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Olefin cross-metathesis based approach for the stereoselective total synthesis of (+)-cardiobutanolide

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ABSTRACT

Olefin cross-metathesis approach to (+)-cardiobutanolide has been achieved starting from D-mannitol utilizing Sharpless kinetic resolution and Sharpless asymmetric dihydroxylation.

The potent polyketide constituent of the annonaceae plant family,[1] (+)-cardiobutanolide **1**, pharmacologically active[2] product was isolated from the stem bark of *Goniothalamus cardiopetalus*, along with three known styryllactones.[3] Styryllactones possess pesticidal, ratogenic, and cytotoxic activity against human tumor cell lines.[2] The first total synthesis of cardiobutanolide was reported by Murga and co-workers by employing an *anti*-selective boronate aldol reaction of L-erythrulose derivative.[4a] So far, four total syntheses and a formal approach have been disclosed toward the synthesis of **1** since the isolation.[4,5] Of the four total syntheses of **1**, we reported a chiron approach-based strategy, using diacetone D-glucose[5] as the starting material involving the key steps of Mitsunobu stereoinversion, ethyl diazoacetate addition, and selective reduction of the ketone. In continuation with our program on the total synthesis of bio-active natural products,[6] we revisited the synthesis of cardiobutanolide based on an olefin cross-metathesis approach starting from D-mannitol. Herein, we report a flexible and practical synthesis of (+)-**1**, the key features of which include olefin cross-metathesis and Sharpless asymmetric dihydroxylation.

With renewed interest we undertook the synthesis of this molecule in a bid to develop a schematically different route viz. olefin cross-metathesis protocol. Since styryllactones also possess, amongst varied biological activities, cytotoxicity with remarkable *anti*-tumor properties,[2,3] congeners of **1** may have comparable profile. Consequently, it was thought that the presence of diverse aryl moieties may contribute or amplify the activity. Taking a cue from this logic, a flexible strategy was developed that could potentially generate a library of natural product-like molecules by adopting an olefin cross-metathesis reaction between a variety of aryl vinyl carbinols (or any predesigned aryl constituents) and vinyl butyrolactone moieties, the product(s) of which on asymmetric dihydroxylation reaction with either AD-mix-α or -β afforded the whole gamut of stereoisomers as well. Alongside this, the first synthesis of C(5), C(6)-*epi*-cardiobutanolide **15**, a non-natural product is also reported emanating from the minor product of asymmetric dihydroxylation reaction.

The retrosynthetic analysis of (+)-**1** is shown in Scheme 1. The envisioned strategy derives C(3) and C(4) stereocenters of **1** from C(3) and C(4) of D-mannitol while other stereocenters are differently generated. Thus, compound **1** could be obtained from the corresponding allylic alcohol **2** by an asymmetric dihydroxylation, which in turn could be obtained from olefin cross-metathesis reaction between vinyl 3-hydroxy butyrolactone derivative **3** and phenyl vinyl carbinol **4a**. The butyrolactone derivative **3** could be synthesized from D-mannitol, while the phenyl vinyl carbinol **4a** can be accessed easily from Sharpless kinetic resolution protocol.

Thus, the synthesis of **1** began following the literature procedure (Scheme 2). For instance, the known[7] **6** obtained from D-mannitol, was subjected to hydroboration followed by the oxidation with H_2O_2 in THF resulted in the desired regioisomer as the major product **7a** in a ratio of 85:15 (65%). Alcohol **7a** was protected (TPSCl/imidazole/CH_2Cl_2/0 °C to rt) as its TPS ether **7b** (95%). Cleavage of the 1,2-*o*-isopropylidine group with $ZnNO_3$[8] in acetonitrile at 60 °C provided the diol **8**, followed by a one-step conversion (TPP/imidazole/I_2/toluene/100 °C) that provided the olefin **5a**

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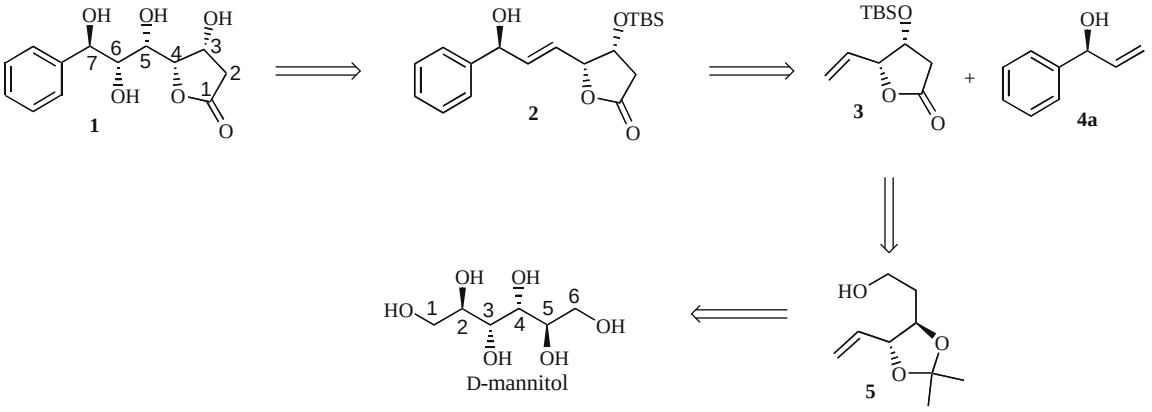
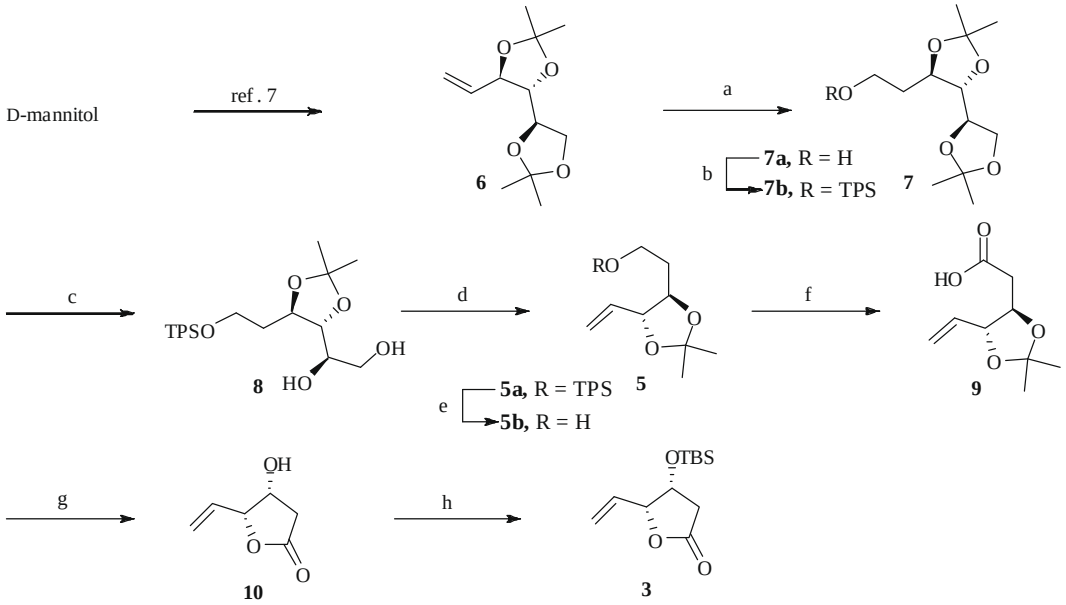


Scheme 1. Retrosynthetic analysis.

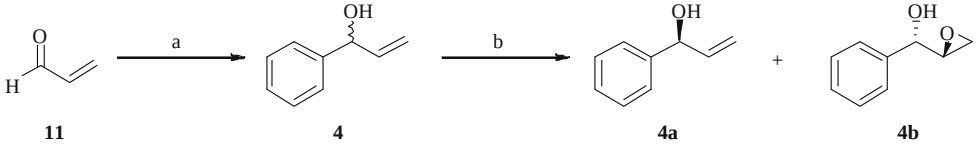


Scheme 2. Reagents and conditions: (a) (i) BH_3·DMS, THF, 0 °C, 3 h; (ii) H_2O_2, aq NaOH, 0 °C, 4 h, 65% (over two steps); (b) imidazole, TPSCl, CH_2Cl_2, 0 °C to rt, 30 min, 95%; (c) $ZnNO_3$, CH_3CN, 60 °C, 8 h; (d) PPh_3, imidazole, I_2, toluene, 100 °C, 3 h, 60% (over two steps); (e) TBAF, THF, 0 °C, 2 h, 80%; (f) PDC, DMF, rt, overnight, 50%; (g) PTSA, MeOH, 8 h, 70%; (h) imidazole, TBSCl, CH_2Cl_2, 2 h, 85%.

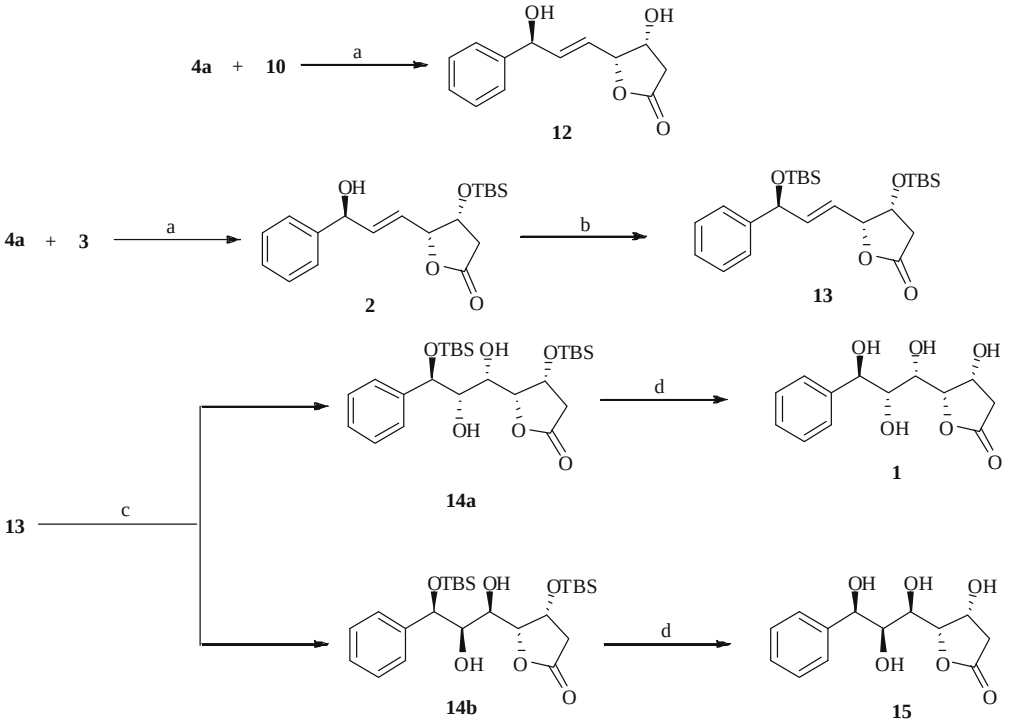
(60%, over two steps). The deprotection (TBAF/THF/0 °C) of silyl ether **5a** resulted in alcohol **5b** (80%), which was then oxidized (PDC/DMF/rt/12 h) to acid **9** (50%). Treatment of acid **9** with PTSA/MeOH resulted in the deprotection of 3,4-*o*-isopropylidine group with the simultaneous lactone ring formation to afford **10** (70%).

On the other hand, the fragment **4a** was synthesized starting from acrolein (Scheme 3), which on Grignard reaction (PhMgBr/THF/0 °C to rt) gave the phenyl vinyl carbinol[9] **4** (75%). Later, **4** on Sharpless kinetic resolution furnished enantiomerically pure phenyl vinyl carbinol **4a** (40%).[10]

Olefin cross-metathesis[6a,11] reaction (Grubbs' cat-II/CH_2Cl_2/rt) between the lactone **10** and phenyl vinyl carbinol **4a** in a 1:1.5 ratio resulted in **12** (70%) as an exclusively *E*-isomer without self dimerisation of lactone (Scheme 4). But we were unable to separate allyl alcohol **12** in pure form due to its co-elution with Grubbs' catalyst. Hence, a practical way thought out by us was to protect (TBSCl/imidazole/CH_2Cl_2/rt/2 h) the 3-hydroxyl group of the lactone **10** as its TBS ether **3** first and conduct the cross-metathesis reaction. Accordingly, the cross-metathesis reaction between lactone **3** and phenyl vinyl carbinol **4a** under the above-cited reaction conditions furnished compound **2** (60%) as an exclusive *E*-isomer. Later, allyl alcohol **2** was purified and subjected to asymmetric dihydroxylation to result in an unisolable mixture of products. Consequently, allyl alcohol **2** was treated with TBSCl under conventional conditions to afford disilyl ether **13** (80%). Asymmetric



Scheme 3. Reagents and conditions: (a) PhMgBr, THF, 0 °C, 40 min, 75%; (b) (+)-DIPT (0.6 equiv), Ti(O^iPr)$_4$ (0.5 equiv), CHP (0.6 equiv), CH_2Cl_2, −24 °C.



Scheme 4. Reagents and conditions: (a) Grubbs' II (10 mol %), CH_2Cl_2, rt, 60%; (b) imidazole, TBSCl, CH_2Cl_2, 2 h, 80%; (c) AD-mix-β, OsO_4, $^tBuOH/H_2O$ (1:1), 70%; (d) Amberlyst 15, CH_3CN, 90%.

dihydroxylation of **13** with AD-mix-β provided the desired product as the major isomer **14a** (70%) in a ratio of 90:10. Treatment of the major isomer with Amberlyst 15 resin in acetonitrile gave the desired natural product **1** {$[\alpha]_D^{25}$ +7.4 (*c* 0.30, MeOH)} in 90% yield. Similarly, the minor isomer **14b** was also treated with Amberlyst 15 resin in acetonitrile to give the diastereoisomer **15** in comparable yields. The physical and spectroscopic data of the synthetic sample **1** were identical to those of the reported natural and synthetic products.[4,5,12] Though the overall yield obtained herein is 5% through a 12-step sequence in comparison to 9% obtained in a 11-step linear synthesis,[4b,5] the combinatorial advantages of the strategy remain intact.

In conclusion, we have performed a divergent, stereoselective synthesis of (+)-cardiobutanolide by means of a versatile strategy. Olefin cross-metathesis, asymmetric dihydroxylation, and Sharpless kinetic resolution were the key steps involved to accomplish the synthesis of (+)-cardiobutanolide **1**.[12]

Acknowledgments

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12. *Spectral data for selected compounds*: *Compound* **9**: colorless sirup. $[\alpha]_D^{25}$ −9.26 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.85–5.75 (m, 1H), 5.34 (d, 1H, *J* = 17.3 Hz), 5.26 (d, 1H, *J* = 10.2 Hz), 4.05 (d, 2H, *J* = 3.5 Hz), 2.55 (t, 2H, *J* = 2.3 Hz), 1.4 (d, 6H, *J* = 4.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.2, 134.4, 119.8, 109.7, 82.5, 76.3, 36.7, 27.0, 26.9; IR (KBr): 3510, 3075, 2942, 1720, 1640, 1465, 1410, 1370, 990 cm^{-1}. *Compound* **10**: colorless sirup. $[\alpha]_D^{25}$ +118.95 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.02–5.90 (m, 1H), 5.54 (dt, 1H, *J* = 17.3, 1.3 Hz), 5.48 (dt, 1H, *J* = 10.5, 1.3 Hz), 4.85 (t, 1H, *J* = 5.6 Hz), 4.48 (td, 1H, *J* = 5.2, 1.3 Hz), 2.79 (dd, 1H, *J* = 5.2, 17.5 Hz) 2.52 (dd, 1H, *J* = 1.3, 17.3 Hz); IR (neat): 3485, 3065, 2932, 1760, 1642, 1412, 1375, 995 cm^{-1}; EIMS: *m*/*z* 100 $(M-28)^+$; Anal. Calcd for $C_6H_8O_3$: C, 56.24; H, 6.29. Found: C, 56.22; H, 6.32. *Compound* **3**: colorless sirup. $[\alpha]_D^{25}$ −51.76 (*c* 0.85, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.90 (ddd, 1H, *J* = 3.0, 10.5, 16.9 Hz), 5.25 (d, 1H, *J* = 16.9 Hz), 5.16 (d, 1H, *J* = 10.5 Hz), 4.13–4.08 (m, 1H), 3.61 (s, 1H), 2.48 (dd, 1H *J* = 2.2, 15.8 Hz), 2.15 (dd, 1H, *J* = 8.6, 15.4 Hz), 0.86 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.9, 131.7, 119.9, 85.5, 70.7, 39.2, 25.6, −4.9; IR (neat): 3070, 2932, 1760, 1640, 1465, 1415, 1375, 990, 910 cm^{-1}; ESIMS: *m*/*z* 265 $(M+Na)^+$, 260 $(M+NH_4)^+$ 243 $(M+H)^+$; Anal. Calcd for $C_{12}H_{22}O_3Si$: C, 59.46; H, 9.15. Found: C, 59.44; H, 9.16. *Compound* **2**: light yellow solid. $[\alpha]_D^{25}$ +12.09 (*c* 0.55, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.25 (m, 5H), 6.04 (dd, 1H *J* = 4.9, 15.8 Hz), 5.92 (dd, 1H *J* = 6.7, 15.8 Hz), 5.25 (d, 1H, *J* = 4.9 Hz), 4.78 (dd, 1H, *J* = 4.1, 6.7 Hz), 4.45 (br s, 1H), 2.65 (dd, 1H, *J* = 5.2, 16.9 Hz), 2.41 (dd, 1H, *J* = 1.5, 16.9 Hz), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.1, 142.0, 138.0, 128.5, 127.9, 126.2, 123.8, 84.6, 74.0, 70.6, 39.3, 25.5, −4.8, −4.9; IR (KBr): 3460, 3020, 2938, 1762, 1675, 1472, 1380, 970 cm^{-1}; ESIMS: *m*/*z* 371 $(M+Na)^+$; Anal. Calcd for $C_{19}H_{28}O_4Si$: C, 65.48; H, 8.10. Found: C, 65.47; H, 8.13. *Compound* **13**: light colorless sirup. $[\alpha]_D^{25}$ −25.97 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.31 (m, 5H), 5.99 (d, 2H, *J* = 3.3 Hz), 5.29 (s, 1H), 4.76 (dd, 1H, *J* = 3.3, 6.4 Hz), 4.46 (t, 1H, *J* = 5.2 Hz), 2.70 (dd, 1H, *J* = 4.9, 16.9 Hz), 2.48 (dd, 1H, *J* = 1.5, 16.9 Hz), 1.51 (br s, OH), 0.96 (s, 18H), 0.11 (s, 12H); IR (neat): 3025, 2932, 1760, 1670, 1471, 1375, 965 cm^{-1}; ESIMS: *m*/*z* 480 $(M+NH_4)^+$; Anal. Calcd for

$C_{25}H_{42}O_4Si_2$: C, 64.88; H, 9.15. Found: C, 64.86; H, 9.13. *Compound* **14b**: colorless sirup. $[\alpha]_D^{25}$ +15.55 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–7.29 (m, 5H), 5.23 (br s, OH), 5.21 (d, 1H, *J* = 3.0 Hz), 5.03 (t, 1H, *J* = 3.0 Hz), 4.73 (d, 1H, *J* = 4.1 Hz), 4.24 (br s, 1H), 3.86 (t, 1H, *J* = 2.6 Hz), 2.67 (d, 2H, *J* = 4.9 Hz), 0.91 (s, 18H), 0.12 (s, 12H); IR (thin film): 3485, 2932, 1760, 1458, 1372, 1246 cm^{-1}; ESIMS: *m*/*z* 514 $(M+NH_4)^+$; Anal. Calcd for $C_{25}H_{44}O_6Si_2$: C, 60.44; H, 8.93. Found: C, 60.46; H, 8.95. *Compound* **14a**: White solid. $[\alpha]_D^{25}$ −51.76 (*c* 1.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.31–7.24 (m, 5H), 4.73 (d, 1H, *J* = 7.8 Hz), 4.50 (t, 1H, *J* = 3.6 Hz), 4.24 (dd, 1H, *J* = 3.1, 9.3 Hz), 3.81 (d, 1H, *J* = 7.8 Hz), 3.60 (t, 1H, *J* = 9.3 Hz), 2.91 (br s, OH), 2.59 (dd, 1H, *J* = 4.6, 17.1, 21.8 Hz), 2.28 (t, 1H, *J* = 5.2 Hz), 0.89 (s, 9H), 0.78 (s, 9H), 0.03 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.7, 140.1, 128.4, 128.1, 127.4, 127.1, 82.4, 76.4, 75.0, 75.0, 68.6, 65.8, 39.8, 25.7, 25.5, −4.4, −4.8, −5.1, −5.3; IR (KBr): 3490, 2955, 1760, 1468, 1370, 1257 cm^{-1}; ESIMS: *m*/*z* 514 $(M+NH_4)^+$, 497 $(M+H)^+$; HRMS: calcd *m*/*z* 519.2574 ($C_{13}H_{16}O_6Na$). Found *m*/*z* 519.2563, ppm error −2.1494. *Compound* **15**: light yellow sirup. $[\alpha]_D^{25}$ +73.86 (*c* 0.22, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.43–7.27 (m, 5H), 5.29 (br s, OH), 5.16 (d, 1H, *J* = 4.5 Hz), 5.02 (t, 1H, *J* = 4.1 Hz), 4.79 (d, 1H, *J* = 3.7 Hz), 4.34 (br s, 1H), 4.06 (dd, 1H, *J* = 3.0, 4.5 Hz), 2.69–2.66 (m, 1H), 2.34–2.25 (m, 1H). *Compound* **1**: White crystalline solid. $[\alpha]_D^{25}$ +7.47 (*c* 0.30, MeOH); ^1H NMR (300 MHz, acetone-d_6): δ 7.44 (t, 2H, *J* = 6.9 Hz), 7.35–7.23 (m, 3H), 4.87 (t, 1H, *J* = 6.9 Hz), 4.61 (d, 1H, *J* = 3.02 Hz), 4.50–4.44 (m, 1H), 4.34–4.05 (br s, 1H), 3.80–3.71 (m, 1H), 2.84 (m, 1H, overlapped by residual water), 2.32 (dd, 1H, *J* = 6.0, 17.3 Hz); ^{13}C NMR (75 MHz, acetone-d_6): δ 176.8, 144.1, 129.8, 129.2, 128.9, 83.7, 76.7, 69.6, 69.5, 69.4, 40.5; IR (KBr): 3510, 3468, 2932, 1760, 1471, 1210 cm^{-1}; HRMS: calcd *m*/*z* 291.0844 ($C_{13}H_{16}O_6Na$). Found *m*/*z* 291.0832, ppm error −4.3224.