New Tetrahydrofuran-Type Sesquilignans of *Saururus chinensis* Root

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Three new tetrahydrofuran-type sesquilignans, called saucerneol A, saucerneol B and saucerneol C were isolated from the underground parts of *Saururus chinensis* (Saururaceae), together with known lignans, di-*O*-methyltetrahydrofuriguaiacin B, machilin D and machilin D 4-methyl ether. Their structures were established from several spectral data.

Key words *Saururus chinensis*; Saururaceae; tetrahydrofuran-type sesquilignan; saucerneol

Saururus chinensis BAILL (Saururaceae) is a perennial herbaceous plant that has been used in the treatment of edema, jaundice and gonorrhea in Korean folk medicine.[1] In our previous work on *S. chinensis* Herbs, we reported two hepatoprotective flavonol glucuronides[2] and diastereomeric hepatoprotective lignans, sauchinone, sauchinone A and 1′-episauchinone.[3,4] To isolate another bioactive compound from this plant, further work on the methanolic extract of underground parts of *S. chinensis* resulted in the isolation of three new tetrahydrofuran-type sesquilignans and three known lignans. Complete assignment of all the resonances in the NMR spectra led to the identification of these compounds. Among them, **1**, **2** and **3** were identified as di-*O*-methyltetrahydrofuriguaiacin B (**1**), machilin D (**2**) and 4-methoxymachilin D (**3**) by comparison of their spectral data with those reported in the literature,[5—11] respectively. And then, **4**, **5** and **6** were identified as new tetrahydrofuran-type sesquilignans and called saucerneol A (**4**), saucerneol B (**5**) and saucerneol C (**6**) on the basis of their spectral data, respectively.

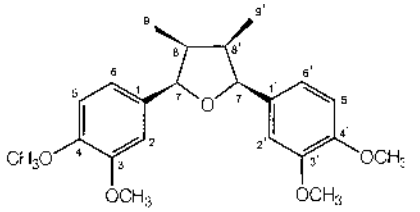
Experimental

General Experimental Procedures Merck Si gel 60 (230—400 mesh) was used for column chromatography. UV spectra were obtained on a Shimadzu UV-2101 spectrophotometer, and IR spectra on a Perkin Elmer 1710 spectrophotometer. The ^{1}H and ^{13}C measurements were carried out in a Bruker AMX 400 spectrometer operating at 400 and 100 MHz, respectively. Data processing was carried out on an Aspect X32 computer with UXNMR software with Bruker microprograms. Standard pulse sequences were used for ^{1}H–^{1}H COSY (PO=45° or 90°), NOESY (mixing time varying between 0.5 and 1.2 s) and HMBC [1/2J=70 ms for $J_{C,H}$=7 Hz]. The experiments were carried out at 300 K. An internal lock was applied and the reference was set to the solvent peak ($CDCl_3$, 7.27 for ^{1}H and 77.2 for ^{13}C; CD_3OD, 3.31 for ^{1}H and 49.2 for ^{13}C). HR-MS were measured on a JEOL JMS AX 505 WA spectrometer, and optical rotations on a JASCO DIP-1000 polarimeter.

Plant Material *S. chinensis* was cultivated in the Medicinal Plant Garden, College of Pharmacy, Seoul National University and identified by Dr. D. S. Han, an emeritus professor of the College of Pharmacy, Seoul National University. A voucher specimen has been deposited in the Herbarium of the Medicinal Plant Garden, College of Pharmacy, Seoul National University.

Extraction and Isolation The air-dried, powdered underground parts of *S. chinensis* (5.5 kg) were defatted with *n*-hexane and then extracted with MeOH in an ultrasonic apparatus which, upon removal of the solvent *in vacuo*, yielded a methanolic extract (900 g). This MeOH extract was then suspended in distilled water and partitioned successively with EtOAc and *n*-BuOH. The EtOAc fraction (100 g) was fractionated by extensive column chromatography over silica gel using $CHCl_3$: MeOH gradient and yielded nine major fractions (fr. 1—fr. 9). Following silica gel column chromatography of fr. 3 with a solvent gradient of ethyl acetate in *n*-hexane yielded 10 subfractions (fr. 3-1—fr. 3-10). Among them, fr. 3-2 yielded **1** by an additional purification step on the RP-HPLC. Compounds **2** and **3** were isolated through Sephadex LH-20 column chromatography of fr. 3-4 with *n*-hexane–CH_2Cl_2–MeOH and RP-HPLC. And then, **5**, **6** and **7** were isolated by RP-HPLC from fr. 3-6. A HPLC (Hitachi L-6200, Japan) system equipped with a UV-visible detector and Microsorb C18 80-299-C5 semi-preparative column (Rainin Inst. Co.) was used for purification. The conditions for HPLC were a mixture of AcCN, MeOH and H_2O (40 : 40 : 20) as mobile phase and were detected at 254 nm.

Di-*O*-methyltetrahydrofuriguaiacin B (**1**): Amorphous powder, $C_{22}H_{28}O_5$, $[\alpha]_D$ +43° (*c*=0.5, $CHCl_3$). UV λ_{max} (MeOH) nm: 280, 235. IR (KBr) cm^{-1}: 2959, 1591, 1515, 1417, 1255, 1235, 1159, 1136, 1028, 814, 761. EI-MS *m/z* (rel. int.): 372 (44) $[M]^+$, 206 (100), 191 (83), 175 (77), 165 (23),



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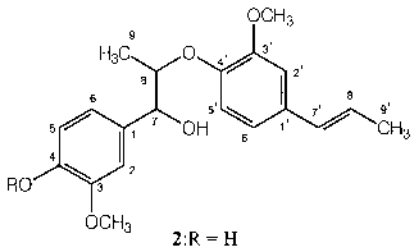
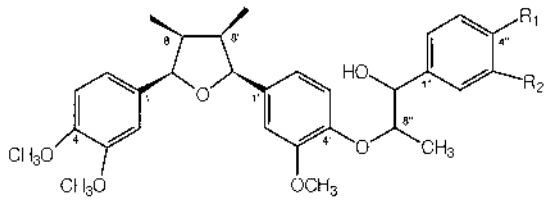


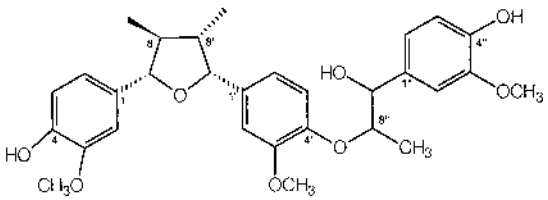
2:R = H

3:R = CH_3



4:R_1 = OCH_3, R_2 = OCH_3

5:R_1, R_2 = $-OCH_2O-$



6

Chart 1. Compounds Isolated from Underground Parts of *S. chinensis*

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91 (12), 77 (13). ^{1}H-NMR ($CDCl_3$) δ: 0.67 (6H, d, J=6.6 Hz, H-9, 9′), 2.23 (2H, m, H-8, 8′), 3.83 (6H, s, 2×OC$\underline{H}_3$), 3.86 (6H, s, 2×OC$\underline{H}_3$), 5.42 (2H, d, J=6.4 Hz, H-7, 7′), 6.82 (6H, s, aromatic protons). ^{13}C-NMR ($CDCl_3$) δ: 14.7 (C-9, 9′), 44.0 (C-8, 8′), 55.7 (2×O$\underline{C}H_3$), 55.9 (2×O$\underline{C}H_3$), 83.5 (C-7, 7′), 109.7 (C-2, 2′), 110.8 (C-5, 5′), 118.4 (C-6, 6′), 134.0 (C-1, 1′), 147.9 (C-4, 4′), 148.6 (C-3, 3′).

Machilin D (**2**): Colorless oil, $C_{20}H_{24}O_5$, $[\alpha]_D$ −160° (c=0.7, $CHCl_3$). UV λ_{max} (MeOH) nm: 260. IR (KBr) cm^{-1}: 3444 (OH), 2950, 2870, 1590, 1490. EI-MS m/z (rel. int.): 344 (38) $[M]^+$, 191 (35), 164 (100), 153 (50), 91 (21), 77 (17), 57 (10). ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, d, J=6.1 Hz, H-9), 1.86 (3H, dd, J=1.5, 6.6 Hz, H-9′), 3.88 (3H, s, –OC$\underline{H}_3$), 3.90 (3H, s, –OC$\underline{H}_3$), 4.06 (1H, m, H-8), 4.59 (1H, d, J=8.3 Hz, H-7), 5.59 (1H, br s, –OH), 6.12 (1H, m, H-8′), 6.34 (1H, dd, J=1.5, 16.3 Hz, H-7′), 6.82—6.97 (6H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$) δ: 151.0 (C-3′), 146.8 (C-3, 4′), 145.7 (C-4), 133.7 (C-1′), 132.2 (C-1), 130.7 (C-7′), 125.1 (C-8′), 120.9 (C-6), 119.2 (C-6′), 119.0 (C-5′), 114.3 (C-5), 109.6 (C-2′), 109.4 (C-2), 84.4 (C-8), 78.7 (C-7), 56.0 (OCH_3), 56.1 (OCH_3), 18.6 (C-9′), 17.3 (C-9).

4-Methoxymachilin D (**3**): Colorless oil, $C_{21}H_{26}O_5$, $[\alpha]_D$ −160° (c=0.7, $CHCl_3$). UV λ_{max} (MeOH) nm: 260. IR (KBr) cm^{-1}: 3444 (OH), 2950, 2870, 1590, 1490. EI-MS m/z (rel. int.): 358 (9) $[M]^+$, 191 (5), 164 (100), 91 (6), 77 (5), 57 (6). ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, d, J=6.1 Hz, H-9), 1.85 (3H, dd, J=1.5, 6.7 Hz, H-9′), 3.85 (3H, s, –OC$\underline{H}_3$), 3.86 (3H, s, –OC$\underline{H}_3$), 3.90 (3H, s, –OC$\underline{H}_3$), 4.07 (1H, m, H-8), 4.61 (1H, d, J=8.3 Hz, H-7), 6.12 (1H, m, H-8′), 6.34 (1H, dd, J=1.5, 15.7 Hz, H-7′), 6.82—6.97 (6H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$) δ: 150.9 (C-3′), 149.1 (C-3), 149.0 (C-4), 146.8 (C-4′), 133.6 (C-1′), 132.6 (C-1), 130.5 (C-7′), 125.0 (C-8′), 120.1 (C-6), 119.1 (C-6′), 118.9 (C-5′), 111.0 (C-5), 110.1 (C-2′), 109.2 (C-2), 84.3 (C-8), 78.5 (C-7), 55.8, 56.0 (OCH_3), 18.5 (C-9′), 17.2 (C-9).

Saucerneol A (**4**): Amorphous powder, $C_{32}H_{40}O_8$, $[\alpha]_D$ −83° (c=0.7, $CHCl_3$). UV λ_{max} (MeOH) nm: 232, 281. IR (KBr) cm^{-1}: 3444 (OH), 2918, 1606, 1521, 1454, 1264, 1138, 1030. EI-MS m/z (rel. int.): 552 (46) $[M]^+$, 534 (30), 358 (18), 206 (100), 192 (88), 178 (64), 165 (47), 91 (9). ^{1}H-NMR (CD_3OD) δ: 7.08 (1H, d, J=1.3 Hz, H-2′), 7.01 (1H, d, J=8.4 Hz, H-5′), 6.99 (1H, dd, J=1.4, 8.2 Hz, H-6″), 6.96 (1H, d, J=1.4 Hz, H-2″), 6.96 (1H, d, J=8.2 Hz, H-5″), 6.94 (1H, dd, J=1.3, 8.4 Hz, H-6′), 6.92 (1H, br s, H-2), 6.88 (1H, d, J=8.2Hz, H-5), 6.83 (1H, br d, J=8.2 Hz, H-6), 5.45 (2H, d, J=6.3 Hz, H-7, 7′), 4.69 (1H, d, J=6.1 Hz, H-7″), 4.44 (1H, m, H-8″), 3.87 (3H, s, –OC$\underline{H}_3$), 3.84 (3H, s, –OC$\underline{H}_3$), 3.82 (6H, s, 2×OC$\underline{H}_3$), 3.81 (3H, s, –OC$\underline{H}_3$), 2.29 (2H, m, H-8, 8′), 1.07 (3H, d, J=6.1 Hz, H-9″), 0.66 (6H, d, J=6.1 Hz, H-9, 9′). HR-EI-MS m/z 552.6579 (Calcd for $C_{32}H_{40}O_8$ 552.6648).

Saucerneol B (**5**): Amorphous powder, $C_{31}H_{36}O_8$, $[\alpha]_D$ −58° (c=0.6, $CHCl_3$). UV λ_{max} (MeOH) nm: 260. IR (KBr) cm^{-1}: 3444 (OH), 2918, 1606, 1512, 1454, 1264, 1138, 1030. EI-MS m/z (rel. int.): 536 (65) $[M]^+$, 518 (24), 355 (38), 192 (84), 178 (60), 145 (45), 117 (15), 91 (12). ^{1}H-NMR (CD_3OD) δ: 7.07 (1H, d, J=1.8 Hz, H-2′), 6.98 (1H, d, J=8.2 Hz, H-5′), 6.97 (1H, dd, J=1.9, 8.2 Hz, H-6″), 6.92 (1H, d, J=1.9 Hz, H-2″), 6.91 (1H, d, J=8.2 Hz, H-5″), 6.83 (1H, dd, J=1.8, 8.2 Hz, H-6′), 6.81 (1H, overlap, H-2), 6.78 (1H, d, J=8.2 Hz, H-5), 6.76 (1H, dd, J=1.1, 8.2 Hz, H-6), 5.42 (2H, s, OCH_2O), 5.42 (2H, d, J=6.0 Hz, H-7, 7′), 4.69 (1H, d, J=6.2 Hz, H-7″), 4.44 (1H, m, H-8″), 3.86 (3H, s, –OC$\underline{H}_3$), 3.82 (3H, s, –OC$\underline{H}_3$), 3.81 (3H, s, –OC$\underline{H}_3$), 2.27 (2H, m, H-8, 8′), 1.08 (3H, d, J=6.2 Hz, H-9″), 0.66 (6H, d, J=6.1 Hz, H-9, 9′). HR-EI-MS m/z 536.6119 (Calcd for $C_{31}H_{36}O_8$ 536.6220).

Saucerneol C (**6**): Amorphous powder, $C_{30}H_{36}O_8$, $[\alpha]_D$ −66° (c=0.7, $CHCl_3$). UV λ_{max} (MeOH) nm: 232, 281. IR (KBr) cm^{-1}: 3444 (OH), 2918, 2870, 1606, 1512, 1454, 1264, 1138, 1030. EI-MS m/z (rel. int.): 524 (24) $[M]^+$, 506 (26), 344 (14), 192 (100), 165 (30), 145 (31), 137 (16), 91 (9). ^{1}H-NMR (CD_3OD) δ: 7.07 (1H, d, J=1.7 Hz, H-2′), 7.00 (1H, d, J=1.8 Hz, H-2″), 6.99 (1H, d, J=8.1 Hz, H-5), 6.98 (1H, d, J=1.7 Hz, H-2), 6.95 (1H, dd, J=1.7, 8.1 Hz, H-6′), 6.88 (1H, dd, J=1.7, 8.1 Hz, H-6), 6.84 (1H, dd, J=1.8, 8.3 Hz, H-6″), 6.83 (1H, d, J=8.1 Hz, H-5′), 6.76 (1H, d, J=8.3 Hz, H-5″), 5.11 (1H, d, J=8.3 Hz, H-7), 4.64 (1H, d, J=6.6 Hz, H-7″), 4.42 (1H, q, J=6.6 Hz, H-8″), 4.36 (1H, d, J=9.5 Hz, H-7′), 3.87 (3H, s, 4″-OCH_3), 3.83 (3H, s, 4-OCH_3), 3.84 (3H, s, 4′-OCH_3), 2.25 (1H, m, H-8), 1.79 (1H, m, H-8′), 1.07 (1H, d, J=6.1 Hz, H-9″), 1.01 (1H, d, J=6.6 Hz, H-9′), 0.65 (1H, d, J=6.8 Hz, H-9). HR-EI-MS m/z 524.6135 (Calcd for $C_{30}H_{36}O_8$ 524.6110).

Results and Discussion

The underground parts of *S. chinensis* were extracted with *n*-hexane and then MeOH. The latter extract was suspended in distilled water and partitioned successively with EtOAc and *n*-BuOH. The EtOAc fraction (100 g) was fractionated by successive chromatographies on silica gel columns using $CHCl_3$: MeOH gradient and yielded three lignan-containing subfractions. These subfractions were chromatographed on RP-HPLC resulting three known lignans (**1**—**3**) and three new sesquilignans (**4**—**6**). Their structures were established on the basis of EI-MS, ^{1}H-, ^{13}C-NMR, DEPT, ^{1}H–^{1}H COSY, HETCOR, HMBC as well as NOE experiments. All molecular ion peaks could be obtained by EI-MS and their molecular formulae were obtained by HR-MS.

Compounds **1**, **2** and **3** were identified as all-*cis* isomer di-*O*-methyl-tetrahydrofuroguaiacin B, machilin D and 4-methoxymachilin D by comparison with previously reported spectral data,[5—11] respectively.

The EI-MS of **4** showed the molecular ion peak at m/z 552, and the molecular formula was determined as $C_{32}H_{40}O_8$ on the basis of HR-EI-MS. The ^{1}H-NMR spectrum showed nine aromatic signals between δ 6.81 and 7.08 and five methoxy groups between δ 3.81 and 3.87, all belonging to three partially methoxylated aromatic systems. Six aliphatic methines and three methyl groups pointed to three phenylpropanoid moieties. In the ^{1}H-NMR spectrum, two methine signals at δ 2.29 (2H, m, H-8, 8′) coupled with two methine groups at δ 5.45 (2H, d, J=6.3 Hz, H-7, 7′) as well as with nearly equivalent methyl groups at δ 0.66 (6H, d, J=6.1 Hz, H-9, 9′) and these were assigned to a substituted tetrahydrofuran moiety. The proton shifts as well as the corresponding shifts in the ^{13}C-NMR spectrum are characteristic for *cis*-oriented aryl/methyl and *cis*-oriented methyl/methyl substituents at the tetrahydrofuran ring.[12,13]

The proton of an oxygenated methine group at δ 4.44 (H-8″) coupled with the protons of a methine at δ 4.69 (1H, d, J=6.1 Hz, H-7″) and a methyl group at δ 1.07 (3H, d, J=6.1 Hz, H-9″) in the ^{1}H-NMR spectrum. A comparison of the chemical shifts of H-7″, H-8″, C-7″, C-8″ and C-9″ (methyl group) with published data of related 8.*O*.4′-type neolignans proved to be helpful for determination of the relative configuration of these methine groups. The *erythro*-orientation of the ether and the hydroxyl group and the *threo*-configuration of these groups can be distinguished by their different chemical shift ranges: methine group bearing the hydroxyl group (*erythro*: δ_H 4.75—4.85, δ_C 72.6—73.3; *threo*: δ_H 4.60—4.66, δ_C 77.5—78.7), methine group bearing the ether group (*erythro*: δ_H 4.33—4.38, δ_C 81.8—82.6; *threo*: δ_H 4.03—4.18, δ_C 82.6—86.1) and methyl group (*erythro*: δ_C 12.6—13.7; *threo*: δ_C 16.2—17.3).[7,14—16] The chemical shift of H-7″ as well as the shifts of C-7″ and C-9″ of **4** were in agreement with a *threo*-orientation of the hydroxyl and the ether group. The large coupling constant ($J_{7'',8''}$=6.1 Hz) was also in accordance with the *threo*-configuration (lit: J=2.7—4.4 Hz, *erythro*-isomer; J=8.0—8.6 Hz, *threo*-isomer).[7,17,18] From the above results, compound **4** was determined as rel-2β-3,4-dimethoxyphenyl-5β-[3-methoxy-4-{*threo*-3-hydroxy-3-(3,4-dimethoxyphenyl)}isopropoxy phenyl]-3β,4β-dimethyltetrahydrofuran and termed as saucerneol A.[19]

The EI-MS of **5** showed the molecular ion peak at m/z 536, and the molecular formula was determined to be $C_{31}H_{36}O_8$ on the basis of HR-EI-MS. The ^{1}H- and ^{13}C-NMR spectra of **4** and **5** were very similar (Table 1). However, the ^{1}H- and ^{13}C-NMR spectra of **5** lacked the signals of two methoxyl

Table 1. ^{13}C-NMR Data of **4**—**6** (100 MHz, CD_3OD)

	4	5	6
1	136.7	136.7	136.4
2	112.1	112.2	112.8
3	151.5	151.5	151.4
4	147.8	147.8	148.0
5	117.8	117.8	117.7
6	120.0	120.1	120.9
7	85.4	85.4	84.3
8	44.7	44.6	47.0
9	14.8	14.7	15.3
1′	135.4	136.7	133.0
2′	111.6	108.0	111.7
3′	150.2	149.0	148.9
4′	149.6	148.1	147.5
5′	112.7	108.7	116.2
6′	120.1	120.7	120.7
7′	85.4	85.6	89.1
8′	44.5	44.7	49.1
9′	14.8	14.7	14.9
1″	135.2	135.2	133.7
2″	112.1	112.2	111.9
3″	150.3	150.3	148.8
4″	150.1	150.1	146.3
5″	112.6	112.6	115.8
6″	121.0	121.0	121.2
7″	78.0	78.0	78.3
8″	81.6	81.7	81.8
9″	16.5	16.5	16.7
$-OCH_2O-$	—	102.3	—
$-OCH_3$	56.4	56.5	56.4
	56.5	56.5	56.5
	56.5	56.6	56.6
	56.5		
	56.6		

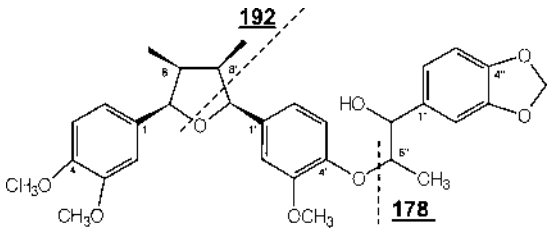

Fig. 1. EI-MS Fragmentation of **5**

groups and showed the signal of one additional methylenedioxy group (δ_H; 5.92, 2H, δ_C; 102.26). The binding site of this methylenedioxy group was proposed by the fragmentation pattern observed in the EI-MS (Fig. 1) and determined using the HMBC spectrum. From the above results, compound **5** was determined to be rel-2β-3,4-dimethoxyphenyl-5β-[3-methoxy-4-{*threo*-3-hydroxy-3-(3,4-methylenedioxyphenyl)}isopropoxyphenyl]-3β,4β-dimethyltetrahydrofuran and called as saucerneol B.[19]

The EI-MS of **6** showed the molecular ion peak at *m*/*z* 524, and the molecular formula was determined as $C_{30}H_{36}O_8$ on the basis of HR-EI-MS. The fragmentation pattern of EI-MS of **6** was similar to those of **4**. However, the ^{1}H-NMR shifts for the tetrahydrofuran moiety as well as the corresponding ^{13}C shifts were quite different. These shifts are characteristic for a tetrahydrofuran ring with a *cis*-configuration of one aryl and methyl substituent as well as a *trans*-configuration of the

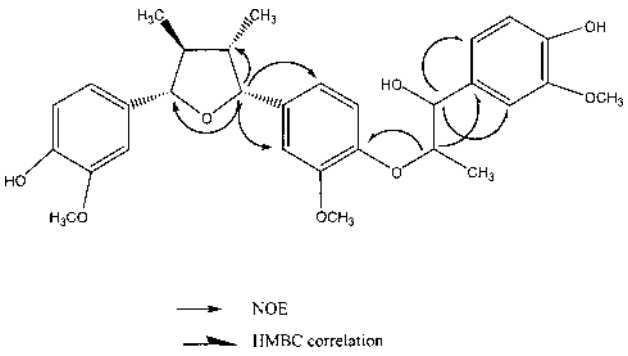

Fig. 2. Important NOE and HMBC Correlations of **6**

other aryl and methyl group, whereas the two methyl groups are *trans*-oriented to each other. The ^{1}H- and ^{13}C-NMR data of the third phenylpropanoid moiety were in agreement with those of **4** except for lack of two methoxyl groups. Due to the asymmetric stereochemistry of the tetrahydrofuran substituent it had to be determined which of the two aryl substituents showed a *cis*-orientation to the neighboring methyl group. This was deduced from the HMBC spectrum and the NOE experiments (Fig. 2). From the above results, compound **6** was determined as rel-2α-3-hydroxy-4-methoxyphenyl-5α-[3-methoxy-4-{*threo*-3-hydroxy-3-(4-hydroxy-3-methoxyphenyl)}isopropoxyphenyl]-3β,4α-dimethyltetrahydrofuran and called as saucerneol C.[19]

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