A Short and Enantioselective Synthesis of Colletodiol

Laurent Ferrié, Patrice Capdevielle, Janine Cossy*

Laboratoire de Chimie Organique associé au CNRS, ESPCI, 10 Rue Vauquelin, 75231 Paris Cedex 05, France
Fax +33(1)40794660; E-mail: janine.cossy@espci.fr

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Abstract: A 12-step enantioselective synthesis of colletodiol has been achieved using a cross-coupling metathesis and a Sharpless dihydroxylation as the key steps.

Key words: cross-metathesis, colletodiol, Sharpless dihydroxylation

Colletodiol is a 14-membered bis-macrolactone, which was isolated as a metabolite of the fungi *Colletrichum capsici* and *Chaetomium funicola* in 1966[1] and 1969,[2] respectively. In 1968,[3] three other 14-membered ring bis-macrolactones were isolated from *C. capsici*: colletol (**2**), colletoallol (**3**) and grahamimycin A (**4**). The interest in this group of unsymmetrical bis-macrolactones was shown in 1980, when the isolation and the significant antibacterial activity of grahamimycin A (**4**) and A1 (**5**) against a variety of pathogenic microorganisms were described.[4] These compounds are active against several species of bacteria, blue-green algae, free algae and different fungi. Even if colletodiol (**1**) exhibits only mild antibiotic properties, this compound is of particular interest as it can be transformed to grahamimycin A in one step by oxidation.[5] The absolute and relative stereochemistry of colletodiol (**1**) was established by total synthesis by Seebach[6] and Mitsunobu,[7] but both groups encountered difficulties as low yields were obtained for the macrolactonization. The macrolactonization problems to colletodiol (**1**) were solved by using DCC/DMAP[8] or Yamaguchi's conditions.[9]

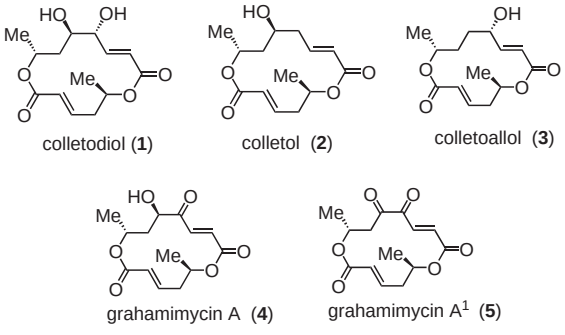
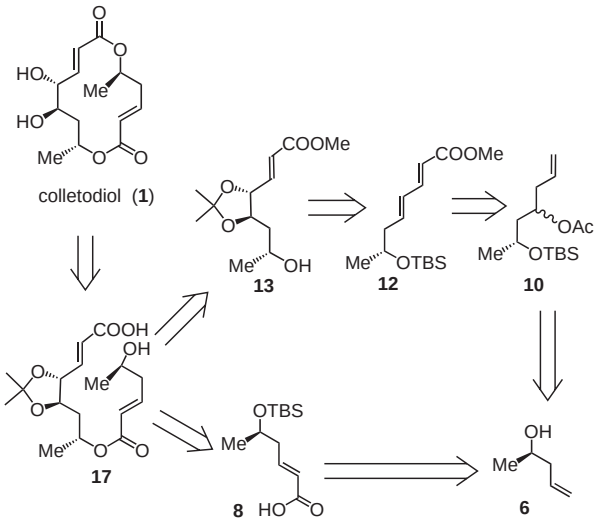


Figure 1 Natural bis-macrolactones.

Here, we would like to report a short and efficient synthesis of colletodiol (**1**) by using a cross-metathesis reaction and a regioselective dihydroxylation of a conjugated diene. Our retrosynthetic analysis of colletodiol envisioned a macrolactonization of hydroxyacid **17** which could be obtained by esterification of acid **8** by alcohol **13**. Compound **8** should be synthesized from the commercially available (*R*)-(–)-4-penten-2-ol (**6**) by using a cross-metathesis reaction with acrylic acid. On the other hand, diene **12**, precursor of intermediate **13**, should be obtained from the homoallylic acetate **10** by achieving a cross-metathesis reaction with methyl acrylate followed by the β-elimination of acetic acid. (*R*)-(–)-4-Penten-2-ol (**6**) should be also the starting material that can be used to prepare the homoallylic acetate **10** (Scheme 1).



Scheme 1 Retrosynthetic analysis.

The synthesis of compound **8** was achieved from the commercially available (*R*)-(–)-4-penten-2-ol (**6**). After protection of the hydroxyl group using *tert*-butyldimethylsilyl chloride [TBSCl (1.05 equiv), Et_3N (2 equiv), DMAP (0.2 equiv), CH_2Cl_2 24 h, r.t.], the obtained silyl ether **7** (89% yield) was treated with acrylic acid (3 equiv) in the presence of the Grubbs–Hoveyda catalyst (3 mol%) in CH_2Cl_2 at room temperature for 48 hours to produce the cross-metathesis product **8** in 97% yield (Scheme 2). The homoallylic alcohol **7** was also used to prepare hydroxyester **14**. After oxidative cleavage of the double bond present in **7** by ozone[10] [O_3, CH_2Cl_2, –78 °C; then Et_3N (2 equiv), r.t., 2 h], aldehyde **9** was obtained in 92% yield. In order to transform aldehyde **9** into the dienoic ester **12**,

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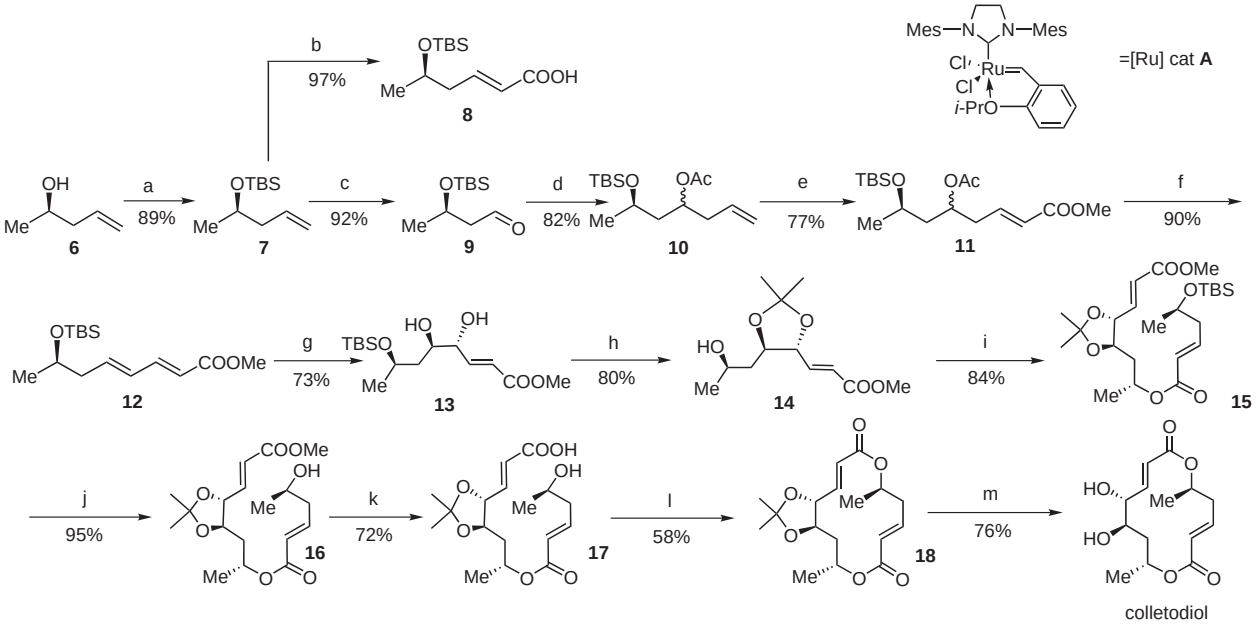

Scheme 2 a) TBSCl (1.05 equiv), Et_3N (2 equiv), DMAP (0.2 equiv), CH_2Cl_2, 24 h, r.t.; b) [Ru] cat **A** (3 mol%), acrylic acid (3 equiv), CH_2Cl_2; c) O_3, CH_2Cl_2, –78 °C; then Et_3N (2 equiv), r.t., 2 h; d) allylMgCl, 30 min, THF, –20 °C; then in situ Ac_2O (5 equiv), pyridine (5 equiv), 8 h, r.t.; e) [Ru] cat **A** (3 mol%), methyl acrylate (5 equiv), CH_2Cl_2; f) DBU (1.1 equiv), DME 16 h, r.t.; g) modified AD-mix β, OsO_4 (2 mol%), $(DHQD)_2PHAL$ (4 mol%), $MeSO_2NH_2$ (1 equiv), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv), *t*-BuOH–H_2O; h) PPTS (1.2 equiv), MeOH, 24 h, r.t.; then dimethoxypropane (10 equiv) and *p*-toluenesulfonic acid (5 mol%); i) 2,4,6-trichlorobenzoyl chloride (1.7 equiv), Et_3N (3 equiv), carboxylic acid **8** (1.5 equiv) in Et_2O, 2 h, r.t., filtration and evaporation of the solvent, then addition of **14** in toluene, 90 °C, 3.5 h; j) TBAF (5 equiv), PhCOOH (5 equiv), THF–H_2O, 96 h, r.t.; k) LiOH (1.2 equiv), THF–H_2O, 16 h; l) DCC (5 equiv), DMAP (5 equiv), CH_2Cl_2, reflux, 12 h; m) Dowex® 50W-8H$^+$ resin, MeOH, reflux, 8 h.

compound **9** was first treated with allylmagnesium chloride in THF at –20 °C and after 30 minutes, the intermediate alkoxide was trapped in situ by addition of acetic anhydride (3 equiv) and pyridine (3 equiv).

The homoallylic acetate **10**[11] was isolated as a 60:40 mixture of two diastereoisomers in 82% yield. The transformation of **10** into diene **12** was achieved in two steps. The first step is a cross-metathesis performed between compound **10** and methyl acrylate (3 equiv) in the presence of the Grubbs–Hoveyda catalyst (3 mol%) in CH_2Cl_2 at room temperature. After 70 hours, the unsaturated ester **11**[11] was isolated in 77% yield. The second step is the acetate elimination using DBU (1.1 equiv) in DME (r.t., 16 h) which produced diene **12** in 90% yield. The Sharpless dihydroxylation[12] applied to **12** using $(DHQD)_2$-PHAL yielded regioselectively diol **13** accompanied by the regioisomer **13′**[13] in a ratio of 10:1. After separation of the two regioisomers **13** and **13′** by chromatography, **13** was isolated in 73% yield. The monoprotected triol **13** was directly subjected to a deprotection–protection step [PPTS (1.2 equiv) in the presence of MeOH, 24 hours, room temperature; then dimethoxypropane (10 equiv) and *p*-toluenesulfonic acid (5 mol%)] to produce selectively the five-membered ring acetonide **14** in 80% yield.

Having synthesized the two main fragments of colletodiol, esterification of the carboxylic acid **8** by alcohol **14** using 2,4,6-trichlorobenzoyl chloride (DMAP, toluene, 90 °C, 3 h) furnished ester **15** in 84% yield. After deprotection of the hydroxy group present in **15** (TBAF, $PhCO_2H$, THF–H_2O, 96 h), the hydroxy ester **16** was isolated in 95% yield and then saponified [LiOH, 1.2 equiv), THF–H_2O, 16 h, r.t.] to produce the hydroxy acid **17** in 82% yield. Following the known procedure for macrolactonization[8] (DCC/DMAP/CH_2Cl_2, reflux), **17** was transformed to **18** in 58% yield and then, this macrolactone was deprotected (Dowex 50W-8H+, MeOH, reflux) in 76% yield, to afford colletodiol (**1**) as pure white crystals. The spectral and physical data for the isolated material were in accordance with the data reported in the literature (^{1}H NMR, ^{13}C NMR, IR, optical rotation and melting point).[14]

The synthesis of colletodiol was achieved in 12 steps from (*R*)-(–)-4-penten-2-ol (**6**) with an overall yield of 7%.

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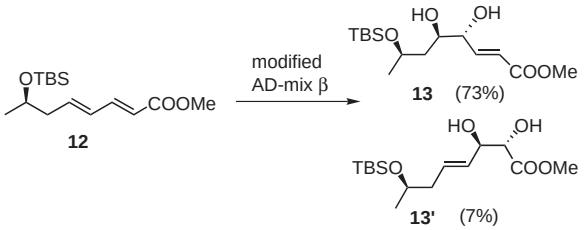
(13) Dihydroxylation of **12** gives a mixture of **13** and **13′** in a 10:1 ratio (Scheme 3).



Scheme 3

(14) Colletodiol(**1**): mp 163–165 °C; R_f = 0.35 [toluene–dioxane–AcOH, 20:10:1 (v/v/v)]; $[\alpha]_D$ +35.6 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.73 (m, 2 H), 6.13 (d, *J* = 15.6 Hz, 1 H), 5.73 (d, *J* = 15.4 Hz, 1 H), 5.31 (m, 1 H), 5.18 (m, 1 H), 4.07 (dd, *J* = 8.5, 5.5 Hz, 1 H), 3.67 (dd, *J* = 8.0, 6.0 Hz, 1 H), 2.87 (br s, OH, 1 H), 2.72 (br s, OH, 1 H), 2.52 (m, 1 H), 2.22 (dt, *J* = 12.4, 11.4 Hz, 1 H), 2.01 (dd, *J* = 15.0, 3.5 Hz, 1 H), 1.50 (ddd, *J* = 15.8, 6.0, 2.0 Hz, 1 H), 1.36 (d, *J* = 6.5 Hz, 3 H), 1.34 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 165.1, 146.3, 144.1, 125.7, 123.9, 74.0, 71.9, 68.7, 67.9, 41.1, 36.3, 20.4, 18.1. IR: 3600–3100 (br), 2980, 2934, 1748, 1716, 1653, 1444, 1347, 1314, 1261, 1172, 1105, 1034, 985, 916, 859, 824, 791, 742, 706, 631, 600 cm^{-1}.