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SYNTHESIS OF ETHERS OF (+)-USNINIC ACID PYRAZOLE DERIVATIVES

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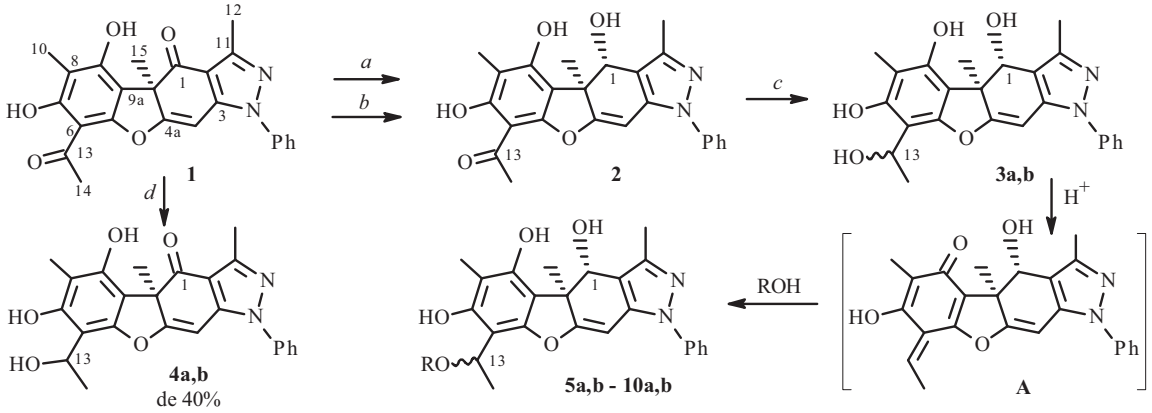
The reduction of usninic acid pyrazole derivatives by complex boron hydrides under various conditions was studied. New ether derivatives containing added alcohols were obtained upon reduction of the carbonyl. The reaction occurred presumably through a quinonemethide intermediate.

Keywords: (+)-usninic acid, reduction, ethers.

Synthetic transformations of natural metabolites in order to enhance their biological activity and prepare compounds with novel biological properties represent a well known strategy in medicinal chemistry. Usninic acid is the main secondary metabolite of several lichens and exhibits various types of biological activity [1]. The present work is a continuation of our research on the reactivity of this interesting metabolite and its derivatives.

Usninic acid contains several structural elements that can be reduced [1]. However, the literature suggests that only the C–C double bond (C^4–C^{4a}) can be reduced selectively and in good yield by hydrogen upon hydrogenation in the presence of a Pd catalyst [2]. The carbonyls (C^1=O and C^{11}=O) of usninic acid are reduced by $NaBH_4$. However, both the selectivity and yields of the resulting alcohols are low [3]. The reduction by $NaBH_4$ of a usninic acid pyrazole derivative (**1**) occurs differently. We found previously that the reduction of **1** at low temperature (–20°C, THF) occurred regio- and stereoselectively at the C^1 carbonyl [3] (Scheme 1). Further treatment of **2** with $NaBH_4$ at higher temperature (50°C) reduced the second carbonyl to give **3a** and **3b** (mixture of stereoisomers at C^{13}). The formation of **2** occurred in high yield (96%). However, the reduction of the second carbonyl was not stereoselective and occurred in 71% yield.



5: R = CH_3; **6:** R = CH_2CH_3; **7:** R = $CH_2(CH_2)_2CH_3$
8: R = CH_2Ph; **9:** R = $CH_2CH{=}CH_2$; **10:** R = $CH_2C{\equiv}CH$

a. $NaBH_4$/THF, –20°C; *b*. Bu_4NBH_4/THF, 50°C; *c*. $NaBH_4$/THF, 50°C; *d*. THF·BH_3/L-proline, PhMe, 110°C

Scheme 1

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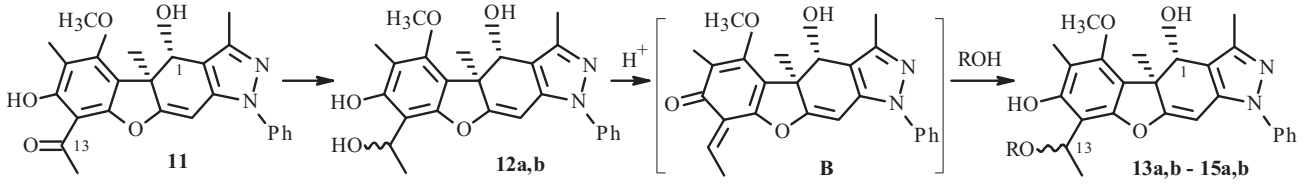
Herein we present results of a study of the specifics and conditions of the reduction of the C^{13} carbonyl.

We attempted to reduce C^{13}=O by other complex boron hydrides although it was not reduced by Bu_4NBH_4, which is a milder reductant than $NaBH_4$ (Scheme 1). However, this reductant did reduce selectively and in high yield the endocyclic carbonyl (C^1=O) without requiring the use of low temperatures.

Because of the formation of a mixture of stereoisomers upon reduction of C^{13}=O, we attempted stereoselective reduction of this group by the chiral reductant THF·BH_3/L-proline (generated *in situ*), the use of which for reduction of acetophenone showed 99% enantioselectivity [4]. Asymmetric reduction of **2** by this system formed a complicated product mixture. The product mixture was much simpler upon reduction of **1** (Scheme 1). However, C^1=O was not reduced whereas C^{13}=O was reduced with moderate stereoselectivity. According to the PMR spectrum, compounds **4a** and **4b** were formed with *de* 40%.

Returning to the reduction by $NaBH_4$, we attempted to explain the much lower yield of C^{13}=O reduction products than that from reduction of C^1=O. In our opinion, this could be related to the generation of a reactive *p*-quinonemethide intermediate (A) upon treatment of the reaction mixture with HCl solution, which was used to destroy the excess of reductant after the reaction (Scheme 1) [5]. This species could be responsible for the occurrence of side reactions, which would reduce the yield of the desired products. The *p*-quinonemethide A could react preferentially with a nucleophile present in the reaction medium without undergoing self-condensation. In fact, we observed that ethers **5a** and **5b** and **6a** and **6b** (mixtures of diastereomers) formed upon addition of methanol or ethanol during work up of the reaction mixture by HCl. The yields of the resulting ethers were in fact greater than those of alcohols **3a** and **3b** (Scheme 1). We attempted to expand the breadth of the reaction by using *n*-BuOH and benzyl, allyl, and propargyl alcohols. As expected, *O*-alkylation occurred. However, the yields of the derivatives of the aforementioned alcohols (**7a**,**b–10a**,**b**) were lower despite the fact that a significant excess of the alcohol was used.

The formation mechanism of ethers of substituted *p*-hydroxybenzyl alcohols with methanol in acidic medium was reported [6]. It was shown that a series of *p*-methoxybenzyl alcohols did not react with MeOH under acidic conditions and that the electron-donating effects of the OH and MeO groups were similar. In order to confirm the hypothesis that the formation mechanism of **5a**,**b–10a**,**b** was similar, we prepared **11** (Scheme 2), which contained a 9-MeO group and; therefore, did not form in acidic medium the *p*-quinonemethide species. The absence of the *p*-quinonemethide species in the reaction medium was confirmed by the fact that the reduction of **11** by $NaBH_4$ occurred practically without side reactions. Both carbonyls were reduced upon heating in THF to form **12a**,**b** in high yield (Scheme 2). The nucleophile was added under more forcing conditions, i.e., prolonged refluxing, upon adding the alcohols to the reaction mixture. The addition products of methyl, ethyl, and *n*-butyl alcohols could be isolated in low yields. For the others (benzyl, allyl, propargyl), the ethers were present in trace amounts. Ethers **13a**,**b–15a**,**b** could be formed through *o*-quinonemethide intermediate B, for the generation of which more forcing conditions than for *p*-quinonemethide A were required [7].



13: R = CH_3; **14:** R = CH_2CH_3; **15:** R = $CH_2(CH_2)_2CH_3$

Scheme 2

Thus, the reduction of the acetophenone carbonyl in the usninic acid pyrazole derivative by $NaBH_4$ in the presence of alcohols occurred with formation of mixtures of diastereomeric ethers. The addition of the alcohols was substantially hindered if the phenol *p*-OH was protected by a methyl. The observed trends suggested that the reaction occurred through formation of a *p*-quinonemethide intermediate. This opens new synthetic possibilities for usninic acid derivatives.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded on a Bruker DRX-500 spectrometer at operating frequency 500.13 MHz for ^{1}H and 125.76 MHz for ^{13}C. IR spectra were taken on a Vector 22 spectrometer. Mass spectra (ionizing-electron energy 70 eV) were obtained on a DFS high-resolution mass spectrometer. Melting points were measured on a Kofler stage. Compound **2** was synthesized by the literature method [3]; compound **11**, as before [8]; *N*-methyl-*N*-nitrosourea and diazomethane, according to the literature [9]. The course of reactions was monitored using PMR spectra. Column chromatography used silica gel (60–200 μm, Merck). Atomic numbering in the compounds was given for assigning resonances in PMR spectra, was based on generally accepted numbering for usninic acid, and did not always agree with the systematic atomic numbering.

Reaction of 1 with $NaBH_4$ in the Presence of L-proline. A suspension of $NaBH_4$ (60 mg) in THF (3 mL) at 0°C was stirred, treated dropwise with a solution of I_2 (130 mg) in THF (3 mL), cooled, added to a mixture of proline (11 mg) and toluene (3 mL), stirred at room temperature for 10 min, heated to 100°C, treated with a solution of **1** (200 mg) in toluene (5 mL), stirred at 110°C for 20 min, cooled to room temperature, and treated with Et_2O (10 mL) and $NaHCO_3$ solution (20 mL, 10%). The organic layer was separated, washed with H_2O (2×), and dried over calcined $MgSO_4$. The solvent was removed. The product was obtained by column chromatography over silica gel (60–200 μm) with elution by $CHCl_3$.

(4a*R*)-8-(*S*-1-Hydroxyethyl)-5,7-dihydroxy-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4(4a*H*)-one (4a), (4a*R*)-8-(*R*-1-hydroxyethyl)-5,7-dihydroxy-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4(4a*H*)-one (4b) (**4a**:**4b** ratio, 7:3 according to PMR data), yield 22%.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.50 and 1.56 (3H, 2d, J = 6.5, H-14), 1.77 and 1.76 (3H, 2s, H-15), 2.12 and 2.11 (3H, 2s, H-10), 2.57 (3H, s, H-12), 2.69 and 2.75 (1H, 2br.s, 13-OH), 5.16 and 5.30 (1H, 2q, J = 6.5, H-13), 5.34 (1H, 2q, J = 6.5, H-13), 6.12 and 6.09 (1H, 2s, H-4), 7.40-7.60 (5H, m, H-arom), 8.40 (1H, s, 9-OH), 10.17 and 10.10 (1H, 2s, 7-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.9 and 7.7 (C-10), 13.2 (C-12), 21.8 and 21.6 (C-14), 30.3 and 30.5 (C-15), 61.0 and 61.2 (C-9b), 66.1 (C-13), 88.0 (C-4), 101.3 (C-6), 103.6 and 103.9 (C-2), 108.8 and 108.5 (C-8), 110.6 (C-9a), 123.8, 128.4, 129.5, and 137.9 (2C, C, 2C, and C, all arom), 148.7 and 148.5 (C-11), 151.2 (C-3), 152.4 and 151.6 (C-7), 153.0 (C-5a), 155.4 (C-9), 174.3 and 174.5 (C-4a), 196.4 (C-1).

Found: fragment ion *m*/*z* 400.1407 $[M - H_2O]^+$, $C_{24}H_{20}O_4N_2$.

Reaction of 3 and 11 with $NaBH_4$ in the Presence of Alcohols. A solution of **3** (or **11**) (1 mmol) in THF (20 mL) was treated with a suspension of $NaBH_4$ (50 mg) in THF (5 mL); heated to 50°C; stirred for 2 h; cooled to room temperature; and treated with the appropriate alcohol (1 mL), dilute HCl until the pH was ~5, and CH_2Cl_2 (30 mL). The mixture was washed with H_2O (2×) and dried over calcined $MgSO_4$. The solvent was removed. The product was obtained by column chromatography over silica gel (60–200 μm) with elution by $CHCl_3$.

(4*R*,4a*S*)-8-(*S*-1-Methoxyethyl)-4,4a-dihydro-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4,5,7-triol (5a), (4*R*,4a*S*)-8-(*R*-1-methoxyethyl)-4,4a-dihydro-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4,5,7-triol (5b) (**5a**:**5b** ratio, ~1:1 according to PMR spectra), yield 85%.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.38 and 1.39 (3H, s, H-15), 1.46 and 1.48 (3H, d, J = 6.5, H-14), 2.07 (3H, s, H-10), 2.37 (3H, s, H-12), 4.57 (1H, br.s, 1-OH), 4.72 and 4.73 (1H, q, J = 6.5, H-13), 5.37 (1H, br.s, H-1), 5.79 (1H, s, H-4), 7.27–7.43 (5H, s, H-arom), 8.23 and 8.24 (1H, s, 9-OH), 8.27 and 8.31 (1H, s, 7-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.6 (C-10), 12.6 (C-12), 16.4 (C-15), 21.5 and 21.6 (C-14), 51.9 (C-9b), 57.3 (C-16), 73.0 and 73.1 (C-13), 74.9 (C-1), 88.1 (C-4), 102.3 (C-8), 106.8 (C-9a), 107.3 (C-6), 111.7 (C-2), 123.4, 127.3, 129.3, and 138.4 (2C, C, 2C, and C, all arom), 138.75 (C-3), 146.74 (C-11), 150.14 (C-7), 153.0 and 153.1 (C-5a), 154.9 (C-9), 168.7 (C-4a).

Found: fragment ion *m*/*z* 402.1570 $[M - MeOH]^+$, $C_{24}H_{22}O_4N_2$.

(4*R*,4a*S*)-8-(*S*-1-Ethoxyethyl)-4,4a-dihydro-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4,5,7-triol (6a), (4*R*,4a*S*)-8-(*R*-1-ethoxyethyl)-4,4a-dihydro-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4,5,7-triol (6b) (**6a**:**6b** ratio, ~1:1 according to PMR spectra), yield 77%.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.23 (3H, t, J = 7, H-17), 1.34 (3H, s, H-15), 1.47 (3H, 2d, J = 6.5, H-14), 2.07 (3H, s, H-10), 2.37 (3H, s, H-12), 3.56 (2H, q, J = 7, H-16), 4.64 (1H, br.s, 1-OH), 4.82 and 4.83 (1H, q, J = 6.5, H-13), 5.31 and 5.34 (1H, br.s, H-1), 5.79 (1H, s, H-4), 7.26–7.47 (5H, m, H-arom), 8.14 and 8.18 (1H, s, 7-OH), 8.48 (1H, s, 9-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.6 (C-10), 12.6 (C-12), 15.0 (C-17), 16.5 (C-15), 21.5 and 21.7 (C-14), 51.9 and 52.1 (C-9b), 65.0 (C-16), 73.0 and 73.2 (C-13), 74.8 and 74.9 (C-1), 88.0 and 88.1 (C-4), 102.3 (C-6), 106.8 (C-2), 107.4 (C-8), 111.8 (C-9a), 123.4, 127.3, 129.2, and 138.4 (2C, C, 2C, and C, all arom), 138.5 (C-3), 146.6 (C-11), 150.5 (C-7), 153.0 and 153.1 (C-5a), 145.9 (C-9), 168.8 (C-4a).

Found: fragment ion *m*/*z* 402.1571 $[M - EtOH]^+$, $C_{24}H_{22}O_4N_2$.

(4*R*,4a*S*)-8-(*S*-1-Butoxyethyl)-4,4a-dihydro-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4,5,7-triol (7a), (4*R*,4a*S*)-8-(*R*-1-butoxyethyl)-4,4a-dihydro-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4,5,7-triol (7b) (**7a**:**7b** ratio, ~1:1 according to PMR spectra), yield 68%.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.92 (3H, 2q, J = 6.5, H-19), 1.38 (2H, m, H-18), 1.40 (3H, 2s, H-15), 1.49 (3H, 2d, J = 6.5, H-14), 1.60 (2H m, H-17), 2.09 (3H, s, H-10), 2.38 (3H, 2s, H-12), 3.51 (2H, m, H-16), 4.22 and 4.29 (1H, br.s, 1-OH), 4.83 (1H, 2q, J = 6.5, H-13), 5.40 (1H, br.s, H-1), 5.81 (1H, 2s, H-4), 7.28–7.50 (5H, m, H-arom), 8.19 and 8.23 (1H, s, 7-OH), 8.50 (1H, 2s, 9-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.6 (C-10), 12.7 (C-12), 13.7 (C-19), 16.4 (C-15), 19.1 (C-18), 21.4 and 21.5 (C-14), 31.6 (C-17), 52.0 (C-9b), 69.5 (C-16), 73.4 (C-13), 75.1 (C-1), 88.2 (C-4), 102.3 (C-6), 106.8 (C-2), 107.3 (C-8), 111.6 (C-9a), 123.3, 127.2, 129.1, and 138.4 (2C, C, 2C, and C, all arom), 138.8 (C-3), 146.5 (C-11), 150.4 (C-7), 153.0 (C-5a), 154.9 (C-9), 168.6 (C-4a).

Found: fragment ion *m*/*z* 402.1571 $[M - C_4H_9OH]^+$, $C_{24}H_{22}O_4N_2$.

(4*R*,4a*S*)-8-(*S*-1-Benzyloxyethyl)-4,4a-dihydro-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4,5,7-triol (8a), (4*R*,4a*S*)-8-(*R*-1-benzyloxyethyl)-4,4a-dihydro-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4,5,7-triol (8b) (**8a**:**8b** ratio, ~1:1 according to PMR spectra), yield 59%.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.39 and 1.42 (3H, s, H-15), 1.54 and 1.55 (3H, d, J = 6.5, H-14), 2.13 (3H, s, H-10), 2.36 and 2.37 (3H, 2s, H-12), 4.07 (1H, d, J = 7, 1-OH), 4.47 and 4.62 (1H each, 2d, J = 10.5, H-16), 4.97 (1H, q, J = 6.5, H-13), 5.35 (1H, br.s, H-1), 5.78 (1H, s, H-4), 7.28–7.38 and 7.39–7.50 (10H, 2m, H-arom), 8.05 and 8.09 (1H, 2s, 9-OH), 8.32 and 8.54 (1H, 2s, 7-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.7 (C-10), 12.5 (C-12), 16.5 and 16.6 (C-15), 21.5 and 21.6 (C-14), 52.0 and 52.1 (C-9b), 65.0 (C-16), 72.6 and 72.8 (C-13), 74.7 (C-1), 88.1 and 88.2 (C-4), 101.8 and 101.9 (C-6), 107.0 (C-2), 107.7 (C-8), 111.9 (C-9a), 123.3, 126.9, 127.3, 128.3, 129.2, 129.9, 136.8, and 138.6 (12C, all arom), 138.5 (C-3), 146.9 (C-11), 150.6 (C-7), 153.3 (C-5a), 154.9 (C-9), 168.9 (C-4a).

Found: fragment ion *m*/*z* 402.1570 $[M - C_7H_9OH]^+$, $C_{24}H_{22}O_4N_2$.

(4*R*,4a*S*)-8-(*S*-1-Allyloxyethyl)-4,4a-dihydro-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4,5,7-triol (9a), (4*R*,4a*S*)-8-(*R*-1-allyloxyethyl)-4,4a-dihydro-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4,5,7-triol (9b) (**9a**:**9b** ratio, ~1:1 according to PMR spectra), yield 46%.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.36 (3H, s, H-15), 1.49 (3H, 2d, J = 6.5, H-14), 2.06 (3H, s, H-10), 2.34 (3H, s, H-12), 4.06 (1H, m, H_a-16), 4.43 (1H, m, H_b-16), 4.43 (1H, br.s, 1-OH), 4.89 (1H, q, J = 6.5, H-13), 5.23 (1H, m, H_a-18), 5.27 (1H, br.s, H-1), 5.34 (1H, m, H_b-18), 5.77 (1H, s, H-4), 5.89 (1H, m, H-17), 7.25–7.50 (5H, m, H-arom), 8.20 and 8.24 (1H, 2s, 7-OH), 8.28 (1H, s, 9-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.6 (C-10), 12.7 (C-12), 16.4 (C-15), 21.5 (C-14), 52.0 (C-9b), 70.1 (C-16), 72.6 (C-13), 75.0 (C-1), 88.1 (C-4), 101.9 (C-6), 106.9 (C-2), 107.4 (C-8), 111.6 (C-9a), 117.9 (C-18), 123.3, 127.3, 129.3, and 138.4 (2C, C, 2C, and C, all arom), 133.4 (C-17), 138.8 (C-3), 146.5 (C-11), 150.6 (C-7), 153.2 (C-5a), 154.9 (C-9), 168.6 (C-4a).

Found: fragment ion *m*/*z* 402.1570 $[M - C_3H_5OH]^+$, $C_{24}H_{22}O_4N_2$.

(4*R*,4a*S*)-8-(*S*-1-Propargyloxyethyl)-4,4a-dihydro-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4,5,7-triol (10a), (4*R*,4a*S*)-8-(*R*-1-propargyloxyethyl)-4,4a-dihydro-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4,5,7-triol (10b) (**10a**:**10b** ratio, ~1:1 according to PMR spectra), yield 45%.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.36 (3H, s, H-15), 1.50 and 1.53 (3H, d, J = 6.5, H-14), 2.06 (3H, s, H-10), 2.34 (3H, s, H-12), 2.44 and 2.47 (1H each, 2d, J = 3, H-18), 4.18 (1H, br.s, 1-OH), 4.10 (1H, m, H_a-16), 4.24 (1H, m, H_b-16), 5.07 (1H, q, J = 6.5, H-13), 5.40 (1H, br.s, H-1), 5.82 (1H, s, H-4), 7.29–7.50 (5H, m, H-arom), 7.78 (1H, s, 9-OH), 8.21 (1H, s, 7-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.6 (C-10), 12.7 (C-12), 16.4 (C-15), 21.2 and 21.3 (C-14), 52.0 (C-9b), 56.3 (C-16), 72.2 and 72.4 (C-13), 75.1 (C-1), 75.1 (C-18), 78.5 (C-17), 88.3 (C-4), 101.1 (C-6), 107.1 (C-2), 107.6 (C-8), 111.5 (C-9a), 123.4, 127.3, 129.1, and 138.4 (2C, C, 2C, and C, all arom), 138.7 (C-3), 146.5 (C-11), 150.9 (C-7), 153.5 (C-5a), 154.7 (C-9), 168.5 (C-4a).

Found: fragment ion *m*/*z* 402.1570 $[M - C_3H_3OH]^+$, $C_{24}H_{22}O_4N_2$.

(4*R*,4a*S*)-8-(*S*-1-Hydroxyethyl)-4,4a-dihydro-5-methoxy-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4,7-diol (12a), (4*R*,4a*S*)-8-(*R*-1-hydroxyethyl)-4,4a-dihydro-5-methoxy-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4,7-diol (12b) (**12a**:**12b** ratio, ~1:1 according to PMR spectra), yield 95%.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.42 and 1.45 (3H, 2s, H-15), 1.47 and 1.48 (3H, 2d, J = 6.5, H-14), 2.12 and 2.13 (3H, 2s, H-10), 2.36 and 2.44 (3H, 2s, H-12), 3.86 (3H, s, 9-OMe), 4.14 (1H, br.s, 1-OH), 4.50 and 5.00 (1H, 2br.s, 13-OH), 5.16 and 5.30 (1H, 2q, J = 6.5, H-13), 5.28 and 5.39 (1H, 2br.s, H-1), 5.79 and 5.82 (1H, 2s, H-4), 7.28–7.50 (5H, m, H-arom), 9.10 and 9.18 (1H, 2s, 7-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 9.1 and 9.2 (C-10), 12.5 and 12.6 (C-12), 18.3 and 18.4 (C-15), 23.0 and 23.1 (C-14), 53.0 (C-9b), 61.5 (OMe), 65.4 and 66.1 (C-13), 74.5 (C-1), 88.6 (C-4), 108.8 and 109.0 (C-6), 112.1 and 112.2; 112.3 and 112.4 (C-8 and C-9a), 114.3 and 114.5 (C-2), 123.0, 126.9, 129.1, and 139.0 (2C, C, 2C, and C, all arom), 138.0 (C-3), 147.7 and 147.9 (C-11), 152.3 and 152.5 (C-7), 153.2 and 153.3 (C-5a), 155.8 (C-9), 168.5 and 168.7 (C-4a).

Found: fragment ion *m*/*z* 416.1725 $[M - H_2O]^+$, $C_{25}H_{24}O_4N_2$.

(4*R*,4a*S*)-8-(*S*-1-Methoxyethyl)-4,4a-dihydro-5-methoxy-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4,7-diol (13a), (4*R*,4a*S*)-8-(*R*-1-methoxyethyl)-4,4a-dihydro-5-methoxy-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4,7-diol (13b) (**13a**:**13b** ratio, ~1:1 according to PMR spectra), yield 37%.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.49 (3H, 2s, H-15), 1.49 and 1.51 (3H, 2d, J = 6.5, H-14), 2.14 (3H, 2s, H-10), 2.52 (3H, 2s, H-12), 3.40 and 3.45 (3H, 2s, 13-OMe), 3.89 and 3.90 (3H, 2s, 9-OMe), 4.03 (1H, d, J = 4.5, 1-OH), 4.78 and 4.87 (1H, 2q, J = 6.5, H-13), 5.40 (1H, d, J = 4.5, H-1), 5.83 (1H, s, H-4), 7.32–7.57 (5H, m, H-arom), 8.39 and 8.49 (1H, 2s, 7-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 9.1 and 9.2 (C-10), 12.1 and 12.9 (C-12), 18.5 and 18.7 (C-15), 20.8 and 21.0 (C-14), 53.1 and 53.2 (C-9b), 61.5 and 61.6 (9-OMe), 74.1 (C-1), 75.1 and 75.3 (C-13), 88.1 and 88.2 (C-4), 106.4 and 106.6 (C-6), 112.3, 112.4, 112.5, and 112.6 (C-8 and C-9a), 114.5 (C-2), 123.4, 127.7, 129.3, and 137.5 (2C, C, 2C, and C, all arom), 138.2 (C-3), 147.1 (C-11), 153.4, 153.5, 153.6, and 153.7 (C-7 and C-5a), 155.3 (C-9), 170.0 (C-4a).

Found: fragment ion *m*/*z* 416.1725 $[M - MeOH]^+$, $C_{25}H_{24}O_4N_2$.

(4*R*,4a*S*)-8-(*S*-1-Ethoxyethyl)-4,4a-dihydro-5-methoxy-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4,7-diol (14a), (4*R*,4a*S*)-8-(*R*-1-ethoxyethyl)-4,4a-dihydro-5-methoxy-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4,7-diol (14b) (**14a**:**14b** ratio, ~1:1 according to PMR spectra), yield 13%.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.23 (3H, t, H-17), 1.45, 1.47, 1.48, and 1.50 (3H each, m, H-14 and H-15), 2.12 and 2.13 (3H, 2s, H-10), 2.45 (3H, s, H-12), 3.57 (2H, q, H-16), 3.87 (3H, s, 9-OMe), 4.11 (1H, d, J = 5, 1-OH), 4.87 (1H, 2q, J = 6.5, H-13), 5.40 (1H, d, J = 5, H-1), 5.85 (1H, 2s, H-4), 7.26–7.57 (5H, m, H-arom), 8.68 and 8.69 (1H, 2s, 7-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 8.7 and 8.8 (C-10), 12.4 (C-12), 14.7 (C-17), 18.0 and 18.1 (C-15), 20.0 and 21.0 (C-14), 52.7 and 52.8 (C-9b), 61.1 and 61.2 (OMe), 65.0 (C-16), 72.8 and 73.1 (C-13), 74.3 (C-1), 88.5 and 88.6 (C-4), 106.5 and 106.7 (C-6), 111.8, 111.9, and 112.0 (C-8 and C-9a), 114.5 (C-2), 122.6, 126.4, 128.7, and 138.9 (2C, C, 2C, and C, all arom), 136.7 (C-3), 147.4 (C-11), 153.1, 153.2, and 153.3 (C-7 and C-5a), 155.0 (C-9), 168.1 (C-4a).

Found: fragment ion *m*/*z* 416.1725 $[M - EtOH]^+$, $C_{25}H_{24}O_4N_2$.

(4*R*,4a*S*)-8-(*S*-1-Butoxyethyl)-4,4a-dihydro-5-methoxy-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4,7-diol (15a), (4*R*,4a*S*)-8-(*R*-1-butoxyethyl)-4,4a-dihydro-5-methoxy-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4,7-diol (15b) (**15a**:**15b** ratio, ~1:1 according to PMR spectra), yield 20%.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.92 (3H, 2q, J = 7, H-19), 1.39 (2H, m, H-18), 1.50 (3H, 2s, H-15), 1.47 and 1.51 (3H, 2d, J = 6.5, H-14), 1.61 (2H, m, H-17), 2.14 and 2.15 (3H, 2s, H-10), 2.47 (3H, 2s, H-12), 3.51 and 3.55 (2H, t and m, J = 6.5, H-16), 3.89 and 3.90 (3H, s, 9-OMe), 4.13 and 4.15 (1H, br.s, 1-OH), 4.87 (1H, 2q, J = 6.5, H-13), 5.4 (1H, d, J = 5, H-1), 5.88 (1H, s, H-4), 7.28–7.59 (5H, m, H-arom), 8.71 and 8.72 (1H, 2s, 7-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 9.1 and 9.2 (C-10), 12.7 (C-12), 13.7 (C-19), 18.3 and 18.5 (C-15), 19.1 (C-18), 21.0 and 21.2 (C-14), 31.5 and 31.6 (C-17), 53.0 and 53.1 (C-9b), 61.5 (OMe), 69.7 (C-16), 73.4 and 73.6 (C-13), 74.6 (C-1), 88.8 and 88.9 (C-4), 106.9 and 107.1 (C-6), 112.1, 112.2, 112.2, and 112.3 (C-8 and C-9a), 114.7 and 114.8 (C-2), 122.9, 126.7, 129.0, and 139.2 (2C, C, 2C, and C, all arom), 137.0 (C-3), 147.7 (C-11), 153.4, 153.5, and 153.6 (C-7 and C-5a), 155.2 and 155.3 (C-9), 168.4 (C-4a).

Found: fragment ion *m*/*z* 416.1725 $[M - C_4H_9OH]^+$, $C_{25}H_{24}O_4N_2$.

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