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Two approaches for efficient synthesis of (−)-colletol

Samir BouzBouz* and Janine Cossy

Laboratoire de Chimie Organique UMR 7084, CNRS, ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05, France

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Abstract—The synthesis of (−)-colletol was achieved from (*R*)-pent-4-en-2-ol by using enantioselective allyltitanations to control the stereogenic centers at C5 and cross-metathesis, ring-closing metathesis reactions to control the configuration of the double bonds.

(−)-Colletol (**1**) is a 14-membered bis-macrolactone isolated from the fermentation broth of *Collectotrichum capsici* in 1973 along with related bis-lactones colletodiol (**2**), colletoketol (**3**), and colletallol (**4**)[1] (Fig. 1). Although no biological activity was reported for these macrolactones, interest in these compounds was stimulated when the isolation of grahamimycin A_1 (**5**), which displayed potent activity against bacteria, algae, and fungi was reported.[2,3] These macrolactones can result from a biosynthesis via the macrodiolide colletotriene (**6**)[4] (Fig. 1).

The promising biological activity and the unique structure of this family of macrolactones make them attractive synthetic targets and there have been several synthesis of colletol.[5]

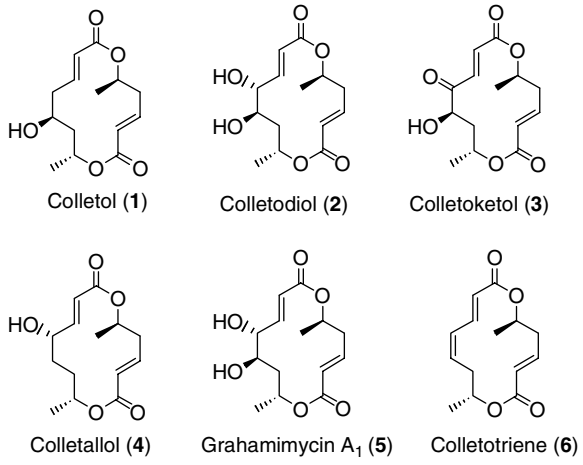
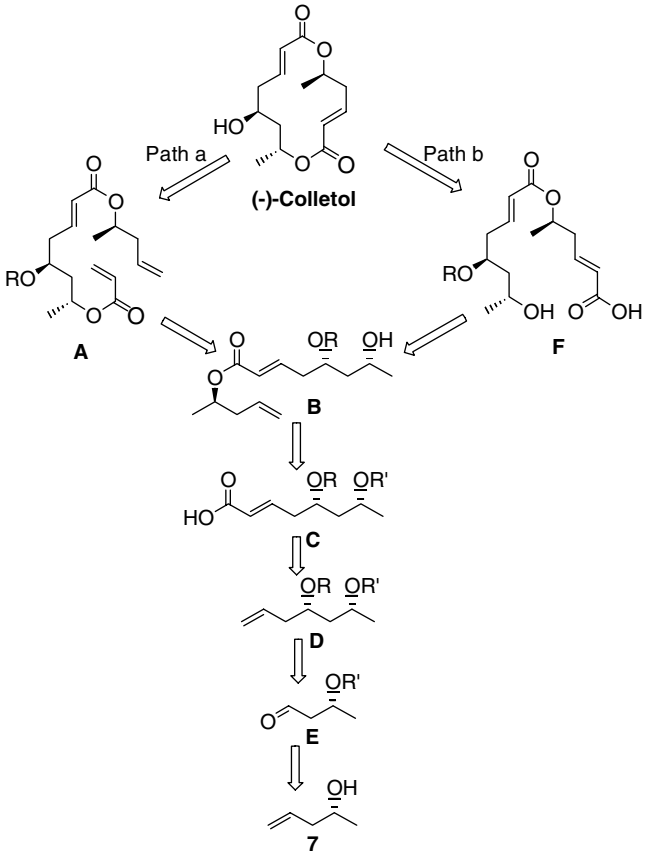


Figure 1. Natural 14-membered macrolactones.

The two possible pathways, implying a common intermediate **B** (Scheme 1), have been envisaged for obtaining the 14-membered ring present in (−)-colletol (**1**)



Scheme 1. Retrosythetic analysis of (−)-colletol.

* Corresponding author. Fax: +33 0140794660; e-mail: samir.bouzbouz@wanadoo.fr

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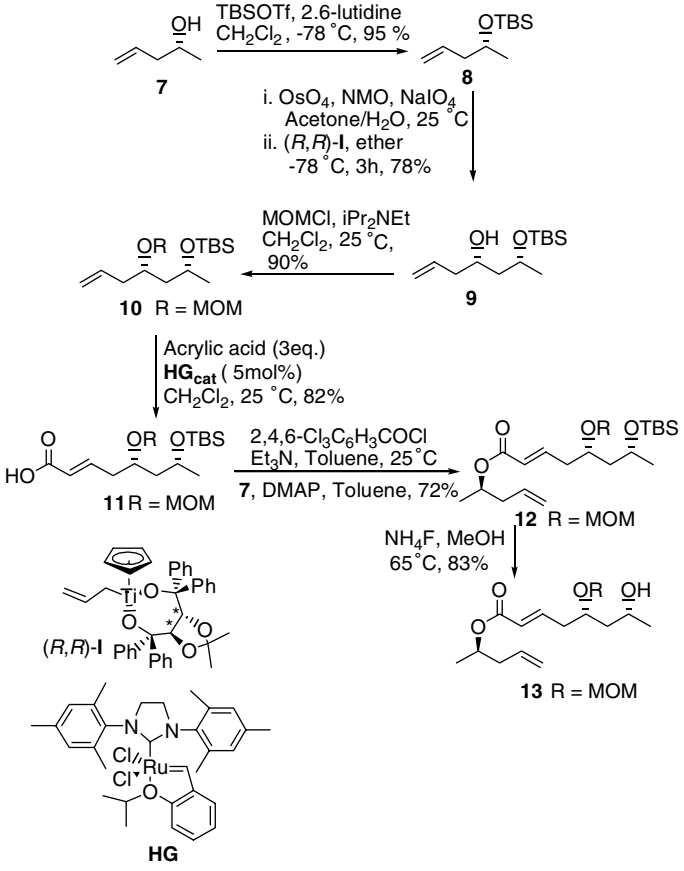
(Scheme 1). One involves a macrolactonization and the second one involves a ring-closing metathesis (RCM) as we wanted to examine the potential of metathesis reactions in the synthesis of (−)-colletol. The synthesis of (−)-colletol should be achieved in a limited number of steps using enantioselective allyltitanations[6] to produce the *syn* 1,3-diol units.[7]

A first retrosynthetic analysis envisioned the formation of the macrolactone by using a ring-closing metathesis (RCM), applied to compound **A** and involved an activated olefin and a non-activated olefin. Compound **A** should be synthesized from **B** by esterification with acryloyl chloride. The unsatured carboxylic acid **C**, precursor of **B**, should be obtained by using a cross-metathesis (CM) between the homoallylic alcohol **D** and acrylic acid. The optically active *syn* 1,3-diols present in **D** should be obtained from the optically active commercially available homoallylic alcohol **7**[8] via the protected β-hydroxy-aldehyde **E** by utilizing an enantioselective allyltitanation (Scheme 1, path a).

A second retrosynthetic analysis involving a penultimate macrolactonization of the seco-acid **F** was envisaged. In this scheme, the two *E*-double bonds will be introduced by using two cross-metatheses, one between **D** and acrylic acid (C2–C3) and one chemoselective CM between **B** and acrylic acid (C8–C9) (Scheme 1, path b).

The synthetic scheme to prepare compound **A** began with the preparation of the pure *syn* 1,3-diol **9** from the commercially available (*R*)-pent-4-en-2-ol. After protection of the hydroxy group of (*R*)-pent-4-en-2-ol **7** (TBSOTf, 2,6-lutidine, −78 °C, 95% yield), the silyl ether **8** was oxidatively cleaved (OsO_4, NMO then $NaIO_4$, acetone/H_2O = 3/1) to produce an aldehyde of type **E**, which was directly treated with the optically active allyltitanium complex (*R*,*R*)-**I** and transformed to the *syn* 1,3-diol **9** with a good diastereoselectivity (dr >95/5) in 78% overall yield from **7**. After protection of the hydroxy group (MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 25 °C, yield = 90%), the resulting compound **10** was involved in a CM reaction with acrylic acid (3 equiv) in the presence of the Hoveyda-Grubbs catalyst (**HG** 5 mol %, CH_2Cl_2, 25 °C, 16 h) and transformed to the *E*-unsaturated carboxylic acid in 82% yield and with a *E*/*Z* ratio of 20/1. In order to introduce the non-activated olefin, which will be involved in the RCM, carboxylic acid **11** was treated with (*R*)-pent-4-en-2-ol under the Yamaguchi's conditions (2,4,6-$Cl_3C_6H_3COCl$, Et_3N, DMAP, 25 °C). Ester **12**[9] was isolated in 72% yield and then converted to alcohol **13**[10] using NH_4F in refluxing methanol for 12 h (yield 83%)[11] (Scheme 2).

A ring-closing metathesis reaction has been achieved on **14** in order to obtain the macrolactone ring of (−)-colletol. At first, compound **13** was esterified using acryloyl



Scheme 2. Synthesis of the common fragment **13**.

chloride (*i*-Pr_2NEt, CH_2Cl_2, −78 °C, yield = 92%) and the obtained unsaturated ester **14** was treated with the Hoveyda-Grubbs catalyst **HG** (5 mol %) in CH_2Cl_2 ($c = 10^{-3}$ M, 25 °C). After 72 h, macrolactone **15** was obtained in 32% as a mixture of two inseparable isomers, *E*,*E*/*E*,*Z* in a ratio of 2.8/1 in favor of the *E*,*E*-isomer.[12] To our knowledge, no precedent of a formation of 14-membered macrolactone of the type **15** by a RCM with 25 °C in the presence of Hoveyda-Grubbs catalyst **HG** was deferred.

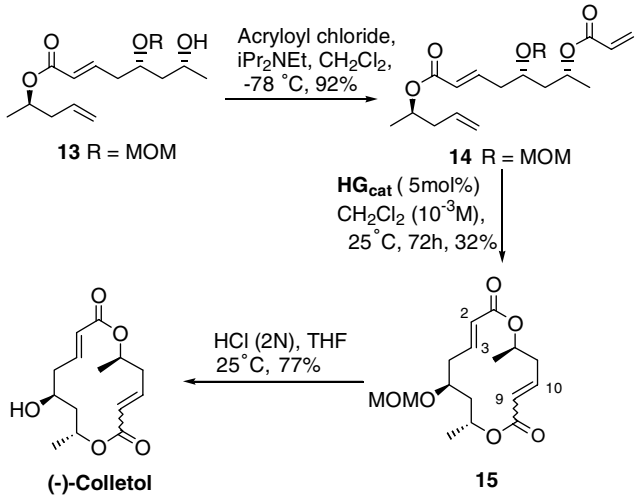
After deprotection (HCl, THF, 24 h, 25 °C), the inseparables (−)-colletol **1** and its (*E*,*Z*)-isomer[13,14] were isolated in 77% yield in a ratio of 2.8/1 (Scheme 3).

To our knowledge, it is the first time that a 14-membered macrolactone can be synthesized from an α,β-unsaturated acrylate using a RCM, however the yield is modest as well as the *E*,*E*/*Z*,*E* ratio of the formed olefins. It is worth noting that the ring-closing metathesis of α,β-unsaturated acrylate by using second generation Grubbs catalyst affords cyclic dimers or trimers.[15,16]

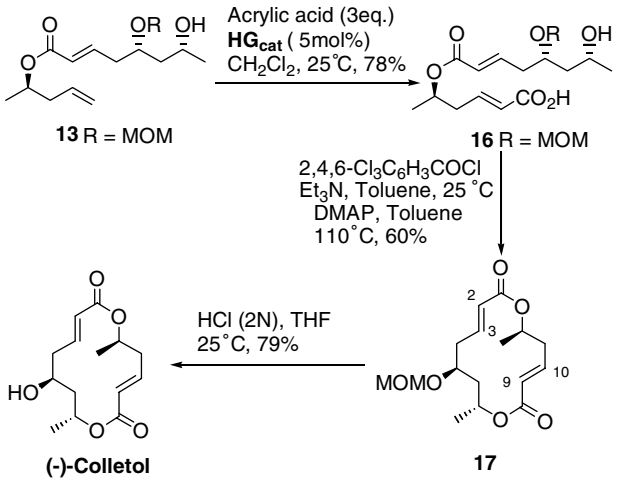
Due to this non-stereoselective RCM, compound **13** has been transformed to acrylic acid **16** in order to achieve a macrolactonization. Compound **13** was submitted to a CM using acrylic acid (**HG** 5 mol %, CH_2Cl_2, 25 °C, 16 h) to form the conjugated unsaturated acid **16** as a 20/1 mixture of *E*/*Z* isomers in 78% yield. The obtained seco-acid **16** was macrolactonized under the Yamaguchi's conditions[17] (2,4,6-$Cl_3C_6H_3COCl$, Et_3N, DMAP, toluene) to afford the macrolactone **17** in 60% yield, which after treatment with HCl was converted to (−)-colletol[18] (Scheme 4).

The spectra and physical data for the isolated material were in accordance with the data reported in the literature (^1H NMR, ^{13}C NMR, IR).

By using a macrolactonization and two CM, (−)-colletol was obtained in nine steps with an overall yield of 12%. This synthesis is the shortest synthesis described up to now.



Scheme 3. Synthesis of (−)-colletol by RCM.



Scheme 4. Synthesis of (−)-colletol by macrolactonization.

Acknowledgments

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References and notes

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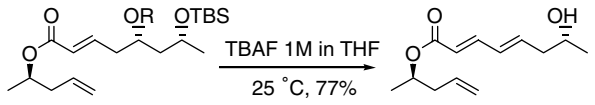
8. Commercially available (*R*)-pent-4-en-2-ol **7** is sold at Aldrich ~ $80/g.
9. Spectral data for common intermediate **12**: $[\alpha]_D^{25}$ +5.3 (*c* 1.23, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.90 (td, *J* = 7.5 and 15.8 Hz, 1H), 5.81 (dt, *J* = 1.5 and 15.8 Hz, 1H), 5.71 (m, 1H), 5.09–4.92 (m, 3H), 4.58 (m, 2H), 3.87 (ddd, *J* = 6.0, 12.0, and 18.4 Hz, 1H), 3.76 (ddd, *J* = 6.4, 11.7, and 12.8 Hz, 1H), 3.32 (s, 3H), 2.50–2.19 (m, 4H), 1.74 (td, *J* = 6.4 and 13.9 Hz, 1H), 1.47 (ddd, *J* = 6.0, 12.4, and 13.9 Hz, 1H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.11 (d, *J* = 6.0 Hz, 3H), 0.83 (s, 9H), 0.02 and 0.01 (2s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 165.7 (s), 144.9 (d), 133.7 (d), 124.0 (d), 117.6 (t), 95.4 (t), 73.5 (d), 69.8 (d), 65.6 (d), 55.6 (q), 44.4 (t), 40.3 (t), 37.4 (t), 25.8 (3q), 23.7 (q), 19.5 (q), 18.0 (s), −4.3 (q), −4.7 (q). IR (neat) ν (cm^{-1}): 2934, 2856, 1718, 1655, 1256, 1034. MS *m*/*z*: 400 (M^+, absent), 343 (M−*t*-Bu, 6), 299 (3), 253 (19), 213 (49), 198 (16), 169 (21), 159 (100), 145 (80), 133 (30), 101 (29), 89 (25), 73 (26), 59 (11).

10. Spectral data for common intermediate **13**: $[\alpha]_D^{25}$ +49.3 (*c* 1.8, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.92 (td, $J = 7.5$ and 15.4 Hz, 1H), 5.86 (dt, $J = 1.5$ and 15.4 Hz, 1H), 5.75 (m, 1H), 5.06 (m, 2H), 5.02 (m, 1H), 4.70 (m, 2H), 3.95 (m, 2H), 3.39 (s, 3H), 2.95 (sl, 1H, OH), 2.50–2.25 (m, 4H), 1.74 (m, 1H), 1.58 (ddd, $J = 3.2$, 4.8, and 16 Hz, 1H), 1.25 (d, $J = 6.4$ Hz, 3H), 1.18 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 165.6 (s), 144.0 (d), 133.5 (d), 124.3 (d), 117.6 (t), 95.3 (t), 75.8 (d), 70.0 (d), 66.6 (d), 55.8 (q), 43.2 (t), 40.2 (t), 37.3 (t), 23.6 (q), 19.4 (q). IR (neat) ν (cm^{-1}): 3457, 2934, 1714, 1654, 1266, 1032. MS *m*/*z*: 286 (M^+, absent), 287 (M+1, 0.05), 227 (1), 211 (1), 198 (30), 169 (56), 154 (4),139 (41), 113 (22), 101 (100), 81 (12), 69 (54).
11. The treatment of **12** by TBAF does not lead to compound **13** but to diene **12′**.



12 R = MOM **12'**

12. The *E*/*Z* ratio has been determined by ^1H NMR. Spectral data for compound **15**: Major isomer *EE*: ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.75–6.60 (2ddd, $J_{2-3} = J_{9-10} =$ 15.8 Hz, 2H, H_3, H_{10}), 5.81 (dt, $J = 1.5$ and 15.8 Hz, 1H), 5.77 (dt, $J = 1.5$ and 15.4 Hz, 1H), 5.30–5.12 (m, 2H), 4.73 (m, 2H), 3.85 (m, 1H), 3.40 (s, 3H), 2.71 (m, 1H), 2.52 (td, $J = 3.7$ and 12.8 Hz, 1H), 2.25 (m, 2H), 1.90 (td, $J = 3.4$ and 15.4 Hz, 1H), 1.36 (d, $J = 6.4$ Hz, 3H), 1.31 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 166.1 (s), 165.3 (s), 144.3 (d), 143.6 (d), 126.2 (d), 124.9 (d), 95.8 (t), 74.3 (d), 68.4 (d), 68.0 (d), 55.8 (q), 40.9 (t), 38.8 (t), 37.0 (t), 20.5 (q), 18.3 (q). MS *m*/*z*: 312 (M^+, absent), 281 (0.07), 251 (3), 206 (8), 180 (26), 157 (33), 127 (23), 115 (78), 95 (63), 68 (100). For minor isomer *EZ*: ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.64 (m, 1H, H_3), 6.32 (td, $J = 6.4$ and 11.7 Hz, 1H, H_{10}), 5.97 ($d_{apparent}$, $J = 11.7$ Hz, 1H, H_9), 5.79 (td, $J = 2.6$ and 15.8 Hz, 1H, H_2), 5.33 (m, 1H), 4.80 (m, 1H), 4.73 (m, 2H), 3.94 (m, 1H), 3.40 (s, 3H), 2.41–2.0 (m, 5H), 1.81 (m, 1H), 1.28 (d, $J = 6.8$ Hz, 3H), 1.24 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 165.2 (s), 164.4 (s), 144.5 (d), 141.8 (d), 124.5 (d), 123.5 (d), 95.2 (t), 73.0 (d), 67.7 (d), 67.3 (d), 55.5 (q), 41.9 (t), 38.6 (t), 31.1 (t), 20.6 (q), 17.8 (q). MS *m*/*z* 312 (M^+, absent), 281 (0.19), 251 (2), 206 (5), 183 (61), 157 (7), 121 (55), 113 (100), 95 (48), 68 (43). For two isomers: IR (neat) ν (cm^{-1}): 2933, 1717, 1655, 1260, 1032.
13. Spectral data for (−)-colletol *E*/*Z* isomer: ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.65 (m, 1H, H_3), 6.34 (td, $J = 6.4$ and 11.3 Hz, 1H, H_{10}), 5.97 ($d_{apparent}$, $J = 11.3$ Hz, 1H, H_9), 5.79 (td, $J = 2.6$ and 15.8 Hz, 1H, H_2), 5.32 (m, 1H), 4.81 (m, 1H), 4.10 (m, 1H), 2.68–2.23 (m, 4H), 2.05 (m, 1H), 1.79 (ddd, $J = 3.4$, 8.3, and 14.3 Hz, 1H), 1.70 (br s, 1H, OH), 1.29 (d, $J = 6.8$ Hz, 3H), 1.26 (d, $J = 6.0$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 165.2 (s), 164.4 (s), 144.2 (d), 142.0 (d), 124.4 (d), 123.6 (d), 68.0 (d), 67.7 (d), 67.4 (d), 43.7 (t), 41.3 (t), 31.2 (t), 20.5 (q), 17.8 (q). MS *m*/*z* 312 (M^+, absent), 281 (0.19), 251 (2), 206 (5), 183 (61), 157 (7), 121 (55), 113 (100), 95 (48), 68 (43). IR (neat) ν (cm^{-1}): 3350, 2984, 2922, 1709, 1653, 1258, 1177.
14. In Ref. 5e O'Doherty and all was obtained the (−)-colletol **1** and its (*Z*,*E*)-isomer in a 1:1 mixture from colletodiol.
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18. Spectroscopic data of (−)-colletol: $[\alpha]_D^{25}$ −13.5 (*c* 0.32, $CHCl_3$). ^1H NMR δ: 6.72 (ddd, $J = 4.9$, 9.0, and 15.8 Hz, 1H), 6.72 (ddd, $J = 6.8$, 8.3, and 15.4 Hz, 1H), 5.80 (dt, $J = 1.13$ and 15.8 Hz, 1H), 5.77 (d, $J = 0.75$ and 15.4 Hz, 1H), 5.30–5.12 (m, 2H), 4.05 (m, 1H), 2.57–2.47 (m, 2H), 2.36–2.20 (m, 2H), 1.99 (dt, $J = 3.0$ and 15.8 Hz, 1H), 1.51 (ddd, $J = 3.0$, 6.0, and 15.8 Hz, 1H), 1.36 (d, $J = 6.4$ Hz, 3H), 1.35 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR δ: 166.0 (s), 165.3 (s), 144.0 (d), 143.8 (d), 126.2 (d), 125.1 (d), 68.4 (d), 68.2 (2d), 40.9 (t), 40.3 (t), 40.1 (t), 20.6 (q), 18.2 (q). IR (neat) ν (cm^{-1}): 3350, 2984, 2922, 1709, 1653, 1258, 1177.