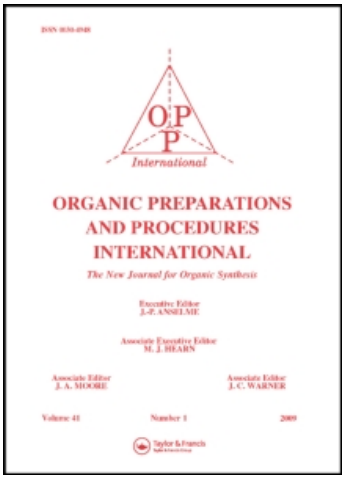

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RACEMIC TOTAL SYNTHESES OF ISOAUSTROBAILICNAN-1 AND OF SOME RELATED ARYLTETRALIN LACTONES

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RACEMIC TOTAL SYNTHESES OF ISOAUSTROBAILIGNAN-1 AND OF SOME RELATED ARYLTETRALIN LACTONES†

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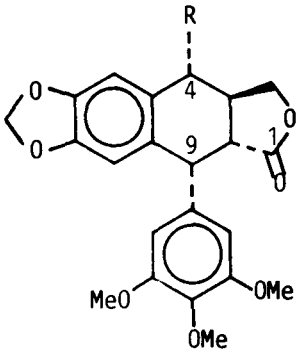
Natural lignans belonging to the aryltetralin lactone series, such as podophyllotoxin 1 or its 4-deoxy analogue 2, exhibit various biological properties, including anticancer activity.[1] A member of this series, austrobailignan-1 3[2] is characterized by the unusual substitution pattern of the aryl substituent (3'-methoxy and 4',5'-methylenedioxy). The 9-epimer of 2, namely (+)-isodeoxypodophyllotoxin, as well as analogous compounds having the same trans-anti stereochemistry, still exhibit a significant cytotoxicity,[3] which is a justification of the interest devoted to their syntheses.



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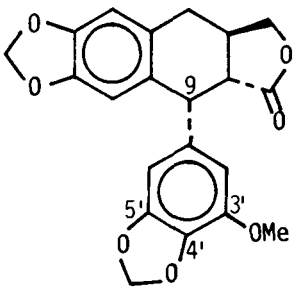
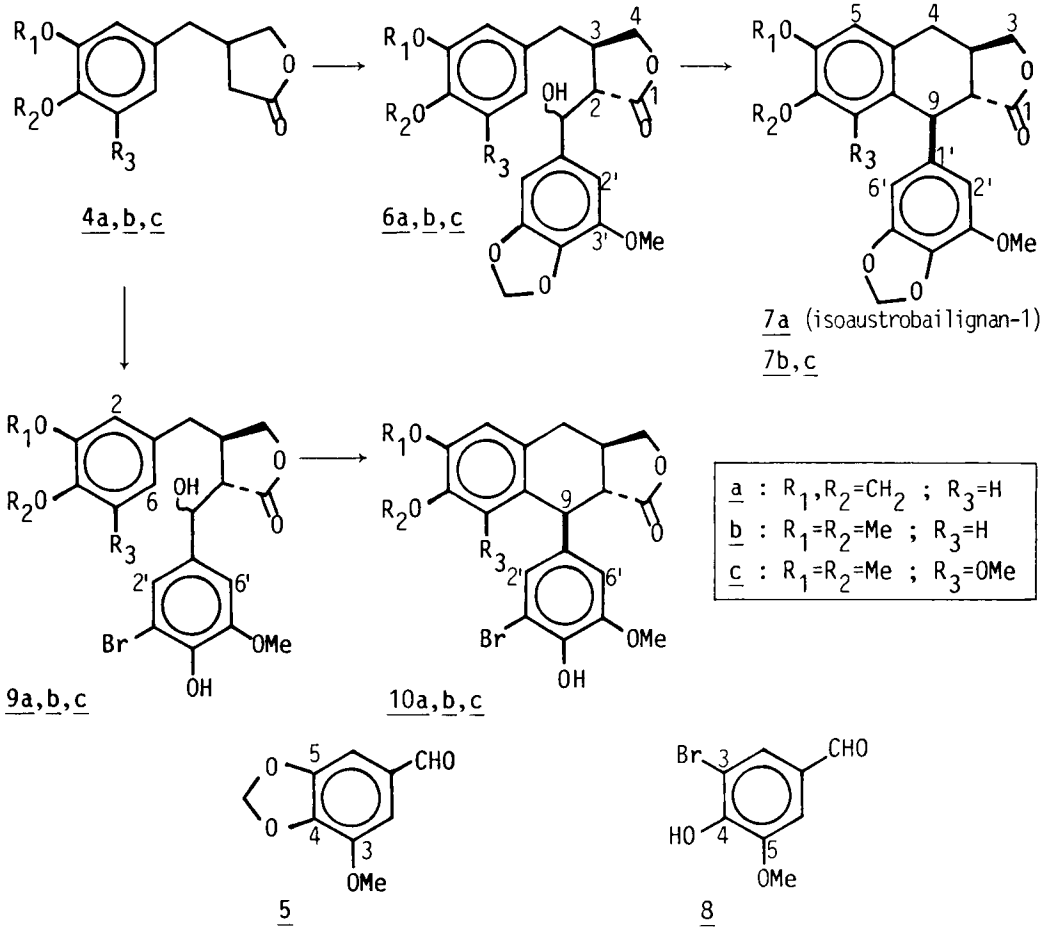


3

The following reaction scheme is an application of the general scheme formerly developed in our laboratory.[4] It leads to aryltetralin lactones of the so-called "iso" series, which all have a relative trans-anti configuration with a pseudo-equatorial aryl substituent.



We synthesized racemic isoaustrobailignan-1 **7a** as follows. ß-Piperonyl-ɣ-butyrolactone **4a**[5] was α-hydroxyalkylated with Stevenson's aldehyde **5**[6] using LHDS as the base, and afforded an approximately equimolar mixture of the epimeric

alcohols **6a** in 79% yield. In both epimers **6a**, the lactone ring is *trans* disubstituted. The mixture of alcohols **6a** was intramolecularly cyclized by means of CF_3CO_2H at room temperature, giving crystalline isoaustrobailignan-1 **7a** in 57% yield. The 350 MHz ^1H NMR spectrum of **7a** indicated that the vicinal protons at the 3a, 9a and 9 positions are axial (J_{3a-9a} = 13.3 Hz, J_{9a-9} = 10.5 Hz) and thus confirmed the *trans*-*anti* structure of **7a** (see Experimental section for full NMR data). As can be predicted from its rigid structure, compound **7a** has a high melting point 281-282° and a low solubility in usual solvents. The aryltetralin lactones **7b** and **7c** which are closely related to **7a** were synthesized in a similar fashion from the corresponding ß-benzyl-γ-butyrolactones **4b**[7] and **4c**[5] respectively.

The syntheses of the (3-bromo-4-hydroxyaryl)tetralin lactones **10a-c** were next undertaken following the same scheme as above. The lactones **4a-c** were separately α-hydroxyalkylated with the aldehyde **8**,[8] using a fivefold excess of LHDS, thus leading to the corresponding epimeric mixture of alcohols **9a-c**, respectively. The latter were intramolecularly cyclized by means of CF_3CO_2H in CH_2Cl_2, and afforded the corresponding crystalline tetralins **10a-c** in good yields.

The results of the pharmacological tests performed with the above compounds will be published separately.

EXPERIMENTAL SECTION

IR spectra were recorded with a Nicolet 5DX spectrophotometer. ^1H NMR spectra were recorded with Varian EM 390 and Cameca 350 spectrometers, using Me_4Si as an internal standard. Mass spectra (MS) were recorded with a Varian MAT 311 spectrometer. The microanalyses were performed by "Service Central d'Analyse", Vernaison. Abbreviations : LHDS, lithium hexamethyldisilylazide ; RT, room temperature ; RP, reduced pressure.

2-[(3'-Methoxy-4',5'-methylenedioxyphenyl)hydroxymethyl]-3-(3,4-methylenedioxybenzyl)-4-butanolide **6a** (2 epimers).- In a 100 mL three-necked flask equipped with a magnetic stirrer, a nitrogen inlet, a thermometer and a septum, a solution of n-BuLi in hexane (1.6 N, 23.6 mL, 37.8 mmol) was placed by means of a syringe, followed by the addition at -10° of hexamethyldisilylamine (8.76 mL, 41.5 mmol). After stirring for 15 min, a mixture of ß-piperonyllactone **4a**[5] (2.08 g, 9.45 mmol) and the aldehyde **5**[6] (1.7 g, 9.45 mmol) in dry benzene (25 mL) was quickly added at RT, and the resulting mixture was vigorously stirred for 4 min. After hydrolysis with aqueous 50% HCl solution (25 mL) previously cooled to -20°, the organic layer was separated and the aqueous phase was extracted 4 times with CH_2Cl_2. The combined organic phases were washed with aqueous 5% $NaHCO_3$ solution and then with brine and were finally dried ($MgSO_4$) and evapored under RP. The pale yellow oily residue was chromatographed over silica gel (40 g) and was eluted with 200:1 CH_2Cl_2-MeOH, thus affording an amorphous mixture of both epimeric alcohols **6a** (3 g, 79%).

Anal. Calcd. for $C_{21}H_{20}O_8$: C, 62.99 ; H, 5.03 ; O, 31.97

Found: C, 63,10 ; H, 5.29 ; O, 31.81

IR (Nujol) 3476(OH), 1757 (C=O), 1636, 1503 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.9-6.3 (m, 5) aryl H, 6.06 (s, 2) OCH_2O, 6.0 (s, 2) OCH_2O, 5.3 (d, J = 3 Hz) and 4.82 (d, J = 6.5 Hz) (1) CHOH, 4.60-4.0 (m, 2) CH_2OCO, 3.96 and 3.90 (2s, 3) OCH_3 of both epimers, 3.30-2.10 (m, 4).

Isoaustrobailignan-1 **7a**.- In a 50 mL two-necked flask equipped with a magnetic stirrer and a nitrogen inlet, a solution of the alcohols **6a** (3 g, 7.5 mmol) in CF_3CO_2H (15 mL) was stirred at

RT for 3 hrs. After concentration of the mixture under RP, the residue was crystallized from $CHCl_3$ providing **7a** (1.6 g, 57%) as a white solid, mp. 281-282°.

Anal. Calcd. for $C_{21}H_{18}O_7$: C, 65.94 ; H, 4.76

Found: C, 65.51 ; H, 4.75

MS. Calcd : 382.1049. Found: 382.1056. m/e 382(100%), 297, 267, 230, 165, 152, 84. IR (Nujol) 1775 (C=O), 1636, 1509 cm^{-1}. ^1H NMR, 350 MHz ($CDCl_3$): δ 6.59 (s, 1) H-5, 6.48 (s, 1) H-2', 6.35 (s, 1) H-8, 6.29 (s, 1) H-6', 5.95 (s, 2) OCH_2O, 5.89 (s, 2) OCH_2O, 4.52 (dd, 1, $J_{3\alpha-3a}$ = 6.4 Hz, J_{AB} = 8.6 Hz) H-3α, 4.03 (d, 1, J_{9-9a} = 10.5 Hz) H-9, 3.99 (dd, 1H, $J_{3\beta-3a}$ = 10.7 Hz, J_{AB} = 9.0 Hz) H-3β, 3.91 (s, 3) OCH_3, 2.97 (dd, 1, $J_{4\alpha-3a}$ = 4.7 Hz, J_{AB} = 15.5 Hz) H-4α, 2.89 (dd, 1, $J_{4\beta-3\alpha}$ = 10.9 Hz, J_{AB} = 15.4 Hz) H-4β, 2.59 (m, 1) H-3a, 2.50 (dd, 1, $J_{9a-9} \approx 10.5$ Hz, J_{3a-9a} = 13.3 Hz) H-9a.

2-[(3'-Methoxy-4',5'-methylenedioxyphenyl)hydroxymethyl]-3-(3,4-dimethoxybenzyl)-4-butanolide **6b** (2 epimers).- The β-veratryl-lactone **4b**[7] (2 g, 8.5 mmol) and the aldehyde **5** (1.53 g, 8.5 mmol) were treated with LHDS (33.9 mmol) in C_6H_6 (25 mL) in the same way as above. The reaction mixture was worked up and the residue was chromatographed over silica gel (30 g) and eluted with 200:1 CH_2Cl_2-MeOH, thus affording an amorphous mixture of both epimeric alcohols **6b** (3 g, 86%).

Anal. Calcd. for $C_{22}H_{24}O_8$: C, 63.45 ; H, 5.81 ; O, 30.74

Found: C, 62.69 ; H, 5.89 ; O, 30.74

IR (Nujol) 3500 (OH), 1763 (C=O), 1636, 1515 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 6.93-6.40 (m, 5) aryl H, 6.06 (s, 2) OCH_2O, 5.30 and 4.84 (2d, 1) CHOH of both epimers, 4.56-4.0 (m, 2) CH_2OCO, 3.96, 3.87 and 3.83 (3s, 9) OCH_3, 2.93-2.13 (m, 4) aliph. H.

9-(3'-Methoxy-4',5'-methylenedioxyphenyl)-6,7-dimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-c]furan-1(3H)-one **7b**.- Treatment of the mixture of alcohols **6b** (2.4 g, 5.8 mmol) with CF_3CO_2H (15 mL) in the same way as above, gave the aryltetralin lactone **7b** (2 g, 71%), mp. 213-215° (CH_2Cl_2/Et_2O). This compound gave erratic microanalytical data. IR (Nujol) 1775 (C=O), 1636, 1515 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 6.66 (s, 1) H-5, 6.56 (d, 1, J = 1.5 Hz) H-2', 6.43 (s, 1) H-8, 6.40 (d, 1, J = 1.5 Hz) H-6', 6.0 (s, 2) OCH_2O, 4.56 (dd, 1) H-3α, 4.26-4.0 (m, 2) H-9,H-3β, 3.93 and 3.90 (2s, 6) OCH_3-3',6, 3.65 (s, 3) OCH_3-7, 3.10-2.83 (m, 2) H-4α, H-4β, 2.70-2.30 (m, 2) H-3a, H-9a.

2-[(3'-Methoxy-4',5'-methylenedioxyphenyl)hydroxymethyl]-3-(3,4,5-trimethoxybenzyl)-4-butanolide **6c** (2 epimers).- The β-(trimethoxybenzyl) lactone **4c**[5] (2.26 g, 8.5 mmol) and the aldehyde **5** (1.53 g, 8.5 mmol) were treated with LHDS (33.9 mmol) in C_6H_6 (25 mL) in the usual way. The reaction product was worked up and chromatographed over silica gel (80 g). Elution with 200:1 CH_2Cl_2-MeOH afforded an amorphous mixture of both epimeric alcohols **6c** (2.8 g, 76%).

Anal. Calcd. for $C_{23}H_{26}O_9$: C, 61.88 ; H, 5.87 ; O, 32.25

Found: C, 61.72 ; H, 5.87 ; O, 31.97

IR (Nujol) 3480 (OH), 1783 (C=O), 1636, 1593, 1509 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 6.75-6.15 (m, 4) aryl H, 6.05 (s, 2) OCH_2O, 5.33 and 4.86 (2d, 1) CHOH of both epimers, 4.6-4.0 (m, 2) CH_2OCO, 3.96, 3.93 and 3.83 (3s, 12) OCH_3, 3.3-2.1 (m, 4) aliph. H.

9-(3'-Methoxy-4',5'-methylenedioxyphenyl)-6,7,8-trimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-c]furan-1(3H)-one **7c**.- Treatment of the alcohols **6c** (2.6 g, 5.8 mmol) with CF_3CO_2H (15 mL) gave the aryltetralin lactone **7c** (2.3 g, 92%), mp. 147-148° (Et_2O).

Anal. Calcd. for $C_{23}H_{24}O_8$. 0.25 H_2O: C, 63.78 ; H, 5.72

Found: C, 63.99 ; H, 5.65

IR (Nujol) 1761 (C=O), 1636, 1599, 1509 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 6.63 (d, 1, J = 1.5 Hz) H-2', 6.53 (s, 1) H-5, 6.33 (d, 1, J = 1.5 Hz) H-6', 5.93 (s, 2) OCH_2O, 4.65-4.25 (m, 3) CH_2-3, H-9, 3.93 (s, 6), 3.80 (s, 3) OCH_3-3', 3.27 (s, 3) OCH_3-8, 3.05 -2,8 (m, 2) CH_2-4, 2.6-2.15 (m, 2) H-3a,H-9a.

2-[(3'-Bromo-4'-hydroxy-5'-methoxyphenyl)hydroxymethyl]-3-(3,4-methylenedioxybenzyl)-4-butanolide **9a** (2 epimers).- A solution of the lactone **4a** (2.5 g, 11.3 mmol) in C_6H_6 (30 mL) was added to a solution of LHDS (56.3 mmol, 5 equ.) in hexane, followed by bromovanillin **8**[8] (2.6 g, 11.3 mmol) in a mixture of C_6H_6 (15 mL) and HMPT (15 mL), and the resulting solution was stirred at RT for 15 min. The reaction product was worked up and chromatographed over silica gel (100 g). Elution with 200:3 CH_2Cl_2-MeOH afforded an amorphous mixture of the alcohols **9a** (5 g, 98%).

Anal. Calcd. for $C_{20}H_{19}BrO_7$: C, 53,23 ; H, 4.24 ; O, 24.82

Found: C, 52.44 ; H, 4.61 ; O, 24.43

IR (Nujol) 3380 (OH), 1757 (C=O), 1605, 1503 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.30-6.33 (m, 5) aryl H, 6.30 (s, 1) phenol OH, 5.97 (s, 2) OCH_2O, 5.23 (d, J = 3 Hz) and 4.83 (d, J = 7 Hz)(1) CHOH of both epimers, 4.6-3.9 (m, 2) CH_2OCO, 3.86 and 3.92 (2s, 3), OCH_3 of both epimers, 3.0-2.0 (m, 4) aliph. H.

9-(3'-Bromo-4'-hydroxy-5'-methoxyphenyl)-6,7-methylenedioxy-3a,4,9,9a-tetrahydronaphtho[2,3-c]furan-1(3H)-one **10a**.- Treatment of the alcohols **9a** (4g, 8.9 mmol) in CH_2Cl_2 (80 mL) with CF_3CO_2H (15 mL) at RT under N_2 for 10 hrs gave the

crystalline aryltetralin lactone **10a** (2.8 g, 74%), mp. 274-277° (Me_2CO).

Anal. Calcd. for $C_{20}H_{17}BrO_6.0.25\ H_2O$: C,54.85; H,4.04; Br,18.26; O,21.94

Found: C,54.82; H,4.19; Br,18.01; O,22.26

IR (Nujol) 3386 (OH), 1775 (C=O), 1605, 1503 cm^{-1}. ^1H NMR ($CDCl_3$, DMSO) : δ 9.21 (s, 1) phenol OH, 6.93 (d, 1) H-2', 6.84 (d, 1) H-6', 6.71 (s, 1) H-5, 6.23 (s, 1) H-8, 5.96 (s, 2) OCH_2O, 4.50 (dd, 1) H-3α, 4.15-3.90 (m, 2) H-9a, H-3β, 3.84 (s,3) OCH_3, 3.10-2.4 (m, 4) aliph. H.

2-[(3'-Bromo-4'-hydroxy-5'-methoxyphenyl)hydroxymethyl]-3-(3,4-dimethoxybenzyl)-4-butanolide **9b** (2 epimers).- A solution of the lactone **4b** (2 g, 8.5 mmol) and bromovanillin **8** (2 g, 8.6 mmol) in a mixture of benzene (40 mL) and HMPT (10 mL) was added to a solution of LHDS (43.3 mmol, 5 equ.) in hexane as described before. The reaction mixture was worked up and the final residue was chromatographed over silica gel (80 g). Elution with 200:1 CH_2Cl_2-MeOH afforded an amorphous mixture of the epimeric alcohols **9b** (2.5 g, 64%).

Anal. Calcd. for $C_{21}H_{23}BrO_7$: C, 53.97 ; H, 4.96

Found: C, 53.31 ; H, 5.01

IR (Nujol) 3476 (OH), 1757 (C=O), 1605, 1587, 1515 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.16 (s, 1) phenol OH, 6.86-6.20 (m, 5) aryl H, 5.27 (m, 1) CHOH, 4.46-3.90 (m, 2) CH_2OCO, 3.83 (s, 3) OCH_3, 3.76 (s, 6) OCH_3, 3.10-2.0 (m, 4) aliph. H.

9-(3'-Bromo-4'-hydroxy-5'-methoxyphenyl)-6,7-dimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-c]furan-1(3H)-one **10b**.- Treatment of the alcohols **9b** (2.4 g, 5.1 mmol) in CH_2Cl_2 (25 mL) with CF_3CO_2H (8 mL) gave the crystalline aryltetralin lactone **10b** (1,8 g, 78%), mp. 190-192° (Me_2CO/Et_2O).

Anal. Calcd. for $C_{21}H_{21}BrO_6$: C, 56.14 ; H, 4.71 ; Br, 17.78 ; O, 21.37

Found: C, 55.87 ; H, 4.74 ; Br, 17.81 ; O, 21.57

IR (Nujol) 3452 (OH), 1775 (C=O), 1605, 1509 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.93 (d, 1) H-2', 6.90 (s, 1) H-6', 6.70 (s, 1) H-5, 6.40 (s, 1) H-8, 5.90 (s, 1) phenol OH, 4.56 (dd, 1) H-3α, 4.33-3.98 (m, 2) H-9, H-3β, 3.90 (s, 6) OCH_3-6', 3.66 (s, 3) OCH_3-7, 3.20-2.80 (m, 2) CH_2-4, 2.63-2.20 (m, 2) H-3a, H-9a.

2-[(3'-Bromo-4'-hydroxy-5'-methoxyphenyl)hydroxymethyl]-3-(3,4,5-trimethoxybenzyl)-4-butanolide **9c** (2 epimers).- A solution of the lactone **4c** (3 g, 11.27 mmol) and bromovanillin **8** (2.6 g, 11.27 mmol) in a mixture of benzene (50 mL) and HMPT (10 mL) was added to a solution of LHDS (56.3 mmol) in hexane. The final residue was chromatographed over silica gel (100 g). Elution with 200:5 CH_2Cl_2-MeOH afforded an amorphous mixture of the epimeric alcohols **9c** (5.6 g, 99%).

Anal. Calcd. for $C_{22}H_{25}BrO_8$: C, 53.13 ; H, 5.07 ; O, 25.73

Found: C, 53.14 ; H, 5.36 ; O, 25.32

IR (Nujol) 3392 (OH), 1763 (C=O), 1684, 1593, 1503 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.26 (d, 1) H-2', 6.51 (d, 1) H-6', 6.2 and 6.1 (2s, 2) H-2,6, 5.30 and 4.90 (2d, 1) CHOH, 4.66-4.0 (m, 2) CH_2OCO, 4.0-3.80 (12) OCH_3, 2.90-2.10 (m,4) aliph. H.

9-(3'-Bromo-4'-hydroxy-5'-methoxyphenyl)-6,7,8-trimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-c]furan-1(3H)-one **10c**.- Treatment of the alcohols **9c** (4 g, 8.04 mmol) in CH_2Cl_2 (80 mL) with CF_3CO_2H (12 mL) gave the aryltetralin lactone **10c** (3 g, 79%), mp. 199-201° (Me_2CO/Pet. ether).

Anal. Calcd. for $C_{22}H_{23}BrO_7$: C, 55.13 ; H, 4.84 ; Br, 16.67 ; O, 23.36

Found: C, 55.35 ; H, 4.93 ; Br, 16.63 ; O, 23.25

IR (Nujol) 3404 (OH), 1775 (C=O), 1599, 1496 cm^{-1}. ^1H NMR

($CDCl_3$) : δ 7.11 (d, 1, J = 1.8 Hz) H-2', 6.73 (d, 1, J = 1.8 Hz) H-6', 6.53 (s, 1) H-5, 5.86 (s, 1) phenol OH, 4.66-4.20 (m, 2) H-3α, H-9, 4.13-3.90 (m, 1) H-3β, 3.96, 3.90 and 3.76 (3s, 9) OCH_3, 3.23 (s, 3) OCH_3-8, 3.03-2.83 (m, 2) CH_2-4, 2.60-2.23 (m, 2) H-3a, H-9a.

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