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Studies on the Michael addition of naphthoquinones to sugar nitro olefins: first synthesis of polyhydroxylated hexahydro-11*H*-benzo[*a*]carbazole-5,6-diones and hexahydro-11b*H*-benzo[*b*]carbazole-6,11-diones

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ABSTRACT

A strategy for the synthesis of the novel (6b*R*,7*R*,8*S*,9*S*,10*S*,10a*R*)-8-(benzyloxy)-7,9,10-trihydroxy-6b,7,8,9,10,10a-hexahydro-11*H*-benzo[*a*]carbazole-5,6-dione is reported. The key steps were the Michael addition of 2-hydroxy-1,4-naphthoquinone to 1-nitrocyclohexene or 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-D-*xylo*-hex-5-enefuranose and the diastereoselective intramolecular Henry reaction of 3-*O*-benzyl-5,6-dideoxy-5-C-(3′-hydroxy-1′,4′-naphthoquinon-2′-yl)-1,2-*O*-isopropylidene-6-nitro-α-D-glucofuranose to give the key (1*S*,2*S*,3*S*,4*R*,5*R*,6*R*)-3-(benzyloxy)-1,2,4-trihydroxy-5-(3′-hydroxy-1′,4′-naphthoquinon-2′-yl)-6-nitrocyclohexane. When 2-hydroxy-1,4-naphthoquinone was replaced by (1,4-dimethoxynaphthalen-2-yl)lithium, the novel (1*R*,2*S*,3*S*,4*R*,4a*S*,11b*S*)-2-(benzyloxy)-1,3,4-trihydroxy-1,2,3,4,4a,5-hexahydro-11b*H*-benzo[*b*]carbazole-6,11-dione was obtained.

1. Introduction

Quinones and naphthoquinones are of perennial chemical interest due to the widespread occurrence of the quinone nucleus in natural products that have important biological functions, together with their industrial applications and the biological activity shown by a number of quinone-containing compounds.[1] Specifically, 2-hydroxy-1,4-naphthoquinones are of interest as pigments[2] and because of their cytotoxic properties, which have been attributed to the presence of the quinone moiety.[1f,g,3,4] For example, parvaquone (**I**) is a hydroquinone that has been used against *Theileria parva*, a microscopic parasite that causes East Coast Fever (theileriosis).[5] From a chemical point of view, particular interest has been focussed on 3-phenyl-2-hydroxynaphthoquinones because they have proven to be convenient precursors for the synthesis of polycyclic naphthoquinone derivatives, including 5*H*-benzo[*b*]carbazole-6,11-diones (**II**),[6] which display antineoplastic activity. This behavior has been related to the presence in the structure of an embedded 2-phenylnaphthalene subunit (highlighted in blue in Fig. 1) in a planar conformation. This unit facilitates intercalation between adjacent pairs of DNA bases and, therefore, interferes with DNA replication and transcription.[7] In addition, the quinone moiety present in the 5*H*-benzo[*b*]carbazole ring skeleton explains its

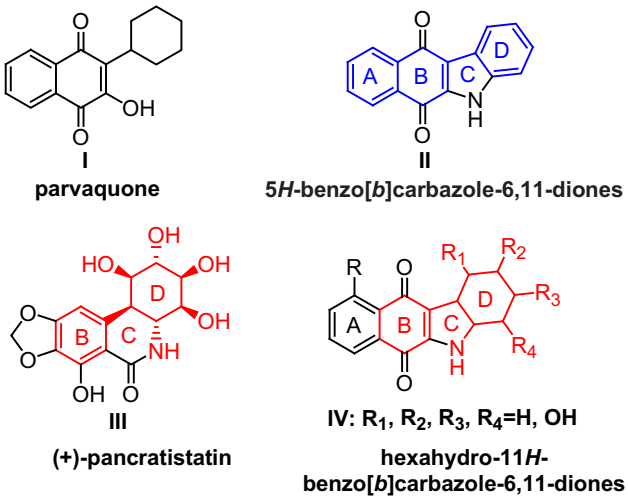

Fig. 1. Polycyclic compounds of biological interest.

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cytotoxic properties and facilitates the strength of intercalative binding to DNA through the formation of charge-transfer interactions with the electron-rich DNA bases.[8]

(+)-Pancratistatin (**III**) is an Amaryllidaceae alkaloid[9] that exhibits high levels of antitumor and antiviral activity as it displays strong toxicity against human tumor cells and is able to induce apoptosis in cancer cells by targeting their mitochrondria.[10] From a structural point of view, this compound consists of a phenanthridinone skeleton with a *trans*-fused BC bicyclic subunit and a D ring bearing six contiguous stereogenic centers.

Hexahydro-11b*H*-benzo[*b*]carbazole-6,11-diones (**IV**) are de novo designed tetracyclic naphthoquinone derivatives that have an ABCD ring system closely related to that of 5*H*-benzo[*b*]carbazole-6,11-diones (**II**). In addition, their highly oxygenated members (R_1=R_2=R_3=R_4=OH) include a structural subunit (highlited in red in Fig. 1), that is, also embedded in (+)-pancratistatin (**III**). These unique structural features and potential pharmacological interest make them particularly attractive targets for synthetic and biological studies.

Nitrocompounds are very versatile in organic synthesis due to their ready availability and ease of transformation into a wide variety of functionalities.[11] The chemistry of these compounds is dominated by the electron-withdrawing character of the nitro group. Thus the nitroaldol condensation (Henry reaction) is a classical method for carbon–carbon bond formation in which a carbonyl compound is coupled with a nitroalkane, a process that can result in the formation of one or two chiral centers.[11c,12] The intramolecular modality makes this a powerful method for the preparation of nitrocycloalkanes and this reaction is of appreciable interest for the transformation of nitro sugars into cyclopentane and cyclohexane derivatives.[12c,13] Nitroalkenes can act as potent Michael acceptors and, in fact, conjugate addition of nucleophiles to nitroolefins is another important tool for the creation of carbon–carbon bonds and carbon–heteroatom bonds.[12c,13] After employing these two powerful methods for the construction of cabon–carbon bonds, the nitro group can be transformed into a variety of funcitionalities—including amino groups by reduction.[12c]

In connection with our continued interest in nitro compounds[12c] and quinones, including 5*H*-benzo[*b*]carbazole-6,11-diones (**II**),[6] a few years ago we envisaged that the then unexplored[3,14,15] Michael addition of 2-hydroxy-1,4-naphthoquinone (**3**) to nitrocyclohexenes **4a** should give the novel 2-(2-nitrocyclohexyl)-3-hydroxynaphthalene-1,4-diones **2a**. We also reasoned that this quinone should provide access to the novel 1,2,3,4,4a,5-hexahydro-11b*H*-benzo[*b*]carbazole-6,11-diones **1a** by means of a heteroannulation process involving the reduction of the nitro group to amino and the subsequent Michael addition of the amino group to its quinone system (Scheme 1). We report here a full account of studies that have been previously unreported or have been published as preliminary reports[14,16] on the synthesis of targets **IV** according to the synthetic plan outlined in Scheme 1.

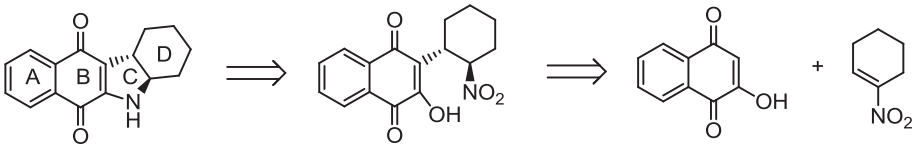
2. Results and discussion

Our preliminary studies on this project were aimed at the synthesis of the D ring unsubstituted model target **1a**. We started its synthesis taking advantage of the nucleophilic properties conferred to 2-hydroxy-1,4-naphthoquinones by their enol moiety.[3,14,15] Thus, the addition of commercially available 2-hydroxy-1,4-naphthoquinone (**3**) to nitrocyclohexene **4a**[17] provided the *trans*-2-naphthyl-1-nitrocyclohexane racemic mixture **2a** only (the thermodynamically more stable isomers) (Scheme 2),[3,14] as a result of a thermodynamically controlled Michael addition of the quinone to the nitro olefin. The structure of compound **2a** was easily established from its spectroscopic and analytical data. In fact, in the ^{1}H NMR spectrum a double triplet (*J* 11.6 and 4.0 Hz) was observed at 3.71 ppm due to the proton in the position α-to the quinone unit, together with a second double triplet at 5.40 ppm (*J* 11.6 and 4.0 Hz) due to the proton in the position α-to the nitro group. The multiplicity of both signals and the values for the coupling constants are consistent with an equatorial disposition of both the nitro and the quinone substituents on the cyclohexane ring.

Catalytic hydrogenation of nitrocyclohexylnaphthoquinone **2a** afforded the expected aminocyclohexylnaphthoquinone **5a**, probably via triol intermediate, which results from the simultaneous reduction of the nitro group and the quinone moiety followed by spontaneous oxidation under the work-up conditions.[18] When a solution of **5a** in dioxane was heated under reflux for 5 h, a mixture of the isomeric indolequinones **1a** (20% yield) and **7a** (25% yield) resulted and these were clearly differentiated by their infrared spectra.[18,19] The infrared spectrum of **1a** contained, at 1681 cm^{-1}, the only typical band described for 1,4-naphthoquinones. On the other hand, isomer **7a** showed the expected two bands for 1,2-naphthoquinones at 1670 and 1628 cm^{-1}.

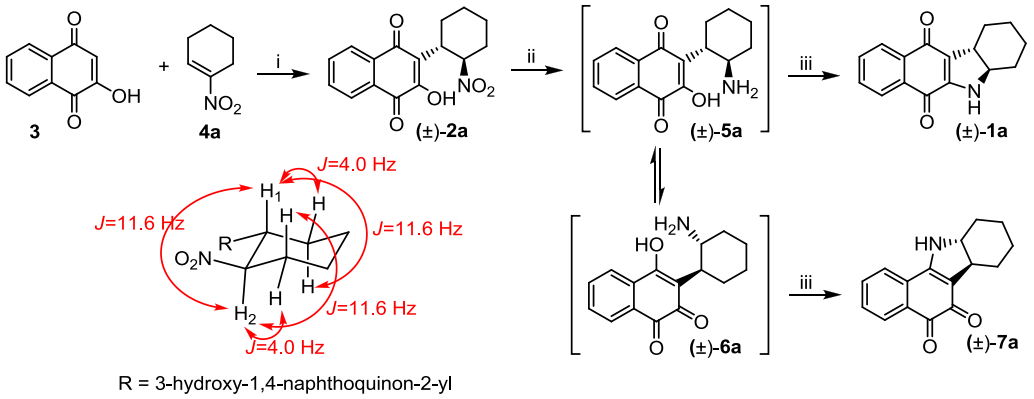
Benzocarbazolediones **1a** and **7a** should result from the conjugate addition of the amino group to the quinone moiety of tautomers **5a** and **6a**, respectively, followed by dehydration (Scheme 3).[6d] The conjugate addition of the amino group of compound **5a** to the quinone moiety should give intermediate **8** and, upon dehydration, this should irreversibly provide the novel tetracyclic quinone **1a**. Alternatively, compound **5a** could tautomerize to compound **6a**, via intermediates **9** and **10**, and this could be followed by the conjugate addition of the amino group of **6a** to its quinone subunit, a reaction that should result in the formation of intermediate **11**, from which quinone **7a** should be irreversibly formed by dehydration. The low yield achieved in these processes may be related to the trans disposition of the quinone and the amino substituents on the cyclohexane ring of **5a** and **6a**, a structural feature that precludes the planar conformation required for efficient formation of the nitrogen ring.

In the context of our continuous interest in novel synthetic applications of nitro sugars,[12c,13a,b,16,20] we decided to explore the extension of this methodology to the highly polysubstituted nitrocyclohexene **4b** (Scheme 4), with the aim of preparing the similar highly functionalized indoloquinones **1b** and **7b** (Scheme 6) for chemical and biological studies.

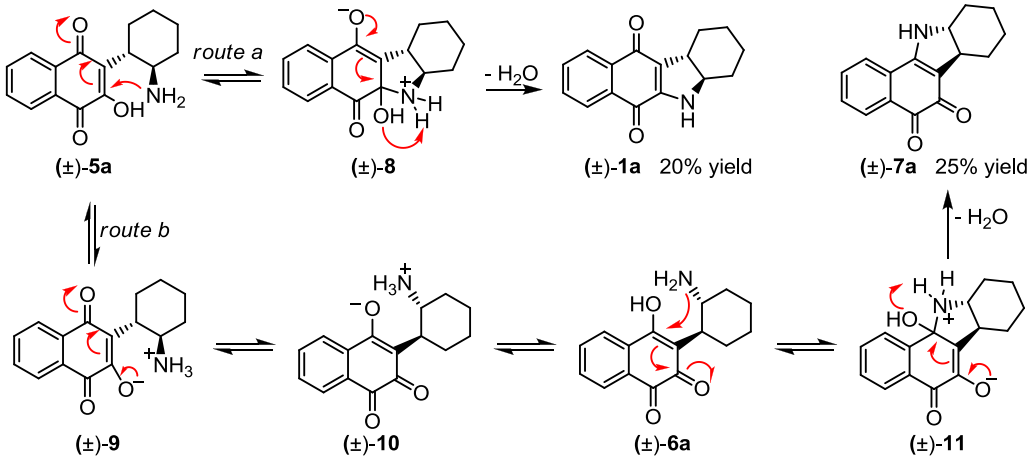


1a **2a** **3** **4a**

Scheme 1. Retrosynthetic plan for the preparation of hexahydro-11b*H*-benzo[*b*]carbazole-6,11-dione (**1a**).



Scheme 2. Reagents and conditions: (i) K_2CO_3, DMF, 90 °C, 16 h, 95%; (ii) H_2, Pd/C, MeOH, rt, 24 h, 80%; (iii) 1,4-dioxane, reflux, 5 h, 20% for **1a** and 25% for **7a**.

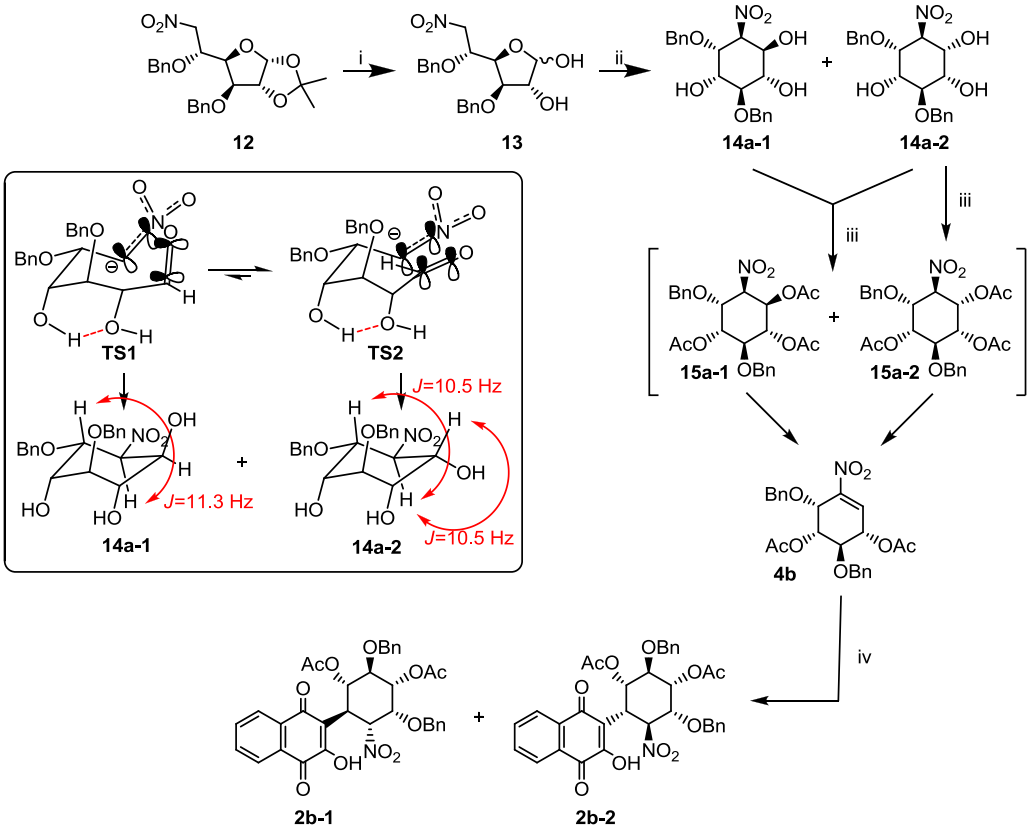


Scheme 3. Proposed mechanism to obtain benzocarbazoldiones **1a** and **7a**.

Nitrocyclohexene **4b** was prepared from diacetone-D-glucose via its nitro sugar derivative **12**, as depicted in Scheme 4.[21] Removal of the isopropylidene protecting group of **12**,[20b] by treatment with a trifluoroacetic acid/water mixture, was followed by treatment of the resulting nitroglucofuranose **13** with sodium bicarbonate in order to promote an intramolecular Henry reaction. This provided a mixture of the expected epimeric nitrocyclohexanes **14a-1** and **14a-2**, which were isolated in 22% yield and 52% yield, respectively, after column chromatography. The structural assignment for **14a-1** and **14a-2** was carried out by 1D and 2D NMR studies. For **14a-1**, the proton chemical shift at 5.0 ppm (d, *J* 11.3 Hz), due to the proton in the position α-to the nitro group, provides evidence for an axial–axial coupling with the proton α-to the adjacent benzyloxy group. The absence of coupling with the proton α-to the hydroxy group is consistent with an axial–equatorial disposition. On the other hand, compound **14a-2** shows a triplet at 4.84 ppm (*J* 10.5 Hz) for the proton in the position α-to the nitro group. The coupling constant values are in accordance with an axial disposition of this proton and its neighboring protons.

The outcome of this reaction can be explained as depicted in Scheme 4,[13c] assuming that abstraction of a proton α-to the nitro group of nitro sugar **13** results in the formation of a nitronate. This compound undergoes an intramolecular Henry reaction via the six-membered cyclic transition states **TS1** and **TS2**, with the bulky benzyloxy and nitro groups oriented equatorially and the hydroxy groups in axial dispositions, with stabilization through intramolecular hydrogen bonds. The transition state **TS2**, which is stabilized by the π-orbital overlap of C=O and C=N of the nitronate allowed by their parallel alignment, provided nitrocyclohexane **14a-2** through attack of the nitronate anion to the *Si*-face of the C=O group. On the other hand, the orthogonal orientation of C=O and C=N in transition state **TS1** precludes the π-orbital overlap and disfavors this transition state, making the formation of nitrocyclohexane **14a-1** less favored.

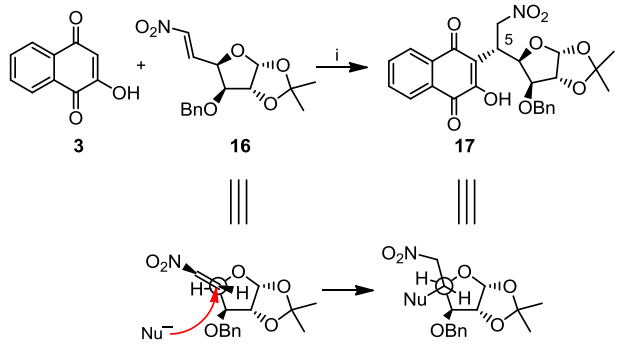
According to our plan, when compound **14a-2** was subjected to Ballini and Palestine's conditions for the dehydration of β-nitro alkanols (Ac_2O, DMAP),[22] the desired polysubstituted nitrocyclohexene **4b** was isolated in only 26% yield, probably due to elimination of one acetoxy group from the tri-*O*-acetyl derivative **15a-2**. In addition, when this protocol was applied to the mixture **14a-1**+**14a-2**, the nitro olefin **4b** was also obtained in 35% yield, probably via the mixture **15a-1**+**15a-2**. Continuing with our plan, the Michael addition of 2-hydroxy-1,4-naphthoquinone (**3**) to this nitrocyclohexene **4b** led to the formation of an inseparable equimolar mixture of compounds **2b-1** and **2b-2**. The mass spectrum of this mixture confirmed the molecular weight expected for these epimers and the 1:1 ratio was established from the ^{1}H NMR spectrum, by comparison of the intensities of the signals due to the acetyl substituents. A trans disposition for the naphthyl and nitro substituents was tentatively proposed on the basis that the ^{1}H NMR spectrum of this mixture includes a doublet of doublets (*J* 11.8 and 2.6 Hz) at 5.86 ppm. This requires an equatorial disposition of both the nitro and the quinone substituents. Unfortunately, the Michael addition of **3** to **4b** occurred without stereochemical control despite the variety of substituents present in the cyclohexane ring. This result is probably due to the fact that both faces of the C=C double



Scheme 4. Reagents and conditions: (i) TFA, H_2O, rt, 17 h; (ii) $NaHCO_3$, MeOH, H_2O, rt, 14 h, 22% for **14a-1** and 52% for **14a-2**; (iii) DMAP, Ac_2O, Et_2O, 0 °C, 1 h, 26% from **14a-2** or 35% from mixture **14a-1**+**14a-2**; (iv) **3**, K_2CO_3, THF, rt, 16 h, 57%.

bond in compound **4b** are equally hindered by the adjacent acetoxy and benzyloxy groups.

The global low yield achieved for the transformation of the mixture **14a-1**+**14a-2** into nitrocyclohexene **4b**, together with the lack of stereoselectivity in the Michael addition of **3** to **4b** and the inseparable nature of the resulting mixture of aducts **2b-1**+**2b-2**, led us to abandon this synthetic plan in favor of the alternative synthesis outlined in Scheme 5. This approach involved the introduction of the quinone unit prior to the Henry cyclization. This novel plan started with the nitro olefin **16**,[23] reaction of which with naphthoquinone **3** provided compound **17** with high diastereoselectivity (96% de) and in excellent yield (98%). The spectroscopic properties of **17** did not allow assignment of the configuration of the new stereogenic center at C-5, but this compound could be crystallized and its structure was firmly established by means of X-ray diffraction (Fig. 2).[24]



Scheme 5. Reagents and conditions: (i) K_2CO_3, THF, rt, 35 h, 96% de, 98% yield.

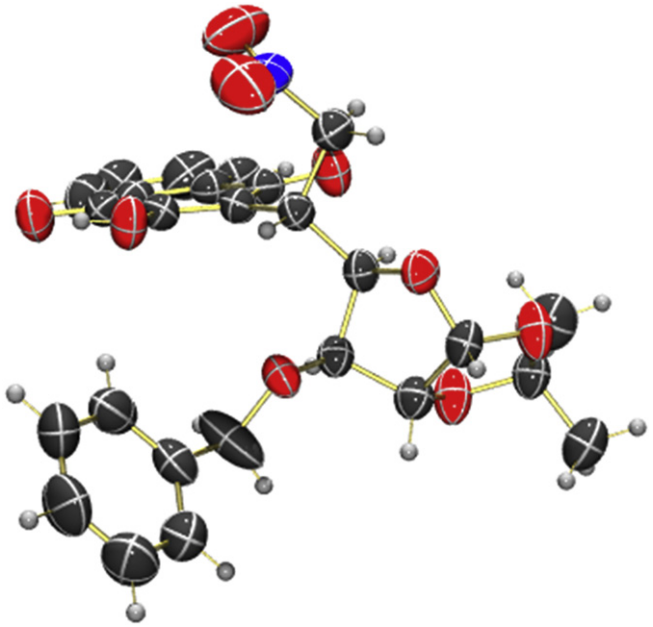
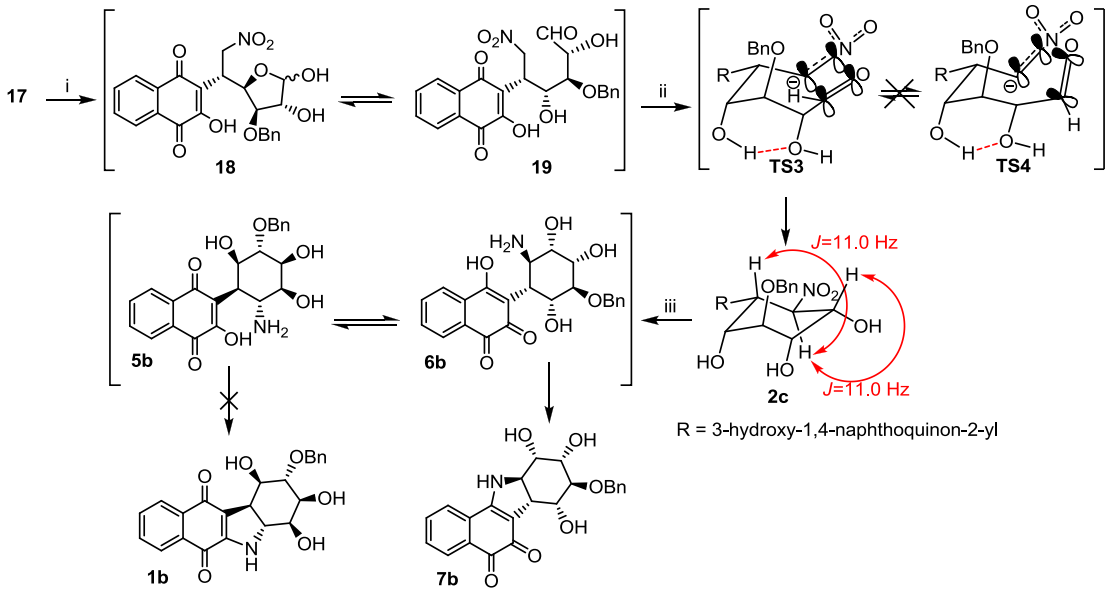


Fig. 2. ORTEP diagram of compound **17**.

The stereoselectivity achieved in this reaction can be easily explained in terms of the Felkin–Anh model (Scheme 5).[25] Thus, it was assumed that the thermodynamically more stable conformation of nitro olefin **16** involves an orthogonal disposition of its double bond with respect to the nearest electronegative substituent (the ring oxygen), together with the nitro group



Scheme 6. Reagents and conditions: (i) CH_2Cl_2, H_2O, TFA, rt, 5 h; (ii) Na_2CO_3, MeOH, H_2O, rt, 12 h, 90% from **17**; (iii) a: H_2 (1 atm), Ni-Raney, MeOH, rt, 5 h; b: 1,4-dioxane, reflux, 12 h, 32%.

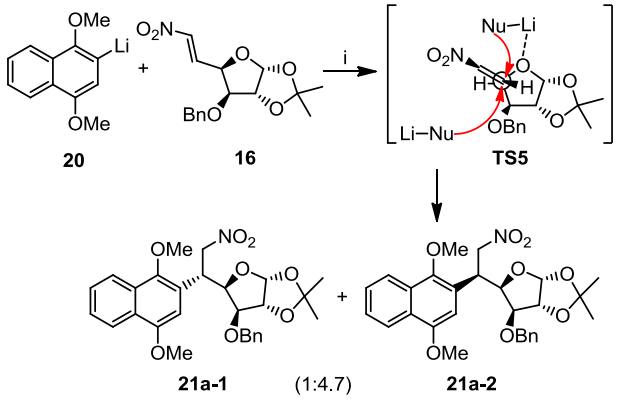
directed toward the smaller substituent. The most favored attack by the hydroxyquinone **3** corresponds to an approach to the double bond by the opposite face to that containing the electronegative oxygen. This explains the high diastereoselectivity achieved in this reaction.

As the final part of our plan, treatment of **17** with a trifluoroacetic acid/water mixture at rt gave the desired compound **18** (Scheme 6) by removal of the isopropylidene protecting group. When **18** was directly reacted with sodium carbonate, naphthyl-*muco*-inositol **2c** was the only product, which resulted from an intramolecular Henry reaction of the nitronate of compound **19** (the open form of compound **18**).

Compound **2c** was easily characterized from its spectroscopic properties. The absence from the ^{13}C NMR spectrum of any signal due to the $CH_2{-}NO_2$ group confirmed that the desired nitroaldol cyclization had occurred. On the other hand, the ^1H NMR spectrum showed a triplet at 6.03 ppm (J 11.0 Hz) and this was assigned to the highly deshielded proton α-to the nitro group. The coupling constant clearly indicates a double axial coupling of this proton with its neighboring protons, which in turn allowed us to establish the axial disposition of all these protons and therefore the equatorial disposition of the hydroxynaphthoquinonyl, nitro, and hydroxyl groups. The diastereoselectivity observed in this cyclization was explained assuming that the two six-membered cyclic transition states **TS3** and **TS4** are possible, both of which have an equatorial disposition of their bulky hydroxynaphthoquinonyl and nitro groups. Transition state **TS3** is probably strongly stabilized because a parallel alignment of C=N and C=O groups of the nitronate of **19** could allow efficient π-orbital overlap. This might explain the formation of compound **2c** only.

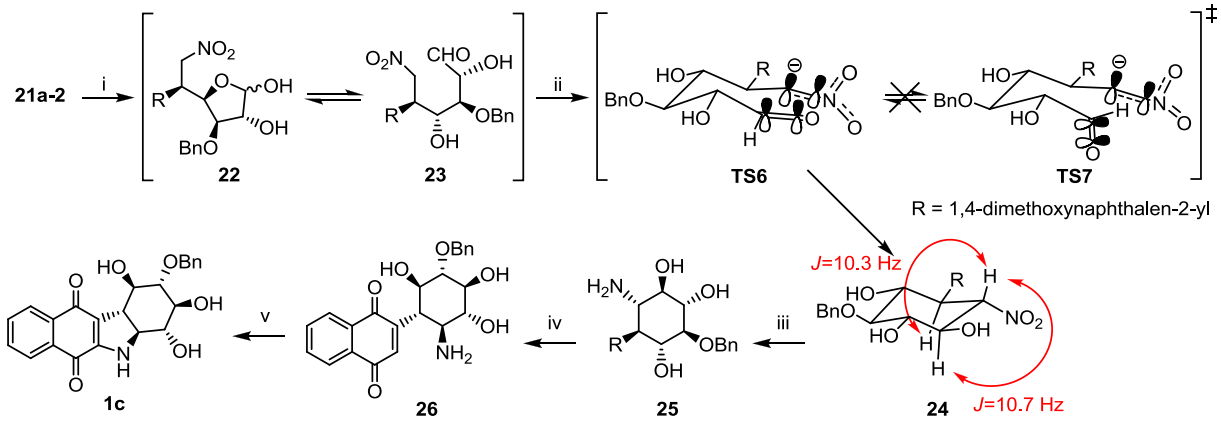
Finally, proceeding as for compound **2a**, catalytic hydrogenation of nitroinositolquinone **2c** should result in a mixture of tautomers **5b** and **6b**, and conjugate addition of the amino functionality to their respective quinone moieties followed by dehydration should provide a mixture of indoloquinones **1b** (as the minor component) and **7b** (as the major component), respectively. However, surprisingly only one product was obtained and this had the molecular formula $C_{23}H_{21}NO_6$, as expected for both indoloquinones **1b** and **7b** (Scheme 6). This compound was tentatively characterized as isomer **7b**, on the basis of the similarities of its infrared spectrum and the infrared spectrum of compound **7a**. The global yield now achieved (32%) was significantly lower than for **1a**+**7a** (45%). This was attributed to the presence of substituents on the cyclohexane ring of tautomers **5b** and **6b**, since no debenzylated or other side-products were observed in the crude mixture. This structural factor that probably makes the transformation of **6b** into **7b** more difficult and impedes the transformation of **5b** into **1b**.

Compound **1c** (Scheme 8), a diastereoisomer of compound **1b**, could be prepared when a slight modification was introduced in this synthetic sequence. Reaction of 2-bromo-1,4-dimethoxynaphthalene[26] with *tert*-butyllithium in tetrahydrofuran produced (1,4-dimethoxynaphthalen-2-yl)lithium (**20**), which was reacted with sugar nitro olefin **16** to give an epimeric mixture of the expected Michael adducts **21a-1**+**21a-2** (65% de) due to attack of the organolithium derivative on both faces of the double bond of **16** (Scheme 7).



Scheme 7. Reagents and conditions: (i) THF, −78 °C, 4 h, 65% de, 77% yield of **21a-1**+**21a-2**, 54% of **21a-2** after crystallization.

The moderate stereoselectivity achieved, which was opposite to that produced by the Michael addition of 2-hydroxy-1,4-naphthoquinone **3** to compound **16**, should be due to chelation of the lithium atom with the furanose ring oxygen favoring the attack of the lithium salt on the most hindered face of the double bond.[27] The mixture of **21a-1** and **21a-2** could not be separated by column chromatography, but the main epimer **21a-2** was isolated in 54%



Scheme 8. Reagents and conditions: (i) 1,4-dioxane, H_2O, TFA, 50 °C, 16 h; (ii) $NaHCO_3$, MeOH, H_2O, rt, 24 h, 87% from **21a-2**; (iii) H_2 (1 atm), Ni-Raney, MeOH, rt, 3 h, 95%; (iv) CAN, CH_3CN, H_2O, 0 °C, 1 h, 92%; (v) THF, 60 °C, 24 h, 20%.

yield by crystallization. Moreover, the minor epimer **21a-1** was isolated as a sticky oil containing small amounts of **21a-2**. The L-idofuranose configuration of **21a-2** was firmly established by X-ray diffraction (Fig. 3).[24] Removal of the acetonide protecting group of **21a-2** with trifluoroacetic acid (Scheme 8), followed by treatment of the resulting furanose **22** with sodium bicarbonate, allowed us to obtain 87% yield of naphthylcyclohexane **24**. Alternative cyclization subproducts were not detected by TLC or by ^{1}H NMR spectroscopy. The configuration of compound **24** was easily established from the ^{1}H NMR spectrum, which included at 5.15 ppm a doublet of doublets (J 10.3 and 10.7 Hz) corresponding to the highly deshielded hydrogen α-to the nitro group. This signal can be explained in terms of double axial coupling between this proton and its neighboring protons. This result requires an equatorial disposition for the dimethoxynaphthalenyl, nitro and hydroxy substituents.

The high diastereoselectivity observed in this process was again explained by assuming the presence of stabilized six-membered cyclic transition states with the bulkiest substituents in equatorial disposition. The parallel alignment of C=O and C=N present in the transition state **TS6** allows a high level of stabilization by π-orbital overlap, which in turn prevents the formation of less stabilized transition state **TS7** and explains the exclusive formation of the diastereomer **24**. Catalytic hydrogenation of naphthylnitrocyclohexane **24** results in its efficient transformation into the corresponding aminocyclohexane **25**. Finally, treatment of this compound with cerium ammonium nitrate gave aminocyclohexanenaphthoquinone **26**, which, on heating in tetrahydrofuran, provided a low yield of a dark purple compound. ^{1}H and ^{13}C NMR spectroscopy allow us identify this product as hexahydro-11b*H*-benzo[*b*]carbazole-6,11-dione **1c**, which also showed the expected molecular formula of $C_{23}H_{21}NO_6$ in its HRMS. The infrared spectrum included at 1661 cm^{-1} the only typical band reported for 1,4-naphthoquinones. The formation of this compound might occur by conjugate addition of the amino group to the quinone moiety of compound **26** followed by spontaneous oxidation of the resulting naphthol. The trans disposition of the amino and quinone substituents on the cyclohexane ring disfavors the formation of the pentacyclic nitrogen ring of **1c**, and this would explain the low efficiency of this intramolecular addition.

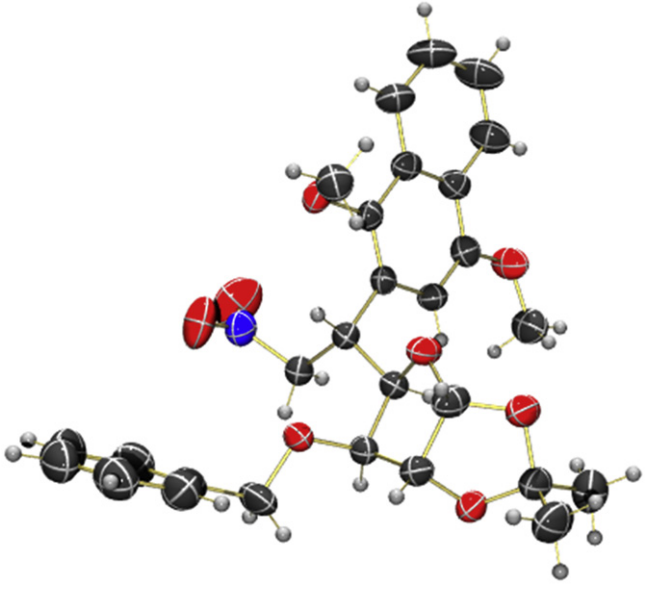


Fig. 3. ORTEP diagram of compound **21a-2**.

In conclusion, we have developed novel chemical applications of nitro compounds and these have allowed the first reported synthesis of (6b*R*,7*R*,8*S*,9*S*,10*S*,10a*R*)-8-(benzyloxy)-7,9,10-trihydroxy-6b,7,8,9,-10,10a-hexahydro-11*H*-benzo[*a*]carbazole-5,6-dione **7b** and (1*R*,2*S*,3-*S*,4*R*,4a*S*,11b*S*)-2-(benzyloxy)-1,3,4-trihydroxy-1,2,3,4,4a,5-hexahydro-11b*H*-benzo[*b*]carbazole-6,11-dione **1c**, two novel benzocarbazoldiones, the two first examples of two novel families of compounds of probable biological interest, on account of their structural relationship with benzo[*b*]carbazoldiones **II** and (+)-pancratistatin (**III**).

The routes involved in the preparation of benzocarbazolediones **1a**, **1c**, **7a**, and **7b** include novel chemistry. It consists of the first reported example on the addition of quinones to nitro olefins,[14] which allowed to prepare compounds **2b** and **2c**, the two first examples of naphthoquinones bearing a highly functionalized cyclohexane ring linked to their C-2 position. They can then be considered as novel derivatives of parvaquone (2-cyclohexyl-3-hydroxy-1,4-naphthoquinones **I**), a hydroxyquinone that displays interesting biological properties.

Work is now in progress aimed at the optimization of the synthetic routes here reported, as a preliminary step for the preparation of libraries of type **1**, **2**, **7**, and **26** naphthoquinone derivatives from the plethora of hexoses for future chemical and biological studies.

3. Experimental section

3.1. General

Melting points were determined on a Kofler Thermogerate apparatus and are uncorrected. Infrared spectra were recorded on a JASCO FT/IR-400 spectrophotometer. Nuclear magnetic resonance spectra were recorded, unless otherwise specified, on a Bruker DPX-250 apparatus using deuterochloroform solutions containing

tetramethylsilane as internal standard. ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q) or quintuplet (p). All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Mass spectra were obtained on an HP 5988A mass spectrometer, using the electron impact (EI) or the chemical ionization (CI) techniques. Elemental analyses were performed on EA 1108 CHNS Fisons. Thin layer chromatography (TLC) was performed using Merck GF-254 type 60 silica gel and dichloromethane/methanol or ethyl acetate/hexane mixtures as eluants; the TLC spots were visualized with ultraviolet light or iodine vapor. Column chromatography was carried out using Merck type 9385 silica gel. Solvents were purified as per Ref. 28. Solutions of extracts in organic solvents were dried with anhydrous sodium sulfate.

*3.1.1. (±)-2-Hydroxy-3-((1S,2R)-2-nitrocyclohexyl)naphthalene-1,4-dione (±-**2a**).* An oven-dried round-bottomed flask was charged with 2-hydroxynaphthalene-1,4-dione (**3**) (0.400 g, 2.30 mmol), 1-nitrocyclohexene (**4a**) (0.350 g, 2.76 mmol), anhydrous potassium carbonate (0.635 g, 4.60 mmol), and dry tetrahydrofuran (16 mL). The mixture was heated at 50 °C during 20 h under a nitrogen atmosphere and the reaction was quenched with water (30 mL) and acidified with several drops of 1.0 M hydrochloric acid. The reaction mixture was extracted with dichloromethane (3×15 mL) and the combined organic extracts were dried with anhydrous sodium sulfate. After filtration and evaporation of the solvent under vacuum, column chromatography of the crude product on silica gel (5% methanol in dichloromethane) afforded (**±**)-**2a** (0.614 g, 89% yield). Orange solid; mp 181–183 °C; IR (ν, cm^{-1}, NaCl) ν=1673, 1644, 1540, 1367; ^{1}H NMR (δ, ppm, $CDCl_3$): 1.38–1.64 (m, 2H, CH_2), 1.73–2.08 (m, 5H, 2× CH_2+CH*H*), 2.33–2.51 (m, 1H, CH*H*), 3.71 (td, 1H, *J*=11.6, 4.0 Hz, CH), 5.40 (td, 1H, *J*=11.6, 4.0 Hz, CH–NO_2), 7.67 (td, 1H, *J*=7.6, 1.5 Hz, Ar–H); 7.76 (td, 1H, *J*=7.6, 1.5 Hz, Ar–H), 8.05 (dd, 1H, *J*=7.6, 1.5 Hz, Ar–H), 8.11 (dd, 1H, *J*=7.6, 1.5 Hz, Ar–H); ^{13}C NMR (δ, ppm, $CDCl_3$): δ=24.2, 25.0, 28.4, 32.1, 38.5, 85.9, 121.6, 126.2, 127.0, 129.0, 132.7, 133.1, 135.2, 153.4, 181.0, 183.7; MS (FAB) (*m*/*z*, %): 302 $[M+H]^+$ (12), 137 (100). Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found C, 63.54; H, 5.28; N, 4.78.

*3.1.2. (±)-2-((1S,2R)-2-Aminocyclohexyl)-3-hydroxynaphthalene-1,4-dione (±-**5a**).* A suspension of compound (±)-**2a** (0.100 g, 0.33 mmol) and 10% palladium on activated charcoal (0.100 g) in methanol (20 mL) was degassed under a nitrogen atmosphere. This mixture was stirred at rt during 24 h under a hydrogen atmosphere and the catalyst was filtered off. Removal of the solvent under vacuum produced a crude red solid of (±)-2-((1*S*,2*R*)-2-aminocyclohexyl)-3-hydroxynaphthalene-1,4-dione (±-**5a**) (0.090 g, 100%), which was used in the next reaction without further purification.

*3.1.3. (±)-(4aR,11bS)-1,2,3,4,4a,5-Hexahydro-11bH-benzo[b]carbazole-6,11-dione (±-**1a**) and (±)-(6bS,10aR)-6b,7,8,9,10,10a-hexahydro-11H-benzo[a]carbazole-5,6-dione (±-**7a**).* A round-bottomed flask was charged with crude amino derivative (±)-**5a** (0.090 g, 0.33 mmol) and 1,4-dioxane (20 mL) and the mixture was heated under reflux for 5 h. The mixture was cooled to rt and benzo[*b*]carbazole-6,11-dione derivative (±)-**1a** (0.018 g) was isolated by filtration. The mother liquors were concentrated to dryness under vacuum and the crude residue was submitted to column chromatography on silica gel (5% methanol in dichloromethane) to afford benzo[*a*]carbazole-5,6-dione derivative (±)-**7a** (0.022 g).

*3.1.3.1. (±)-(4aR,11bS)-1,2,3,4,4a,5-Hexahydro-11bH-benzo[b]carbazole-6,11-dione (±-**1a**).* Violet solid (20% yield); mp higher than 300 °C, IR (ν, cm^{-1}, NaCl): 2935, 1681; ^{1}H NMR (δ, ppm, DMSO-d_6): 1.16–2.27 (m, 8H, 4× CH_2), 2.50–2.65 (m, 1H, CH), 3.43–3.59 (m, 1H, CH), 7.57–7.94 (m, 4H, 4× Ar–H), 9.21 (br s, 1H, NH); ^{13}C NMR (δ, ppm, DMSO-d_6): 24.3, 25.3, 28.4, 30.0, 47.5, 67.7, 115.7, 124.2, 127.4, 127.7, 131.5, 131.6, 133.9, 161.1, 171.2, 183.6; MS (FAB) (*m*/*z*, %): 253 $[M]^+$ (63), 195 (100). HRMS calcd for $C_{16}H_{15}NO_2$ $[M]^+$ 253.110279; found 253.109090.

*3.1.3.2. (±)-(6bS,10aR)-6b,7,8,9,10,10a-Hexahydro-11H-benzo[a]carbazole-5,6-dione (±-**7a**).* Orange solid (25% yield); IR (ν, cm^{-1}, NaCl): 2931, 1670, 1628; ^{1}H NMR (δ, ppm, CD_3COCD_3): 1.28–1.92 (m, 6H, 3× CH_2), 2.20–2.31 (m, 1H, CH), 2.56–2.74 (m, 2H, CH_2), 3.19–3.33 (m, 1H, CH), 6.65 (br s, 1H, NH), 7.68 (td, 1H, *J*=7.5, 1.6 Hz, Ar–H), 7.76 (td, 1H, *J*=7.5, 1.6 Hz, Ar–H), 7.91–7.99 (m, 2H, 2× Ar–H); ^{13}C NMR (δ, ppm, CD_3COCD_3): 26.3, 27.6, 30.6, 32.7, 50.7, 70.3, 124.5, 127.0, 127.1, 133.6, 135.8, 135.9, 136.2, 156.4, 181.5, 182.0; MS (FAB, *m*/*z*, %): 253 $[M]^+$ (91), 224 (100); HRMS calcd for $C_{16}H_{15}NO_2$ $[M]^+$ 253.110279; found 253.109088.

*3.1.4. 1L-3,5-Di-O-benzyl-6-deoxy-6-nitro-muco-inositol (**14a**-**1**) and 1L-2,6-di-O-benzyl-3-deoxy-3-nitro-chiro-inositol (**14a**-**2**).* A solution of 3,5-di-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-6-nitro-α-D-glucofuranose (**12**) (0.103 g, 0.241 mmol) in water (6 mL) and trifluoroacetic acid (6 mL) was stirred at rt during 17 h. The solvent was evaporated under vacuum and the residue was coevaporated with toluene (3×6 mL). The unstable yellow oil obtained was dissolved in methanol (7 mL), 2% sodium bicarbonate aqueous solution (2.5 mL) was added, and the mixture was stirred at rt during 14 h. The reaction mixture was quenched by acidification with acid resin, the solids were filtered off, the solvent was removed under vacuum, and the residue was purified by column chromatography (AcOEt/hexane, 2:3) to give the *muco*-inositol **14a**-**1** and the *chiro*-inositol **14a**-**2**.

*3.1.4.1. 1L-3,5-Di-O-benzyl-6-deoxy-6-nitro-muco-inositol (**14a**-**1**).* Yellow oil (22% yield); IR (ν, cm^{-1}): 3410; 1559; 1376; ^{1}H NMR (δ, ppm, $CDCl_3$): 2.68 (br s, 3H, 3× OH); 3.47–3.50 (m, 1H, H-1); 3.54 (d, 1H, *J*=2.3 Hz, H-5); 3.62 (dd, 1H, *J*=2.4 Hz, H-1); 4.43–4.55 (m, 3H, –OCH_2Ph, H-6); 4.73–4.79 (m, 2H, –OCHPh, H-4); 5.00 (d, 1H, *J*=11.3 Hz, H-3); 7.19–7.37 (m, 10H, 10× Ar–H); ^{13}C NMR (δ, ppm, $CDCl_3$): 69.6, 72.6, 74.6, 75.3, 75.9, 78.0, 79.8, 86.7, 128.0–128.7, 137.3, 138.1; MS (CI, *m*/*z*, %): 390 $[MH]^+$ (1); 341 (2); 298 (2), 91 $[PhCH_2]^+$ (100).

*3.1.4.2. 1L-2,6-Di-O-benzyl-3-deoxy-3-nitro-chiro-inositol (**14a**-**2**).* Yellow oil (52% yield); IR (ν, cm^{-1}): 3410; 1559; 1376; ^{1}H NMR (δ, ppm, $CDCl_3$): 3.28 (br s, 3H, 3× OH); 3.90 (t, 1H, *J*=2.9 Hz, H-3); 4.06 (br s, 2H, H-2+H-4); 4.22–4.30 (m, 2H, H-1+H-5); 4.40–4.58 (m, 4H, 2× OCH_2Ph); 4.84 (t, 1H, *J*=10.5 Hz, H-6); 7.23–7.40 (m, 10H, 10× Ar–H); ^{13}C NMR (δ, ppm, $CDCl_3$): 69.1, 70.4, 71.2, 72.8, 72.9, 72.9, 76.0, 76.2, 88.7, 127.7–128.7, 136.7, 137.2; MS (CI, *m*/*z*, %): 388 $[M-H]^+$, (2); 370 (2); 298 (4); 181 (25); 91 $[PhCH_2]^+$ (100).

*3.1.5. (1R,2R,3S,6R)-2,6-Bis(benzyloxy)-5-nitrocyclohex-4-ene-1,3-diyl diacetate (**4b**).* A mixture of inositols **14a**-**1** and **14a**-**2** (113 mg, 0.29 mmol) in Et_2O (11 mL) was cooled to 0 °C under a nitrogen atmosphere and a catalytic amount of 4-(dimethylamino)pyridine and acetic anhydride (1.30 mL) were added. The reaction mixture was stirred until complete conversion (TLC analysis), then acidified to pH 6 with 10% hydrochloric acid and the stirring was continued for 1 h. The mixture was diluted with water (10 mL), extracted with ethyl acetate (3×10 mL), and the combined organic extracts were dried over anhydrous sodium sulfate and concentrated to dryness under vacuum. The residue was purified by column chromatography (ethyl acetate/hexane 1:5) to give nitrocyclohexene **4b** (46.2 mg, 35% yield). Yellow oil; $[\alpha]_D^{20}$ +0.07 (*c* 0.6, $CHCl_3$). IR (ν, cm^{-1}, NaCl): 1530; 1365; 1745; ^{1}H NMR (δ, ppm, $CDCl_3$): δ=1.95 (s, 3H, OCH_3); 1.98 (s, 3H, OCH_3); 4.19 (dd, 1H, *J*=7.8, 9.9 Hz, H-2); 4.59–4.76 (m, 4H, 2× CH_2Ph); 4.98–5.04 (m, 2H, H-1+H-6); 5.52

(dd, 1H, *J*=2.6, 7.8 Hz, H-3); 7.06 (d, 1H, *J*=2.7 Hz, H-4); 7.21–7.32 (m, 10H, 10× Ar–H); ^{13}C NMR (δ, ppm, $CDCl_3$): 20.6, 20.7, 70.8, 71.2, 72.3, 74.9, 75.0, 75.8, 127.8, 127.9, 128.1, 128.2, 128.5, 132.3, 137.3, 137.7, 148.1, 169.8, 169.9 ppm. MS (*m*/*z*, %): 456 $[MH]^+$ (8); 91 $[PhCH_2]^+$ (90). Anal. Calcd for $C_{24}H_{25}NO_8$: C, 63.29; H, 5.53; N, 3.08. Found C, 63.58; H, 5.79; N, 2.90.

*3.1.6. (1S,2R,3R,4R,5R,6R)-+(1S,2R,3R,4R,5S,6S)-2,6-Di-O-benzyloxy-4-(3′-hydroxy-1′,4′-naphthoquinon-2′-yl)-5-nitrocyclohexan-1,3-dyil diacetate (**2b**-**1**+**2b**-**2**).* To a solution of nitrocyclohexene **4b** (25.7 mg, 0.056 mmol) in dry tetrahydrofuran (1.0 mL), 2-hydroxy-1,4-naphthoquinone (**3**) (15.6 mg, 0.113 mmol), and anhydrous potassium carbonate (31.6 mg, 0.226 mmol) were added and the suspension was stirred under a nitrogen atmosphere at rt for 16 h. The mixture was acidified with 10% hydrochloric acid, the tetrahydrofuran was removed under vacuum and the aqueous phase was extracted with dichloromethane (3×5 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to dryness under vacuum. The residue was purified by column chromatography (ethyl acetate/hexane 1:1) to yield an inseparable mixture of nitrocyclohexanes **2b**-**1** and **2b**-**2** (20.4 mg, 57% yield). Orange oil; IR (ν, cm^{-1}, NaCl): 3326; 1671; 1649; 1555; 1367; ^{1}H NMR (δ, ppm, $CDCl_3$): 1.74 (s, 3H, CH_3); 1.78 (s, 3H, CH_3); 1.92 (s, 3H, CH_3); 1.94 (s, 3H, CH_3); 4.16–4.38 (m, 3H); 4.58–4.76 (m, 11H); 5.03–5.17 (m, 2H); 5.47–5.67 (m, 3H); 5.86 (dd, 1H, *J*=2.6, 11.8 Hz); 7.22–7.42 (m, 20H, 20× Ar–H); 7.63–7.80 (m, 4H, 4× Ar–H); 7.94–8.20 (m, 4H, 4× Ar–H); ^{13}C NMR (δ, ppm, $CDCl_3$): 20.4, 20.5, 20.7, 34.1, 37.0, 70.7, 72.6, 73.5, 73.6, 75.1, 75.3, 75.7, 77.4, 77.5, 77.9, 78.0, 82.1, 82.9, 126.4–128.5, 128.9, 129.2, 132.8, 133.1, 133.2, 135.2, 135.6, 136.9, 137.0, 138.0, 138.1, 155.7, 169.8, 169.9, 180.6, 182.7, 184.4; MS (CI, *m*/*z*, %): 630 $[MH]^+$ (5); 91, $[CH_2Ph^+]$ (100).

*3.1.7. 3-O-Benzyl-5,6-dideoxy-5-C-(3′-hydroxy-1′,4′-naphthoquinon-2′-yl)-1,2-O-isopropylidene-6-nitro-α-D-glucofuranose (**17**).* An oven-dried round-bottomed flask was charged with 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-D-*xylo*-hex-5-enefuranose (**16**) (0.590 g, 1.83 mmol), 2-hydroxy-1,4-naphthoquinone (**3**) (0.312 g, 2.12 mmol), anhydrous potassium carbonate (0.510 g, 3.65 mmol), and dry tetrahydrofuran (17 mL). The suspension was stirred at rt under a nitrogen atmosphere during 35 h, the reaction was quenched with water (30 mL) and acidified with several drops of 1.0 M hydrochloric acid. The resulting mixture was extracted with dichloromethane (3×15 mL) and the combined organic extracts were dried with anhydrous sodium sulfate. After filtration and evaporation of the solvent under vacuum, column chromatography of the crude product on silica gel (methanol in dichloromethane 1:60 to 1:30 gradient) afforded compound **17** (0.892 g, 1.79 mmol) as a solid, which was crystallized from dichloromethane/heptane. Yellow solid (98% yield), mp 130–131 °C; $[\alpha]_D^{20}$ +45.6 (*c* 1.1, $CHCl_3$); IR (ν, cm^{-1}, NaCl): 3359, 1669, 1648, 1552, 1380; ^{1}H NMR (δ, ppm, $CDCl_3$): 1.33 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 1.61 (br s, 1H, OH), 3.73 (d, 1H, *J*=3.0 Hz, H-3), 4.24 (d, 1H, *J*=11.6 Hz, CH_2Ph), 4.38 (ddd, 1H, *J*=4.6, 9.7 Hz, *J*=10.1 Hz, H-5), 4.51 (d, 1H, *J*=11.6 Hz, CH_2Ph), 4.61 (d, 1H, *J*=4.0 Hz, H-2), 4.90 (dd, 1H, *J*=3.0, 9.7 Hz, H-4), 4.90 (dd, 1H, *J*=4.6, 12.2 Hz, H-6), 5.00 (dd, 1H, *J*=10.1, 12.2 Hz, H-6), 5.98 (d, 1H, *J*=4.0 Hz, H-1), 7.07–7.15 (m, 5H, 5× H–Ar), 7.69–7.83 (m, 2H, H-6′+H-7′), 8.04–8.09 (m, 2H, H-5′+H-8′); ^{13}C NMR (δ, ppm, $CDCl_3$): 26.1, 26.6, 35.1, 71.4, 75.9, 78.1, 80.7, 81.5, 104.7, 111.8, 117.7, 126.1, 126.9, 127.7, 128.1, 129.0, 132.3, 133.0, 135.1, 136.2, 154.7, 180.4, 183.2; MS (CI, *m*/*z*, %): 496 $[MH]^+$ (1), 480 $[M-CH_3]^+$ (2), 438 $[M-C_3H_6O]^+$ (11), 91 $[PhCH_2]^+$ (100). Anal. Calcd for $C_{26}H_{25}NO_9$: C, 63.03; H, 5.09; N, 2.83. Found: C, 62.74; H, 5.15; N 2.81.

*3.1.8. 2-((1R,2R,3S,4S,5S,6R)-3-(Benzyloxy)-2,4,5-trihydroxy-6-nitrocyclohexyl)-3-hydroxynaphthalene-1,4-dione (**2c**).* A solution of glucofuranose derivative **17** (0.250 g, 0.51 mmol) in dichloromethane (1 mL), water (3 mL), and trifluoroacetic acid (6 mL) was stirred at rt during 5 h. The solvent was evaporated and the residue was coevaporated with toluene (3×5 mL) to yield the 3-*O*-benzyl-5,6-dideoxy-5-*C*-(3′-hydroxy-1′,4′-naphthoquinon-2′-yl)-6-nitro-D-glucose **18** as an unstable yellow oil, which was dissolved in methanol (12 mL) and 2% sodium carbonate aqueous solution (4 mL). After stirring the mixture at rt during 12 h, the reaction was quenched by acidification with acid resin, filtered, and the solvent was evaporated under vacuum. The resulting residue was subjected to chromatography on silica gel (dichloromethane/methanol/acetic acid 10:0.5:0.2) affording nitrocyclohexane **2c** (0.213 g, 0.46 mmol). Amorphous orange solid (90% yield); $[\alpha]_D^{20}$ +60.8 (*c* 4.5, CH_3COCH_3). IR (ν, cm^{-1}, NaCl): 3393, 1672, 1647, 1552, 1371; ^{1}H NMR (δ, ppm, CD_3COCD_3): 3.98 (t, 1H, *J*=3.2 Hz, H-3), 4.24–4.29 (m, 2H, H-2+H-4), 4.39 (dd, 1H, *J*=3.0, 11.0 Hz, H-1), 4.46 (d, 1H, *J*=11.0 Hz, H-5), 4.72 (d, 1H, *J*=11.8 Hz, CH_2–Ph), 4.82 (d, 1H, *J*=11.8 Hz, CH_2–Ph), 6.03 (t, 1H, *J*=11.0 Hz, H-6), 7.29–7.56 (m, 5H, 5× H–Ar), 7.76–7.89 (m, 2H, H-6′+H-7′), 8.04–8.11 (m, 2H, H-5′+H-8′); ^{13}C NMR (δ, ppm, CD_3COCD_3): 40.8, 73.2, 73.5, 73.8, 74.5, 78.5, 87.3, 119.1, 127.5, 128.0, 129.5, 130.0, 131.3, 133.9, 134.9, 136.6, 139.7, 159.2, 182.7, 185.4; MS (CI, *m*/*z*, %): 349 $[MH-BnO]^+$ (20), 281 $[M-C_{10}H_6O_3]^+$ (14), 91 $[Bn]^+$ (100). Anal. Calcd for $C_{23}H_{21}NO_9$: C, 60.66; H, 4.65; N, 3.08. Found: C, 60.73; H, 4.98; N, 2.65.

*3.1.9. (6bR,7R,8S,9S,10S,10aR)-8-(Benzyloxy)-7,9,10-trihydroxy-6b,7,8,9,10,10a-hexahydro-11H-benzo[a]carbazole-5,6-dione (**7b**).* A degassed suspension of nitrocyclohexane derivative **2c** (0.052 g, 0.11 mmol) and Raney-nickel (0.100 g) in methanol (5 mL) was stirred under a hydrogen atmosphere at rt during 5 h. The catalyst was filtered off and the solvent evaporated, providing the amino intermediate **6b** as a yellow oil, which was directly dissolved in 1,4-dioxane (5 mL) and heated under reflux during 12 h. The solvent was evaporated and the crude solid was subjected to column chromatography on silica gel (10% methanol in dichloromethane) to afford benzo[*a*]carbazoledione **7b** (0.016 g, 0.04 mmol). Red solid (32% yield); mp 193–194 °C (methanol); $[\alpha]_D^{20}$ −112.3 (*c* 0.34, CH_3OH); IR (ν, cm^{-1}, NaCl): 3341, 1671, 1623; ^{1}H NMR (δ, ppm, CD_3OD): 3.37–3.57 (m, 2H, H-7+H-8), 3.77 (t, 1H, *J*=2.7 Hz, H-9), 3.85 (dd, 1H, *J*=3.4, 10.4 Hz, H-6b), 3.97–4.09 (m, 2H, H-10+H-10a), 4.53 (d, 1H, *J*=12.0 Hz, CH_2–Ph), 4.60 (d, 1H, *J*=12.0 Hz, CH_2–Ph), 7.16–7.29 (m, 5H, 5× H–Ar), 7.51–7.67 (m, 2H, H-2+H-3), 7.86–7.91 (m, 2H, H-1+H-4); ^{13}C NMR (δ, ppm, $CDCl_3$): 48.6, 62.1, 68.9, 73.4, 74.0, 74.5, 81.8, 120.7, 126.5, 126.8, 128.9, 129.0, 129.5, 133.2, 135.3, 135.7, 139.6, 157.3, 180.6, 182.4; MS (CI, *m*/*z*, %): 409 $[MH_2]^+$ (42), 408 $[MH]^+$ (37), 358 (17), 185 (100). HRMS calcd for $C_{23}H_{21}NO_6$ $[M]^+$ 407.136890; found 407.136881.

*3.1.10. 3-O-Benzyl-5,6-dideoxy-5-C-(1′,4′-dimethoxynaphthalen-2′-yl)-1,2-O-isopropyliden-6-nitro-β-L-idofuranose (**21a**-**2**).* A 2.1 M solution in hexanes of *tert*-butyllithium (1.9 mL, 4.04 mmol, 2.5 equiv) was added dropwise to a solution of 2-bromo-1,4-dimethoxynaphthalene (540 mg, 2.02 mmol, 1.2 equiv) in dry tetrahydrofuran (4 mL) at −78 °C under nitrogen atmosphere. After 15 min a solution of nitro olefin **16** (520 mg, 1.61 mmol) in dry tetrahydrofuran (4 mL) was added to the mixture and after 4 h at −78 °C, the reaction was quenched with saturated aqueous ammonium chloride solution (10 mL). The aqueous layer was extracted with dichloromethane (3×20 mL) and the pooled organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to dryness under reduced pressure. The residue was purified by column chromatography (ethyl acetate/hexane, 1:6) providing a mixture of **21a**-**1** and **21a**-**2** (640 mg, 77% yield) as a yellow solid (diastereoisomeric ratio=50:1 determined by ^{1}H NMR). Major diastereoisomer (**21a**-**2**) was isolated from this mixture in 54% yield by crystallization from hexane. Colorless solid: mp 145–147 °C;

$[\alpha]_D^{20}$ −86.4 (*c* 1.5, $CHCl_3$); IR (*ν*, cm^{-1}, NaCl): 1558; 1367; ^1H NMR (*δ*, ppm, $CDCl_3$): 1.29 (s, 3H, CH_3); 1.47 (s, 3H, CH_3); 3.79 (s, 3H, OCH_3); 3.83 (d, 1H, *J*=2.8 Hz, H-3); 3.93 (s, 3H, OCH_3); 4.50 (d, 1H, *J*=12.0 Hz, CH_2Ph); 4.60 (dd, 1H, *J*=8.0, 2.8 Hz, H-4); 4.63 (d, 1H, *J*=3.7 Hz, H-2); 4.70–4.74 (m, 1H, H-5); 4.75 (d, 1H, *J*=12.0 Hz, CH_2Ph); 4.80 (dd, 1H, *J*=12.9, 4.3 Hz, H-6); 5.01 (dd, 1H, *J*=12.9, 9.6 Hz, H-6); 5.92 (d, 1H, *J*=3.7 Hz, H-1); 6.62 (s, 1H, H-3′); 7.33–7.42 (m, 5H, 5× H–Ph); 7.46 (dd, 1H, *J*=8.3, 7.1 Hz, H-6′); 7.52 (dd, 1H, *J*=8.3, 7.1 Hz, H-7′); 8.01 (d, 1H, *J*=8.3 Hz, H-8′); 8.19 (d, 1H, *J*=8.3 Hz, H-5′); ^{13}C NMR (*δ*, ppm, CD_3OD): 26.1, 26.6, 37.7, 55.5, 62.5, 71.4, 75.7, 79.7, 81.2, 82.0, 102.0, 104.5, 111.7, 122.2, 122.3, 124.1, 125.6, 126.3, 126.7, 127.2, 128.2, 128.4, 128.7, 136.9, 148.2, 152.2; MS (CI, *m*/*z*, %): 509 (4, M^+); 91 (25, $[PhCH_2]^+$); 29 (100). Anal. Calcd for $C_{28}H_{31}NO_8$: C, 66.00; H, 6.13; N, 2.75. Found: C, 66.08, H, 6.33; N, 2.45.

*3.1.11. 3-O-Benzyl-5,6-dideoxy-5-C-(1′,4′-dimethoxynaphthalen-2′-yl)-6-nitro-β-L-idofuranose (**22**).* A solution of idofuranose **21a-2** (0.390 g, 0.76 mmol) in 1,4-dioxane (6 mL), water (2 mL), and trifluoroacetic acid (4 mL) was stirred at 50 °C during 16 h. The solvent was evaporated and the residue was coevaporated with toluene (3×5 mL) to give the 3-*O*-benzyl-5,6-dideoxy-5-*C*-(3′-hydroxy-1′,4′-naphthoquinon-2′-yl)-6-nitro-β-L-idofuranose (**22**) as a colorless oil, which was used in the next reaction without further purification.

*3.1.12. (1R,2S,3S,4R,5S,6S)-3-(Benzyloxy)-5-(1′,4′-dimethoxynaphthalen-2′-yl)-6-nitrocyclohexane-1,2,4-triol (**24**).* A 2% aqueous solution of sodium bicarbonate (4 mL) was added to a solution of **22** (390 mg, 0.76 mmol) in methanol (12 mL) and the mixture was stirred at rt for 24 h. The reaction mixture was acidified with acid resin, filtered, and the solvents were evaporated under vacuum. The residue was purified by column chromatography (dichloromethane/methanol/acetic acid, 10:0.5:0.2) to obtain nitrocyclohexanetriol **24** (310 mg, 87% yield from **21a-2**). White amorphous solid. $[\alpha]_D^{20}$ +15.7 (*c* 2.00, $CHCl_3$); IR (*ν*, cm^{-1}, NaCl): 3434; 1557; 1371; ^1H NMR (*δ*, ppm, CD_3COCD_3): 3.61 (t, 1H, *J*=8.8 Hz, H-3); 3.75 (ddd, 1H, *J*=4.3, 8.8, 9.1 Hz, H-2); 3.91 (s, 3H, OCH_3); 3.96–4.06 (m, 1H, H-5); 4.02 (s, 3H, OCH_3); 4.09–4.15 (m, 1H, H-4); 4.21 (ddd, 1H, *J*=4.6, 9.1, 10.3 Hz, H-1); 4.45 (d, 1H, *J*=4.3 Hz, OH-2); 4.75 (d, 1H, *J*=4.6 Hz, OH-1); 4.95–5.01 (m, 3H, OH-4+CH_2Ph); 5.15 (t, 1H, *J*=10.3 Hz, H-6); 7.21 (s, 1H, H-3′); 7.24–7.35 (m, 3H, 3× H–Ar); 7.40–7.58 (m, 4H, 2× H–Ph+H-6′+H-7′); 7.98–8.19 (m, 2H, H-5′+H-8′); ^{13}C NMR (*δ*, ppm, CD_3COCD_3): 45.4, 57.1, 64.0, 75.0, 76.0, 76.3, 76.5, 86.9, 92.7, 103.8, 123.8, 124.0, 126.7, 127.2, 127.8, 128.3, 128.9, 129.4, 129.7, 130.2, 141.4, 150.8, 153.8; MS (CI, *m*/*z*, %): 469 (5, M^+); 133 (100); 91 (25, $[PhCH_2]^+$). Anal. Calcd for $C_{25}H_{27}NO_8$: C, 63.96; H, 5.80; N, 2.98. Found: C, 63.71; H, 5.59; N 3.29.

*3.1.13. (1R,2S,3S,4R,5S,6S)-6-Amino-3-(benzyloxy)-5-(1′,4′-dimethoxynaphthalen-2′-yl)cyclohexane-1,2,4-triol (**25**).* A degassed suspension of compound **24** (61 mg, 0.13 mmol) and Ni-Raney (0.100 g) in methanol (5 mL) was stirred under a hydrogen atmosphere at rt during 3 h. The suspension was filtered over Celite and the filtrate was concentrated to dryness under vacuum providing the amino derivative **25** (53 mg, 95% yield) as a colorless oil, which was reacted without further purification.

*3.1.14. (1R,2S,3S,4R,5S,6S)-6-Amino-3-O-benzyloxy-1,2,4-trihydroxy-5-(1′,4′-naphthoquinon-2′-yl)cyclohexane (**26**).* A solution of cerium ammonium nitrate (200 mg, 0.36 mmol) in acetonitrile (1 mL) and water (1 mL), was added to a solution of compound **25** (53 mg, 0.12 mmol) in acetonitrile (9 mL) and water (1 mL) at 0 °C and the reaction mixture was stirred for 1 h. The solution was concentrated to dryness under vacuum and the solid residue was dissolved in acetone (1 mL). The solids were filtered off and the filtrate was concentrated to dryness under vacuum to give compound **26** (45 mg, 92% yield) as a yellow oil, which was used without further purification.

*3.1.15. (1R,2S,3S,4R,4aS,11bS)-2-(Benzyloxy)-1,3,4-trihydroxy-1,2,3,4,4a,5-hexahydro-11bH-benzo[b]carbazole-6,11-dione (**1c**).* A solution of compound **26** (45 mg, 0.11 mmol) in dry tetrahydrofuran (3 mL) was stirred and heated at 60 °C during 24 h. The solvent was removed under vacuum and the residue purified by preparative TLC (dichloromethane/methanol, 9:1) providing the benzo[*b*]carbazoledione **1c** (9.0 mg, 20% yield). Violet solid: mp higher than 260 °C; $[\alpha]_D^{20}$ +26.0 (*c* 0.10, CH_3COCH_3); IR (*ν*, cm^{-1}, NaCl): 3434 (b, OH+NH); 1661 (m, CO); ^1H NMR (*δ*, ppm, CD_3COCD_3,): 2.80 (s, 1H, OH); 3.57 (dd, 1H, *J*=7.3, 9.9 Hz, H-11b); 3.73 (ddd, 1H, *J*=3.1, 7.5, 9.9 Hz, H-4a); 4.36 (d, 1H, *J*=3.4 Hz, OH); 4.63–4.69 (m, 1H, H-2); 4.87 (d, 1H, *J*=11.7 Hz, CH_2Ph); 4.87–4.91 (m, 2H, H-1+H-4); 5.11 (d, 1H, *J*=11.7 Hz, CH_2Ph); 5.17 (d, 1H, *J*=1.3 Hz, H-3); 7.26–7.51 (m, 6H, 5× H–Ar+H-7); 7.68 (td, 1H, *J*=1.3, 7.5 Hz, H-10); 7.94–8.03 (m, 2H, H-8+H-9), 11.42 (br s, 1H, NH); ^{13}C NMR (*δ*, ppm, CD_3COCD_3): 42.0, 67.2, 70.6, 71.3, 76.3, 78.4, 85.9, 124.2, 127.3, 129.1, 129.8, 130.0, 130.8, 131.5, 131.9, 134.1, 137.2, 141.5, 157.7, 177.2, 182.9; MS (FAB$^+$, *m*/*z*, %): 407 (1, M^+); 390 (5, $[M-OH]^+$); 91 (100, $[PhCH_2]^+$); HRMS calcd for $C_{23}H_{21}NO_6$ $[M]^+$ 407.136890; found 407.136897.

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