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Preliminary studies on the incorporation of sugars into naphthoquinones: synthesis of (1*R*,2*S*,3*S*,4*R*,4a*S*,11b*S*)-2-(benzyloxy)-1,2,3,4,4a,5-hexahydro-1,3,4-trihydroxy-11b*H*-benzo[*b*]carbazole-6,11-dione

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Abstract—The first total synthesis of (1*R*,2*S*,3*S*,4*R*,4a*S*,11b*S*)-2-(benzyloxy)-1,2,3,4,4a,5-hexahydro-1,3,4-trihydroxy-11b*H*-benzo[*b*]carbazole-6,11-dione from D-glucose is described. The key steps of this synthesis are the stereoselective Michael addition of 2-lithium-1,4-dimethoxynaphthalene to 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-D-*xilo*hex-5-enefuranose followed by the enantioselective intramolecular Henry reaction of 3-*O*-benzyl-5,6-dideoxy-5-*C*-(1,4-dimethoxynaphthalene-2-yl)-6-nitro-β-L-idofuranose to the key (1*R*,2*S*,3*S*,4*R*,5*S*,6*S*)-3-(benzyloxy)-5-(1,4-dimethoxynaphthalene-2-yl)-1,2,4-trihydroxy-6-nitrocyclohexane.

Naphthoquinones are of perennial chemical interest due to the widespread occurrence of the naphthoquinone nucleus in natural products, from simple hydroxynaphthoquinones such as lawsone, the main component of a natural dye, to complex structures such as the trimeric hydroxynaphthoquinone conocurvone, a potential anti-HIV agent.[1] The chemistry of naphthoquinones is mainly dependent on the substituents on the quinone moiety. Thus 1,4-naphthoquinones bearing a phenyl substituent attached to its C-2 position proved to be convenient precursors for the synthesis of polycyclic naphthoquinone derivatives that exhibit anti-neoplasic[2] activity, such as indolonaphthoquinones,[3] benzofuronaphthoquinones,[4] and benzopyronaphthoquinones.[5] The similar transformation of related, less abundant, 2-cyclohexyl-1,4-naphthoquinones[6] into promising 1,2,3,4,5,6-hexahydroindolonaphthoquinones **9**[7] has not been studied, probably due to the lack of available methods for the preparation of highly functionalized cyclohexylnaphthoquinones.

On the other hand, nitrocompounds are compounds of great versatility in organic synthesis due to their easy availability and transformation into a wide variety of functionalities.[8] Their chemistry is largely dominated by the electron withdrawing character of the nitro group. Thus the nitroaldol condensation (the Henry reaction) is a classical method for carbon–carbon formation, which couples a carbonyl compound with a nitroalkane and can result in the formation of one or two stereogenic centers.[9] Its intramolecular modality has proven to be a powerful method for the preparation of nitrocycloalkanes. On the other hand, nitroalkenes are potent dienophiles in the Diels–Alder reaction and they give easily addition reactions with a great variety of nucleophiles. Their chemistry has been the object of several reviews.[10] Persual of the literature indicates that reactions of nitroalkenes with 1,4-naphthoquinones has not yet been described.

Our continuous interest into indolonaphthoquinones[11] together with our recent interest in nitrosugars[12] led us to develop the first total synthesis of a highly functionalized indolonaphthoquinone (compound **9**) by a route including two key steps: a Michael addition of naphthalene **1** to nitrosugar **2** and an intramolecular Henry reaction of nitrosugar derivative **4** (Scheme 1).

Reaction of bromonaphthalene **1**[13] with *t*-BuLi in THF at −78 °C, followed by the addition of sugarnitroethylene

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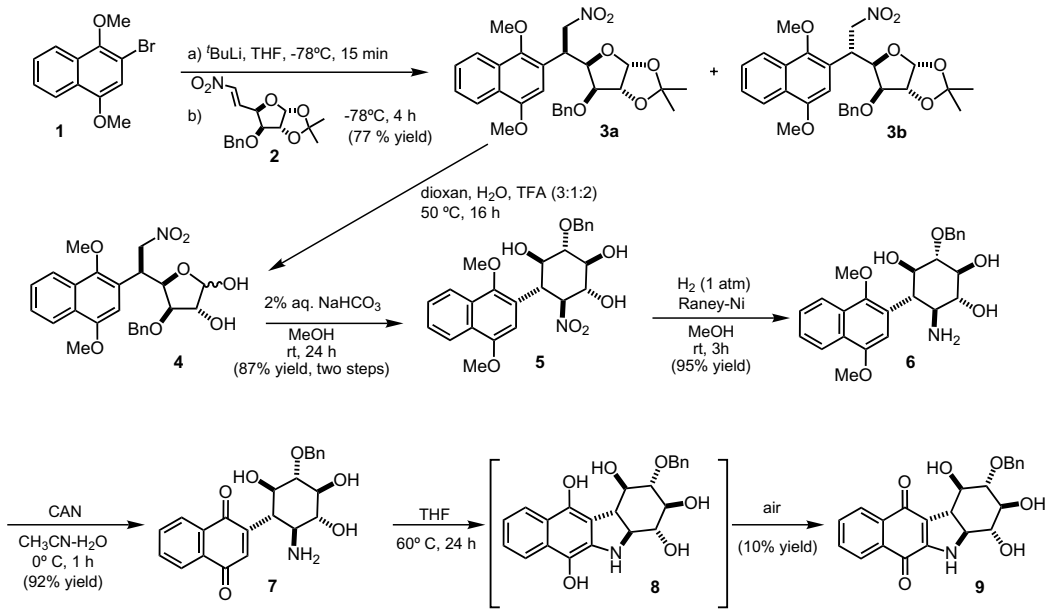


Scheme 1.

2[14] to the resulting 2-lithionaphthalene of **1** gave a 4.7:1.0 epimeric mixture **3a** and **3b**[15] of the expected adduct, as a result of the attack of the organolithium derivative of **1** on both faces of the nitroethylene moiety of **2**. This moderate stereoselectivity should be due to the preferential attack on the *si*-face of the double bond. This was confirmed when the structure of **3a**[16] was firmly established by X-ray diffraction (Fig. 1).

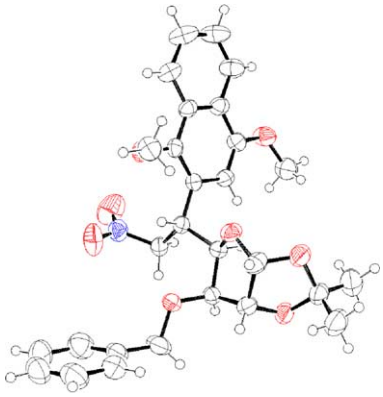


Figure 1. ORTEP diagram corresponding to the X-ray molecular structure of compound **3a.**

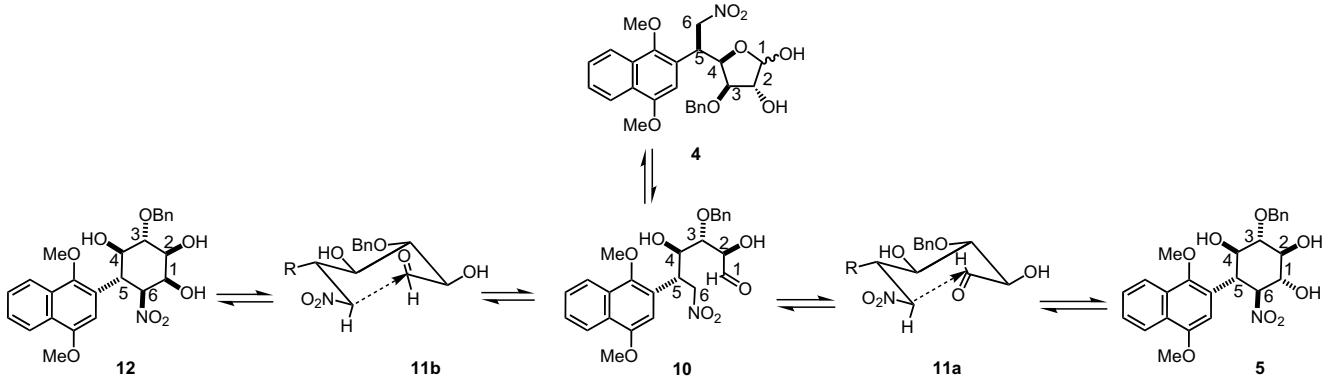
Removal of acetonide protecting group of **3a** with TFA followed by treatment of the resulting furanose **4** with 2% aqueous sodium bicarbonate allowed us to obtain a 87% yield of naphthalenecyclohexane **5**. The alternative cyclization product was not detected by TLC nor by ^{1}H NMR. The configuration of compound **5** was easily established from its ^{1}H NMR spectrum, which includes at 5.15 ppm a pair of doublets ($J_{1,6}$ = 10.3 Hz, $J_{5,6}$ = 10.7 Hz) corresponding to the highly deshielded hydrogen at position C_6 bearing the NO_2. This signal can be explained in terms of di-axial couplings between H_5 and H_6 and between H_1 and H_6.

Formation of compound **5** may occur as indicated in Scheme 2. The intramolecular Henry reaction in the open form **10** of nitrosugar **4** probably gives a mixture of nitrocyclohexanes **5** and **12** via the corresponding chair transition states **11a** and **11b**, both having an equatorial nitro group. Compounds **5** and **12** could easily revert to compound **10** by a retro-Henry reaction. At the equilibrium, compound **5** should be favored with respect to compound **12**, because **11a** is thermodynamically more stable than **11b**, where the carbonyl is axial. This explains the highly remarkable stereoselectivity of the cyclization.

Catalytic hydrogenation of naphthylnitrocyclohexane **5** allowed its efficient transformation into the corresponding aminocyclohexane **6**. Finally, treatment of this compound with CAN gave aminocyclohexanenaphthoquinone **7**, which on heating in THF provided a poor yield of a dark purple compound tentatively identified as hexahydroindolonaphthoquinone **9** from its spectroscopical data.[15] Formation of this compound might occur by conjugate addition of the amino group to the quinone moiety followed by oxidation of the resulting naphthol **8**. The unfavorable attack of the amino to the quinone **7** would justify the low efficiency of the intramolecular addition leading the pentacyclic nitrogen ring of **8**.

In conclusion, we have developed the first total synthesis of a polyhydroxylated 2-nitrocyclohexane-1,4-naphthoquinones (compound **5**) together with the first total synthesis of a polyhydroxylated hexahydroindolonaph thoquinone (compound **9**), the later being a new class of compound that should exhibit antibiotic properties on the basis of their structural similarities to kinamycin antibiotics.[17]

Work is now in progress to extend this new route for nitrocyclohexanenaphthoquinones **5** in order to prepare



Scheme 2.

a wide range of indolonaphthoquinones **9** for chemical and biological studies.

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15. All new compounds gave satisfactory spectroscopical and analytical data. Selected physical and spectroscopic data are as follows. Compound **3a**: $[\alpha]_D^{20} = -86.4$ (*c* 1.5, $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 1.29$ (s, 3H, CH_3); 1.47 (s, 3H, CH_3); 3.79 (s, 3H, OCH_3); 3.83 (d, 1H, $J_{3,4} = 2.8$ Hz, H-3); 3.93 (s, 3H, OCH_3); 4.50 (d, 1H, $J_{H,H} = 12.0$ Hz, CH_2Ph); 4.60 (dd, 1H, $J_{4,5} = 8.0$ Hz, $J_{3,4} = 2.8$ Hz, H-4); 4.63 (d, 1H, $J_{1,2} = 3.7$ Hz, H-2); 4.70–4.74 (m, 1H, H-5); 4.75 (d, 1H, $J_{H,H} = 12.0$ Hz, CH_2Ph); 4.80 (dd, 1H, $J_{6,6} = 12.9$ Hz, $J_{5,6} = 4.3$ Hz, H-6); 5.01 (dd, 1H, $J_{6,6} = 12.9$ Hz, $J_{5,6} = 9.6$ Hz, H-6); 5.92 (d, 1H, $J_{1,2} = 3.7$ Hz, H-1); 6.62 (s, 1H, H-8); 7.33–7.42 (m, 5H, 5 × Ar–H); 7.46 (dd, 1H, $J_{10,11} = 8.3$ Hz, $J_{11,12} = 7.1$ Hz, H-11); 7.52 (dd, 1H, $J_{12,13} = 8.3$ Hz, $J_{11,12} = 7.1$ Hz, H-12); 8.01 (d, 1H, $J_{12,13} = 8.3$ Hz, H-13); 8.19 (d, 1H, $J_{10,11} = 8.3$ Hz, H-10). ^{13}C NMR ($CDCl_3$): $\delta = 26.1$, 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, MH^+); 420 (2); 91 (25, Bn^+); 29 (100). Compound **5**: $[\alpha]_D^{20} = +15.7$ (*c* 2.00, $CHCl_3$). ^1H NMR (CD_3COCD_3): $\delta = 3.61$ (dd, 1H, $J_{3,4} = 8.8$ Hz, $J_{3,2} = 8.5$ Hz, H-3); 3.75 (ddd, 1H, $J_{1,2} = 9.1$ Hz, $J_{2,3} = 9.1$ Hz, $J_{2,OH} = 4.3$ 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, $J_{1,6} = 10.3$ Hz, $J_{1,2} = 9.1$ Hz, $J_{1,OH} = 4.6$ Hz, H-1); 4.45 (d, 1H, $J_{2,OH} = 4.3$ Hz, OH-2); 4.75 (d, 1H, $J_{1,OH} = 4.6$ Hz, OH-1); 4.95–5.01 (m, 3H, CH_2–Ph + OH-4); 5.15 (dd, 1H,$J_{5,6} = 10.7$ Hz, $J_{1,6} = 10.3$ Hz, H-6); 7.21 (s, 1H, H-8); 7.24–7.35 (m, 3H, 3 × Ar–H); 7.40–7.58 (m, 4H, 4 × Ar–H); 7.99–8.19 (m, 2H, 2 × Ar–H). ^{13}C NMR (CD_3COCD_3): $\delta = 45.4$, 57.1, 64.0, 75.0, 76.0, 76.3, 76.4, 86.9, 92.7, 103.7, 123.8, 124.0, 126.7, 127.2, 127.8, 128.3, 128.9, 129.4, 129.7, 130.2, 130.1, 141.4, 150.8, 153.8. MS (FAB): *m/z* (%) = 469 (5, M^+); 133 (100); 91 (25, Bn^+); 29 (100). Compound **9**: $[\alpha]_D^{20} = +26.0$ (*c* 0.10, acetone). ^1H NMR (CD_3COCD_3): $\delta = 2.64$ (s, 1H, OH); 2.80 (s, 1H, OH); 3.57 (dd, 1H, $J_{4a,11b} = 9.9$ Hz, $J_{1,11b} = 7.3$ Hz, H-11b); 3.73 (ddd, 1H, $J_{4a,11b} = 9.9$ Hz, $J_{4,4a} = 7.5$ Hz, $J_{4a,5} = 3.1$ Hz, H-4a); 4.36 (d, 1H, $J_{H,OH} = 3.4$ Hz, OH); 4.63–4.69 (m, 1H, H-2); 4.87 (d, $J_{H,H} = 11.7$ Hz, CH_2Ph); 4.87–4.91 (m, 2H, H-1 + H-4); 5.11 (d, 1H, $J_{H,H} = 11.7$ Hz, CH_2Ph); 5.17 (d, 1H, $J_{2,3} = 1.3$ Hz, H-3); 7.26–7.51 (m, 6H, 6 × Ar–H); 7.68 (td, 1H, $J_{H,H} = 7.5$ Hz, $J_{H,H} = 1.3$ Hz, Ar–H); 7.94–8.03 (m, 2H, 2 × Ar–H); 11.58 (br s, 1H, NH). ^{13}C NMR (CD_3COCD_3): $\delta = 42.0$, 67.2, 70.6, 71.3, 76.3, 78.4, 85.8, 124.1, 127.2, 129.1, 129.7, 129.9, 130.7, 131.4, 131.9, 134.1, 137.1, 141.4, 157.6, 177.3, 182.9. MS (FAB): *m/z* (%) = 407 (1, M^+); 390 (5, M^+–OH).
16. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 254541 **3a**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK fax: (+44)1223-336-033; email: deposit@ccdc.cam.ac.uk. Crystallographic data for **3a**. $C_{28}H_{31}NO_8$, $M = 509.54$, $T = 293(2)$ K. Monoclinic, space group P 21 with $a = 9.7351(10)$, $b = 12.9049(13)$, $c = 11.950(11)$ Å, $\alpha = 90°$, $\beta = 108.266(2)°$, $\gamma = 90°$, $V = 1323.6(2)$ Å^3, Dc ($Z = 4$) = 'not measured'. $F(000) = 540$, absorption coefficient = 0.094 cm^{-1}. Data were obtained on an Enraf-Nonius CAD4-Mach3 diffractometer (graphite crystal monochromator, $\lambda = 1.5418$ Å) using the $\omega = 2\theta$ scan method; absorption corrections were applied. Refinement, with anisotropic displacement parameters applied to each of the non-hydrogen atoms, was by full-matrix least squares on F^2 (SHELXL-93) using all data; $w^2R = [(\Sigma w(F_o^2 - F_c^2)^2/\Sigma w (F_o^2)^2]^{1/2}$.
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