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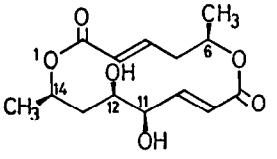
TOTAL SYNTHESIS OF COLLETODIOL

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

Summary: Colletodiol and 6-epi-colletodiol were synthesized from (5S,2E)-5-tetrahydropyranyloxy-2-hexenoic acid and p-toluenesulfonylethyl (4R,5R,7R,2E)-7-hydroxy-4,5-dimethylmethylenedioxy-2-octenoate.

Colletodiol has been isolated from the culture filtrates of Colletotrichum capsici[1] and the centers of chiralities have been confirmed to be 6R, 11R, 12R, and 14R.[2]

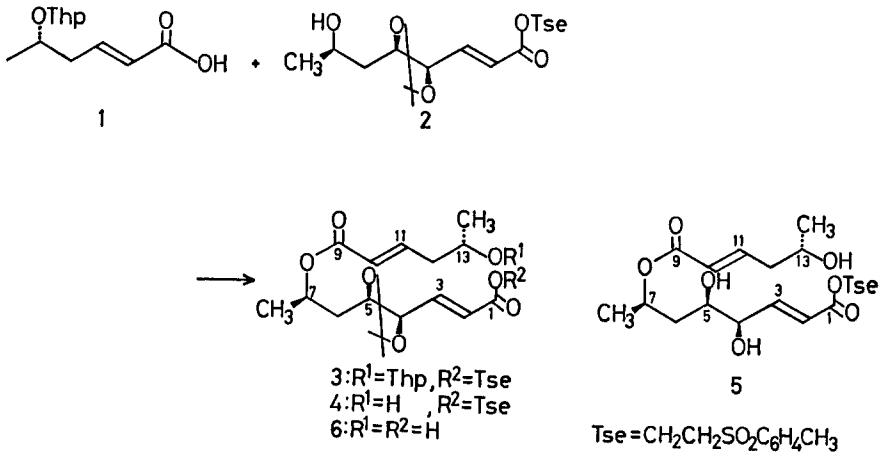


Colletodiol

In a previous paper, we have described the preparation of (5S,2E)-5-tetrahydropyranyloxy-2-hexenoic acid (1) and p-toluenesulfonylethyl (4R,5R,7R,2E)-7-hydroxy-4,5-dimethylmethylenedioxy-2-octenoate (2) which correspond to O-1∼C-6 and O-7∼C-14 fragments of colletodiol.[3] In this communication, we wish to report the total synthesis of colletodiol and 6-epi-colletodiol from 1 and 2.

Condensation of 1 with 2 was performed by Yamaguchi method.[4] Thus, 1 was at first treated with 2,4,6-trichlorobenzoyl chloride in the presence of triethylamine in tetrahydrofuran (THF) at room temperature for 2 h, filtered, and the filtrate was evaporated to sirup. The resulting mixed anhydride was allowed to react with 2 in the presence of 4-dimethylaminopyridine (DMAP) in toluene at room temperature for 24 h to afford protected seco-acid (3) in 47% yield.[5] On treatment with 2.9 molar amounts of $HgCl_2$ in CH_3CN-H_2O (8 : 1) at room temperature for 45 h, 3 gave acetonide (4) and deacetonided product (5) in 66% and 11% yields, respectively.[6] Treatment of 4 with DBU[7] in benzene at room temperature for 11 h afforded the seco-acid (6) of colletodiol in nearly quantitative yield. Although NMR spectrum of the product indicated presence of small amounts of impurity, it was used in lactonization step without further purification.

In order to lactonize with inversion of the configuration at the alcoholic part, 6 (0.130 mmol) was allowed to react with diethyl azodicarboxylate (DEAD; 0.260 mmol) and triphenylphosphine (TPP; 0.260 mmol) in toluene (25 ml) at -10 °C



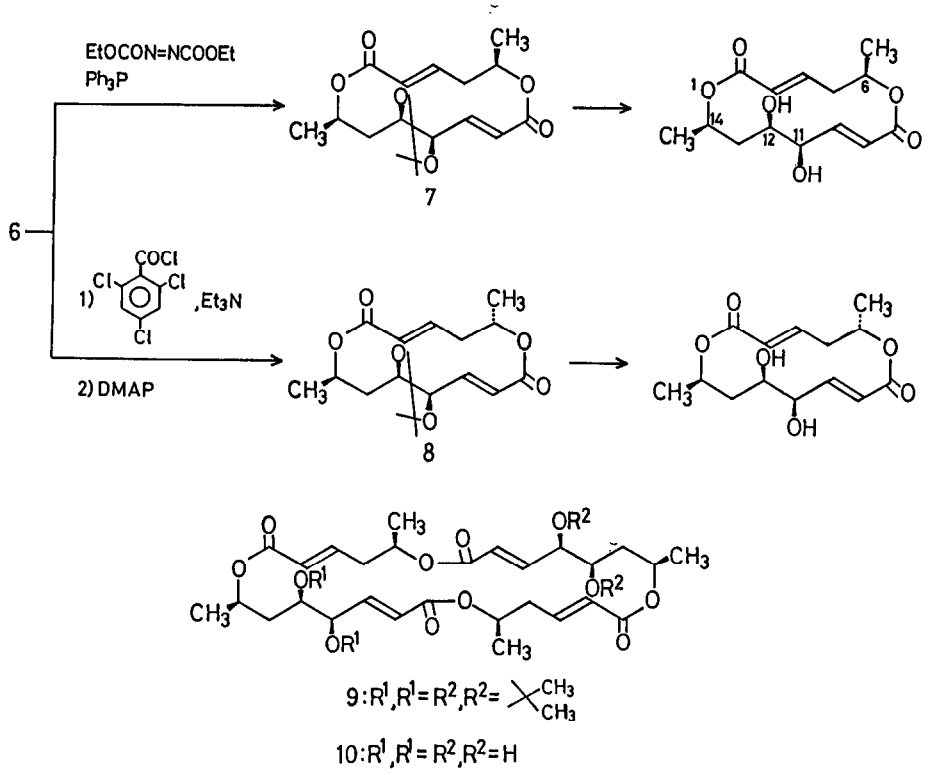
for 96 h and then 0 °C for 19 h to give protected colletodiol (7) and 28-membered lactone (9) in 45% and 29% yields, respectively.[5,8]

Hydrolysis of the acetonide group of 7 (CF_3COOH-CH_3CN-H_2O = 2 : 2 : 1, 0 °C to room temperature, 1 h) gave colletodiol in 57% yield. After one recrystallization from acetone-light petroleum, the synthetic colletodiol exhibited mp 163-165 °C and $[\alpha]_D$ +26° (c 0.31, $CHCl_3$). When the product was again recrystallized from the same solvent system, the specific rotation rose to +35° (c 0.16, $CHCl_3$) which is consistent with reported value.[9]

6-Epi-colletodiol was prepared by the use of Yamaguchi method[4] in lactonization step. Thus, 6 (0.719 mmol) was treated with 2,4,6-trichlorobenzoyl chloride (1.54 mmol) and triethylamine (1.69 mmol) in THF (6 ml) at room temperature for 2 h. Triethylamine hydrochloride was filtered off and the filtrate was diluted with toluene (380 ml). The resulting solution was added dropwise to toluene (75 ml) containing DMAP (4.60 mmol) over a period of 5.5 h at 95 °C. The reaction was continued for 40 min at this temperature, protected 6-epi-colletodiol (8) being obtained in 52% yield.[5] Contrary to the case of lactonization by the use of DEAD and TPP, the formation of the corresponding 28-membered lactone could not be detected.

Hydrolysis of the acetonide group of 8 under the same conditions described above afforded 6-epi-colletodiol with mp 163-164 °C and $[\alpha]_D$ +99° (c 0.50, $CHCl_3$) in 91% yield.

Treatment of protected 28-membered lactone (9) in CF_3COOH-CH_3CN-H_2O (2 : 2 : 1, 0 °C to room temperature, 2.5 h) gave tetrahydroxy lactone (10) in 23% yield (mp 80-82 °C, $[\alpha]_D$ -25° (c 0.04, $CHCl_3$).



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References and Notes

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2) a) R. Amstutz, E. Hungerbühler, and D. Seebach, Helv. Chim. Acta, 64, 1769 (1981). See also, b) J. MacMillan and T. J. Simpson, J. Chem. Soc. Perkin I, 1973, 1487.
3) H. Tsutsui and O. Mitsunobu, the preceding communication.
4) J. Inagawa, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, Bull. Chem. Soc. Jpn., 52, 1989 (1979).
5) NMR data of representative compounds (ppm from Me_4Si). 3: oil, NMR (CCl_4); 0.9-2.1 (CH_3 (d) at positions 7 and 13, $-(CH_2)_3-$ (m), H-6 (m)), 1.35 (br s, $(CH_3)_2C$), 2.1-2.5 (m, H-12), 2.4 (s, $CH_3C_6H_4-$), 3.39 (br t, $-CH_2SO_2-$), 3.4-4.2 (m, H-4, H-5, H-13, $-OCH-OCH_2-$), 4.34 (br t, $-CO_2-CH_2-CH_2-$), 4.6 (br s,

-OCH-OCH_2-), 4.7-5.3 (m, H-7), 5.72 (d, H-2, H-10), 6.38-7.1 (m, H-3, H-11), 7.26 and 7.7 (d, aromatic-H). 4: oil, $[\alpha]_D$ +13.7 (c 1.8, $CHCl_3$). NMR ($CDCl_3$); 1.22 and 1.30 (d, CH_3 at C-7 and C-13, J = 6 Hz), 1.39 (s, $(CH_3)_2C<$), 1.7-2.1 (m, H-6), 2.1-2.4 (m, H-12), 2.32 (s, OH), 2.43 (s, $CH_3C_6H_4$-), 3.47 (t, -CH_2SO_2-), 3.6-4.3 (m, H-4, H-5, H-13), 4.42 (t, -CO_2CH_2-CH_2-), 4.8-5.35 (sextet, H-7), 5.83 (dm, H-2, H-10, $J_{2,3} = J_{10,11}$ = 16 Hz), 6.5-7.1 (m, H-3, H-11), 7.3 and 7.75 (d, aromatic-H). 6: oil, NMR ($CDCl_3$); 1.22 and 1.31 (d, CH_3 at C-7 and C-13), 1.4 (s, $(CH_3)_2C<$), 1.3-2.1 (m, H-6), 2.3 (br t, H-12), 3.5-4.3 (m, H-4, H-5, H-13), 4.75-5.4 (sextet, H-7), 5.75 (d, H-10, $J_{10,11}$ = 16 Hz), 5.96 (d, H-2, $J_{2,3}$ = 16 Hz), 6.5-7.25 (m, H-3, H-11), 6.83 (s, OH). 7: oil, M^+ = 324. NMR ($CDCl_3$); 1.1-1.55 (CH_3 at C-6 or C-14, and $(CH_3)_2C<$), 1.35 (d, CH_3 at C-6 or C-14), 1.9 (br t, H-5), 2.2-2.6 (m, H-13), 3.7-4.3 (m, H-11, H-12), 4.55-5.4 (m, H-6, H-14), 5.63 (d, H-3, $J_{3,4}$ = 16 Hz), 5.95 (d, H-9, $J_{9,10}$ = 16 Hz), 6.25-7 (m, H-4, H-10). 8: oil, M^+ = 324. NMR ($CDCl_3$); 1.29 and 1.4 (d, CH_3 at C-6 and C-14), 1.4 (s, $(CH_3)_2C$), 1.75-2.2 (m, H-13), 2.2-3.15 (m, H-5), 3.6-4.2 (m, H-11, H-12), 4.8-5.55 (m, H-6, H-14), 5.68 (d, H-3, $J_{3,4}$ = 16 Hz), 5.98 (d, H-9, $J_{9,10}$ = 16 Hz), 6.4-7.2 (m, H-4, H-10). 6-Epi-colletodiol: NMR ($CDCl_3$); 1.36 and 1.4 (d, CH_3 at C-6 and C-14), 1.6-2 (m, H-13), 2-3.2 (m, H-5), 3.3-4.3 (m, H-11, H-12, OH), 4.9-5.5 (m, H-6, H-14), 5.68 (d, H-3, $J_{3,4}$ = 16 Hz), 6.15 (d, H-9, $J_{9,10}$ = 16 Hz), 6.4-7.4 (m, H-4, H-10).

6) Meyers and Brinkmeyer have reported that dithianyl and tetrahydropyranyl groups could be simultaneously removed by treatment with $HgCl_2$. A. I. Meyers and R. S. Brinkmeyer, Tetrahedron Lett., 1975, 1749. In order to examine the stereochemistry of the deprotection process using $HgCl_2$, methyl (5S,2E)-5-tetrahydropyranyloxy-2-hexenoate[3] was hydrolyzed under the same conditions described in the text. The optical purity of the resulting methyl 5-hydroxy-2-octenoate (bp 78 °C/0.45 Torr, Kugelrohr) was estimated to be 96% by comparison of specific rotation with that of the sample obtained by acid (HCl) hydrolysis of the same substrate.

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9) Lit.[2b,10] mp 162-164 °C or 163-164 °C. Lit.[1,10] $[\alpha]_D$ +36° (c 1.0, $CHCl_3$).

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