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A convenient approach to total synthesis of synargentolide-B from L-ascorbic acid and D-ribose

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ABSTRACT

A convenient and practical approach for the total synthesis of naturally occurring lactone synargentolide-B has been accomplished in 14 steps from the commercially available L-ascorbic acid and D-ribose involving Bestmann–Ohira reaction, zinc mediated allylation, ring closing-metathesis, and cross-metathesis reactions. The highlight of our strategy describes a one-pot reaction involving stereoselective addition of allylzinc reagent and selective reduction of terminal alkyne to obtain the key advanced intermediates.

The α,β-unsaturated δ-lactone moiety is a ubiquitous motif present in a large number of natural products displaying a wide range of potent biological activities. It has been shown that the unsaturated moiety plays an essential role in the biological activity, due to its potential to act as a Michael acceptor in the presence of protein functional groups.[1] The synthetic and natural products possessing α,β-unsaturated δ-lactone moiety gained attention of researchers due to their cytotoxic and anti-tumor properties.[2] In addition they inhibit HIV protease,[3] induce apoptosis[4] and have proven to be anti-leukemic[5] along with having many other immunosuppressive properties.[6]

The α,β-unsaturated δ-lactone of synargentolide-B (**1**), was isolated in 1998 by Rivett's group from *Syncolostemon argenteus*, a South African genus.[7] In 2013 Prasad et al.[8a] attained its total synthesis making use of Wittig–Horner and RCM reactions as the key steps and also established its absolute stereochemistry. Sabitha et al.[8b], also reported its total synthesis from D-mannitol and D-ribose using a tandem ring-closing/cross-metathesis (RCM/CM) and the second-generation Hoveyda–Grubbs catalyst.

As continuation of our research program directed toward the total synthesis of bioactive molecules from cheap and readily available starting materials,[9] we have developed an efficient strategy utilizing Bestmann–Ohira, zinc allylation, ring-closing metathesis (RCM), and cross-metathesis (CM) reactions, for the convergent stereoselective synthesis of synargentolide-B (**1**). Our approach to the synthesis of synargentolide-B is based on stereoselective addition of an allylzinc reagent as well as controlled reduction of a terminal alkyne for an advanced intermediate, starting from abundantly available L-ascorbic acid and D-ribose in 14 steps.

As shown retrosynthetically in Scheme 1, synthesis of synargentolide-B could be accomplished with two different olefins, **15** and exocyclic olefin **9**. The exocyclic olefin would be started from the TBS-protected D-ribose (**5**), that would be subjected to Bestmann–Ohira reaction to furnish the triple bond compound **6**, which would be followed by zinc allylation to give **7**, which would be further reacted with acryloyl chloride and RCM cyclization for the key intermediate **9**. The other key intermediate olefin **15** was obtained from L-ascorbic acid by a standard carbohydrate chemistry procedure to obtain epoxide (**10**), which was regioselectively opened with $LiAlH_4$ to furnish an alcohol compound (**11**). The alcohol was benzoylated and acetonide was deprotected and the obtained diol compound was converted to the olefinic diol followed by acylation to give **15**.

Based on the above mentioned plan, synthesis of synargentolide-B (**1**) was initiated from commercially available L-ascorbic acid (Scheme 3) and D-ribose (Scheme 2). The primary hydroxyl group of 2,3-*O*-isopropylidine-D-ribose was protected as silyl ether by *tert*-butyldimethylsilyl chloride (TBDMSCl) and imidazole to give the known hemiacetal **5**[10] in 90% yield. A solution of hemiacetal **5** in dry methanol was subjected to undergo Bestmann–Ohira reaction[11] with gradual addition of dimethyl (1-diazo-2-oxopropyl)phosphonate and K_2CO_3 at 55 °C, 8 h leading to acetylenic moiety in a 65% yield. The free hydroxyl moiety of **6** was subsequently subjected to oxidation with sodiumperiodate to give corresponding aldehyde, followed by allylation using activated zinc

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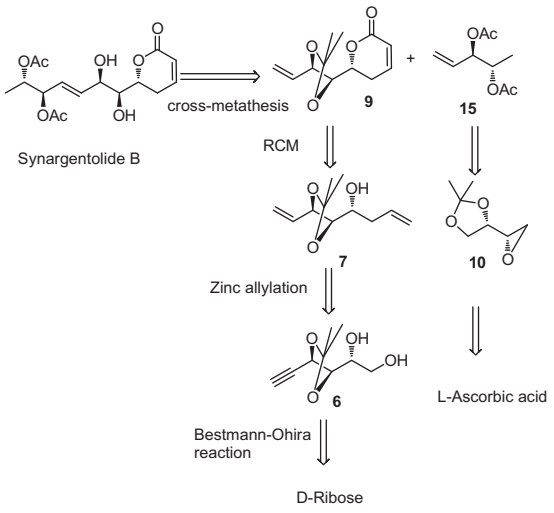
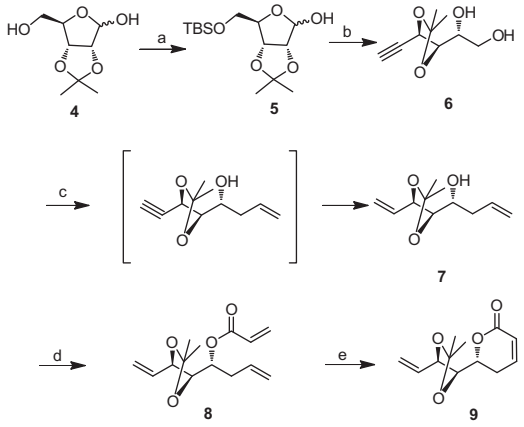
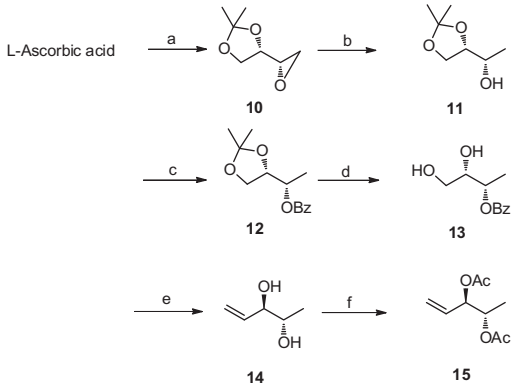


Scheme 1. Retrosynthetic analysis of synargentolide B.



Scheme 2. Reagents and conditions: (a) TBDMSCl, DMF, rt, 1 h, 90%; (b) Bestmaan–Ohira reaction, reflux, 8 h, 65%; (c) Zn, allyl bromide, THF-DMF, 0 °C to rt, 4 h, 85%; (d) acryl chloride, Et_3N, DMAP, rt, 0.5 h, 91%; (e) Grubb's first generation (5 mol %) DCM, reflux, 3 h, 89%.



Scheme 3. Reagents and conditions: (a) Refs. [13,14]; (b) $LiAlH_4$, THF, reflux, 3 h, 85%; (c) benzoyl chloride, Et_3N, DMAP, DCM, rt, 3 h, 95%; (d) PTSA, MeOH, rt 2 h, 86%; (e) (i) $NaIO_4$, $MeOH/H_2O$, rt, 2 h, (ii) vinyl magnesium bromide, THF, −20 °C to rt, 5 h, 58% (over all two steps); (f) Ac_2O, pyridine, DCM, rt, 4 h, 92%.

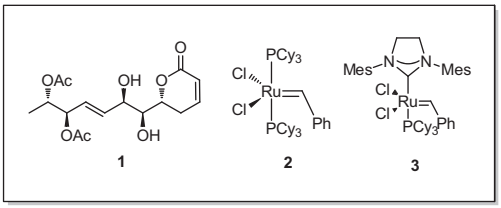
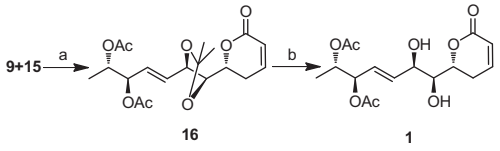


Figure 1. Synargentolide B, Grubb's I and II generation compounds.



Scheme 4. Reagents and conditions: (a) Grubb's second generation, DCM, reflux, 6 h, 67%; (b) PTSA, MeOH, reflux, 12 h, 78%.

metal to facilitate the reduction of triple bond to double bond[12] for the formation of **7** in a single step, with a good yield and better stereoselectivity with diastereomeric ratio 80:20. Acryloylation of **7** with acryloyl chloride furnished the acrylate **8** in 91% yield, which was then subjected to ring-closing metathesis in the presence of the first generation Grubbs' catalyst (**2**. in Fig. 1) in DCM at reflux conditions to produce 6-membered lactone[8b] as a single product **9** in 89% yield.

3,4-*O*-Isopropylidene-L-threitol was derived from L-ascorbic acid according to Abushanab's method.[13] The epoxide **10** can be obtained from 3,4-*O*-isopropylidene-L-threitol by the procedure already known in the literature.[14] The regioselective opening of the epoxide with Lithium aluminum hydride in dry THF at 0–60 °C provided a secondary alcohol **11** in 85% yield, The secondary alcohol was benzoylated under standard conditions (BzCl, Et_3N, DMAP, DCM) to give **12** in 90% yield, which on acetonide deprotection with para toluene sulfonic acid (PTSA) in MeOH afforded diol **13**. The oxidative cleavage with $NaIO_4$ led to the aldehyde, which was vinylated under Grignard reaction conditions. Vinylation was accompanied by ester cleavage and the resultant olefinic diol **14** was obtained.[15] The diol was acetylated with Ac_2O in the presence of pyridine to give 92% of the olefinic fragment **15**.[16]

With the key intermediates **9** and **15** in hand, we focused on the synthesis of synargentolide-B (Scheme 4). It was achieved by the coupling of both the fragments, diacetate olefin **15** and exocyclic olefin **9** via an olefin cross-metathesis reaction by using Grubb's second generation[17] G-II catalyst **3** (Fig. 1) to give acetonide protected synargentolide-B (**16**), which was subsequently treated with PTSA in MeOH at 65 °C to afford synargentolide-B (**1**). The spectroscopic data[18] were in agreement with the recently synthesized structure of synargentolide-B.[8a,8b] This method is regarded as the best procedure from the view point of the number of steps (14) and the overall yield (21%).

In conclusion, a convergent, stereoselective synthesis of synargentolide-B has been achieved from the commercially available, L-ascorbic acid and D-ribose via a short and (14 steps) high yielding route (21% overall yield). The prominent steps involved in the one-pot transformation involved are stereoselective addition of an allylzinc reagent as well as controlled reduction of a terminal alkyne in the presence of active zinc, construction of exocyclic olefin unit by RCM, and coupling of two fragments via olefin cross-metathesis reaction.

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18. *Spectral data for selected compounds:* (*R*)-1-((4*R*,5*R*)-5-ethynyl-2, 2-dimethyl-1, 3-dioxolan-4-yl) ethane-1, 2-diol (**6**) $[\alpha]_D^{27}$ +7.39 (*c* = 0.55 DCM) [lit.[11] $[\alpha]_D^{27}$ +7.24 (*c* 0.55, DCM)]. IR (KBr) ν_{max} = 3289, 2920, 1212, 1064 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.7 (dd, *J* = 4.72, 2.13, 1.98 Hz, 1H); 4.14 (d, *J* = 5.17, 1.52 Hz, 1H); 3.89 (m, 1H); 3.68–3.81 (m, *J* = 5.18, 3.18 Hz, 2H); 2.57 (d, *J* = 2.13 Hz, 1H); 1.51 (s, 3H); 1.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 110.80, 81.87, 81.48, 74.67, 71.46, 66.50, 63.1, 26.7, 25.85 ppm.
(R)-1-((4R,5R)-2, 2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)but-3-en-1-ol (**7**). $[\alpha]_D^{27}$ +131 (*c* = 1.0, MeOH) [lit.,[8b] $[\alpha]_D^{27}$ +135 (*c* 1.0, MeOH)];. IR (KBr) ν_{max} = 3477, 3080, 2987, 2931, 1728, 1643, 1372, 1215, 1170, 1057, 921, 876 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.86 (m, 2H); 5.44 (d, *J* = 17.09 Hz, 1H); 5.27 (d, *J* = 10.22 Hz, 1H); 5.15 (m, 2H); 4.47 (t, *J* = 7.82, Hz, 1H); 3.88 (m, 1H); 3.75 (dd, *J* = 7.93, 4.42 Hz, 1H); 2.24 (m, , 2H); 1.45 (s, 3H); 1.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 136.37, 134.05, 118.61, 118.27, 108.99, 82.51, 78.25, 70.26, 37.97, 26.93, 26.93 ppm. MS (ESI): *m*/*z* = 199 $[M+H]^+$. HRMS: calcd for $C_{11}H_{19}O_3$ $[M+H]^+$: 199.1255: found: 199.1250.
(R)-6-((4R,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-5,6-dihydro-2H-pyran-2-one (**9**): $[\alpha]_D^{27}$ +3.9 (*c* = 1.1, MeOH) [lit.,[8b] $[\alpha]_D^{27}$ +3.7 (*c* 1.1, MeOH)]. IR (KBr) ν_{max} = 2925, 2855, 1746, 1599, 1488, 1239, 1105, 1026 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 6.92 (ddd, *J* = 10.10, 7.10, 2.91 Hz, 1H); 6.04 (dt, *J* = 10.10, 2.91 1H); 5.95 (ddd, *J* = 16.99, 10.99, 5.99 Hz, 1H); 5.45 (d, *J* = 16.99 Hz, 1H); 5.29 (d, *J* = 9.99 Hz, 1H); 4.46 (quin, *J* = 6,99 Hz, 2H); 3.92 (t, *J* = 6.98 Hz, 1H); 2.55 (m, 2H); 1.44 (s, 3H); 1.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 162.8, 144.7, 135.09, 121.13, 118.33, 109.89, 80.55, 79.85, 77.88, 27.75, 26.8, 25.64 ppm. MS (ESI): *m*/*z* = 225 $[M+H]^+$. HRMS: calcd for $C_{12}H_{16}O_4Na$ $[M+Na]^+$: 247.0935: found: 247.0940.
(2S,3R)-pent-4-ene-2,3-diyl diacetate (**15**): $[\alpha]_D^{27}$ −9.6(*c* = 0.9, MeOH) [lit.,[8b] $[\alpha]_D^{27}$ −10.5 (*c* 0.8, MeOH)]. IR (KBr) ν_{max} 2925, 1739, 1598, 1482, 1372, 1242, 1113, 751 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.78 (m, 1H); 5.38–5.26 (m, 3H); 5.08 (m, 1H); 2.10 (s, 3H); 2.05 (s, 3H); 1.21 (d, *J* = 6.60 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 170.26, 169.90, 131.87, 119.24, 75.51, 70.39, 21.05, 20.96, 14.83 ppm. MS (ESI): *m*/*z* = 209 $[M+Na]^+$.
Synargentolide-B (**1**) $[\alpha]_D^{27}$ +27.1 (*c* = 0.2, DCM) [lit.,[8a] $[\alpha]_D^{27}$ +26.3 (*c* = 0.2, DCM)]. IR (KBr) ν_{max} = 3326, 2934, 2862, 1728, 1489, 1366, 1222, 1110, 1037, 770 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.95 (ddd, *J* = 9.78, 5.27, 3.28 Hz, 1H); 6.03 (dt, *J* = 9.78, 1.50 Hz, 1H); 5.89 (dd, *J* = 15.81, 5.27 Hz, 1H); 5.81 (dd, *J* = 15.81, 6.77 Hz, 1H); 5.33 (dd, *J* = 6.40, 3.76 Hz, 1H); 5.07 (dq, *J* = 6.40, 3.76 Hz, 1H); 4.52 (m, 1H); 4.48 (m, 1H); 3.71 (dd, *J* = 6.81, 2.67 Hz, 1H); 2.58 (m, 2H); 2.09 (s, 3H); 2.05 (s, 3H); 1.21 (d, *J* = 6.40 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 170.45, 170.29, 163.73, 145.80, 134.17, 126.66, 120.93, 76.83, 74.97, 74.26, 70.50, 69.50, 25.52, 21.13, 21.09, 15.08 ppm. MS (ESI): *m*/*z* = 365 $[M+Na]^+$. HRMS: calcd for $C_{16}H_{22}O_8Na$ $[M+Na]^+$: 365.1212: found: 365.1208.