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Asymmetric total synthesis of (+)-cardiobutanolide via an iterative asymmetric dihydroxylation in PEG

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ABSTRACT

The stereoselective total synthesis of (+)-cardiobutanolide, a polyhydroxylated natural product, is achieved in high yield through Lu and Guo diene synthesis, Sharpless asymmetric dihydroxylation, and one-pot deprotection–lactonization. The utility of a recyclable reagent system in PEG for asymmetric dihydroxylation is demonstrated.

Polyhydroxylated five- and six-membered ring lactones are common scaffolds present in natural products isolated from several species of Annonanceae family.[1,2] These include (+) cardiobutanolide **1a**, goniofufurone (**1b**), etharvendiol (**1c**), and altholactone (**1e**) besides others (Fig. 1). These natural products can be considered as consisting of an aryl group, a polyhydroxy component, and a lactone ring. The plants from which these compounds have been isolated display various therapeutic activities in traditional medicine in the treatment of rheumatism, edema, and as mosquito repellents.[3] Extensive investigations from the research group of McLaughlin resulted in the isolation and characterization of a series of styryllactones, possessing pesticidal, ratogenic, and embryotoxic activity and significant to marginal cytotoxic activity against human tumor cell lines.[4] The styryllactone, namely, cardiobutanolide was isolated from the stem bark of *Goniothalamus cardiopetalus* together with four known styryllactones.[5]

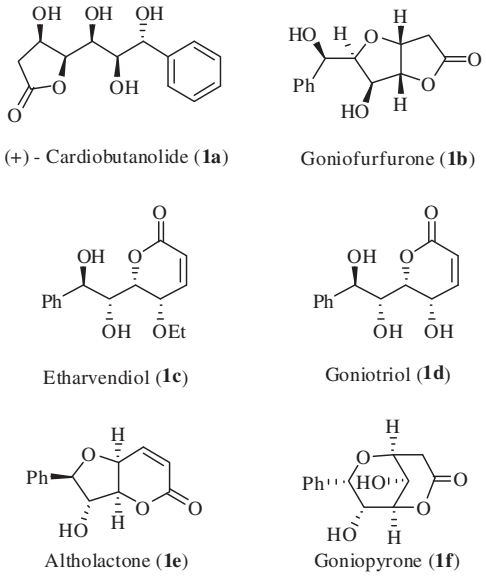
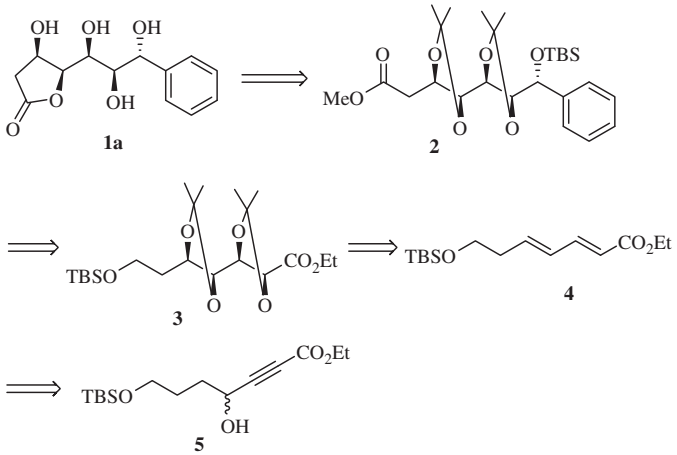


Figure 1. Structure of styryllactones.

Herein, we wish to communicate a short and high yielding total synthesis of (+)-cardiobutanolide.[6] The key steps are the not so well-exploited diene ester synthesis, double Sharpless asymmetric dihydroxylation in polyethylene glycol (PEG), and one-pot deprotection–lactonization. Accordingly, we envisaged the retrosynthetic pathway (Scheme 1). The title compound (**1a**) can be obtained from globally protected aryl pentol acid **2**, through one-pot deprotection–lactonization. Compound **2** was prepared from compound **3**, which in turn was obtained by means of double asymmetric



Scheme 1. Retrosynthetic analysis.

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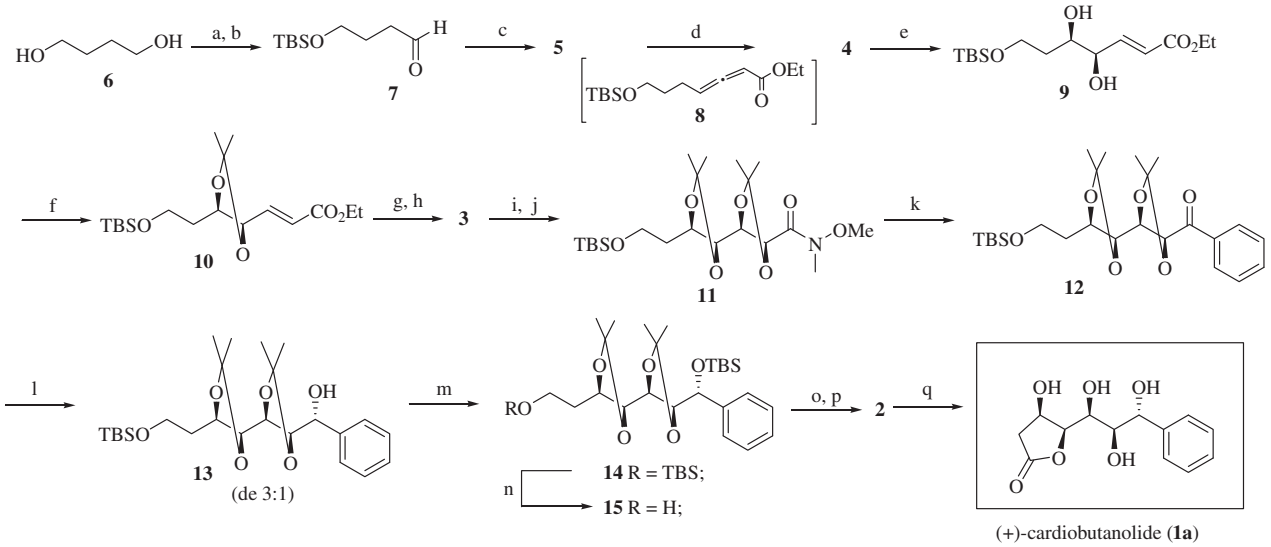

Scheme 2. Reagents and conditions: (a) TBSCl, imidazole, CH_2Cl_2, 30 min, 78%; (b) $(COCl)_2$, DMSO, −78 °C, 2 h, 87%; (c) ethyl propiolate, LiHMDS, THF, −78 °C, 2 h, 77%; (d) PPh_3, benzene, rt, 3 h, 82%; (e) $(DHQD)_2PHAL$ (2 mol %), OsO_4 (0.5 mol %), NMO·H_2O, PEG-400 MW, 0 °C, 30 h, 84%; (f) 2,2-DMP, CSA (5 mol %), CH_2Cl_2, 0 °C, 30 min, 85%; (g) (DHQD)2PHAL (2 mol %), OsO4 (0.5 mol %), PEG-400 MW (recovered system from step e) and NMO·H_2O, 0 °C, 30 h, 80%; (h) 2,2-DMP, CSA (5 mol %), CH_2Cl_2, rt, 2 h, 75%; (i) LiOH, THF–H_2O (7:3), 0 °C, 3 h; (j) NH(Me)(OMe)·HCl, DCC, TEA, DMAP, CH_2Cl_2, rt, 3 h (80% for two steps); (k) PhMgBr, THF, rt, 1 h, 85%; (l) $NaBH_4$, $CeCl_3·7H_2O$, MeOH, −78 °C, 30 min, 74%; (m) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 82%; (n) CSA (cat), MeOH, 20 °C, 2 h, 85%; (o) BAIB, TEMPO, CH_3CN–H_2O (1:1), 0 °C to rt, 3 h; (p) CH_2N_2, ether, 0 °C, 30 min, 90% (for two steps); (q) TFA–H_2O (9:1), concd HCl, CH_2Cl_2, 0 °C to rt, 3 h, 80%.

dihydroxylation of diene ester **4**. Compound **4** was obtained from the isomerization of 4-hydroxy-2-ynoic acid **5**, which was in turn prepared from 1,4-butane-diol (**6**) and ethyl propiolate.

The synthesis commenced from commercially available 1,4-butanediol (**6**) which was transformed to the γ-hydroxy ethyl propiolate derivative (**5**), a critical intermediate for diene synthesis. The selective mono silylation of diol **6** followed by Swern oxidation of alcohol using oxalyl chloride and DMSO in dichloromethane at −78 °C gave aldehyde **7**. This was then subjected to the crucial step to append the ethyl propiolate group. The lithiated ethyl propiolate in THF was added to aldehyde **7** at −78 °C to yield γ-hydroxy ethyl propiolate derivative **5**. Following the protocol reported by Lu and Guo,[7] the hydroxy ethyl propiolate **5** was stirred in benzene in the presence of PPh_3 to yield the (*E*,*E*) diene ester **4** in 82% yield via allene intermediate **8** which isomerizes to stable diene ester. The enantio and regioselective Sharpless asymmetric dihydroxylation[8] of diene ester **4** was achieved in a stepwise manner for easy isolation. Thus **4** on exposure to $(DHQD)_2PHAL/OsO_4/NMO·H_2O$ in PEG as reported by us[9] provided diol **9** (>90% ee by HPLC). The acetonide was prepared under standard conditions using 2,2-dimethoxypropane (2,2-DMP) and catalytic camphor sulfonic acid (CSA) in dichloromethane for 30 min at 0 °C provided **10** in 85% yield.

Acetonide (**10**) was subjected to second Sharpless asymmetric dihydroxylation[10] under the same reaction medium to provide diisopropylidine derivative **3** after acetonide formation with 2,2-DMP and CSA in dichloromethane at room temperature for 2 h in 75% yield with good diastereoselectivity (8:2).[11]

Hydrolysis of ester **3** with LiOH and amidation with Weinreb salt provided amide **11** in 80% yield (for two steps). Exposure of this to PhMgBr in THF at room temperature for 1 h gave aryl ketone **12** in 85% yield. This reaction and the previous asymmetric dihydroxylation reaction allow in theory to create diversity in both stereochemistry of hydroxyl groups and also in introducing substituted aryl groups for analoging. The diastereoselective reduction of prochiral ketone **12** using $NaBH_4$ and $CeCl_3·7H_2O$ in MeOH at −78 °C produced the desired alcohol **13** with reasonable diastereoselectivity (3:1), which was separated by silica gel chromatography.[12a–c] The silylation of the benzylic hydroxyl group in dichloromethane was achieved with TBSOTf/2,6-lutidine at 0 °C for 1 h to give **14** in 82% yield. The selective deprotection of the primary silyl ether was accomplished with catalytic CSA in methanol at 20 °C to get the alcohol **15**. The exhaustive oxidation of primary alcohol **15** to carboxylic acid followed by esterification furnished globally protected aryl pentol acid **2** in 90% yield (for two steps). The obvious deprotection under aq TFA in the presence of a drop of concd HCl in dichloromethane at 0 °C allowed concomitant removal of isopropylidine groups and silyl ether and also lactonization to furnish the natural product (+)-cardiobutanolide.[13] The spectral features were in complete agreement with those reported in the literature[5,6] (Scheme 2).[14]

In conclusion, the total synthesis of (+)-cardiobutanolide was achieved through the application of diene ester synthesis, Sharpless asymmetric dihydroxylation protocol in PEG, and global deprotection–lactonization in one-pot as key steps.

Acknowledgment

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References and notes

1. For a review on styryllactones from Goniothalamus species, see: Blàzquez, M. A.; Bermejo, A.; Zafra-Polo, M. C.; Cortes, D. *Phytochem. Anal.* **1999**, *10*, 161.
2. (a) Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504; (b) Zafra-Polo, M. C.; Figadère, B.; Gallardo, T.; Tormo, J. R.; Cortès, D. *Phytochemistry* **1998**, *48*, 1087; (c) Cavè, A.; Figadère, B.; Laurens, A.; Cortés, D. *Prog. Chem. Org. Nat. Prod.* **1997**, *70*, 81.
3. On the cytotoxic activity and other bioactivity of styryllactones, see: Mereyala, H. B.; Joe, M. *Curr. Med. Chem.: Anti-Cancer Agents* **2001**, *1*, 293.
4. For a review on the synthesis of styryllactones until 2004, see: Mondon, M.; Gesson, J. P. *Curr. Org. Synth.* **2006**, *3*, 175.
5. Hisham, A.; Toubi, M.; Shuaily, W.; Bai, M. D. A.; Fujimoto, Y. *Phytochemistry* **2003**, *62*, 597.
6. For earlier synthetic approaches of (+)-cardiobutanolide, see: (a) Krishna, P. R.; Kumas, E. S. *Tetrahedron Lett.* **2009**, *50*, 6676; (b) Prasad, K. R.; Gholap, S. L. *J. Org. Chem.* **2008**, *73*, 2916; (c) Ruiz, P.; Murga, J.; Carda, M.; Marco, J. A. *J. Org. Chem.* **2005**, *70*, 713; (d) Matsuura, D.; Takabe, K.; Yoda, H. *Tetrahedron Lett.* **2006**, *47*, 1371; (e) Krishna, P. R.; Reddy, P. V. N. *Tetrahedron Lett.* **2006**, *47*, 4627; (f) Garg, A.; Singh, R. P.; Singh, V. K. *Tetrahedron* **2006**, *62*, 11240.
7. Guo, C.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1993**, 394.
8. Xu, D.; Crispino, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570–7571.

9. Chandrasekhar, S.; Narasihmulu, Ch.; Sultana, S. S.; Reddy, N. R. *Chem. Commun.* **2003**, 1716.
10. Gao, D.; O'Doherty, G. A. *Org. Lett.* **2005**, *6*, 1069.
11. The double dihydroxylation was also achieved in a similar sequence using AD mix β, the product was obtained in similar yield and selectivity albeit requiring longer reaction times (3–5 days).
12. (a) Murphy, P. J.; Dennison, S. T. *Tetrahedron* **1993**, *49*, 6695; (b) Yi, X.; Meng, Y.; Hua, X.; Li, Ch. *J. Org. Chem.* **1998**, *63*, 7472; (c) Seyden-Penne, J. *Reductions by the Alumino and Borohydridesin Organic Synthesis*; VCH: New York, 1991.
13. The overall yield of **1a** is 5.2% (15 mg of **1a** was isolated from 500 g of stem bark powder of *Goniothalamus cardiopetalus*).
14. *Spectral data of selected compounds*:
Compound **10**: Colorless oil; $[\alpha]_D^{29}$ +6.2 (*c* 0.75, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.92–6.84 (dd, *J* = 15.1, 5.2 Hz, 1H), 6.13–6.07 (dd, *J* = 15.1, 1.5 Hz, 1H), 4.27–4.14 (m, 3H), 3.89–3.66 (m, 3H), 1.84–1.77 (m, 2H), 1.39 (d, *J* = 9.8, 6H), 1.27 (t, *J* = 7.5 Hz, 3H), 0.86 (s, 9H), 0.03 (d, *J* = 1.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 143.9, 122.5, 109.1, 80.0, 77.6, 60.0, 59.4, 35.0, 27.1, 26.5, 25.8, 14.1, −5.4; (ESI-MS): *m/z* 359 (M^++H); HRMS: calcd for $C_{18}H_{34}NaO_5Si$: 381.2068 (M^++Na), found: 381.2080.
Compound **3**: Colorless oil; $[\alpha]_D^{27}$ +14.7 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.55 (d, *J* = 7.5 Hz, 1H), 429–4.12 (m, 4H), 3.85–3.70 (m, 3H), 1.84–1.75 (m, 2H), 1.46–1.24 (m, 15H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 111.3, 108.8, 96.1, 79.7, 77.3, 75.5, 73.9, 61.3, 59.8, 35.9, 27.5, 26.5, 25.9, 14.2, −5.3; (ESI-MS): *m/z* 433 (M^++H); HRMS: calcd for $C_{21}H_{40}NaO_7Si$: 455.2436 (M^++Na), found: 455.2455.
Compound **13**: Colorless oil; $[\alpha]_D^{28}$ +11.5 (*c* 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.27 (m, 5H), 5.01 (d, *J* = 3.7 Hz, 1H), 4.34 (m, 1H), 3.99–3.89 (m, 2H), 3.61 (m, 2H), 2.60 (d, *J* = 1.1 Hz, 1H), 2.34 (dd, *J* = 8.8, 1.1 Hz, 1H), 1.41–1.24 (m, 14H), 0.90 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.7, 128.5, 128.4, 126.9, 109.9, 108.5, 80.8, 80.7, 79.0, 75.8, 74.7, 73.7, 59.9, 35.7, 29.6, 27.4, 27.2, 26.8, 26.4, 25.8, 18.2, −5.3; (ESI-MS): *m/z* 489 (M^++Na); HRMS: calcd for $C_{25}H_{42}NaO_6Si$: 489.2643, (M^++Na), found: 489.2606.
Compound **2**: Colorless oil; $[\alpha]_D^{27}$ −1.3 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.70 (m, 1H), 7.52 (m, 2H), 7.31 (d, *J* = 4.5 Hz, 2H), 4.88 (d, *J* = 5.28 Hz, 1H), 4.34–4.27 (m, 1H), 4.20 (m, 1H), 4.07 (d, *J* = 6.0 Hz, 2H), 3.7 (s, 3H), 2.7 (m, 1H), 2.37 (m, 1H), 1.40–1.26 (m, 12H), 0.92 (s, 9H), 0.09 (s, 3H), −0.1 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 140.0, 127.7, 127.3, 109.3, 108.9, 80.2, 79.2, 75.3, 74.3, 73.0, 51.6, 37.7, 29.7, 27.3, 26.7, 25.8, −4.8, −4.9; (ESI-MS): *m/z* 517 (M^++Na); HRMS: calcd for $C_{26}H_{42}NaO_7Si$: 517.2592 (M^++Na), found: 517.2634.
Compound **1**: White crystalline solid; mp: 194–196 °C; $[\alpha]_D^{27}$ +5.7 (*c* 0.3, MeOH) [lit.[5] mp 189–190 °C; $[\alpha]_D$ +6.4 (*c* 0.28, MeOH)]; ^1H NMR (300 MHz, acetone-d_6): δ 7.44 (d, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 4.79 (d, *J* = 7.2 Hz, 1H), 4.77 (br s, 1H), 4.72 (d, *J* = 3.3 Hz, 1H), 4.62 (br s, 1H), 4.56 (m, 1H), 4.40 (d, *J* = 4.8 Hz, 1H), 4.05 (d, *J* = 6.4 Hz, 1H), 3.91 (d, *J* = 7.2 Hz, 1H), 3.84 (s, 1H), 2.91 (m, 1H, overlapped by residual water), 2.38 (d, *J* = 17.3 Hz, 1H); ^{13}C NMR (150 MHz, acetone-d_6): δ 176.1, 144.2, 128.5, 127.9, 127.7, 86.7, 75.4, 74.1, 70.2, 68.6, 40.4; IR υ_{max} (KBr): 3434 (br, OH), 1759 (C=O) cm^{-1}; (ESI-MS): *m/z* 291 (M^++Na); HRMS: calcd for $C_{13}H_{16}NaO_6$: 291.0839 (M^++Na), found: 291.0838.