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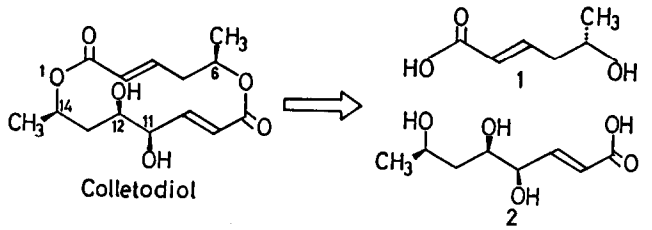
PREPARATION OF O-1∼C-6 AND O-7∼C-14 FRAGMENTS OF COLLETODIOL

Hironori Tsutsui and Oyo Mitsunobu*
Department of Chemistry, College of Science and Engineering, Aoyama Gakuin University, Chitosedai, Setagayaku, Tokyo 157, Japan

Summary: (5S,2E)-5-Tetrahydropyranyloxy-2-hexenoic acid and p-toluenesulfonylethyl (4R,5R,7R,2E)-7-hydroxy-4,5-dimethylmethylenedioxy-2-octenoate were prepared from ethyl acetoacetate and D-glucose, respectively.

Colletodiol, a metabolite of the plant pathogen, Colletotrichum capsici, was isolated by Grove et al.[1] and shown to be a 14-membered cyclic dilactone. The absolute configuration has been determined to be 6R, 11R, 12R, 14R by Amstutz, Hungerbühler, and Seebach.[2] In this communication, we wish to report the preparation of the O-1∼C-6 and O-7∼C-14 segments of colletodiol.[3]

Scheme 1

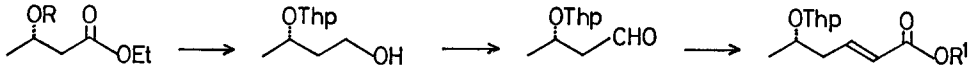


The basic design for the synthesis of colletodiol was planned as follows. The bond disconnections at the two ester functions produce O-1∼C-6 segment (1; hydrophobic fragment) and O-7∼C-14 segment (2: hydrophilic fragment) which would be derived from ethyl acetoacetate and D-glucose, respectively. Convergence of these two fragments into colletodiol requires esterification with retention of the configuration at the C-7 position of 2 and lactonization of the resulting seco-acid with inversion of the configuration at the hydroxyl group attached-carbon atom. Since esterification and lactonization procedures with different stereochemical outcome are now available, these transformation would be accomplished without difficulty.

Hydrophobic fragment 6b was prepared as outlined in Scheme 2. Ethyl acetoacetate was treated with baker's yeast to give ethyl (S)-(+)-3-hydroxybutylate

(3a) in 36% yield ($[\alpha]_D$ +41.6° (c 0.50, $CHCl_3$); optical purity is 97%).[4] The 3a was subsequently converted into tetrahydropyranyl ether (3b: dihydropyrane, p-TsO$^-$ HPy$^+$, CH_2Cl_2, room temperature, 28 h) in 72% yield.[5] The ester 3b was reduced by $LiAlH_4$ giving alcohol (4: ether, 0 °C, 0.5 h, then room temperature, 3.5 h) in 71% yield.[5] The oxidation of 4 by PCC in the presence of AcONa (CH_2Cl_2, room temperature, 5 h)[6] quantitatively afforded the corresponding aldehyde (5) which was, without purification, allowed to react with methoxycarbonylmethylenetriphenylphosphorane (benzene, reflux, 8.5 h) to give methyl (5S,2E)-5-tetrahydropyranyloxy-2-hexenoate (6a) and its Z-isomer (6a') in 53% and 4% yields, respectively. The E-olefin and Z-olefin were separated by silica gel column chromatography (AcOEt-hexane = 1 : 8).[5] As indicated by gas chromatography-mass spectrum, 6a was a 1 : 4 mixture of diastereo isomers (retention time; 3 min and 5.4 min). Saponification of 6a (0.1 M LiOH in THF-H_2O (1 : 1), room temperature, 13.5 h) quantitatively gave the desired (5S,2E)-5-tetrahydropyranyloxy-2-hexenoic acid (6b: overall yield from 3a is 27%).[5]

Scheme 2



3a: R=H
3b: R=Thp

4

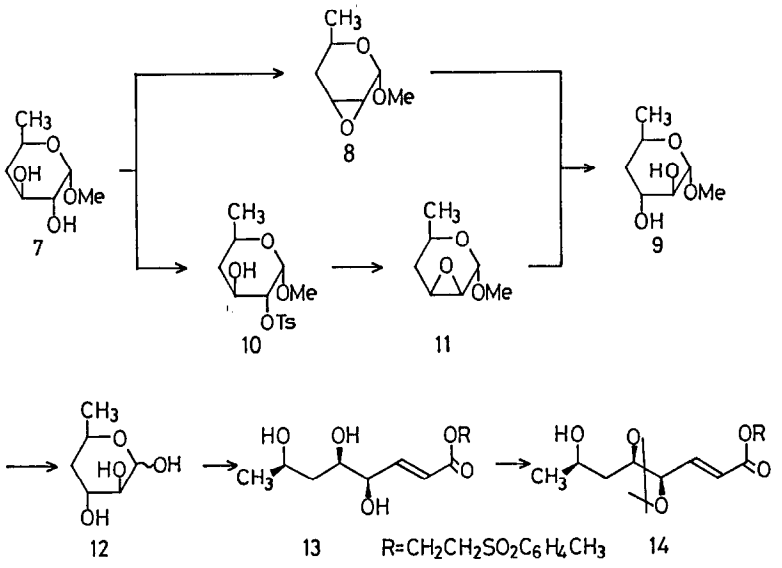
5

6a: R¹=Me
6b: R¹=H

In order to prepare the hydrophilic fragment from D-glucose, the hydroxyl groups at C-2 and C-3 should be inverted. At the outset, methyl 4,6-dideoxy-α-D-xylo-hexopyranoside (7)[7] was converted into methyl 2,3-anhydro-4,6-dideoxy-α-D-ribo-hexopyranoside (8),[8] followed by treatment with 1 M KOH in water under reflux for 4.5 h to afford methyl 4,6-dideoxy-α-D-arabino-hexopyranoside (9: bp 108-110 °C/0.40 Torr (Kugelrohr); $[\alpha]_D$ +101° (c 0.60, MeOH)) and 7 in 22% and 43% yields, respectively. On the other hand, selective transformation of 7 to 9 could be achieved via methyl 2,3-anhydro-4,6-dideoxy-α-D-lyxo-hexopyranoside (11). Thus, 7 was converted into monotosylate (10)[9] which was treated with MeONa in MeOH under reflux for 2.5 h to give 11 (bp 85-95 °C/25 Torr (Kugelrohr); $[\alpha]_D$ +69° (c 0.60, MeOH)) in 58% yield. Hydrolysis of 11 (1 M KOH in water, reflux, 1.4 h) gave 9 in 93% yield without any detectable formation of undesired 7 (tlc and vpc). Hydrolysis of 9 (Dowex 50(H^+), reflux, 2 h) afforded the corresponding free sugar (12) in quantitative yield. The reaction of 12 with p-toluenesulfonylethoxycarbonylmethylenetriphenylphosphorane[10] (benzene, reflux, 6.5 h) gave p-toluenesulfonylethyl (3R,4R,6R,2E)-3,4,6-trihydroxy-2-octenoate (13) in 67% yield. Acetonidation of 13 (Me_2CO, $(MeO)_2CMe_2$, p-TsOH, room temperature, 60 h) afforded the desired hydrophilic fragment 14 in 75% yield (overall yield from 10 is 27%).[5]

Both fragments 6b and 14 were thus available and have successfully been linked together to prepare colletodiol. This conversion will be described in the accompanying communication.

Scheme 3



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References and Notes

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5) All compounds are characterized by elemental analyses and/or NMR spectroscopy. Significant NMR data are the following (δ, ppm from Me_4Si). 3b: bp 100-115 °C/7 Torr. $[\alpha]_D$ +11.4° (c 0.5, $CHCl_3$). NMR (CCl_4); 1.1 (d) and 1.23 (d)(H-4, $J_{3,4}$ = 6 Hz), 1.2 (t, CH_3CH_2-), 1.2-2 (m, $-(CH_2)_3-$), 2.33 (d) and 2.4 (d) (H-2), 3.2-4.3 (m, H-3 and -O-CH-O-CH_2-), 4.04 (q, CH_3CH_2-), 4.65 (br s, -O-CH-O-CH_2-). 4: bp 73-75 °C/0.5 Torr. $[\alpha]_D$ +37.3° (c 0.5, $CHCl_3$). NMR (CCl_4); 1.12 (d) and 1.21 (d) (H-4, $J_{3,4}$ = 6 Hz), 1.3-2 (m, H-2 and $-(CH_2)_3-$),

3.3-4.2 (m, H-1, H-3, and -OCH-OC$\underline{H}_2$-), 3.57 (s, OH), 4.62 (br s, -OC$\underline{H}$-OCH$_2$-). 6a: bp 107-112 °C/0.55 Torr (Kugelrohr). $[\alpha]_D$ -13° (c 0.5, $CHCl_3$). The tetrahydropyranyl groups of 6a and 6a' were removed and the resulting hydroxyesters showed following NMR data. Hydroxyester from 6a (CCl_4); 1.18 (d, H-6, $J_{5,6}$ = 6 Hz), 2.32 (br t, H-4), 3.68 (s, CH_3O-), 3.5-4.3 (m, H-5), 3.93 (s, OH), 5.81 (dt, H-2, $J_{2,3}$ = 16 Hz, $J_{2,4} > 0$), 6.94 (dt, H-3, $J_{3,4}$ = 7 Hz). Hydroxyester from 6a' (CCl_4); 1.17 (d, H-6, $J_{5,6}$ = 6.4 Hz), 2.7 (br t, H-4), 3.28 (br s, OH), 3.6 (s, CH_3O-), 3.7-4.1 (m, H-5), 5.7 (dt, H-2, $J_{2,3}$ = 12 Hz, $J_{2,4} > 0$), 6.3 (dt, H-3, $J_{3,4}$ = 7 Hz). 6b: oil. NMR (CCl_4); 1.12 (d) and 1.22 (d) (H-6, $J_{5,6}$ = 6 Hz), 1-2 (m, -$(CH_2)_2$-), 2.2-2.6 (m, H-4), 3.2-4.2 (m, H-5 and -OCH-OC$\underline{H}_2$-), 4.65 (br s,-OC$\underline{H}$-OCH$_2$-), 5.74 (dt, H-2, $J_{2,3}$ = 16 Hz, $J_{2,4} > 0$), 6.6-7.4 (m, H-3), 10.85 (s, -COOH). 14: mp 86 °C. $[\alpha]_D$ +7.7° (c 0.5, $CHCl_3$). M^+ = 412. NMR ($CDCl_3$); 1.19 (d, H-8, $J_{7,8}$ = 6.2 Hz), 1.41 (s, $(CH_3)_2C<$), 1.71 (br t, H-6), 2.42 (s, $\underline{CH}_3C_6H_4$-), 3.05 (br s, OH), 3.46 (t, -CH_2-SO_2-), 3.55-4.3 (m, H-4, 5, 7), 4.41 (t, -OC$\underline{H}_2$-CH_2-), 5.83 (dd, H-2, $J_{2,3}$ = 16 Hz, $J_{2,4} > 0$), 6.72 (dd, H-3, $J_{3,4}$ = 5 Hz), 7.28 (d, 2H, aromatic-H), 7.72 (d, 2H, aromatic-H).

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