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ISOTEUFLIDIN, A NEO-CLERODANE DITERPENOID FROM *TEUCRIUM CHAMAEDRYS*, AND REVISED STRUCTURES OF TEUCRINS F AND G*†

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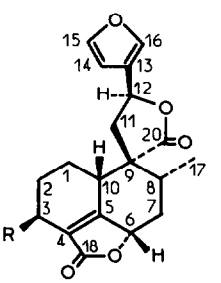
Key Word Index—*Teucrium chamaedrys*, Labiatae, diterpenoids, neo-clerodane derivative, isoteuflidin, teucrin F, teucrin G

Abstract—A new neo-clerodane diterpenoid, isoteuflidin, was isolated from the aerial part of *Teucrium chamaedrys* Its structure, 15,16-epoxy-3β-hydroxy-19-nor-neo-cleroda-4,13(16),14-triene-18,6α 20,12*S*-diolide, was established mainly by spectroscopic means and by comparison with closely related compounds In addition, the previously proposed structures for teucrins F and G [15,16-epoxy-4β,7α-dihydroxy-neo-cleroda-2,13(16),14-triene-18,19 20,12*S*-diolide and 2ξ,3ξ 15,16-diepoxy-4β,7ξ-dihydroxy-neo-cleroda-13(16),14-diene-18,19 20,12*S*-diolide, respectively] were revised establishing that their secondary hydroxyl group must be placed at the C-6β position instead of the C-7 position

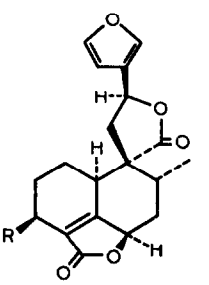
INTRODUCTION

The diterpenoids of *Teucrium chamaedrys* L (Labiatae) have been the subject of a number of investigations [1–10] In continuation of our work [7–10] on this botanical species we have isolated a new diterpenoid, isoteuflidin (**1**), from a sample of plant material collected in Spain In addition, from *T chamaedrys* collected in Italy we have now isolated six neo-clerodane diterpenoids teucvin (**3**) [11–13], teucvidin (**4**) [13], teuflin [6, 14], teucrin A [1–4, 6, 7] and a mixture of teucrins F and G [1, 5, 6] Two of these diterpenoids, teucvin (**3**) and teucvidin (**4**), have not been previously described as constituents of *T chamaedrys* collected in Spain [7–10] and in eastern Europe [1–6], showing that the nature of the diterpenoid fraction of *T chamaedrys* collected in different countries is not the same, as we have pointed out earlier [15] for other *Teucrium* spp

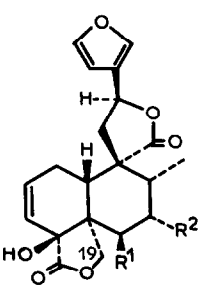
Furthermore, from a chemotaxonomic point of view it is important to note that teucrins F (**5**) and G (**6**), together with teucrin B [5, 6], are the only neo-clerodane diterpenoids isolated from *Teucrium* species for which structures lacking the common C-6 oxygenated function have been attributed However, a careful spectroscopic study of the monoacetyl derivatives of teucrins F and G showed that the structures of these diterpenoids are correctly represented by the formulae **7** and **8**, respectively, instead of the formulae **5** and **6** [5, 6] Thus, teucrin B [5, 6] is for the present the only neo-clerodane diterpenoid found in *Teucria* which is not oxidized at the C-6 position, but, in our opinion, the structure attributed to this



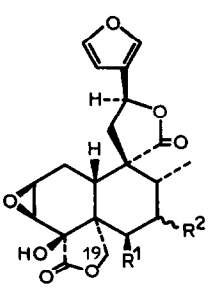
1 R OH
3 R H



2 R OH
4 R H



	R^1	R^2
5	H	OH
7	OH	H
9	OAc	H



	R^1	R^2
6	H	OH
8	OH	H
10	OAc	H

*Dedicated to the memory of the late Professor Dr Luis M Sánchez de la Torre, University of Oviedo, Spain

†This work is a part of the Ph D Thesis of M -C Rodríguez

compound [15,16-epoxy-1ξ,7ξ-dihydroxy-neo-clerodа-13(16),14-diene-18,19 20,12-diolide] [5, 6] requires further support

RESULTS AND DISCUSSION

Isoteuflidin (**1**) had a $C_{19}H_{20}O_6$ molecular formula and its ^{1}H NMR spectrum (Table 1) was almost identical with that reported for teuflidin (**2**), a diterpenoid previously found in *T flavum* [16] and *T chamaedrys* [9], whose structure was firmly established by its X-ray diffraction analysis [16] In fact, the only remarkable difference between the ^{1}H NMR spectra of compounds **1** and **2** was the signal due to the C-10 proton, which appeared at δ 3 27 in **2** [16] and at higher field in **1** (δ 2 69, Table 1) This behaviour clearly established that isoteuflidin (**1**) possessed its C-10 hydrogen atom *trans* to the C-20 lactone function and, consequently, it had an H-10β configuration [9, 11–14, 16] Moreover, the C-6 proton resonance of the new diterpenoid (**1**, $\delta_{H\text{-}6}$ 4 80) was in agreement with a C-6α configuration for the closure of the C-18–C-6 lactone ring [9, 12, 13], because in the 10β-neoclerodan-4-en-18,6β-olide derivatives such as teuflin [14] and 6-epiteucrin A [9] the C-6α proton appeared at lower field (δ 5 75 and 5 85, respectively) than in isoteuflidin (**1**) Thus, it was clear that isoteuflidin possessed H-6β and H-10β configurations as in teucvin (**3**) [11–13] and teucrin A [1–4, 7, 9] Inspection of the ^{13}C NMR spectra (Table 2) of isoteuflidin (**1**), teuflidin (**2**) [16] and teucvin (**3**) [16, 17] confirmed all the above conclusions and established that the secondary hydroxyl group of compound **1** was at the C-3 position as in teuflidin (**2**) [16] The C-3–C-5 and C-18 carbon atom resonances of the new diterpenoid (**1**) were almost identical (Table 2) with those of teuflidin (**2**), and the C-6–C-9, C-11–C-17 and C-20 carbon atom resonances were identical in **1** and teucvin (**3**), whereas the variations observed in the $\delta_{C\text{-}1}$, $\delta_{C\text{-}2}$, $\delta_{C\text{-}4}$ and $\delta_{C\text{-}10}$ values (Table 2) were in complete agreement with the structural differences between these three compounds [9, 14, 16, 17]

Furthermore, isoteuflidin (**1**) and teucvin (**3**) showed identical CD curves for their α,β-unsaturated γ-lactone chromophore (see Experimental and ref [13]), thus establishing the same absolute configuration in both compounds Application of Horeau's method [18] to isoteuflidin (**1**, see Experimental) established as *S* the stereochemistry of its C-3 hydroxyl group, and thus a 3β-

Table 1 ^{1}H NMR data of compounds **1**, **9** and **10** (300 MHz, $CDCl_3$, TMS as internal standard, *J* values in Hz)*

	1	**9**	**10**
H-1α	†	2 12‡	1 90 *td*
			$J_{1\alpha\ 1\beta} = J_{1\alpha,10\beta} = 13\ 6$, $J_{1\alpha\ 2\alpha} = 1\ 8$
H-1β	†	2 58‡	2 57‡
H-2	†	6 10 *ddd*	3 62 *dt*
		$J_{2\ 3} = 9\ 8$, $J_{2\ 1A} = 5\ 3$, $J_{2\ 1B} = 2\ 2$	$J_{2\alpha,3\alpha} = 3\ 6$, $J_{2\alpha\ 1\alpha} = J_{2\alpha\ 1\beta} = 1\ 8$
H-3	4 57 *m*	5 55 *ddd*	3 25 *d*
	$W_{1/2} = 8$	$J_{3\ 2} = 9\ 8$, $J_{3,1A} = 2\ 4$, $J_{3\ 1B} = 1\ 3$	$J_{3\alpha\ 2\alpha} = 3\ 6$
H-6	4 80 *tt*	5 42 *br dd*	5 33 *dd*
	$J_{6\beta\ 7\alpha} = J_{6\beta\ 7\beta} = 9$, $J_{6\beta\ 3\alpha} = J_{6\beta,10\beta} = 1\ 4$	$J_{6\alpha\ 7\alpha} = 2\ 5$, $J_{6\alpha\ 7\beta} = 3\ 5$	$J_{6\alpha\ 7\alpha} = 1\ 8$, $J_{6\alpha\ 7\beta} = 4$
H-7α	†	2 35 *td*	2 21 *ddd*
		$J_{7\alpha,7\beta} = J_{7\alpha\ 8\beta} = 14\ 6$, $J_{7\alpha,6\alpha} = 2\ 5$	$J_{7\alpha\ 7\beta} = 15$, $J_{7\alpha\ 8\beta} = 12\ 7$, $J_{7\alpha\ 6\alpha} = 1\ 8$
H-7β	†	1 70 *dt*	1 69 *dt*
		$J_{7\beta\ 7\alpha} = 14\ 6$, $J_{7\beta,8\beta} = J_{7\beta\ 6\alpha} = 3\ 5$	$J_{7\beta\ 7\alpha} = 15$, $J_{7\beta\ 6\alpha} = J_{7\beta\ 8\beta} = 4$
H-8β	†	2 12‡	2 03‡
H-10β	2 69 *td*	2 62 *dd*	2 57‡
	$J_{10\beta\ 1\alpha} = J_{10\beta\ 1\beta} = 8$, $J_{10\beta\ 6\beta} = 1\ 4$	$J_{10\beta\ 1\alpha} = 13\ 7$, $J_{10\beta\ 1\beta} = 5\ 9$	
H-11A	2 57 *dd*	2 48 *dd*	2 44 *dd*
	$J_{11A\ 11B} = 14$, $J_{11A\ 12} = 8\ 4$	$J_{11A\ 11B} = 14\ 2$, $J_{11A\ 12} = 9\ 2$	$J_{11A\ 11B} = 14.3$, $J_{11A\ 12} = 8\ 7$
H-11B	2 61 *dd*	2 56 *dd*	2 57‡
	$J_{11B\ 11A} = 14$, $J_{11B\ 12} = 8\ 7$	$J_{11B\ 11A} = 14\ 2$, $J_{11B,12} = 8\ 4$	
H-12	5 49 *dd*	5 42 *dd*	5 45 *t*
	$J_{12\ 11A} = 8\ 4$, $J_{12,11B} = 8\ 7$	$J_{12\ 11A} = 9\ 2$, $J_{12\ 11B} = 8\ 4$	$J_{12,11A} = J_{12\ 11B} = 8\ 7$
H-14	6 39 *dd*	6 41 *dd*	6 40 *dd*
	$J_{14,15} = 1\ 6$, $J_{14\ 16} = 0\ 9$	$J_{14\ 15} = 1\ 7$, $J_{14\ 16} = 0\ 7$	$J_{14\ 15} = 1\ 6$, $J_{14\ 16} = 1$
H-15	7 45 *t*	7 46 *t*	7 46 *t*
	$J_{15\ 14} = J_{15,16} = 1\ 6$	$J_{15\ 14} = J_{15\ 16} = 1\ 7$	$J_{15\ 14} = J_{15,16} = 1\ 6$
H-16	7 47 *m*, $W_{1/2} = 4$	7 47 *m*, $W_{1/2} = 3$	7 47 *m*, $W_{1/2} = 4$
Me-17	1 07 *d*, $J_{17\ 8} = 6\ 8$	1 01 *d*, $J_{17\ 8} = 6\ 8$	0 97 *d*, $J_{17\ 8} = 6\ 8$
H-19A	—	4 17 *d*, $J_{19A,\ 19B} = 11\ 4$	4 12 *d*, $J_{19A\ 19B} = 11\ 8$
H-19B	—	4 54 *d*, $J_{19B,19A} = 11\ 4$	4 53 *d*, $J_{19B\ 19A} = 11\ 8$
-OAc	—	2 05 *s*	2 05 *s*

*Spectral parameters were obtained by first order approximation All these assignments have been confirmed by double resonance experiments

†Could not be identified

‡Overlapped signal

Table 2 ^{13}C NMR chemical shifts ($CDCl_3$ solution, δ values from TMS) of compounds 1–3 and 9

	1	2*	3*	9
C-1	19 6 *t*†	17 7 *t*	21 6 *t*	25 3 *t*
C-2	30 9 *t*	29 8 *t*	19 7 *t*	125 7 *d*
C-3	58 1 *d*	58 7 *d*	24 7 *t*	129 9 *d*
C-4	127 8 *s*	128 7 *s*	126 1 *s*	76 0 *s*
C-5	165 1 *s*	165 7 *s*	162 1 *s*	48 0 *s*
C-6	78 0 *d*	76 2 *d*	78 3 *d*	68 2 *d*
C-7	35 2 *t*	35 6 *t*	35 3 *t*	32 0 *t*
C-8	35 7 *d*	36 2 *d*	35 7 *d*	33 0 *d*
C-9	53 9 *s*	52 1 *s*	53 5 *s*	51 7 *s*
C-10	42 2 *d*	38 6 *d*	41 9 *d*	37 3 *d*
C-11	40 7 *t*	38 8 *t*	40 6 *t*	42 7 *t*
C-12	71 9 *d*	72 2 *d*	71 9 *d*	72 2 *d*
C-13	125 0 *s*	125 3 *s*	124 9 *s*	124 8 *s*
C-14	108 1 *d*	107 9 *d*	108 0 *d*	108 1 *d*
C-15	144 2 *d*	144 2 *d*	144 2 *d*	144 4 *d*
C-16	139 7 *d*	139 5 *d*	139 6 *d*	139 7 *d*
C-17	16 9 *q*	14 3 *q*	17 0 *q*	16 5 *q*
C-18	172 1 *s*	172 0 *s*	173 0 *s*	177 5 *s*‡
C-19	—	—	—	69 0 *t*
C-20	175 5 *s*	177 5 *s*	175 9 *s*	176 1 *s*‡
–OAc	—	—	—	170 2 *s*
	—	—	—	21 5 *q*

*Taken from refs [16, 17]
†SFORD multiplicity
‡These assignments may be interchanged

hydroxyl configuration in the neo-clerodane hydrocarbon skeleton [19]

Finally, since the C-17 methyl proton resonances of isoteuflidin (**1**) and teucvin (**3**) were almost identical (δ 1 07 and 1 05, respectively, Table 1 and refs [11–13]), and the $\delta_{C\text{-}8}$ value was the same in both compounds (δ35 7, Table 2), it was evident [20, 21] that isoteuflidin (**1**) possessed a 12*S*-configuration such as teucvin [11–13] Thus, the new diterpenoid isolated from *T chamaedrys* collected in Spain is 15,16-epoxy-3β-hydroxy-19-nor-neocleroda-4,13(16),14-triene-18,6α 20,12*S*-diolide (**1**)

Since teucrins F and G are compounds difficult to separate chromatographically one from another [5], the mixture of these compounds was subjected to acetic anhydride–pyridine treatment for 24 hr at room temperature to afford their monoacetyl derivatives, which were easily separated by column chromatography (see Experimental) These derivatives showed physical and spectroscopic data identical with those reported [5] for the corresponding monoacetyl derivatives of teucrins F and G A careful study of the ^{1}H NMR spectra of these derivatives (Table 1) showed that, although the most significant part of the previously proposed structures for teucrins F (**5**) and G (**6**) was correct, the location of their secondary hydroxyl group must be at the C-6β position (**7** and **8**, respectively) instead of the C-7α position [5, 6] This conclusion was firmly supported by the following arguments (a) The ^{1}H NMR spectra of the monoacetyl derivatives of teucrins F (**9**) and G (**10**) showed clear patterns for a (C)–CHOAc–CH_2–CH(Me)–(C) grouping (see Table 1, signals of H-6α, H-7α, H-7β, H-8β and 3H-17) and not for an isomeric (C)–CH_2–CHOAc–CH(Me)–(C) arrangement Double resonance experiments showed that the geminal proton of the acetoxyl group (δ 5 42 and 5 33 in **9** and **10**, respectively, Table 1) was coupled only with a vicinal methylene grouping (signals at δ 1 70 and 2 35, and δ 1 69 and 2 21, in **9** and **10**, respectively), and not with the C-8 methine proton (δ 2 12 and 2 03 in **9** and **10**, respectively) (b) Neither of the two protons at C-19 in **9** and **10** showed any long-range coupling in their ^{1}H NMR spectra (Table 1) The requirement for the existence of such a long-range coupling [22, 23], which has been observed (J = 2 5 Hz) in some neo-clerodan-18,19-olides lacking a substituent at C-6 [24–26], is the existence of an axial proton at C-6 Thus, compounds **9** and **10** possessed their acetoxyl group at the C-6β position (c) The ^{13}C NMR spectrum of teucrin F monoacetate (**9**, Table 2) also confirmed this point The C-6–C-9 and C-11–C-17 carbon atom resonances of **9** (Table 2) were almost identical with those of the corresponding carbon atoms of teugin diacetate [27], a neo-clerodane diterpenoid with an isomeric structure (2β-hydroxyl, Δ^3) to that of teucrin F (**7**) The chemical shift value of the C-17 carbon atom in the monoacetyl derivative **9** (δ 16 5) excluded the C-7 position for the acetoxyl group, since, in this case, a chemical shift value between δ 10 6 and 12 0 would be expected for the C-17 carbon atom [28–30]

Accordingly from all the above data, it is evident that teucrins F and G must be represented by the formulae **7** and **8**, respectively The previous mistake in assigning the structures (**5** and **6**) of these diterpenoids might have been due to the ^{1}H NMR field (60 and/or 100 MHz) utilized in the first work [5] instead of a 300 MHz field utilized by us In addition, the reason for locating the secondary hydroxyl group of these diterpenoids at the C-7α position because the enol-acetate of the ketoderivative of teucrin F showed for its enolic proton a singlet in the ^{1}H NMR spectrum [5] was not conclusive, since in the neo-clerodane diterpenoids there are some cases in which the H-7β–H-8β and H-7 (olefinic)–H-8β coupling values are zero or close to zero [15, 31]

Finally, the configuration of the oxirane ring of teucrin G was not previously established [5], but the data collected in Table 1 show that it must be β-oriented, since the coupling values between the C-2 and C-1 protons ($J_{2,1\alpha} = J_{2,1\beta} = 1\,8$ Hz) were only compatible with a 2β,3β-oxirane configuration (see the molecular model of teucrin G)

EXPERIMENTAL

Mps are uncorr For general details on methods, see refs [7–10, 15] Plant materials were collected in July 1981, near Ciruelos del Pinar, Guadalajara, Spain (voucher specimens were deposited in the Herbarium of the Faculty of Pharmacy, Madrid 'Complutense' University), and in July 1982, at Prealpi Lombarde, Italy (voucher specimens were deposited in the Herbarium of the Dipartimento di Biologia of the University of Milan, Italy)

Isolation of isoteuflidin (**1**) Dried and finely powdered *T chamaedrys* L aerial parts (Spanish sample, 2 19 kg) were extracted with Me_2CO as previously described [7–10] The chromatographic fractions (3 5 g) containing predominantly teucrin A [1–4, 7, 9] were crystallized from Me_2CO–Et_2O yielding pure teucrin A (3 g) The crystallization solvents were evaporated to dryness to give 450 mg of a 5 1 (TLC) mixture of

teucrin A (less polar constituent, silica gel plates, EtOAc–*n*-hexane, 4 1, as eluent) and isoteuflidin (**1**) After repeated and careful column chromatography (silica gel Merck, No 7734, deactivated with 15% H_2O, eluent EtOAc–*n*-hexane, 4 1) of this mixture, 41 mg of pure **1** (0 0018% on dry plant material) were obtained mp 215–217° (from EtOAc–*n*-hexane), $[\alpha]_D^{27}$ + 156 0° (*c* 0 152, $CHCl_3$), IR ν_{max}^{KBr} cm^{-1} 3580, 3460, 3155, 3130, 2980, 2950, 2930, 2880, 1760 (br), 1720, 1695, 1603, 1505, 1475, 1380, 1355, 1270, 1180, 1020, 970, 880, 803, 730, UV λ_{max}^{EtOH} nm (log ε) 223 (3 93), ^{1}H NMR (300 MHz, $CDCl_3$) see Table 1, ^{13}C NMR (20 15 MHz, $CDCl_3$) see Table 2, EIMS (direct inlet) 75 eV, *m/z* (rel int) 344 $[M]^+$ (3), 326 (8), 300 (18), 299 (14), 281 (6), 255 (19), 232 (12), 231 (13), 204 (14), 199 (13), 187 (14), 178 (28), 173 (26), 161 (25), 149 (20), 147 (20), 133 (25), 115 (21), 105 (37), 96 (66), 95 (100), 94 (60), 91 (50), 81 (64), 77 (46), 65 (30), 53 (31), 41 (48), CD curve nm ($\Delta\varepsilon$) 264 (0), 228 (+ 14 0), 215 (0), 210 (− 6 4) (*c* 0 843, MeOH) (Found C, 66 42, H, 5 70 $C_{19}H_{20}O_6$ requires C, 66 27, H, 5 85%)

Application of Horeau's method to isoteuflidin (**1**) This was performed in the usual manner [18] Compound **1** (28 mg), (±)-α-phenyl butyric anhydride (170 mg) in pyridine (2 ml) soln, 16 hr at room temp $\alpha_1 = +0\,661$, $\alpha_2 = +0\,639$, $\alpha_1 - 1\,1\alpha_2 = -0\,042$ Configuration 3*S*

Extraction and isolation of the diterpenoids from the Italian sample Dried and finely powdered *T chamaedrys* L aerial parts (Italian sample, 1 62 kg) were extracted with Me_2CO as described above The extract (36 g) was chromatographed on a silica gel column (Merck, No 7734, deactivated with 15% H_2O, 800 g) Elution with petrol–EtOAc (3 2) yielded teucvidin (**4**, 150 mg) [13], and elution with EtOAc–petrol (3 2) yielded, in order of elution, teuflin (100 mg) [14], teucvin (**3**, 210 mg) [11–13] and 80 mg of a mixture of teucrins F and G (**7** and **8**) [1, 5, 6] Finally, elution with EtOAc yielded teucrin A (500 mg) [1–4, 6, 7]

The previously known diterpenoids were identified by their physical (mp, $[\alpha]_D$) and spectroscopic (IR, UV, ^{1}H NMR, MS) data and by comparison (mmp, TLC) with authentic samples

Preparation and isolation of teucrins F and G monoacetates (**9** *and* **10**) The mixture (70 mg) of teucrins F and G (**7** and **8**) was treated with Ac_2O–pyridine (3 ml, 1 1) for 24 hr at room temp Work-up in the usual manner yielded 71 mg of a mixture of compounds **9** and **10**, which was chromatographed on a silica gel column eluted with EtOAc–petrol (2 1) yielding pure **10** (11 mg, less polar compound) and **9** (30 mg)

6-*Acetyl teucrin F* (**9**) Mp 225–227° (EtOAc–*n*-hexane), $[\alpha]_D^{28}$ + 6 9° (*c* 0 248, $CHCl_3$), IR ν_{max}^{KBr} cm^{-1} 3440, 3155, 3130, 3050, 2980, 2940, 2890, 2860, 1790, 1770, 1735, 1605, 1510, 1480, 1375, 1270, 1160, 1030, 1005, 955, 880, 855, 790, 740, 730, 720, ^{1}H NMR (300 MHz, $CDCl_3$) see Table 1, ^{13}C NMR (20 15 MHz, $CDCl_3$) see Table 2, EIMS (direct inlet) 75 eV, *m/z* (rel int) 416 $[M]^+$ (1 2), 399 (0 8), 398 (0 7), 357 (1 6), 356 (1 6), 312 (66), 267 (24), 218 (36), 200 (20), 199 (23), 185 (24), 173 (21), 159 (24), 145 (24), 133 (26), 105 (30), 96 (73), 95 (80), 94 (36), 91 (41), 81 (54), 69 (38), 55 (18), 43 (100) (Found C, 63 59, H, 5 76 Calc for $C_{22}H_{24}O_8$ C, 63 45, H, 5 81%) Lit [5] mp 225–227°, identical IR and ^{1}H NMR spectra

6-*Acetyl teucrin G* (**10**) Mp 229–232° (EtOAc–*n*-hexane), $[\alpha]_D^{28}$ + 38 2° (*c* 0 112, $CHCl_3$), IR ν_{max}^{KBr} cm^{-1} 3400, 3155, 3145, 3130, 3060, 3020, 2985, 2970, 2940, 2890, 1775, 1770, 1740, 1600, 1505, 1475, 1375, 1250, 1195, 1170, 1160, 1040, 1025, 1010, 975, 880, 860, 850, 803, 755, 665, ^{1}H NMR (300 MHz, $CDCl_3$), see Table 1, EIMS (direct inlet) 75 eV, *m/z* (rel int) 432 $[M]^+$ (3), 414 (2), 404 (1 5), 390 (2 5), 389 (3), 372 (5), 344 (4), 328 (7), 296 (4), 283 (6), 265 (5), 234 (11), 215 (15), 201 (13), 187 (13), 178 (15), 173 (15), 161 (17), 159 (18), 145 (16), 133 (20), 119 (17), 105 (28), 96 (45), 95 (71), 94 (49), 91 (40), 81 (66), 67 (19), 55 (26), 43 (100) (Found C, 60 89, H, 5 63 Calc for $C_{22}H_{24}O_9$ C, 61 10, H, 5 59%) Lit [5] a vitreous mass (no mp given), identical IR and ^{1}H NMR spectra

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