4,5-Dihydro-2,5-dimethyl-3-iodo-6*H*-cyclopenta[*b*]thiophene (4a): yield 6.4 g (46% from **3a**); bp 96–98 °C (1.2 mm).

3-Iodo-2-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene (4b):[18] yield 9.0 g (65% from **3b**); bp 103–107 °C (0.8 mm) [lit.[18] bp 146–150 °C (12 mm)].

3-Iodo-2-methyl-4,5,6,7-tetrahydro-8*H*-cyclohepta[*b*]thiophene (4c): yield 10.7 g (73% from **3c**); bp 104–106 °C (0.5 mm); mp 40–41 °C (ethanol).

4,5,6,7,8,9-Hexahydro-3-iodo-2-methylcycloocta[*b*]thiophene (4d): yield 11.0 g (72% from **3d**); bp 113–114 °C (0.5 mm).

2,5-Dimethyl-3-iodo-4,5,6,7-tetrahydro-8*H*-cyclohepta[*b*]thiophene (4e): yield 10.0 g (65% from **3e**); bp 142–143 °C (2.5 mm).

2,7-Dimethyl-3-iodo-4,5,6,7-tetrahydro-8*H*-cyclohepta[*b*]thiophene (4f): yield 11.6 g (76% from **3f**); bp 142–143 °C (2.5 mm).

General Procedure for the Ring-Opening of the 3-Iodothiophenes. The 3-iodothiophenes **4a–f** (5.0 mmol) were each dissolved in 25 mL of anhydrous ether in a round-bottomed flask equipped with a rubber septum and a magnetic stirring bar. The flask was flushed with nitrogen, and the reaction was conducted under a nitrogen atmosphere. Phenyllithium (5.5 mmol) in ether was introduced with a syringe. The alkylating agent (5.5 mmol) was introduced after an appropriate period of time (15 min for the cyclopenta and tetrahydrobenzo derivatives, 2 h for the cyclohepta derivatives, and 1 h for the cycloocta derivative).

When ethyl bromoacetate was used as alkylating agent, the alkylation was allowed to proceed for 3–4 min only, in order to prevent resinification. Thereafter, the crude products were hydrolyzed by adding 25 mL of 5 M NaOH and 5 mL of ethanol and stirring for 2 h. The reaction mixture was then poured into water and washed with ether. The water phase was made acidic by hydrochloric acid and extracted with ether. The ether phase was washed with water, dried ($MgSO_4$), and evaporated.

When benzyl chloride was used as alkylating reagent, the reaction mixture was left 2 h before being quenched with water. The aqueous phase was extracted with ether, and the ethereal phase was washed with water, dried ($MgSO_4$), and evaporated.

From the crude products the following compounds were obtained in the pure state as indicated in Table I (together with yields and physical data): **1-(benzylthio)-4-methyl-2-(1-propynyl)cyclopentene (10a)**, **1-(benzylthio)-2-(1-propynyl)cyclohexene (10b)**, **1-(benzylthio)-2-(1-propynyl)cycloheptene (10c)**, **1-(benzylthio)-2-(1-propynyl)cyclooctene (10d)**, **1-(benzylthio)-4-methyl-2-(1-propynyl)cycloheptene (10e)**, **2-(benzylthio)-4-methyl-1-(1-propynyl)cycloheptene (10f)**, **[4-methyl-2-(1-propynyl)-cyclopenten-1-yl]thioacetic acid (10g)**, **[2-(1-propynyl)-cyclohexen-1-yl]thioacetic acid (10h)**, **[2-(1-propynyl)-cycloheptan-1-yl]thioacetic acid (10i)**, **[2-(1-propynyl)-cyclooctan-1-yl]thioacetic acid (10j)**.

2-(Methylthio)-1-formylcyclohexene (13). Sodium metal (7.4 g, 0.32 mol) was dissolved in 300 mL of absolute ethanol. The solution was then cooled to 0 °C, and 16 g (0.33 mol) of methanethiol was added, followed by 36 g (0.25 mol) of 2-chloro-1-formylcyclohexene.[17] After 15 min the mixture was heated, and reflux was maintained for 2 h. The ethanol was stripped off, and the residue was dissoved in ether, washed with water, dried ($MgSO_4$), and evaporated. The crude product was recrystallized from hexane: yield 32 g (65%); mp 46–47 °C; bp 141–143 °C (11 mm); IR (KBr) 1665 (C=O), 1580 cm^{-1} (C=C).

1-(Methylthio)-2-(2,2-dichloroethenyl)cyclohexene (14) was prepared according to Normant et al.[20] from 3.0 g (0.019 mol) of **13**. The crude product was chromatographed on silica gel by using hexane–ethyl acetate 95/5 as eluent; yield 2.2 g (50%). The compound was used in the next step without further characterization.

1-(Methylthio)-2-(1-propynyl)cyclohexene (10k) was prepared from 0.65 g (2.9 mmol) of **14** according to Normant et al.[20] The crude product was allowed to crystallize at −20 °C and was recrystallized from a small amount of hexane at −20 °C. For the yield and physical data see Table I.

(20) Villieras, J.; Pierrot, P.; Normant, J. F. *Synthesis* **1975**, 458.

Acknowledgment. We are grateful to Mr. G. Skarping for performing the capillary column chromatography of the methyl-substituted cyclohepta[*b*]thiophene systems. Grants from the Swedish Natural Science Council to T. F. and S. G. are gratefully acknowledged.

Registry No. 3a, 77416-12-7; **3b**, 40808-50-2; **3c**, 77416-13-8; **3d**, 77416-14-9; **3e**, 77416-15-0; **3f**, 77416-16-1; **4a**, 77416-17-2; **4b**, 77416-18-3; **4c**, 77416-19-4; **4d**, 77416-20-7; **4e**, 77416-21-8; **4f**, 77416-22-9; **7a**, 77416-23-0; **7b**, 77416-24-1; **10a**, 77416-25-2; **10b**, 77416-26-3; **10c**, 77416-27-4; **10d**, 77416-28-5; **10e**, 77416-29-6; **10f**, 77416-30-9; **10g**, 77416-31-0; **10h**, 77416-32-1; **10i**, 77416-33-2; **10j**, 77416-34-3; **10k**, 77416-35-4; **13**, 49571-45-1; **14**, 77416-36-5; 2-chloro-1-formylcyclohexene, 1680-73-5.

Supplementary Material Available: Table III showing elemental analyses and ^1H NMR data of compounds **3a–f**, **4a–f**, **7a–b**, **13**, and **14** (3 pages). Ordering information is given on any current masthead page.

C(15) Configuration of Isopimaren-15,16-diols and Sandaracopimaren-15,16-diols[1]

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The naturally occurring tricarbocyclic diterpenes of the pimarane skeletal type contain an increasing number of 15,16-diols (**1**). Whereas the stereochemistry of their rigid nuclear framework and of the substituents attached thereto could be determined readily by the spectral methods of analysis developed during the last three decades, the C(15) configuration has remained obscure in many cases in view of the nonrigid nature of the C(13)-attached dihydroxyethyl side chain. Recently there were introduced two procedures for the elucidation of the C(15) stereochemistry by ^{13}C NMR spectral analysis of cyclization products of the natural substances.[2,3] One of these new methods, developed for the analysis of pimaren-15,16-diols (**2**), was based on the isomerization of the olefinic diols into rigid (hydroxymethyl)tetrahydrofurans (**3**) and ^{13}C NMR spectral inspection thereof.[2] Since, in principle, this simple procedure is applicable also to sandaracopimaren-15,16-diols (**4**) and isopimaren-15,16-diols (**5**), its efficacy was investigated on diols derived from methyl sandaracopimarate (**6**) and virescenol B diacetate (**7**).

(1) Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. 73. For the previous paper see: E. Wenkert, E. W. Hagaman, N.-y. Wang, G. E. Gutowski, and J. C. Miller, *Heterocycles*, **15**, 255 (1981).

(2) E. Wenkert, P. Ceccherelli, M. S. Raju, J. Polonsky, and M. Tingoli, *J. Org. Chem.*, **44**, 146 (1979).

(3) E. Wenkert, M. S. Raju, P. Ceccherelli, M. Curini, M. Tingoli, and R. Pellicciari, *J. Org. Chem.*, **45**, 741 (1980).

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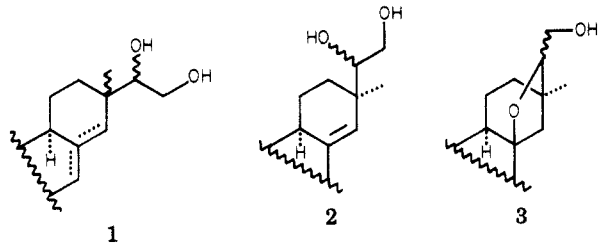

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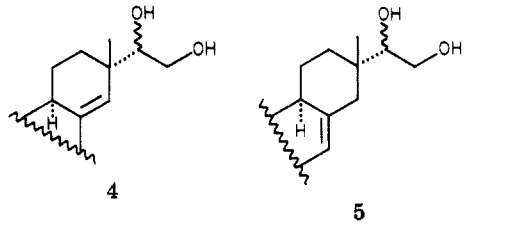

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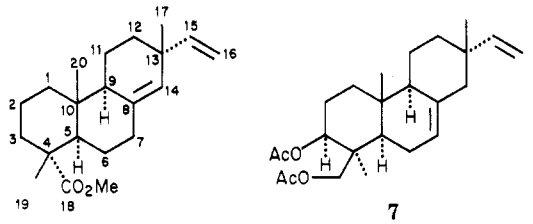
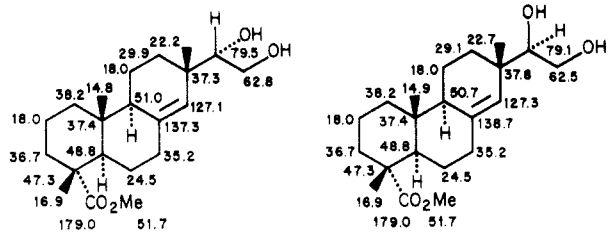


6 7

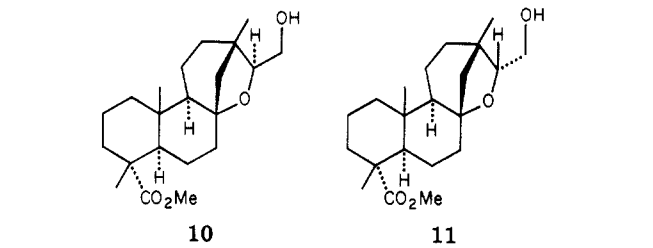
Oxidation of methyl sandaracopimarate (6) with osmium tetraoxide yielded diols 8 and 9, whose treatment with



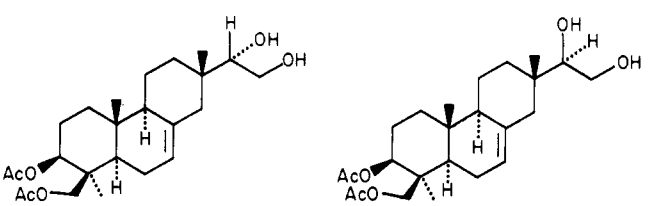
8 9

hydrogen chloride led to isomers 10 and 11, respectively. Similarly, exposure of the diol mixture 12 and 13, prepared earlier from virescenol B diacetate,[3] to acid produced tetrahydrofurans 14a and 15a. Jones oxidation of alcohol 14a gave acid 14b, while the same oxidation of 15a afforded acid 15b and a degradation product, γ-lactone 16.[4]

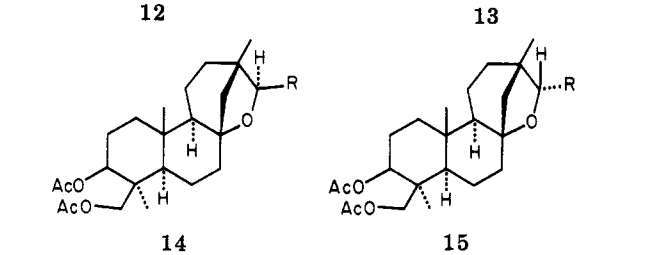
As in the earlier ^{13}C NMR spectral studies of the C(15) epimer pairs of 15,16-diols derived from pimarol[2] as well as from virescenol B (12 and 13)[3] a comparison of the carbon shifts between the C(15) epimers in the present investigation, i.e., the δ values depicted in formulas 8 and 9, indicates the shift differences to be too low to be of stereochemically diagnostic value. On the other hand, a comparison of the shifts of the rigid tetracycles 10, 14a, and 14b with their C(15) epimers 11, 15a, and 15b, respectively (cf. Table I), reveals expectedly strong changes for carbons 12 and 14–17. Thus acid-induced isomerization of pimarenic 15,16-diols and ^{13}C NMR spectral analysis of the resultant (hydroxymethyl)tetrahydrofurans[5] is now a general, short method for the determination of the C(15) configuration of such natural products.[6]



10 11

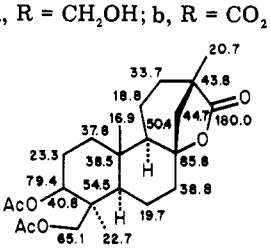


12 13



14 15

a, R = CH_2OH; b, R = CO_2H



16

Experimantal Section

Melting points were determined on a Reichert micro hot stage and are uncorrected. Infrared spectra of CCl_4 solutions were recorded on an Acculab 5 spectrophotometer and ^1H MMR spectra of $CDCl_3$ solutions (Me_4Si, δ 0) were obtained on JEOL IMN-C-60 HL and Varian EM390 spectrometers. Carbon-13 NMR spectra of $CDCl_3$ solutions were run on a Varian XL-100-15 spectrometer operating at 25.02 MHz in the Fourier transform mode. The carbon shifts on formulas 8, 9, and 16 are in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm.

Methyl 15,16-Dihydro-15,16-dihydroxysandaracopimarates (8 and 9). Osmium tetraoxide, 0.75 g (3 mmol), was added slowly to a stirred solution of 1.00 g (3 mmol) of methyl sandaracopimarate (6) in 30 mL of dioxane and the stirring was continued for 48 h. A stream of hydrogen sulfide gas was passed through the mixture for 1 h and the latter was filtered through Celite. The filtrate was evaporated under vacuum and the resultant residue chromatographed on silica gel. Elution with 50:1 chloroform–methanol yielded first 500 mg of semisolid C(15) *R* alcohol 9; ^1H NMR δ 0.81, 0.97, 1.20 (s, 3 each, 3 Me), 3.62 (s, 3, OMe), 5.20 (s, 1, H-14).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.10; H, 9.70.

Further elution gave 400 mg of semisolid C(15) *S* alcohol 8; ^1H NMR δ 0.80, 0.98, 1.20 (s, 3 each, 3 Me), 3.63 (s, 3, OMe), 5.28 (s, 1, H-14).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.08; H, 9.72.

(4) The reproducible formation of a lactone with concomitant loss of the hydroxymethyl group in the oxidation of solely one of the two (hydroxymethyl)tetrahydrofuran isomers may be of stereochemical significance. But more stereoisomer pairs will have to be tested before the isomerizaiton–oxidation procedure can be used as a chemical method of diagnosis of the C(15) configuration of 15,16-diols.

(5) In view of the a priori possibility of the isomerization leading to β-hydroxytetrahydropyrans it is useful to test the product structure by oxidation (e.g., 14a → 14b or 15a → 15b) or other techniques.

(6) The carbon shifts of lactone 16 are depicted in the formula. In order to differentiate between its C(7) and C(12) shifts, the ^{13}C NMR spectra of its 7-deuterio derivative, prepared by the interaction of the 15,16-diol from virescenol B diacetate (7) with deuterium chloride and subsequent oxidation, have been inspected.

Table I. ^{13}C Chemical Shifts of Tetracycles 10, 11, 14, and 15[a]

	10[b]	11[b]	14a[c]	15a[c]	14b[c]	15b[c]
C(1)	38.3	39.2	37.8	37.9	37.7	37.8
C(2)	18.4	18.8	23.3	23.3	23.3	23.5
C(3)	36.5	36.6	79.7	79.6	79.6	79.8
C(4)	47.2	47.3	40.7	40.7	40.7	40.9
C(5)	49.6	49.6	54.7[d]	54.6	54.6	54.7[d]
C(6)	23.3	23.2	21.3	21.1	21.3	21.1
C(7)	39.8	39.8	40.4	40.4	39.7	40.0
C(8)	84.2	84.3	83.8	83.4	86.2	86.1
C(9)	54.8	55.1	54.4[d]	54.6	53.9	54.4[d]
C(10)	37.9	38.1	38.1	38.1	38.1	38.4
C(11)	17.4	17.5	18.7	19.0	18.7	18.4
C(12)	39.0	32.3	38.1	32.1	37.5	32.8
C(13)	41.9	41.6	41.8	41.4	44.8	44.6
C(14)	44.6	47.6	44.2	47.1	43.2	47.5
C(15)	82.0	85.3	82.0	85.2	81.3	82.2
C(16)	64.1	61.7	64.0	61.3	176.1	173.5
C(17)	20.4	23.2	20.3	23.0	21.7	24.0
C(18)	178.6	178.8	22.6	22.5	22.6	22.8
C(19)	17.1	17.2	64.9	64.9	65.0	65.2
C(20)	16.1	16.1	16.5	16.5	16.5	16.5

[a] In parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] $\delta(OMe) = 51.7$ ppm. [c] Acetate $\delta(CO) = 170.3 \pm 0.4$ ppm and $\delta(Me) = 20.9 \pm 0.1$ ppm. [d] Signals in any vertical column may be interchanged.

Methyl 16-Hydroxy-8α,15(*S*)-oxy-8,14,15,16-tetrahydrosandaracopimarate (10). A solution of 200 mg of diol **8** in 100 mL of dry chloroform was saturated with hydrogen chloride gas and kept at room temperature for 48 h. It was mixed with 100 mL of water and the organic solution washed with a saturated sodium bicarbonate solution and with water and dried (Na_2SO_4). It then was evaporated and the residue chromatographed on silica gel. Elution with 32:1 chloroform–methanol led to the recovery of 65 mg of starting diol and 110 mg of semisolid alcohol **10**; ^1H NMR δ 0.98, 1.00, 1.15 (s, 3 each, 3 Me), 3.2–3.7 (m, 3, OCH, OCH_2), 3.63 (s, 3, OMe).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.78; H, 9.95.

Methyl 16-Hydroxy-8α,15(*R*)-oxy-8,14,15,16-tetrahydrosandaracopimarate (11). The same hydrogen chloride treatment of a solution of 200 mg of diol **9** in 100 mL of dry chloroform led to the recovery of 50 mg of starting diol and 100 mg of semisolid alcohol **11**; ^1H NMR δ 0.95, 1.02, 1.18 (s, 3 each, 3 Me), 3.3–3.8 (m, 3, OCH, OCH_2), 3.62 (s, 3, OMe).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.82; H, 9.89.

16-Hydroxy-8α,15ζ-oxy-7,8,15,16-tetrahydrovirescenol B Diacetate (14a and 15a). The identical treatment of a solution of 1.20 g of the diol **12** and **13** mixture[3] in 200 mL of dry chloroform yielded 1.20 g of crude alcohols, whose chromatography on silica gel and elution with 200:1 chloroform–methanol gave first crystalline C(15) *S* alcohol **14a**: mp 172 °C; ^1H NMR δ 0.98, 1.00, 1.01 (s, 3 each, 3 Me), 1.98, 2.00 (s, 3 each, 2 Ac Me), 3.2–3.8 (m, 3, OCH, OCH_2), 4.13 (4-line AB, 2, J = ca. 11 Hz, $AcOCH_2$), 4.50 (t, 1, J = 8 Hz, AcOCH).

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.07. Found: C, 68.18; H, 9.40.

Further elution yielded crystaline C(15) *R* alcohol **15a**; mp 175–176 °C; ^1H NMR δ 0.97, 1.05, 1.05 (s, 3 each, 3 Me), 2.00, 2.01 (s, 3 each, 2 Ac Me), 3.4–3.8 (m, 3, OCH, OCH_2), 4.12 (4-line AB, 2, J = ca. 11 Hz, $AcOCH_2$), 4.50 (t, 1, J = 8 Hz, AcOCH).

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.07. Found: C, 68.12; H, 9.37.

Jones Oxidation of Alcohols 14a and 15a. A solution of 1.0 mmol of Jones reagent (prepared from a solution of 70 g of chromium trioxide in 500 mL of water and 61 mL of concentrated sulfuric acid) was added slowly to a stirred solution of 290 mg of alcohol **14a** in 50 mL of acetone at 0 °C. After 0.5 h the mixture was decomposed with 5% sodium bisulfite solution, diluted with 150 mL of water, and extracted exhaustively with ether. The extract was dried (Na_2SO_4) and evaporated. Chromatography of the residue over silica gel and elution with 200:1 chloroform–methanol gave 60 mg of starting material. Elution with 20:1 chloroform–methanol afforded 150 mg of semisolid acid **14b**; ^1H NMR δ 0.98, 1.05, 1.08 (s, 3 each, 3 Me), 2.01, 2.05 (s, 3 each, 2 Ac Me), 4.10 (s, 1, H-15), 4.18 (4-line AB, 2, J = ca. 11 Hz, OCH_2), 4.50 (t, 1, J = 8 Hz, OCH).

Anal. Calcd for $C_{24}H_{36}O_7$: C, 66.03; H, 8.31. Found: C, 66.21; H, 8.20.

A solution of 250 mg of alcohol **15a** in 40 mL of acetone was treated with 0.90 mmol of Jones reagent as above. Elution of the chromatography column with chloroform yielded 90 mg of semisolid lactone **16**: IR 1770 (s, C=O), 1730 (s, C=O) cm^{-1}; ^1H NMR δ 1.05, 1.05, 1.18 (s, 3 each, 3 Me), 2.03, 2.06 (s, 3 each, 2 Ac Me), 4.23 (4-line AB, 2, J = ca. 11 Hz, OCH_2), 4.50 (t, 1, J = 8 Hz, OCH).

Anal. Calcd for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 68.21; H, 8.36.

Elution with 200:1 chloroform–methanol gave 30 mg of starting alcohol and elution with 20:1 chloroform–methanol led to 100 mg of semisolid acid **15b**; ^1H NMR δ 0.93, 0.97, 1.00 (s, 3 each, 3 Me), 1.96, 1.98 (s, 3 each, 2 Me), 4.08 (s, 1, H-15), 4.20 (4-line AB, 2, J = ca. 11 Hz, OCH_2), 4.55 (t, 1, J = 8 Hz, OCH).

Anal. Calcd for $C_{24}H_{36}O_7$: C, 66.03; H, 8.31. Found: C, 65.91; H, 8.56.

Acknowledgment. We are indebted to Dr. Bernard Delmond (Institut du Pin, Université de Bordeaux I) for a generous sample of sandaracopimaric acid and P.C., M.C., and R.P. to the CNR (Rome) for financial supporot in Perugia.

Registry No. 6, 1686-54-0; **8**, 77494-88-3; **9**, 77549-65-6; **10**, 77494-89-4; **11**, 77549-66-7; **12**, 72478-93-4; **13**, 72478-94-5; **14a**, 77494-90-7; **14b**, 77494-91-8; **15a**, 77549-67-8; **15b**, 77549-68-9; **16**, 77494-92-9.

A Short Route to Pyrenophorin and Vermiculine

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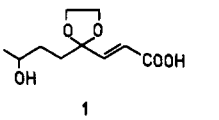
We report a new synthesis, from a common intermediate, of the monomeric units **1** and **2**, which correspond (and have been converted) to the dimeric macrolide (dilide) antibiotics (±)-pyrenophorin[2] (**3**) and (±)-vermiculine[3] (**4**).



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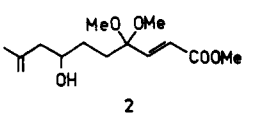

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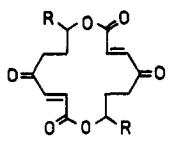

3 R = CH_3

4 R = CH_2COCH_3

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