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

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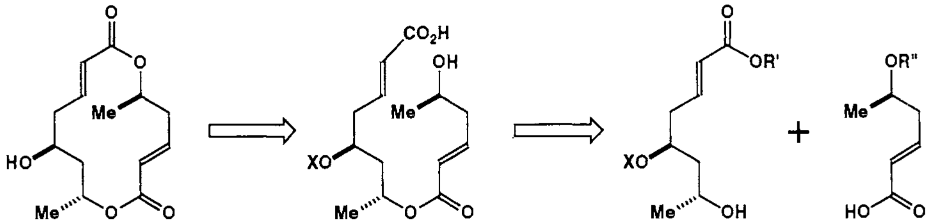
Total synthesis of (-)-colletol was achieved using palladium-catalyzed hydrogenolysis of optically active (*E*)-4,5-epoxy-2-alkenoates to (*E*)-5-hydroxy-2-alkenoates with formic acid as a key step for preparation of the intermediate hydroxy ester segments.

(-)-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]



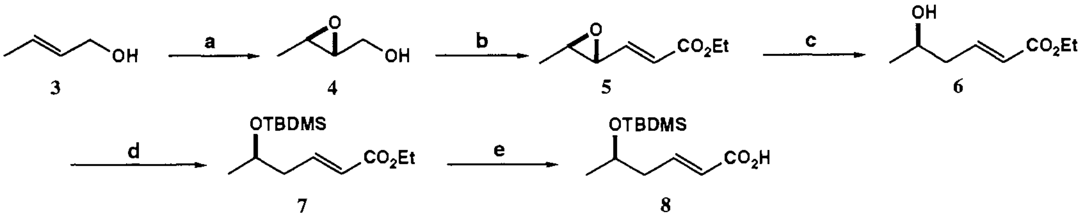
(-)-Colletol (**1**)

X=MOM

2

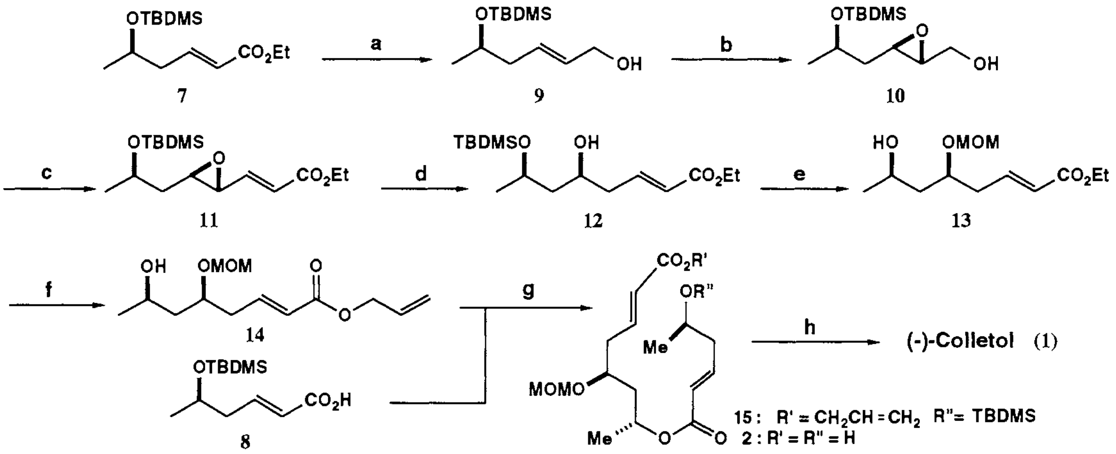
Scheme 1.

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.

References

1) J. MacMillan and T. J. Simpson, *J. Chem. Soc., Perkin Trans. 1*, **1973**, 1487.
2) G. E. Keck and J. A. Murry, *J. Org. Chem.*, **56**, 6606 (1991).
3) M. Oshima, H. Yamazaki, I. Shimizu, M. Nisar, and J. Tsuji, *J. Am. Chem. Soc.*, **111**, 6280 (1989).
4) F. J. Dommerholt, L. Thijs, and B. Zwanenburg, *Tetrahedron Lett.*, **32**, 1495 (1991); H. Tone, T. Nisi, Y. Oikawa, and O. Yonemitsu, *Chem. Pharm. Bull.*, **37**, 1167 (1989).
5) B. E. Rossiter, T. Katsuki, and K. B. Sharpless, *J. Am. Chem. Soc.*, **103**, 464 (1981); Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, and K. B. Sharpless, *ibid.*, **109**, 5765 (1987).
6) J. Otera, T. Yano, A. Kawabata, and H. Nozaki, *Tetrahedron Lett.*, **21**, 2383 (1986).
7) S. Hanessian, D. Delorme, and Y. Dufresne, *Tetrahedron Lett.*, **25**, 2515 (1984).
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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