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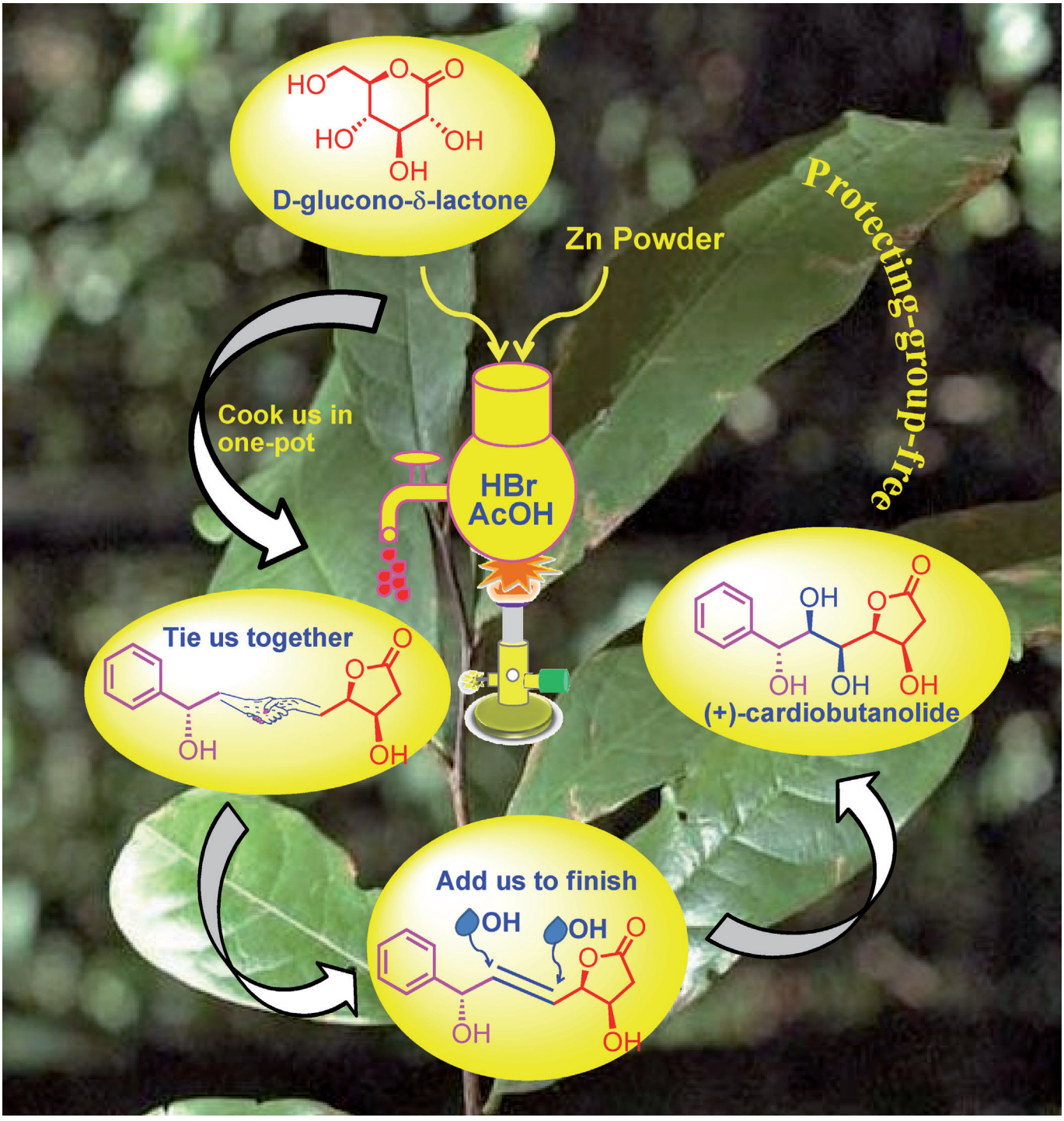
Step-Economic and Protecting-Group-Free Total Synthesis of (+)-Cardiobutanolide

Rodney A. Fernandes* and Pullaiah Kattanguru[a]



Abstract: A short protecting-group-free synthesis of (+)-cardiobutanolide is reported. We have modified a one-pot conversion of D-glucono-δ-lactone into the building block β-hydroxy-γ-lactone. A series of cross-metathesis reactions and dihydroxylations either under the Sharpless conditions or achiral 4-methylmorpholine *N*-oxide (NMO) conditions were used to synthesize (+)-cardiobutanolide and its various diastereomers. In this endeavour, we have achieved a step-economic and protecting-group-free synthesis of (+)-cardiobutanolide in 22.4% overall yield from D-glucono-δ-lactone. A cross-metathesis reaction that is compatible with hydroxy groups and a substrate controlled Upjohn dihydroxylation reaction are key steps in the synthesis. The synthesis is highly efficient and competitive with previous reports.

Keywords: asymmetric dihydroxylation · cardiobutanolide · cross-metathesis · natural products · styryllactones

Introduction

(+)-Cardiobutanolide (**1**), a styryllactone (Figure 1), was isolated from *Goniothalamus cardiopetalus* trees of the family *Annonaceae* in 2003 by Hisham et al.[1] The plant family *Annonaceae* have yielded different types of natural products, such as acetogenins,[2] isoquinoline alkaloids,[3] and terpenoid compounds.[4] Styryllactones are mainly isolated from the genus *Goniothalamus* and are known to have antitumor, teratogenic, pesticidal, cytotoxic, embryotoxic, and other biological activities.[5] (+)-Cardiobutanolide is a target of synthetic interest. It contains a γ-lactone and polyhydroxy groups, which account for five contiguous stereocenters. Nearly a decade after it was first isolated, there have been nine reported syntheses of cardiobutanolide and/or its diastereomers.[6] The first synthesis was reported by Murga and co-workers.[6a] through an *anti*-selective boronate aldol reaction of an L-erythrulose derivative in 9% overall yield. The synthesis by Yoda and Co-workers used D-glucuronolactone and involves a long synthetic route (9% overall yield).[6b] A synthesis from D-glucose derivative was reported by Krishna et al.[6c] in 8% overall yield. This was followed by a formal synthesis by Singh and co-workers[6d] from a furanose derivative. Prasad et al.[6e] developed a longer synthetic route from D-(−)-tartaric acid in 18% overall yield. The synthesis also involved inversion of configuration and multiple protecting groups. Krishna et al.[6f] then reported a non-sugar-based synthesis of **1** through Sharpless kinetic resolution, cross-metathesis, and Sharpless asymmetric dihydroxylation (2% overall yield). Yadav et al.[6g] developed a synthesis from the chiral pool material D-gluconolactone in 13% overall yield. A sequential double asymmetric dihydroxylation of a diene has been demonstrated by Chandrasekhar et al.[6h] to achieve the synthesis of **1** over a lengthy linear sequence in 5% overall yield. A recent synthesis by Pal and Shaw[6i] used a chiral building block approach starting from 3,4,6-tri-*O*-benzyl-D-glucal and involved cross-metathesis and asymmetric dihydroxylation as key steps (2% overall yield). A review of literature syntheses indicates that most strategies were designed with the use and/or replacement and removal of one or multiple protecting groups. The syntheses were dramatically lengthened by use of these protecting groups.

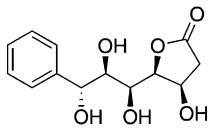


Figure 1. Structure of **1**.

With the availability of many new synthetic methods, especially skeleton-constructing reactions with tolerance for various functional groups, protecting-group-free synthesis is practical and in high demand.[7] With our interest in designing strategies for the total syntheses of natural products[8] we became interested in the development of a protecting-group-free synthesis of **1** from the cheap and commercially available material D-glucono-δ-lactone. Our detailed retrosynthetic approach towards developing a protecting-group-free synthesis of **1** is outlined in Scheme 1. Our approach is built on an interesting report by Song and Hollingsworth[9] about a one-pot conversion of D-glucono-δ-lactone **7** into the key building block γ-lactone **3a**. We visualized a cross-metathesis of **3a** would lead to **5** or **2** depending on the olefin partners **6** or **4**, respectively. Asymmetric dihydroxylation of **5** (with or without protecting groups) would lead to **1**. Similarly, asymmetric dihydroxylation and ketone reduction of **2** or the reverse sequence would also give **1**. The strategy holds potential for the syntheses of analogues of **1**, especially at the aryl end. Apart from the syntheses of analogues, stereochemical variation could also be possible by using enantiomers of **6** and/or **3a**.[9]

Results and Discussion

The synthesis commenced with the conversion of **7** into the key building block γ-lactone **3a** or **3b**. The synthesis of **3a** from D-mannitol over a lengthy sequence of ten steps is known.[6f] Song and Hollingsworth[9] reported a promising 58% yield (25 g scale reaction of **7**) in the one-pot conversion of **7** to **3a**. However, repetition of this reaction by Brimble and co-workers[10] resulted in only a 7% yield after numerous attempts. Our efforts towards refinement of this

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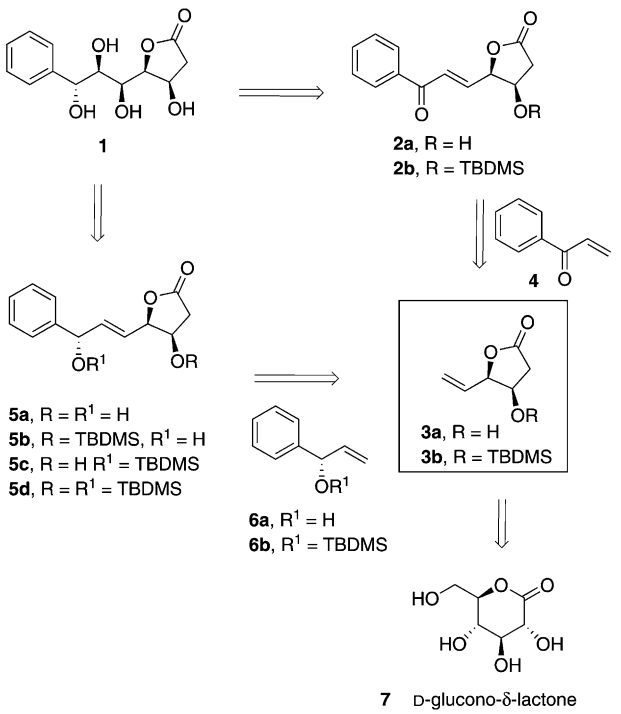
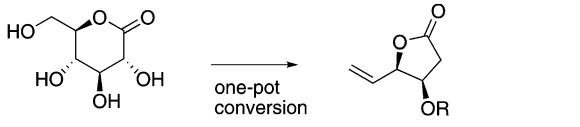


Scheme 1. Retrosynthesis of **1**. TBDMS = *tert*-butyldimethylsilyl.

reaction are presented in Table 1. When the reported procedure[9] was attempted, we encountered similar lower yields (Table 1, entry 1, 12%). The reaction was messy, involves froth formation and requires careful handling, especially while adding Zn dust. When the Zn dust treatment was carried out at 0°C initially and then the reaction heated to reflux, the yield improved to 24% of **3a** (Table 1, entry 2). However, when the HBr treatment was shortened to 1 h at 50°C instead of overnight reaction,[9] the yield improved to 45% (Table 1, entry 3). A combination of HBr treatment at 50°C for 1 h and Zn dust addition at −10°C over 1 h and then warming to room temperature over 2 h further improved the yield to 51% (Table 1, entry 4). This procedure was reproducible on less than four grams of **7**. The β-hydroxy group of the crude product of the reaction in Table 1, entry 4 on protection with a silyl group gave **3b** in 44% yield (Table 1, entry 5). When the reaction was washed with water and not treated with base, the γ-lactone **3c** with an acetate group was obtained in 45% yield (Table 1, entry 6).

Table 1. One-pot conversion of **7** into **3**.



7 D-glucono-δ-lactone

3a, R = H **3b**, R = TBDMS
3c, R = Ac

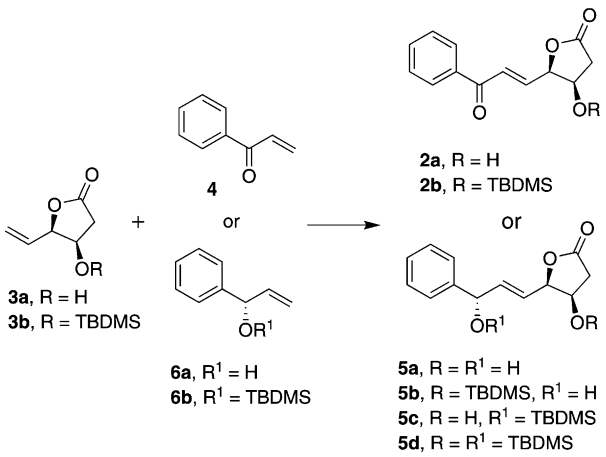
Entry	Reaction conditions	Product (Yield [%])
1	i) 33% HBr in AcOH, 60°C, 1 h, RT, overnight; ii) Zn dust, AcOH/H_2O (1:1), RT, 2 h, reflux, 1 h, KOH.[9]	**3a** (12)
2	i) 33% HBr in AcOH, 60°C, 1 h, RT, overnight; ii) Zn dust, AcOH/H_2O (1:1), 0°C, 1 h, RT, 2 h, reflux, 1 h, KOH.	**3a** (24)
3	i) 33% HBr in AcOH, 50°C, 1 h; ii) Zn dust, AcOH/H_2O (1:1), 0°C, 1 h, RT, 2 h, heated at 60°C, 1 h, KOH.	**3a** (45)
4	i) 33% HBr in AcOH, 50°C, 1 h; ii) Zn dust, AcOH/H_2O (1:1), −10°C, 1 h, RT, 2 h, heated at 60°C, 1 h, KOH.	**3a** (51)
5	i) 33% HBr in AcOH, 50°C, 1 h; ii) Zn dust, AcOH/H_2O (1:1), −10°C, 1 h, RT, 2 h, heated at 60°C, 1 h, KOH. iii) imidazole, TBDMSCl, CH_2Cl_2, 0°C to RT, 12 h.	**3b** (44)
6	i) 33% HBr in AcOH, 50°C, 1 h. ii) Zn dust, AcOH/H_2O (1:1), −10°C, 1 h, RT, 2 h, heated at 60°C, 1 h, H_2O.	**3c** (45)

The lactones **3a** and **3b** were used in the cross-metathesis reaction with a suitable olefin partner **4**, **6a**, or **6b**. The results are shown in Table 2.

The cross-metathesis[11] reaction of commercially available phenylvinyl ketone **4** with **3a** did not occur with Grubbs second generation (G-II) catalyst (Table 2, entry 1). Compound **4** decomposed, whereas unreacted **3a** was recovered. The reaction was achieved with the use of the Grubbs-Hoveyda[11a,12] catalyst (G-H-II) to give **2a** in 48% yield (Table 2, entry 2). Similarly, the reaction of **4** with **3b** also worked with the G-H-II catalyst to give **2b** in 41% yield (Table 2, entry 4). The reaction of commercially available **6a** and unprotected **3a** also occurred with only the G-H-II catalyst (10 mol%) to provide **5a** in 72% yield (Table 2, entry 6). In the reaction with G-II catalyst, **6a** dimerized and **3a** was recovered[13] (entry 5). The reaction of **6a** with **3b** occurred with the G-II and G-H-II catalysts in 72% and 63% yields, respectively, to give **5b** (Table 2, entries 7 and 8). When **6b** was treated with **3a** in the presence of the G-II or G-H-II catalysts, **5c** was obtained in low yields of 12% and 18%, respectively (Table 2, entries 9 and 10). The reaction of **6b** and **3b** with the hydroxy groups protected, failed with the G-II catalyst and resulted in recovery of the starting materials (Table 2, entry 11). However, the reaction worked with the G-H-II catalyst, albeit with lower yield of 28% of **5d** (Table 2, entry 12). The lower yield could be attributed to the bulky silyl groups in the vicinity of the double bonds in both **3b** and **6b**, which results in steric crowding. The Grubbs first generation catalyst was ineffective for all of the above reactions.

With the skeletal structures **2a–b** and **5a–d** in hand, we moved to introduce the remaining hydroxy groups. The Sharpless asymmetric dihydroxylation[14] (SAD) of **2a** gave a complex mixture with inseparable compounds (Scheme 2). We believe partial hemiacetal formation could lead to mixture of products. We planned to reduce the carbonyl group and then proceed with dihydroxylation. Towards this end, a (*R*)-(Me)-Corey-Bakshi-Shibata (CBS)

Table 2. Cross-metathesis of **3a**/**3b** with **4**, **6a** or **6b**.[a]



Entry	4/6	3a/3b	G-II catalyst Yield [%] (time [h])	G-H-II catalyst Yield [%] (time [h])	Product
1	**4**	**3a**	NR (72)[b]	–	**2a**
2	**4**	**3a**	–	48 (72)	
3	**4**	**3b**	NR (72)[b]	–	**2b**
4	**4**	**3b**	–	41 (72)	
5	**6a**	**3a**	NR (72)[c]	–	**5a**
6	**6a**	**3a**	–	72 (48)[d]	
7	**6a**	**3b**	72 (72)	–	**5b**
8	**6a**	**3b**	–	63 (96)	
9	**6b**	**3a**	12 (120)	–	**5c**
10	**6b**	**3a**	–	18% (120)	
11	**6b**	**3b**	NR (72)[e]	–	**5d**
12	**6b**	**3b**	–	28% (72)	

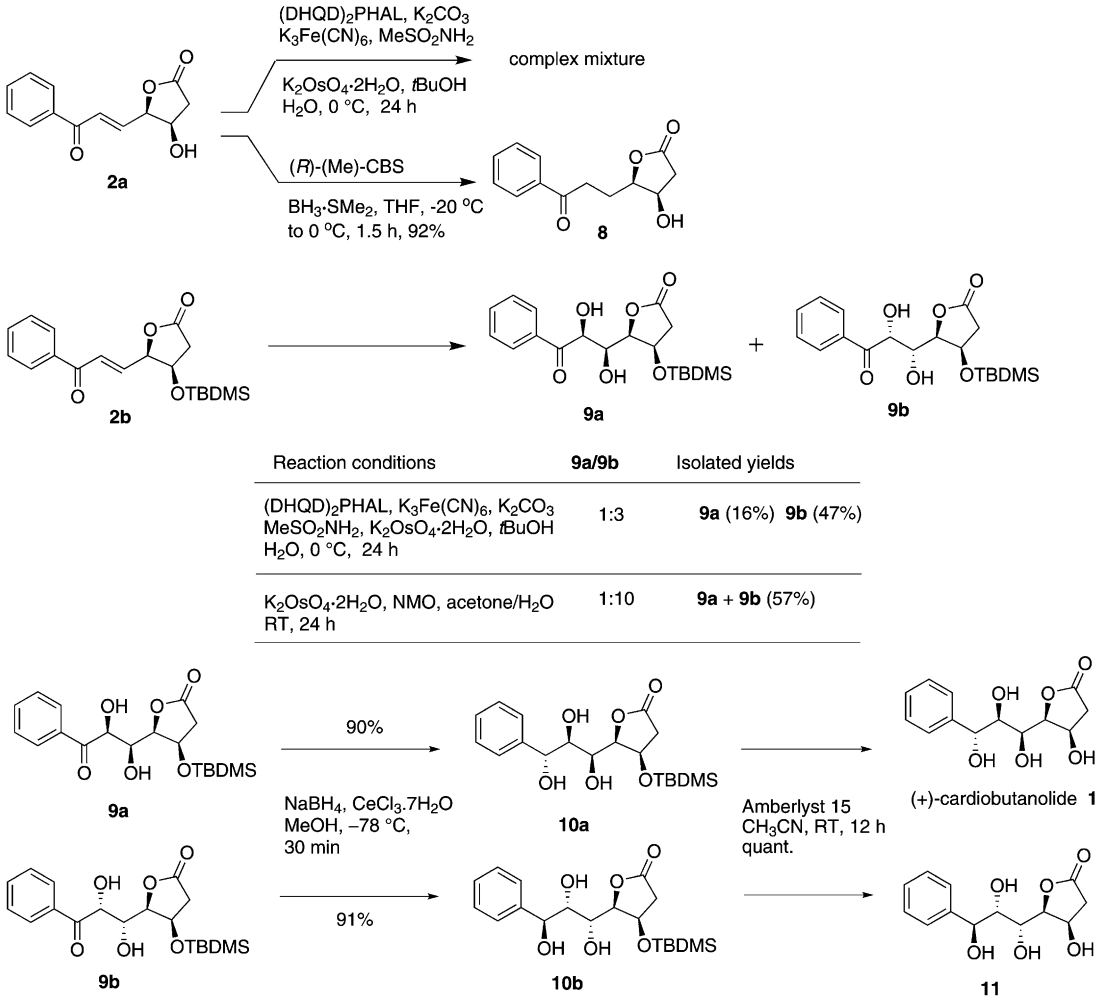
[a] The G-I catalyst was ineffective in all cases. Unless otherwise mentioned, all reactions were carried out with catalyst (5 mol%) in anhydrous CH_2Cl_2 at reflux. [b] Whereas **4** decomposed, **3a** or **3b** were recovered. [c] Whereas **3a** was recovered, **6a** dimerized. [d] 10 mol% of G-H-II catalyst was used. [e] Starting materials recovered. NR = no reaction.

asymmetric reduction[15] of **2a** was executed. However, a conjugate addition occurred instead of ketone reduction to provide **8** in 92% yield. The chelation of the borane reagent with the free hydroxy group could be the reason for delivery of the hydride for conjugate addition. The SAD reaction of **2b** gave **9a** and **9b** in a 1:3 diastereomeric ratio.[16] These diastereoisomers could be efficiently separated to furnish **9a** and **9b** in 16 and 47% yields, respectively. When dihydroxylation was carried out without the $(DHQD)_2$-PHAL ligand and with NMO, the Upjohn process,[17] **9a** and **9b** were formed in a 1:10 ratio[16] (57% combined yield). Thus, the former SAD reaction on **2b** was a mismatched case, in which strong substrate control is evident from the latter reaction without the use of a ligand.[18] The ketone of **9a** was subjected to reduction with $NaBH_4$ in the presence of $CeCl_3{\cdot}7H_2O$ to provide **10a** in 90% yield. Similarly, the same reaction with **9b** gave **10b** in 91% yield. Other diastereomers were not isolated in this reduction reaction.[19] Cleavage of the TBDMS group in **10a** yielded **1** quantitatively ($[\alpha]_D^{25} = +7.6$ ($c = 0.2$, MeOH), lit.[1] $[\alpha]_D^{24} = +6.4$ ($c = 0.28$, MeOH)). The spectral and analytical data of **1** are identical to that reported in the literature.[1,6a,e] Similarly, on removal of the TBDMS group, **10b** provided the diastereomer **11** quantitatively.

The SAD reaction of **5b** gave a mixture of **9a** and **9b** in a 1:3 ratio after 12 h (Scheme 3). We isolated **9a** and **9b** in 21 and 65% yield respectively. The same reaction when carried out for a shorter time of 2 h gave keto-compound **2b** in 65% yield.[20] Thus, the oxidation of the benzylic hydroxy group occurred prior to dihydroxylation. The dihydroxylation reaction of **5b** without the chiral ligand and using the Upjohn process[17] gave **9a** and **9b** (51%) in a 1:7 ratio. In this case the benzylic alcohol oxidation also occurred. The reaction also confirmed a strong substrate control.[18] We cross-checked the oxidation of the benzylic hydroxy group with the SAD reaction of (±)-**6a**. After a 12 h reaction we isolated a mixture of (−)-**12**[21] and **13** (mixture of diastereomers)[22] in 37 and 36% yield, respectively (Scheme 3). The dihydroxylation reaction of **5c** was not attempted because of lower yields in its preparation by cross-metathesis (Table 2, entries 9 and 10).

From the SAD reaction of **5d** with the $(DHQD)_2$-PHAL ligand, we isolated three diastereomers **14a** (31%), **14b** (37%), and a minor unidentifiable diastereomer **14c** (7%). This reaction is reported in the literature by Krishna et al.[6f] to give the two expected diastereomers in a 9:1 ratio. However, we noted discrepancies in the results we obtained in comparison with Krishna's report. The ^{1}H NMR spectral data of **14b** and **14c** matched exactly with the major and minor diastereomers reported by Krishna et al.[6f] However, there was no description of **14a**. Further elaboration of **14b** by cleavage of the silyl ether groups yielded the diastereomer **15** in quantitative yield, the ^{1}H and ^{13}C NMR spectra of which matched with the data reported by Krishna for **1**.[6f] As reported by Krishna et al., **1** has a signal at $\delta = 83.7$ ppm in the ^{13}C NMR spectrum, which corresponds to C5, which we also detected at $\delta = 82.7$ ppm for **15**. In the original report of its isolation, natural **1** has the same signal at 86.57 ppm. The earlier syntheses of **1** reported this peak as follows: Murga[6a] (86.6 ppm), Prasad[6e] (86.6 ppm), Yadav[6g] (88.4 ppm), Chandrasekhar[6h] (86.7 ppm), and Shaw[6i] (86.6 ppm). Thus, a difference of approximately $\Delta\delta = 3.0$ ppm was detected for this peak in compound **15** relative to actual **1**. On the contrary, we found that the diastereomer **14a** quantitatively gave **1** after deprotection of the silyl groups. The signal at $\delta = 86.7$ ppm and all data exactly match the original isolation report as well other syntheses.[1,6a,e,g,h,i]

Thus, we believe that Krishna et al.[6f] did not isolate the chromatographically late-eluting diastereomer **14a** in the SAD reaction of **5d** (see the Experimental Section) but reported **14b** and **14c** with incorrect assignment of structure, and that **14b** gives **1**. As pure diastereomer **5d** cannot give three products in the SAD reaction, we consider **14c** to arise from the minor *Z* diastereomer of **5d** (which might be formed during the cross-metathesis reaction in a trace amount, though not detected in the NMR spectra) or by some other reaction. But we could not unambiguously



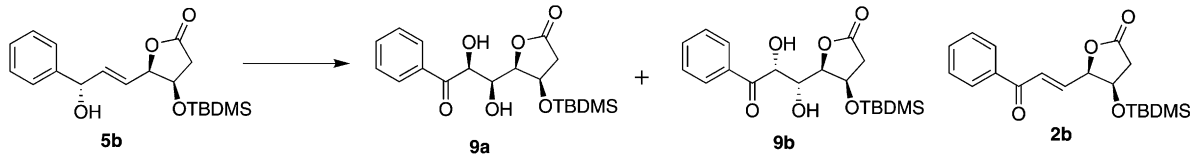
Scheme 2. SAD reaction of **2a** and **2b** and synthesis of **1**.

assign the absolute structure for **14c**. We also observed a mismatch in the SAD reaction, wherein **14a** and **14b** were formed in a 1:1.2 ratio. The dihydroxylation reaction of **5d** without the chiral ligand but with NMO gave **14a** (15%) and **14b** (47%) in a 1:3 ratio, which confirms substrate control (Scheme 3).[18]

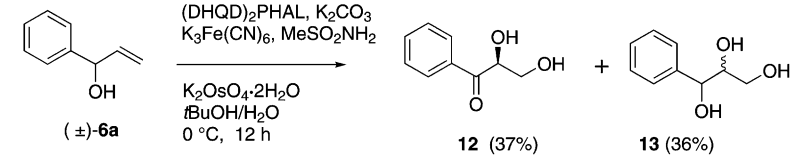
For a practical, step-economic, and protecting-group-free synthesis of **1**, we used **5a**, as shown in Scheme 4. The SAD reaction of **5a** under standard Sharpless conditions with the $(DHQD)_2$-PHAL ligand for 12 h at 0°C gave a complex mixture of inseparable products. However, when the reaction time was reduced to 2 h we obtained the benzylic alcohol oxidation product **2a** in 92% yield rather than dihydroxylation products. The dihydroxylation of **5a** without the Sharpless conditions but with NMO gave a diastereomeric mixture (**15**/**1**, dr = 1:4) from which we isolated **15** in 15% yield and **1** in 61% yield. We believe that the substrate control is more from the benzylic alcohol part than the lactone part in compound **5a**, where **1** is the major product.

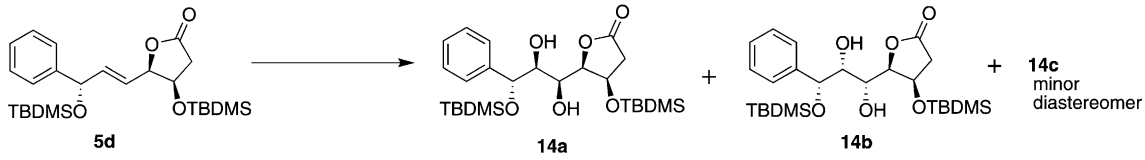
Conclusions

In conclusion we have demonstrated a reliable modification of one-pot conversion of D-glucono-δ-lactone into the β-hydroxy-γ-lactone **3**. Further, a series of cross-metathesis reactions were carried out to construct the olefins that are the skeletal structures of cardiobutanolide. These olefins were subjected to a dihydroxylation reaction either under Sharpless conditions or achiral NMO conditions. Some of the intermediates were efficiently converted into **1** and its various diastereomers. Finally, we have achieved a practical, step-economic, and protecting-group-free synthesis of **1**[23] in 22.4% overall yield from D-glucono-δ-lactone. A cross-metathesis reaction between **3a** and **6a** that is compatible with hydroxy groups and a substrate-controlled dihydroxylation reaction are key steps in the synthesis. The synthesis is highly efficient and competitive with previous reports in literature.

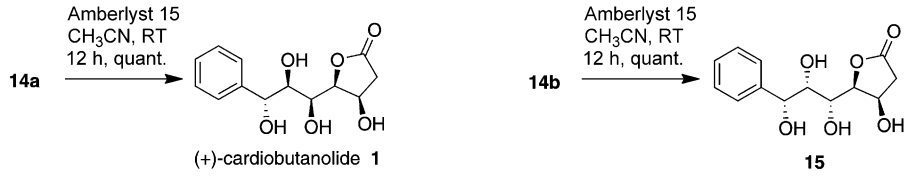


Reaction conditions	9a/9b/2b	Isolated yields
$(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3 $MeSO_2NH_2$, $K_2OsO_4{\cdot}2H_2O$, *t*BuOH H_2O, 0 °C, 12 h	1 : 3 : 0	**9a** (21%), **9b** (65%)
$(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3 $MeSO_2NH_2$, $K_2OsO_4{\cdot}2H_2O$, *t*BuOH H_2O, 0 °C, 2 h	only **2b** (65%)	
$K_2OsO_4{\cdot}2H_2O$, NMO, acetone/H_2O RT, 24 h	1 : 7 : 0	**9a** + **9b** (51%)





Reaction conditions	14a/14b/14c	Isolated yields
$(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3 $MeSO_2NH_2$, $K_2OsO_4{\cdot}2H_2O$, *t*BuOH H_2O, 0 °C, 48 h	1 : 1.2 : 0.22	**14a** (31%), **14b** (37%), **14c** (7%)
$K_2OsO_4{\cdot}2H_2O$, NMO, acetone/H_2O RT, 24 h	1 : 3 : 0	**14a** (15%), **14b** (47%)



Scheme 3. SAD reaction of **5b** and **5d** and synthesis of **1**.

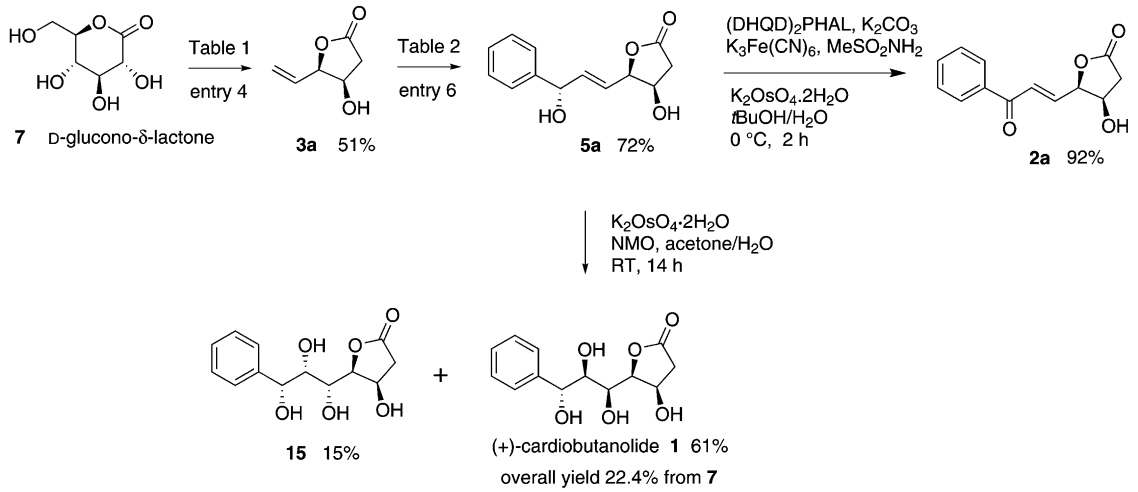
Experimental Section

General Information

Flasks were oven or flame dried and cooled in a desiccator. Anhydrous reactions were carried out under an atmosphere of Ar or N_2. Solvents and reagents were purified by standard methods. Zn powder was obtained from a local commercial source and was 325 mesh. Thin layer chromatography was performed on EM 250 Kieselgel 60 F254 silica gel plates. The spots were visualized by staining with $KMnO_4$ or by UV lamp. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, and chemical shifts are based on the tetramethylsilane signal at $\delta = 0.00$ pm for ^{1}H NMR spectra and the $CDCl_3$ signal at $\delta = 77.00$ ppm (t) or the $[D_6]$acetone signal at 29.80 ppm (septet) in ^{13}C NMR spectra. IR samples were prepared by evaporation from $CHCl_3$ on CsBr plates or as KBr pellets. High-resolution mass spectra were obtained in positive electrospray ionization mode.

*(4R,5R)-4-Hydroxy-5-vinyldihydrofuran-2(3H)-one (**3a**)*

Reaction conditions were as stated in Table 1, entry 4. Hydrogen bromide in acetic acid (HBA, 33%, 16 mL) was added to **7** (4.0 g, 22.45 mmol) and the reaction mixture stirred at 50 °C for 1 h. The mixture was then cooled to room temperature and excess HBA was removed under reduced pressure. The resultant syrupy liquid was dissolved in 50% aqueous acetic acid (40 mL), then cooled to −10 °C and zinc powder (8.07 g, 123.49 mmol, 5.5 equiv) was added in portions over 1 h at −10 °C. The mixture was stirred and warmed to room temperature over 2 h and then heated to 60 °C for an additional 1 h. The mixture was then filtered and the filtrate concentrated under reduced pressure. The residue was dissolved in water (30 mL), cooled to 0 °C, and the pH ad-



Scheme 4. Protecting-group-free synthesis of **1**.

justed to 10 by slow addition of KOH pellets to precipitate the remaining zinc as the insoluble hydroxide and to affect C3 deacetylation. After filtration, the basic filtrate was acidified to pH 5 with concentrated hydrochloric acid at 0 °C. Water was removed under reduced pressure and the residue was dissolved in cold ethanol. Precipitated potassium chloride was removed by filtration and the filtrate was concentrated. The residue was purified by chromatography on a silica gel column with petroleum ether/EtOAc (1:1) as eluent to give **3a** (1.46 g, 51 %). $[\alpha]_D^{25} = +45.3$ ($c = 0.8$, $CHCl_3$), lit.[9] $[\alpha]_D = +43$ ($c = 1.15$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}_{max} = 3447, 2934, 1771, 1639, 1432, 1413, 1333, 1309, 1203, 1158, 1080, 1017, 990, 962, 901, 884, 833, 796\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 6.01–5.92 (m, 1H), 5.59–5.49 (m, 2H), 4.94–4.91 (m, 1H), 4.56–4.53 (m, 1H), 2.80 (dd, $J = 17.7$, 5.4 Hz, 1H), 2.63 (dd, $J = 17.7$, 1.3 Hz, 1H), 2.27 ppm (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 176.1, 130.2, 120.6, 84.9, 69.4, 38.6$ ppm; HRMS: *m/z*: calcd for $[C_6H_8O_3+H]^+$: 129.0552; found: 129.0551.

*(4R,5R)-4-tert-Butyldimethylsilyloxy-5-vinyldihydrofuran-2(3H)-one (**3b**)*

By using similar procedure as above with **7**, 4.0 g, the crude hydroxy lactone **3a** (1.70 g, 13.27 mmol) obtained was dissolved in anhydrous CH_2Cl_2 (30 mL), then imidazole (1.80 g, 26.54 mmol, 2.0 equiv) and *tert*-butyldimethylsilyl chloride (2.99 g, 19.90 mmol, 1.5 equiv) were added at 0 °C. The reaction mixture was stirred at room temperature for 12 h and then diluted with CH_2Cl_2 (10 mL), H_2O (10 mL), and extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on a silica gel column with petroleum ether/EtOAc (9:1) as eluent to afford **3b** (2.38 g, 44 %) as a colorless oil: $[\alpha]_D^{25} = +15.9$ ($c = 1.0$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}_{max} = 2956, 2932, 2859, 1781, 1473, 1259, 1206, 1149, 1096, 1029, 946, 841, 779\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.91$–5.82 (m, 1H), 5.33–5.25 (m, 2H), 4.67 (dd, $J = 7.2$, 4.2 Hz, 1H), 4.40–4.37 (m, 1H), 2.61 (dd, $J = 17.2$, 5.4 Hz, 1H), 2.37 (dd, $J = 17.2$, 2.1 Hz, 1H), 0.76 (s, 9H), −0.05 (s, 3H), −0.06 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 175.2, 131.8, 119.9, 85.4, 70.7, 39.3, 25.6, 18.0, -4.9, -5.0$ ppm; HRMS: *m/z*: calcd for $[C_{12}H_{22}O_3Si+H]^+$: 243.1415; found: 243.1418.

*(4R,5R)-4-Acetyloxy-5-vinyldihydrofuran-2(3H)-one (**3c**)*

Reaction conditions were as stated in Table 1, entry 6. HBA in acetic acid (33 %, 16 mL) was added to **7** (4.0 g, 22.45 mmol) and the reaction mixture stirred at 50 °C for 1 h. The mixture was then cooled to room temperature, excess HBA was removed under reduced pressure. The resultant syrupy liquid was dissolved in 50 % aqueous acetic acid (40 mL), then cooled to −10 °C and zinc powder (8.07 g, 123.49 mmol, 5.5 equiv) was added in portions over 1 h at −10 °C. The mixture was warmed to room temperature over 2 h and then heated to 60 °C for an additional 1 h. The mixture was then filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in water (30 mL) and extracted with CH_2Cl_2 (3×40 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on a silica gel column with petroleum ether/EtOAc (7:3) as eluent to give **3c** (1.72 g, 45 %). $[\alpha]_D^{25} = +29.6$ ($c = 1.0$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}_{max} = 3091, 2998, 2938, 1789, 1747, 1649, 1432, 1375, 1237, 1149, 1062, 990, 942, 903, 761, 708\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.88$–5.80 (m, 1H), 5.55–5.52 (m, 2H), 5.39 (dd, $J = 10.7$, 1.2 Hz, 1H), 5.03 (td, $J = 4.9$, 1.1 Hz, 1H), 2.91 (dd, $J = 18.2$, 6.3 Hz, 1H), 2.65 (dd, $J = 18.2$, 2.0 Hz, 1H), 2.08 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.7, 169.8, 129.5, 120.5, 82.7, 70.8, 35.9, 20.7$ ppm; HRMS: *m/z*: calcd for $[C_8H_{10}O_4+H]^+$: 171.0657; found: 171.0652.

General Procedure for Cross-Metathesis Reactions

G-H-II, G-II, or G-I catalyst (5 mol %) was added to a stirred and degassed solution of **3a–b** (1 equiv) and **4** or **6a-b** (1.2–5.0 equiv) in anhydrous CH_2Cl_2 at room temperature and the mixture stirred at reflux for 48–144 h. The mixture was cooled to room temperature, filtered through a small pad of silica gel, and the filtrate concentrated. The residue was purified by chromatography on a silica gel column with petroleum ether/EtOAc to give **2a–b** or **5a–d** (for yields see Table 2). The *Z* isomer was not formed within the detectable limit of the ^1H NMR spectra of the isolated products. The G-I catalyst was ineffective in cross-metathesis reaction in all cases.

*(4R,5R)-4-Hydroxy-5-[(E)-3-oxo-3-phenylprop-1-en-1-yl]dihydrofuran-2(3H)-one (**2a**)*

The reaction of **3a** (50 mg, 0.39 mmol), **4** (260 mg, 1.95 mmol, 5.0 equiv), and the G-H-II catalyst (12.2 mg, 0.0195 mmol, 5 mol %) gave **2a** (43.6 mg, 48 %) as a colorless solid: m.p. 148–150 °C; $[\alpha]_D^{25} = +39.3$ ($c = 0.3$, MeOH); IR (KBr): $\tilde{\nu}_{max} = 3407, 1777, 1623, 1382, 1315, 1276, 1197, 1161, 1134, 1073, 975, 895, 775, 701\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.98$ (d, $J = 7.3$ Hz, 2H), 7.61 (t, $J = 7.4$ Hz, 1H), 7.50 (t, $J = 7.6$ Hz, 2H), 7.40 (dd, $J = 15.4$, 1.7 Hz, 1H), 7.04 (dd, $J = 15.5$, 4.1 Hz, 1H), 5.21 (td, $J = 3.9$, 1.8 Hz, 1H), 4.77 (ddd, $J = 5.3$, 3.9, 1.3 Hz, 1H), 2.88 (dd, $J = 17.7$, 5.5 Hz, 1H), 2.72 (dd, $J = 17.6$, 1.3 Hz, 1H), 1.79 ppm (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 189.9, 174.7, 138.6, 136.7, 133.7, 128.9, 128.8, 127.6, 83.0, 69.4, 38.5$ ppm; HRMS: *m/z*: calcd for $[C_{13}H_{12}O_4+H]^+$: 233.0814; found: 233.0823.

*(4R,5R)-4-tert-Butyldimethylsilyloxy-5-[(E)-3-oxo-3-phenylprop-1-en-1-yl]dihydrofuran-2(3H)-one (**2b**)*

The reaction of **3b** (20 mg, 0.082 mmol), **4** (22 mg, 0.165 mmol, 2.0 equiv), and the G-H-II catalyst (2.6 mg, 0.004 mmol, 5 mol%) gave **2b** (11.7 mg, 41%) as a yellow solid: m.p. 74–76 °C; $[\alpha]_D^{25} = +35.1$ ($c = 0.5$, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max} = 2931, 2858, 1770, 1674, 1629, 1270, 1203, 1158, 1098, 1038, 919, 835, 778, 711\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.99–7.96$ (m, 2H), 7.61–7.56 (m, 1H), 7.51–7.47 (m, 2H), 7.27 (dd, $J = 15.5$, 1.7 Hz, 1H), 6.98 (dd, $J = 15.5$, 4.5 Hz, 1H), 5.14 (td, $J = 4.4$, 1.7 Hz, 1H), 4.69–4.66 (m, 1H), 2.81 (dd, $J = 17.3$, 5.4 Hz, 1H), 2.54 (dd, $J = 17.3$, 2.1 Hz, 1H), 0.81 (s, 9H), 0.06 (s, 3H), 0.04 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 189.2$, 174.6, 139.8, 137.1, 133.2, 128.7, 128.6, 126.9, 83.2, 70.3, 39.2, 25.6, 25.5, 17.9, −5.0, −5.1 ppm; HRMS: *m/z*: calcd for $[C_{19}H_{26}O_4Si+H]^+$: 347.1679; found: 347.1673.

*(4R,5R)-4-Hydroxy-5-[(S,E)-3-hydroxy-3-phenylprop-1-en-1-yl]dihydrofuran-2(3H)-one (**5a**)*

The reaction of **3a** (130 mg, 1.01 mmol), (*S*)-phenylvinyl carbinol **6a** (204 mg, 1.52 mmol, 1.5 equiv), and the G-H-II catalyst (63.3 mg, 0.101 mmol, 10 mol%) gave **5a** (171 mg, 72%) as a colorless soild: m.p. 83–85 °C; $[\alpha]_D^{25} = +6.2$ ($c = 0.5$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}_{max} = 3425$, 2925, 2854, 1777, 1493, 1454, 1405, 1328, 1162, 1076, 1016, 970, 906, 761, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.40–7.29$ (m, 5H), 6.14 (ddd, $J = 15.7$, 5.5, 1.1 Hz, 1H), 5.97 (ddd, $J = 15.7$, 6.3, 1.3 Hz, 1H), 5.27 (d, $J = 5.4$ Hz, 1H), 4.92 (dd, $J = 6.2$, 3.7 Hz, 1H), 4.52 (t, $J = 4.2$ Hz, 1H), 2.94 (br s, 1H, OH), 2.78 (dd, $J = 17.7$, 5.4 Hz, 1H), 2.72 (br s, 1H, OH), 2.62 ppm (dd, $J = 17.7$, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 176.3, 141.7, 137.8, 128.6, 127.9, 126.5, 126.4, 123.3, 84.4, 73.7, 69.8, 38.5 ppm; HRMS: *m/z*: calcd for $[C_{13}H_{14}O_4+Na]^+$: 257.0790; found: 257.0793.

*(4R,5R)-4-(tert-Butyldimethylsilyloxy)-5-[(S,E)-3-hydroxy-3-phenylprop-1-en-1-yl]dihydrofuran-2(3H)-one (**5b**)*

The reaction of **3b** (300 mg, 1.24 mmol), (*S*)-phenylvinylcarbinol **6a** (200 mg, 1.49 mmol, 1.2 equiv), and the G-II catalyst (52.6 mg, 0.062 mmol, 5 mol%) gave **5b** (310 mg, 72%) as colorless solid: m.p. 99–101 °C; $[\alpha]_D^{25} = +8.8$ ($c = 0.4$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}_{max} = 3450$, 2955, 2930, 2858, 1784, 1464, 1259, 1215, 1161, 1096, 1025, 974, 954, 906, 840, 760, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.37–7.27$ (m, 5H), 6.08 (ddd, $J = 15.6$, 5.4, 0.7 Hz, 1H), 5.94 (ddd, $J = 15.6$, 7.3, 1.3 Hz, 1H), 5.29 (d, $J = 5.4$ Hz, 1H), 4.83 (dd, $J = 7.3$, 4.0 Hz, 1H), 4.50–4.47 (m, 1H), 2.72 (dd, $J = 17.2$, 5.4 Hz, 1H), 2.50 (dd, $J = 17.2$, 1.9 Hz, 1H), 1.98 (br s, 1H, OH), 0.87 (s, 9H), 0.06 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 175.3$, 142.0, 138.1, 128.5, 127.8, 126.3, 123.8, 84.7, 73.9, 70.6, 39.4, 25.5, 18.0, −4.96, −5.0 ppm; HRMS: *m/z*: calcd for $[C_{19}H_{28}O_4Si+Na]^+$: 371.1655; found: 371.1662.

*(4R,5R)-5-[(S,E)-3-(tert-Butyldimethylsilyloxy)-3-phenylprop-1-en-1yl]-4-hydroxydihydrofuran-2(3H)-one (**5c**)*

The reaction of **3a** (20 mg, 0.156 mmol), **6b** (46 mg, 0.187 mmol, 1.2 equiv), and the G-H-II catalyst (4.9 mg, 0.0078 mmol, 5 mol%) gave **5c** (9.8 mg, 18%) as colorless oil. $[\alpha]_D^{25} = -20.1$ ($c = 0.2$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}_{max} = 3465$, 2929, 2857, 1773, 1638, 1472, 1258, 1163, 1118, 1017, 907, 877, 838, 760, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.38–7.26 (m, 5H), 6.15 (ddd, $J = 15.5$, 4.8, 1.1 Hz, 1H), 5.91 (ddd, $J =$ 15.5, 6.3, 1.5 Hz, 1H), 5.32 (d, $J = 4.8$ Hz, 1H), 4.94–4.92 (m, 1H), 4.50 (td, $J = 4.5$, 1.1 Hz, 1H), 2.78 (dd, $J = 17.6$, 5.4 Hz, 1H), 2.63 (dd, $J =$ 17.6, 1.2 Hz, 1H), 1.98 (br s, 1H, OH), 0.94 (s, 9H), 0.10 (s, 3H), −0.01 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 175.1$, 142.7, 140.5, 128.4, 127.5, 125.9, 120.1, 83.7, 74.3, 69.6, 38.6, 25.8, 18.3, −4.8, −4.9 ppm; HRMS: *m/z*: calcd for $[C_{19}H_{28}O_4Si+Na]^+$: 371.1655; found: 371.1664.

*(4R,5R)-4-(tert-Butyldimethylsilyloxy)-5-[(S,E)-3-(tert-butyldimethylsilyloxy)-3-phenylprop-1-en-1-yl]dihydrofuran-2(3H)-one (**5d**)*

The reaction of **3b** (30 mg, 0.124 mmol), **6b** (46 mg, 0.185 mmol, 1.5 equiv), and the G-H-II catalyst (3.9 mg, 0.0062 mmol, 5 mol%) gave **5d** (16 mg, 28%) as colorless oil. $[\alpha]_D^{25} = -44.1$ ($c = 0.4$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}_{max} = 3028$, 2956, 2930, 2887, 2858, 1790, 1464, 1472, 1362, 1258, 1204, 1159, 1121, 1026, 973, 952, 905, 880, 838, 776, 758, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.31–7.22$ (m, 5H), 5.97–5.96 (m, 2H), 5.25 (d, $J = 2.5$ Hz, 1H), 4.75 (dd, $J = 7.1$, 3.9 Hz, 1H), 4.43–4.40 (m, 1H), 2.71 (dd, $J = 17.2$, 5.2 Hz, 1H), 2.46 (dd, $J = 17.2$, 1.7 Hz, 1H), 0.90 (s, 9H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), −0.06 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 175.3$, 143.0, 140.3, 128.2, 127.2, 126.0, 121.1, 85.2, 74.3, 70.8, 39.5, 25.8, 25.7, 18.2, 18.0, −4.9, −4.94, −5.0 ppm; HRMS: *m/z*: calcd for $[C_{25}H_{42}O_4Si_2+Na]^+$: 485.2519; found: 485.2511.

*(4R,5R)-4-Hydroxy-5-(3-oxo-3-phenylpropyl)dihydrofuran-2(3H)-one (**8**):*

$BH_3{\cdot}Me_2S$ (0.05 mL, 0.516 mmol, 1.2 equiv) was added to a stirred solution of (*R*)-2-methyl-CBS-oxazaborolidine (1.0 M solution in toluene, 0.52 mL, 0.52 mmol, 1.2 equiv) in anhydrous THF (15 mL) at 0 °C. After stirring for 30 min, the solution was cooled to −20 °C and a solution of **2a** (100 mg, 0.43 mmol) in anhydrous THF (5 mL) was added dropwise over 10 min. The reaction mixture was warmed to 0 °C over 1 h and then quenched with MeOH (1 mL). The solution was stirred for 15 min at room temperature and concentrated. The residue was purified by chromatography on a silica gel column with petroleum ether/EtOAc (1:1) as eluent to afford **8** (92.8 mg, 92%) as colorless solid: m.p. 121–123 °C; $[\alpha]_D^{25} = +52.9$ ($c = 0.75$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}_{max} = 3398$, 2929, 2857, 1770, 1679, 1598, 1449, 1407, 1203, 1161, 1079, 1025, 982, 883, 756, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.97$ (d, $J = 8.1$ Hz, 2H), 7.61–7.58 (m, 1H), 7.50–7.46 (m, 2H), 4.47–4.39 (m, 2H), 3.32 (dt, $J =$ 18.5, 6.0 Hz, 1H), 3.25–3.16 (m, 1H), 2.78 (dd, $J = 17.7$, 5.4 Hz, 1H), 2.60 (d, $J = 17.6$ Hz, 1H), 2.40–2.31 (m, 1H), 2.27–2.17 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 200.2$, 175.8, 136.2, 133.7, 128.7, 128.1, 84.5, 68.6, 39.0, 34.4, 22.0 ppm; HRMS: *m/z*: calcd for $[C_{13}H_{14}O_4+H]^+$: 235.0970; found: 235.0979.

*(4R,5R)-4-(tert-Butyldimethylsilyloxy)-5-[(1S,2S)-1,2-dihydroxy-3-oxo-3-phenylpropyl]dihydrofuran-2(3H)-one (**9a**) and (4R,5R)-4-(tert-butyldimethylsilyloxy)-5-[(1R,2R)-1,2-dihydroxy-3-oxo-3-phenylpropyl]dihydrofuran-2(3H)-one (**9b**)*

$K_2OsO_4{\cdot}2H_2O$ (0.53 mg, 0.00145 mmol, 0.5 mol%) was added to a mixture of $K_3Fe(CN)_6$ (334 mg, 1.015 mmol, 3.5 equiv), K_2CO_3 (140 mg, 1.015 mmol, 3.5 equiv) and $(DHQD)_2PHAL$ (2.5 mg, 0.0032 mmol, 1.1 mol%) in *t*BuOH-H_2O (1:1, 4 mL) cooled at 0 °C followed by methanesulfonamide (30.3 mg, 0.32 mmol, 1.1 equiv). After stirring for 5 min at 0 °C, **2b** (100 mg, 0.29 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid Na_2SO_3. The stirring was continued for an additional 45 min and the solution was extracted with EtOAc (5×10 mL). The combined organic phases were washed with KOH (2 N), water, brine, then dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on a silica gel column with petroleum ether/EtOAc (4:1) as eluent to give **9b** (52 mg, 47%) as a white solid. Further elution gave **9a** (17 mg, 16%) as a colorless oil. Data for **9a**: $[\alpha]_D^{25} = +18.7$ ($c = 0.7$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}_{max} = 3456$, 2950, 2931, 2859, 1790, 1689, 1599, 1472, 1409, 1264, 1210, 1162, 1126, 1087, 1030, 981, 947, 840, 779, 745, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.97–7.95$ (m, 2H), 7.65–7.61 (m, 1H), 7.49 (t, $J = 7.8$ Hz, 2H), 5.21–5.20 (m, 1H), 4.83–4.80 (m, 1H), 4.64 (dd, $J = 6.6$, 4.2 Hz, 1H), 4.49 (dd, $J = 6.6$, 3.0 Hz, 1H), 4.07 (br s, 1H, OH), 2.80 (dd, $J = 17.5$, 5.5 Hz, 1H), 2.57 (dd, $J = 17.5$, 2.0 Hz, 1H), 1.71 (br s, 1H, OH), 0.96 (s, 9H), 0.20 (s, 3H), 0.19 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.6$, 174.2, 134.1, 133.7, 128.8, 128.6, 128.56, 84.5, 73.2, 71.6, 69.5, 39.7, 25.7, 25.3, 17.9, −4.3, −4.6 ppm; HRMS: *m/z*: calcd for $[C_{19}H_{28}O_6Si+H]^+$: 381.1733; found: 381.1732. Data for **9b**: m.p. 136–138 °C; $[\alpha]_D^{25} = -19.4$ ($c = 0.6$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}_{max} = 3368$, 2930, 2857, 1795, 1693, 1407, 1267, 1200, 1146, 1113, 1091, 1040, 983, 874, 839, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.94–7.92$ (m, 2H), 7.65–7.61 (m, 1H), 7.51 (t, $J = 7.7$ Hz, 2H), 5.37 (d, $J = 3.9$ Hz, 1H), 4.58 (dd, $J = 4.2$, 3.0 Hz, 1H), 4.46–4.38 (m, 2H), 4.11 (br s, 1H, OH), 2.78 (dd, $J = 17.2$, 4.7 Hz, 1H), 2.50 (d, $J = 17.2$ Hz, 1H), 2.26 (br s, 1H, OH), 0.67 (s, 9H), 0.04 (s, 3H), −0.10 ppm (s, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ = 199.6, 175.0, 134.2, 132.9, 129.0, 128.6, 82.5, 73.2, 68.6, 68.5, 39.9, 25.3, 17.7, −4.8, −5.7 ppm; HRMS: *m/z*: calcd for $[C_{19}H_{28}O_6Si+H]^+$: 381.1733; found: 381.1726.

*Dihydroxylation of **2b** Under Upjohn Conditions[17] to give **9a** and **9b***

NMO (16.9 mg, 0.144 mmol, 2.0 equiv) and $K_2OsO_4{\cdot}2H_2O$ (1.33 mg, 0.0036 mmol, 5 mol%) were added to a solution of **2b** (25 mg, 0.072 mmol) in acetone/water (4:1, 2 mL) at room temperature and stirred for 24 h. The mixture was then quenched with solid Na_2SO_3 and stirred for 1 h. Water was added and the solution was extracted with EtOAc (3×10 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on a silica gel column with petroleum ether/EtOAc (3:1) as eluent to afford a mixture of **9a** and **9b** (15.6 mg, 57%) as waxy solid. Analysis of this mixture by ^{1}H NMR spectroscopy indicated **9a**/**9b** = 1:10.

*(4R,5R)-4-(tert-Butyldimethylsilyloxy)-5-[(1S,2R,3R)-1,2,3-trihydroxy-3 phenylpropyl]dihydrofuran-2(3H)-one (**10a**)*

Cerium chloride heptahydrate (30 mg, 0.079 mmol, 1.2 equiv) was added to a stirred solution of **9a** (25 mg, 0.066 mmol) in methanol (2 mL) at room temperature and then cooled to −78 °C. Sodium borohydride (3.0 mg, 0.079 mmol, 1.2 equiv) was added in one portion and stirred for 30 min. After warming to room temperature, the reaction was quenched with water (3 mL) and extracted with EtOAc (3×5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on a silica gel column with petroleum ether/EtOAc (1:1) as eluent to give **10a** (22.6 mg, 90%) as a white solid: m.p. 110–112 °C; $[\alpha]_D^{25} = -12.4$ (c = 0.3, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3447, 3019, 2930, 2857, 1778, 1464, 1258, 1216, 1164, 1097, 1027, 947, 915, 840, 806, 760, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.30 (m, 5H), 4.94 (d, J = 5.0 Hz, 1H), 4.56–4.50 (m, 1H), 4.49 (t, J = 4.9 Hz, 1H), 4.25 (dd, J = 5.2, 2.4 Hz, 1H), 3.83 (d, J = 3.2 Hz, 1H), 3.43 (br s, 1H, OH), 3.22 (br s, 1H, OH), 2.85 (br s, 1H, OH), 2.70 (dd, J = 17.3, 5.8 Hz, 1H), 2.53 (dd, J = 17.3, 2.8 Hz, 1H), 0.80 (s, 9H), 0.05 (s, 3H), 0.03 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6, 140.4, 128.7, 128.1, 126.3, 84.3, 75.9, 73.4, 69.3, 69.2, 39.2, 25.5, 17.7, −4.6, −5.0 ppm; HRMS: *m/z*: calcd for $[C_{19}H_{30}O_6Si+H]^+$: 383.1890; found: 383.1895.

*(4R,5R)-4-(tert-Butyldimethylsilyloxy)-5-[(1R,2S,3S)-1,2,3-trihydroxy-3-phenylpropyl]dihydrofuran-2(3H)-one (**10b**)*

The title compound was prepared from **9b** (55 mg, 0.145 mmol) by a similar procedure as described for **10a**, to give **10b** (50.3 mg, 91%) as a white solid: m.p. 114–115 °C; $[\alpha]_D^{25} = +25.0$ (c = 1.0, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3432, 2930, 2858, 1775, 1411, 1255, 1208, 1161, 1092, 1039, 954, 906, 839, 779, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 5H), 5.05 (d, J = 4.5 Hz, 1H), 4.53 (t, J = 3.7 Hz, 1H), 4.36 (dd, J = 9.3, 3.3 Hz, 1H), 4.13 (d, J = 8.4 Hz, 1H), 3.96 (d, J = 3.8 Hz, 1H), 3.14 (br s, 2H, OH), 2.97 (br s, 1H, OH), 2.64 (dd, J = 17.3, 4.9 Hz, 1H), 2.36 (d, J = 17.3 Hz, 1H), 0.80 (s, 9H), 0.06 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.7, 140.0, 128.6, 127.8, 125.8, 81.9, 77.1, 72.7, 68.5, 66.7, 39.7, 25.5, 25.47, 17.8, −4.9, −5.3 ppm; HRMS: *m/z*: calcd for $[C_{19}H_{30}O_6Si+H]^+$: 383.1890; found: 383.1893.

*(4R,5S)-4-Hydroxy-5-[(1S,2R,3R)-1,2,3-trihydroxy-3-phenylpropyl]dihydrofuran-2(3H)-one, (+)-cardiobutanolide (**1**)*

Amberlyst 15 resin (10 mg) was added to a stirred solution of **10a** (13 mg, 0.034 mmol) in anhydrous MeCN (2 mL) at 0 °C. The reaction was then warmed to room temperature and stirred for 12 h. The mixture was filtered through a small pad of celite and washed with EtOAc (30 mL). The filtrate was concentrated to give virtually pure **1** (9.1 mg, quant) as a colorless solid: m.p. 190–191 °C; $[\alpha]_D^{25} = +7.6$ (c = 0.2, MeOH), lit.[1] m.p. 189–190 °C, $[\alpha]_D^{24} = +6.4$ (c = 0.28, MeOH); IR (KBr): $\tilde{\nu}_{max}$ = 3517, 3478, 3377, 2925, 2853, 1759, 1638, 1455, 1373, 1275, 1209, 1169, 1106, 1078, 1056, 1028, 1012, 986, 917, 858, 790, 774, 774, 702 cm^{-1}; ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 7.45 (d, J = 7.0 Hz, 2H), 7.30 (t, J = 7.3 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 4.79 (d, J = 7.2 Hz, 1H), 4.60 (t, J = 4.1 Hz, 1H), 4.56 (dd, J = 7.8, 3.5 Hz, 1H), 4.39 (d, J = 7.7 Hz, 1H), 3.90 (d, J = 6.9 Hz, 1H), 2.85 (dd, J = 17.2, 5.2 Hz, 1H), 2.37 ppm (dd, J = 17.2, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, [D$_6$]acetone); δ = 176.3, 144.2, 128.6, 127.9, 127.8, 86.7, 75.3, 74.0, 70.1, 68.5, 40.4 ppm; HRMS: *m/z*: calcd for $[C_{13}H_{16}O_6+Na]^+$: 291.0845; found: 291.0851.

*(4R,5S)-4-Hydroxy-5-[(1R,2S,3S)-1,2,3-trihydroxy-3-phenylpropyl]dihydrofuran-2(3H)-one (**11**)*

The title compound was prepared from **10b** (50 mg, 0.13 mmol) by a similar procedure as described for **1**, to give **11** (35 mg, quant) as a white solid: m.p. 155–156 °C; $[\alpha]_D^{25} = +47.4$ (c = 0.5, MeOH); IR (KBr): $\tilde{\nu}_{max}$ = 3427, 2925, 2854, 1757, 1605, 1443, 1336, 1295, 1233, 1171, 1109, 1011, 906, 768, 705 cm^{-1}; ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 7.44 (d, J = 7.2 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2H), 7.24–7.21 (m, 1H), 4.80 (d, J = 7.6 Hz, 1H), 4.79 (s, 1H, OH), 4.64 (dd, J = 4.8, 3.4 Hz, 1H), 4.51 (br s, 1H, OH), 4.47 (dd, J = 9.4, 3.2 Hz, 1H), 4.41–4.37 (m, 1H), 4.20 (br s, 1H, OH), 3.90–3.86 (br d, 1H, OH), 3.74 (d, J = 7.3 Hz, 1H), 2.88 (dd, J = 17.3, 5.2 Hz, 1H), 2.35 ppm (d, J = 17.3 Hz, 1H); ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 176.3, 144.3, 128.7, 127.8, 82.7, 75.2, 74.6, 68.6, 67.7, 39.6 ppm; HRMS: *m/z*: calcd for $[C_{13}H_{16}O_6+Na]^+$: 291.0845; found: 291.0834.

*Sharpless Asymmetric Dihydroxylation of **5b** to afford **9a** and **9b***

$K_2OsO_4{\cdot}2H_2O$ (0.126 mg, 0.000344 mmol, 0.4 mol%) was added to a mixture of $K_3Fe(CN)_6$ (85.6 mg, 0.26 mmol, 3.0 equiv), K_2CO_3 (35.9 mg, 0.26 mmol, 3.0 equiv) and $(DHQD)_2PHAL$ (0.67 mg, 0.00086 mmol, 1 mol%) in *t*BuOH/H_2O (1:1, 2 mL), cooled at 0 °C followed by methanesulfonamide (8.2 mg, 0.086 mmol, 1.0 equiv). After stirring for 5 min at 0 °C, **5b** (30 mg, 0.086 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 12 h and then quenched with solid Na_2SO_3. The stirring was continued for an additional 45 min and the solution extracted with EtOAc (5×10 mL). The combined organic phases were washed with KOH (2 N), water and brine, then dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on a silica gel column with petroleum ether/EtOAc (4:1) as eluent to give **9b** (21.3 mg, 65%) as a colorless solid. Further elution gave **9a** (6.9 mg, 21%) as a colorless oil. **9a**: $[\alpha]_D^{25} = +18.4$ (c = 0.2, $CHCl_3$); **9b**: $[\alpha]_D^{25} = -19.0$ (c = 0.4, $CHCl_3$).

*Dihydroxylation of **5b** under Upjohn Conditions[17] to give **9a** and **9b***

NMO (20.2 mg, 0.172 mmol, 2.0 equiv) and $K_2OsO_4{\cdot}2H_2O$ (1.6 mg, 0.0043 mmol, 5 mol%) were added to a solution of **5b** (30 mg, 0.086 mmol) in acetone/water (4:1, 1.2 mL) at room temperature and stirred for 12 h. The mixture was then quenched with solid Na_2SO_3 and stirred for 1 h. Water was added and the solution extracted with EtOAc (3×10 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on a silica gel column with petroleum ether/EtOAc (3:1) as eluent to afford a mixture of **9a** and **9b** (16.7 mg, 51%) as a waxy solid. Analysis of this mixture by ^{1}H NMR spectroscopy indicated **9a**/**9b** = 1:7.

*Sharpless Dihydroxylation of (±)-**6a***

$K_2OsO_4{\cdot}2H_2O$ (1.1 mg, 0.003 mmol, 0.4 mol%) was added to a mixture of $K_3Fe(CN)_6$ (736 mg, 2.235 mmol, 3.0 equiv), K_2CO_3 (309 mg, 2.235 mmol, 3.0 equiv) and $(DHQD)_2PHAL$ (5.8 mg, 0.00745 mmol, 1 mol%) in *t*BuOH-H_2O (1:1, 8 mL) cooled at 0 °C followed by methanesulfonamide (71 mg, 0.745 mmol, 1.0 equiv). After stirring for 5 min at 0 °C, (±)-**6a** (100 mg, 0.745 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 12 h and then quenched with solid Na_2SO_3. The stirring was continued for an additional 45 min and the solution extracted with EtOAc (5×10 mL). The combined organic phases were washed with KOH (2 N), water, and brine, then dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on a silica gel column with petroleum ether/EtOAc (1:1) as eluent to give (−)-**12**[21] (46 mg, 37%) as a colorless solid and further elution provided **13**[22] (45 mg, 36%) as a colorless oil. Data for (−)-**12**:[21] Mp 80–82 °C; $[\alpha]_D^{25} = -33.6$ (c = 0.4, CH_2Cl_2) lit.[21] for (*R*)-enantiomer, $[\alpha]_D^{23} = +72.1$ (c = 8.0, CH_2Cl_2); IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3447, 3066, 2928, 2884, 1686, 1597, 1580,

1450, 1401, 1319, 1264, 1229, 1182, 1118, 1603, 1002, 978, 962, 885, 847, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.95$ (d, $J = 7.3$ Hz, 2H), 7.64 (t, $J = 7.4$ Hz, 1H), 7.54 (t, $J = 7.7$ Hz, 2H), 5.21–5.15 (m, 1H), 4.04 (s, 1H, OH), 4.02 (d, $J = 10.2$ Hz, 1H), 3.77 (dd, $J = 11.6$, 4.2 Hz, 1H), 2.22 ppm (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 199.4$, 134.3, 133.4, 129.0, 128.5, 74.6, 65.3 ppm. Data for **13**:[22] IR ($CHCl_3$): $\tilde{\nu}_{max} =$ 3401, 1647, 1456, 1316, 1217, 1154, 1106, 1031, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): mixture of diastereomers (ca. 1:1), $\delta = 7.30$–7.25 (m, 10H), 4.78 (d, $J = 4.1$ Hz, 1H), 4.58 (d, $J = 6.9$ Hz, 1H), 4.18 (br s, 1H, O*H*), 3.95 (br s, 2H, OH), 3.74 (br d, 3H), 3.64–3.60 (m, 3H), 3.56–3.36 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): mixture of diastereomers (ca. 1:1), $\delta = 140.5$, 140.4, 128.4, 128.3, 128.0, 127.6, 126.7, 126.3, 76.0, 75.2, 74.9, 74.6, 63.0, 62.5 ppm.

*(4R,5R)-4-(tert-Butyldimethylsilyloxy)-5-[(1S,2S,3R)-3-(tert-butyldimethylsilyloxy)-1,2-dihydroxy-3-phenylpropyl]dihydrofuran-2(3H)-one (**14a**) and (4R,5R)-4-(tert-butyldimethylsilyloxy)-5-[(1R,2R,3R)-3-(tert-butyldimethylsilyloxy)-1,2-dihydroxy-3-phenylpropyl]dihydrofuran-2(3H)-one (**14b**)*

$K_2OsO_4.2H_2O$ (0.55 mg, 0.0015 mmol, 1.0 mol%) was added to a mixture of $K_3Fe(CN)_6$ (300 mg, 0.907 mmol, 6.0 equiv), K_2CO_3 (126 mg, 0.907 mmol, 6.0 equiv) and $(DHQD)_2PHAL$ (4.7 mg, 0.006 mmol, 4.0 mol%) in *t*BuOH/H_2O (1:1, 2 mL) cooled at 0 °C, followed by methanesulfonamide (14 mg, 0.15 mmol, 1.0 equiv). After stirring for 5 min at 0 °C, the solution of **5d** (70 mg, 0.15 mmol) in *t*BuOH (1 mL) was added in one portion. The reaction mixture was stirred at 0 °C for 48 h and then quenched with solid Na_2SO_3. The stirring was continued for an additional 45 min and the solution extracted with EtOAc (5×10 mL). The combined organic phases were washed with KOH (2N), water, and brine, then dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on a silica gel column with petroleum ether/EtOAc (5:1) as eluent to give **14b** (28 mg, 37%) as colorless oil. Further elution with petroleum ether/EtOAc (4:1) gave **14c** (5.2 mg, 7%) as colorless oil. Elution then with petroleum ether/EtOAc (7:3) gave **14a** (23.3 g, 31%) as a colorless oil. Data for **14a**: $[\alpha]_D^{25} = -40.5$ ($c = 0.4$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}_{max} = 3461$, 3020, 2957, 2931, 2859, 1779, 1472, 1405, 1388, 1362, 1258, 1216, 1163, 1097, 1061, 1023, 948, 860, 839, 806, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.40$–7.27 (m, 5H), 4.85 (d, $J = 6.6$ Hz, 1H), 4.57–4.50 (m, 1H), 4.47–4.45 (m, 1H), 4.41 (dd, $J = 5.8$, 1.6 Hz, 1H), 3.72–3.67 (m, 1H), 3.06 (br s, 1H, OH), 2.67 (dd, $J = 17.2$, 5.8 Hz, 1H), 2.56 (dd, $J = 17.2$, 3.3 Hz, 1H), 2.27 (br s, 1H, OH), 0.85 (s, 9H), 0.84 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), −0.16 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.6$, 141.3, 128.5, 128.0, 127.0, 85.5, 76.6, 74.9, 69.0, 67.8, 39.2, 25.8, 25.7, 18.1, 17.8, −4.6, −4.8, −4.81, −5.1 ppm; HRMS: *m*/*z*: calcd for $[C_{25}H_{44}O_6Si_2+Na]^+$: 519.2574; found: 519.2570. Data for **14b**: $[\alpha]_D^{25} = -28.0$ ($c = 0.5$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}_{max} = 3480$, 3022, 2955, 2931, 2859, 1790, 1472, 1363, 1258, 1162, 1090, 1036, 953, 839, 809, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.34$–7.28 (m, 5H), 4.79 (d, $J = 7.9$ Hz, 1H), 4.56–4.54 (m, 1H), 4.33 (dd, $J = 9.3$, 3.3 Hz, 1H), 3.84 (d, $J = 7.8$ Hz, 1H), 3.68 (t, $J = 8.8$ Hz, 1H), 3.00 (s, 1H, OH), 2.65 (dd, $J = 17.2$, 4.8 Hz, 1H), 2.38 (d, $J = 17.2$ Hz, 1H), 2.36 (s, 1H, OH), 0.89 (s, 9H), 0.78 (s, 9H), 0.05 (s, 3H), 0.04 (s, 6H), −0.22 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 175.1$, 140.1, 128.4, 128.1, 127.1, 82.4, 76.4, 75.0, 68.6, 65.8, 39.8, 25.7, 25.5, 18.0, 17.8, −4.5, −4.9, −5.2 −5.4 ppm; HRMS: *m*/*z*: calcd for $[C_{25}H_{44}O_6Si_2+Na]^+$ 519.2574; found: 519.2568. Data for **14c**: $[\alpha]_D^{25} = -3.6$ ($c = 0.5$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}_{max} = 3436$, 3019, 2930, 2957, 1788, 1650, 1464, 1260, 1100, 1048, 839, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.39$–7.29 (m, 5H), 5.44 (d, $J = 2.3$ Hz, 1H), 5.23 (d, $J = 2.9$ Hz, 1H), 5.07 (t, $J = 4.1$ Hz, 1H), 4.80 (d, $J = 3.9$ Hz, 1H), 4.28 (s, 1H), 3.89 (t, $J = 2.8$ Hz, 1H), 2.75 (dd, $J = 18.6$, 5.3 Hz, 2H), 0.89 (s, 18H), 0.12 (s, 6H), −0.01 (s, 3H), −0.03 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 175.5$, 139.4, 128.7, 128.2, 125.9, 87.6, 82.5, 77.2, 75.9, 74.2, 36.2, 25.5, 18.1, −5.1, −5.4 ppm; HRMS: *m*/*z*: calcd for $[C_{25}H_{44}O_6Si_2+Na]^+$: 519.2574; found: 519.2565.

*(4R,5S)-4-Hydroxy-5-[(1R,2S,3R)-1,2,3-trihydroxy-3-phenylpropyl]dihydrofuran-2(3H)-one (**15**)*

The title compound was prepared from **14b** (45 mg, 0.0906 mmol) by a similar procedure as described for **1** to give **15** (24.2 mg, quant) as white solid: m.p. 168–170 °C; $[\alpha]_D^{25} = +5.4$ ($c = 0.5$, MeOH); IR (KBr): $\tilde{\nu}_{max} = 3452$, 3022, 2926, 2854, 1773, 1652, 1458, 1262, 1122, 1028, 908 cm^{-1}; ^1H NMR (400 MHz, [D_6]acetone): $\delta = 7.44$ (d, $J = 7.1$ Hz, 2H), 7.32 (t, $J = 7.4$ Hz, 2H), 7.25 (t, $J = 7.3$ Hz, 1H), 4.87 (d, $J = 7.2$ Hz, 1H), 4.62 (d, $J = 4.0$ Hz, 1H), 4.58 (br s, 1H, OH), 4.48 (dd, $J = 9.0$, 3.4 Hz, 1H), 4.32 (br s, 1H, OH), 4.04 (br s, 2H, OH), 3.79–3.72 (m, 2H), 2.88–2.84 (m, overlapped by residual water, 1H), 2.30 ppm (d, $J = 17.3$ Hz, 1H); ^{13}C NMR (100 MHz, [D_6]acetone): $\delta = 176.0$, 142.9, 128.9, 128.2, 127.9, 82.7, 75.72, 75.7, 68.6, 68.5, 39.6 ppm; HRMS: *m*/*z*: calcd for $[C_{13}H_{16}O_6+Na]^+$: 291.0845; found: 291.0852.

*Synthesis of **1** by Dihydroxylation of **5a***

NMO (30 mg, 0.256 mmol, 2.0 equiv) and $K_2OsO_4{\cdot}2H_2O$ (2.36 mg, 0.0064 mmol, 5 mol%) were added to a solution of olefin **5a** (30 mg, 0.128 mmol) in acetone/water (4:1, 2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 14 h. The mixture was then quenched with solid Na_2SO_3 and stirred for 1 h. Water was added and the solution extracted with EtOAc (3×10 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on a silica gel column with petroleum ether/EtOAc (1:4) as eluent to give (+)-cardiobutanolide **1** (21 mg, 61%) as a white solid: m.p. 190–191 °C; $[\alpha]_D^{25} = +7.7$ ($c = 0.5$, MeOH). Further elution gave the diastereomer **15** (5.1 mg, 15%) as white solid: m.p. 168–170 °C; $[\alpha]_D^{25} = +5.6$ ($c = 0.3$, MeOH).

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[23] A provisional process patent on this work has been filed, application no. 1780/MUM/2012.

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