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Methyl dodonates, a new type of diterpenes with a modified clerodane skeleton from *Dodonaea viscosa*☆

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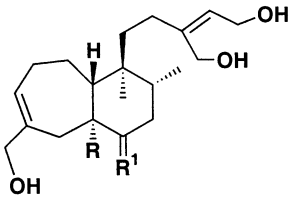
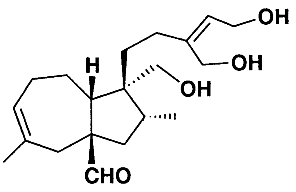
Abstract—Three new modified clerodanes (**10**, **12**, **17**) containing a tricyclo[5.4.0.0^{1,3}]undecane ring system were isolated from *Dodonaea viscosa*. These types of compounds have not been found in nature until now, but they have been proposed as hypothetical intermediates in the biogenetic pathway of diterpenes possessing bicyclo[5.4.0]undecane or bicyclo[5.3.0]decane ring systems. In support of this hypothesis, **17** was transformed into the bicyclo[5.4.0]undecane derivative **20**. Additionally, we isolated the new 5,10-secoclerodane **21** and several known diterpenes. The structures were elucidated by spectroscopic methods, chemical reactions and X-ray diffraction analysis. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Clerodanes whose decaline nucleus has been modified to a bicyclo[5.4.0]undecane (like jewenol B (**1**)[1] or pilosanone B (**2**)[2]) or to a bicyclo[5.3.0]decane (like portulal (**3**)[3]) have been isolated from several *Portulaca* species (Portulacacea) and also from some species of Asteraceae.[7,8] Several biogenetic pathways[2–7] have been postulated to explain the formation of their unique structures. Most of them[2,4–6] (Scheme 1) propose a cyclopropyl clerodane diterpenoid (tricyclo[5.4.0.0^{1,3}]undecane) as the key intermediate in the process. These types of compounds have not been found so far in nature, but they have been synthesized from the hydroxy-acid **7**.[9,10]



1 R = OH, R^1 = 2 H
2 R = H, R^1 = O



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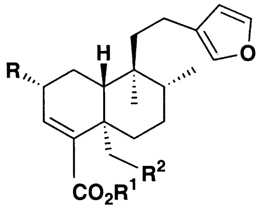

4 R = R^1 = H, R^2 = OH
5 R = H, R^1 = Me, R^2 = OH
6 R = OH, R^1 = Me, R^2 = H

In our ongoing search for new metabolites, we have isolated the methyl dodonates A (**10**), B (**12**) and C (**17**) from *D. viscosa*. These new clerodane derivatives contain a tricyclo[5.4.0.0^{1,3}]undecane nucleus. In addition, the new 5,10-secoclerodane, dodonolide (**21**), the known clerodanes **4**, **6** and **7**, and the labdane diol **9**, were isolated from the plant. This paper describes the structure elucidation of the new compounds and the transformation of methyl dodonate C (**17**) into **20**, a compound with a

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Keywords: natural products; terpenes and terpenoids; clerodanes; diterpenes.

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† In memoriam.

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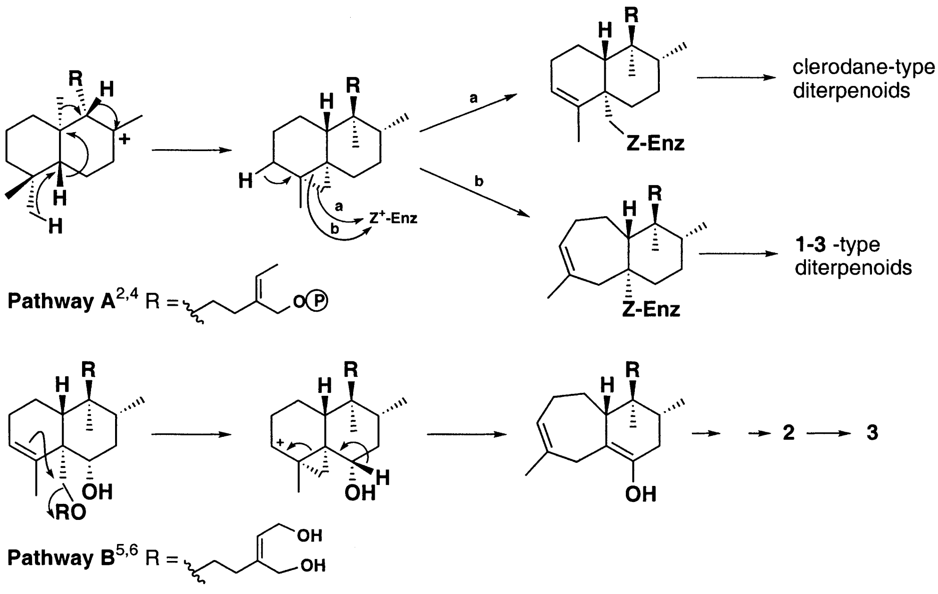
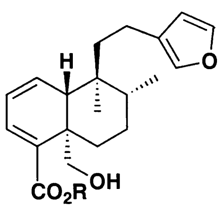
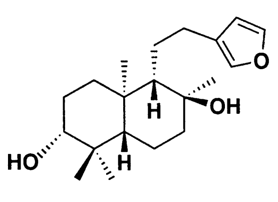


Scheme 1. Proposed biogenetic pathways of *Portulaca*-type diterpenes.

bicyclo[5.4.0]undecane ring system. This transformation and the chemical composition found in *D. viscosa* could provide significant clues in the understanding of the biogenesis of these diterpenes.



7 R = H
8 R = Me



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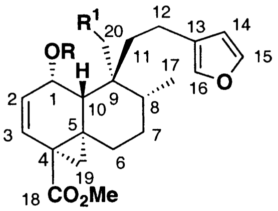
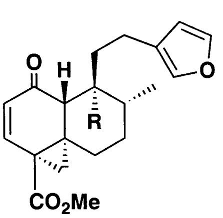
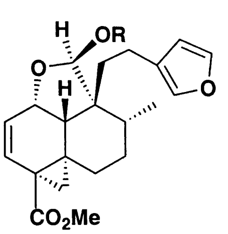


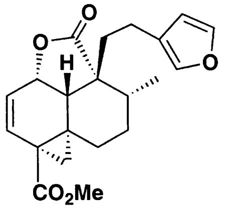
10 R = R^1 = H
11 R = Ac, R^1 = H
12 R = H, R^1 = OH
13 R = H, R^1 = OAc
14 R = R^1 = OAc



15 R = Me
16 R = CHO



17 R = H
18 R = Ac



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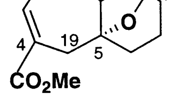

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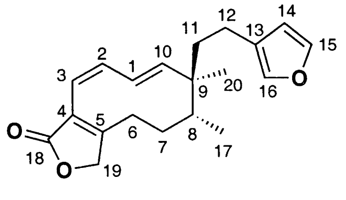

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2. Results and discussion

The fresh leaves of *D. viscosa* were rinsed with EtOAc. The concentrated extract crystallized spontaneously to afford large amounts of a mixture of hautriwaic acid (**4**)[11–13] and its dehydroderivative **7**[9,14] (ca 4:1 ratio). These compounds were characterized as the methyl esters **5** and **8**. Exhaustive chromatographic purifications of the non-methylated mother liquors of **4** and **7** gave 2α-hydroxy methyl

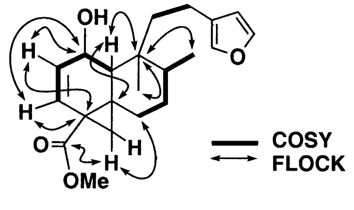

Figure 1. Planar structure of methyl dodonate A (**10**).

Table 1. ^{1}H NMR data of compounds **10**–**21**

H	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**
1	4.47 dd 6.3, 4.2	5.50 dd 6.3, 4.5	4.34 dd 6.6, 3.6	4.47 dd 6.6, 3.6	5.52 dd 6.5, 4.4	–	–	4.68 dd 6.3, 3.9	4.74 dd 6.3, 3.5	4.93 dd 6.5, 4.2	6.41 dd 12, 5.5	5.78 dd 17, 2.4
2	5.75 dd 9.9, 6.3	5.79 dd 9.9, 6.3	5.80 dd 10, 6.6	5.79 dd 10, 6.6	5.79 dd 10.2, 6.5	5.73 d 10.2	5.81 d 10.2	5.63 dd 10, 6.3	5.63 dd 10, 6.3	5.68 dd 9.9, 6.5	5.81 ddd 12, 5.5, 2	6.30 dd 11.4, 2.4
3	6.46 d 9.9	6.51 d 9.9	6.47 d 10	6.47 d 10	6.51 d 10.2	7.25 d 10.2	7.36 d 10.2	6.66 d 10	6.68 d 10	6.87 d 9.9	6.76 d 5.5	6.03 d 11.4
6	1.56 m^{a}	1.70 m^{a}	1.62 m^{a}	1.5–1.8 m^{a}	1.5–1.9 m^{a}	1.70 m^{a}	1.95 m^{a}	1.85 m^{a}	1.95–2.05 m^{a}	1.8–1.94 m^{a}	1.5–1.8 m^{a}	2.20 m^{a}
	1.56 m^{a}	1.50 m^{a}	1.50 m^{a}	1.5–1.8 m^{a}	1.5–1.9 m^{a}	1.58 m^{a}	1.60 m^{a}	1.50 m^{a}	1.42 m^{a}	1.45–1.65 m^{a}	1.5–1.8 m^{a}	2.20 m^{a}
7	1.42 m^{a}	1.70 m^{a}	1.40 m^{a}	1.5–1.8 m^{a}	1.78 m^{a}	1.58 m^{a}	1.70 m^{a}	1.82 m^{a}	1.85 dt 10.2, 5.4	1.8–1.94 m^{a}	1.5–1.8 m^{a}	1.76 br
	1.42 m^{a}	1.50 m^{a}	1.40 m^{a}	1.5–1.8 m^{a}	1.60 m^{a}	1.58 m^{a}	1.70 m^{a}	1.42 m^{a}	1.54 m	1.45–1.65 m^{a}	1.5–1.8 m^{a}	1.60 m^{a}
8	1.62 m^{a}	1.65 m^{a}	1.68 m^{a}	1.76 m^{a}	1.72 m^{a}	1.70 m^{a}	1.80 m^{a}	2.00 m^{a}	1.95–2.05 m^{a}	2.07 qd 6.9, 3.3	1.78 brq 6.5	1.54 m^{a}
10	1.68 d 4.2	1.89 d 4.5	1.76 d 3.6	1.86 d 3.6	2.04 m^{a}	2.65 s	2.97 s	2.13 d 3.9	2.17 d 3.5	2.28 d 4.2	2.35 dd 5.5, 2	5.85 d 17
11	1.93 ddd 14.7, 12.9, 4.2	1.70 m^{a}	2.03 td 14.4, 3.6	1.90 m^{a}	1.90 m^{a}	2.86 ddd 14.1, 12.9, 5	2.65 m^{a}	1.7–2.1 m^{a}	1.95–2.05 m^{a}	2.16 ddd 15, 11, 6.5	2.11 ddd 15, 11, 8	1.64 m^{a}
	1.78 ddd 14.7, 12.9, 5.4	1.52 m^{a}	1.71 m	1.90 m^{a}	1.50 m^{a}	1.58 m^{a}	2.35 m^{a}	1.7–2.1 m^{a}	1.95–2.05 m	1.95 ddd 15,11.2, 6	1.83 dd 15, 6.5	1.42 m^{a}
12	2.43 td 14.7, 5.4	2.40 td 14.2, 5.4	2.38 td 14.4, 4.6	2.2–2.5 m^{a}	2.41 td 14.2, 5.3	2.37 td 12.9, 4.5	2.45 m^{a}	2.44 td 14, 4.5	2.35–2.5 m	2.46–2.62 m^{a}	2.64 dddd 17, 11, 6.5, 2	2.26 m^{a}
	2.31 td 14.7, 4.2	2.31 td 14.2, 4.5	2.22 td 14.4, 3.6	2.2–2.5 m^{a}	2.33 td 14.2, 4.1	2.20 td 12.9, 5	2.30 m^{a}	2.37 td 14, 6	2.35–2.5 m	2.46–2.62 m^{a}	2.47 dd 17, 8	2.26 m^{a}
14	6.27 dd 1.7, 0.9	6.32 brs	6.25 brs	6.28 brs	6.33 brs	6.28 brs	6.27 brs	6.27 brs	6.27 brs	6.26 dd 1.8, 0.9	6.06 d 2	6.23 brs
15	7.35 t 1.7	7.34 t 1.5	7.32 t 1.5	7.37 t 1.5	7.35 t 1.5	7.32 t 1.5	7.36 brs	7.35 brs	7.36 t 1.5	7.37 t 1.8	7.30 dd 2, 0.5	7.32 t 1.5
16	7.22 brs	7.23 brs	7.21 brs	7.24 brs	7.24 brs	7.21 m	7.24 brs	7.25 brs	7.25 brs	7.24 brs	–	7.17 brs
17	0.87 d 6	0.88 d 6	0.95 d 6.9	1.04 d 6.6	1.05 d 6.3	0.90 d 6.6	1.06 d 6.6	1.05 d 6.6	0.92 d 6.9	1.38 d 6.9	0.90 d 6.5	0.87 d 6.5
19$_{\text{pro-R}}$	1.94 d 4.5	1.98 d 4.5	1.90 d 4.2	1.92 d 4.5	1.96 d 4.5	2.15 d 4.5	2.21 d 4.8	1.66 d 3.6	1.68 d 3.3	1.64 d 4.2	2.73 d 13.5	4.73 d 17.5
19$_{\text{pro-S}}$	1.59 d 4.5	1.52 d^{a} 4.5	1.71 d 4.2	1.72 d 4.5	1.52 d 4.5	0.85 d 4.5	1.06 ^{a}	1.35 ^{a}	1.44 ^{a}	1.25 d 4.2	2.45 d 13.5	4.62 d 17.5
20	1.15 s	1.01 s	4.14 d 12 3.41 d 12	4.68 d 12 4.58 d 12	4.57 d 12 4.45 d 12	0.97 s	9.81 s	5.51 s	5.23 s	–	4.78 s	1.04 s
OMe	3.72 s	3.73 s	3.70 s	3.73 s	3.74 s	3.78 s	3.79 s	3.73 s	3.72 s	3.75 s	3.75 s	
OAc		2.02 s		2.06 s	2.04 s				2.05 s			

Spectra recorded in $CDCl_3$ solutions at 300 or 500 MHz.

[a] Superimposed signals.

hardwickate (**6**),[10,15] *ent*-15,16-epoxy-9αH-labda-13(16), 14-diene-3β, 8α-diol (**9**),[16] methyl dodonates A (**10**), B (**12**) and C (**17**) and dodonolide (**21**).

The mass spectrum of methyl dodonate A (**10**) showed a molecular ion at *m/z* 344, in agreement with the molecular formula $C_{21}H_{28}O_4$. The ^{1}H NMR spectrum showed some similarities with those of compounds **4–8** such as the presence of a β-substituted furan [(IR: 1500, 873 cm^{-1}), δ_H 6.27 (1H, dd, J=1.7, 0.9 Hz), 7.35 (1H, t, J=1.7 Hz) and 7.22 (1H, m)], a secondary [δ_H 0.87 (3H, d, J=6 Hz)] and a tertiary [δ_H 1.15 (3H, s)] methyl groups. In addition, the IR absorption at 1717 cm^{-1} and the signals at δ_H 3.72 (3H, s), and δ_C 172.6 (s) and 52.1 (q), revealed the presence of a carbomethoxy group in the molecule. All these facts allowed us to propose a clerodane type skeleton for compound **10**. This compound also possesses a methine bearing a hydroxyl group [IR: 3470 cm^{-1}, δ_H 4.47 (1H, dd, J=6.3, 4.2 Hz), δ_C 64.5, d], a double bond [IR: 1650 cm^{-1}, δ_H 5.75 (1H, dd, J=9.9, 6.3 Hz), 6.46 (1H, d, J=9.9 Hz), δ_C 124.7 (d) and 131.4 (d)], five sp^3 methylenes, two sp^3 methines and three quaternary sp^3 carbons. The ^{1}H–^{1}H COSY spectrum revealed connectivities from C-10 to C-3 in ring A, C-6 to C-17 in ring B and C-11 to C-12 (Fig. 1). This spectrum also showed the presence of an isolated methylene whose proton signals appeared as an AB system at δ_H 1.94 and 1.59 (J=4.5 Hz) and correlated, in the HETCOR spectrum, with the signal at δ_C 32.8 (t). The long-range ^{1}H–^{13}C correlations exhibited by the FLOCK spectrum (Fig. 1) confirmed that **10** possessed a clerodane-type framework and established, by the cross peaks of the signal at δ_H 1.94 with C-6 and C-18, that the isolated methylene corresponds to C-19. The geminal coupling constant of the C-19 methylene protons (4.5 Hz) and the chemical shift of the quaternary carbons C-4 (δ_C 30.1) and C-5 (δ_C 34.1) led us to propose that C-19 is part of a cyclopropane ring. The presence of this ring satisfies the eight degrees of unsaturation required by the molecular formula. The ^{13}C NMR data (Table 2) provided strong support for the proposed structure. The assignments were deduced from HETCOR and FLOCK spectra. Thus, the planar structure of methyl dodonate A was assigned as **10**, a modified clerodane containing a tricyclo[5.4.0.0^{1,3}]undecane ring system. We suggest the name dodonane for this new carbon skeleton.

Biogenetic considerations based on the co-occurrence with compounds **4**, **6** and **7** suggested the relative stereochemistry of a neo-clerodane diterpene for **10**. Comparison of the chemical shift of the C-17 and C-20 methyl groups with those of related compounds,[6,17,18] suggested an A/B *trans* ring junction. Consequently, the cyclopropane ring must be α-oriented. The H-1/H-10 coupling constant (4.2 Hz) indicated a β-equatorial disposition of H-1 and therefore an α-axial orientation of the C-1 hydroxy group. This orientation provided an explanation for the unusual low field shift of H-19$_{\text{pro-S}}$ (δ_H 1.59), which is due to the deshielding effect of an α-axial hydroxy group, that is coplanar to C-19. Another deshielding effect attributable to the C-18 carbomethoxy group was responsible for the unusual paramagnetic shift of the H-19$_{\text{pro-R}}$ (δ_H 1.94). Acetylation of compound **10** proceeded slowly and with poor yields. In the ^{1}H NMR spectrum (Table 1) of acetyl derivative **11**, the expected low field shift for H-1 was observed, but the chemical shift for the C-19 protons remained, almost the same, as in **10**. Contrarily, no deshielding effect was observed in the ^{1}H NMR spectrum of Jones oxidation product **15**, which showed H-19$_{\text{pro-S}}$ at δ_H 0.85 (d,

Table 2. ^{13}C NMR data of compounds **10–21**

C	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**
1	64.5 d	66.7 d	62.8 d	63.4 d	65.9 d	196.9 s	195.8 s	71.5 d	72.7 d	70.9 d	138.7 d	124.0 d[a]
2	124.7 d	120.7 d	124.2 d	124.4 d	120.5 d	125.5 d	124.7 d	120.1 d	119.4 d	117.0 d	126.3 d	133.2 d
3	131.4 d	132.8 d	131.7 d	131.2 d	132.7 d	145.9 d	147.4 d	135.6 d	136.0 d	138.5 d	134.9 d	119.8 d
4	30.1 s	29.9 s	30.5 s	30.7 s	30.7 s	30.8 s	31.5 s	32.8 s[b]	32.7 s	32.4 s	131.2 s	123.4 s[a]
5	34.1 s	33.4 s	32.6 s	32.6 s	32.4 s	32.3 s	32.6 s	36.7 s	36.2 s	35.0 s	95.2 s	158.4 s[a,c]
6	31.9 t	31.7 t	32.1 t	32.0 t	31.8 t[b]	31.5 t	31.3 t[b]	32.8 t[b]	30.2 t[b]	31.8 t	40.0 t	28.8 t
7	29.5 t	29.3 t	28.7 t	29.2 t	29.3 t	30.0 t	30.6 t	30.6 t	32.5 t	29.7 t	29.8 t	33.2 t[c]
8	38.3 d	38.4 d	38.7 d	38.6 d	38.5 d	37.2 d	36.6 d	32.5 d	32.4 d	33.7 d	41.8 d	41.3 d[a,c]
9	40.8 s	40.5 s	43.6 s	43.1 s	43.4 s	41.1 s	?	51.2 s	51.3 s	51.3 s	51.6 s	41.9 s
10	43.3 d	42.5 d	44.0 d	43.6 d	42.3 d	51.0 d	50.8 d	43.2 d	42.9 d	42.2 d	61.0 d	144.8 d
11	37.8 t	38.1 t	30.8 t	31.5 t	31.8 t[b]	37.1 t	31.3 t	28.8 t	30.2 t[b]	33.5 t	25.7 t	40.7 d
12	17.9 t	17.8 t	17.6 t	17.7 t	17.6 t	18.5 t	18.9 t	19.0 t	19.1 t	20.0 t	21.4 t	19.8 t
13	125.4 s	124.9 s	125.1 s	124.8 s	124.4 s	125.5 s[b]	124.4 s[b]	125.0 s	124.8 s	124.0 s	117.7 s	125.4 s
14	110.9 d	111.0 d	110.9 d	110.8 d	110.9 d	111.0 d	110.9 d	111.0 d	110.9 d	110.7 d	108.9 d	110.9 d
15	142.8 d	142.9 d	142.8 d	143.0 d	143.0 d	142.6 d	143.0 d	143.0 d	143.0 d	143.3 d	142.6 d	142.7 d
16	138.4 d	138.6 d	138.5 d	138.6 d	138.7 d	138.6 d	138.7 d	138.7 d	138.7 d	138.8 d	149.9 s	138.5 d
17	15.0 q	15.0 q	15.7 q	16.4 q	16.8 q	15.2 q	15.8 q	17.0 q	16.5 q	15.8 q	17.5 q	17.3 q
18	172.6 s	172.3 s	172.3 s	172.3 s	171.9 s	170.9 s	170.5 s	171.9 s	171.6 s	171.3 s	168.0 s	174.9 s
19	32.8 t	31.8 t	32.5 t	32.4 t	31.9 t	36.1 t	37.5 t	36.2 t	36.0 t	37.1 t	35.4 t	71.6 t
20	17.3 q	17.1 q	60.3 t	65.2 t	65.4 t	14.8 q	205.8 d	100.0 d	97.8 d	178.0 s	71.5 d	14.6 q[a]
OMe	52.1 q	52.2 q	52.2 q	52.2 q	52.3 q	52.6 q	52.6 q	52.1 q	52.1 q	52.4 q	52.0 q	–
OAc		170.2 s 21.7 q		170.6 s 21.1 q	170.7 s 170.2 s 21.5 q 21.1 q				169.9 s 21.2 q			

Spectra recorded in $CDCl_3$ solutions at 75 or 125 MHz at room temperature.

[a] Broad, low-intensity signal.

[b] Superimposed signals.

[c] Signal observed only in the spectrum determined at 55°C.

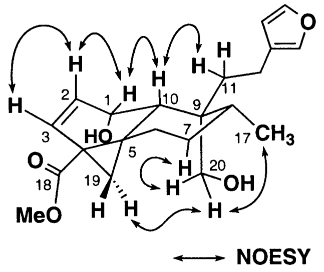

Figure 2. NOESY correlations of methyl dodonate B (**12**).

J=4.5 Hz). Other changes observed for the α,β-unsaturated ketone **15** were the low field shift of H-3 (δ_H 7.25, d, J=10.2 Hz) and H-10 (δ_H 2.65, s) and the diamagnetic shift of the C-20 methyl group. The ^{13}C NMR spectrum of **15** showed a signal for an additional ketone carbonyl group at δ_C 196.9, which supports the proposed structure (Table 2).

Methyl dodonate B (**12**) differs from **10** by the presence of an additional hydroxy group at C-20. Accordingly, the molecular peak at m/z 360 established a molecular formula $C_{21}H_{28}O_5$. The ^{1}H NMR data of **12** revealed the presence of only one methyl group (δ_H 0.95, J=6.9 Hz, H_3-17) and an additional AB system at δ_H 4.14 and 3.41 (J=12 Hz) assigned to the C-20 hydroxymethyl group. The ^{13}C NMR spectrum showed the C-20 methylene signal at δ_C 60.3. The long-range C–H couplings for H-10/C-20 and H-20 (δ_H 3.41)/C-9, C-10, confirmed the position of the hydroxymethyl group. The remaining resonances of **12** showed chemical shifts very similar to those of **10**. They were assigned by 2D-NMR experiments as shown in Tables 1 and 2. The relative stereochemistry of **12** was deduced from NOESY correlations (Fig. 2) between H-1/H-2, H-10 and H-11 which established that H-1, H-10 and the side chain at C-9 were on the same side of the molecule, biogenetically, the β-side. NOESY interactions of H-20 (δ_H 4.14)/H-7_α, H-$19_{\text{pro-S}}$ and those of H-20 (δ_H 3.41)/H-17 confirmed the α-orientation of C-17, C-20 and the cyclopropane ring (C-19).

Treatment of **12** with acetic anhydride in pyridine afforded the mono and diacetyl derivatives **13** and **14**, respectively. The keto-aldehyde **16** and the lactone **19** were obtained upon oxidation of **12** with pyridinium chlorochromate. The ^{13}C NMR spectrum of compound **16** showed three carbonyl resonances at δ_C 170.5, 195.8 and 205.8; they were assigned to the C-18 carbomethoxy, C-1 ketone and C-20 aldehyde group, respectively. In the ^{1}H NMR spectrum, the H-3 signal was observed at δ_H 7.36 and the signal for the aldehyde proton (H-20) at δ_H 9.81.

In the NMR spectra of the major oxidation product **19**, the H-1 and C-1 signals appeared shifted to lower field (δ_H 4.93; δ_C 70.9) when compared with those of **12** and a new carbonyl signal at δ_C 178.0 (C-20) was observed. Attainment of lactone **19** strongly supports the 1,3-diaxial disposition in **12** of the C-1–OH and the C-20–hydroxymethyl functionalities.

The molecular formula of methyl dodonate C (**17**) was determined as $C_{21}H_{26}O_5$ by EIMS [m/z 358 $(M)^+$]. The IR spectrum showed absorptions for hydroxyl (3374 cm^{-1}), ester (1719 cm^{-1}), double bond (1650 cm^{-1}) and β-substituted furan (1502, 872 cm^{-1}). The ^{1}H NMR spectrum of **17** was very similar to that of **12**, except for the chemical shift of H-1 (δ_H 4.68, dd, J=6.3, 3.9 Hz) and the presence of a singlet signal at δ_H 5.51 instead of the AB system of the C-20 methylene protons in **12**. In the HETCOR NMR spectrum, the signal at δ_H 5.51 correlated with the signal at δ_C 100.0 and the H-1 resonance with the signal at δ_C 71.5. These facts strongly suggested the presence of a 20,1-lactol ring in the molecule. This was supported by the attainment of γ-lactone **19** by oxidation of **17**. Accordingly, the structure of methyl dodonate C was formulated as **17**. Its relative stereochemistry (except that at C-20) was assumed to be the same as that of **10** and **12** by spectroscopic and biogenetic data considerations.

At this point, it was necessary to establish unambiguously, the structure and relative stereochemistry of the methyl

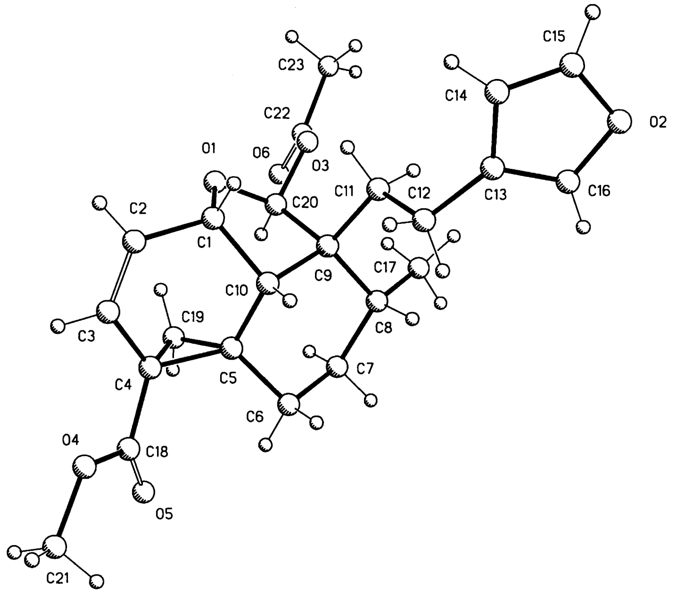

Figure 3. Stereoscopic view of compound **18**.

dodonates. This was achieved by means of an X-ray diffraction analysis on the acetyl derivative **18**, obtained by acetylation of compound **17**. The resulting thermal ellipsoid diagram obtained from data collected at 20°C is shown in Fig. 3. This result established the relative configuration of **18** and confirmed the structure of **17**. The structure of **12** was established by chemical correlation of **12** and **17** through the 20,1-olide **19**.

On the other hand, methyl dodonate C (**17**) was transformed into the rearranged derivative **20** by treatment with trifluoroacetic acid (55.8% yield). This transformation was accompanied by loss of a water molecule from **17**, as indicated by the EI mass spectrum of **20**, which showed a molecular ion at *m/z* 340 in accordance with the molecular formula $C_{21}H_{24}O_4$. The spectral data revealed the elimination of the oxygenated function at C-1 and the opening of the cyclopropane ring with concomitant 6 → 7 expansion of ring A to generate a cycloheptadiene conjugated with the C-18 carbomethoxy group. Thus, the IR spectrum showed an absorption at $1704\ \mathrm{cm}^{-1}$ due to an α,β,γ,δ-unsaturated ester. The ^{1}H NMR spectrum showed signals for the 1,3-diene system at δ_H 6.41 (H-1), 5.81 (H-2) and 6.76 (H-3). The C-19 protons appeared as an AB system at δ_H 2.73 and 2.45 (J=13.5 Hz), and the H-10 signal was observed at δ_H 2.35. The ^{13}C NMR spectrum exhibited signals at δ_C 138.7 d (C-1), 126.3 d (C-2), 134.9 d (C-3), 131.2 s (C-4), 61.0 d (C-10), 168.0 s (C-18) and 35.4 t (C-19). The proposed structural changes in ring A were confirmed by the HMBC cross-peaks of H-10 with C-1, C-2, C-9, and those of the protons of C-19 with C-3, C-4, C-6, C-18, and the singlet at δ_C 95.2 assigned to a tertiary carbon bearing an oxygenated function (C-5). The oxygenation at C-5 together with the presence of only two furan proton signals [δ_H 6.06 (H-14) and 7.30 (H-15)] and the highfield-shift of H-20 (δ_H 4.78 brs) were consistent with the formation of a tetrahydrofuran and a cyclohexane rings as represented in **20**. The first ring results from attack of the C-20 oxygen to C-5 and the second from electrophilic attack of C-20 to the furan ring followed by regeneration of its aromaticity. This was supported by the ^{1}H–^{13}C correlations of C-13/H-12, H-12′, H-15, H-20; C-16/H-12, H-14, H-15, H-20; and C-20/ H-8, H-11.

Regarding the relative stereochemistry of **20**, the α-orientation of C-20 in **17** forces the formation of the ether linkage to C-5 on the α-face of compound **20**. This was verified by the NOESY correlations (Fig. 4) of H-10/H-1, H-8; H-1/H-12 and mainly by the correlation of H-20/H_3-17, which also established as R^* the stereochemistry at C-20.

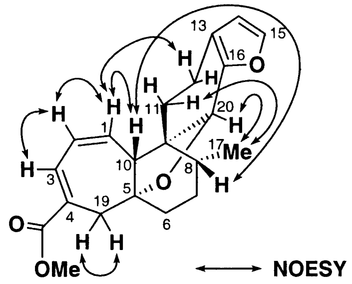

Figure 4. NOESY correlations of compound (**20**).

The mass spectrum of dodonolide was consistent with a molecular formula $C_{20}H_{24}O_3$. Its structure was established as the 5,10-secoclerodane **21** based on the following evidences. Its IR spectrum showed absorptions for β-substituted furan (1501, $874\ \mathrm{cm}^{-1}$), α, β-unsaturated-γ-lactone ($1749\ \mathrm{cm}^{-1}$) and double bond (1642, 1615, $1585\ \mathrm{cm}^{-1}$) functionalities. The ^{1}H NMR spectrum showed signals for a β-substituted furan (Table 1) and two signals at δ_H 0.87 (3H, d, J=6.5 Hz) and 1.04 (3H, s) assigned to the C-17 and C-20 methyl groups, respectively. The AB system at δ_H 4.73 and 4.62 (J=17.5 Hz) was ascribed to the C-19 methylene. The presence of two conjugated double bonds was evident from the signals at δ_H 5.85 (1H, d, J=17 Hz), 5.78 (1H, dd, J=17, 2.4 Hz), 6.30 (1H, dd, J=11.4, 2.4 Hz) and 6.03 (1H, d, J=11.4 Hz) assigned to H-10, H-1, H-2 and H-3, respectively. The assignments were based on the cross peaks and the H-3/H-19 (δ_H 4.62) long-range coupling observed in the COSY spectrum. The magnitudes of J_{1-10}=17 Hz and J_{2-3}=11.4 Hz established the geometry of the C-1–C-10 and C-2 double bonds as *trans* and *cis*, respectively. The above-mentioned long-range coupling led us to suspect the existence of an additional double bond at C-4, whose presence was confirmed by the ^{13}C NMR spectrum. The occurrence of three conjugated C=C bonds in **21** strongly supports the presence of a 10-membered ring. At this point it is important to remark that only 18 carbon signals were observed in the spectrum determined at room temperature. The 20 expected carbon signals of **21** were observed when the spectrum was recorded at 55°C. In both spectra, some carbon resonances (four at room temperature and six at 55°C) appeared as broad, low intensity signals. These facts revealed that dodonolide exist as a mixture of conformers like that observed in tonalensin, a quite similar 5,10-secoclerodane isolated from *Salvia tonalensis*[19] whose structure was unambiguously determined by X-ray analysis.[20]

Additionally, in the low field region of the ^{13}C NMR spectrum (room temperature) only 10 resonances were observed: one carbonyl (C-18), four signals ascribed to the furan ring (C-13–C-16), and five additional signals assigned to the vinylic carbons C-10 (δ_C 144.8), C-1 (δ_C 124.0), C-2 (δ_C 133.2), C-3 (δ_C 119.8) and C-4 (δ_C 123.4). The HMBC spectrum showed long-range cross peaks of H-3 and the C-19 protons with a very low-intensity carbon resonance at δ_C 158.4 attributed to C-5. The signal for C-8 could not be located in this spectrum. Nevertheless, both signals (C-5 and C-8) were observed in the spectrum determined at 55°C. The assignments for the other carbons of **21** are shown in Table 2.

The conformational changes of dodonolide seem to affect mainly the carbons at 1,4,5,7,8 and 20. This and the severe overlapping of the methine and methylene proton signals as two broad envelopes rendered ambiguous the NOESY NMR data. Therefore, the relative stereochemistry at C-8 and C-9 of dodonolide was based only on biogenetic considerations.

3. Conclusions

In spite of the fact that cyclopropyl clerodanes (dodonanes) had not been isolated until now, they had been proposed as intermediates in the biosynthesis of clerodanes containing bicyclo[5.4.0]undecane or bicyclo[5.3.0]decane ring systems.[2,4–6] In this way, their isolation and subsequent transformation of dodonane **17** into **20**, a derivative containing a bicyclo[5.4.0]undecane ring system, provide additional support to these speculations.

4. Experimental

4.1. General experimental procedures

Optical rotations were measured with JASCO-DIP-360 polarimeter. IR spectra were recorded with a NICOLET-FTIR-Magna 750 spectrometer and NMR spectra with a Varian UNITY 300 or 500. Chemical shifts were reported using residual $CHCl_3$ (δ_H 7.26; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad) δ_C 77.0; s, C; d, CH; t, CH_2; q, CH_3) as internal standard. EIMS spectra were obtained with a JEOL JMS-AX505HA spectrometer. Precoated TLC plates Alugram® Sil G/UV_{254} were used for analytical TLC and MN-Kieselgel G was used for preparative column chromatography.

Vegetal material. Leaves of *D. viscosa* Jacq. were collected in Cuernavaca (Morelos State, Mexico) in August 1998. A voucher specimen (MEXU-961425) was deposited at the National Herbarium.

Extraction and isolation. Fresh leaves (4.4 kg) were rinsed three times with EtOAc (10 L) to give 364 g of extract, which crystallized on standing. The crystals consisting of a mixture of **4** and **7** (ca. 4:1 ratio) were filtered off, dissolved in Me_2CO, decolored with activated charcoal and crystallized to give 28.6 g (0.065% fresh weight) of the mixture. A portion of this mixture (1.745 g) was methylated with CH_2N_2 to give after column chromatography (hexane/EtOAc, 17:3) 1.399 g of **5** and 341.4 mg of **8**. The rest of the non-methylated extract (326 g) was chromatographed on a silica gel column using as eluant hexane with increasing amounts of EtOAc (column A). The first fractions eluted with hexane/EtOAc 4:1 contained compound **10**. The latter was purified by column chromatography (hexane/EtOAc, $10:0 \rightarrow 0:10$, column B). Fractions eluted from column B with hexane/EtOAc 19:1 were chromatographed on a silica gel column (hexane/$CHCl_3$/Me_2CO, 20:3:1) to give fractions **a** and **b**. Fraction **a** was purified by repeated column chromatography eluted with the latter solvent system to give compound **10** (2.1798 g, 0.0495% fresh weight). Compound **21** (2.915 g, 0.066% fresh weight) was crystallized from fraction **b**. The mother liquors of **10** and **21** contained crude **6**. Compound **6** was purified by column chromatography (hexane/*i*PrOH, 49:1) followed by percolation through alumina (hexane/EtOAc, 2:3) and further chromatography on a silica gel column (hexane/EtOAc, 199:1) to obtain 3.27 g (0.0743% fresh weight) of compound **6**. Fractions eluted from column A with hexane/EtOAc, 4:1 (subsequent to the elution of **10**) and 3:2 were combined and chromatographed on a silica gel column (hexane/EtOAc, $17:3 \rightarrow 3:1 \rightarrow 13:7$). An additional amount (5.84 g, 0.132% fresh weight) of the mixture of **4** and **7** crystallized from fractions eluted with hexane/EtOAc, 3:1. The mother liquors were purified on a silica gel column (hexane/$CHCl_3$/Me_2CO, 11:1.5:2.5) to afford compound **12** (1.467 g, 0.0333% fresh weight). Fractions eluted with hexane/EtOAc 17:3 contained a mixture of **9**, **17** and flavonoid-type compounds. This mixture was chromatographed on a silica gel column (hexane/*i*PrOH, 19:1). Two fractions, **c** and **d** were obtained. In fraction **c**, compound **17** as well as flavonoids were present. Percolation of this fraction through alumina with EtOAc (to eliminate the flavonoids) followed by flash chromatography (silica gel 230–400, hexane/$CHCl_3$/Me_2CO, 10:1.5:1) afforded **17** (313 mg, 0.0071% fresh weight). Percolation of fraction **d** through alumina with EtOAc afforded **9** (7.542 g, 0.171% fresh weight).

4.1.1. Methyl dodonate A (10). Colorless crystals, mp 132–133°C; $[\alpha]_D=+39°$ (c 0.15, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3470, 1717, 1650, 1500, 873 cm^{-1}; EIMS at m/z 344 $[M]^+$, 326, 312, 297, 283, 245, 203, 189, 162, 149, 121, 95, 81. For ^1H and ^{13}C data, see Tables 1 and 2.

4.1.2. Methyl dodonate B (12). Colorless crystals, mp 162–165°C; $[\alpha]_D^{20}=-5°$ (c 0.16, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3374, 1719, 1650, 1500, 873 cm^{-1}; EIMS at m/z 360 $[M]^+$, 342, 327, 310, 297, 282, 253, 203, 189, 162, 149, 95, 81. For ^1H and ^{13}C data, see Tables 1 and 2.

4.1.3. Methyl dodonate C (17). Pale yellow oil; IR ($CHCl_3$) ν_{max}: 3401, 1721, 1645, 1501, 874 cm^{-1}; EIMS at m/z 358 $[M]^+$, 340, 326, 312, 281, 231, 230, 215, 171, 162, 149, 121, 95, 81. For ^1H and ^{13}C data, see Tables 1 and 2.

4.1.4. Dodonolide (21). Colorless crystals, mp 117–118°C; $[\alpha]_D=-87°$ (c 0.19, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 1749, 1642, 1615, 1585, 1501, 988, 874 cm^{-1}; EIMS at m/z 312 $[M]^+$, 297, 283, 256, 231, 189, 161, 121, 95, 81. For ^1H and ^{13}C data, see Tables 1 and 2.

4.1.5. Acetylation of 10. Ac_2O (1 mL) was added to a solution of **10** (114 mg, 0.33 mmol) in pyridine (1 mL). The reaction mixture was stirred at 90°C for 72 h. Ice was added and the mixture was extracted with EtOAc, washed consecutively with 5% HCl, $NaHCO_3$ saturated solution and water, and dried over anhydrous Na_2SO_4. Purification by silica gel chromatography (hexane/EtOAc, 19:1) gave unreacted **10** (57.6 mg, 50.5%) and **11** (19.8 mg, 15.5%) as crystals from EtOAc–hexane; mp 117–118°C; IR ($CHCl_3$) ν_{max}: 1724, 1655, 1501, 874 cm^{-1}; EIMS at m/z 386 $[M]^+$, 354, 344, 326, 312, 283, 231, 203, 162, 131, 81, 43. For ^1H and ^{13}C data, see Tables 1 and 2.

4.1.6. Oxidation of 10. Jones reagent was added drop-wise to a stirred solution of **10** (81 mg, 0.24 mmol) in Me_2CO (8 mL) at 0°C, until persistence of the reagent color. The reaction mixture was stirred for 20 min at 0°C. The solvent was removed using an air stream. The residue was diluted with water and extracted with EtOAc (3×, 8 mL). The combined organic phases were washed with water, dried over Na_2SO_4, and purified over silica gel (hexane/EtOAc, 9:1). There was obtained 31.3 mg (38.9%) of **15** as oil. IR ($CHCl_3$) ν_{max}: 1728, 1672, 1630, 1500, 873 cm^{-1}; EIMS at m/z 342 $[M]^+$, 326, 311, 283, 247, 178, 149, 121, 95, 83, 81. For ^1H and ^{13}C data, see Tables 1 and 2.

4.1.7. Acetylation of 12. Ac_2O (0.5 mL) was added to a solution of **12** (49.2 mg, 0.14 mmol) in pyridine (0.5 mL). The reaction mixture was stirred at room temperature for 1 h and worked up as described for the acetylation of **10**. The residue was subjected to silica gel column chromatography (hexane/EtOAc, 9:1) to give 31 mg (55.7%) of **13** and 21.3 mg (34.7%) of **14**.

Compound **13**: Pale yellow oil. IR ($CHCl_3$) ν_{max}: 3530, 1723, 1660, 1500, 872 cm^{-1}; EIMS at *m/z* 402 $[M]^+$, 384, 370, 352, 342, 324, 282, 229, 201, 175, 162, 149, 121, 95, 81, 43. For ^1H and ^{13}C data, see Tables 1 and 2.

Compound **14**: Pale yellow oil; IR ($CHCl_3$) ν_{max}: 1733, 1662, 1502, 872 cm^{-1}; EIMS at *m/z* 444 $[M]^+$, 412, 384, 352, 342, 324, 311, 282, 229, 201, 175, 162, 149, 95, 81, 43. For ^1H and ^{13}C data, see Tables 1 and 2.

4.1.8. Oxidation of 12. Pyridinium chlorochromate (103 mg, 0.99 mmol) was gradually added to a solution of **12** (42.2 mg, 0.12 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 7 h at room temperature. The solvent was removed with an air stream. The residue was taken in Me_2CO and filtered to eliminate the excess of reagent and purified by preparative TLC (hexane/EtOAc, 4:1, 4×) to give **16** (7.1 mg, 16.9%) and **19** (5.1 mg, 12.2%).

Compound **16**: Pale yellow oil; IR ($CHCl_3$) ν_{max}: 1763, 1720, 1682, 1620, 1500, 874 cm^{-1}. For ^1H and ^{13}C data, see Tables 1 and 2.

Compound **19**: Pale yellow oil; IR ($CHCl_3$) ν_{max}: 1768, 1723, 1652, 1502, 873 cm^{-1}. EIMS at *m/z* 356 $[M]^+$, 324, 310, 296, 262, 215, 202, 187, 175, 157, 105, 95, 81. For ^1H and ^{13}C data, see Tables 1 and 2.

4.1.9. Acetylation of 17. Ac_2O (1 mL) was added to a solution of crude **17** (213 mg, 0.59 mmol) in pyridine (1 mL). The reaction mixture was stirred for 2 h at room temperature and worked up as described for the acetylation of **10**. The residue was subjected to silica gel column chromatography (CH_2Cl_2/Me_2CO, 19:1) and crystallization from hexane afforded 143.7 mg (60.4%) of **18** as colorless crystals, mp 121–123°C; IR ($CHCl_3$) ν_{max}: 1740, 1724, 1650, 1501, 873 cm^{-1}; EIMS at *m/z* 400 $[M]^+$, 385, 369, 358, 340, 311, 281, 258, 231, 199, 171, 149, 121, 95, 81, 43. For ^1H and ^{13}C data, see Tables 1 and 2.

4.1.10. Oxidation of 17. Jones reagent was added drop wise to a stirred solution of **17** (68.8 mg, 0.19 mmol) in Me_2CO (5 mL) at 0°C, until persistence of the reagent color. The reaction mixture was stirred for 15 min at 0°C. The solvent was removed using an air stream and the residue was worked up as described for the oxidation of **10**. The residue was purified over a silica gel column (hexane/EtOAc/MeOH, 19:1:0.05) to afford compound **19** (41.3 mg, 68.4%) identical in every respect with the product obtained from **12**.

4.1.11. Rearrangement of 17. Trifluoroacetic acid (0.2 mL, 2.6 mmol) was added to a stirred solution of **17** (50 mg, 0.14 mmol) in anhydrous CH_2Cl_2 (10 mL) at room temperature, under N_2. The reaction mixture was stirred for 7 h, washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4 and chromatographed over a silica gel column (hexane/Me_2CO, 49:1) to give 26.5 mg (55.8%) of **20** as a pale yellow oil; IR ($CHCl_3$) ν_{max}: 1704, 1620, 1610, 1502, 962, 896, 847 cm^{-1}; EIMS at *m/z* 340 $[M]^+$, 325, 310, 283, 223, 195, 160, 147, 131, 115, 91, 77, 55. For ^1H and ^{13}C data, see Tables 1 and 2.

4.2. Crystallographic study

A single crystal of compound **18** ($0.80\times0.40\times0.36$ mm^3) was used for the X-ray study. Data were collected on a Siemens P4/PC diffractometer using MoK_α radiation. Crystal data: $C_{23}H_{28}O_6$, orthorhombic, space group $P2_12_12$, a=17.291 (2) Å, b=17.968 (2) Å, c=6.894 (1) Å, V=2141.9 (5) $Å^3$, Z=4, D_{calcd}=1.242 Mg/m^3, $F(000)$=856. The structure was solved by direct methods[21] and refined by full matrix least-squares[22] with anisotropic temperature factors for non-hydrogen atoms converged at the discrepancy R factor=0.0601 for 2182 observed reflections. Crystallographic data (excluding structure factors) have been deposited as supplementary material.

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