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# Stereoselective Total Synthesis of (+)-Cardiobutanolide

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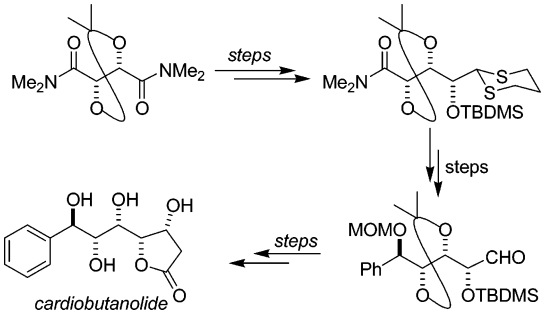
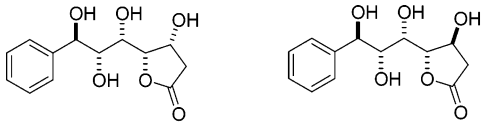


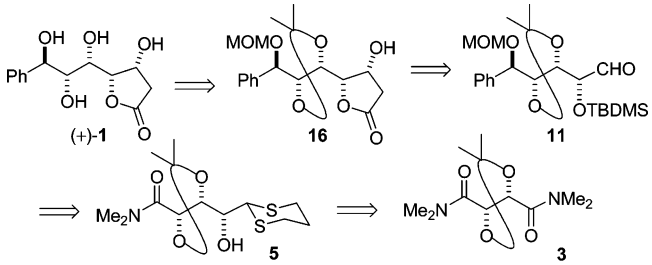

Stereoselective synthesis of styryllactone (+)-cardiobutanolide was accomplished in good overall yield from D-(−)-tartaric acid. Key features of the synthesis include the elaboration of a γ-hydroxy butyramide obtained from the dimethylamide of tartaric acid, involving a combination of the addition of 1,3-dithian-2-yllithium and stereoselective reduction.

Styryllactones are potent biologically active oxygenated compounds isolated from the trees of genus *Goniothalamus* of the plant family Annonaceae grown in South East Asia.[1] Extensive investigations from the research group of McLaughlin resulted in the isolation and characterization of a series of styryllactones, possessing pesticidal, ratogenic, embryo toxic activity and significant to marginal cytotoxic activity against human tumor cell lines.[2] Recently, a new styryllactone cardiobutanolide **1**[3] was isolated from the stem bark of *Goniothalamus cardiopetalus*, together with four known styryllactones by Hisham et al. The structure of (+)-cardiobutanolide **1** was deduced by extensive 1D and 2D NMR spectral analysis and mass spectroscopic techniques. Three total syntheses and a formal approach have been disclosed for the synthesis **1** since the isolation. Murga et al.[4a] reported the first synthesis of cardiobutanolide employing an *anti* selective boronate aldol reaction of L-erythrulose derivative in 9% overall yield. Yoda et al.[4b] accomplished the synthesis of **1** in 9% overall yield employing a lengthy sequence from D-glucuronolactone. Another approach for the synthesis of **1** from 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose, derived from D-glucose was also reported in 8% overall yield by Krishna et al.[4c] Recently, Singh et al.[4d] disclosed a formal approach to **1** from a furanose derivative. We have been involved in the synthesis of bio-active natural products and have recently accomplished the total synthesis of a number of styryllactones from a single synthetic precursor derived from chiral pool tartaric acid.[5] A key step in our synthesis is the elaboration of a γ-hydroxy butyramide easily accessed from the *bis*-dimethylamide of tartaric acid by a combination of Grignard reagent addition and stereoselective reduction. In continuation of this strategy, herein we report the synthesis of cardiobutanolide in high overall yield from D-(−)-tartaric acid.




Our approach for the synthesis of (+)-cardiobutanolide **1** is based on the elaboration of aldehyde **11** comprising the masked tetrol unit. Synthesis of **11** was anticipated from γ-hydroxybutyramide **5**, the synthesis of which was envisaged by the combination of a controlled addition of 1,3-dithian-2-yllithium and stereoselective reduction of the resultant ketone (Scheme 1).

**SCHEME 1. Retrosynthesis for (+)-Cardiobutanolide 1**




Accordingly, the synthetic sequence commenced with the addition of 1.2 equiv of 1,3-dithian-2-yllithium to the bis-dimethylamide of tartaric acid **3** resulting in the ketoamide **4** in 71% yield along with traces (2−5%) of the corresponding diketone. Stereoselective reduction of the ketone in **4** with $NaBH_4/CeCl_3 \cdot 7H_2O$ furnished the alcohol **5** as a single diastereomer in 97% yield after chromatography.[6] Protection of the free hydroxy group in **5** as the corresponding TBDMS ether **6** was effected with TBDMSOTf in 98% yield. Addition of

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(1) For a review on the cytotoxic activity and other bioactivity of styryllactones, see: (a) Mereyala, H. B.; Joe, M. *Curr. Med. Chem. Anti-Cancer Agents* **2001**, *1*, 293. (b) Blàzquez, M. A.; Bermejo, A.; Zafra-Polo, M. C.; Cortes, D. *Phytochem. Anal.* **1999**, *10*, 161.

(2) For a review on the synthesis of styryllactones until 2004, see: Mondon, M.; Gesson, J.-P. *Curr. Org. Synth.* **2006**, *3*, 175.

(3) Hisham, A.; Toubi, M.; Shuaily, W.; Bai, M. D. A.; Fujimoto, Y. *Phytochemistry* **2003**, *62*, 597.

(4) (a) Ruiz, P.; Murga, J.; Carda, M.; Marco, J. A. *J. Org. Chem.* **2005**, *70*, 713. (b) Matsuura, D.; Takabe, K.; Yoda, H. *Tetrahedron Lett.* **2006**, *47*, 1371. (c) Radhakrishna, P.; Reddy, P. V. N. *Tetrahedron Lett.* **2006**, *47*, 4627. (d) Garg, A.; Singh, R. P.; Singh, V. K. *Tetrahedron* **2006**, *62*, 11240.

(5) (a) Prasad, K. R.; Gholap, S. L. *Synlett* **2005**, 2260. (b) Prasad, K. R.; Gholap, S. L. *J. Org. Chem.* **2006**, *71*, 3643. (c) Prasad, K. R.; Gholap, S. L. *Tetrahedron Lett.* **2007**, *48*, 4679. (d) Prasad, K. R.; Gholap, S. L. *J. Org. Chem.* **2008**, *73*, 2. (e) Prasad, K. R.; Dhaware, M. G. *Synlett* **2007**, 1112. (f) Prasad, K. R.; Dhaware, M. G. *Synthesis* **2007**, 3697.

(6) Formation of other diastereomer was not observed within detectable limits in $^1H$ NMR.

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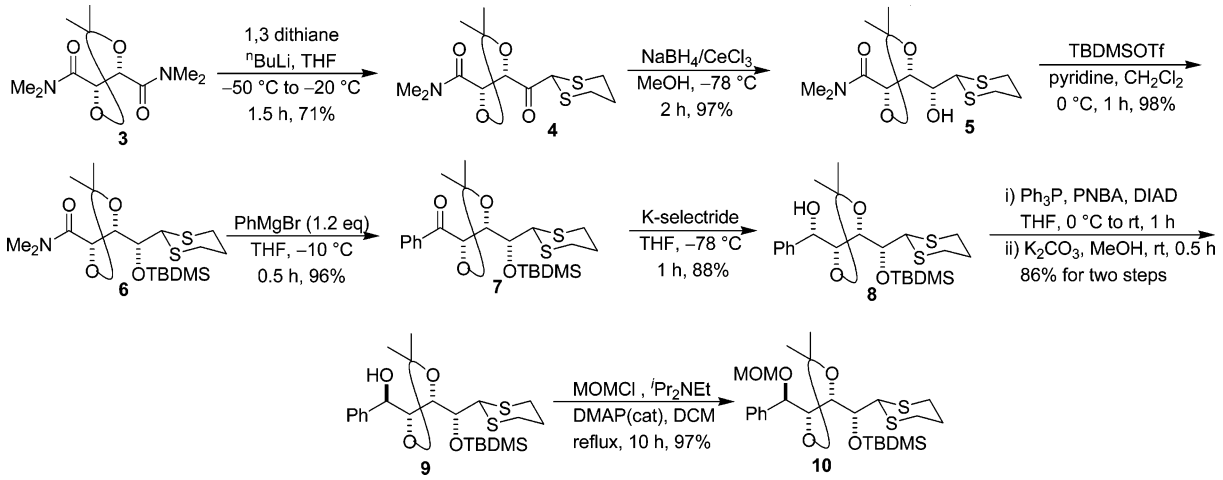
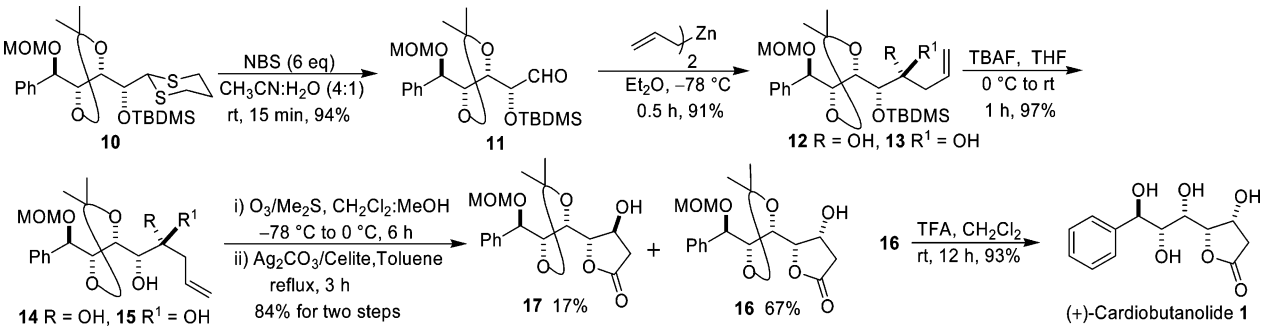
**SCHEME 2. Stereoselective Synthesis of Masked Tetrol 10**




**SCHEME 3. Stereoselective Synthesis of (+)-Cardiobutanolide 1**




phenylmagnesium bromide to **6** proceeded smoothly affording the ketone **7** in 96% yield. Stereoselective reduction of the ketone **7** with K-Selectride in THF at −78 °C resulted in a separable mixture of alcohols in 92:8 ratio, with **8** being the major diastereomer isolated in 88% yield after chromatography. Mitsunobu inversion of the benzylic hydroxy group in **8** with DIAD, $Ph_3P$ and *p*-nitrobenzoic acid, and subsequent hydrolysis of the *p*-nitrobenzoyl ester furnished the epimerized alcohol **9** in 86% yield for two steps. The free hydroxy group in **9** was protected as the corresponding methoxymethyl (MOM) ether **10** using standard conditions in 97% yield. Thus, the key masked tetrol unit **10** was synthesized in **8** steps with 48% overall yield from the *bis*-dimethylamide of tartaric acid **3** (Scheme 2).

*N*-Bromosuccinimide mediated oxidative cleavage of the dithiane[7] in **10** was found to be facile resulting in the aldehyde **11** in 94% yield. Addition of allylmagnesium bromide to the aldehyde **11** afforded an inseparable diastereomeric mixture of homoallylic alcohols **12** and **13** (dr 48:52) in 92% combined yield. Reaction of aldehyde **11** with diallylzinc[8] prepared in situ from allylmagnesium bromide and $ZnCl_2$ resulted in an improved ratio (dr 80:20) of homoallylic alcohols **12** and **13** in 91% yield. Deprotection of the silyl group in **12** and **13** with TBAF furnished an inseparable mixture of diols **14** and **15** respectively in 97% yield. Ozonolysis of diastereomeric mixtures of diols **14** and **15** produced the corresponding lactols, which on oxidation with silver carbonate impregnated on celite[9] afforded easily separable mixtures of γ-lactones **16** and **17** in 67% and 17% yields respectively. Treatment of γ-lactone **16** with trifluoroacetic acid in moist dichloromethane at room temperature underwent smooth deprotection of the MOM ether and acetonide to afford (+)-cardiobutanolide **1** in 93% yield. Similarly, deprotection of the lactone **17** furnished (+)-3-*epi*-cardiobutanolide **2** in 94% yield (Scheme 3). The spectral data of **1** is in complete agreement with that reported in literature.[4a]

In conclusion, a facile and efficient stereoselective synthesis of (+)-cardiobutanolide was accomplished in 24% overall yield in 14 steps from the readily available dimethylamide **3** derived from D-(-)-tartaric acid. Pivotal reaction sequence include the elaboration of a γ-hydroxy butyramide, involving a combination of the addition of 1,3-dithian-2-yllithium and stereoselective reduction.

## Experimental Section

**Preparation of (4*S*,5*R*)-5-(1-Oxo(1,3-dithian-2-yl))-*N*,*N*,2,2-tetramethyl-1,3-dioxolane-4-carboxamide (4).** To a pre cooled (−50 °C) solution of 1,3-dithiane (1.18 g, 9.8 mmol) in dry THF (10 mL) was added *n*-BuLi (6.1 mL of 1.6 M solution in hexane, 9.8 mmol) dropwise under argon atmosphere. It was slowly allowed to warm to −20 °C and stirred for 1 h at the same temperature to generate 1,3-dithian-2-yllithium. The resultant THF solution of 1,3-dithian-2-yllithium was then cautiously added to a precooled (−20 °C) solution of bis-dimethylamide **3** (2.0 g, 8.2 mmol) dropwise via syringe under argon atmosphere. Progress of the reaction was

(7) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.
(8) Kishi, Y.; Nagaoka, H. *Tetrahedron* **1981**, *37*, 3873.

(9) (a) Balogh, V.; Fetizon, M.; Golfier, M. *J. Org. Chem.* **1971**, *36*, 1339. (b) Clive, D. L. J.; Murthy, K. S. K.; Wee, A. G. H.; Prasad, J. S.; da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Evans, C. F.; Haugen, R. D.; Heerze, L. D.; Barrie, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 3018. (c) Chandrasekhar, M.; Chandra, K. L.; Singh, V. K. *J. Org. Chem.* **2003**, *68*, 4039.

monitored by TLC and after the reaction was complete (0.5 h), it was cautiously quenched by addition of saturated solution of $NH_4Cl$ (10 mL). It was then poured into water (20 mL) and extracted with ether (3 × 25 mL). Combined ethereal extracts were washed with brine (30 mL) and dried ($Na_2SO_4$). Evaporation of the solvent and silica gel column chromatography of the residue using petroleum ether/EtOAc (7:3) as eluent yielded **4** (1.86 g, 71%) as a white solid: mp 74−76 °C; $[\alpha]_D$ −70.8 (*c* 1.2, $CHCl_3$); IR (KBr) 2939, 2832, 1707, 1651, 1495, 1378, 1265, 1087 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.52 (d, $J$ = 5.7 Hz, 1H), 4.85 (d, $J$ = 5.7 Hz, 1H), 4.73 (s, 1H), 3.45−3.31 (m, 1H), 3.24−3.10 (m, 1H), 3.16 (s, 3H), 3.00 (s, 3H), 2.66−2.48 (m, 2H), 2.22−1.94 (m, 2H), 1.47 (s, 3H), 1.43 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 200.5 (C), 167.6 (C), 112.1 (C), 79.3 (*C*H), 76.1 (*C*H), 39.8 (CH), 36.8 (*C*$H_3$), 35.8 (*C*$H_3$), 26.1 (*C*$H_3$), 25.8 (*C*$H_3$), 24.9 (*C*$H_2$), 24.7 (*C*$H_2$); HRMS for $C_{13}H_{21}NO_4S_2$ + Na calcd 342.0812, found 342.0810. Anal. Calcd for $C_{13}H_{21}NO_4S_2$: C, 48.88; H, 6.63; N, 4.38; S, 20.08. Found: C, 49.03; H, 6.55; N, 4.48; S, 20.19.

**Preparation of ((4*S*,5*S*)-5-((*R*)-(1,3-Dithian-2-yl)(*tert*-butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(phenyl)-methanone (7).** To a precooled (−10 °C) solution of the silyl ether **6** (0.8 g, 1.8 mmol) in dry THF (12 mL) was added a freshly prepared THF solution of PhMgBr (4.5 mL of 0.5 M solution in THF, 2.2 mmol) dropwise under argon atmosphere. The reaction mixture was stirred for 0.5 h at the same temperature. It was then cautiously quenched by addition of saturated $NH_4Cl$ (15 mL). The reaction mixture was then extracted with ether (3 × 20 mL), and the combined ethereal extracts were washed with brine (25 mL) and dried ($Na_2SO_4$). Evaporation of the solvent and silica gel column chromatography of the residue with petroleum ether/EtOAc (95:5) as eluent afforded ketone **7** (0.83 g, 96%) as a white solid: mp 68−69 °C; $[\alpha]_D$ +21.6 (*c* 1.2, $CHCl_3$); IR (KBr) 2931, 2690, 1597, 1451, 1371, 1257, 1057, 845, 778, 688 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.08 (d, $J$ = 7.5 Hz, 2H), 7.63−7.42 (m, 3H), 5.24 (d, $J$ = 6.6 Hz, 1H), 4.83 (t, $J$ = 6.3 Hz, 1H), 4.32 (d, $J$ = 3.6 Hz, 1H), 4.00 (t, $J$ = 4.8 Hz, 1H), 2.92−2.67 (m, 4H), 2.07−1.98 (m, 1H), 1.93−1.75 (m, 1H), 1.52 (s, 3H), 1.32 (s, 3H), 0.90 (s, 9H), 0.19 (s, 3H), 0.11 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 197.4 (C), 135.7 (C), 133.4 (CH), 129.4 (CH), 128.4 (CH), 111.1 (C), 78.9 (CH), 78.3 (CH), 75.5 (CH), 51.8 (CH), 31.3 ($CH_2$), 30.4 ($CH_2$), 26.9 ($CH_3$), 26.1 ($CH_2$), 26.0 ($CH_3$), 25.9 ($CH_3$), 18.4 (C), −4.2 ($CH_3$), −4.4 ($CH_3$); HRMS for $C_{23}H_{36}O_4S_2Si$ + Na calcd 491.1724, found 491.1722. Anal. Calcd for $C_{23}H_{36}O_4S_2Si$: C, 58.93; H, 7.74; S, 13.68. Found: C, 58.94; H, 7.61; S, 13.79.

**Preparation of (*R*)-((4*R*,5*S*)-5-((*R*)-(1,3-Dithian-2-yl)(*tert*-butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(phenyl)methanol (9).** To a precooled (0 °C) solution of **8** (0.6 g, 1.3 mmol) in dry THF (12 mL) were added triphenylphosphine (0.5 g, 1.9 mmol) and *p*-nitrobenzoic acid (0.3 g, 1.9 mmol) under argon atmosphere and allowed to stir for 10 min. DIAD (0.3 mL, 0.3 mmol) was introduced in the reaction mixture over period of 15 min at the same temperature. The reaction mixture was warmed to room temperature and stirred at room temperature for 2 h. After the reaction was complete (TLC), solvent was removed under reduced pressure and the crude ester thus obtained was purified by column chromatography to yield the corresponding *p*-nitrobenzoate ester (0.73 g, 92%) as pale yellow solid (for characterization, see the Supporting Information).

To a methanol (12 mL) solution of the *p*-nitrobenzoate ester (0.77 g, 1.24 mmol) obtained above was added $K_2CO_3$ (0.34 g, 2.5 mmol) and the mixture stirred for 0.5 h at room temperature. After the reaction was complete (TLC), the reaction mixture was poured in to water (15 mL) and extracted with diethyl ether (3 × 20 mL). Combined ethereal extracts were washed with brine (25 mL) and dried over $Na_2SO_4$. Evaporation of the solvent and silica gel column chromatography of the residue using petroleum ether/EtOAc (9:1) as eluent afforded **9** (0.55 g, 94%) as a colorless oil: $[\alpha]_D$ −13.2 (*c* 1, $CHCl_3$); IR (neat) 3450, 2931, 1471, 1371, 1252, 1132, 1068, 941, 837, 776, 702 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.44−7.23 (m, 5H), 4.96 (d, $J$ = 4.8 Hz, 1H), 4.36 (dd, $J$ = 7.5, 3.3 Hz, 1H), 4.25 (dd, $J$ = 7.5, 5.4 Hz, 1H), 4.15 (d, $J$ = 4.5 Hz, 1H), 3.41 (dd, $J$ = 4.5, 3.3 Hz, 1H), 3.04 (s, 1H), 2.84−2.71 (m, 4H), 2.08−1.81 (m, 2H), 1.40 (s, 6H), 0.92 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 139.6 (C), 128.5 (CH), 128.0 (CH), 126.9 (CH), 109.6 (C), 80.3 (CH), 79.0 (CH), 74.5 (CH), 74.0 (CH), 52.8 (CH), 31.0 ($CH_2$), 30.5 ($CH_2$), 27.5 ($CH_3$), 27.1 ($CH_3$), 26.1 ($CH_2$), 26.0 ($CH_3$), 18.6 (C), −3.8 ($CH_3$), −4.5 ($CH_3$); HRMS for $C_{23}H_{38}O_4S_2Si$ + Na calcd 493.1881, found 493.1879.

**Preparation of (*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-((4*S*,5*R*)-5-((*R*)-(methoxymethoxy)(phenyl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde (11).** A solution of **10** (0.42 g, 0.8 mmol) in acetonitrile (5.0 mL) was added dropwise over a period of 5 min to a solution of *N*-bromosuccinimide (0.85 g, 4.8 mmol) in 4:1 mixture of acetonitrile/water (10 mL) at room temperature. The reaction mixture was stirred for 10 min at same temperature. After the reaction was complete (TLC), saturated solution of sodium sulfite (5 mL) was added to the reaction mixture and stirred for 5 min. The reaction mixture was then extracted with ether (3 × 15 mL), and the combined ethereal extracts were washed with 1 M solution of aqueous sodium bicarbonate (15 mL), water (15 mL), and brine (20 mL) and dried over $Na_2SO_4$. Evaporation of the solvent and silica gel column chromatography of the residue with petroleum ether/EtOAc (95:5) as eluent afforded aldehyde **11** (0.32 g, 94%) as colorless oil: $[\alpha]_D$ −22.8 (*c* 1, $CHCl_3$); IR (neat) 2934, 2859, 1737, 1467, 1375, 1253, 1217, 1151, 1084, 922, 839 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.65 (s, 1H), 7.39−7.28 (m, 5H), 4.76 (d, $J$ = 6.1 Hz, 1H), 4.56 (s, 3H), 4.43 (dd, $J$ = 7.6, 2.0 Hz, 1H), 4.31 (dd, $J$ = 7.4, 6.3 Hz, 1H), 3.87 (d, $J$ = 1.3 Hz, 1H), 3.38 (s, 1H), 1.37 (s, 3H), 1.35 (s, 3H), 0.93 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 203.3 (C), 137.9 (C), 128.5 (CH), 128.3 (CH), 127.7 (CH), 110.3 (C), 94.1 ($CH_2$), 79.8 (CH), 78.6 (CH), 78.1 (CH), 77.6 (CH), 56.0 ($CH_3$), 27.2 ($CH_3$), 26.7 ($CH_3$), 25.8 ($CH_3$), 18.2 (C), −4.5 ($CH_3$), −5.1 ($CH_3$); HRMS for $C_{22}H_{36}O_6Si$ + Na calcd 447.2181, found 447.2179.

**Preparation of ((1*S*)-2-Hydroxy-1-((4*S*,5*R*)-5-((*R*)-(methoxymethoxy)(phenyl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-pent-4-enyloxy)(*tert*-butyl)dimethylsilane (12 and 13).** To a precooled (0 °C) solution of allylmagnesium bromide (0.5 M solution in ether, 3 mL, 1.5 mmol) in dry ether (6.0 mL) was added a solution of $ZnCl_2$ (0.5 M solution in ether, 4 mL, 2 mmol) dropwise under argon atmosphere. The reaction mixture was warmed to room temperature and after stirring for 5 min at room temperature, it was cooled to −78 °C and **11** (0.35 g, 0.82 mmol) in ether (3.0 mL) was added dropwise over period of 15 min. Progress of the reaction was monitored by TLC and after the reaction was complete (15 min), it was cautiously quenched by addition of saturated solution of $NH_4Cl$ (5 mL) and poured in to water (10 mL). The reaction mixture was then extracted with ether (3 × 15 mL) and the combined ethereal extracts were washed with brine (20 mL) and dried ($Na_2SO_4$). Evaporation of the solvent and silica gel column chromatography of the residue with petroleum ether/EtOAc (9:1) as eluent afforded an inseparable diastereomeric mixture (dr 80:20) of homoallylic alcohols **12** and **13** (0.34 g, 91%) as a colorless oil: IR (neat) 3509, 2933, 1642, 1465, 1374, 1251, 1149, 1080 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.44−7.26 (m, 5H), 5.93−5.76 (m, 1H), 5.20−5.09 (m, 2H), 4.81−4.75 (m, 1H), 4.65−4.50 (m, 2H), 4.40−4.19 (m, 1H), 4.26−4.20 (m, 1H), 3.68−3.81 (m, 1H), 3.37 (S, 1H), 3.07 (d, $J$ = 5.9 Hz, 1H), 2.44−2.22 (m, 2H), 1.44−1.35 (m, 6H), 0.94−0.90 (m, 9H), 0.11−0.01 (m, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 137.8, 135.1, 135.0, 128.7, 128.4, 128.2, 128.18, 128.1, 127.8, 117.6, 117.4, 109.9, 79.8, 79.6, 78.4, 77.9, 77.8, 75.0, 74.4, 72.4, 55.9, 55.8, 38.7, 38.6, 27.4, 27.3, 27.0, 26.9, 26.2, 25.9, 18.5, 18.3, −3.9, −4.3, −4.4, −4.6; HRMS for $C_{25}H_{42}O_6Si$ + Na calcd 489.2651, found 489.2648.

**Preparation of (4*R*,5*S*)-Dihydro-5-((4*R*,5*R*)-5-((*R*)-(methoxymethoxy)(phenyl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-**

**hydroxy-furan-2(3*H*)-one (16) and (4*S*,5*S*)-Dihydro-5-((4*R*,5*R*)-5-((*R*)-(methoxymethoxy)(phenyl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-hydroxy-furan-2(3*H*)-one (17).** Ozone was bubbled through a precooled (−78 °C) solution of diols **14** and **15** (0.15 g, 0.43 mmol) in 4:1 mixture of $CH_2Cl_2$:MeOH (15 mL) containing solid $NaHCO_3$ (20 mg) till the pale blue color persisted. Excess ozone was flushed off with oxygen and dimethyl sulfide (0.5 mL) was added. The reaction mixture was warmed to 0 °C, and stirred at the same temperature for 6 h. The reaction mixture was concentrated under reduced pressure and filtered through a short pad of Celite. The Celite pad was washed with EtOAc (25 mL). Evaporation of the solvent yielded the crude lactol, which was subjected to the next reaction without further purification.

To a solution of the crude lactol obtained above in 15 mL of toluene was added $Ag_2CO_3$ impregnated on Celite (0.72 g, 0.86 mmol, 33% impregnation) under argon atmosphere. The reaction mixture was kept at 110 °C and stirred at the same temperature for 3 h. It was then cooled to room temperature, filtered through a pad of Celite and the Celite pad was washed with EtOAc (25 mL). Evaporation of the solvent and silica gel column chromatography of the residue using petroleum ether:EtOAc (4:6) as eluent yielded lactone **16** (0.1 g, 67%) as colorless oil: $[\alpha]_D$ −8.2 (*c* 1, $CHCl_3$); IR (neat) 3447, 2935, 1785, 1456, 1373, 1248, 1153, 1034 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.42−7.28 (m, 5H), 4.83 (d, $J$ = 6.3 Hz, 1H), 4.70−4.51 (m, 3H), 4.59 (dd, $J$ = 7.5, 2.6 Hz, 1H), 4.39 (dd, $J$ = 7.5, 6.3 Hz, 1H), 4.16 (dd, $J$ = 6.0, 2.6 Hz, 1H), 3.39 (s, 3H), 2.74 (dd, $J$ = 17.7, 7.4 Hz, 1H), 2.58 (dd, $J$ = 17.7, 5.1 Hz, 1H), 1.44 (s, 3H), 1.37 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 174.6 (C), 137.3 (C), 128.7 (CH), 128.5 (CH), 127.3 (CH), 111.0 (C), 94.4 (CH), 80.8 (CH), 79.6 (CH), 77.7 (CH), 77.2 (CH), 68.9 (CH), 56.2 ($CH_3$), 38.3 ($CH_2$), 27.4 ($CH_3$), 26.6 ($CH_3$); HRMS for $C_{18}H_{24}O_7$ + Na calcd 375.1422, found 375.1420. Lactone **17** was isolated in 17% (0.025 g) as colorless oil: $[\alpha]_D$ −21.8 (*c* 1.1, $CHCl_3$); IR (neat) 3447, 2936, 1883, 1456, 1373, 1165, 1026, 889 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.40−7.28 (m, 5H), 4.80 (d, $J$ = 5.9 Hz, 1H), 4.63 (d, $J$ = 6.8 Hz, 1H), 4.58 (d, $J$ = 6.8 Hz, 1H), 4.51 (d, $J$ = 6.4 Hz, 1H), 4.32 (dd, $J$ = 8.0, 6.0 Hz, 1H), 4.20 (dd, $J$ = 8.8, 0.8 Hz, 1H), 4.08 (s, 1H), 3.38 (s, 3H), 2.93 (dd, $J$ = 18.0, 6.4 Hz, 1H), 2.35 (dd, $J$ = 18.0, 1.6 Hz, 1H), 1.34 (s, 3H), 1.29 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 176.2 (C), 137.5 (C), 128.6 (CH), 128.5 (CH), 127.3 (CH), 110.4 (C), 94.6 (CH), 85.7 (CH), 79.1 (CH), 78.4 (CH), 77.7 (CH), 70.3 (CH), 56.1 ($CH_3$), 38.2 ($CH_2$), 27.1 ($CH_3$), 26.3 ($CH_3$); HRMS for $C_{18}H_{24}O_7$ + Na calcd 375.1422, found 375.1420.

**Preparation of (+)-Cardiobutanolide (1).** To a solution of **16** (60 mg, 0.17 mmol) in 5 mL of moist dichloromethane was added trifluoroacetic acid (0.12 mL, 1.7 mmol) at room temperature. The reaction mixture was allowed to stir for 12 h at the same temperature. After the reaction was complete (TLC), the solvent was removed under reduced pressure and the residue obtained was purified by silica gel column chromatography using petroleum ether: EtOAc (2:8) as an eluent to give **1** (42 mg, 93%) as a crystalline solid: mp 192−193 °C; $[\alpha]_D$ +7.5 (*c* 0.8, MeOH) [lit.[3] mp 189−190 °C; $[\alpha]_D$ +6.4 (*c* 0.28, MeOH)]; IR (KBr) 3516, 3476, 2933, 1758, 1495, 1319, 1208, 1028 $cm^{-1}$; $^1H$ NMR (400 MHz, $CD_3COCD_3$) $\delta$ 7.44 (d, $J$ = 7.5 Hz, 2H), 7.30 (t, $J$ = 7.2 Hz, 2H), 7.22 (t, $J$ = 7.2 Hz, 1H), 4.80 (dd, $J$ = 7.2, 5.0 Hz, 1H), 4.67 (d, $J$ = 5.0 Hz, 1H), 4.63 (bs, 2H), 4.57 (dd, $J$ = 7.5, 3.1 Hz, 1H), 4.40 (t, $J$ = 4.5 Hz, 1H), 4.34 (d, $J$ = 5.3 Hz, 1H), 3.92 (td, $J$ = 7.9, 1.5 Hz, 1H), 3.83 (d, $J$ = 8.4 Hz, 1H), 2.93−2.80 (m, 1H, overlapped by residual $H_2O$), 2.38 (d, $J$ = 17.1 Hz, 1H); $^{13}C$ NMR (100 MHz, $CD_3COCD_3$) $\delta$ 176.1 (C), 144.2 (C), 128.6 (CH), 128.0 (CH), 127.9 (CH), 86.6 (CH), 75.7 (CH), 74.2 (CH), 70.4 (CH), 68.7 (CH), 40.4 ($CH_2$); HRMS for $C_{13}H_{16}O_6$ + Na calcd 291.0847, found 291.0845.

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**Supporting Information Available:** General experimental procedures and spectroscopic data for the compounds and copies of $^1H$ NMR and $^{13}C$ NMR spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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