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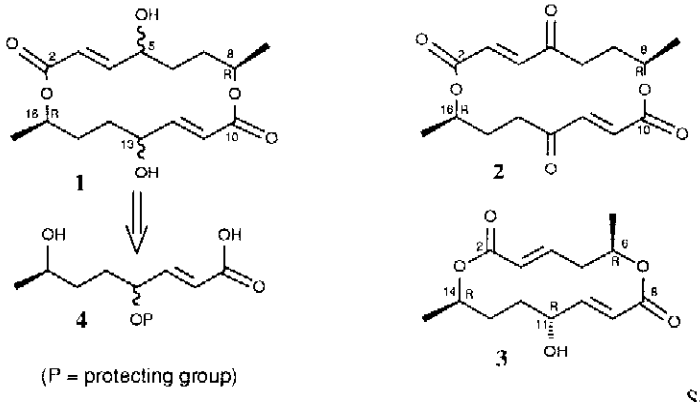
TOTAL SYNTHESIS OF THE MACRODIOLIDE PYRENOPHOROL

F.J. Dommerholt, L. Thijs and B. Zwanenburg*
Department of Organic Chemistry, University of Nijmegen,
Toernooiveld, 6525 ED Nijmegen, The Netherlands.

Abstract:
By means of a total synthesis, the absolute configuration of the naturally occurring macrodiolide pyrenophorol has been established. An essential step is the photo-induced rearrangement of an α,β-epoxy diazomethyl ketone to produce a 4-hydroxy-2-alkenoate. The two lactone units have been introduced in two successive steps.

The sixteen-membered dilactone pyrenophorol **1**, has been isolated from culture filtrates of the fungi *Byssochlamys nivea*[1] and *Stemphylium radicinum*[2]. The relative and absolute configuration of the respective stereogenic centres have not been determined hitherto. Pyrenophorin **2** (scheme 1), which has also been iso-



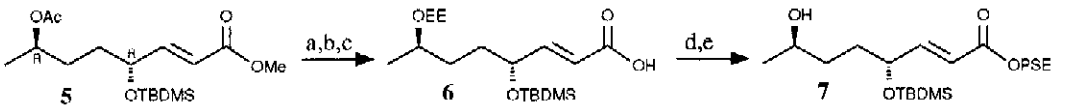
Scheme 1

lated from culture filtrates of *Stemphylium radicinum*[3], is structurally related to pyrenophorol and has the *R*-configuration at both C_8 and C_{16}. It is therefore reasonable to assume that the corresponding carbon atoms in pyrenophorol have the same absolute configuration. In this paper the absolute configuration of the naturally occurring pyrenophorol will be established by means of a total synthesis. Retrosynthetically, a dimerization of 4,7-dihydroxy-2(*E*)-octenoic acid **4** with an appropriate protection of the 4 hydroxyl function, would seem a logical approach for the construction of dilactone **1**[4].

Such a half of pyrenophorol is also present as the C_8-C_{14} moiety in colletallol **3**, the total synthesis of which is described in the accompanying paper[5]. We prepared methyl 7(*R*)-acetoxy-4(*R*)-tert. butyldimethylsilyloxy-2(*E*)-octenoate **5** (scheme 2) as the principal building block for colletallol. Incorporation of its C_4-chirality into the dilactone will ultimately lead to *RRRR*-"pyrenophorol"[6]. Compound **5** was converted into the corresponding hydroxy acid **4** (P= Si-t-$BuMe_2$) by successive treatment with NaOMe and pig liver esterase.

Several attempts to dimerize this compound were made, however, without success; only polymeric products or intramolecular Michael adducts were obtained.

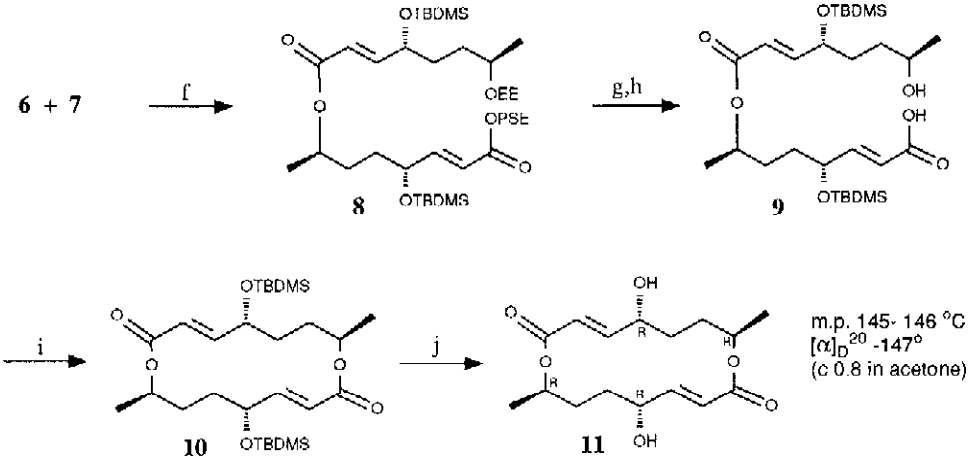
Subsequently, assembly of the target molecule in two successive lactonization steps was undertaken. For this purpose the principal building block **5** was converted into compounds **6** and **7** having a free carboxylic acid function and a free 7-hydroxy group, respectively (scheme 2). In the colletallol synthesis the ethoxy



a. NaOMe, MeOH, 0 °C (85%)
b. ethyl vinyl ether, PPTS, CH_2Cl_2 (99%)
c. LiOH, THF/H_2O– 1/1 (98%)
d. $HOCH_2CH_2SO_2Ph$, DCC, DMAP, CH_2Cl_2 (68%)
e. $MgBr_2$, Et_2O (99%)

Scheme 2

ethyl (EE) and β-phenylsulfonyl ethyl-group (PSE) were of crucial importance as protecting functions. DCC-coupling of the C_2-C_8 unit **6** with the C_{10}-C_{16} fragment **7** furnished compound **8**, which after removal of the EE and PSE protecting groups, gave the seco-macrolide **9** (scheme 3). The second lactonization step was



m.p. 145- 146 °C
$[\alpha]_D^{20}$ -147°
(c 0.8 in acetone)

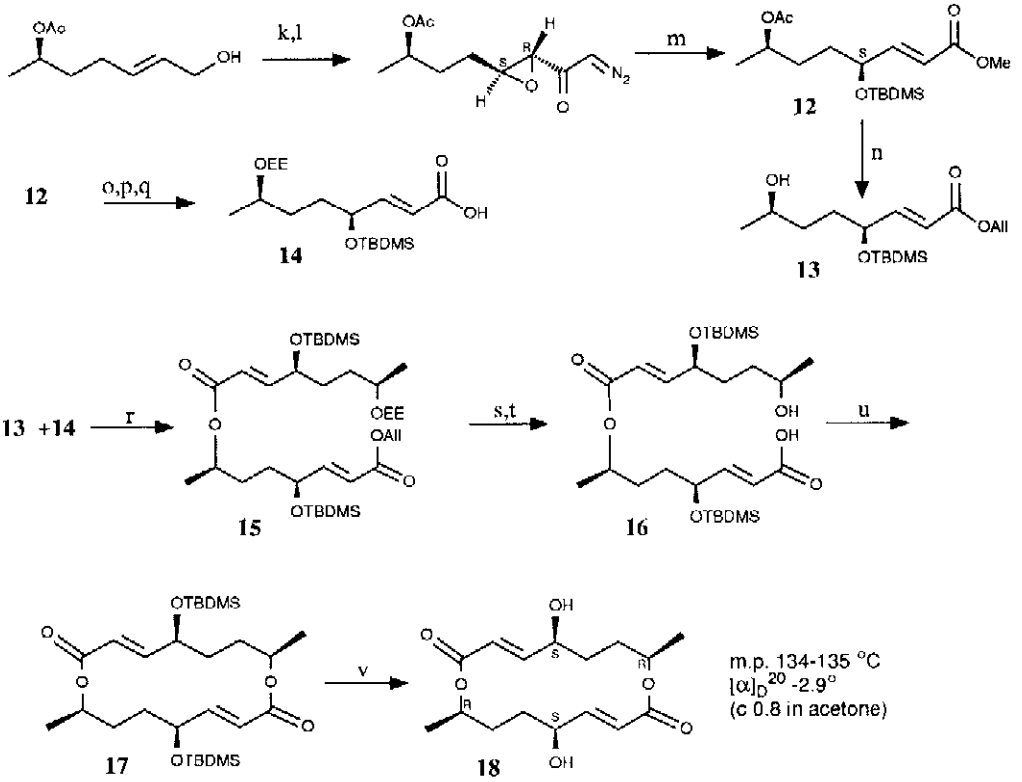
f. DCC, DMAP, CH_2Cl_2 (73%)
g. $MgBr_2$, Et_2O (93%)
h. DBU, benzene (72%)
i. 2,6-$Cl_2C_6H_3C(O)Cl$, Et_3N; DMAP, toluene, Δ (80%)
j. n-Bu_4NF, THF (80%)

Scheme 3

accomplished with the Yamaguchi macrolactonization reaction[7] using 2,6-dichlorobenzoyl chloride. The dilactone **10**, which was obtained in good yield, was finally desilylated yielding "pyrenophorol" **11** with the 5*R*,8*R*,13*R*,16*R* configuration, m.p. 145-146 °C and $[\alpha]_D^{20}$ -147°. The natural product has a m.p. 135 °C and

an $[\alpha]_D^{20}$ -3°[1]. Comparison of these physical data reveals clearly that the stereochemistry of the synthesized product **11** differs from that of the natural pyrenophorol.

At this stage the configuration at C_8 and C_{16} were determined unambiguously by oxidation of both hydroxy functions with PCC. The diketo-compound obtained in this manner, proved to be identical to natural *R,R*-pyrenophorin, establishing the *R*-configuration at C_8 and C_{16}. It was therefore decided to change the configuration at C_5 and C_{13}. The required building block, i.e. methyl 7(*R*)-acetoxy-4(*S*)-tert. butyldimethylsilyloxy-2(*E*)-octenoate **12**, could readily be prepared following the same strategy as used for **5**, the only difference being the chiral inductor in the Sharpless epoxidation[8] (scheme 4). In this sequence we made effective



k. L(+)-DET, tBuOOH, $Ti(OiPr)_4$, mol sieves, CH_2Cl_2	(77%)	p. ethyl vinyl ether, PPTS, CH_2Cl_2	(98%)
l. RuO_4, $CH_3CN/CCl_4/H_2O$= 2/2/3; $ClCOOiBu$, NEt_3; CH_2N_2	(63%)	q. LiOH, THF/H_2O= 1/1	(97%)
m. hυ, MeOH; TBDMSCl, imidazole, DMF	(60%)	r. DCC, DMAP, CH_2Cl_2	(75%)
n. K_2CO_3, allyl alcohol	(66%)	s. $MgBr_2$, Et_2O	(94%)
o. NaOMe, MeOH, 0 °C	(87%)	t. $Pd(PPh_3)_4$, morpholin, THF	(77%)
		u. 2,6-$Cl_2C_6H_3C(O)Cl$, NEt_3; DMAP, toluene, Δ	(79%)
		v. n-Bu_4NF, THF	(95%)

Scheme 4

use of the photo-induced rearrangement of epoxy diazomethyl ketones, as a synthetic method for the prepa-

ration of 4-hydroxy 2-alkenoates[9].

A modified synthetic route was followed for the construction of the dilactone **18** (scheme 4). Reaction of the building block **12** with allylic alcohol gave in one step the 7-hydroxy allyl ester **13**. This hydroxy ester was coupled with carboxylic acid **14** to give the "half-lactone" **15**. The required acid **14** was obtained in three steps from **12** in the same manner as **6** from **5** (scheme 2). Removal of the EE and allyl protecting functions from product **15**, then furnished seco-compound **16**. Macrolactonization of **16** as before, gave dilactone **17** which on desilylation produced the target molecule **18**. Most gratifyingly, the m.p. (134-135 °C), $[\alpha]_D^{20}$ (-2.9°) and spectral data (^{1}H-NMR, IR, MS) were in full agreement with those of the natural compound. This clearly establishes the 5*S*,8*R*,13*S*,16*R* configuration for natural pyrenophorol.

References and notes

1. Z. Kis, P. Furger and H.P. Sigg, Experienta,25, 123 (1969).
2. J.F. Grove, J. Chem. Soc. (C), 2261 (1971).
3. S. Nozoe, K. Hirai, K. Tsuda, K. Ishibashi, M. Shirasaka, Tetrahedron Lett., 4675 (1965).
4. For the construction of the dilactone skeleton, dimerization of a C_4-functionalized 7-hydroxy-2-octenoic acid has been used by several authors, however a protected 4 hydroxy derivative, viz. 4-tert. butyldimethylsilyloxy-7-hydroxy-2(E)-octenoic acid has only been described by F.L.M. Smeets and B. Zwanenburg, unpublished results.
5. F.J. Dommerholt, L. Thijs and B. Zwanenburg, An enantioselective total synthesis of the macrodiolide (-)-(*RRR*)-colletallol, preceding paper.
6. For the sake of convenience we use here the name pyrenophorol for the dilactone of type **1**, despite the fact that the stereochemical configuration of the respective stereogenic centres differs from that of the natural product.
7. J. Inanaga, K. Hirata, H. Sacki, T. Katsuki and M. Yamaguchi, Bull. Chem. Soc. Japan, 52, 1989 (1979).
8. Y. Gao, R.M. Hanson, J.M. Klunder, S.Y. Ko, H. Masamune and B. Sharpless, J. Am. Chem. Soc.,109, 5765 (1987).
9. L. Thijs, F.J. Dommerholt, F.M.C. Leemhuis and B. Zwanenburg, Tetrahedron Lett., 31, 6589 (1990).

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