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Chiral Synthesis of (-)-Colletol Based on Palladium-Catalyzed Reductive Cleavage of Alkenyloxiranes with Formic Acid

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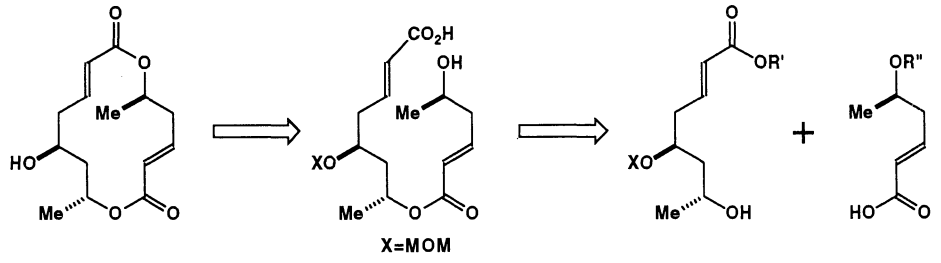
Total synthesis of (-)-colletol was achieved using palladium-catalyzed hydrogenolysis of optically active (*E*)-4,5-epoxy-2-alkenoates to (*E*)-5-hydroxy-2-alkenoates with formic acid as a key step for preparation of the intermediate hydroxy ester segments.

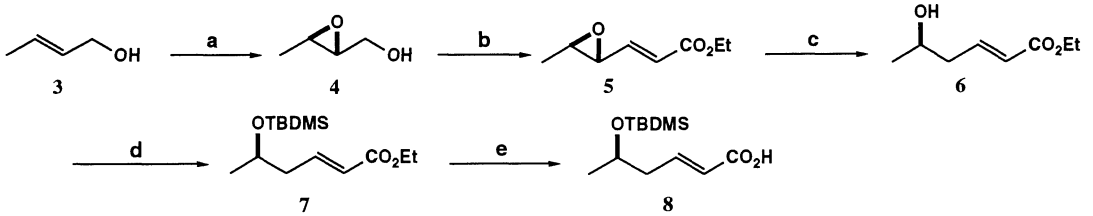
(-)-Colletol (**1**) is a 14-membered bismacrolactone isolated from the fermentathoin broth of *Colletotrichum capsici* in 1973 along with related bislactones, colletodiol, colletoketol, and colletallol.[1] Recently, Keck's group reported the first total synthesis of **1** involving stereoselelective addition of triphenylallystannane to an aldehyde mediated by a Lewis acid.[2] Herein we wish to report a synthesis of **1** by stereoselective construction of two optically active hydroxy ester segments **6** and **12** using palladium-catalyzed hydrogenolysis of optically active alkenyloxiranes[3] and macrolactonization by Yamaguchi-Yonemitsu method.[4]



(-)-Colletol (**1**) **2**

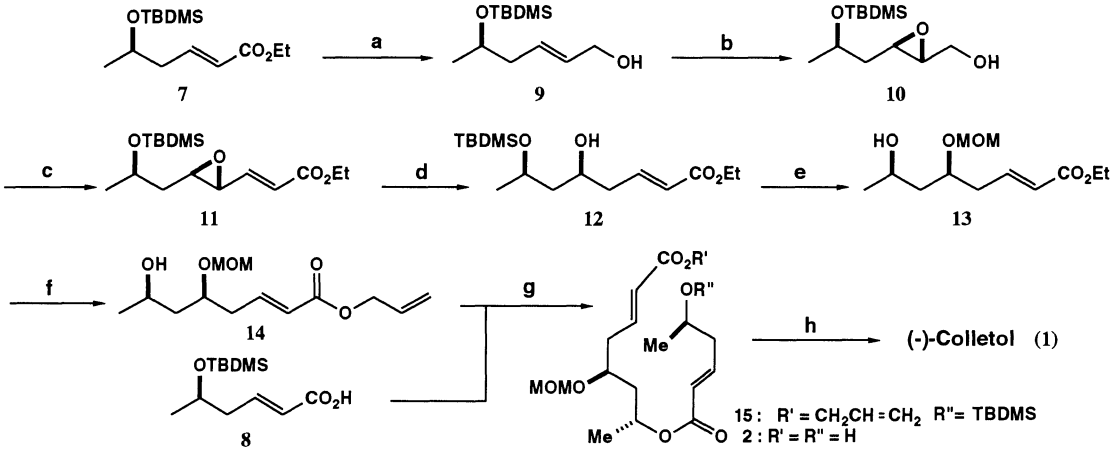
Scheme 1.

Optically active hydroxy esters **6** and **12** were prepared from alkenyl oxiranes **5** and **11**, respectively. Sharpless asymmetric epoxidation of (*E*)-2-buten-1-ol (**3**)[5] followed by Swern oxidation and subsequent Horner-Emmons reaction gave the alkenyloxirane **5**. The epoxy group of **5** was reduced selectively with formic acid in the presence of $Pd_2(dba)_3CHCl_3$-PPh_3 as a catalyst to give the optically active alcohol **6** in 84% yield. Protection of the hydroxy group (TBDMSCl, 92%) and alkaline hydrolysis (3M KOH, 83%) gave the carboxylic acid **8**.



Scheme 2. (a) TBHP, $Ti(O^iPr)_4$, (-)-DET, CH_2Cl_2, -25 °C, 55%; (b) (1) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; (2) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 34%, 2 steps; (c) 2.5 mol% $Pd_2(dba)_3CHCl_3$, 2 mol% Ph_3P, HCO_2H-Et_3N, dioxane, rt, 84%; (d) TBDMSCl, imidazole, 92%; (e) 3 M KOH, EtOH, 83% (1 M = 1 mol dm^{-3})

The other segment **13** was prepared from the hydroxy ester **7**. Reduction of **7** (DIBAH, 93%) gave the allylic alcohol **9**. By a similar procedure, the allylic alcohol **9** was converted into the hydroxy ester **12** via an optically active epoxy alcohol **10** and the alkenyloxirane **11** in 55% yield. The hydroxy group was protected with MOMCl and the TBDMS ether was deprotected with 1M HCl to give the ester **13** in 83% yield.



Scheme 3. (a) DIBAH, Et_2O, -78 °C, 93%; (b) TBHP, $Ti(O^iPr)_4$, (-)-DET, CH_2Cl_2, -25 °C, 91%; (c) (1) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; (2) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 85%; (d) 2.5 mol% $Pd_2(dba)_3CHCl_3$, 2.3 mol% Ph_3P, HCO_2H-Et_3N, dioxane, 72%; (e) (1) MOMCl, $^iPr_2EtN$, CH_2Cl_2, 85%; (2) 1 M HCl, THF, 98%; (f) CH_2=$CHCH_2OH$, $ClBu_2Sn$-O-$SnBu_2OH$, toluene, reflux, 93%; (g) (1) DCC, DMAP, Et_2O, 68%; (2) 1 M HCl, THF, 91%; (3) 2 mol% $Pd_2(dba)_3CHCl_3$, 24.5 mol% Ph_3P, HCO_2H-Et_3N, dioxane, reflux, 71%; (h) (1) 2,6-dichlorobenzoylchloride, Et_3N, DMAP, toluene, 84%; (2) TMSBr, CH_2Cl_2, -30 °C, 71% (1 M = 1 mol dm^{-3})

The ethyl ester **13** was converted into the allyl ester **14** prior to coupling with **8** by Otera method.[6] Esterification of **8** and **14** using DCC gave **15** in 68% yield. Deprotection of TBDMS ether and removal of allylic moiety with formic acid using palladium catalyst gave the hydroxy carboxylic acid **2** in 64% yield. Finally, lactonization of **2** was carried out using 2,6-dichlorobenzoyl chloride and subsequent deprotection of MOM group with TMSBr[7] gave (-)-**1**[8,9] in 60% yield from **2**.

This synthetic method of hydroxy esters described in this paper provides a promising method for 1,3-polyols which are present in a number of polyene macrolide antibiotics. This research was finnancially supported by Grant-in-Aids for Scientific Research on Priority Areas (No. 05234228) from Ministry of Education, Science and Culture and the Asahi Glass Foundation for Industrial Technology.

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8) (-)-Colletol (**1**): $[\alpha]^{24}_D$=-3.3° (c1.04, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.62-6.73 (m, 2H), 5.79 (d, *J*=15.0 Hz, 1H), 5.76 (d, *J*=15.4 Hz, 1H), 5.24 (m, 1H), 5.17 (m, 1H), 4.02 (m, 1H), 2.48-2.54 (m, 2H), 2.20-2.33 (m, 2H), 1.97 (ddd, *J*=2.93, 2.93, 15.75 Hz, 1H), 1.50 (ddd, *J*=2.93, 6.23, 15.76 Hz, 1H), 1.35 (d, *J*=6.59 Hz, 3H), 1.34 (d, *J*=6.60 Hz, 3H); HRMS (CI) Found : 269.1416. Calcd for $C_{14}H_{21}O_5$ (MH+) 269.1389.
9) The enantiomeric excess of (-)-**1** was >99% confirmed by NMR after converting to its (+)- and (-)-MTPA esters.

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