21. Synthesis of the Oviposition-Deterring Pheromone (ODP) in *Rhagoletis cerasi* L.

Preliminary Communication

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For the assignment of the configuration at C(8) and C(15) of the natural oviposition-deterring pheromone **1** in *Rhagoletis cerasi* L., the four possible stereoisomers of **1** are synthesized. By condensing the C_6 building blocks (5*R*)-**4** and (5*S*)-**4** with the boron enolates of the C_{10} building blocks (4*S*)-**13** and (4*R*)-**13**, followed by decarboxylative dehydration, all stereoisomers of **16** are available *(Scheme 5)*. Glucosylation of **16** followed by formation of the taurin amide gives, after deprotection, the four stereoisomers (8*R*,15*R*)-**1**, (8*S*,15*R*)-**1**, (8*R*,15*S*)-**1**, and (8*S*,15*S*)-**1** *(Scheme 6)*.

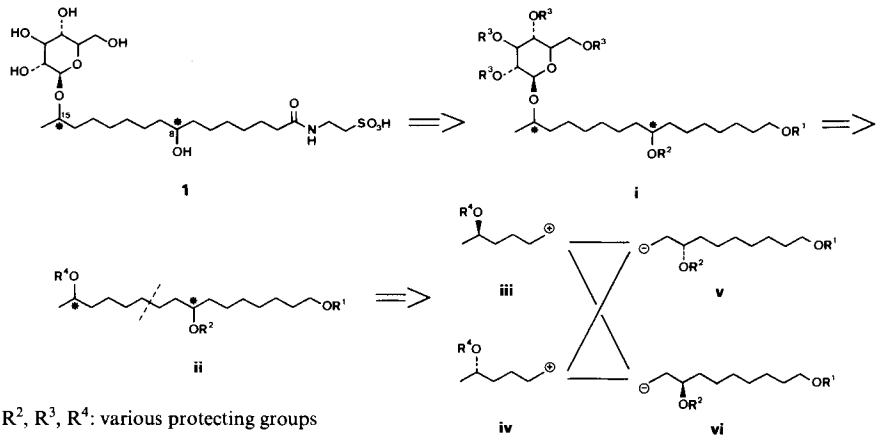
1. Introduction. – The European cherry fruit fly *Rhagoletis cerasi* L. lays one single egg into half-ripe cherries. It was demonstrated in field tests that double or triple ovipositions into the same fruit did occur with a much lower frequency than would be expected if deposition had occurred randomly [1]. Consequently, the hypothesis was put forward that the females mark the fruits, and it was speculated that the observed dragging of the fly's ovipositor over the fruit surface might be connected with the postulated marking procedure [2].

Traces of a secretion possibly connected with this marking procedure were isolated and reapplied to cherries under field conditions. The infestation rate was in fact reduced by up to 90% [3]. Isolation and purification of the active component made a partial structural analysis of the oviposition-deterring pheromone (ODP) possible [4]. Its constitution, a *N*-15-[(β-D-glucopyranosyl)oxy]-8-hydroxypalmitoyltaurin (= 2-{[15-[(β-D-glucopyranosyl)oxy]-8-hydroxyhexadecanoyl]amino}ethanesulfonic acid; **1**), contains two chiral centers, C(8) and C(15). Since the assignment of the configuration was not possible by spectroscopic means, we decided to synthesize the four possible stereoisomers and compare their biological and physical properties with those of natural **1**.

2. Results and Discussion. – The syntheses of the four possible stereoisomers of ODP **1** were planned according to the concept presented in *Scheme 1*. By bond formation between the (*R*)- and (*S*)-configurated C_6 synthons **iii** and **iv** with the (*R*)- and (*S*)-configurated C_{10} synthons **v** and **vi**, all stereoisomers of the selectively protected triol **ii** are available. Glucosylation of HO–C(15) (→**i**) and oxidation at C(1) to a carboxylic acid followed by the formation of the taurin amide leads, after deprotections, to the four possible stereoisomers of **1**.

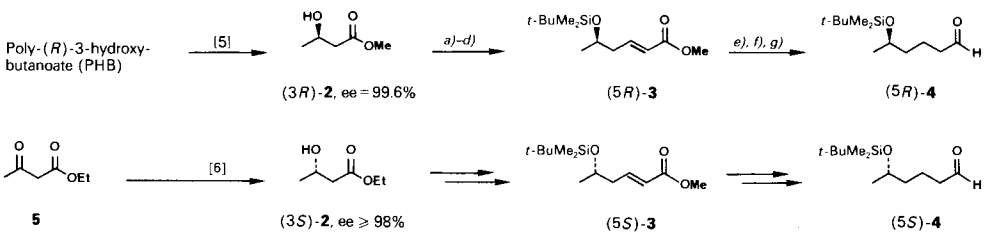
*The C_6 Building Blocks (5*R*)-**4** and (5*S*)-**4** (Scheme 2)*. The starting material for the synthesis of (5*R*)-**4** is available by depolymerization of poly-(*R*)-3-hydroxybutanoate

Scheme 1



R^1, R^2, R^3, R^4: various protecting groups

Scheme 2



a) (*t*-Bu)Me_2SiCl, imidazol, DMF, r.t. (94%); *b*) DIBAL, toluene/THF, 0° (81%); *c*) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78° (98%); *d*) $Ph_3PCHCOOMe$, CH_2Cl_2, r.t. (89%); *e*) H_2, cat. $Pd/BaSO_4$, AcOEt, r.t. (94%); *f*) DIBAL, toluene/THF, 0° (92%); *g*) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78° (92%).

(PHB). Heating PHB-containing material to 160° in the presence of MeOH and tetraethoxytitanium as catalyst [5] gave the ester (3*R*)-**2**. Its enantiomeric purity was checked by acylation with (+)-(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoylchloride ($CF_3C(Ph)(MeO)COCl$). By comparing the MeO ^{1}H-NMR signal of the minor (*S*)-isomer with the ^{13}C-satellite of the MeO signal of the major (*R*)-isomer, the enantiomeric excess was determined to be 99.6%.

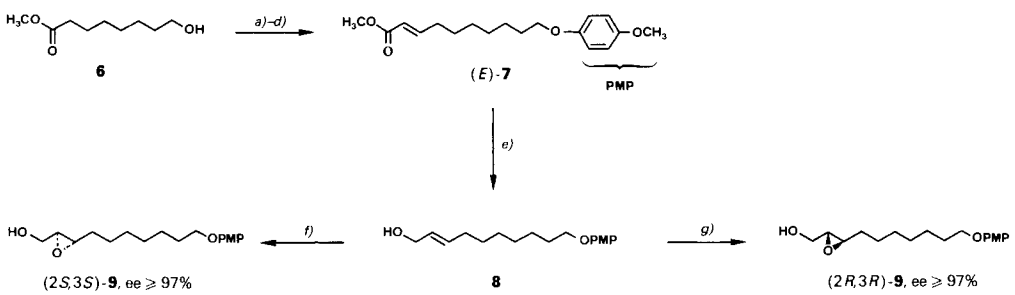
Then, (3*R*)-**2** was silylated, reduced and oxidized to the corresponding aldehyde which was transformed by *Wittig* olefination (→(5*R*)-**3**), hydrogenation, diisobutylaluminium hydride (DIBAL) reduction, and *Swern* oxidation to the C_6 building block (5*R*)-**4** ($[\alpha]_D$, see the *Table*).

Baker's-yeast reduction of ethyl acetoacetate (**5**) provided the starting material (3*S*)-**2** for the (*S*)-configurated C_6 building block [6]. Its optical purity (92%) was increased to ≥ 98% by several crystallizations of the corresponding 3,5-dinitrobenzoate derivative [6a]. Then, (3*S*)-**2** was transformed into (5*S*)-**4** ($[\alpha]_D$, see the *Table*) by the same sequence as described for (5*R*)-**4**.

Table. *Optical Rotations* $[\alpha]_D^{20}$ *of Intermediates* **4**, **9**, **13**, *and* **16** *and of the Stereoisomers of* **1**

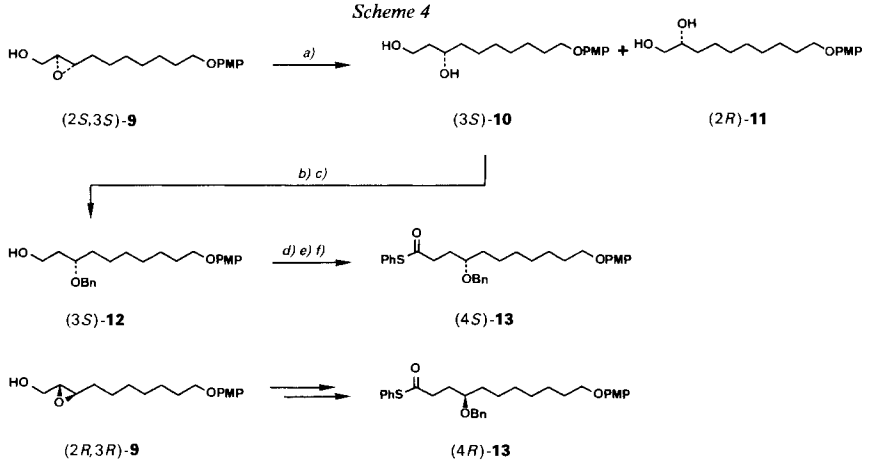
	$[\alpha]_D^{20}$		$[\alpha]_D^{20}$
(5*R*)-**4**	−17.4 (*c* = 1.107, $CHCl_3$)	(2*R*,9*S*)-**16**	−19.0 (*c* = 0.990, $CHCl_3$)
(5*S*)-**4**	+16.9 (*c* = 1.009, $CHCl_3$)	(2*R*,9*R*)-**16**	+ 5.6 (*c* = 1.419, $CHCl_3$)
(2*S*,3*S*)-**9**	−17.4 (*c* = 0.933, EtOH)	(2*S*,9*S*)-**16**	− 4.8 (*c* = 1.525, $CHCl_3$)
(2*R*,3*R*)-**9**	+17.5 (*c* = 0.316, EtOH)	(2*S*,9*R*)-**16**	+19.3 (*c* = 1.278, $CHCl_3$)
(4*S*)-**13**	+16.6 (*c* = 0.865, $CHCl_3$)	(8*R*,15*R*)-**1**	−19.3 (*c* = 0.280, MeOH)
(4*R*)-**13**	−16.5 (*c* = 0.985, $CHCl_3$)	(8*S*,15*R*)-**1**	−17.9 (*c* = 0.235, MeOH)
		(8*R*,15*S*)-**1**	−16.9 (*c* = 0.455, MeOH)
		(8*S*,15*S*)-**1**	−15.8 (*c* = 0.190, MeOH)

Scheme 3



a) $MeOC_6H_4OH$, PPh_3, EtOOCN=NCOOEt, THF, 80° (68%); *b*) $LiAlH_4$, Et_2O, 0° (90%); *c*) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78° (92%); *d*) $Ph_3PCHCOOMe$, CH_2Cl_2, r.t. (90% (*E*)–**7**, 7% (*Z*)–**7**); *e*) DIBAL, toluene/THF, −20° (97%); *f*) (+)-L-EtOOCCH(OH)CH(OH)COOEt, $(i\text{-PrO})_4Ti$, CH_2Cl_2, −68°; *t*-BuOOH, toluene, −20°; recryst. form hexane/$(i\text{-Pr})_2O$ (87%); *g*) as *f*), but with (−)-D-EtOOCCH(OH)CH(OH)COOEt (74%).

Scheme 4



PMP = 4-MeOC_6H_4

a) $[(CH_3OCH_2CH_2O)_2AlH_2]Na$, toluene, r.t. (93% (3*S*)-**10** and 2% (2*R*)-**11**); *b*) C_6H_5CHO, cat. conc. H_2SO_4, DMSO, r.t. (quant.); *c*) DIBAL, hexane, 70° (90%); *d*) $Me_2C{=}CBrNMe_2$ [10], C_6H_6, r.t.; NaCN, DMF, 130° (92%); *e*) NaOH, $HOCH_2CH_2OH$, 180° (92%); *f*) $Me_2C{=}CClNMe_2$ [10], $CHCl_3$, 0°; C_6H_5SH, pyridine, 0° (87%).

*The C_{10} Building Blocks (4S)-***13** *and (4R)-***13** (*Schemes 3* and *4*). The common starting material for both enantiomers was methyl 8-hydroxyoctanoate (**6**) [7]. Its primary-alcohol function which is the precursor of the carboxylic-acid moiety in our target molecule was protected under *Mitsunobu* conditions as 4-methoxyphenyl (PMP) ether [8]. Chain extension by *Wittig* olefination of the corresponding aldehyde (→**7**) and DIBAL reduction yielded the allyl alcohol **8**. Asymmetric *Sharpless* epoxidation [9] of **8** using either (+)-L- or (−)-D-diethyltartrate gave the crystalline epoxides (2*S*,3*S*)-**9** and (2*R*,3*R*)-**9**, respectively. By crystallization, the enantiomeric excess of both enantiomers could be raised to ⩾ 97% (see *Table*). Again, the optical purity was determined by acylation with $CF_3C(Ph)(MeO)COCl$ and NMR analysis.

Red-Al reduction of the epoxide (2*S*,3*S*)-**9** yielded mainly the 1,3-diol (3*S*)-**10**. The 1,2-diol (2*R*)-**11** which was obtained as a side product could not be removed by chromatography. Treatment of this mixture with sodium periodate, however, resulted in oxidative cleavage of the undesired (2*R*-**11**) only, giving a separable mixture of a C_9 aldehyde and the 1,3-diol (3*S*)-**10**. The protection of the secondary-alcohol function in (3*S*)-**10** was achieved by a regioselective reductive opening of the corresponding *O*,*O*-benzylidene derivative yielding (3*S*)-**12** in 90%. For chain extension, the primary alcohol (3*S*)-**12** was converted most conveniently into its bromide with 1-bromo-2,*N*,*N*-trimethyl-1-propenyl-amine [10]. Substitution with cyanide, hydrolysis, and esterification finally gave the thioester (4*S*)-**13** (see *Table*).

Starting from the epoxide (2*R*,3*R*)-**9**, the phenylthioester (4*R*)-**13** was obtained by the analogous reaction sequence in an overall yield of 55% (see *Table*).

Condensation of the C_6 and C_{10} Building Blocks (*Scheme 5*). The aldehyde (5*R*)-**4** was condensed at −78° in anhydrous CH_2Cl_2 with the preformed (*Z*)-*O*-boron enolate [11][1]) derived from the thioester (4*S*)-**13**. After flash chromatography of the crude reaction product, a 1:1 mixture of the two β-hydroxy thioesters (8*S*,10*S*,11*R*,15*R*)-**14**[2]) and (8*S*,10*R*,11*S*,15*R*)-**14**[2]) was isolated in 84% yield. On hydrolysis, a 1:1 mixture **15** of the corresponding acids was obtained. Their decarboxylative dehydration with *N*,*N*-dimethylformamide- bis(2,2-dimethylpropyl) acetal [12] in refluxing xylene yielded in an E_2 elemination [13] exclusively the (*E*)-olefin (2*R*,9*S*)-**16**.

By the analogous sequence, the remaining three stereoisomers of the backbone (2*R*,9*R*)-, (2*S*,9*S*)-, and (2*S*,9*R*)-**16** were synthesized (see *Table*).

Glycosylation of the Stereoisomers **16** *(Scheme 6)*. The glycosylation of the silyl ether (2*R*,9*S*)-**16** was achieved using tetra-*O*-pivaloylglucopyranosyl fluoride [14] and $BF_3 \cdot Et_2O$ in CH_2Cl_2. The reaction occurred stereospecifically due to the directing influence of the 2-pivaloyloxy substituent [15] leading to the β-D-glucoside (2*R*,9*S*)-**17**. The formation of an orthoester which often complicates the *Koenigs-Knorr* reaction [16] in the case of 2-acetoxy substituents was completely suppressed. The acyl protective groups of the glucose moiety were successfully hydrolyzed in MeOH at 100° using a catalytic amount of NaOMe. Benzylation of the free OH groups followed by oxidative cleavage of the PMP ether and *Jones* oxidation at C(1) gave the carboxylic acid (8*S*,15*R*)-**18** in 63%

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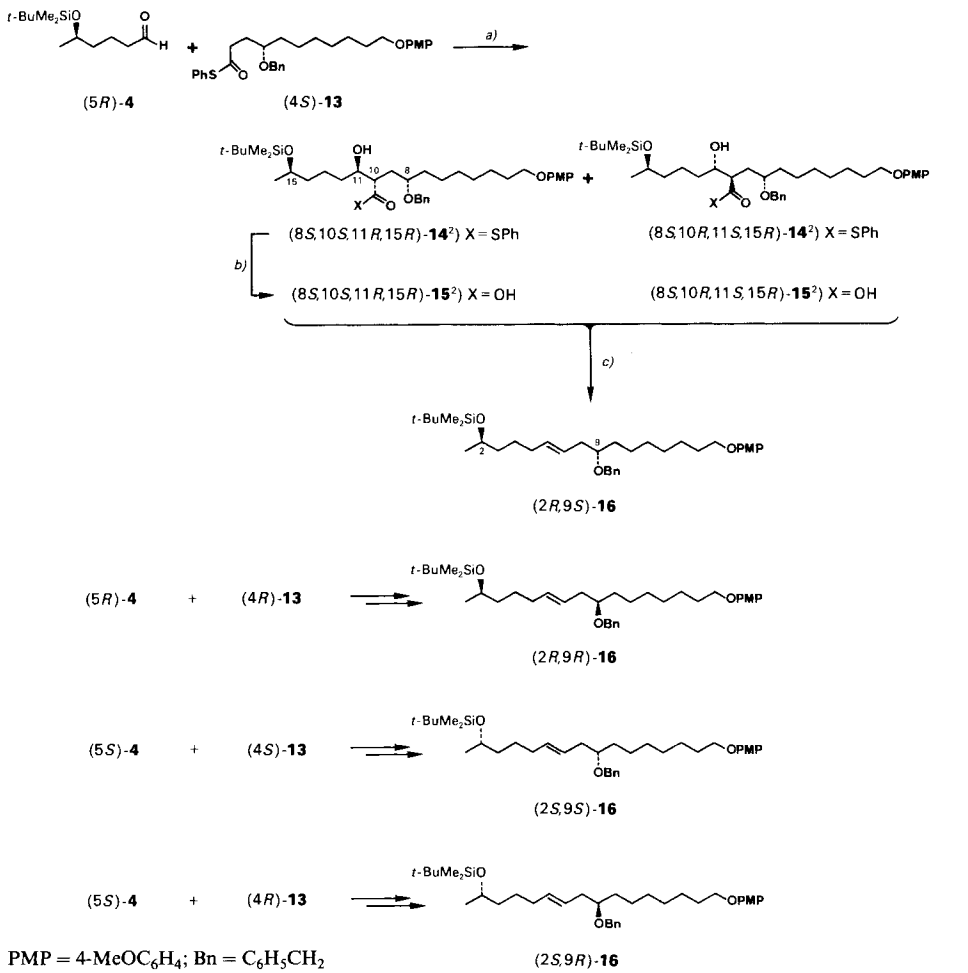
[1]) The enolate was prepared by addition of 9-borabicyclo[3.3.1]nonane (9-BBN) triflate to the thioester (4*S*)-**13** in anhydrous CH_2Cl_2 containing $(i\text{-}Pr)_2EtN$ at −78°. After 1 h stirring at −78° and 1 h at 0°, the enolate was cooled to −78° for the reaction with the aldehyde (5*R*)-**4**.

[2]) Arbitrary numbering.

Scheme 5



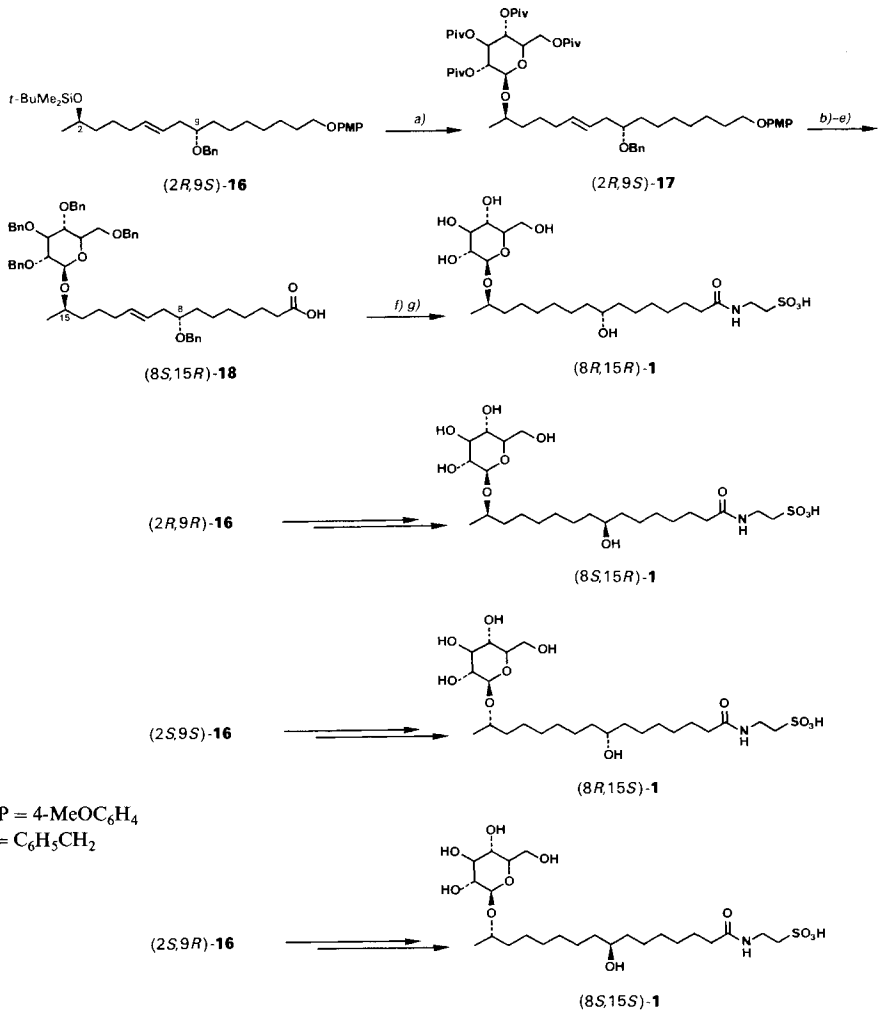
a) (9-BBN)OTf, (i-Pr)$_2$NEt, CH_2Cl_2, −78°; 30% H_2O_2, MeOH, 0° (84%; 1:1); *b*) LiOH, MeOH/H_2O, r.t.; NaOH, dioxan/H_2O, reflux (89%; 1:1); *c*) *N*,*N*-dimethylformamide-bis(2,2-dimethylpropyl)acetal, xylene, reflux (88%).

overall yield. The activated ester of **18**, obtained with hydroxysuccinimide and DCC, was transformed into the taurin amide. Hydrogenolysis finally yielded the (8*R*,15*R*)-isomer of **1** in 92% yield (see *Table*).

The other three isomers, namely (8*S*,15*R*)-**1**, (8*R*,15*S*)-**1**, and (8*S*,15*S*)-**1**, were synthesized by the same sequence (see *Table*).

For the assignment of the configuration of natural ODP at C(8) and C(15), the ^{1}H-NMR data of natural **1** were compared with the ones of the four synthetic stereoisomers. The only significant difference is observed for H–C(15) and CH_3–C(15). The

Scheme 6



PMP = 4-$MeOC_6H_4$
Bn = $C_6H_5CH_2$

a) 2,3,4,6-Tetra-*O*-pivaloyl-α-D-glucopyranosyl fluoride, $BF_3 \cdot Et_2O$, CH_2Cl_2, r.t. (71%); *b*) cat. Na, MeOH, 100° (quant.); *c*) $C_6H_5CH_2Br$, NaH, DMF, r.t. (89%); *d*) $Ce(NH_4)_2(NO_3)_6$, $MeCN/H_2O$, 0° (78%); *e*) CrO_3, H_2SO_4, Me_2CO, 0° (90%); *f*) hydroxysuccinimide, DCC, $MeOCH_2CH_2OMe$, r.t.; $H_2NCH_2CH_2SO_3H$, NaOH, MeOH, r.t. (96%); *g*) H_2, cat. Pd/C, MeOH (93%).

chemical shifts for natural ODP are 3.85 and 1.16 ppm, respectively [4], whereas the corresponding protons of (8*R*,15*S*)-**1** and (8*S*,15*S*)-**1** resonate at 3.81 and 1.22 ppm. The two isomers (8*R*,15*R*)-**1** and (8*S*,15*R*)-**1**, however, show the same chemical shifts as the natural product. Its configuration at C(15) is, therefore, determined to be (*R*). For a final assignment of the configuration at C(8) of natural ODP, the biological activity of the two

C(8) epimers (8*R*,15*R*)-**1** and (8*S*,15*R*)-**1** is currently compared with the one of natural ODP[3]).

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[3]) *E. Städler* and *E. F. Boller* from the *Swiss Federal Research Station for Fruit-Growing, Viticulture, and Horticulture*, CH–8820 Wädenswil, are currently evaluating the biological activities in electrophysiological experiments and field tests.