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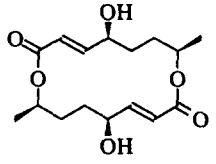
A total synthesis of the (5*R*,8*S*,13*R*,16*S*)-isomer of pyrenophorol

S. Amigoni and Y. Le Floc'h *

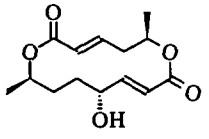
Laboratoire de Synthèses et Activations de Biomolécules, ESA 6052, E.N.S.C.R., Avenue du Général Leclerc, F-35700 Rennes, France

Abstract: The first total synthesis of the (5*R*,8*S*,13*R*,16*S*)-isomer **3** of pyrenophorol is described using a retrosynthetic scheme based on two consecutive double bond cleavages. The title compound **3** was prepared in 14 steps with an overall yield of 4.5% starting from the key synthon 6, readily prepared from (*S*)-(−)-ethyl lactate. © 1997 Elsevier Science Ltd

The natural macrodiolides are compounds produced by microorganisms such as *Stemphilium radicium* for pyrenophorol **1** and *Colletotrichum capri* for colletallol **2**.[1] They are divided into two groups: compounds having a C_2 symmetry and a 16-membered ring such as pyrenophorol **1**, and those having an unsymmetrical 14-membered ring like colletallol **2** (Figure 1).



(5*S*,8*R*,13*S*,16*R*)-Pyrenophorol **1**



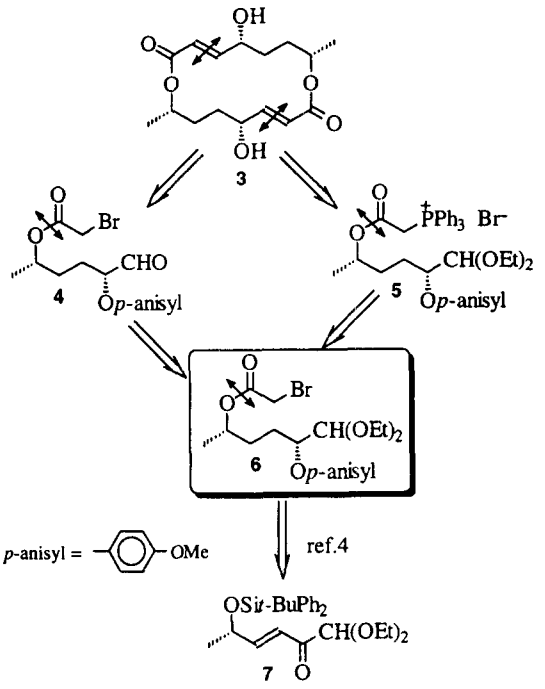
(6*R*,11*R*,14*R*)-Colletallol **2**

Figure 1. Two natural macrodiolides.

They were first studied for their biological properties but then rapidly became interesting synthetic targets. Many syntheses are already reported in the literature.[2] However, in spite of the similarities of their skeletons, a general synthetic strategy allowing full control of both ring size and the configuration of stereogenic carbons was lacking. We thus elaborated a new general synthetic scheme starting from a key synthon, the (3*E*,5*S*)-1,1-diethoxy-5-t-butyldiphenylsilyloxy-hex-3-en-2-one **7**, easily obtained from (*S*)-ethyl lactate.[3] We recently applied this new method to the synthesis of a 14-membered macrodiolide, the (6*R*,11*R*,14*S*)-isomer of colletallol.[4] This paper aims at extending our strategy for obtaining **3** which is a representative example of the symmetrical 16-membered macrodiolides (Scheme 1). Pyrenophorol **1** which is the natural isomer was synthesized by Kibayashi *et al.*[5] and by Zwanenburg *et al.*[6] by means of two successive esterifications. Since it is biologically inactive, we thus decided to synthesize the enantiomer **3** in order to study structure–activity relationships and to demonstrate the potential of our strategy.

The novelty of our synthesis consisted in the retrosynthetic cleavage of the double bonds which involved a cycle building by two successive Wittig reactions, one intramolecular, the second intermolecular. This choice avoided the lower yields generally obtained during macrolactonizations. The first retrosynthetic cleavage led to an unsaturated ω-aldehydo phosphonium salt. The second one produced two fragments, the aldehyde **4** and the ylide corresponding to the phosphonium salt **5**. With regard to the symmetric macrocycle **3**, both fragments proceeded from the same ester acetal **6**. A dimerization process of an ω-aldehydo ylide easily accessible from aldehyde **4** could have been

* Corresponding author. Email: ylefloch@aol.com



Scheme 1. Retrosynthetic analysis of the *ent*-pyrenophorol **3**.

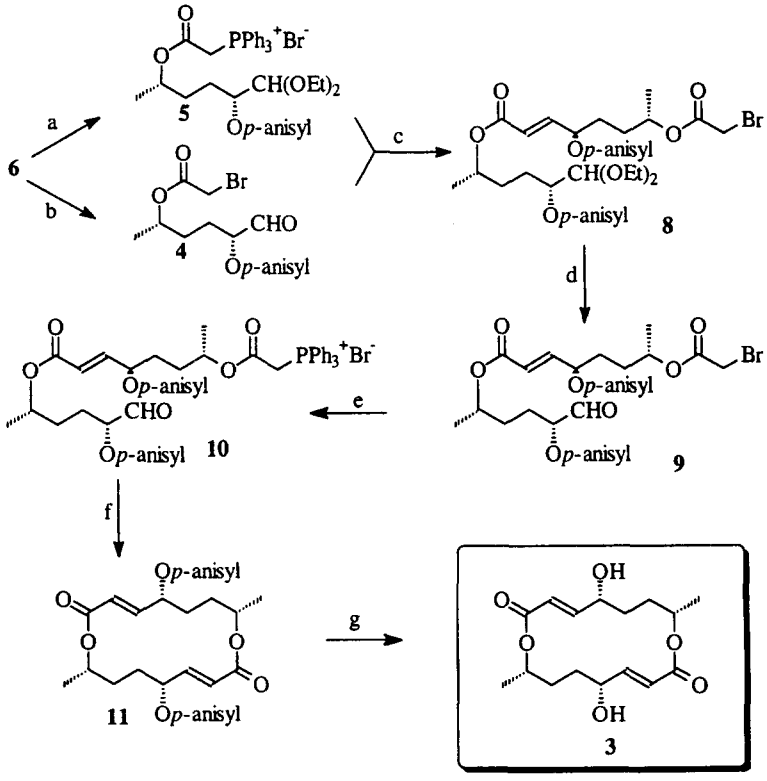
possible. However, previous studies in the laboratory indicated that even under high dilution conditions, the competitive formation of monomers, (*E*,*Z*)-dimers and (*E*,*E*,*E*)-trimers occurred.[7]

Synthon **6** was derived from enone **7** in 5 steps. This key intermediate possessed both asymmetric centers that permitted absolute configurational control of the target molecule. The choice of the commercialy available ethyl lactate enantiomer determined the desired configuration of carbon 5. The second center proceeded from the stereocontrolled reduction by Corey and Link's[8] catalysts of enone **7**; its absolute configuration is conditioned by the choice of the CBS catalyst configuration. The catalyst with an (*S*) configuration afforded (2*S*,5*S*) allylic alcohol with 95% de and 86% yield. After catalytic hydrogenation of the double bond, the saturated alcohol was protected as a para anisyl ether with inversion of configuration. It thus possessed the (2*R*,5*S*)-configuration as indicated for compound **6**. This latter was then obtained by the deprotection of the alcohol function in position 5 and its esterification with bromoacetic acid. The overall yield for this key intermediate was 25%.[4]

The phosphonium salt **5** formation was quantitative starting from compound **6** by addition of triphenylphosphine.[4] The aldehyde **4** was also prepared from ester **6** *via* the formolysis of the acetal function (HCOOH, rt)[9] (Scheme 2).

The first Wittig reaction gave (*E*) olefin **8** in 75% yield. This compound comprised all the asymmetric carbons of the target molecule as well as the two ester functions. The formolysis of the acetal function followed by the addition of triphenylphosphine afforded compound **10** in quantitative yields. The intramolecular Wittig reaction under high dilution conditions with 6 equiv of TEA furnished the protected macrodiolide **11** in 51% yield. The cleavage of the ether function by CAN[10] gave the (5*R*,8*S*,13*R*,16*S*)-isomer of pyrenophorol **3** in 84%. This target compound was obtained enantiomerically pure in a 4.5% global yield. Spectral data underlined the C_2 symmetry of the macrocycle in agreement with the retrosynthetic study.

In conclusion, it seems important to note that this strategy is highly flexible and should control the configuration of every stereogenic center. Indeed, (*R*)-ethyl lactate is commercially available and the



a- PPh_3, CH_3CN, rt, 12 h, quant ; b- HCO_2H, rt, 2 h, quant ; c- TEA, CH_3CN, 70°C, 48 h, (75 %) ; d- HCO_2H, rt, 2 h, quant ; e- PPh_3, CH_3CN, rt, 12 h, quant ; f- TEA, CH_3CN, 70°C, 42 h, (51%) ; g- CAN, CH_3CN/H_2O, -10°C, 30 min, (84 %).

Scheme 2.

reduction of enone **7** can be achieved either with the oxazaborolidine with *R* or *S* configuration to afford (2*R*) or (2*S*) allylic alcohol. Our strategy could thus afford any isomer of pyrenophorol, and furthermore stereoselective modifications of the enone **7**[11] should open this method to other synthetic analogues.

Experimental section

General procedure

Melting points are uncorrected. Optical rotations were measured at 25°C. IR spectra were recorded on a FT-IR spectrometer. ^1H NMR spectra were recorded at 400 MHz and ^{13}C NMR at 100 MHz in $CDCl_3$. Mass spectra were obtained at 70eV either in EI mode (HRMS) or using CI/NH_3 (MS). All separations were carried out under flash chromatographic conditions on Merck silica gel Geduran Si60 (230–240 mesh) using as eluent mixtures of ether (E) and low-boiling (<60°C) petroleum ether (PE). CH_2Cl_2 was distilled from P_2O_5, toluene from $CaCl_2$ and THF from sodium/benzophenone.

Bromoacetic acid, (2R,5S)-1-formyl-2-(4'-methoxyphenoxy)-5-hexyl ester 4

A solution of acetal **6** (0.09 g, 0.2 mmol) and formic acid (0.2 mL, 5.2 mmol, 26 equiv) in CH_2Cl_2 (0.4 mL) was stirred at rt overnight. The mixture was concentrated and the formic acid removed under vacuum to give **4** as a colourless oil (0.075 g, quant). ^1H NMR: δ 9.76 (d, *J*=2.0 Hz, 1H), 6.83 (s, 4H), 5.02 (m, 1H), 4.43 (m, 1H), 3.78 (m, 2H), 3.77 (s, 3H), 1.95–1.65 (m, 4H), 1.29 (d, *J*=6.1 Hz,

3H). ^{13}C NMR: δ 19.7, 26.0, 26.1, 30.7, 55.7, 72.5, 81.9, 114.9, 116.5, 151.5, 154.7, 166.9, 202.7. $[\alpha]^{25}_D$ +55.2 (*c* 0.62; CH_2Cl_2). IR 1728.1, 1510.2 cm^{-1}. R_f=0.55 (E/PE) (50/50). HRMS (EI) for $C_{15}H_{19}BrO_5$ calcd: 358.0416, found: 358.0424.

Olefin ***8***

To a solution of phosphonium salt **5** (0.12 g, 0.18 mmol) and TEA (0.025 mL, 0.18 mmol, 1 equiv) in CH_3CN (30 mL) was added aldehyde **4** (0.075 g, 0.2 mmol, 1.1 equiv) dissolved in CH_3CN (2 mL). The mixture was heated at 30°C overnight and the solvent evaporated. Chromatography on silica gel (E/PE (10/90)) afforded **8** (0.090 g, 75%). ^1H NMR: δ 6.86 (m, 9H), 5.98 (dd, *J*=15.8 Hz and 1.5 Hz, 1H), 5.00 (m, 2H), 4.68 (m, 1H), 4.45 (d, *J*=5.1 Hz, 1H), 4.17 (m, 1H), 3.77 (s, 2H), 3.76 (s, 6H), 3.75–3.40 (m, 4H), 1.79 (m, 8H), 1.27 (d, *J*=6.6 Hz, 3H), 1.23 (d, *J*=6.1 Hz, 3H), 1.22 (t, *J*=7.1 Hz, 3H), 1.12 (t, *J*=7.1 Hz, 3H). ^{13}C NMR: δ 15.3, 15.4, 19.7, 19.8, 19.9, 25.7, 25.9, 26.2, 30.5, 30.8, 31.4, 31.6, 31.8, 55.7, 64.1, 64.2, 71.6, 72.7, 73.1, 80.0, 80.3, 103.4, 103.5, 114.6, 116.9, 117.4, 122.5, 146.4, 146.5, 151.9, 153.0, 154.1, 154.3, 165.7, 166.8, 166.9. $[\alpha]^{25}_D$ +27.8 (*c* 0.72; CH_2Cl_2). IR 1714.6, 1680.0, 1600.9, 1510.0 cm^{-1}. R_f=0.40 (E/PE) (50/50). HRMS (EI) for $C_{34}H_{47}BrO_{10}$ calcd: 694.2353, found: 694.2353.

Aldehyde ***9***

A solution of acetal **8** (0.090 g, 0.13 mmol) and formic acid (0.2 mL, 5.2 mmol, 40 equiv) in CH_2Cl_2 (0.2 mL) was stirred overnight at rt. The mixture was concentrated under vacuum to give **9** as a colourless oil (0.08 g, quant). ^1H NMR: δ 9.69 (d, *J*=2.1 Hz, 1H), 6.93 (dd, *J*=15.8 Hz and 5.1 Hz, 1H), 6.80 (s, 8H), 5.99 (dd, *J*=15.8 Hz and 1.5 Hz, 1H), 5.00 (m, 2H), 4.70 (m, 1H), 4.40 (m, 1H), 3.78 (s, 2H), 3.76 (s, 6H), 1.80 (m, 8H), 1.27 (d, *J*=6.1 Hz, 3H), 1.25 (d, *J*=6.6 Hz, 3H). ^{13}C NMR: δ 19.9, 19.7, 26.2, 30.4, 30.9, 31.1, 55.7, 70.4, 72.7, 76.9, 82.1, 114.7, 114.9, 116.5, 116.8, 122.1, 147.0, 151.6, 151.8, 154.3, 154.7, 165.7, 166.9, 202.8. $[\alpha]^{25}_D$=+38,8 (*c* 0.62; CH_2Cl_2). IR 1735.2, 1707.5 and 1658.0 cm^{-1}. R_f=0.40 (E/PE) (50/50). LRMS (CI/NH_3): m/z 639.9, 638.2, 377.9, 375.9, 221.0. HRMS (FAB) for $C_{30}H_{37}BrO_7$ calcd: 620.1621, found: 620.1624.

Aldehydo-phosphonium salt ***10***

A solution of aldehyde **9** (0.075 g, 0.12 mmol) with triphenylphosphine (0.045 g, 0.17 mmol, 1.4 equiv) in CH_3CN (20 mL) was stirred at rt overnight. The solvent was removed and the crude product was washed with ethyl ether (3×50 mL) to give the phosphonium salt **10** (0.12 g, quant). ^1H NMR: δ 9.69 (d, *J*=2.0 Hz, 1H), 7.85 (m, 15H), 6.88 (dd, *J*=15.8 and 4.6 Hz, 1H), 6.80 (m, 8H), 5.95 (d, *J*=15.8 Hz, 1H), 5.61 (m, 1H), 5.50 (m, 1H), 5.00–4.44 (4m, 4H), 3.75 and 3.40 (2s, 6H), 2.00–1.48 (m, 8H), 1.26 (d, *J*=6.6 Hz, 3H), 1.05 (d, *J*=6.6 Hz, 3H). ^{13}C NMR: δ 19.5 and 20.0, 26.1, 30.3, 30.8, 31.0, 55.7, 65.9, 70.4, 74.1, 82.1, 114.7, 114.9, 116.5, 116.8, 118.0 (d, J_{CP}=88.7 Hz), 122.0, 128.5–135.2, 147.0, 151.6, 151.7, 154.2, 154.7, 164.2, 165.7. $[\alpha]^{25}_D$ +28.3 (*c* 0. 47; CH_2Cl_2). IR 1710–1655 cm^{-1}. R_f=0.00 (E/PE) (50/50)

(5R,8S,11R,16S)-Protected isomer of pyrenophorol ***11***

The aldehydo-phosphonium salt **10** (0.12 g, 0.13 mmol) was dissolved in CH_3CN (40 mL) and was added dropwise over 30 h to a solution of TEA (135 mL, 0.89 mmol, 7 equiv) in CH_3CN (10 mL). The mixture was heated and stirred for 12 h. The solvent was evaporated and chromatography on silica gel (E/PE (50/50)) afforded **11** as a white powder (0.03 g, 51%). ^1H NMR: δ 6.89 (dd, *J*=15.8 Hz and 6.6 Hz, 2H), 6.80 (s, 8H), 5.98 (dd, *J*=15.8 Hz and 1.0 Hz, 2H), 5.10 (m, 2H), 4.54 (m, 2H), 3.78 (s, 6H), 2.80–1.65 (m, 8H), 1.24 (d, *J*=6.6 Hz, 6H). ^{13}C NMR: δ 18.4, 28.5, 28.6, 28.7, 55.7, 69.6, 76.9, 114.7, 117.0, 123.8, 146.1, 151.2, 154.3, 165.1. $[\alpha]^{25}_D$ +90.6 (*c* 0.16; CH_2Cl_2). IR 1735.9; 1707.8 et 1658.6 cm^{-1}. R_f=0.20 E/EP (50/50). LRMS (CI/NH_3): m/z 542.6, 527.4, 360.6. HRMS (EI) for $C_{30}H_{36}O_8$ calcd: 524.2410, found: 524.2407. Mp=166°C.

(5R,8S,11R,16S)-Isomer of pyrenophorol 3

To a solution of compound **11** (0.01 g, 0.02 mmol) in a mixture CH_3CN/H_2O (3/1) (7 mL) was added CAN (0.010 g, 0.06 mmol, 3 equiv) at −10°C. After 30 min the reaction was over. The crude mixture was extracted with CH_2Cl_2 (20 mL). The organic layer was dried ($MgSO_4$), concentrated and chromatography on silica gel (E/EP (70/30)) gave **3** as a white powder (0.005 g, 84%). ^{1}H NMR; δ 6.92 (dd, *J*=15.8 Hz and 5.1 Hz, 2H), 5.99 (dd, *J*=15.8 Hz and 1.5 Hz, 2H), 5.15 (m, 2H), 4.31 (m, 2H), 2.22 (d, *J*=6.1 Hz, 2H), 2.00–1.60 (m, 8H), 1.29 (d, *J*=6.6 Hz, 6H). ^{13}C NMR: δ 18.2, 28.9, 30.4, 69.8, 70.4, 122.1, 149.5, 164.9. $[\alpha]^{25}_D$ +17.0 (*c* 0.06; CH_2Cl_2). IR 3400.0, 1720.5 and 1650.3 cm^{-1}. R_f=0.20 (E). LRMS (CI/NH_3): m/z 330.3 and 313.2. HRMS (FAB) for $C_{16}H_{24}O_6$ calcd: 313.1651, found: 313.1654. Mp=123°C.

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