Short Communication

Syntheses of Monilidiol and Dechloromonilidiol, Phytotoxic Octaketides of *Monilinia fructicola*†

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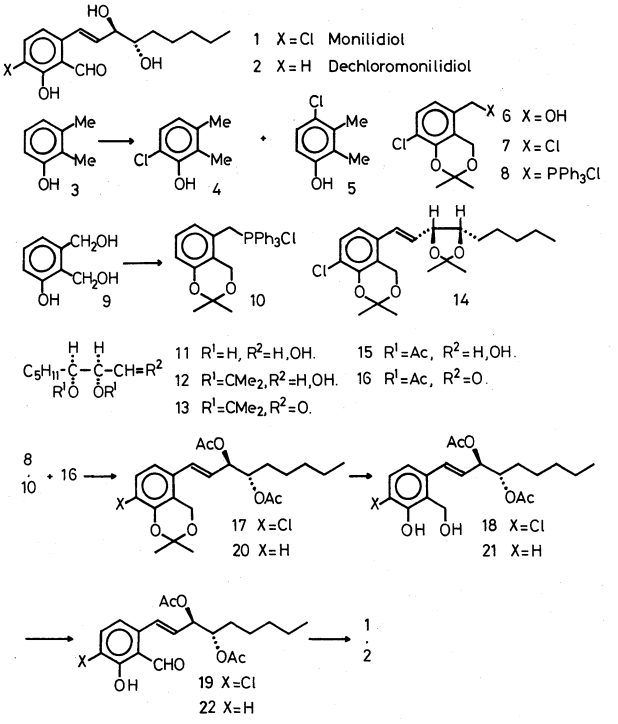
Monilidiol (**1**) and dechloromonilidiol (**2**) were isolated from the culture filtrate of benomyl-resistant strains of cherry brown rot fungus *Monilinia fructicola* and shown to exhibit phytotoxic and antibacterial properties.[1] They have a salicylaldehyde-type octaketide structure bearing an unsaturated side chain with two asymmetric centers at the glycol moiety. The absolute configuration of **1** was determined by the spectrometric and degradation process.*[1] In this paper, we describe the first total syntheses of optically active monilidiol (**1**) and dechloromonilidiol (**2**) in a stereo-controlled fashion.

These molecules were constructed from two parts, *i.e.* an aromatic moiety and an aliphatic one with adequate stereochemistry, using the Wittig reaction between them.

The aromatic synthon of monilidiol was prepared from 2,3-dimethylphenol (**3**). Treatment of **3** with sulfuryl chloride in refluxing carbon tetrachloride gave a mixture of 6-chloro-2,3-dimethylphenol (**4**) and its 4-chloro-isomer (**5**) in a quantitative yield (**4**:**5**=6:4). The 6-chloro-isomer (**4**) was



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*1 In ref. 1, the stereochemistry of asymmetric centers of **2** was estimated to be the same as that of monilidiol (**1**).

acetylated and successively treated with i) *N*-bromosuccinimide, ii) sodium acetate, iii) potassium hydroxide or lithium aluminum hydride and iv) 2,2-dimethoxypropane. The resulting hydroxyacetonide (**6**) (*ca.* 50% from **4**) was converted to a corresponding chloride (**7**) with triphenylphosphine–carbon tetrachloride[2] and then to a phosphonium salt (**8**) in a 70% overall yield.

On the other hand, the aromatic moiety (**10**) for dechloromonilidiol (**2**) was derived from 2,3-bishydroxymethylphenol (**9**)[3] as in the case of monilidiol.

The aliphatic synthon for **1** and **2** was prepared by adding *n*-pentylmagnesium bromide in tetrahydrofuran–hexamethylphosphoric triamide to isopropylidene-D-glyceraldehyde at a low temperature. This gave, with more than 90% stereoselectivity, an *erythro*-adduct[4] which was hydrolyzed in the acidic medium to give (2*R*, 3*S*)-1,2,3-octanetriol (**11**). **11** was converted to (2*S*, 3*S*)-2,3-isopropylidenedioxyoctanal (**13**) *via* (2*R*, 3*S*)-2,3-isopropylidenedioxy-1-octanol (**12**) by treating with i) pivaloyl chloride, ii) 2,2-dimethoxypropane, iii) potassium hydroxide and iv) oxalyl chloride–dimethylsulfoxide.[5] A Wittig reaction between **8** and **13** gave a product (**14**) with the desired stereochemistry. However, attempts to selectively hydrolyze the six-membered acetal ring in the aromatic moiety of **14** proved unsuccessful. The intermediate (**12**) was then treated with i) benzyl bromide–sodium hydride, ii) Amberlyst 15, iii) acetic anhydride and iv) hydrogen–palladium on barium sulfate to afford (2*R*, 3*S*)-2,3-diacetoxy-1-octanol (**15**) (an 87% overall yield from **12**) which was oxidized[5] to (2*S*, 3*S*)-2,3-diacetoxyoctanal (**16**) in a 77.6% yield.

A Wittig reaction between **8** and **16** (in ether and *n*-butyllithium, at room temperature) afforded the desired **17** (a 91% yield) [(*E*)-17:(*Z*)-17 = 4:1] which was hydrolyzed with aqueous acetic acid to give a diol **18** in a 74% yield. The *Z*-isomer of **18** was removed effectively by preparative thin layer chromatography. Oxidation of **18** with active manganese dioxide gave monilidiol diacetate (**19**) in a quantitative yield and saponification of **19** with potassium carbonate yielded monilidiol (**1**) in an 84.6% yield. The spectroscopic and physical properties of synthetic **1** were identical with those of natural monilidiol.

Using a similar method, dechloromonilidiol (**2**) was synthesized from **10** and **16**, and the synthetic **2** was also identical with the natural one in all respects.

Satisfactory analytical data have been obtained for the intermediates and products. Their selected characteristics are: **6**: ^{1}H-NMR $\delta_{TMS}^{ODCl_3}$ 1.576 (6H, $CH_3 \times 2$), 4.507 ($C\underline{H}_2$–OH), 4.880 ($C\underline{H}_2$–O–C–), 6.816 (1H, d, J=8.2 Hz), 7.218 (1H, d, J=8.2 Hz). **11**: mp 104~105°C, $[\alpha]_D^{20}$ −21.4° (c=0.98, EtOH), tribenzoate of **11**: mp 89.5~90.5°C, $[\alpha]_D^{20}$ +48.1° (c=1.5, $CHCl_3$). **16**: $[\alpha]_D^{22}$ −22.8° (c=0.92, $CHCl_3$), IR ν_{max}^{film} cm^{-1}: 2740, 1748, 1375, 1240, 1220, 1050, 965. Synthetic **1**: mp 135.5~136.5°C, $[\alpha]_D^{21}$ +20.8° (c=0.24, MeOH), [Natural **1**[1]: mp 136~137°C, $[\alpha]_D^{20}$ +20° (MeOH)], Synthetic **2**: mp 124~125°C, $[\alpha]_D^{22}$ +19.3° (c=0.41, MeOH), [Natural **2**[1]: mp 123~125°C, $[\alpha]_D^{20}$ +20.5°(MeOH)].

By the present study, we have synthetically established not only the absolute configuration of monilidiol (**1**) as 3-chloro-6-[(3′*R*, 4′*S*)-3′, 4′-dihydroxy-1′-(*E*)-nonenyl]-2-hydroxybenzaldehyde and dechloromonilidiol (**2**) as 2-[(3′*R*, 4′*S*)-3′,4′-dihydroxy-1′-(*E*)-nonenyl]-6-hydroxybenzaldehyde but also the synthetic method toward the salicylaldehyde-type polyketide. Synthesis of structurally related natural compounds[6] and biological tests are in progress and the details will be published later.

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