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Synthesis of (±)-3,3′-bis(4-hydroxy-2*H*-benzopyran): a literature correction

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Abstract—The synthesis of bisbenzopyran-4-ol (**1**) was performed through the key steps of iodination, nickel(0)-modified Ullmann-type reaction, hydrogen-transfer hydrogenation and diastereoselective reduction. The X-ray diffraction experiment of compound **9** confirmed that the reported structure in the literature was not the real natural product. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Aloe barbadensis Mill. is well reputed in the folklore of medicine for the treatment of wounds, burns, asthma, and ulcers.[1–3] Faizi et al.[4] reported a new bisbenzopyran structured compound **1a** {$[\alpha]_D$=+128 ($CHCl_3$, *c* 0.14)} from the roots of *A. barbadensis*. According to the reported data,[4] the natural product is optically active, but the reported structure **1a** is a *meso*-isomer, thus, we suspected that C-3 and C-3′ had the (*S*,*S*) or (*R*,*R*) configuration,[5] as in **1b**. Recently, a comprehensive review[6] also cited this *meso*-isomer **1a** as the unique structure occurring in nature. In order to determine the right structure and unravel the absolute configuration of **1b**, we synthesized compound **1a** and its stereoisomers.[7] The retrosynthesis shows that **1b** can be constructed from its dimer precursor **2** which is prepared from the iodo-benzopyran-4-one **3** (Fig. 1).

2. Results and disccusion

Thus, starting from the conveniently available compound **4**, benzopyran-4-one (**6**) was prepared according to the literature.[8,9] Directed iodination of **6** to **3** was unsuccessful, thus the resulting compound **6** was treated with piperidine[10] in refluxing methanol to afford the enamino ketone **7** in 95% yield. Subsequent treatment of **7** with a chloroform solution of I_2 gave 3-iodo-6-methoxy-4*H*-1-benzopyran-4-one (**3**) in 80% yield. In this step, the yield of **3** was improved to be over 90% in the presence of 2 equiv. of pyridine. Although the mechanism of iodination is still unclear,[10] the presence of organic bases, such as piperidine and pyridine, will restrain **7** from going back to **6** (Scheme 1).

Generally, for the synthesis of **1** from **3**, an Ullmann-type homo-coupling reaction was considered as the first choice. Unfortunately, the isolated yield of dimer **2** was no more than 20% under the standard reaction conditions whether in Cu-mediated[11] coupling (either with DMF, $PhNO_2$ or pyridine as solvent) or with Ni(0) as catalyst.[12] Recently, a new Ullmann-type reagent system, $NiCl_2(PPh_3)_2/PPh_3/Zn/NaH$/toluene, has been developed after screening some additives and solvents in our laboratory.[13] Using this reagent system (0.5 equiv. of the catalyst), the yield of dimer **2** was nearly quantitative (Scheme 1).

Then, it was observed that the dimer **2**, which was sparingly reactive under standard catalytic hydrogenation.[14]

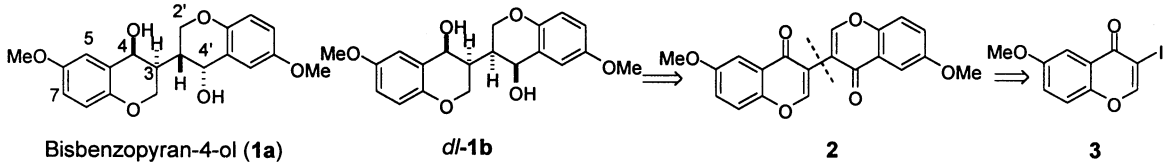

Figure 1. Isomers of bisbenzopyran and retrosynthesis of *dl*-**1b**.

Keywords: total synthesis; Ullmann-type reaction; hydrogenation; X-ray.

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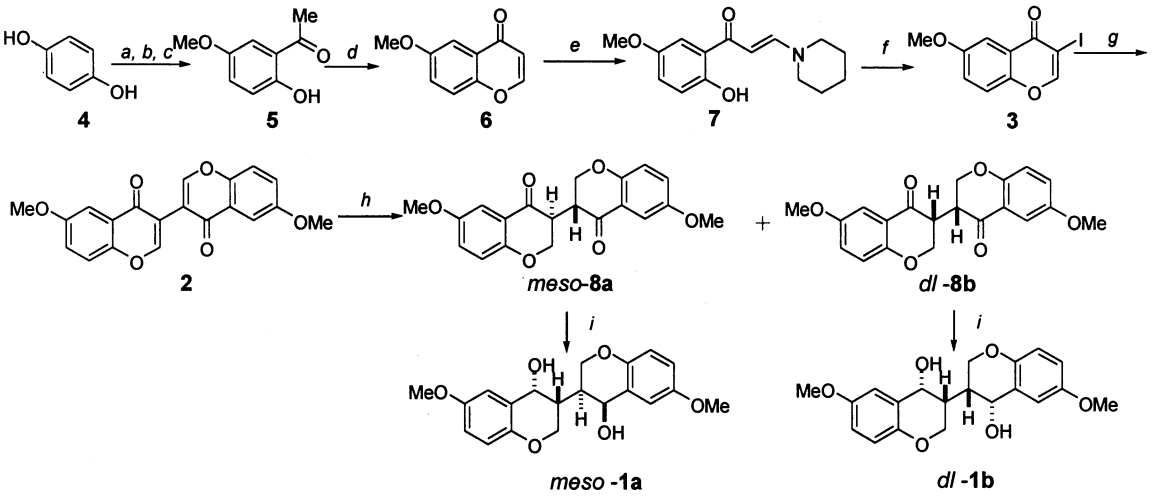


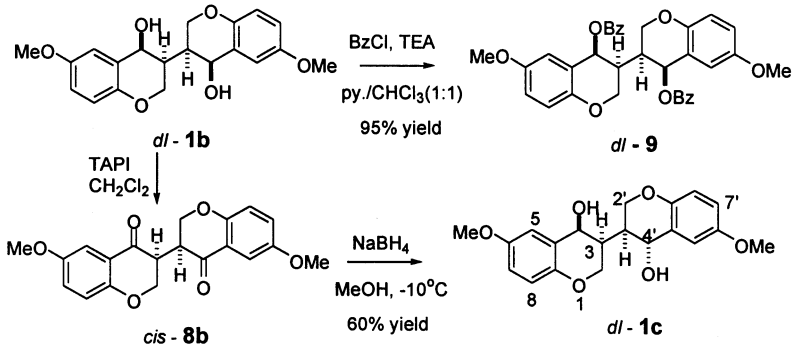
Scheme 1. *Reagents and conditions*: (a) Ac_2O, conc. H_2SO_4; (b) $AlCl_3$, 160°C; (c) K_2CO_3, Me_2SO_4, 40–50% for three steps; (d) Na, HCO_2Et; H_2SO_4 (6N), 80%; (e) Piperidine, MeOH, 95%; (f) I_2, $CHCl_3$, 2 equiv. of pyridine, 95%; (g) $NiCl_2(PPh_3)_2$, PPh_3, Zn, NaH, toluene, 95%; (h) 10% Pd–C, $HCOONH_4$, THF–MeOH (4:1), 25°C, 85%, *meso*-**8a**/*dl*-**8b**=3:7 (determined by 300 MHz ^{1}H NMR spectra); (i) $NaBH_4$–$CeCl_3{\cdot}7H_2O$, MeOH, 95%.

Table 1. Comparing the ^{1}H NMR (300 MHz) data ($CDCl_3$, *J* values in Hz) of synthetic samples (**1b** and **9**) with the reported product (**1**)

Protons	Reported product[4]	Compound *dl*-**1b**	Compound **9**
2a, 2′a	4.24 dd (9.1, 6.8)	4.24 dd (9.8, 4.0)	4.36–4.47 m
2e, 2′e	3.85 dd (9.1, 3.8)	4.13 t (10.8)	
3, 3′	3.09 m	2.19 m	2.46 m
4, 4′	4.73 d (4.1)	4.99 s	6.39 s
5, 5′	6.87 d (1.8)		7.03 d (2.5)
7, 7′	6.80 dd (8.1, 1.8)	6.77–6.84 m	6.84–6.74 m
8, 8′	6.88 d (8.1)		
OCH_3	3.88 s	3.77 s	3.72 s

Interestingly, could be reduced smoothly under the conditions[15] of 10% Pd–C/$HCOONH_4$ in the co-solvents THF–MeOH yielding **8a** and **8b**, subject to the precondition that compound **2** was stored in a refrigerator overnight before hydrogenation. Nevertheless, the hydrogenation of dimer **2** did not occur when the dimer was stored at room temperature overnight after it recrystallized from CH_2Cl_2/MeOH (4:1). The reduction of the ketones **8a** and **8b** with $NaBH_4/CeCl_3{\cdot}7H_2O$ in methanol[16] afforded the target molecules *meso*-**1a** and *dl*-**1b**, respectively. In addition to the optical activity, it was also found that the synthetic *meso*-isomer **1a** with the (*S*,*R*)/(*R*,*S*)-configuration of C-3 and C-3′ did not dissolve in $CDCl_3$, which was used by Faizi et al. as solvent[4] for ^{1}H NMR indicating that *meso*-**1a** could not be the natural product.

Surprisingly, the ^{1}H NMR, ^{13}C NMR and the FT-IR of our synthetic product *dl*-**1b** was greatly different from the reported one (Table 1). The reported chemical shift of the 3-position hydrogen was at unreasonably lowfield (δ=3.09 ppm) while the same hydrogen of the synthetic sample is at just 2.19 ppm. The NOESY spectrum displayed through space connectivity between H-4 and H-3 suggesting their *cis* relationship. This situation is the same as that described in the literature.[4] To confirm the relative configuration of our synthetic product *dl*-**1b**, the corresponding compound **9** was prepared where the hydroxyl group was protected as benzoylate (Scheme 2). The shift of 3-position hydrogen of **9** is downshifted, due to the deshielding effect of benzene ring. An X-ray diffraction experiment performed on **9** furnished a 3D ORTEP diagram (Fig. 2) which fully supported the structure described on the basis of our synthetic method. The monomers are linked with each other through equatorial linkage of C-3 and C-3′ as described in the literature. The NOESY spectrum of **1b** also indicates that H-3 and H-4 are in *cis*-orientation. Therefore, such a structure of **1b** was ruled out from the reported natural product.



Scheme 2. Protection of *dl*-**1b** and preparation of compound *dl*-**1c**.

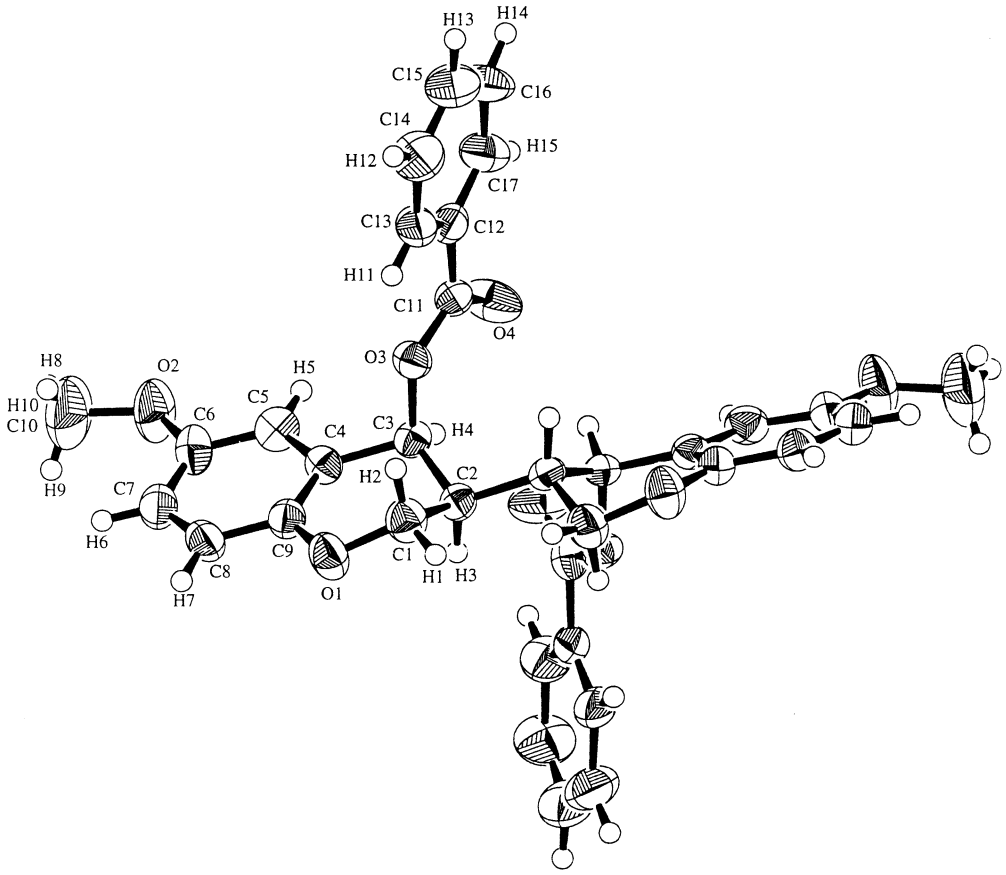


Figure 2. X-Ray ORTEP Diagram of compound **9**.

Furthermore, compound *dl*-**1c** was prepared through the reduction of *dl*-**8b** with $NaBH_4$ in methanol for comparison. The NOESY spectrum of **1c** shows that H-3 and H-4 have a *cis*-orientation, H-3′ and H-4′ are *trans*-oriented. The ^{13}C NMR of *dl*-**1c** is similar to that of compound *dl*-**1b**, but it is still very different from the reported data. The IR spectrum of **1b** does not show the two diagnostic sharp peaks at 3650 and 3550 cm^{-1} which were reported in the literature,[4] but only a broad peak at 3447 cm^{-1}. All the results mentioned above suggest that the reported structure in the literature should be exclusive from **1a**–**1c**.[7]

3. Conclusions

In summary, we have developed a concise strategy for the total synthesis of bis-(4-hydroxy-2*H*-benzopyran), using Ni(0)-catalyzed Ullmann-type coupling reaction and hydrogen-transfer hydrogenation as key steps. At the same time, we confirmed that the reported structure of bisbenzopyran (**1a**) was not the real natural product, and the proposed biosynthesis pathway in literature[4] must also not be correct.[17]

4. Experimental

4.1. General procedure

Solvents (THF, MeOH, pyridine, $CHCl_3$, benzene, EtOH, ethylacetate (EtOAc), pet. ether (PE)) were used without further purification. Benzoyl chloride was distilled over anhydrous KOH. $NaBH_4$ was purchased from Aldrich Co., 10% Pd/C from Fluka Co. HCO_2NH_4 was recrystallized in $EtOH/H_2O$ (95:5). ^1H NMR (300 MHz) spectra were recorded in $CDCl_3$ and chemical shifts are given in ppm. Column chromatography was performed with 300–400 mesh silica gel using flash column techniques. Elemental analyses were performed by EA-MOD 7106. Low-resolution mass spectra were recorded on a Finigan-4201 spectrometer, high-resolution MS on a Concept-1H spectrometer and IR on a FTS-185 spectrometer. The melting points were not corrected. Characterization of compounds **2** and **3** had been reported in our previous work.[13]

4.1.1. 3,3′-Bis(3,4-dihydro-4-hydroxy-6-methoxy-2*H*-benzopyran) (1b). A 100 mL flask was charged with 3,3′-bis(6-methoxychromone) (**2**) (88 mg, 0.25 mmol) (the solid sample was stored at 0°C overnight, after it was recrystallized at room temperature), 10% Pd/C (44 mg, 50 wt%), HCO_2NH_4 (472 mg, 7.5 mmol) and 20 mL of co-solvents THF–MeOH (4:1) then sealed with a rubber septum. The mixture was stirred at room temperature for 6 h, then filtered, and washed with CH_2Cl_2. The filtrate was concentrated in vacuo. The white solid (75 mg, 0.21 mmol) was obtained in 85% yield after flash column chromatography on silica gel (EtOAc/PE=1:4). **8b**: [Found: C, 67.76; H, 5.19. $C_{20}H_{12}O_6$ requires C, 67.80; H, 5.07%]; EI-MS (*m*/*z*): 354 [M^+], 336, 321, 203, 178, 151. IR (KBr) ν_{max}: 2868, 1674, 1617, 1586, 1493, 842, 759 cm^{-1}. ^1H NMR

($CDCl_3$, 300 MHz): δ 7.34 (2H, d, *J*=3.2 Hz, H-5, 5′), 7.11 (2H, dd, *J*=9.2, 3.2 Hz, H-7, 7′), 6.92 (2H, d, *J*= 9.2 Hz, H-8, 8′), 4.63 (2H, t, *J*=11.5 Hz, H-2a, 2′a), 4.49 (2H, dd, *J*=11.0, 4.9 Hz, H-2e, 2′e), 3.43 (2H, dd, *J*=10.1, 4.9 Hz, H-3a, 3′a), 3.80 (6H, s, 2×OCH_3).

To the mixture of **8a** and **8b** (60 mg, 0.17 mmol) and $CeCl_3{\cdot}7H_2O$ (300 mg, 0.81 mmol) was added 15 mL of MeOH. $NaBH_4$ (23 mg, 0.68 mmol) was added in portions. The reaction mixture was stirred at 0°C for 2 h, quenched with 5 mL of 5% HCl, extracted with EtOAc. The combined organic layers were washed with 20% $NaHCO_3$ (aq.) and brine, dried over Na_2SO_4. The white solid **1b** (42 mg, 0.12 mmol) was obtained in 70% yield after column chromatography (silica gel; EtOAc/PE=2:5).

EI-MS (*m*/*z*): 358 (M^+), 340, 239, 149, 97, 71, 57; IR (KBr) ν_{max}: 3447 (br s, OH), 2926, 2835, 1625, 1591, 875, 807, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.84–6.77 (6H, m, Ar–H), 5.00 (2H, s, H-4, 4′), 4.23 (2H, d, *J*=10.8 Hz, H-2β, 2′β), 4.12 (2H, d, *J*=10.8 Hz, H-2α, 2′α), 3.77 (6H, s, OCH_3), 2.19 (2H, m, H-3, 3′); ^{13}C NMR ($CDCl_3$, 75 MHz): 153.64, 148.12, 124.37, 117.69, 116.76, 114.01, 64.75, 63.75, 55.84, 35.82. HRMS. $[M-H_2O]^+$ found: 340.1362. $[C_{20}H_{22}O_6-H_2O]$ requires 340.1311.

Dibenzoylate of compound **1b** (**9**): substrate **1b** (8 mg, 0.022 mmol) was dissolved in 1.0 mL of pyridine–$CHCl_3$ (1:1) in a 5 mL dried flask. Triethylamine (60 μL, 0.43 mmol) and benzoyl chloride (30 μL, 0.26 mmol) were added via a syringe. The mixture was stirred at room temperature for 15 min. The reaction was quenched with 2 mL H_2O, diluted with 10 mL EtOAc. The organic layer was washed with saturated $CuSO_4$ (aq.) and brine, dried over Na_2SO_4. The white solid **9** (12 mg, 0.21 mmol) was obtained in 96% yield after column chromatography (silica gel; EtOAc/PE=1:4).

Compound **9** was recrystallized in benzene–EtOH (1:1), and the single crystal was selected for X-ray experiment.

Mp 260–262°C. Colorless prism. $C_{34}H_{30}O_8$, *M*=566.61, monoclinic. Space group *C*2(#5), *a*=20.790(4), *b*= 6.729(4), *c*=15.323(4) Å, β=136.830(5)°, *V*=1466.7(9) $Å^3$, *Z*=2, Dc=1.283 g cm^{-3}, *F*(000)=596.00, μ (MoKc)= 0.91 cm^{-1}, final R,R_w, 0.059, 0.058. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 163336.

EI-MS (*m*/*z*): 566 (M^+), 494, 323, 307, 282, 162, 105, 77; IR (KBr) ν_{max}: 2928, 2829, 1710, 1600, 1584, 1500, 709 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.03 (4H, dd, *J*=7.0, 1.4 Hz, H-2 on Bz), 7.54 (2H, t, *J*=7.4 Hz, H-4 on Bz), 7.34 (4H, t, *J*=7.4 Hz, H-3 on Bz), 7.03 (2H, d, *J*=2.8 Hz, H-5, 5′), 6.80 (2H, dd, *J*=9.0, 2.8 Hz, H-7, 7′), 6.76 (2H, d, *J*=9.0 Hz, H-8, 8′), 6.39 (2H, br s, H-4e, 4′), 4.45 (2H, dd, *J*=10.8, 2.0 Hz, H-2e, 2′), 4.39 (2H, t, *J*=11.0 Hz, H-2a, 2′a), 3.70 (6H, s, 2×OCH_3), 2.45 (2H, m, H-3); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.61, 153.49, 148.29, 133.32, 129.85, 129.79, 128.47, 120.46, 117.86, 117.37, 114.88, 66.42, 63.80, 55.82, 35.15. HRMS (EI). M^+ found: 566.1909. $C_{34}H_{30}O_8$ requires 566.1941.

4.1.2. (±)-(*S*,*S*)-3,4-(*S*,*R*)-3′,4′-(*S*,*S*)-3,3′-Bis(3,4-dihydro-4-hydroxy-6-methoxy-2*H*-benzopyran) (1c). Compound **1b** (16 mg, 0.044 mmol) was dissolved in 10 mL of CH_2Cl_2 and Dess–Martin periodinane (TAPI) (28 mg, 0.066 mmol) was added in portions. The mixture was stirred at room temperature for 30 min. The reaction was quenched with 10 mL saturated $Na_2S_2O_{3(aq.)}$, $Na_2CO_{3(aq.)}$, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4. The solution was concentrated and the residue was used directly for next reduction. $NaBH_4$ (46 mg, 1.36 mmol) was added in portions to a solution of crude **8b** in 10 mL of MeOH. The mixture was stirred at 0°C for 30 min, then quenched with 5 mL of 5% HCl, and extracted with EtOAc. The combined organic layers were washed with 20% $NaHCO_3$ (aq.) and brine, dried over Na_2SO_4. The desired product (**1c**) (9 mg, 0.026 mmol) was isolated in 60% yield after column chromatography (silica gel; EtOAc/PE=1:2).

EI-MS (*m*/*z*): 358 (M^+), 340, 322, 188, 178, 162, 152, 137, 91; IR (KBr) ν_{max}: 3478 (br s, OH), 2955, 2837, 1586, 1496, 877, 817 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.90 (1H, d, *J*=2.0 Hz, H-5′), 6.74–6.82 (5H, m, Ar–H), 4.90 (1H, d, *J*=4.9 Hz, H-4′), 4.72 (1H, d, *J*=1.5 Hz, H-4), 4.36 (1H, dd, *J*=11.5, 2.7 Hz, H-2′), 4.27 (1H, ddd, *J*=10.7, 2.3, 1.5 Hz, H-2), 4.12 (1H, d, *J*=11.1 Hz, H-2), 4.02 (1H, dd, *J*=11.5, 5.8 Hz, H-2′), 3.76 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 2.98 (2H, br s, OH, D_2O exchange), 2.12 (1H, m, H-3), 1.89 (1H, tt, *J*=10.0, 3.4 Hz, H-3′); ^{13}C NMR ($CDCl_3$, 75 MHz): 153.94, 153.53, 148.55, 148.24, 123.66, 123.65, 117.70, 117.61, 116.81, 116.39, 114.18, 113.80, 66.53, 64.61, 64.54, 63.51, 55.82 (two carbons), 37.51, 37.09. HRMS. M^+ found: 358.1417. $C_{20}H_{22}O_6$ requires 358.1416.

Acknowledgements

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5. Herein, the (*S*,*S*)/(*R*,*R*) is just preferred for the easy discussion according to the structure shown in Fig. 1. The configurations of compound **9** and **1c** are the same as above. Obviously, they are not the absolute configuration.
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all of the stereoisomers of this structure, and none of them is similar to the nature product (according to ^{1}H NMR spectra). Therefore, the reported structure in literature is not correct.

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17. The real natural product might be (+)-pinoresinol. See: Kostava, I.; Dichev, D.; Mikhova, B.; Iossifova, T. *Phytochemistry* **2000**, *53*, 827. We compared the ^{13}C NMR, ^{1}H NMR and MS of compound **1** with those of (+)-pinoresinol. They are almost same. Therefore, the real natural product is mostly (+)-pinoresinol and the structure determination of Faizi's group is completely wrong.