Stereoselective Total Synthesis of (–)-(6*R*,11*R*,14*R*)-Colletallol via RCM Protocol

Palakodety Radha Krishna,* D. Venkata Ramana, B. Karunakar Reddy

D-211, Discovery Laboratory, Organic Chemistry Division-III, Indian Institute of Chemical Technology, Hyderabad 500607, India
Fax +91(40)27193158; E-mail: prkgenius@iict.res.in

Received 21 August 2009

Abstract: The total synthesis of (–)-colletallol via a ring-closing metathesis protocol is reported.

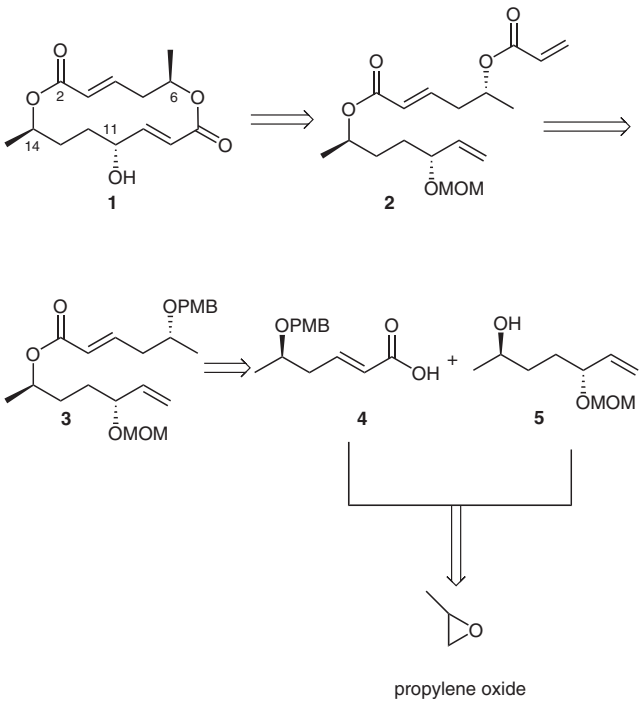
Key words: (–)-colletallol, ring-closing metathesis (RCM), Grubbs II catalyst, Jacobsen's hydrolytic kinetic resolution (HKR)

Colletallol (**1**), a diolide belonging to a series of structurally related macrolides, was isolated from plant pathogen *Colletrichum capsici*.[1] This diolide and its congeners attracted the attention of many synthetic organic chemists worldwide since isolation, but only two syntheses of **1** were reported so far, out of which one was an enantioselective total synthesis by Zwanenburg et al.[2] using epoxy diazomethyl ketone as the starting material and its photo-induced rearrangement to 4-hydroxy-2-alkenoate as the useful intermediate en route and the other one being a racemic synthesis way back in 1985.[3] Subsequently, a 14-epimer was synthesized by Floćh et al.[4] using two consecutive Wittig olefination reactions as an alternative methodology to classical macrolactonization strategy. As a part of our ongoing program on the metathesis-based synthesis of natural products,[5] herein we describe a stereoselective total synthesis of natural (–)-colletallol (**1**) via Grubbs catalyst assisted ring-closing metathesis protocol of the corresponding diester derivative **2** (Scheme 1).

The retrosynthetic analysis envisioned for **1** is depicted in Scheme 1, using a ring-closing metathesis (RCM) of the corresponding diester derivative **2** followed by the deprotection of the MOM protecting group. Compound **2** in turn could be synthesized from **3** on PMB deprotection and acryloylation. Compound **3** should be accessible through the esterification of acid **4** with alcohol **5** that were independently synthesized from the commercially available propylene oxide as starting material.

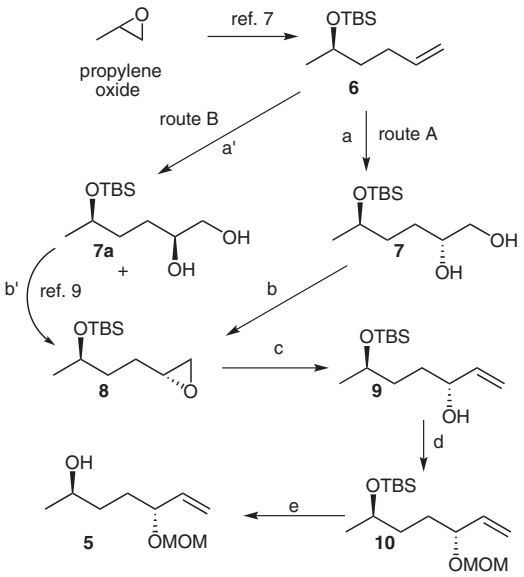
Thus, the synthesis began in the direction of accessing both the acid **4** and the alcohol **5** components independently. Firstly, acid **4** was accessed based on the literature procedure[6] wherein the synthesis of its enantiomer was reported.

Subsequently, alcohol **5** was also prepared from propylene oxide (Scheme 2) using a literature-inspired route.[7] Accordingly, propylene oxide upon Jacobsen's hydrolytic kinetic resolution[8]/epoxide ring-opening reaction with allyl magnesium chloride and protection of the ensuing hydroxyl group as its silyl ether afforded **6**. The terminal olefin was used in two ways, firstly Sharpless asymmetric dihydroxylation (AD-mix-β, *t*-BuOH–H_2O (1:1), 48 h) furnished diol **7** (84%) albeit in 63% de. Further purification of **7** led to diminished yields. Consequently, an alternate Jacobsen's hydrolytic kinetic resolution (HKR) based strategy was adopted and the loss in chemical yield was circumvented by a two-step recycling of the resoluted diol **7a** into the requisite epoxide **8**.[9] Thus both enhanced chemical and optical yields were met through this strategy. Epoxide **8** obtained by both methods was found to have comparable spectral data. Later, ring-opening reaction[10] ($Me_3S^+I^-$, THF, –20 °C to r.t., 3 h) of epoxide **8** gave allylic alcohol **9** (85%) which was protected as its MOM ether **10** under conventional conditions. TBS deprotection (TBAF, THF, r.t., 2 h) in **10** furnished the corresponding alcohol **5** (85%) as the suitable intermediate for the next reaction.



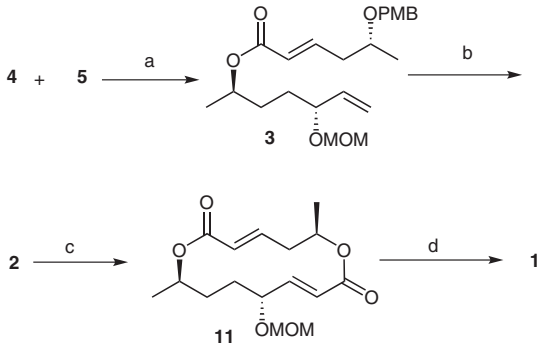
Scheme 1 Retrosynthetic analysis

SYNLETT 2009, No. 18, pp 2924–2926
Advanced online publication: 02.10.2009
DOI: 10.1055/s-0029-1218270; Art ID: G27209ST



Scheme 2 Reagents and conditions: route A: (a) AD-mix-β, *t*-BuOH–H_2O (1:1), 48 h, 84%, 63% de; (b) i) TsCl, Et_3N, CH_2Cl_2, r.t.; ii) K_2CO_3, MeoH, r.t., 1 h, 72% (over two steps); route B: (a′) (i) MCPBA, $CHCl_3$, 0 °C to r.t., 2 h, 90%; (ii) (*R*,*R*)-(salen)CoIII(OAc), 0.55 equiv H_2O, r.t., 18 h,; (b′) ref. 9; (c) *n*-BuLi, $Me_3S^+I^-$, THF, –20 °C to r.t., 3 h, 85%; (d) MOMCl, DIPEA, DMAP (cat.) CH_2Cl_2, 0 °C to r.t., 8 h, 98%; (e) TBAF, THF, r.t., 2 h, 85%.

Having both the intermediates **4** and **5** in hand, the next task was to couple them as an ester (Scheme 3). Accordingly, esterification (DCC, DMAP, CH_2Cl_2, r.t.) of **4** and **5** afforded **3** (80%) which was characterized by its spectral data. For instance, ^{1}H NMR spectrum of ester **3** revealed the characteristic signals due to the ester-linked proton shifting downfield to δ = 4.90–4.98 ppm as a multiplet while the rest of the protons resonated at their expected chemical shifts. Also, the characteristic olefinic protons present in conjugation with the α,β-unsaturated ester revealed the α-proton at δ = 5.57–5.67 ppm integrating for 1 H, while the β-proton appeared at δ = 6.85–6.94 ppm. The terminal olefinic protons integrating for 3 H retained their expected chemical shifts. The HRMS was in good agreement {*m/z* calcd for $C_{23}H_{34}O_6Na$ [M + Na]$^+$: 429.2253; found: 429.2263} with the expected structure. Next, the PMB group was deblocked under DDQ conditions; the corresponding hydroxyl group was acryloylated (acryloyl chloride, DIPEA, CH_2Cl_2, r.t.) to furnish the crucial intermediate **2** (95%). Diester **2** was then subjected to ring-closing metathesis reaction (Grubbs II, toluene, reflux, 4 h) to afford diolide **11** in good yields albeit as an *E*/*Z* mixture in a 85:15 ratio.[11] The required *E*-isomer was purified by column chromatography and characterized by its spectral data. For instance, the ^{1}H NMR spectrum of (*E*)-**11** displayed the absence of chemical shifts due to terminal olefinic protons, the emergence of two nonequivalent α-protons: one at δ = 5.79 ppm as a doublet (*J* = 15.1 Hz) and the other at δ = 5.87 ppm as a double doublet (*J* = 16.1, 1.4 Hz); while one of the two β-protons appearing at δ = 6.68–6.75 ppm as a multiplet and the other one at δ = 6.81 ppm as a double doublet (*J* = 15.6, 4.3 Hz) of the α,β-unsaturated esters marked the formation of the product. The HRMS spectrum displayed the *m/z* [M + Na]$^+$ 335.1475, calculated 335.1470 for the molecular formula $C_{16}H_{24}O_6Na$. Later, deprotection of MOM ether in **11** under Hannessian conditions[12] resulted in the natural product **1** (95%). The physical and spectroscopic data of synthetic **1** is consistent with the reported values.[1,2,13]



Scheme 3 *Reagents and conditions*. a) DCC, DMAP, CH_2Cl_2, r.t., 80%; b) (i) DDQ, CH_2Cl_2, 0 °C to r.t., 95%; (ii) acryloyl chloride, DIPEA, CH_2Cl_2, 4 h, r.t., 95%; c) Grubbs II (10 mol%), toluene, reflux, 4 h, 80%; d) TMSCl, *n*-$Bu_4N^+Br^-$, CH_2Cl_2, –10 °C to 0 °C, 2 h, 95%.

In summary, synthesis of (–)-colletallol was accomplished via the RCM of the highly substituted diester **2** with Grubbs II catalyst in good yields and selectivity. The key intermediates **4** and **5** were accessed from a common, inexpensive starting material viz. (±)-propylene oxide through simple transformations using Jacobsen's HKR protocol as the means of introducing chirality.

Acknowledgment

Two of the authors (D. V. R. and B. K. R.) thank the CSIR, New Delhi for the financial support in the form of fellowships.

References and Notes

(1) (a) MacMillan, J.; Pryce, R. J. *Tetrahedron Lett.* **1968**, 5497. (b) MacMillan, J.; Simpson, T. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1487.
(2) Dommerholt, F. J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1991**, *32*, 1495.
(3) Wakamatsu, T.; Yamada, S.; Ozaki, Y.; Ban, Y. *Tetrahedron Lett.* **1985**, *26*, 1989.
(4) Amigoni, S. J.; Toupet, L. J.; Le Floćh, Y. J. *J. Org. Chem.* **1997**, *62*, 6374.
(5) (a) Radha Krishna, P.; Narsingam, M. *Tetrahedron Lett.* **2004**, *45*, 4773. (b) Radha Krishna, P.; Srinivas, P. R. *Tetrahedron* **2007**, *63*, 3995. (c) Radha Krishna, P.; Krishnarao, L. *Synlett* **2007**, 1742. (d) Radha Krishna, P.; Srinivas, R. *Tetrahedron: Asymmetry* **2007**, *18*, 2197. (e) Radha Krishna, P.; Dayaker, G. *Tetrahedron Lett.* **2007**, *48*, 7279. (f) Radha Krishna, P.; Narsingam, M. *Tetrahedron Lett.* **2007**, *48*, 8721. (g) Radha Krishna, P.; Srinivas, R. *Tetrahedron: Asymmetry* **2008**, *19*, 1160. (h) Radha Krishna, P.; Srinivas, P. R. *Synlett* **2009**, 209.
(6) Sharma, G. V. M.; Babu, K. V. *Tetrahedron: Aymmetry* **2007**, *18*, 2175.

(7) Liu, J.; Zhang, L.; He, L.; Ma, B.; Pan, X.; She, X. *Tetrahedron: Aymmetry* **2008**, *19*, 906.
(8) (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.
(9) Radha Krishna, P.; Srinivas, R. *Tetrahedron Lett.* **2007**, *48*, 2013.
(10) Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Legall, T.; Shin, D.-S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 5449.
(11) (a) Lee, C. W.; Grubbs, R. H. *J. Org. Chem.* **2001**, *66*, 7155. (b) Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 3171. (c) Deiters, A.; Martin, S. *Chem. Rev.* **2004**, *104*, 2199.
(12) Hanessian, S.; Delorme, D.; Dufresne, Y. *Tetrahedron Lett.* **1984**, *25*, 2515.
(13) Spectral Data for Selected Compounds
Compound **5**: colorless liquid; $[\alpha]_D^{25}$ +243.0 (*c* 0.15, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.73–5.58 (m, 1 H), 5.24–5.13 (m, 2 H), 4.64 (d, *J* = 6.8 Hz, 1 H), 4.48 (d, *J* = 6.8 Hz, 1 H), 4.04–3.96 (m, 1 H), 3.83–3.73 (m, 1 H), 3.35 (s, 3 H), 1.68–1.39 (m, 4 H), 1.17 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.0, 117.2, 93.7, 77.4, 67.8, 55.4, 34.7, 31.7, 23.4. MS (EI): *m/z* = 113 [M – OMOM].
Compound **3**: colorless liquid; $[\alpha]_D^{25}$ +90.0 (*c* 0.25, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.3 Hz, 2 H), 6.94–6.85 (m, 1 H), 6.80 (d, *J* = 8.3 Hz, 2 H), 5.80 (d, *J* = 15.6 Hz, 1 H), 5.67–5.57 (m, 1 H), 5.23–5.13 (m, 2 H), 4.98–4.90 (m, 1 H), 4.67–4.61 (m, 1 H), 4.49–4.24 (m, 2 H), 4.37 (d, *J* = 11.2 Hz, 1 H), 3.98–3.90 (m, 1 H), 3.78 (s, 3 H), 3.63–3.56 (m, 1 H), 3.3 (s, 3 H), 2.49–2.4 (m, 1 H), 2.37–2.27 (m, 1 H), 1.67–1.54 (m, 4 H), 1.24 (d, *J* = 5.8 Hz, 3 H), 1.18 (d, *J* = 6.3 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9, 145.1, 137.9, 129.0, 123.5, 117.4, 113.7, 93.6, 77.0, 73.1, 70.6, 70.1, 55.3, 55.2, 39.2, 31.7, 31.1, 19.9, 19.6. HRMS: *m/z* calcd for $C_{23}H_{34}O_6Na$ $[M + Na]^+$: 429.2253; found: 429.2263.
Compound **2**: colorless liquid; $[\alpha]_D^{25}$ +155.9 (*c* 0.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 6.92–6.84 (m, 1 H), 6.39 (d, *J* = 17.0 Hz, 1 H), 6.09 (d, *J* = 17.0, 10.2 Hz, 1 H), 5.90–5.80 (m, 2 H), 5.70–5.61 (m, 1 H), 5.24–5.17 (m, 2 H), 5.12–5.06 (m, 1 H), 4.99–4.93 (m, 1 H), 4.68 (d, *J* = 6.8 Hz, 1 H), 4.52 (d, *J* = 6.8 Hz, 1 H), 4.00–3.94 (m, 1 H), 3.36 (s, 3 H), 2.55–2.44 (m, 2 H), 1.69–1.55 (m, 4 H), 1.28 (d, *J* = 6.3 Hz, 3 H), 1.24 (d, *J* = 6.3 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 165.5, 143.2, 137.9, 130.7, 128.5, 124.5, 117.5, 93.7, 77.0, 71.4, 69.3, 55.4, 38.3, 31.7, 31.2, 20.3, 19.6. HRMS: *m/z* calcd for $C_{18}H_{28}O_6Na$ $[M + Na]^+$: 363.1783; found: 363.1773.
Compound **11**: brown colored liquid; $[\alpha]_D^{25}$ +123.8 (*c* 0.06, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 6.75–6.71 (dd, *J* = 16.1, 5.4 Hz, 1 H), 6.70–6.63 (m, 1 H), 5.82 (d, *J* = 16.1 Hz, 1 H), 5.71 (d, *J* = 15.6 Hz, 1 H), 5.28–5.22 (m, 1 H), 5.16–5.11 (m, 1 H), 4.56 (s, 2 H), 4.44–4.40 (m, 1 H), 3.32 (s, 3 H), 2.54–2.48 (m, 2 H), 2.05–1.97 (m, 2 H), 1.81–1.74 (m, 1 H), 1.67–1.61 (m, 1 H), 1.45 (d, *J* = 6.3 Hz, 3 H), 1.17 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3, 165.5, 149.2, 143.6, 126.2, 122.1, 94.5, 74.0, 69.1, 68.3, 55.4, 40.6, 27.7, 26.5, 20.7, 17.5. HRMS: *m/z* calcd for $C_{16}H_{24}O_6Na$ $[M + Na]^+$: 335.1470; found: 335.1475.
Compound **1**: colorless syrup; $[\alpha]_D^{25}$ –85.5 (*c* 0.1 $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 6.81 (dd, *J* = 15.6, 4.3 Hz, 1 H), 6.75–6.68 (m, 1 H), 5.87 (dd, *J* = 16.1, 1.4 Hz, 1 H), 5.79 (d, *J* = 15.1 Hz, 1 H), 5.26–5.16 (m, 2 H), 4.60 (s, 1 H), 2.53 (m, 1 H), 2.38–2.24 (m, 2 H), 2.17 (d, *J* = 2.9 Hz, 1 H), 1.79–1.67 (m, 2 H), 1.36 (d, *J* = 6.3 Hz, 3 H), 1.19 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 165.6, 150.9, 143.5, 126.2, 121.3, 70.4, 69.1, 68.4, 40.6, 32.2, 29.1, 20.6, 17.4. HRMS: *m/z* calcd for $C_{14}H_{20}O_5Na$ $[M + Na]^+$: 291.1208; found: 291.1210.