Molecular and Crystal Structure of Hyptolide, a Naturally Occurring α,β-Unsaturated δ-Lactone

Sjamsul Achmad,[a] Thomas Høyer,[b] Anders Kjær,[b,*] Lukman Makmur[a] and Rolf Norrestam[c]

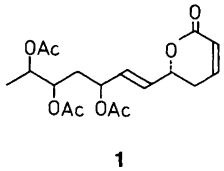
[a]Department of Chemistry, Bandung Institute of Technology, Bandung 40132, Indonesia, [b]Department of Organic Chemistry and [c]Chemistry Department B, The Technical University of Denmark, DK-2800 Lyngby, Denmark

Achmad, S., Høyer, T., Kjær, A., Makmur, L. and Norrestam, R., 1987. Molecular and Crystal Structure of Hyptolide, a Naturally Occurring α,β-Unsaturated δ-Lactone. – Acta Chem. Scand., Ser. B 41: 599–609.

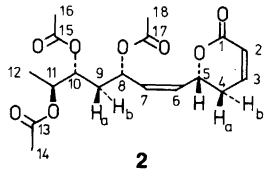
Hyptolide, a six-membered, α,β-unsaturated C_{12} lactone, has been reisolated from *Hyptis pectinata* Poit. Detailed ^1H and ^{13}C NMR spectroscopic studies and a crystal structure determination on the basis of single-crystal X-ray diffraction data collected at 293 K provide evidence for the detailed structure and relative configuration of hyptolide. The crystal structure has been determined from the 2261 most significant X-ray intensities and refined to an *R* factor of 0.065. The space group is $P2_1$ and the cell parameters are a = 7.629(2), b = 24.639(3), c = 10.468(2) Å and β = 90.64(2)°. The absolute configuration is established by synthesis of 10(*S*),11(*R*)-dihydroxydodecanoic acid, the enantiomer of an acid previously produced by exhaustive hydrogenation of hyptolide. On the basis of the combined evidence, supported by chiroptical data, hyptolide can now be formulated as 6*R*-(1*Z*,3*S*,5*R*,6*S*)-5,6-dihydro-6-[3,5,6-tris(acetoxy)-1-heptenyl]-2*H*-pyran-2-one. Its relation to other C_{12}-lactones of natural origin is briefly discussed.

In 1920, Gorter[1] described the isolation of a crystalline lactone, hyptolide, from Indonesian raised material of *Hyptis pectinata* Poit., a labiate indigenous to warm America. His structure proposal,[1] resulting from extensive degradation studies, rested on an erroneous empirical formula, and proved untenable when hyptolide was subjected to a reinvestigation by Birch and Butler[2] in 1964. They formulated hyptolide as **1**, yet without any stereochemical specification except for an expressed preference, founded on IR-data, for (*E*)-configuration around the exocyclic double bond.

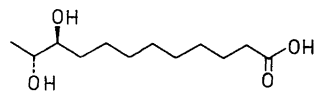
In connection with a broader interest in naturally occurring, unsaturated δ-lactones, the detailed structure of hyptolide became of importance to us. We describe the results of our reinvestigation supporting the formulation of hyptolide as **2**.



1



2



3

Results

Hyptolide was isolated from leaves of *Hyptis pectinata*, essentially as described by Gorter.[1] Its ^{13}C NMR spectrum (Table 1) is in accord with the general structure **1** of Birch and Butler,[2] whereas the ^1H NMR spectrum (Table 2), with its two discernible 10 Hz coupling constants for the two

*To whom correspondence should be addressed.

Table 1. ^{13}C NMR data for hyptolide.[a]

Position[b]	^{13}C δ/ppm[c]	Position[b]	^{13}C δ/ppm[c]
1	163.2	10	70.7
2	121.3	11	70.2
3	144.5	12	14.5
4	29.3	13	170.4*
5	73.6	14	20.84†
6	131.0	15	170.8*
7	130.6	16	20.82†
8	66.3	17	169.5*
9	34.6	18	20.79†

[a]Spectrum measured at 125 MHz in $CDCl_3$; assignments of (C-2)–(C-12) were made by CHORTLE correlation[3] with the unambiguously assigned ^1H NMR spectrum (Table 2). [b]Numbering as shown in formula **2**. [c]Assignments for signals marked with the same symbols may be interchanged.

sets of olefinic protons, is difficult to reconcile with the proposed (*E*)-configuration of the exocyclic double bond in hyptolide.[2] In order to clarify this uncertainty and also to establish the configuration of the four chiral centers in hyptolide, a single crystal X-ray analysis was undertaken.

Structure determination. Single crystals, used for the X-ray diffraction studies, were grown by slow evaporation of an ether solution of hyptolide. The crystals are monoclinic, space group $P2_1$, with the unit cell parameters $a = 7.629(2)$, $b = 24.639(3)$, $c = 10.468(2)$ Å and $\beta = 90.64(2)°$. As the unit cell contains four hyptolide molecules, there are two crystallographically independent molecules in the cell. The structural model, derived by direct methods, was refined to an *R*-value of 0.065 for 2261 significant X-ray reflections collected with Cu*K*α radiation. The most relevant experimental details are given in Table 3.

The average molecular conformation in the crystal structure together with the atomic labelling used in the X-ray study are shown in Fig. 1, and the non-hydrogen atomic coordinates are listed in Table 4. As seen in Fig. 2, the conformations of the two independent molecules are very similar. The largest deviations are observed for the orientation of one of the acetoxy-groups, viz. the torsion angles of the atoms C(8)–O(3)–C(13)–C(14) which differ by 7.5(9)°. The bond distance (e.s.d.'s about 0.01 Å) and bond angle (e.s.d.'s about 0.8°) distributions in the two molecules are also very similar (cf. Table 5). As there are no proper hydrogen bond donors, the molecules are mainly held together in the crystals by weak intermolecular forces, suggesting that both of the two independent molecules can adopt similar, energetically favourable conformations.

The two independent molecules are related to each other by a non-crystallographic symmetry element, a two-fold pseudo-screw axis parallel to the *x* axis. A least-squares fit of the position and translation of the pseudo-screw shows that it passes through [0, 0.163(1), 0.324(2)] with a translation of 0.501(2) unit translations along *a*. The deviations from this pseudo-screw symmetry are small. The largest, about 0.2 Å, are observed for

Table 2. ^1H NMR data for hyptolide.[a]

Position[b]	δ/ppm	$J_{H/H}$/Hz
2	6.04 (1H, ddd)	$^3J_{H(C\text{-}2)/H(C\text{-}3)} = 10.0$ $^4J_{H(C\text{-}2)/H(a)(C\text{-}4)} =$ $^4J_{H(C\text{-}2)/H(b)(C\text{-}4)} = 1.0$
3	6.90 (1H, ddd)	$^3J_{H(C\text{-}3)/H(C\text{-}2)} = 10.0$ $^3J_{H(C\text{-}3)/H(a)(C\text{-}4)} = 6.0$ $^3J_{H(C\text{-}3)/H(b)(C\text{-}4)} = 3.0$
4(a)	2.40[c] (1H, m)	
4(b)	2.45[c] (1H, m)	
5	5.30 (1H, ddd)	$^3J_{H(C\text{-}5)/H_{(ax)}(C\text{-}4)} = 12.0$ $^3J_{H(C\text{-}5)/H_{(eq)}(C\text{-}4)} = 4.5$ $^3J_{H(C\text{-}5)/H(C\text{-}6)} = 7.0$
6	5.78 (1H, dd)	$^3J_{H(C\text{-}6)/H(C\text{-}7)} = 10.0$ $^3J_{H(C\text{-}6)/H(C\text{-}5)} = 7.0$
7	5.54 (1H, m)	
8	5.54 (1H, m)	
9(a)	1.84[c] (1H, m)	
9(b)	2.02[c] (1H, m)	
10	4.94 (1H, m)	
11	5.00 (1H, dq)	$^3J_{H(C\text{-}11)/H(C\text{-}10)} = 2.9$ $^3J_{H(C\text{-}11)/H(C\text{-}12)} = 6.5$
12	1.21 (3H, d)	$^3J_{H(C\text{-}12)/H(C\text{-}11)} = 6.5$
14	2.03[c] (3H, s)	
16	2.04[c] (3H, s)	
18	2.08[c] (3H, s)	

[a]Spectrum measured at 500 MHz in $CDCl_3$; assignments were made on the basis of two-dimensional spectra produced by COSY technique. [b]Numbering are shown in formula **2**. [c]These values may be interchanged.

Table 3. Experimental conditions for the crystal structure determination of hyptolide.

Formula	$C_{18}H_{24}O_8$
Formula weight	368.38
Unit cell volume, V/Å^3	1967.6(8)
Formula units per unit cell, Z	4
Calculated density, D_x/g cm^{-3}	1.244(1)
Radiation	Cu$K\alpha$
Wavelength/Å	1.54184
F(000) value	784
Temperature, T/K	293(1)
Crystal shape	Prismatic
Crystal size/mm	0.18×0.20×0.26
Diffractometer	Enraf-Nonius CAD4
Determination of unit cell:	
Number of reflections used	16
B-range/°	12.4 to 16.2
Intensity data collection:	
Maximum $\sin(\theta)/\lambda$/Å^{-1}	
0.609	
Range of h, k and l	−9 to 9, 0 to 30 and 0 to 12
Standard reflections	(2 −1 2) and (0 5 3)
Intensity instability/%	<2.5
Number of unique reflections	3821
Number of observed reflections	2261
Criterion for significance	$I > 5\sigma(I)$
Absorption correction:	
Linear absorption coefficient/cm^{-1}	7.9
Transmission factor range	0.84 to 0.88
Structure determination technique	Direct methods
Determination of hydrogen atoms	Geometric
Structure refinement:	
Minimization of	Sum of $w\Delta F^2$
Anisotropic thermal model for	Non-hydrogens
Isotropic thermal model for	Hydrogens
Parameters fixed for	Hydrogens
Number of refined parameters	469
Weighting scheme	$1/[\sigma(F)^2 + 0.0004\ F^2]$
Final R	0.065
Final wR	0.086
Final max. shift/sigma	0.2
Final max. and min. in/e·Å^{-3}	0.3 and −0.2

the carbon atoms C(14) and C(16) of two different acetoxy groups.

The molecular fragments formed by C(5)–C(6)=C(7)–C(8) and C(7)–C(8)–C(9)–C(10)–C(15), as well as the three acetoxy groups, are planar in both molecules (r.m.s. deviations from the planes less than 0.05 Å). Least-squares planes through C(1)–C(2)=C(3)–C(4) show that these atoms are coplanar within 0.02 Å in both molecules, and that the C(5) and O(1) atoms deviate by about 0.8 and 0.2 Å, respectively. Thus, the 2*H*-pyran-2-one rings have slightly distorted envelope conformations with the C(5) atoms at the apices.

The structure determination, providing information about the *relative* configuration, was performed on an arbitrarily chosen enantiomer which, on the basis of chemical evidence (*vide infra*), proved to be the enantiomer of hyptolide. Accordingly, the coordinates for the latter can be easily deduced from Table 4 by changing the fractional y coordinates to 1-y, while keeping the x and z coordinates invariant.

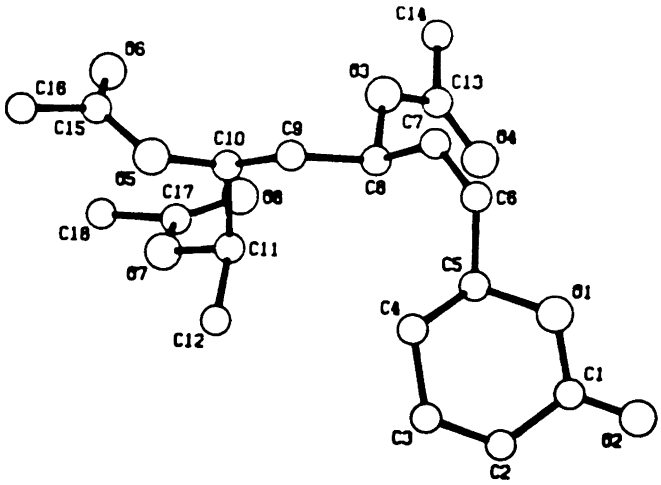


Fig. 1. The molecular conformation found for hyptolide, and the atomic labels used.

Absolute configuration. The structure determination, as described above, defines the relative but not the absolute configuration of hyptolide. In order to establish the latter, recourse was made to both chiroptical measurements and synthetic correlations. In ethanol solution, hyptolide exhibits a positive $n \rightarrow \pi^*$ CD peak of moderate intensity ($\Delta\varepsilon_{257} = +2.3$). This behaviour, together with the ^{1}H NMR spectroscopic evidence for an equatorial position of the side-chain at C-5 (cf. Table 2), points to (*R*)-configuration at this center on the basis of established regularities between the sign of the $n \rightarrow \pi^*$ Cotton effect near 260 nm and the sense of chirality in the C=C−C=O moiety of α,β-unsaturated δ-lactones.[4,5]

Additional evidence was provided by chemical correlation. Birch and Butler[2] converted hyptolide, through exhaustive catalytic hydrogenation, into a mixture of an 8,10,11-trihydroxydodecanoic acid, of unstated rotation, and a dextrorotatory 10,11-dihydroxydodecanoic acid. From our crystal structure it is apparent that the latter must be one of the enantiomers of the *erythro* acid. To decide between these we have synthesized 10(*S*),11(*R*)-dihydroxydodecanoic acid (**3**) through the sequence of reactions presented in Scheme 1, first traversed in the racemic series.

(±)-*erythro*-2,3-Dihydroxybutyric acid[6] (±**4**)* was converted, via its methyl ester (±**5**),[7] into methyl *cis*-2,2,5-trimethyl-1,3-dioxolane-4-carboxylate (±**6**),[7] and further, by DIBAL reduction as known from the *trans* series,[8–10] into the *cis*-aldehyde (±**7**), without any appreciable epi-

*Only one enantiomeric series is depicted in Scheme 1.

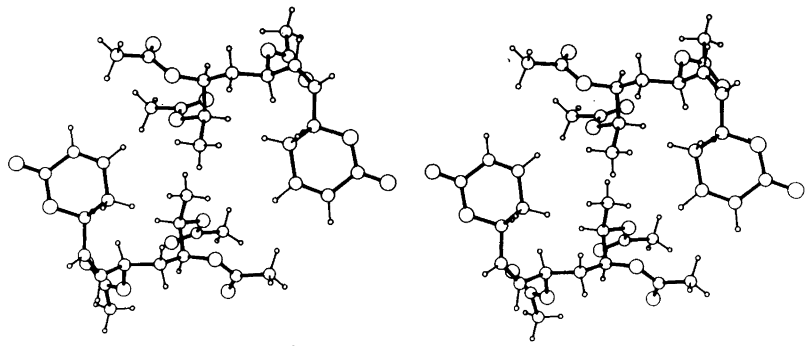


Fig. 2. Stereo drawing of the conformations of the two crystallographically independent hyptolide molecules.

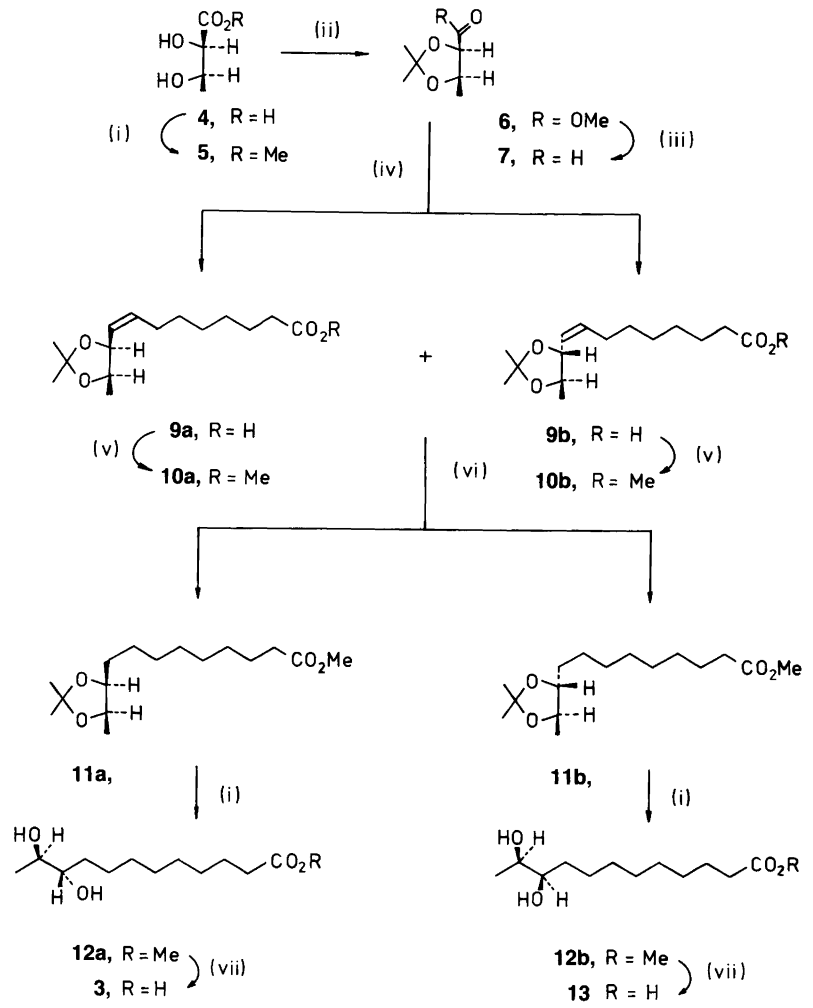
Table 4. Fractional atomic coordinates ($\times 10^4$) and equivalent isotropic thermal parameters ($\times 10^4$ Å^2) of the non-hydrogen atoms. The thermal parameters were estimated as 1/3 trace(U).

Atom	x	y	z	U
O(1)	9952(7)	2201(1)	−2203(5)	538(17)
C(1)	10089(10)	1662(4)	−2466(8)	544(28)
C(2)	10208(12)	1311(4)	−1410(9)	619(30)
O(2)	10212(10)	1522(3)	−3553(6)	788(25)
C(3)	10576(14)	1482(4)	−228(9)	724(35)
C(4)	10744(12)	2076(4)	21(8)	608(30)
C(5)	9529(9)	2367(3)	−916(7)	460(23)
C(6)	9757(10)	2975(4)	−894(7)	496(25)
C(7)	8808(11)	3313(4)	−223(8)	518(25)
C(8)	7364(9)	3172(3)	661(7)	438(22)
C(9)	7980(10)	3191(4)	2026(7)	536(26)
C(10)	6513(9)	3094(4)	3007(7)	471(24)
C(11)	5725(11)	2529(4)	2933(7)	531(26)
C(12)	6996(13)	2052(4)	3120(10)	746(35)
O(3)	5976(7)	3603(3)	559(5)	541(18)
C(13)	4683(11)	3544(4)	−309(9)	590(28)
O(4)	4624(11)	3168(4)	−1020(8)	990(31)
C(14)	3480(15)	3984(5)	−307(15)	1015(50)
O(5)	7369(7)	3153(3)	4232(5)	532(17)
C(15)	6588(13)	3454(4)	5111(8)	608(30)
O(6)	5243(9)	3692(3)	4932(6)	710(23)
C(16)	7571(15)	3453(5)	6309(9)	861(43)
O(7)	4454(7)	2478(3)	3974(5)	517(17)
C(17)	2838(11)	2688(4)	3771(9)	569(29)
O(8)	2383(8)	2849(4)	2746(7)	828(27)
C(18)	1835(12)	2692(4)	4942(10)	735(35)
O(1′)	4968(7)	1013(3)	8746(5)	556(18)
C(1′)	5070(10)	1551(4)	8975(8)	530(26)
C(2′)	5254(13)	1917(4)	7901(9)	716(33)
O(2′)	5182(9)	1702(3)	10068(6)	767(23)
C(3′)	5656(13)	1744(4)	6747(8)	685(33)
C(4′)	5790(11)	1151(4)	6527(8)	637(30)
C(5′)	4629(10)	845(3)	7430(7)	461(22)
C(6′)	4836(10)	235(4)	7394(7)	503(24)
C(7′)	3882(10)	−101(3)	6730(7)	485(23)
C(8′)	2384(9)	50(3)	5834(7)	426(21)
C(9′)	3025(9)	83(3)	4457(7)	466(23)
C(10′)	1578(9)	202(3)	3499(6)	438(22)
C(11′)	694(10)	749(3)	3651(7)	503(24)
C(12′)	1939(12)	1231(4)	3452(9)	694(31)
O(3′)	1094(6)	−383(2)	5836(5)	509(16)
C(13′)	−287(9)	−340(4)	6588(8)	553(27)
O(4′)	−445(9)	20(3)	7349(7)	823(25)
C(14′)	−1570(12)	−786(4)	6354(11)	774(36)
O(5′)	2277(6)	168(3)	2249(5)	515(16)
C(15′)	1482(11)	−119(4)	1355(8)	540(26)
O(6′)	159(9)	−397(3)	1584(6)	813(24)
C(16′)	2272(13)	−54(4)	79(8)	672(31)
O(7′)	−627(6)	793(3)	2640(5)	524(17)
C(17′)	−2193(11)	557(4)	2864(9)	660(31)
O(8′)	−2567(9)	383(4)	3876(7)	1039(35)
C(18′)	−3345(12)	575(5)	1697(11)	844(38)

merisation at C-4 as estimated from GLC analysis. The (4*S*)-*cis* aldehyde (*en*-**7**) is available as a transient intermediate from products arising from cinnamaldehyde[11] or 1-(1,3-dithian-2-yl)-1,2-propanedione[12] in fermenting baker's yeast and has been utilized in chain-extension reactions to give compounds with independently established stereochemistry.[10] Wittig reaction of the aldehyde (±**7**) with the ylide **8** derived from (7-carboxyheptyl)triphenylphosphonium bromide[13] proceeded in moderate yield (see Experimental) to give a mixture of two unsaturated acids, ±**9a** and ±**9b**, accompanied by a minor quantity of the previously unknown 9-methyl-8-decenoic acid (**14a**), obviously deriving from partial cleavage of the acetalic system under basic conditions; a similar, base-induced deacetalisation was observed by Viscontini and Frei[7] in another substrate with a carbonyl group positioned adjacent to the 1,3-dioxolane ring. Only (*Z*)-isomers of ±**9a** and ±**9b** were observed, as estimated from 500 MHz ^{1}H NMR spectroscopic analysis of the mixture. The concomitant formation of the *trans* acid (±**9b**) during the Wittig reaction is attributed to a competing, base-induced epimerisation at C-4 of the *cis* aldehyde (±**7**) prior to the formation of

Table 5. Bond distances (Å) and angles (°) between the non-hydrogen atoms (e.s.d.'s are 0.01 Å and 0.8°, respectively). Related values for the two molecules (having unprimed and primed atomic labels, respectively) are given on each line.

Distances			Angles		
O1 –C1	1.360	1.349	O1 –C1 –C2	116.5	118.7
C1 –C2	1.406	1.449	O1 –C5 –C4	109.0	110.6
C2 –C3	1.334	1.320	C1 –O1 –C5	118.9	117.1
C4 –C5	1.522	1.505	C2 –C1 –O2	124.5	122.5
C6 –C7	1.312	1.299	C3 –C4 –C5	107.4	110.7
C8 –C9	1.500	1.529	C5 –C6 –C7	125.0	126.1
C9 –C10	1.546	1.512	C7 –C8 –C9	111.0	110.4
C10–O5	1.440	1.421	C8 –C9 –C10	114.0	113.4
C11–O7	1.472	1.457	C9 –C8 –O3	105.0	105.3
C13–O4	1.189	1.199	C9 –C10–O5	104.6	108.7
O5 –C15	1.328	1.316	C10–C11–O7	107.7	107.1
C15–C16	1.454	1.480	C11–C10–O5	108.3	108.7
C17–O8	1.192	1.181	C12–C11–O7	105.1	105.5
			O3 –C13–C14	112.7	111.6
			O5 –C15–O6	123.8	121.8
			O6 –C15–C16	124.7	124.9
			O7 –C17–C18	111.0	111.0
O1 –C5	1.443	1.459	O1 –C1 –O2	118.8	118.4
C1 –O2	1.194	1.205	O1 –C5 –C6	105.5	106.7
C3 –C4	1.492	1.483	C1 –C2 –C3	123.1	122.3
C5 –C6	1.508	1.512	C2 –C3 –C4	119.3	118.5
C7 –C8	1.488	1.517	C4 –C5 –C6	112.9	114.8
C8 –O3	1.503	1.451	C6 –C7 –C8	127.0	126.0
C10–C11	1.518	1.516	C7 –C8 –O3	108.5	109.0
C11–C12	1.535	1.536	C8 –O3 –C13	118.9	119.0
O3 –C13	1.342	1.326	C9 –C10–C11	113.4	115.2
C13–C14	1.420	1.490	C10–C11–C12	116.5	113.4
C15–O6	1.193	1.245	C10–O5 –C15	118.1	120.8
O7 –C17	1.352	1.352	C11–O7 –C17	117.3	116.6
C17–C18	1.452	1.498	O3 –C13–O4	122.1	122.7
			O4 –C13–C14	125.2	125.7
			O5 –C15–C16	111.4	113.2
			O7 –C17–O8	121.7	122.3
			O8 –C17–C18	127.3	126.7



Scheme 1. Reagents and conditions: (i) MeOH/HCl; (ii) $Me_2C(OMe)_2$, PTSA; (iii) DIBAL, Et_2O, −50 °C; (iv) $Ph_3P{=}CH(CH_2)_6CO_2H$(**8**), DMSO, NaH, 20 °C, 1 h; (v) CH_2N_2/Et_2O; (vi) a. 5 % Pd/C, H_2, EtOAc; b. separ. SiO_2; (vii) NaOH/MeOH, 20 °C.

the Wittig reaction product. In fact, Servi[10] has demonstrated that the (4*S*)-*cis* aldehyde (*en*-**7**) is converted almost quantitatively into the more stable (4*R*)-*trans* aldehyde on treatment with potassium carbonate in methanol. The major Wittig product is assigned the *cis* configuration (±**9a**) on the basis of ^{1}H NMR evidence. Its methine protons, at C-4 and C-5, are both displaced about 0.4 δ downfield from those of the minor product ±**9b**; its geminal methyl groups are clearly anisochronous, in contrast to the virtually coinciding groups of ±**9b**, and the methyl group at C-5 resonates about 0.15 δ upfield from that of the minor isomer. These are all features distinguishing the structurally analogous *cis* aldehyde (±**7**) (see Experimental) from its *trans*-isomer.[9] The non-separated acid mixture was converted into a mixture of the methyl esters ±**10a** and ±**10b**, and, in turn, on hydrogenation, into the saturated esters ±**11a** and ±**11b**. Chromatographic separation of the latter, followed by acid hydrolysis, yielded the crystalline esters ±**12a** and ±**12b**,

which were finally hydrolyzed to (±)-*erythro*-10,11-dihydroxydodecanoic acid (±**3**) and its (±)-*threo*-isomer (±**13**), respectively.

Repetition of the sequence (Scheme 1), starting from (−)-2(*R*),3(*R*)-dihydroxybutyric acid (**4**),[14,15] proceeded, *via* the methyl esters **5** and **6**, to the aldehyde (**7**), characterized as its 2,4-dinitrophenylhydrazone. Wittig reaction of **7** with the ylide **8** afforded a 4:1 mixture of the acids **9a** and **9b**, further processed, without separation, through the unsaturated methyl esters **10a** and **10b** to the saturated counterparts **11a** and **11b**. Separation of the latter by chromatography, followed by individual acid hydrolysis, yielded the crystalline methyl esters **12a** and **12b**. Finally, alkaline hydrolysis converted the latter into the levorotatory 10(*S*),11(*R*)-dihydroxydodecanoic acid (*erythro* isomer) and the dextrorotatory 10(*R*),11(*R*) isomer (*threo*), respectively.

The X-ray crystal structure presented above, the dextrorotation of the 10,11-dihydroxydodecanoic acid produced upon exhaustive hydrogenation of hyptolide,[2] and the here-described synthesis of the *erythro* acid (**3**) together provide conclusive evidence for the formulation of hyptolide as 6*R*-(1*Z*,3*S*,5*R*,6*S*)-5,6-dihydro-6-[3,5,6-tris(acetoxy)-1-heptenyl]-2*H*-pyran-2-one (**2**), a conclusion supported by our chiroptical data.

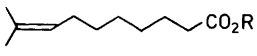
Discussion

Structurally, hyptolide belongs to a group of naturally occurring C_{12} α,β-unsaturated δ-lactones. Other members are: argentilactone (**15**),[16] boronolide (**16**),[17] umuravumbolide (**17**),[18] its deacetyl derivative (**18**),[18] "deacetylboronolide" (**19**),[18] "1′,2′-dideacetylboronolide" (**20**),[19] olguine (**21**)[20] and anamarine (**22**).[21] Apart from the highly reduced argentilactone (**15**), all members derive from taxa belonging to the family Labiatae (genera: *Tetradenia, Iboza* and *Hyptis*), a fact deserving attention in a taxonomic context. Biosynthetically, the structural features of this group of lactones are suggestive of a polyketide derivation, though the implication of carbohydrates cannot be excluded in view of the lack of experimental evidence.

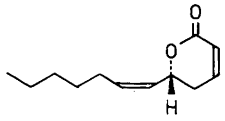
Though highly diversified with regard to extension and stereochemical pattern of acetoxylation, a single regularity is noticeable within the series: the stereochemistry around the ring-carbon to which the side-chain is attached seems invariant throughout this group of lactones with its multifunctionality and variegated hydroxylation patterns, features that have drawn attention to several of its members as synthetic targets.[22-25]

Experimental

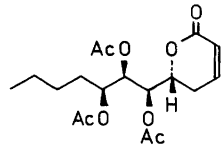
Melting points are uncorrected. ^{13}C NMR spectra (at 125 MHz), as well as ^{1}H NMR spectra and two-dimensional spectra (at 500 MHz) were obtained on a Bruker HX 500 instrument. 90 MHz (^{1}H) and 22.6 MHz (^{13}C) spectra were recorded on Bruker HX 90E and WH-90 instruments, re-



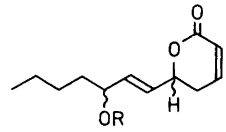
14a R = H
14b R = Me



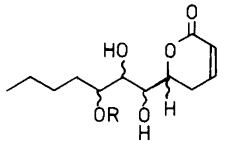
15



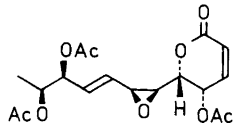
16



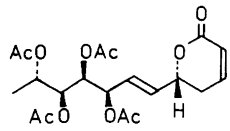
17 R = Ac
18 R = H



19 R = H **20** R = Ac



21



22

spectively, all in $CDCl_3$ with TMS as internal standard. Optical rotations were measured in 1 dm microcells on a Perkin-Elmer 141 polarimeter. The CD spectrum in ethanol was recorded on a Roussel Jouan Dichrographe. Microanalyses were performed at the Leo Company by Mr. G. Cornali and his staff.

Isolation of hyptolide. Leaves of *Hyptis pectinata* Poit. were collected in January 1985 in the Gegerkalong region north of Bandung in Indonesia. The dried, ground leaves (500 g) were extracted with 95 % ethanol and the extract processed further as described by Gorter[1] to give hyptolide (1.5 g) which was purified by repeated recrystallization from ether; m.p. 87–88 °C, $[\alpha]_D^{22}$ +7.6° (*c* 4.0, 94 % ethanol), +11.8° (*c* 4.0, 100 % ethanol), +11.2° (*c* 0.6, chloroform) [lit.: m.p. 88.5 °C,[1,2] $[\alpha]_D^{27}$ +6.75° (*c* 4, 95 % ethanol),[1] $[\alpha]_D^{23}$ +7.43° (ethanol)[2]]. A 0.01 M solution of hyptolide exhibited CD extrema at 257 nm ($\Delta\varepsilon$ +2.3) and 217 nm ($\Delta\varepsilon$ +2.7). For NMR spectroscopic data: see Tables 1 and 2.

*(±)-2,2,5-Trimethyl-*cis*-1,3-dioxolane-4-carboxaldehyde* (±**7**). *(±)-erythro*-2,3-Dihydroxybutyric acid[6] (**4**) was converted into its methyl ester (±**5**) and thence into the known dioxolane ester (±**6**) as previously described.[7] Reduction of the ester with an equimolar quantity of DIBAL was conducted as described by Servi[10] for the *trans* series to give the aldehyde (±**7**) as a colourless liquid, distilled in a 'Kugelrohr' apparatus at 115 °C/41 mmHg (yield 56 %) and homogeneous by GLC. ^{1}H NMR (90 MHz): δ 1.27 (3H, d, J = 6.0 Hz), 1.41 (3H, s), 1.59 (3H, s), 4.22 (1H, dd, J = 7.0 and 3.3 Hz), 4.50 (1H, m), 9.67 (1H, dd, J = 3.3 and 0.5 Hz).

Wittig reaction of the aldehyde (±**7**) *with 8-(tripenylphosphoranylidene)octanoic acid, the ylide derived from* **8**. A solution of sodium hydride (2.75 g, 50 % NaH in oil, 57 mmol) in freshly distilled DMSO (48 ml) was produced by heating in a nitrogen atmosphere at 80 °C for 3 h. The cooled solution was added, in the course of 5 min, to a stirred solution of (7-carboxyheptyl) triphenylphosphonium bromide[13] (15.9 g, 32.8 mmol) in DMSO (50 ml) to produce the anion of the red ylide (**8**).[13] After stirring for an additional 10 min, a solution of the aldehyde (±**7**) (2.08 g, 14.5 mmol) in DMSO (4 ml) was added. After 1 h, additional DMSO (50 ml) was introduced in order to facilitate stirring before the reaction was quenched by adding water (10 ml) to the cooled reaction mixture. Aqueous $NaHSO_4$ (40 ml, 2 M solution) and ice-cold water (50 ml) were added, and the solution was extracted with five 60 ml portions of pentane. The reaction product was transferred to water on extraction with 4 M NaOH (5 ml) followed by water (2×5 ml). Acidification with aqueous $NaHSO_4$ (2M), extraction with pentane (3×20 ml), drying, and evaporation yielded an oily mixture of acids, containing ±**9a** and ±**9b**.

Conversion of the Wittig products ±**9a** *and* ±**9b** *into (±)-methyl dihydroxydodecanoates* ±**12a** *and* ±**12b**. The acids produced in the Wittig reaction were converted into the corresponding methyl esters on treatment with excess ethereal diazomethane. The ester mixture was chromatographed [silica gel column (15×5 cm); ethyl acetate (15 %) in hexane] to give a faster-moving ester fraction (0.27 g) (*vide infra*) and a fraction containing ±**10a** and ±**10b** (1.27 g). The latter was dissolved in ethyl acetate (20 ml) and subjected to catalytic hydrogenation over 5 % palladium-on-carbon (500 mg) to give the saturated esters ±**11a** and ±**11b**, which were separated by repeated chromatography [silica gel column (15×5 cm); ethyl acetate (10 %) in hexane]; the fastest moving band contained the *threo* ester (±**11b**) (157 mg), and the following contained the *erythro* ester (±**11a**) (642 mg), both esters being colourless oils.

(±)-erythro-*Methyl 10,11-dihydroxydodecanoate* (±**12a**). The ester ±**11a** (642 mg, 2.25 mmol) was dissolved in 1 % methanolic HCl (20 ml). After 16 h at 22 °C the solvent was removed and the dihydroxy ester recrystallized from ethyl acetate/hexane as colourless needles (316 mg, 57 %), m.p. 63.0–64.5 °C. Anal. $C_{13}H_{26}O_4$: C,H. ^{1}H NMR (500 MHz): δ 1.15 [3H, d, J = 6.5 Hz, H(C-12)], 1.29–1.33 [10H, m, H(C-4)-H(C-8)], 1.41 [2H, m, H(C-9)], 1.62 [2H, m, H(C-3)], ca. 2.0 (2H, br.s, 2OH), 2.30 [2H, t, J = 7.5 Hz, H(C-2)], 3.61 [1H, dt, J = 6.5 and 3.0 Hz, H(C-10)], 3.66 (3H, s, OMe) and 3.79 [1H, dq, J = 6.5 and 3.0 Hz, H(C-11)].

(±)-threo-*Methyl-10,11-dihydroxydodecanoate* (±**12b**). The ester **11b** was hydrolyzed in the

same manner as (±)-**11a** to give (±)-**12b** as colourless needles (from ethyl acetate/hexane), m.p. 50.5 °C. Anal. $C_{13}H_{26}O_4$: C,H. ^{1}H NMR (500 MHz): δ 1.20 [3H, d, *J* = 6.0 Hz, H(C-12)], 1.29–1.33 [10H, m, H(C-4)-H(C-8)], 1.35–1.40 [2H, m, H(C-9)], 1.62 [2H, m, H(C-3)], ca. 2.0 (2H, br.s, 2OH), 2.30 [2H, t, *J* = 7.5 Hz, H(C-2)], 3.35 [1H, m, H(C-10)], 3.59 [1H, dq, *J* = ca. 6.5 Hz, H(C-11)] and 3.67 (3H, s, OMe).

(±)-erythro-*10,11-Dihydroxydodecanoic acid* (±**3**). The methyl ester ±**12a** (226 mg, 0.92 mmol) was treated with a solution of 1 M KOH (1 ml) in methanol (5 ml) for 16 h to give the corresponding acid (±**3**), crystallizing from ethyl acetate/hexane as colourless needles (136 mg, 64 %), m.p. 78–79 °C. Anal. $C_{12}H_{24}O_4$: C,H. ^{1}H NMR (500 MHz): δ 1.16 [3H, d, *J* = 6.5 Hz, H(C-12)], 1.30–1.40 [10H, m, H(C-4)-H(C-8)], 1.41 [2H, m, H(C-9)], ca. 1.5 (2H, br.s, 20H), 1.64 [2H, quint., *J* = 7.5 Hz, H(C-3)], 2.35 [2H, t, *J* = 7.5 Hz, H(C-2)], 3.63 [1H, m, H(C-10)] and 3.82 [1H, m, H(C-11)].

(±)-threo-*10,11-Dihydroxydodecanoic acid* (±**13**). The (±)-*threo* ester (**12b**) was saponified as described for the (±)-*erythro* isomer to give the racemic *threo* acid (±**13**) as colourless needles from ethyl acetate/hexane, m.p. 87.5–88.5 °C. Anal. $C_{12}H_{24}O_4$: C,H. ^{1}H NMR (500 MHz): δ 1.20 [3H, d, *J* = 7.5 Hz, H(C-12)], 1.30–1.40 [10H, m, H(C-4)-H(C-8)], 1.40 [2H, m, H(C-9)], ca. 1.5 (2H, br.s, 2OH), 1.64 [2H, quint., *J* = ca. 7 Hz, H(C-3)], 2.34 [2H, t, *J* = 7.5 Hz, H(C-2)], 3.34 [1H, m, H(C-10)] and 3.60 [1H, quint., *J* = 6.0 Hz, H(C-11)].

Methyl 9-methyl-8-decenoate (**14b**). The faster-moving fraction from the methyl exter mixture, formed on treating the Wittig reaction products with diazomethane, was identified at **14** through its spectroscopic properties. ^{1}H NMR (90 MHz): δ 1.30 [6H, m, H(C-4)-H(C-6)], ca. 1.6 [2H, m, H(C-3)], 1.58 (3H, s, Me), 1.67 (3H, s, Me), 1.93 [2H, m, H(C-7)], 2.29 [2H, t, *J* = 7 Hz, H(C-2)], 3.64 (3H, s, OMe) and 5.07 [1H, t, *J* = 7 Hz, H(C-8)]. ^{13}C NMR (22.63 MHz): δ 174.3 (C-1), 131.3 and 124.8 (C-8 and C-9, or vice versa), 51.4 (OMe), 34.1, 29.7, 29.2, 29.0, 28.0, 25.7, 25.0 and 17.7. MS: 198 (14, M), 166 (8), 143 (11), 123 (12), 111 (20), 87 (25), 83 (27), 74 (28) and 69 (100, $[Me_2C{=}CHCH_2^+]$).

*Methyl 2(*R*),3(*R*)-dihydroxybutyrate* (**5**). Enantiomerically homogeneous (−)-2(*R*),3(*R*)-dihydroxybutyric acid (**4**)[14,15] {$[\alpha]_D^{25}$ −10.7° (*c* 1.0, water); lit.[26] $[\alpha]_D^{20}$ −10.78° (*c* 1.17, water), m.p. 60–64 °C (no m.p. recorded previously)} was converted into its methyl ester (**5**) as described for the racemate.[7] The product was purified by 'Kugelrohr' distillation at 180 °C/18 mmHg; $[\alpha]_D^{20}$ −16.0° (*c* 1.1, methanol). Anal. $C_5H_{10}O_4$: C,H.

*Methyl 4(*R*),5(*R*)-2,2,5-trimethyl-1,3-dioxolane-4-carboxylate* (**6**). Conversion of **5** into the previously unknown cyclic ester **6** was achieved, in 90 % yield, as described for the racemic series.[7] The ester was purified by 'Kugelrohr' distillation at 130 °C/18 mmHg; $[\alpha]_D^{20}$ −31.4° (*c* 1.25, methanol). Anal. $C_8H_{14}O_4$: C,H.

*4(*R*),5(*R*)-2,2,5-Trimethyl-1,3-dioxolane-4-carboxaldehyde* (**7**). Reduction of the ester **6** was performed as described above for the racemic series to give the aldehyde (**7**) (62 % yield) as a colourless oil which was homogeneous by GLC. For characterization, the aldehyde was converted into its 2,4-dinitrophenylhydrazone by brief heating (2 min) of the aldehyde with 2,4-dinitrophenylhydrazine in dioxane containing a few drops of acetic acid. After chromatography on silica gel (40 % ethyl acetate in hexane) and recrystallization from the same solvents, yellow needles were obtained, m.p. 130–132 °C; $[\alpha]_D^{22}$ −37° (*c* 1.6, chloroform). Anal. $C_{13}H_{16}N_4O_6$: C,H,N. ^{1}H NMR (90 MHz): δ 1.28 (3H, d, *J* = 6.5 Hz), 1.42 (3H, s), 1.56 (3H, s), 4.3–4.8 (2H, m), 7.37 (1H, d, *J* = 7 Hz), 7.91 (1H, d, *J* = 9 Hz), 8.32 (1H, dd, *J* = 9 Hz and 2 Hz), 9.13 (1H, d, *J* = 2 Hz) and 11.1 [1H, br.s (NH)].

*Methyl 10(*S*),11(*R*)-dihydroxydodecanoate* (**12a**). After Wittig reaction and subsequent processing as described above for the racemic series, **12a** was obtained as colourless needles, m.p. 50 °C: $[\alpha]_D^{22}$ −10.4° (*c* 1.1, chloroform). Anal. $C_{13}H_{26}O_4$: C,H.

*10(*S*),11(*R*)-Dihydroxydodecanoic acid* (**3**). Alkaline hydrolysis of **12a** gave the desired acid **3** as colourless needles (from ethyl acetate/pentane); m.p. 77–79 °C, $[\alpha]_D^{22}$ −17.4° (*c* 3.1, ethanol) (lit.[2] m.p. 68–71 °C, $[\alpha]_D^{23}$ +13.8° (ethanol) for the enantiomer). Anal. $C_{12}H_{24}O_4$: C,H. The ^{1}H NMR spectrum was identical with that of the racemate reported above.

10(R),11(R)-Dihydroxydodecanoic acid (**13**). Without further characterization, the crystalline ester **12b** (m.p. 41 °C), produced as described for the racemic series, was hydrolyzed to give the acid **13** as colourless needles, m.p. 74.5–76.0 °C; $[\alpha]_D^{22}$ +16.1° (*c* 0.9, ethanol). Anal. $C_{12}H_{24}O_4$: C,H.

Acknowledgements. The authors are grateful to Mr. D. Ruhiminparaga, Department of Biology, The Institute of Technology, Bandung, Indonesia for his kind assistance with the collection and identification of the plant material. The valuable help of Drs. G. Borch and K. Bock in recording the CD and two-dimensional NMR spectra, respectively, is gratefully acknowledged. The 500 MHz NMR spectra were recorded on an instrument placed at our disposal by The Danish Natural Science Research Council and the Carlsberg Foundation.

References

1. Gorter, K. *Bull. Jard. Bot. Buitenzorg 1* (1920) 327.
2. Birch, A. J. and Butler, D. N. *J. Chem. Soc.* (1964) 4167.
3. Pearson, G. A. *J. Magn. Reson. 64* (1985) 487.
4. Snatzke, G. *Angew. Chem. 80* (1968) 15.
5. Beecham, A. F. *Tetrahedron 28* (1972) 5543.
6. Mugdan, M. and Young, D. P. *J. Chem. Soc.* (1949) 2988.
7. Viscontini, M. and Frei, W. F. *Helv. Chim. Acta 55* (1972) 574.
8. Hatch, R. P., Shringarpure, J. and Weinreb, S. M. *J. Org. Chem. 43* (1978) 4172.
9. DeShong, P., Dickens, C. M., Leginus, J. M. and Whittle, R. R. *J. Am. Chem. Soc. 106* (1984) 5598.
10. Servi, S. *J. Org. Chem. 50* (1985) 5865.
11. Fronza, G., Fuganti, C., Grasselli, P., Majori, L., Pedrocchi-Fantoni, G. and Spreafico, F. *J. Org. Chem. 47* (1982) 3289.
12. Fujisawa, T., Kojima, E., Itoh, T. and Sato, T. *Tetrahedron Lett. 26* (1985) 6089.
13. Dawson, M. I. and Vasser, M. *J. Org. Chem. 42* (1977) 2783.
14. Bachelor, F. W. and Miana, G. A. *Can. J. Chem. 47* (1969) 4089.
15. Bachelor, F. W. and Miana, G. A. *Can. J. Chem. 45* (1967) 79.
16. Priestap, H. A., Bonafede, J. D. and Rúveda, E. A. *Phytochemistry 16* (1977) 1579.
17. Kjær, A., Norrestam, R. and Polonsky, J. *Acta Chem. Scand., Ser. B 39* (1985) 745.
18. Van Puyvelde, L., Dube, S., Uwimana, E., Uwera, C., Dommisse, R. A., Esmans, E. L., Van Schoor, O. V. and Vlietinck, A. J. *Phytochemistry 18* (1979) 1215.
19. Van Puyvelde, L., De Kimpe, N., Dubé, S., Chagnon-Dubé, M., Boily, Y., Borremans, F., Schamp, N. and Anteunis, M. J. O. *Phytochemistry 20* (1981) 2753.
20. Alemany, A., Márquez, C., Pascual, C., Valverde, S., Perales, A., Fayos, J. and Martínez-Ripoll, M. *Tetrahedron Lett.* (1979) 3579.
21. Alemany, A., Márquez, C., Pascual, C., Valverde, S., Martínez-Ripoll, M., Fayos, J. and Perales, A. *Tetrahedron Lett.* (1979) 3583.
22. Fehr, C., Galindo, J. and Ohloff, G. *Helv. Chim. Acta 64* (1981) 1247.
23. O'Connor, B. and Just, G. *Tetrahedron Lett. 27* (1986) 5201.
24. Achenbach, H. and Witzke, J. *Z. Naturforsch. B 35* (1980) 1459.
25. Lichtenthaler, F. W., Lorenz, K. and Ma, W. *Tetrahedron Lett. 28* (1987) 47.
26. White, J. C., Kang, M. and Sheldon, B. G. *Tetrahedron Lett. 24* (1983) 4539.

Received April 16, 1987.