Bull Soc Chim Fr (1995) 132, 114-118

A short and convergent synthesis of dideoxypyrenophorin : a simple model for the construction of 16-membered ring natural macrodiolides

Yves Le Floc'h*, Hervé Dumartin, René Grée

Laboratoire de Synthèses et Activations de Biomolécules, CNRS URA D1467, Ecole Nationale Supérieure de Chimie de Rennes, av du Général-Leclerc, 35700 Rennes, France

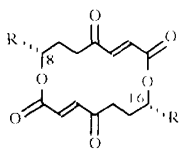
(received 24 October 1994, accepted 20 December 1994)

Summary – The title compound **2** is prepared using a new methodology involving two consecutive Wittig reactions and starting from a simple key molecule, the hydroxy acetal **4**.

macrodiolides / unsaturated dilactones / intramolecular Wittig reaction / dideoxypyrenophorin

Introduction

Macrolides form an important class of natural products and most have potent biological properties, especially in the field of antibiotics. These properties and their complex structure make them interesting target molecules for the organic chemist and many innovative total syntheses have already been described [1-12]. Some of these macrolides have two ester functions and one (*E*) or two (*E,E*) sites of unsaturation and were originally called dilactones; they have now been renamed macrodiolides [2]. These naturally occurring diolides can be divided in two groups, the first having a 14-membered unsymmetrical macrocyclic ring such as colletol [3], colletalol [4], colletodiol [5], colletoketol [6] and grahamimycin A_1 [7], and the second, a 16-membered macrocyclic ring with C_2 symmetry such as pyrenophorin **1a** [8], pyrenophorol [9], vermiculin **1b** [10], elaiophylin [11] and conglobatin [12] (fig 1). Many compounds of the second group show antimicrobial, antibacterial, antiprotozoal or antifungal activity [2]. However, it is interesting to note that few studies dealing with structure-activity relationships have been published for these derivatives [13]. Therefore, it appears to be important to design new, efficient and convergent strategies in order to study the influence of each structural element : ring size, number of double bonds, configuration of the stereogenic centers and nature of the substituents.



1a : R = CH_3, (-)-pyrenophorin
1b : R = CH_2-CO-CH_3, (-)-vermiculin

Fig 1

It is noteworthy that almost [14] all of these compounds were prepared from the corresponding ω-hydroxy acids by a macrodimerization reaction using the conditions of Mitsunobu [15]. This observation prompted us to initiate a synthetic programme in this field and we have already described a new route to 14-26-membered symmetrical macrodiolides involving a dimerization reaction between two ω-aldehydophosphoranes [16]. Since this route is limited to the construction of symmetrical molecules only, we have also reported another, more general, synthesis of macrodiolides, starting from ω-diols and involving two consecutive Wittig reactions [17]. *This has only been performed with simple, unsubstituted, models, even through all the natural products of this family have substituents in positions 8 and 16.* Thus, it is important to establish that this new strategy is also suitable for the preparation of macrodiolides *substituted in these two positions with the same or with different substituents.* The purpose of this paper is to describe a short and versatile synthesis of *meso*-**2a** and *d,l*-**2b** dideoxypyrenophorin which are convenient models for such a construction of various 16-membered macrodiolides.

Results

Due to the C_2 symmetry of the target molecules, the construction of the 16-membered ring needs only two molecules of bromoacetyl bromide, two of triphenylphosphine and two of the key intermediate **4**

* Correspondence and reprints

(fig 2). This alcohol is obtained by reaction of the Grignard reagent prepared from bromobutanal diethylacetal [18] with acetaldehyde. After esterification with bromoacetyl bromide the resulting ester **5** is transformed either into the aldehyde **6** or, in two steps, into the ylid **7**. In that case, the two fragments possess the same methyl group but this could easily be modified by the use of another aldehyde in the first step. A first intermolecular Wittig reaction between **6** and **7** leads to the (*E*) olefin **8** as the only isolated stereoisomer.

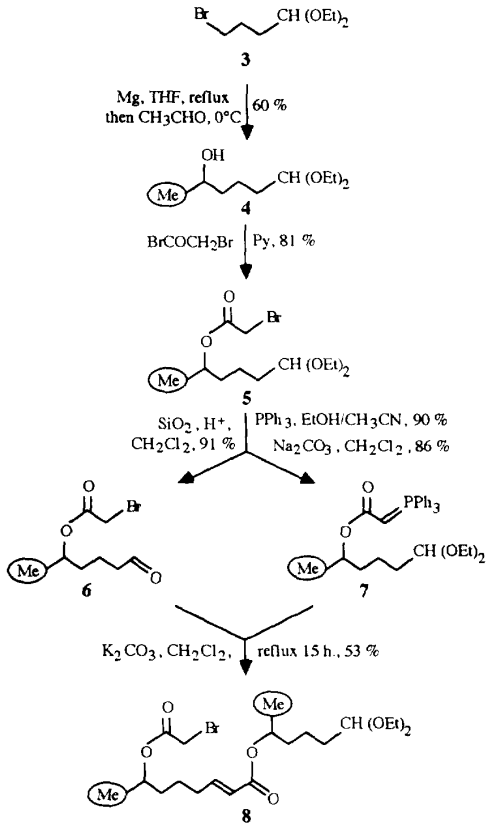


Fig 2

After acetal hydrolysis of **8**, the phosphonium salt **10** is obtained from the aldehyde **9**. The final ring closure occurred conveniently (83% yield) by an intramolecular Wittig reaction under the high-dilution reaction conditions previously described [17]. The macrodiolide **2** is obtained (8 steps, 10% overall yield) as a mixture of *meso*-**2a** and *d,l*-**2b** dideoxypyrenophorin, which were easily separated by flash chromatography. Their structures are unambiguously established by comparison of their physical and spectroscopical data with that found in the literature [13]. This also constitutes a formal synthesis of pyrenophorin since the transformation of **2** into **1a** has already been reported [13] (fig 3).

In conclusion, our strategy towards the synthesis of macrodiolides can easily be extended to derivatives bearing substituents in positions vicinal to the ring oxygen atoms. *This approach appears to be very versatile since both the nature of the two substituents in type* **6** *and* **7** *fragments (by the choice of the starting aldehydes) and the chain length (by selection of appropriate Grignard reagent) can be controlled.* A final key point involving the control of the stereogenic centers and the asymmetric version of these syntheses is under active investigation in our laboratory; the first, optically active, key intermediates have been described recently [20].

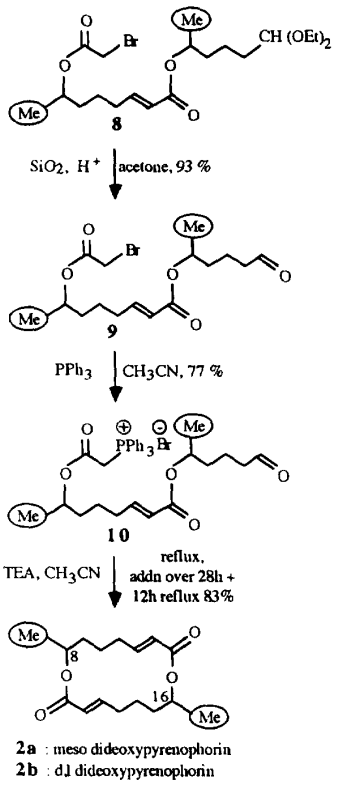


Fig 3

Experimental section

General methods : see reference [16b].

5-Hydroxyhexanal diethylacetal **4** *[18]*

To a 250 mL round-bottomed two-necked flask fitted with a magnetic stir bar, a 100 mL pressure-equalizing addition funnel and a reflux condenser with an outlet to a nitrogen atmosphere was added magnesium turnings (390 mg, 16 mmol, 1.2 equiv) and anhydrous THF (10 mL). The addition funnel was charged with a solution of freshly distilled bromo compound **3** [19] (3 g, 13.3 mmol, 1 equiv) in anhydrous THF (50 mL). Approximately 5 mL of this solution was added slowly with stirring until the Grignard reaction commenced with reflux of solvent. (If the Grignard reaction did not start within a few minutes, a catalytic quantity of 1,2-dibromoethane was required). Generally, the addition was complete in 1 h, and almost all the magnesium had dissolved. The mixture was refluxed for 1 h further. A solution of freshly distilled acetaldehyde (0.6 g, 13.3 mmol, 1 equiv) in anhydrous THF was then transferred to the addition funnel and added over 10 min, with stirring, to the mixture cooled in an ice-bath. After 1 h, the reaction was

quenched by the addition of dilute NH_4Cl. The reaction mixture was extracted with ether (2 × 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. Flash chromatography (40 g of SiO_2; 0-50% ether in petroleum ether) of the residue gave alcohol **4** as a colorless liquid (1.5 g, 60%) :

Rf = 0.11 with ether/petroleum ether 1:1.

IR (neat, KBr) : 3 480 (OH) cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz) : 4.49 (t, 1H, *J* = 6.0 Hz), 3.80 (qt, 1H, *J* = 5.8 Hz), 3.70-3.57 (m, 2H), 3.57-3.43 (m, 2H), 1.75-1.55 (m, 3H, O*H*), 1.55-1.35 (m, 4H), 1.21 (t, 6H, *J* = 7.1 Hz), 1.19 (d, 3H, *J* = 6.0 Hz).

^{13}C NMR ($CDCl_3$, 22.5 MHz) : 102.5, 66.9, 60.5, 60.4, 38.6, 33.2, 22.9, 20.6, 14.9.

Anal calc for $C_{10}H_{21}O_3$: C (63.12), H (11.65), found : C (62.82), H (11.33).

HRMS *m/z* calc for $[M-.H]^+$: 189.1491, found : 189.1496; calc for $[M-.OC_2H_5]^+$: 145.1228, found : 145.1226.

5-(Bromoacetoxy)hexanal diethylacetal **5**

To a 100 mL round-bottomed flask fitted with a magnetic stir bar and a condenser with an outlet to a nitrogen atmosphere was added compound **4** (750 mg, 3.95 mmol, 1 equiv) in anhydrous CH_2Cl_2 (60 mL). The solution was cooled to 0°C with an ice bath and anhydrous pyridine (750 μL, 8.37 mmol, 2.1 equiv) was added. Bromoacetyl bromide (500 μL, 5.64 mmol, 1.43 equiv) was then added dropwise with vigorous stirring; a yellow precipitate started to form immediately. After 2 h, the mixture was concentrated and ether was added. Filtration through a plug of cotton, concentration and flash chromatography (15 g of SiO_2; 20% ether in petroleum ether) of the residue gave bromoester **5** as a colorless liquid (1 g, 81%) :

Rf = 0.50 ether/petroleum ether 1:1.

IR (neat, KBr) : 1 730 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$, 90 MHz) : 4.97 (qt, 1H, *J* = 6.1, 6.1 Hz), 4.47 (t, 1H, *J* = 5.0 Hz), 3.80 (s, 2H), 3.75-3.30 (m, 4H), 1.70-1.40 (m, 6H), 1.26 (d, 3H, *J* = 6.1 Hz), 1.20 (t, 6H, *J* = 7.0 Hz).

^{13}C NMR ($CDCl_3$, 22.5 MHz) : 166.9, 102.8, 73.3, 61.1, 35.5, 33.4, 26.3, 20.6, 19.7, 15.4.

HRMS *m/z* calc for $[M-.OC_2H_5]^+$: 265.0439, found : 265.0439; calc for $[M-.OC_2H_5\text{-}BrCH_2CO_2H]^+$: 127.1123, found : 127.1125.

5-(Bromoacetoxy)hexanal **6**

A 50 mL conical flask fitted with a magnetic stir bar was charged with silica gel (4.5 g) and CH_2Cl_2 (13 mL); 2.5% H_2SO_4 (0.45 g) was then added with vigorous stirring, followed by compound **5** (450 mg, 1.45 mmol, 1 equiv) in CH_2Cl_2 (7 mL). The mixture was stirred overnight at room temperature, filtered and dried ($MgSO_4$). Concentration and flash chromatography (10 g, SiO_2; 10% ether in petroleum ether) of the residue gave aldehyde **6** as a colorless liquid (310 mg, 91%) :

Rf = 0.27 with ether/petroleum ether 1:1.

IR (neat, KBr) : 1 720 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$, 90 MHz) : 9.77 (t, 1H, *J* = 1.5 Hz), 5.50-4.50 (m, 1H), 3.81 (s, 2H), 2.49 (td, 2H, *J* = 5.1, 1.5 Hz), 1.70-1.55 (m, 4H), 1.27 (d, 3H, *J* = 6.3 Hz).

^{13}C NMR ($CDCl_3$, 22.5 MHz) : 201.7, 166.8, 72.7, 43.4, 35.0, 26.2, 19.6, 17.8.

HRMS *m/z* calc for $[M-.(CH_2)_3CHO]^+$: 164.9551, found : 164.9548, calc for $[CH_2 = CH\text{-}CH_2\text{-}CHO]^+$: 70.0419, found : 70.0417.

Ylide **7**

To a 50 mL round-bottomed flask fitted with a magnetic stir bar and an outlet to a nitrogen atmosphere was added compound **5** (1.26 g, 4 mmol, 1 equiv) in solvent (ethanol/CH_3CN 2:1, 63 mL) and triphenylphosphine (1.13 g, 4.3 mmol, 1.1 equiv). The mixture was stirred for 2 d at room temperature, concentrated, diluted with ether and stirred vigorously for 1 h. After filtration, the precipitate was washed with ether and dried under vacuum. The phosphonium salt (2 g, 86%) was isolated as a very hygroscopic white powder (*Rf* = 0.39 CH_2Cl_2/MeOH 9:1). This salt (1 g, 1.75 mmol) was dissolved in CH_2Cl_2 (20 mL) and treated with saturated aqueous Na_2CO_3 (3 × 10 mL). After vigorous shaking and partitioning, the organic phase was washed with water (3 × 20 mL), dried ($MgSO_4$) and concentrated under vacuum to afford phosphorane **7** as a yellow oil (740 mg, 86%) :

^1H NMR (CD_2Cl_2, 90 MHz) : 8.20-7.35 (m, 15H), 4.85-4.58 (m, 1H), 4.36 (t, 1H, *J* = 5.6 Hz), 3.60-3.20 (m, 4H), 2.77 (s, 1H), 1.30-1.20 (m), 1.14 (t, 6H, *J* = 7.0 Hz), 0.96 (d, 3H, *J* = 6.2 Hz).

^{13}C NMR (CD_2Cl_2, 22.5 MHz) : 171.0, 133.4 (d, J_{C-P} = 10.4 Hz), 132.2 (d, J_{C-P} = 3 Hz), 129.0 (d, J_{C-P} = 12.2 Hz), 128.8 (d, J_{C-P} = 92.2 Hz), 103.4, 67.6, 61.3, 36.8, 34.2, 29.9 (d, J_{C-P} = 23.9 Hz), 21.2, 20.5, 15.6.

No more data were available because of the instability of this compound.

Bromoester acetal **8**

To a 100 mL round-bottomed two-necked flask fitted with a magnetic stir bar and a reflux condenser with an outlet to a nitrogen atmosphere was added, with stirring, compound **6** (150 mg, 0.63 mmol, 1 equiv) in anhydrous CH_2Cl_2 (20 mL) and compound **7** (375 mg, 0.76 mmol, 1.2 equiv) in anhydrous CH_2Cl_2 (25 mL). The reaction mixture was allowed to warm to reflux and was left to stir overnight. The solvent was removed and ether (70 mL) was added with vigorous stirring. After filtration and evaporation of the ether, the residue was subjected to a flash chromatography (20 g of SiO_2, 5-10% ether in petroleum ether) affording olefin (*E*)**8** as a colorless liquid (150 mg, 53%) :

Rf = 0.41 with ether/petroleum ether 1:1.

IR (neat, KBr) : 1 710 (C=O), 1 650 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz) : 6.91 (dt, 1H, *J* = 15.6, 6.9 Hz), 5.81 (dt, 1H, *J* = 15.6, 1.5 Hz), 5.05-4.90 (m, 2H), 4.47 (t, 1H, *J* = 5.6 Hz), 3.83 (d, 1H, J_{gem} = 12.1 Hz), 3.79 (d, 1H, J_{gem} = 12.1 Hz), 3.75-3.30 (m, 4H), 2.21 (dm, 2H, *J* = 6.9 Hz), 1.80-1.30 (m, 10H), 1.26 (d, 3H, *J* = 5.4 Hz), 1.24 (d, 3H, *J* = 6.6 Hz), 1.20 (t, 6H, *J* = 7.1 Hz).

^{13}C NMR ($CDCl_3$, 75.5 MHz) : 166.9 (dd, *J* = 7.5, 4.3 Hz), 166.3 (dd, *J* = 6.0, 3.3 Hz), 148.0 (dtd, *J* = 154.7, 6.8, 4.4 Hz), 122.2 (dtd, *J* = 161.7, 4.5, 1.6 Hz), 102.8 (d, *J* = 158 Hz), 73.0 (d, *J* = 146.6 Hz), 70.7 (d, *J* = 147.8 Hz), 61.0 (tq, *J* = 141.3, 1.7 Hz), 35.8 (t, *J* = 122.7 Hz), 35.2 (t, *J* = 126.1 Hz), 33.4 (t, *J* = 125.3 Hz), 31.8 (t, *J* = 128.1 Hz), 26.2 (t, *J* = 153.3 Hz), 23.7 (t, *J* = 123.8 Hz), 20.6 (t, *J* = 125.3 Hz), 20.0 (q, *J* = 126.7 Hz), 19.7 (q, *J* = 127.2 Hz), 15.4 (qt, *J* = 125.9, 2.5 Hz).

Anal calc for $C_{20}H_{35}BrO_6$: C (53.33), H (7.82), found : C (53.69), H (7.65).

HRMS *m/z* calc for $[C_{12}H_{20}O_4{}^{79}Br]^+$: 307.0545, found : 307.0533; calc for $[(C_2H_5O)_2CH]^+$: 103.0759, found : 103.0764.

Bromoester aldehyde **9**

Compound **9** was prepared in the same manner as compound **6** : from compound **8** (180 mg, 0.4 mmol, 1 equiv) treated with a mixture of silica gel (1.8 g), acetone (9 mL) and 2.5% H_2SO_4 (0.6 g), was isolated after flash chromatography (15 g of SiO_2, 0-30% ether in petroleum ether) aldehyde **9** as a colorless liquid (140 μg, 93%) :

Rf = 0.23 with ether/petroleum ether 1:1.

IR (neat, KBr) : 1 720 (C=O), 1 635 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz) : 9.77 (t, 1H, J = 1.5 Hz), 6.92 (dtt, 1H, J = 15.6, 6.9, 3.5 Hz), 5.81 (dt, 1H, J = 15.6, 1.5 Hz), 5.10-4.90 (m, 2H), 3.83 (d, 1H, J_{gem} = 12.1 Hz), 3.79 (d, 1H, J_{gem} = 12.1 Hz), 2.48 (td, 2H, J = 7.3, 1.5 Hz), 2.22 (d, 2H, J = 6.9 Hz), 1.80-1.40 (m, 8H), 1.27 (d, 3H, J = 6.3 Hz), 1.25 (d, 3H, J = 6.3 Hz).

^{13}C NMR ($CDCl_3$, 75.5 MHz) : 202.1 (dt, J = 165.6, 4.8 Hz), 166.9 (dd, J = 7.4, 4.2 Hz), 166.2 (dd, J = 6.3 Hz), 148.4 (d, J = 154.8 Hz), 122.1 (dt, J = 162.2, 5.5 Hz), 72.9 (d, J = 147.9 Hz), 70.2 (d, J = 146.2 Hz), 43.5 (tdt, J = 125.1, 24.1, 3.8 Hz), 35.3 (t, J = 129.1 Hz), 35.2 (t, J = 129.1 Hz), 31.8 (t, J = 128.7 Hz), 26.2 (t, J = 153.4 Hz), 23.7 (t, J = 129.4 Hz), 20.0 (q, J = 126.7 Hz), 19.8 (q, J = 127.2 Hz), 18.0 (t, J = 129.7 Hz).

Anal calc for $C_{16}H_{25}BrO_5$: C (50.94), H (6.68), found : C (51.16), H (6.63).

HRMS m/z calc for $[M\text{-}.OCH(CH_3)(CH_2)_3CHO]^+$: 261.0126, found : 261.0137; calc for $[M\text{-}.MeCHOH(CH_2)_3CHO]^+$: 260.0048, found : 260.0045; calc for $[C_8H_{13}O_2]^+$: 141.0915, found : 141.0915; calc for $[C_8H_{11}O]^+$: 123.0810, found : 123.0806; calc for $[C_6H_{11}O_2]^+$: 115.0759, found : 115.0760.

Phosphonium salt **10**

Compound **10** was prepared in the same manner as the phosphonium salt leading to the ylide **7**. From triphenylphosphine (90 mg, 0.34 mmol, 1 equiv) and compound **9** (130 mg, 0.34 mmol, 1 equiv) in anhydrous acetonitrile (7 mL), after 2 d, was isolated phosphonium salt **10** as a white hygroscopic powder (170 mg, 77%).

^1H NMR ($CDCl_3$, 300 MHz) : 9.76 (t, 1H, J = 1.5 Hz), 8.10-7.60 (m, 15H), 6.83 (dt, 1H, J = 15.6, 6.2 Hz), 5.75 (dt, 1H, J = 15.6, 1.3 Hz), 5.60-5.45 (m, 2H), 4.98 (m, 1H), 4.77 (m, 1H), 2.48 (td, 2H, J = 6.6, 1.5 Hz), 2.10 (td, 2H, J = 6.7, 6.2 Hz), 1.8-1.3 (m, 8H), 1.26 (d, 3H, J = 6.3 Hz), 1.03 (d, 3H, J = 6.3 Hz).

^{13}C NMR ($CDCl_3$, 75.5 MHz) : 202.6 (d, J = 170.4 Hz), 166.2 (dd, J = 6.2, 2.9 Hz), 164.1 (d, J_{C-P} = 3.4 Hz), 148.2 (d, J = 154.4 Hz), 135.2 (dtd, J = 163.5, 6.5 Hz, J_{C-P} = 2.7 Hz), 134.1 (dddd, J = 175.9, 6.9, 6.9 Hz, J_{C-P} = 10.8 Hz), 130.3 (ddd, J = 167.0, 7.3 Hz, J_{C-P} = 13 Hz), 122.1 (dt, J = 161.3, 5.1 Hz), 118.1 (dt, J_{C-P} = 88.8 Hz, J = 8.2), 74.3 (d, J = 147.3 Hz), 70.3 (d, J = 147.3 Hz), 43.5 (tdt, J = 121.7, 24.2, 3.6 Hz), 35.3 (t, J = 133.6 Hz), 34.9 (t, J = 122.6 Hz), 33.5 (dt, J = 134.6 Hz, J_{C-P} = 55.8 Hz), 31.7 (t, J = 126.9 Hz), 23.6 (t, J = 126.21 Hz), 20.0 (q, J = 126.8 Hz), 19.5 (q, J = 127.6 Hz), 18.0 (t, J = 126.9 Hz).

(3E,11E)-8,16-Dimethyl-1,9-dioxacyclohexadeca-3,11-diene-2,10-dione : dideoxypyrenophorin **2**

To a 50 mL round-bottomed two-necked flask fitted with a magnetic stir bar and a reflux condenser with an outlet to nitrogen atmosphere and charged with dry TEA (120 μL, 0.88 mmol, 0.8 equiv) in anhydrous CH_3CN (5 mL), was added compound **10** (70 mg, 0.11 mmol, 1 equiv) in anhydrous CH_3CN (20 mL) at reflux over 28 h. The mixture was refluxed for a further 12 h, concentrated and was subjected to a flash chromatography (4 g of SiO_2, 0-20% ether in petroleum ether) to afford 2 fractions as white crystalline powders : *meso*-diolide **2a** (10.3 mg, 32%) and *d,l*-diolide **2b** (15.6 mg, 51%). These yields were lower when the solution was not sufficiently dilute. The assignment of *meso*- and *d,l*-**2** was given by RS Mali *et al* referenced in [8d].

• meso-*Diolide* **2a**

Rf = 0.38 with ether/pentane 4:6.

IR : see RS Mali *et al* referenced in [8d].

^1H NMR ($CDCl_3$, 300 MHz) : 6.89 (ddd, 2H, J = 15.7, 8.05, 5.7 Hz), 5.84 (dt, 2H, J = 15.7, 15.7, 1.5 Hz), 5.2 (qdd, 2H, J = 6.4, 6.4, 2.1 Hz), 2.4-2.1 (m, 4H), 1.8-1.4 (m, 8H), 1.23 (d, 6H).

^{13}C NMR ($CDCl_3$, 75.5 MHz) : 166.0 (m), 148.4 (ddt, J = 154.9, 6.4, 6.4 Hz), 122.7 (dtd, J = 161.5, 5.3, 1.5 Hz), 70.4 (d, J = 128.4 Hz), 19.4 (q, J = 126.6 Hz).

HRMS m/z calc for $[M]^+$: 280.1674, found : 280.1671, the fragment $[M\text{-}H_2O]^+$: 262 was observed.

• d,l-*Diolide* **2b**

Rf = 0.29 with ether/pentane 4:6.

IR : see RS Mali *et al* referenced in [8d].

^1H NMR ($CDCl_3$, 300 MHz) : 6.95 (ddd, 2H, J = 15.8, 7.6, 5.8 Hz), 5.85 (dt, 2H, J = 15.8, 1.6 Hz), 5.02 (qdd, 2H, J = 6.5, 6.5, 2.9 Hz), 2.4-2.1 (m, 4H), 1.8-1.4 (m, 8H), 1.26 (d, 6H, J = 6.5 Hz).

^{13}C NMR ($CDCl_3$, 75.5 MHz) : 165.9 (m), 148.2 (ddt, J = 154.9, 6.4, 6.4), 122.7 (dt, J = 161.5, 5.2 Hz), 70.2 (d, J = 150.6 Hz), 33.2 (t, J = 123.4 Hz), 30.7 (t, J = 124.3 Hz), 21.9 (t, J = 127.4 Hz), 19.1 (qd, J = 127.4, 2.11 Hz).

HRMS m/z calc for $[M]^+$: 280.1674, found : 280.1671, the fragment $[M\text{-}H_2O]^+$: 262 was observed.

References

1 Reviews on macrolides :
a) Omura S, *Macrolide Antibiotics : Chemistry, Biology and Practice*, Academic, New York, 1984
b) Masamune S, Bates GS, Corcoran JW, *Angew Chem Int Ed Engl* (1977) 16, 585
c) Nicolaou KC, *Tetrahedron* (1977) 33, 683
d) Back TG, *Tetrahedron* (1977) 33, 3041

2 For a review on macrodiolides see reference [1a] pp 538-541

3 Keck GE, Murry JA, *J Org Chem* (1991) 56, 6606 and references cited therein

4 Dommerholt FJ, Thijs L, Zwanenburg B, *Tetrahedron Lett* (1991) 32, 1495 and references cited therein

5 Keck GE, Boden EP, Wiley MR, *J Org Chem* (1989) 54, 896 and references cited therein

6 Millan J Mc, Simpson JT, *J Chem Soc Perkin Trans 1* (1973) 1487

7 Ohta K, Mitsunobu O, *Tetrahedron Lett* (1991) 32, 517

8 *Pyrenophorin* :
a) *structure* : Nozoe S, Hirai K, Tsuda K, Ishibushi K, Shirasaka M, Grove JF, *Tetrahedron Lett* (1965) 4675
b) *hemisyntheses* : Traverso G, Pirillo D, Rescia G, *Il Farmaco Ed Sc* (1979) 34, 409; Trost BM, Gowland FW, *J Org Chem* (1979) 44, 3448; Pirrillo D, Rescia G, Traverso G, De Paoli A, *Il Farmaco Ed Sc* (1979) 35, 324; Hase TA, Ourila A, Homberg C, *J Org Chem* (1981) 46, 3137; Baraldi PG, Barco A, Benetti S, Moroder F, Pollini GP, Simoni D, *J Org Chem* (1983)

48, 1297; Labadie JW, Stille JK, *Tetrahedron Lett* (1983) 24, 4283; Dumont W, Vermeyen C, Krief A, *Tetrahedron Lett* (1984) 25, 2883; Breuilles P, Uguen D, *Tetrahedron Lett* (1984) 25, 5759; Petrini M, Ballini R, Rosini G, Marotta E, *Tetrahedron* (1986) 42, 151; Rao AVR, Reddy KB, Dhar TGM, *Indian J Chem* (1986) 25B, 1014; Zschiesche R, Hafner T, Reissig HU, *Liebigs Ann Chem* (1988) 1169; Breuilles P, Uguen D, *Bull Soc Chim Fr* (1988) 705; Nagooi TK, Scilimati A, Guo Z, Sih CJ, *J Org Chem* (1989) 54, 911; Barre V, Massias F, Uguen D, *Tetrahedron Lett* (1989) 30, 7389; Solladié G, Gerber C, *Synlett* (1992) 449
c) (±)-*Pyrenophorin* : Colvin EW, Purcell TA, Raphael RA, *J Chem Soc Chem Commun* (1972) 1031; Colvin EW, Purcell TA, Raphael RA, *J Chem Soc Perkin Trans 1* (1976) 1718; Gerlach H, Oertle K, Thalmann A, *Helv Chim Acta* (1977) 60, 2860; Bakuzis P, Bakuzis MLF, Weingartner TF, *Tetrahedron Lett* (1978) 27, 2371; Seuring B, Seebach D, *Liebigs Ann Chem* (1978) 2044; Asaoka M, Mukuta T, Takei H, *Tetrahedron Lett* (1981) 22, 735; Bates GS, Ramaswany S, *Can J Chem* (1983) 61, 2466; Derguini F, Linstrumelle G, *Tetrahedron Lett* (1984) 25, 576
d) (−)-*Pyrenophorin* : Seebach D, Seuring B, Kalinowski HO, Lubosch W, Renger B, *Angew Chem Int Ed Engl* (1977) 16, 264; Seuring B, Seebach D, *Liebigs Ann Chem* (1978) 2044; Mali RS, Pohmakotr M, Weidmann B, Seebach D, *Liebigs Ann Chem* (1981) 2272; Hatakeyama S, Satoh K, Sakurai K, Takano S, *Tetrahedron Lett* (1987) 28, 2717; Yoshida M, Harada N, Nakamura H, Kanematsu K, *Tetrahedron Lett* (1988) 29, 6129; Baldwin JE, Adlington RM, Ramcharitar SH, *Synlett* (1992) 875; Machinaga N, Kibayashi C, *Tetrahedron Lett* (1993) 34, 841; Matsushita Y, Furusawa H, Matsui T, Nakayama M, *Chem Lett* (1994) 1083; Nokami J, Taniguchi T, Gomyô S, Kakihara T, *Chem Lett* (1994) 1103
e) for a review, see *Synform* (1986) 4, 259

9 a) (±)-*Pyrenophorol* : Hirao T, Fujihara Y, Kurokawa K, Oshiro Y, Agawa T, *J Org Chem* (1986) 51, 2830
b) b) (−)-*Pyrenophorol* : Dommerholdt FJ, Thijs L, Zwanenburg B, *Tetrahedron Lett* (1991) 32, 1499; Machinaga N, Kibayashi C, *Tetrahedron Lett* (1993) 34, 841

10 a) (±)-*Vermiculin* : Corey EJ, Nicolaou KC, Toru T, *J Am Chem Soc* (1975) 97, 2287; Fukuyama Y, Kirkemo CL, White JD, *J Am Chem Soc* (1977) 99, 646; Hase TA, Ourila A, Holmberg C, *J Org Chem* (1981) 46, 3137
b) (±)-*Vermiculin* : Seebach D, Seuring B, Kalinowski HO, Lubosch W, Renger B, *Angew Chem Int Ed Engl* (1977) 16, 264
c) (−)-*Vermiculin* : Seuring B, Seebach D, *Liebigs Ann Chem* (1978) 2044; Burri KF, Cardone RA, Chen WY, Rosen P, *J Am Chem Soc* (1978) 100, 7069; Noda A, Aoyagi S, Machinaga N, Kibayashi C, *Tetrahedron Lett* (1994) 35, 8237

11 *Elaiophylin* (azalomycin B) : Kaiser H, Keller-Schierlein W, *Helv Chim Acta* (1981) 64, 407; Toshima K, Tatsuta K, Kinoshita H, *Tetrahedron Lett* (1986) 39, 4741; Toshima K, Tatsuta K, Kinoshita M, *Bull Chem Soc Jpn* (1988) 61, 2369

12 *Conglobatin* : Schregenberger C, Seebach D, *Tetrahedron Lett* (1984) 25, 5881; Schregenberger C, and Seebach D, *Liebigs Ann Chem* (1986) 2081

13 It is interesting to note that the CO–CH=CH–CO_2R moiety appears to be essential for biological activity : neither **2a** nor **2b** show any activity with the microorganisms which were affected by **1a** and **1b**; see Mali RS, referenced in [8d]

14 A total synthesis of (−)-vermiculin using a HWE reaction to achieve the closure of the ring is related : see Burri KF, referenced in [10c]; the norpyrenophorin and the (−)-Grahamimycin A_1 syntheses using a cumulenic phosphorane and two consecutive Wittig reactions are also noteworthy : Bestmann HJ, Schobert R, *Angew Chem Int Ed Engl* (1985) 24, 791; *Tetrahedron Lett* (1987) 28, 6587

15 Mitsunobu O, Eguchi M, *Bull Chem Soc Jpn* (1971) 44, 3427; Kurihara T, Nakajima Y, Mitsunobu O, *Synthesis* (1981) 1

16 a) Yvergnaux F, Le Floc'h Y, Grée R, Toupet L, *Tetrahedron Lett* (1989) 30, 7393
b) Le Floc'h Y, Yvergnaux F, Toupet L, Grée R, *Bull Soc Chim Fr* (1991) 128, 16

17 Yvergnaux F, Le Floc'h Y, Grée R, *Tetrahedron Lett* (1989) 30, 7397; Le Floc'h Y, Yvergnaux F, Grée R, *Bull Soc Chim Fr* (1992) 129, 62

18 Kovalev BG, Shamashurin AA, *J Org Chem* USSR (Engl Transl) (1967) 3, 989

19 Masahito S, Mamoru T, Tadashi N, Sohei S, Noboru S, *Synth Commun* (1989) 19, 2431

20 Dumartin H, Le Floc'h Y, Grée R, *Tetrahedron Lett* (1994) 35, 6681