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NEO-CLERODANE DITERPENOIDS FROM *TEUCRIUM PYRENAICUM* AND *T. SUBSPINOSUM*

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Key Word Index—*Teucrium pyrenaicum*; *T. subspinosum*; Labiatae; neo-clerodane derivatives; teupyrins A and B; teuflin; teucrin H2; teucvin; 6α-hydroxyteuscordin.

Abstract—From the aerial parts of *Teucrium pyrenaicum* two new neo-clerodane diterpenoids, teupyrins A and B, have been isolated. The structures of teupyrin A [3β,12*S*-diacetoxy-4α,18; 15,16-diepoxy-6-keto-neo-cleroda-13(16),14-diene-20*R*,19-hemiacetal] and teupyrin B [6α-acetoxy-4α,18; 15,16-diepoxy-3β,12ξ,19-trihydroxy-neo-cleroda-13(16),14-diene] were established mainly by spectroscopic means and, in the case of teupyrin A, by X-ray diffraction analysis. The acetone extract of the aerial parts of *T. subspinosum* yielded four previously known neo-clerodane diterpenoids: teucvin, teuflin, teucrin H2 and 6α-hydroxyteuscordin.

INTRODUCTION

In a previous communication [1], we reported teupyrenone, teupyreinin [2] and teupyreinidin [2] as the major diterpenoid constituents of *Teucrium pyrenaicum* L. A study of the minor diterpene constituents of this plant has now allowed the isolation of two new neo-clerodane derivatives, teupyrin A (**1**) and teupyrin B (**3**).

The aerial parts of *T. subspinosum* Willd. gave four previously known compounds, teucvin [3, 4], teuflin [5, 6], teucrin H2 [7, 8] (identical with teuchamaedryn B [9]) and 6α-hydroxyteuscordin [10], as the sole diterpene constituents of this species.

RESULTS AND DISCUSSION

The first of the new diterpenoids (teupyrin A, **1**), $C_{24}H_{30}O_9$, had an IR spectrum which showed hydroxyl (3480 cm^{-1}), furanic (3150, 3130, 1505, 877 cm^{-1}), acetate (1745, 1235 cm^{-1}) and ketone (1715 cm^{-1}) absorptions. The ^1H NMR spectrum (Table 1) showed signals for a secondary methyl group (δ1.00, *d*, $J = 6.7$ Hz), a β-substituted furan ring (two α-furan protons at δ7.38 and 7.46, and one β-furan proton at δ6.44), an α,α-disubstituted oxirane ring (two protons forming an AB system at δ2.77 and 3.15, $J = 4.2$ Hz), two secondary acetoxyl groups (δ2.07, *s*, 3H, and 1.96, *s*, 3H; geminal protons at δ4.51, *dd*, and 6.02, *dd*, see Table 1) and a hemiacetalic carbon atom without vicinal protons (one-proton doublet at δ5.01, $J = 3.3$ Hz, which collapsed into a singlet after addition of D_2O). The closure of this hemiacetal group was revealed by an AB system due to a methylene group attached to a fully substituted carbon atom (δ_A2.96, δ_B4.41, $J_{AB} = 12.5$ Hz). All the above data were in complete agreement with a structure such as **1** for teupyrin A. One of the secondary acetoxyl groups must be placed at C-12, since its geminal proton appeared as the X part of an ABX system (see Table 1: H-12, H_A-11 and H_B-11 protons) at the same field (δ6.02) as a derivative of auropolin, a neo-clerodane diterpenoid possessing a C-12 acetoxyl group and whose structure was established by X-ray diffraction analysis [11]. The other acetoxyl group could be placed at the C-3 or C-6, because its geminal proton appeared as a double doublet ($J_1 = 6.6$ Hz, $J_2 = 1.5$ Hz) at δ4.51. However, position C-3 is more likely since the C-7 protons of teupyrin A (**1**) were coupled with only one vicinal proton (H-8β, see Table 1). Consequently, the ketone function of this diterpenoid (ν_{CO} 1715 cm^{-1}, δ_{CO} 208.3, *s*, Table 2) must be placed at the C-6 position, thus explaining the high field resonance of the H_A-19 proton (δ2.96), which is inside the shielding cone of the C-6 carbonyl group (see the molecular model of teupyrin A).

The C-20 stereochemistry of teupyrin A (**1**) was established by NOE experiments. Irradiation of the Me-17 protons (δ1.00) of compound **1** produced an NOE enhancement in the signal of the H-20 proton (δ5.01, 12%), thus establishing that the Me-17 and the H-20 proton were on the same side of the plane defined by the hemiacetal ring [2, 12].

In accordance with all the above assignments, acetic anhydride–pyridine treatment of teupyrin A (**1**) gave a monoacetyl derivative (**2**, $C_{26}H_{32}O_{10}$) the IR spectrum of which was devoid of hydroxyl absorption. Moreover, the ^1H NMR spectrum of compound **2** showed the hemiacetalic proton paramagnetically shifted (δ5.99).

As the configuration at C-3 and C-12 of teupyrin A (**1**) could not be established by means of ^1H and ^{13}C NMR spectroscopic data, a single-crystal X-ray determination was undertaken in order to establish the structure and absolute configuration of the derivative **2**, and thus of teupyrin A (**1**). Figure 1 shows the final molecular model of compound **2**, confirming all the above assignments and establishing a 3β and a 12*S* configuration for the two acetoxyl groups and a neo-clerodane [13] absolute stereochemistry for this diterpenoid. Table 3 gives the

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Table 1. ^{1}H NMR data of compounds 1–3 ($CDCl_3$, TMS as int. standard)*

	1†	2‡	3†
H-2β	§	§	1.36 *dddd*
H-3α	4.51 *dd*	4.50 *dd*	4.24 *dd*
H-6β	—	—	4.93 *ddd*
H-7α	2.76 *dd*	§	1.62§
H-7β	2.55 *dd*	§	1.62§
H-8β	2.19 *ddq*	§	1.80 *ddq*
H_A-11	1.68 *dd*	§	1.58 *dd*
H_B-11	2.66 *dd*	§	1.95 *dd*
H-12	6.02 *dd*	6.05 *dd*	4.78 *br d*
H-14	6.44 *dd*	6.39 *dd*	6.37 *dd*
H-15	7.38 *t*	7.40 *m*	7.38 *t*
H-16	7.46 *m*	7.40 *m*	7.36 *m*
Me-17	1.00 *d*	1.08 *d*	0.79 *d*
H_A-18	2.77 *d*	2.75 *d*	2.81 *d*
H_B-18	3.15 *d*	3.18 *d*	2.84 *d*
H_A-19	2.96 *d*	3.01 *d*	3.97 *td***
H_B-19	4.41 *d*	4.21 *d*	4.31 *d*
H-20	5.01 *d* ¶	5.99 *s*	—
Me-20	—	—	0.63 *s*
OAc	2.07 *s*	2.17 *s*	2.06 *s*
	1.96 *s*	2.09 *s*	—
	—	1.98 *s*	—
OH‖	2.77 *d*	—	2.46 *d*
J (Hz)			
2β,2α	§	§	11.5
2β,1α	§	§	11.5
2β,1β	§	§	4.7
2β,3α	1.5	5.4	11.5
3α,2α	6.6	7.0	4.5
6β,7α	—	—	8.9
6β,7β	—	—	6.5
7α,7β	15.8	§	§
7α,8β	10.6	§	9.5
7β,8β	6.5	§	6.4
8β,17	6.7	7.0	6.6
11A,11B	16.0	§	15.9
11A,12	2.4	2.4	2.2
11B,12	11.6	10.0	8.8
12,16	0	0	0.9
14,15	1.7	1.8	1.8
14,16	0.7	0.9	0.9
15,16	1.7	§	1.8
18A,18B	4.2	3.8	3.8
19A,19B	12.5	13.2	12.1
19A,6β	—	—	1.2
OH,19A‖	—	—	12.1
OH,20‖	3.3	—	—

*Spectral parameters were obtained by first order approximation. All these assignments have been confirmed by double resonance experiments.
†At 300 MHz.
‡At 90 MHz.
§Overlapped signal.
¶Collapsed into *s* after addition of D_2O.
‖Disappeared after addition of D_2O.
**Collapsed into *dd* after addition of D_2O.

Table 2. ^{13}C NMR chemical shifts of compounds 1 and 3 ($CDCl_3$, TMS as int. standard)

C	1	3	C	1	3
1	19.0 *t**	20.6 *t*	13	125.8 *s*	130.9 *s*
2	27.2 *t*	32.0 *t*†	14	108.7 *d*	108.2 *d*
3	72.7 *d*	66.1 *d*	15	143.4 *d*	143.7 *d*
4	55.8 *s*	68.2 *s*	16	140.1 *d*	138.3 *d*
5	39.9 *s*	46.5 *s*	17	16.1 *q*	15.4 *q*
6	208.3 *s*	74.6 *d*	18	52.1 *t*	42.0 *t*
7	47.9 *t*	32.6 *t*†	19	55.8 *t*	61.7 *t*
8	37.0 *d*	35.0 *d*	20	94.5 *d*	17.3 *q*
9	48.3 *s*	39.0 *s*	OAc	170.2 *s*	169.6 *s*
10	40.6 *d*	48.1 *d*		169.9 *s*	—
11	35.1 *t*	44.6 *t*		21.6 *q*	21.4 *q*
12	64.8 *d*	63.0 *d*		21.1 *q*	—

*SFORD multiplicity.
†These assignments may be reversed.

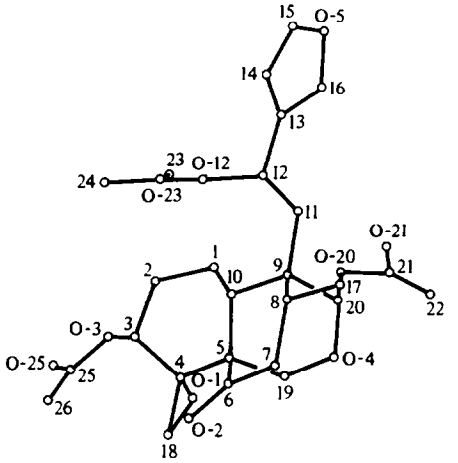


Fig. 1. X-ray molecular model of compound 2.

conformational and configurational analysis for the rings [14, 15] and for their substituents, and also the parameters which define as *S* the configuration of the C-12 asymmetric centre. The *trans*-decalin moiety of compound 2 possesses a twist-boat conformation for ring A and a chair conformation for ring B. This conformation of ring A explains the unusual $J_{3\alpha,2\alpha}$, $J_{3\alpha,2\beta}$ values found in teupyrin A (1, 6.6 and 1.5 Hz, respectively) and its derivative 2 (7.0 and 5.4 Hz, respectively), since in compounds possessing ring A with a chair conformation, such as teulanigeridin [16], the geminal proton of a 3β-acetoxyl group shows $J_{3\alpha,2\alpha}$ and $J_{3\alpha,2\beta}$ values of 5.9 and 11.3 Hz, respectively.

The other new diterpenoid isolated from *T. pyrenaicum*, teupyrin B (3, $C_{22}H_{32}O_7$), showed hydroxyl (3580, 3440 cm^{-1}), furanic (3160, 3150, 1505, 880 cm^{-1}) and acetate (1735, 1250 cm^{-1}) absorptions in its IR spectrum. The ^{1}H and ^{13}C NMR spectra of teupyrin B (3, Tables 1 and 2, respectively) were almost identical with those of teumassilin (4), a neo-clerodane diterpenoid previously isolated from *T. massiliense* [17]. In fact, the only differences were consistent with the presence in the former of an acetoxyl group at the C-6α position (δ2.06, *s*, 3H; ^{13}C NMR signals at δ169.6, *s* and 21.4, *q*; geminal proton

Table 3. Conformational and configurational characteristics of compound 2*

(a) Torsion angles for the rings. Cremer's [14] and Duax's [15] parameters

Ring	τ^1	τ^2	τ^3	τ^4	τ^5	τ^6	τ^7	τ^8	Q(Å)	θ(°)	ϕ(°)	(Å)
A	67	−40	−20	54	−26	−31			0.71	96	−144	$D_2^{10-1} = 0.030$
B	54	−44	44	−56	66	−64			0.58	162	120	$D_s^7 = 0.004$
C	−52	53	−57	55	−51	52			0.53	5	−104	$D_s^{20} = 0.006$
D	4	−6	5	−2	−1				0.05		−119	$D_s^{16} = 0.008$
E	−68	−44	44	61	−61	−57	53	64				$D_s^7 = 0.014$

(b) Configurational angles (°) for the substituents of the rings

Configurational angle	Substituent angle	Ring angle
ρO(3) [C(5)-C(4)-C(3)-O(3)] = τ_0	[C(5)-C(4)-C(3)-O(3)] − τ^1	[C(5)-C(4)-C(3)-C(2)] = −66 − 54 = −120(β)
ρO(20) [C(10)-C(9)-C(20)-O(20)] = τ_0	[C(10)-C(9)-C(20)-O(20)] − τ^1	[C(10)-C(9)-C(20)-O(4)] = 70 + 52 = 122 (α)
ρC(17) [C(10)-C(9)-C(8)-C(17)] = τ_0	[C(10)-C(9)-C(8)-C(17)] − τ^1	[C(10)-C(9)-C(8)-C(7)] = −178 − 54 = −232 ≡ 128 (α)
ρH(10) [C(2)-C(1)-C(10)-H(10)] = τ_0	[C(2)-C(1)-C(10)-H(10)] − τ^1	[C(2)-C(1)-C(10)-C(5)] = −45 − 67 = −112 (β)

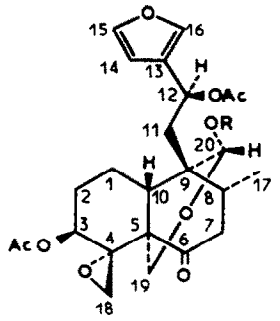
(c) Configuration at the asymmetric C(12) centre and conformation of its substituents

$\rho^1 = \tau^1 - \tau_0$ = [C(9)-C(11)-C(12)-O(12)] − [C(9)-C(11)-C(12)-H(12)] = −69 − 46 = −115
$\rho^2 = \tau^2 - \tau_0$ = [C(9)-C(11)-C(12)-C(13)] − [C(9)-C(11)-C(12)-H(12)] = 173 − 46 = 127

C(12) → *S*

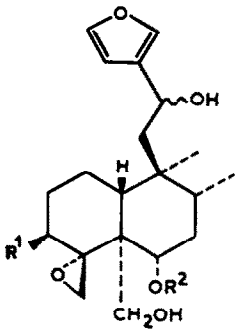
Angle	Conformation
C(9)-C(11)-C(12)-O(12) = −69 (°)	(−sc)
C(9)-C(11)-C(12)-C(13) = 173	(ap)
C(9)-C(11)-C(12)-H(12) = 46	(sc)

*The sense of the rotation is clockwise and the starting point for each ring is: ring A: τ^1 [C(1)-C(10)]; ring B: τ^1 [C(9)-C(8)]; ring C: τ^1 [C(9)-C(20)]; ring D: τ^1 [C(15)-O(5)]; ring E: τ^1 [C(9)-C(8)].



1 R = H

2 R = Ac



	R^1	R^2
3	OH	Ac
4	H	H

at δ4.93, *ddd*, $J_{6\beta,7\alpha}$ = 8.9 Hz, $J_{6\beta,7\beta}$ = 6.5 Hz, $J_{6\beta,19A}$ = 1.2 Hz) and a 3β-hydroxyl group (axial geminal proton at δ4.24, *dd*, $J_{3\alpha,2\alpha}$ = 4.5 Hz, $J_{3\alpha,2\beta}$ = 11.5 Hz; $\delta_{C\text{-}3}$ 66.1, *d*) [16] instead of the C-6α hydroxyl group (H-6β at δ3.61, *ddd*, $J_{6\beta,7\alpha}$ = 9 Hz, $J_{6\beta,7\beta}$ = 6 Hz, $J_{6\beta,19A}$ = 1 Hz) and the C-3 methylene grouping of teumassilin (**4**) [17].

On the other hand, comparison between the ^{13}C NMR spectra of compounds **3** (Table 2) and **4** [17] clearly revealed the presence of a C-6α oxygenated function in both substances, an identical stereochemistry for their C-4, C-5, C-8, C-9 and C-10 asymmetric centres, and also provided conclusive proof of the presence in teupyrin B (**3**) of an equatorial C-3 hydroxyl group. Effectively, the C-5, C-6, C-8, C-9–C-17 and C-20 carbon resonances were identical in both compounds, whereas their chemical shift differences in the C-1–C-4, C-18 and C-19 carbon atoms can only be explained by the introduction in teumassilin (**4**) of an equatorial hydroxyl group on C-3. In particular, the small γ-effect shown by the C-1 carbon atom in compound **3** ($\Delta\delta$ −0.6), compared with the larger value shown by its C-18 carbon atom ($\Delta\delta$ −6.1), clearly confirmed this point [1].

Moreover, the attachment of the acetoxyl group at the C-6α position of teupyrin B was also in agreement with the chemical shift of the C-7 carbon atom, which appeared at δ32.6 or 32.0 (see Table 2) in **3** and at δ34.1 in **4** [17]. Comparison of the chemical shifts of the H-3α, H-6β, 2H-19 and H-12 protons in compounds with free hydroxyl groups at these positions (δ4.14 [2], 3.61, 4.03 (H_A-19), 4.27 (H_B-19) and 4.70 [17], respectively) with those of the corresponding acetyl derivatives (δ5.30 [1], 4.75, 4.40 (H_A-19), 4.80 (H_B-19) and 5.90–6.00 [17], respectively) clearly established that in teupyrin B (**3**, $\delta_{H\text{-}3\alpha}$ 4.24, $\delta_{H\text{-}6\beta}$ 4.93, $\delta_{H_A\text{-}19}$ 3.97, $\delta_{H_B\text{-}19}$ 4.31 and $\delta_{H\text{-}12}$ 4.78) the C-6α hydroxyl group was acetylated.

The stereochemistry at the C-12 centre and the absolute configuration of teupyrin B were not ascertained; however, the decalin moiety of compound **3** is believed to belong to the neo-clerodane [13] series like teupyrenone [1] and teupyrin A (**1**), co-occurring in the same species. Moreover, all the diterpenoids until now isolated from *Teucrium* species [1–12, 16, 17 and references therein], and whose structures have been rigorously established, belong to the neo-clerodane series. These biogenetic reasons are not adequate for suggesting a configuration at

C-12 in teupyrin B, since there are some neo-clerodanes isolated from *Teucria* which possess a 12*R* absolute stereochemistry [2, 12], although a 12*S* configuration is the more common feature.

EXPERIMENTAL

Mps are uncorr. For general details of the collection of *T. pyrenaicum* and the extraction of the diterpenoids, see ref. [1]. *T. subspinosum* was collected in June 1984, at Majorca (Spain), and voucher specimens were deposited in the Herbarium of the Royal Botanic Garden, Madrid.

Isolation of teupyrins A (1) *and B* (3). The chromatographic fractions obtained before elution of teupyreinidin [1] were evaporated to dryness and the residue (600 mg) was chromatographed on a silica gel column (Merck No. 7734, deactivated with 10% H_2O, 100 g) eluted with *n*-hexane–EtOAc (2:1) yielding pure teupyrin A (1, 30 mg). Two chromatographic fractions obtained after elution of teupyreinin [1] were evaporated to dryness and the residue (36 mg) was crystallized from EtOAc–*n*-hexane yielding crystals of pure teupyrin B (3, 7 mg).

Extraction and isolation of the diterpenoids from T. subspinosum. Dried and finely powdered aerial parts (1 kg) of *T. subspinosum* were extracted with Me_2CO (5 l.) at room temp. for 1 week. After filtration, the solvent was evaporated yielding a gum (30 g) which was subjected to dry CC over silica gel (400 g, Merck No. 7734, deactivated with 15% H_2O). Elution with *n*-hexane, *n*-hexane–EtOAc mixtures and pure EtOAc, yielded the following compounds in order of elution: teuflin (100 mg) [5, 6], teucrin H2 (15 mg) [7–9], teucvin (15 mg) [3, 4] and 6α-hydroxyteuscordin (12 mg) [10]. These diterpenoids were identified by their physical (mp, $[\alpha]_D$) and spectroscopic (IR, ^{1}H NMR, MS) data and by comparison (mmp, TLC) with authentic samples.

Teupyrin A (1). An amorphous powder which melted at 78–90°; $[\alpha]_D^{20}$ −204.5° ($CHCl_3$; *c* 0.202); IR ν_{max}^{KBr} cm^{-1}: 3480, 3150, 3130, 2980, 2945, 1745 (br), 1715, 1505, 1440, 1375, 1235 (br), 1105, 1035, 965, 877; ^{1}H NMR (300 MHz, $CDCl_3$): see Table 1; ^{13}C NMR (75.4 MHz, $CDCl_3$): see Table 2; CIMS *m/z* (rel. int.): 463 $[M+1]^+$ (9), 445 (4), 431 (4), 403 (100), 385 (5), 373 (12), 343 (27), 325 (6), 313 (9), 295 (8), 249 (2), 247 (3), 163 (3). (Found: C, 62.05; H, 6.48. $C_{24}H_{30}O_9$ requires: C, 62.32; H, 6.54%.)

Acetylteupyrin A (2). Ac_2O–C_5H_5N treatment of 1 (20 mg) in the usual manner yielded 2 (18 mg after crystallization from MeOH): mp 167–168°; $[\alpha]_D^{24}$ −226.7° ($CHCl_3$; *c* 0.486); IR ν_{max}^{KBr} cm^{-1}: 3160, 3130, 3080, 2980, 2940, 1755 (br), 1710, 1508, 1450, 1370, 1220, 1015, 985, 960, 950, 875; ^{1}H NMR (90 MHz, $CDCl_3$): see Table 1; EIMS (direct inlet) 75 eV, *m/z* (rel. int.): $[M]^+$ absent, 444 $[M-60]^+$ (1), 402 (0.3), 384 (0.5), 325 (1), 265 (1.2), 234 (1.3), 187 (1.6), 167 (4), 97 (5), 94 (3), 91 (5), 81 (5), 69 (4), 43 (100). (Found: C, 61.96; H, 6.21. $C_{26}H_{32}O_{10}$ requires: C, 61.89; H, 6.39%.)

X-Ray structure determination of compound 2. Compound 2 ($C_{26}H_{32}O_{10}$) crystallizes in the space group $P2_12_12_1$, $Z = 4$, with $a = 9.0817$ (3), $b = 33.038$ (5), $c = 7.9758$ (3) Å, its M_r is 504.533 and $D_c = 1.400$ g/cm^3. A crystal of $0.2 \times 0.25 \times 0.32$ mm was used to measure the intensities of 2509 independent Friedel pairs up to $\theta = 65°$. The data were collected on a computer-controlled four-circle diffractometer, using graphite-monochromated CuKα radiation ($\lambda = 1.5418$ Å) and $\omega/2\theta$ scan technique and a scan speed of 1°/min were used. No crystal decomposition was observed during the experiment. No absorption correction was used ($\mu = 8.590$ cm^{-1}). The structure was solved by MULTAN [18], and refined using the 2127 observed reflexions with $I > 2\sigma(I)$. Not all the hydrogen atoms were located on a difference map. In some of the methyl groups their H-atoms were fixed at idealized positions (C–H = 1.00 Å, and H–C–H = 100°) and all of them were included as fixed isotropic contributors in the refinement. Then, a weighting scheme was selected to prevent bias in $\langle w\Delta^2F \rangle$ vs. $\langle F_o \rangle$ and vs. $\langle \sin\theta/\lambda \rangle$. Several cycles of weighted anisotropic refinement using both *hkl* and $\overline{hkl}$ reflexions converged to $R_w = 0.063$ and $R_w = 0.0$ [19].

The absolute configuration of compound 2 was determined using the more relevant Bijvoet pairs with $F_o > 10\sigma(F_o)$. There were 81 pairs with $\Delta F_c > 0.10$, the averaged Bijvoet difference for these were 0.555 for the correct enantiomer vs. 0.638 for the wrong one [20].

The asymmetric parameters for the rings of compound 2 show [15] that ring A has a rotational dominant symmetry but in rings B and C the mirror symmetry is dominant.

A list of structure factors, atomic and anisotropic thermal parameters, hydrogen atom parameters, bond distances, bond angles, torsion angles and conformational parameters are deposited in the Cambridge Crystallographic Data Centre.

Teupyrin B (3). Mp 213–215° (EtOAc–*n*-hexane), $[\alpha]_D^{26}$ +7.1° (MeOH; *c* 0.126); IR ν_{max}^{KBr} cm^{-1}: 3580, 3440, 3160, 3150, 2940, 2880, 1735, 1505, 1455, 1380, 1250, 1090, 1045, 1025, 880; ^{1}H NMR (300 MHz, $CDCl_3$): see Table 1; ^{13}C NMR (75.4 MHz, $CDCl_3$): see Table 2; EIMS (direct inlet) 75 eV, *m/z* (rel. int.): $[M]^+$ absent, 390 $[M-18]^+$ (0.4), 348 (0.2), 330 (0.4), 299 (1), 281 (1), 206 (6), 188 (8), 187 (7), 159 (6), 145 (6), 119 (6), 105 (7), 96 (21), 94 (18), 91 (8), 81 (9), 69 (13), 55 (10), 43 (100). (Found: C, 64.37; H, 7.86. $C_{22}H_{32}O_7$ requires: C, 64.68; H, 7.90%.)

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