** with polyphosphoric acid at 90°C, and obtained **2a** as a single product. Crystallization of **2a** from chloroform and additional chromatography supplied a sample quality, which was sufficiently pure for further synthesis.

The introduction of just one amino group into anthraquinones at a later step in the synthesis is also problematic. Three methods have been described in the literature: reaction of an amine with fluorinated azaanthraquinones[2] and tosyl esters of hydroxyanthraquinones,[15] and the reaction of the anthraquinones in the leuco-form with subsequent oxidation.[2] These procedures give the bis aminated compounds. In order to prepare a monoaminated product we wanted to exchange only one tosyloxy group of the *para* ditosylated material. For tosylation we tried 2-methoxypurpurine[13] as a model compound. Reaction of the purpurine derivative with *p*-tosyl chloride in the presence of bases like triethylamine or pyridine, in analogy to literature procedures,[14,15] yielded a mixture of undefined products. However, phase transfer catalyzed esterification[16] was very suitable. Tosylation of **2a** under these conditions (Scheme 3) afforded **10**.

Treatment of **10** with *N*,*N*-dimethylethylenediamine yielded the desired monoaminated product **1**. However, crystals could not be obtained. Evidence for the structure was furnished by one and two dimensional NMR measurements. Particularly helpful was the observed vicinal $^3J_{H,C}$ coupling of the amino proton to the C-8 atom (Fig. 1) suggesting the localization of the amino group at C-9.

Hetero-Diels–Alder synthesis of tolypocladin and other 1- and 2-azaanthraquinones

The synthesis of tolypocladin derivatives requires the regioselective introduction of the 3-methyl group in benzo[*g*]-isoquinoline-5,10-dione. Cameron[4–6] and Watanabe[17] synthesized bostrycoidin as a product of a series of difficult steps. Recently we published a synthesis of tolypocladin via a keto carboxylic acid under Friedel–Crafts conditions.[8] The main problem was the reaction of 3-methylcinchomeronic acid anhydride with 1,2,4-trimethoxybenzene yielding a mixture of keto carboxylic acids. Unfortunately, the starting material for tolypocladin (**3**) was the minor compound. Krapcho synthesized tolypocladin by cyclization of a benzyl derivative in small amounts.[9] Therefore we proposed a regioselective synthesis of tolypocladin via a hetero-Diels–Alder reaction[18–20] based on the addition of **11** and **12** at low temperatures (Scheme 4). Before starting this total synthesis the desired regioselectivity was predicted by calculating the transition states (see Theoretical investigations).



Scheme 4.

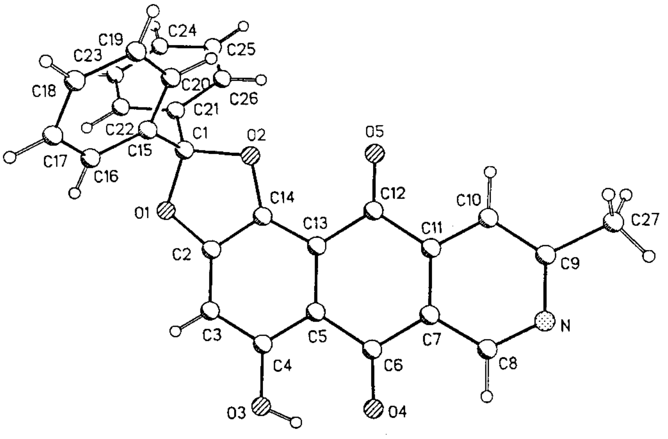


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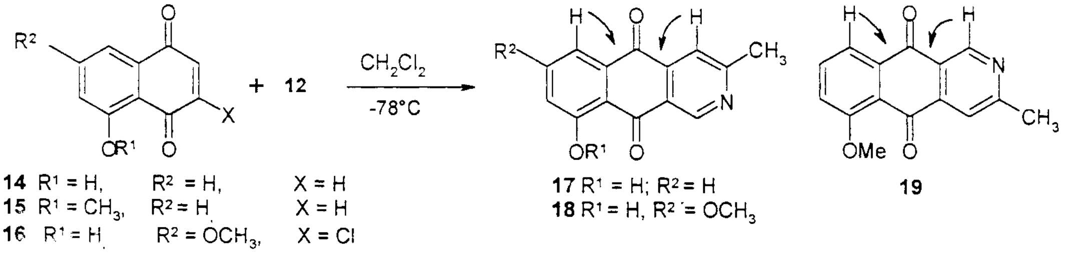
Figure 2.

Starting from 1,5-dinitronaphthalene, and 5,8-dihydroxynapthoquinone, we prepared the following compounds: naphthopurpurine and finally 5-hydroxy-2,2-diphenylnaphtho[1,2-*d*]-1,3-dioxol-6,9-dione (**11**) (Scheme 4).[21] The diene **12** was prepared as described in literature.[22,23] It was impossible to determine the regioselectivity of the hetero-Diels–Alder reaction by NMR methods. Structure **13** (Fig. 2) was therefore established by X-ray analysis. Hydrolysis of **13** (Fig. 5) supplied **3**. Similar to the above reaction, the hetero-Diels–Alder reaction of juglone (**14**), its methyl ether **15** and compound **16** with the diene **12** (Scheme 5) yielded the products 9-hydroxy-3-methyl-2-benzo[*g*]isoquinoline-5,10-dione (**17**) (29%), 6-methoxy-3-methyl-2-benzo[*g*]isoquinoline-5,10-dione (**19**) (19%) and 9-hydroxy-7-methoxy-3-methyl-2-benzo[*g*]isoquinoline-5,10-dione (**18**) (33%). The structure assignments were performed by one- and two-dimensional NMR methods.

The relatively low yields of the hetero-Diels–Alder reaction may result from the reactions of electron-deficiency dienophiles with an electron-deficient azadiene.[19] But the disadvantage of low yields is compensated by a short synthetic route.

Theoretical investigations

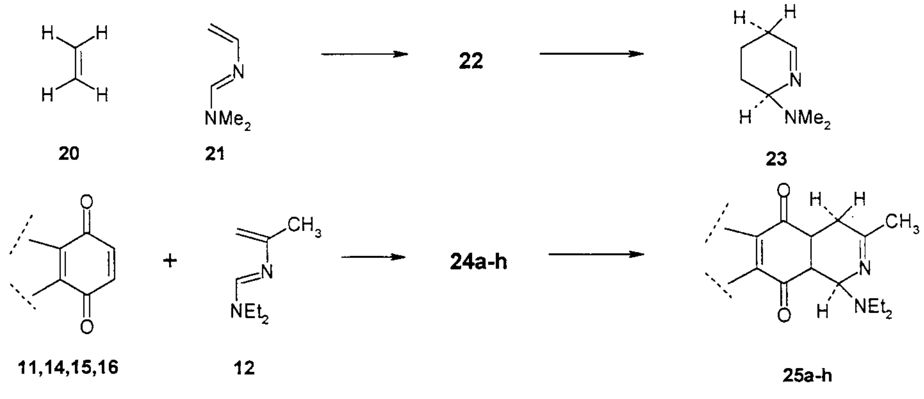
Our calculations were carried out by using Powervamp[24] and the Gaussian 94 suite of programs.[25] The transition structures were calculated by using the NS01A routine. The energy minima of the structures or transition states



Scheme 5.

Table 1. Heat of formation and dihedral angle of compounds of the Hayashi rearrangement

Compound	AM1		PM3	
	Heat of formation [kcal/mol]	Dihedral angle C4–C4a–C5–C5a	Heat of formation [kcal/mol]	Dihedral angle C4–C4a–C5–C5a
8a	312.8	–	304.9	–
8b	312.8	–	304.9	–
Δ(**8a**–**8b**)	0.0		0.0	
7a	−4.2	–	−8.6	–
7b	−3.0	–	−8.3	–
Δ(**7a**–**7b**)	−1.2		−0.3	
9a	54.8	–	47.9	–
9b	54.8	–	47.9	–
Δ(**9a**–**9b**)	0.0		0.0	
2a	−118.9	179.1	−134.8	179.6
2b	−118.9	179.2	−134.9	179.5
Δ(**2a**–**2b**)	0.0	–	0.0	–



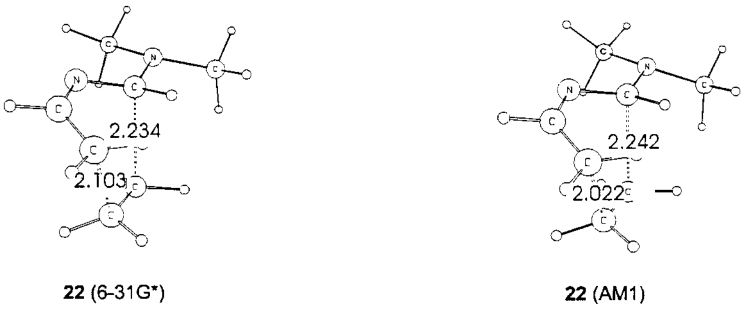
Scheme 6.

were confirmed by calculating the number of the imaginary frequencies (NIMAG). MNDO[26] gives rather unreliable results for calculating anthraquinones. In contrast to this, the semiempirical methods AM1[27] and PM3[28] calculate accurate geometries even in the case of azaanthraquinones.

For the investigation of the Hayashi rearrangement (Scheme 2) we were interested in the heat of formation (Table 1) of the isomers **7a**/**7b** and **9a**/**9b**. We hoped that the thermodynamic stability of the isomeric intermediates expresses the ratio of Hayashi products. Indeed, the calculation of the isomers (Table 1) showed different values for **7a**/**7b**. In agreement with the experiment, **7a** was calculated as being more stable [1.2 kcal/mol (AM1) and 0.3 kcal/mol (PM3)]. The final compounds **2a** and **2b** were calculated as nearly planar. A slight distortion from planar geometry of azaanthraquinones was observed experimentally for isotolypocladin.[8]

Furthermore, we were interested in the theoretical investigations of the regioselectivity of the hetero-Diels–Alder reaction. An asynchronous mechanism for the reaction of 2-azabutadiene with ethylene was considered by Houk.[29]

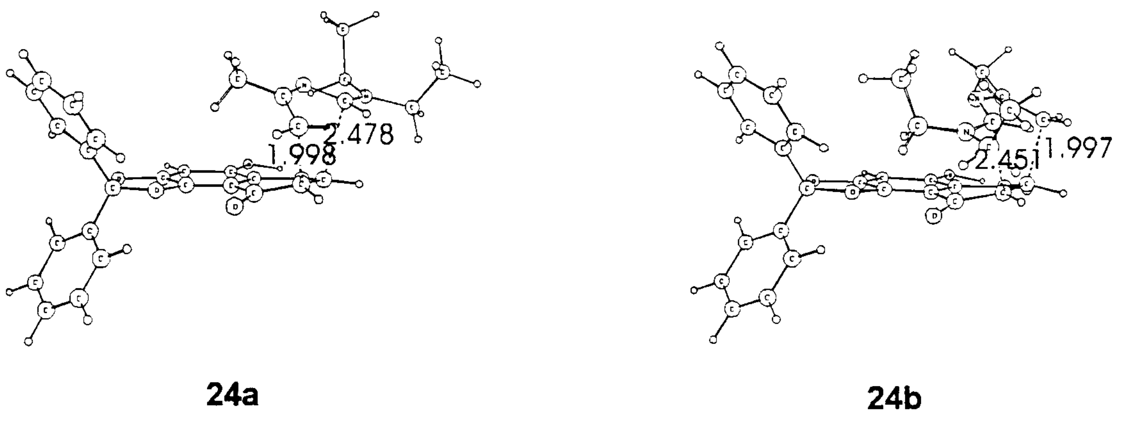
For the experimentally investigated systems, ab inito calculations on a high level (MP4STDQ/MP2/6-31G*//MP/26-31G*) are desired: their results should be close to the experimental values.[29,30] In order to check the application of semiempirical methods for 2-azabutadienes, we compared the ab initio calculated energies with that calculated by the semiempirical method AM1 of a model reaction (Scheme 6, top). The AM1 calculated activation energies (23 kcal/mol) are



22 (6-31G*)

22 (AM1)

Figure 3.



24a

24b

Figure 4.

Table 2. Relative energies of the hetero-Diels–Alder reaction of **21** with ethylene (**20**)

Method	**20**+**21**	**22**[a]	**23**
RHF/6-31G*+ΔZPE[b]	0.0	49.4	−25.0
MP2/6-31G*//6-31G*+ΔZPE[b]	0.0	20.5	−35.3
MP4STDQ/6-31G*//6-31G*+ΔZPE[b]	0.0	25.1	−32.6
AM1	0.0	23.1	−41.4

[a] NIMAG=1.

[b] ZPE (6-31G*) scaled with 0.89.

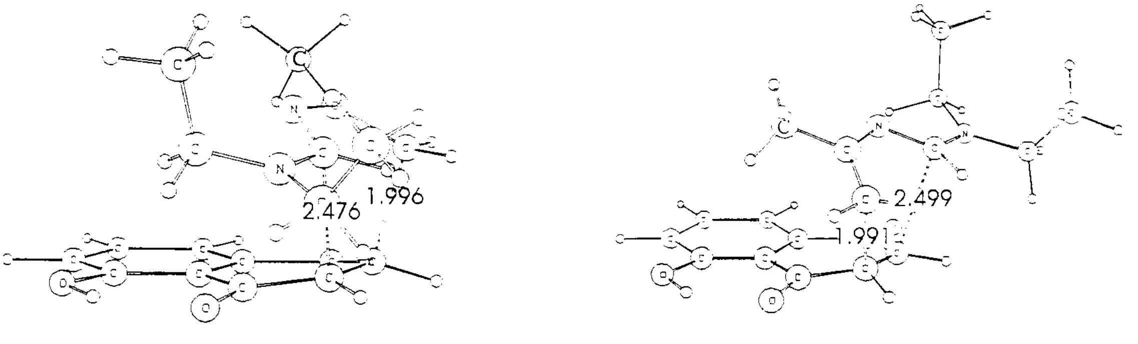
Table 3. Relative energies (AM1) of the hetero-Diels–Alder reaction of **11**, **14**, **15**, and **16** with **12**

Reaction	Energies relative to the products			ΔHf [kcal/mol]
	Product		Transition state	
11+**12**	**25a**	−27.1	**24a**	23.2
	25b	−27.0	**24b**	23.8
14+**12**	**25c**	−32.1	**24c**	22.9
	25d	−31.9	**24d**	23.4
15+**12**	**25e**	−27.3	**24e**	24.3
	25f	−27.6	**24f**	23.7
16+**12**	**25g**	−27.5	**24g**	21.3
	25h	−28.1	**24h**	27.2

close to that calculated at the MP4STQ/6-31G*//6-31G*-level (25.1 kcal/mol) (Table 1). The product with a relative energy of −41.4 kcal/mol was calculated as too stable by AM1. The AM1 calculated bond lengths are similar to those calculated on the 6-31G*-level (Figs. 3 and 4). We conclude that AM1 is suitable to predict the regio-selectivity of the hetero-Diels–Alder reaction of 2-aza-1-(dimethylamino)-butadiene as model compound and with 2-aza-1-(diethylamino)-3-methylbutadiene (Scheme 6, bottom), which we employed in synthesis (Tables 2 and 3, Figs. 3–7).

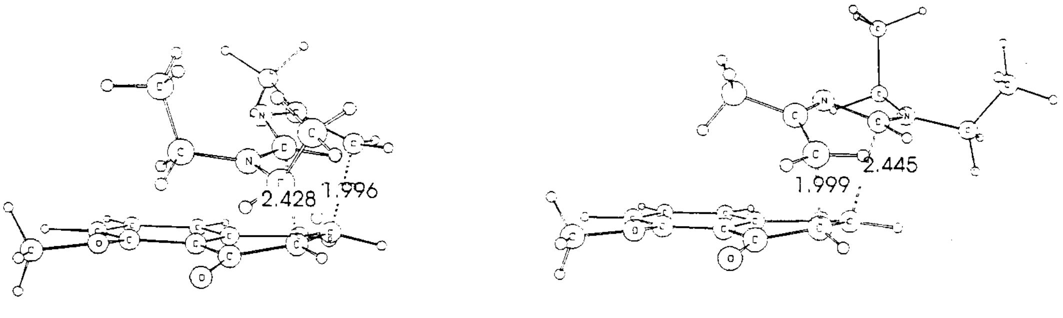
In order to predict the regioselectivity of the hetero-Diels–Alder reaction we calculated the heat of formation of the alternative products and the transition states running through the transition states **24a**–**24h** (Table 3, Figs. 4–7). They are shown in Figs. 4–7 for the reactions of naphthoquinones **11**, **14**, **15** and **16** with the azadiene **12**. As expected, the calculated differences (Table 3) not only of the proposed products but also of the alternative transition states are small but significant. The predicted regioselectivity agrees quite well with the experimental data. The reaction of **16** with **12** is an instructive example of an old theorem: if a reaction is kinetically controlled, the energy level of the transition state is decisive for the product distribution. The product that proceeds through the transition state **24g** leads, as expected, to the thermodynamically less stable isomer.

As indicated by the easy formation of the sodium salt of tolypocladin and by the chemical shift of the hydroxy group at C-7 in the ^{1}H NMR spectra (13.33 for compound **3**), the hydroxy group is the most acidic one. Further evidence for the strong acidic behavior of this hydroxy group is given by the reaction of purpurine with diazomethane yielding 2-methoxypurpurine. For the explanation of these findings



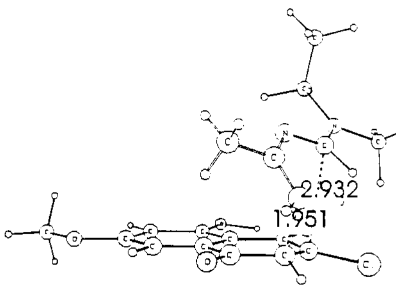
24c **24d**

Figure 5.

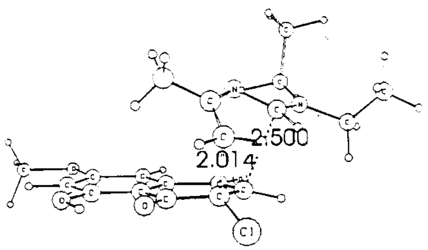


24e **24f**

Figure 6.



24g



24h

Figure 7.

Table 4. Energies of the deprotonation reaction of **3**

Position	AM1 [kcal/mol]	PM3 [kcal/mol]
6	−299.3	−313.2
7	−308.2	−316.1
9	−306.9	−314.1

we suggest the deprotonation reaction ROH+ $CH_3^+ \rightarrow RO^- + CH_4$ at positions 6, 7, and 9 (Table 4) of compound **3**. As one can see, the reaction of the hydroxy group at C-6 results in the lowest energy. Thus our experimental observations were supported by this calculation.

Experimental

Mp: Boetius M (corr.) TLC.: Aluminium foils (sheets) silica gel 60 F_{254} (Merck). Electron impact mass spectra (EI-MS): High resolution seder-fuild mass spectrometer AMD 402. ^1H NMR (300 or 500 MHz) and ^{13}C NMR spectra were recorded on Bruker advance DRX 300 and 500 spectrometers. δ [ppm]. The following starting materials were prepared according to literature procedures: 1-bromo-2,3,4-trimethoxybenzene,[31] pyridine-3,5-dicarboxylic acid anhydride,[2] 2-methoxypurpurine,[13] 5,8-dihydroxynaphthoquinone,[32] naphthopurpurine,[33] 5-hydroxy-2,2-diphenylnaphto[1,2-*d*]-1,3-dioxol-6,9-dione,[21] and 1-(diethylamino)-2-aza-3-methylbutadiene,[22,23] 3-chloro-5-hydroxy-7-methoxy-1,4-naphthoquinone.[34]

4-(2,4,5-Trimethoxybenzoyl)nicotinic acid hydrochloride (7). 4 (18.5 g, 75 mmol) were added to 1.94 g (80 mol) of activated magnesium turnings in 150 ml of dry THF. The reaction mixture was cooled to room temperature and 11.3 ml (75 mmol) of TMEDA were added. The mixture was cooled down to −78°C and a solution of 11.2 g (80 mmol) of pyridine-3,4-dicarboxylic acid anhydride (**6**) in 160 ml dry THF was added. Stirring was continued for 12 h allowing the reaction mixture to come to ambient temperature. The solvent was evaporated in vacuo and 200 ml ice water was added. A yellow–brown slurry precipitated. The water was decanted and the residue was treated with a mixture of isopropanol and diethyl ether. Yellow crystals from ethanol. Yield: 12.5 g (47%). Mp: 187°C. Calcd for $C_{16}H_{16}ClNO_6$ (353.82) C, 54,19; H, 4.65; N, 4.10; Cl, 10.25. Found: C, 54.32; H, 4.56; N, 3.98; Cl 10.02; MS (EI): *m*/*e*= 317.01642 (M+, 100), Calcd 317.08994. ^1H NMR (DMSO): 3.79 (m, 9H, OCH_3), 6.91 (s, 1H, C–H), 6.92 (s, 1H, C–H), 7.66 (d, ^3J=5.3 Hz, 1H, H-5), 8.96 (d, ^3J= 5.3 Hz, 1H, H-6), 9.15 (s, 1H, H-2). ^{13}C NMR (DMSO): 55.6 (OCH_3), 56.2 (OCH_3), 59.8 (OCH_3), 102.6, 106.6, 121.7, 124.6, 143.9, 147.7, 150.0, 153.7, 154.8, 155.5, 164.8, 164.8 (COOH), 192.1 (CO).

6,9-Dihydroxy-7-methoxybenzo[*g*]isoquinoline-5,10-dione (2a). 7 (1.2 g, 3.4 mmol) were added at 90°C to polyphosphoric acid (7 ml of 80% H_3PO_4/10 g of P_4O_{10}). The reaction mixture was stirred for 6 h at 90°C and then cooled to room temperature. The mixture was neutralized with 10% sodium hydroxide solution to pH=6. A reddish–brown precipitate was formed, which was filtered off, washed with water, dried and crystallized from chloroform. Reddish powder. Yield: 694 mg (78%). Mp 242°C (decomp). R_f ($CHCl_3$, MeOH=40:1)=0.8. Anal. Calcd for $C_{13}H_7NO_5$ (257.20): C, 61.98; H, 3.34; N, 5.18. Found: C, 61.50; H, 3.29; N, 5.27. MS (EI); *m*/*e*=257.04901 (M^+); Calcd 257.03242. ^1H NMR ($CDCl_3$): δ=4.03, (s, 3H, OCH_3), 6.76 (s, 1H, H-8); 8.14 (d, ^3J=5.1 Hz, 1H, H-4) 9.09 (d, ^3J=5.1 Hz, 1H, H-3), 9.63 (s, 1H, H-1), 13.20 (s, 1H, OH), 13.38 (s, 1H, OH).

6,9-Bistoluenesulfonyl-7-methoxybenzo[*g*]isoquinoline-5,10-dione (10). Tetrabutylammonium bromide (255 mg, 0.8 mmol), **2a** (533 mg, 1.96 mmol), and *p*-toluenesulfonyl chloride (1.20 g, 6.30 mmol) were added to a mixture of 9.31 ml of 1N sodium hydroxide solution, 77.4 ml of water, and 70.4 ml of CH_2Cl_2. The blue color changed to brown. The organic layer was separated, the water phase was extracted twice with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4. The solvent was removed in vacuo. The yellow residue was chromatographed on silica gel twice (first $CHCl_3$, then $CHCl_3$/acetone=4: 1). The chromatographed powder was crystallized from acetone. Yellow crystals. Yield: 548 mg (48%). Mp: 140–142°C, R_f ($CHCl_3$/acetone=4:1)=0.8. MS (EI): *m*/*e*=578.96411. Anal. Calcd for $C_{28}H_{21}NO_9$ S_2 (579.61): C, 58.02; H, 3.65; N, 2.42. Found: C, 57.90; H, 3.71, N, 2.44. ^1H NMR ($CDCl_3$): 2.42 (s, 3H, CH_3), 222.47 (s, 6H, CH_3), 3.57, (s, 3H, OCH_3), 7.14 (s, 1H, H-8), 7.34 (d, ^3J=11.3 Hz, 4H, H-3), 7.90 (d, ^3J=8.3 Hz, 1H, H-4), 8.99 (d, ^3J=8.3 Hz, 1H, H-3), 9.27 (s, 1H, H-1). ^{13}C NMR ($CDCl_3$): 21.7 (CH_3), 56.6 (OCH_3), 114.1, 118.5, 128.5, 129.1, 129.5, 129.8, 145.3, 142.6, 149.3 (C-1), 154.7, 178.1 (CO), 181.2 (CO).

9-(2-Dimethylaminoethylamino)-6-hydroxy-7-methoxy-benzo[*g*]isoquinoline-5,10-dione (1). 8.37 g of 2-(dimethylamino)ethylamine were added to **10** (548 mg, 0.95 mmol). The mixture was stirred for three days and the color changed to deep blue. The excess of the amine was removed in vacuo. 5 ml 1N NaOH were added, the solution was extracted with $CHCl_3$. The organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The deep blue residue was chromatographed ($CHCl_3$/MeOH=4:1). Yield 74 mg (21%). Mp: 209–210°C. R_f ($CHCl_3$: MeOH=4:1)=0.4. MS (EI): 341.2 (M^+, 100) Anal. Calcd for $C_{18}H_{19}N_3O_4$ (341.54) C, 63.30; H 5.60; N 12.35. Found: C, 62.94; H, 5.51; N, 12.49. ^1H NMR ($CDCl_3$): 2.35 (s, 6H, N(CH_3), 2.65 (t, 2H, ^3J=8.0 Hz, H-3), 9.47 (s, 1H, H-1), 11.08, (t, 1H, ^3J=5.2 Hz, NH). ^{13}C NMR ($CDCl_3$): 36.0 (CH_3), 40.4 (CH_2), 50.7 (OCH_3), 53.1 (CH_2), 93.5 (C-7), 95.0, 105.0, 112.8 (C-3), 121.9, 123.3, 124.4, 133.5, 143.5 (C-1), 144.3, 146.4 (C-4), 172.9 (CO), 176.2 (CO).

9-Hydroxy-3-methyl-6,7-diphenylbenzo[*g*]isoquinoline-[1,2-*d*]-1,3-dioxol-5,10-dione (13). **12** (50 mg, 0.35 mmol) were dropped under argon at −78°C into a solution containing 100 mg (0.27 mmol) of 5-hydroxy-2,2-diphenyl-naphtho[1,2-*d*]-1,3-dioxol-6,9-dione (**11**) in acetonitrile. The solution was warmed up to room temperature and stirred for 12 h. The color changed to yellow. The solvent was evaporated in vacuo, the resulting solid was chromatographed ($CHCl_3$/MeOH=5:1). Crystallization from CH_2Cl_2 gave red needles that were suitable for X-ray investigation. Yield: 36 mg (31%). Mp: 202°C. Anal. Calcd for $C_{27}H_{17}NO_5$ (435.44) C, 74.48; H, 3.94; N, 3.22. Found: C, 73.90; H, 4.12; N, 3.17. MS (EI): *m*/*e*: 435.10940 (M^+); Calcd 435.11067. ^1H NMR ($CDCl_3$): 2.77 (s, 3H, CH_3), 6.82 (s, 1H, H-8) 7.41 (m, 6H, Ph), 7.59 (m, 4H, Ph), 7.88 (s, 1H, H-4), 9.46 (s, 1H, H-1), 13.74 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): 25.26, (CH_3), 104.16, 107.76, 112.80, 118.1, 121.2, 124.4, 126.3, 127.5, 128.5, 129.9, 138.3, 138.8, 140.9, 149.2, 156.2, 163.3, 165.5, 180.3 (CO), 185.3 (CO).

Crystal structure determination

The intensity data were collected on a Nonius Kappa CCD diffractometer, using graphite monochromated MoK_α radiation. Data were corrected for Lorentz and polarization effects, but not for absorption.[35] The structure was solved by direct methods (SHELX[36]) and refined by full-matrix least squares techniques against F_0^2 (SHELXL-97[37]). The hydrogen atoms were included at calculated positions with fixed thermal parameters. All nonhydrogen atoms were refined anisotropically[37]. XP (Siemens Analytical X-ray Instruments, Inc.) was used for structure re-presentation. *Crystal data for **13**:*[38] $C_{27}H_{16}NO_5$, M_r=434.41 g mol^{-1}, red prism, size 0.30×0.20×0.05 mm^3, monoclinic, space group $P2_1/c$, a=15.073 (1), b=17.957 (1), c=8.0219 (7) Å, β=103.81 (1)°, V=2108.5 (3) Å^3, T=−90°C, Z=4, ρ=1.368 g cm^{-3}, μ (MoK_α)=0.95 cm^{-1}, F(000)=900, 2344 reflections in h (−11/12), k (−14,14), l (−6/0), measured in the range $4.18° \leq \theta \leq 17.18°$, completeness $\theta_{max=}$95.8%, 1240 independent reflections, $R_{int=}$ 0.021, 1015 reflections with $F_0 > 4\sigma$ (F_0), 299 parameters, 0 restraints, $R1_{obs=}$0.037, $wR^2_{obs=}$0.103, $R1_{all}$=0.055, $wR^2_{all=}$0.126, GOOF=1.016, largest difference peak and hole: 0.212/−0.166e Å^{-3}.

3-Methyl-6,7,9-trihydroxybenzo[*g*]isoquinoline-5,10-dione (3). 15 ml of 0.2N HCl were added to a solution of 40 mg (0.09 mmol) of **13** in 15 ml EtOH. The mixture was heated under reflux for 5 h. The solvent was removed in vacuo, water was added, the solid was filtered off and the residue was adjusted to pH=6 with 0.1N NaOH and sodium acetate. The solution was extracted once with diethylether and afterwards with chloroform. The combined extracts were concentrated in vacuo. Reddish powder. Yield: 60%. Mp>300°C. R_f (acetone/$CHCl_3$=2:1)=0.6. MS: *m*/*e* found 271.0472 (M^+), Calcd 271.0481. Anal. Calcd for $C_{14}H_9NO_5$ (271.2) C, 62.00; H, 3.34; N, 5.16. Found: C, 61.70; H, 3.68; N, 5.25. ^1H NMR (DMSO): 2.72 (s, 3H, CH_3), 6.74 (s, 1H, H-8), 7.79, (s, 1H, H-4), 9.29 (s, 1H, H-1), 12.80 (broad, 1H, OH), 13.33 (s, 1H, OH-7). ^{13}C NMR (DMSO): 24.7 (CH_3), 105.0, 110.3, 113.0 (C-8), 117.6 (C-4), 124.2, 138.3, 148.0 (C-1), 149.7, 157.30, 160.5, 164.9, 183.0 (CO), 186.0 (CO).

9-Hydroxy-3-methyl-benzo[*g*]isoquinoline-5,10-dione (17). **12** (0.6 g, 4.1 mmol) at −78°C were added to a solution of **14** (1.24 g, 7.12 mmol) in 40 ml CH_2Cl_2. The color changed from yellow to brown and the reaction mixture was allowed to warm up to ambient temperature and was stirred for 48 h. The solution was filtered and the precipitate was chromatographed (CH_2Cl_2). Yield: 499 mg (51%), Mp: 187°C. Anal. Calcd for $C_{14}H_9NO_3$ (239.23) C, 70.27; H, 3.79; N, 5.85. Found: C, 70.77; H, 3.77; N, 6.08. MS (EI): *m*/*e* 239.05920 (M^+), Calcd 239.05824. ^1H NMR ($CDCl_3$): 2.79 (s, 3H, CH_3), 7.37 (d, ^3J=8.4 Hz, ^4J=1.1 Hz, 1H, H-8), 7.71, (dd, ^3J=7.4 Hz, ^3J=8.4 Hz, 1H, H-7), 7.84 (dd, ^3J=7.4 Hz, ^4J=1.1 Hz, 1H, H-6); 7.91 (s, 1H, H-4), 9.46 (s, 1H, H-1), 12.51 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): 25.4 (CH_3), 115.8 (C-9a), 118.6 (C-4), 119.8 (C-6), 123.9 (C-10a), 125.4, (C-8), 133.0 (C-5a), 137.0 (C-7), 138.7 (C-3), 149.2 (C-1), 162.7 (C-9), 166.5 (C-4a), 182.2 (C-5), 188.1 (C-10).

6-Methoxy-3-methyl-benzo[*g*]isoquinoline-5,10-dione (19). **12** (150 mg, 1.1 mmol) were added dropwise at −78°C under vigorous stirring to a solution of 200 mg (1.6 mmol) of **15** in 10 ml CH_2Cl_2. After 2 h the mixture was allowed to warm up to ambient temperature and stirring was continued for a further 2 h. The solution was concentrated under vacuo to one quarter and the residue was treated with 20 ml diethylether. The yellow precipitate was filtered off, dried and purified chromatographically (CH_2Cl_2). Yield: 51 mg (19%). Mp 167°C. Anal. Calcd for $C_{15}H_{11}NO_3$ (253.26) C, 71.14; H, 4.38; N, 5.53. Found: C, 70.58; H, 4.11; N, 5.84. MS (EI): *m*/*e*=253.1. ^1H NMR ($CDCl_3$): 2.76 (s, 3H, CH_3), 7.35 (d, 1H, H-8), 7.75 (dd, 1H, H-7), 7.85 (s, 1H, H-4), 7.88 (d, 1H, H-6), 9.48 (s, 1H, H-1), 12.54 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): 25.4 (CH_3), 56.1 (OCH_3), 118.5 (C-4), 118.8 (C-9), 120.3, 120.7, 124.2 (C-10a), 125.7 (C-7), 136.4 (C-8), 138.7 (C-3), 149.2 (C-1), 163.4 (C-6), 165.6 (C-4a), 184.3 (C-5), 185.8 (C-10).

9-Hydroxy-7-methoxy-3-methylbenzo[*g*]isoquinoline-5,10-dione (18). A solution of 0.16 ml (1.14 mmol) of **12** in abs. THF was added drop by drop to a solution of 0.144 mg (0.6 mmol) of **16** in abs. THF at 0°C. After the addition was completed the solvent was removed in vacuo and the green crude product was purified chromatographically (CH_2Cl_2). Yield: 103 mg (33%). Mp: 195°C. Anal. Calcd for $C_{15}H_{11}NO_3$ (269.26): C, 66.91; H, 4.12; N, 5.20. Found: C, 66.58; H, 3.84; N, 5.40. MS (EI): *m*/*e*. 269.1. ^{1}H NMR ($CDCl_3$): 2.77 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 6.75 (d, *J*=2.5 Hz, 1H, H-8), 7–35 (d, *J*=2.5 Hz, 1H, H-6), 7.87 (s, 1H, H-4), 9.42 (s, 1H, H-1), 12.77 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): 25.3, (CH_3), 56.1 (OCH_3), 107.4 (C-8), 108.2 (C-9a), 110.4 (C-6), 118.5 (C-4), 124.1 (C-10a) 134.5 (C-5a), 138.6 (C-3), 149.1 (C-1), 165.5 (C-7), 165.9 (C-4a), 166.4 (C-9) 182.3 (C-5), 186.2 (C-10).

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (Grant Zi 396/5-1) and by the Bundesminister für Forschung und Technologie, Bonn, Beo Jülich, Germany No 0310591A. We thank Dr Peter Jütten for helpful discussions.

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