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Asymmetric synthesis of (+)-cardiobutanolide

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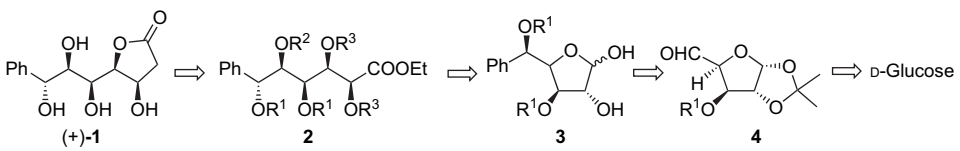
Abstract—A formal total synthesis of (+)-cardiobutanolide has been accomplished from D-glucose, a readily available precursor.

1. Introduction

(+)-Cardiobutanolide **1**, a γ-lactone was isolated in 2003 from *Goniothalamus cardiopetalus* of the family Annonaceae.[1] The related natural products isolated from the same tree have been used as a traditional medicine in Asia to treat rheumatism, edema, and as a mosquito repellent. Because of the structural complexity of having five contiguous chiral centers in the molecule and potential pharmacological activity, (+)-cardiobutanolide **1** has recently attracted the attention of synthetic organic chemists. Two syntheses of the molecule involving chiral starting materials have already appeared in the literature.[2] While this manuscript was in preparation, a third synthesis appeared employing a chiron strategy.[3] For the last several years, we were involved in the synthesis of bioactive natural products having lactone as a sub-unit using sugars as cheap starting materials.[4] In this paper, we report our approach for asymmetric synthesis of (+)-cardiobutanolide **1**.

The retrosynthetic analysis of (+)-**1** is shown in Scheme 1. It was conceived that the five-membered lactone ring can be constructed after Arndt–Eistert homologation of an ester **2**, which can be synthesized from a hemiacetal **3**. The requisite chirality at the 7-carbon of (+)-**1** in the side chain of **3** would be created by a diastereoselective addition of PhMgX to the corresponding aldehyde **4**, which in turn, could be derived from D-glucose. The chirality at the 5- and 6-carbon atoms in the natural product would be directly translated from D-glucose. The other two chiral centers at 3- and 4-carbon atoms would be created by Sharpless asymmetric dihydroxylation reaction.

The synthesis of (+)-cardiobutanolide **1** involved 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylopentodialdo-1,4-furanose **5**, which was readily synthesized from D-glucose using a literature procedure.[5] The diastereoselective addition of PhMgBr to the aldehyde **5** resulted in the unwanted chelation controlled product **6a** and the desired C-5 epimer **6b** in a ratio of 12:1 (Scheme 2). The diastereomeric ratio could be improved by subjecting the mixture to an oxidation (PDC)–reduction ($NaBH_4$) sequence to obtain the desired isomer **6b** in a ratio of 10:1, which could be separated by column chromatography resulting in the pure **6b**. After protecting the benzylic hydroxyl group as a benzyl ether, the acetonide of **7** was hydrolyzed with dilute sulfuric acid in dioxane to provide a hemiacetal whose diol was oxidatively cleaved with $NaIO_4$ to give an aldehyde **8** that was directly subjected to Wittig olefination reaction with a stabilized ylide ($Ph_3P{=}CHCO_2Et$). This gave an inseparable mixture of α,β-unsaturated ester **9** in favor of *E*-isomer (*E*/*Z* ratio=3:1). Our strategy required that the olefination product **9** should have trans geometry for the subsequent incorporation of chiral diol via Sharpless asymmetric dihydroxylation.



Scheme 1. Retrosynthetic analysis.

Keywords: Cardiobutanolide; Asymmetric dihydroxylation; Lactone; D-Glucose.
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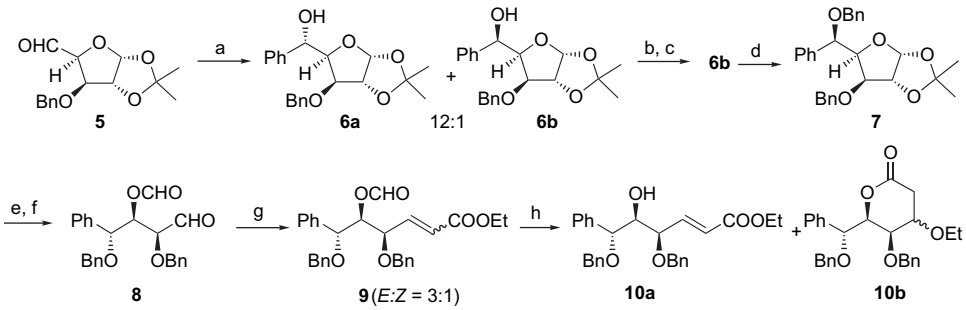


Scheme 2. Reagents and conditions: (a) PhMgBr, THF, 0 °C–rt, 30 min (90%); (b) PDC, CH_2Cl_2, 4 Å MS, catalytic amount of CH_3CO_2H, 6 h (82%); (c) $NaBH_4$, MeOH, 0 °C–rt, 4 h (98%), dr=10:1; (d) NaH, BnBr, TBAI, THF, 0 °C–rt, 2 h (98%); (e) 0.4% H_2SO_4, dioxane, 100 °C, 6 h (80%); (f) $NaIO_4$, H_2O/MeOH, 98%; (g) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 2 h, 98%; (h) K_2CO_3, EtOH, 0 °C–rt (96%).

Keeping this in mind, we envisaged that the cis-isomer of the α,β-unsaturated ester, on exposure to K_2CO_3/EtOH, would provide **10b** after deprotection of the formate ester and lactonization followed by 1,4-addition of an ethoxide group. Under the above basic conditions, the trans-isomer of **9**, after deprotection of the formyl group, would remain as hydroxyl ester **10a** as it would not lactonize because of the geometrical constraint.[6] This was indeed the case. The required *trans*-ester **10a** could be obtained in pure form using the above protocol (Scheme 2). The δ-hydroxyl group of **10a** was protected as the corresponding TIPS ether that was subjected to Sharpless asymmetric dihydroxylation using AD-mix β (Scheme 3). The desired diol **11** was obtained in 94% yield with a ratio of 4:1. The minor isomer could be separated after the formation of acetonide ester **12**. Conversion of **12** to **14** was carried out using the Arndt–Eistert homologation protocol.[7] Thus, the ester **12** was hydrolyzed with LiOH in aqueous methanol to obtain carboxylic acid that was converted into α-diazoketone **13** via reaction of diazomethane with the mixed anhydride. Wolff rearrangement of the **13** using silver benzoate afforded the homologated ester **14** in 68% yield. Exposure of the **14** to TFA/H_2O (10:1) resulted in deprotection of the TIPS ether as well as acetonide with in situ lactonization to give **15** as a clean product (Scheme 3). Since the conversion of **15** into the natural product (+)-**1** has recently been carried out,[3] we stopped our synthesis at this stage.

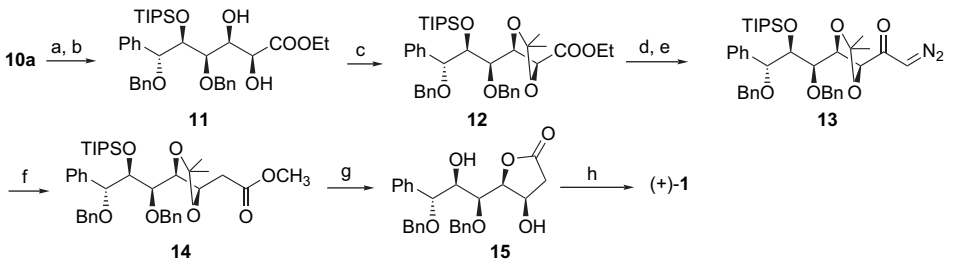
In conclusion, we have achieved a formal total synthesis of (+)-cardiobutanolide **1** from D-glucose, which is a readily available starting material. The key steps in the synthesis are Sharpless asymmetric dihydroxylation, Arndt–Eistert homologation, and lactonization reactions.

2. Experimental

2.1. General methods

Chemicals were purchased and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA400 spectrometer. All chemical shifts are quoted on the δ scale, TMS as internal standard, and coupling constants are reported in hertz. Routine monitoring of reactions were performed by TLC, and using 0.2 mm Kieselgel 60 F_{254} precoated aluminum sheets, commercially available from Merck. Visualization was done by fluorescence quenching at 254 nm, by exposure to iodine vapor. All the column chromatographic separations were done by using silica gel (Acme's, 60–120 mesh). Petroleum ether used was of boiling range 60–80 °C. Reactions that needed anhydrous conditions were run under an atmosphere of nitrogen or argon using flame-dried glassware. The organic extracts were dried over *anhydrous* sodium sulfate. Evaporations of solvents were performed at reduced pressure. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen. Dichloromethane was distilled from CaH_2. AD-mix β and $(DHQD)_2PHAL$ were purchased from Aldrich. $MeSO_2NH_2$, CSA, and 2,2-dimethoxypropane were obtained from Lancaster.

2.1.1. 3-*O*-Benzyl-1,2-*O*-isopropylidene-5-*C*-phenyl-α-L-idopentofuranose (6a and 6b). To a solution of α-D-pentodialdose **5** (8.89 g, 32.0 mmol) in *anhydrous* THF (160.0 mL), PhMgBr (48.0 mL, 1 M soln in THF, 48.0 mmol) was added under an N_2 atmosphere at 0 °C and stirred at room temperature for 12 h. The reaction mixture was quenched with saturated NH_4Cl and extracted with



Scheme 3. Reagents and conditions: (a) TIPSOTf, 2,6-lutidine, DCM, 0 °C–rt (98%); (b) AD-mix β, $(DHQD)_2PHAL$, $MeSO_2NH_2$, *t*-BuOH/H_2O, 0 °C, 24 h (94%), dr 4:1; (c) 2,2-dimethoxy propane, CSA, DCM, 0 °C–rt, 2 h (91%); (d) LiOH·H_2O, MeOH/H_2O (4:1) (91%); (e) Et_3N, ClCOOEt, CH_2N_2, THF, 0 °C–rt (60%); (f) PhCOOAg, Et_3N, MeOH, 2 h (68%); (g) TFA/H_2O (10:1), DCM, 24 h (98%); (h) Ref. 3.

ethyl acetate. The combined organic layers were washed with brine, dried over *anhydrous* Na_2SO_4, and concentrated. The residue was purified over silica gel to give a separable diastereomeric mixture (dr 12:1) of benzylic alcohol **6a** (9.45 g, 83%) and **6b** (0.80 g, 7%). Compound **6a**: IR (thin film, cm^{-1}) 3548, 3020; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.31 (s, 3H), 1.49 (s, 3H), 3.64 (d, J=2.9 Hz, 1H), 4.31 (dd, J=7.3, 4.1 Hz, 1H), 4.43 (ABq, J=11.5 Hz, $\Delta\nu$=98.1 Hz, 2H), 4.61 (d, J=3.7 Hz, 1H), 5.06 (d, J=7.3 Hz, 1H), 6.02 (d, 3.4 Hz, 1H), 7.26–7.41 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.2, 26.8, 71.8, 72.4, 82.1, 82.2, 84.5, 105.2, 111.9, 127.1, 127.7, 128.0, 128.1, 128.4, 128.6, 136.9, 139.6. MS (FAB) 357 (M^++1). Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79; found: C, 70.71; H, 6.83.

2.1.2. 3-*O*-Benzyl-1,2-*O*-isopropylidene-5-*C*-phenyl-α-D-glucopentofuranose (6b). To a solution of alcohol **6a** and **6b** (5.36 g, 15.05 mmol) in dry DCM (90.0 mL), PDC (8.49 g, 22.58 mmol), powdered 4 Å MS (12.04 g), and glacial acetic acid (600 μL) were added. The reaction was exothermic, refluxing gently and the orange color of the solution turned to dark brown within 5 min. The reaction mixture was stirred for 6 h; Celite was added and again stirred for 10 min. The reaction mixture was filtered over silica gel under vacuo and washed with DCM. The organic layer was concentrated to yield the ketone (4.37 g, 82%). The ketone (4.37 g, 12.34 mmol) was dissolved in MeOH (40.0 mL) and cooled to 0 °C. To this cooled solution $NaBH_4$ (1.87 g, 49.39 mmol) was added portion wise and stirred for 4 h. The reaction mixture was quenched with saturated NH_4Cl and MeOH was removed on a rotavapor. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine and placed over *anhydrous* Na_2SO_4. The organic layer was concentrated in vacuo and chromatographed over silica gel to give a separable diastereomeric mixture (10:1) of alcohol **6b** (3.91 g, 89%) and **6a** (0.38 g, 9%) as a syrup. Compound **6b**: $[\alpha]_D^{25}$ −85.18 (c 1.35, $CHCl_3$); IR (thin film, cm^{-1}) 3550, 3045; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.31 (s, 3H), 1.46 (s, 3H), 4.00 (d, J=2.4 Hz, 1H), 4.32 (dd, J=5.9, 3.2 Hz, 1H), 4.57 (ABq, J=11.5 Hz, $\Delta\nu$=90.6 Hz, 2H), 4.62 (d, J=3.9 Hz, 1H), 5.10 (d, J=6.1 Hz, 1H), 6.03 (d, J=3.9 Hz, 1H), 7.26–7.39 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.1, 26.7, 71.9, 72.2, 81.6, 82.4, 82.7, 105.1, 111.6, 126.0, 127.6, 128.0, 128.4, 128.7, 136.6, 141.2. MS (FAB) 357 (M^++1). Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79; found: C, 70.84; H, 6.71.

2.1.3. 3,5-Di-*O*-benzyl-1,2-*O*-isopropylidene-5-*C*-phenyl-α-D-glucopentofuranose (7). To a suspension of NaH (0.67 g, 16.8 mmol) in *anhydrous* THF (50.0 mL), alcohol **6b** (3.0 g, 8.4 mmol) in *anhydrous* THF (10.0 mL) was slowly added at 0 °C, stirred for 30 min, followed by addition of benzyl bromide (1.10 mL, 9.26 mmol) and a catalytic amount of TBAI. The resulting mixture was stirred at room temperature for 2 h, quenched with NH_4Cl, and extracted with ether. The organic layer was washed with brine, dried over *anhydrous* Na_2SO_4, and concentrated in vacuo. The residue was purified over silica gel to give the benzyl ether **7** (3.68 g, 98%) as a white solid. Mp 68–69 °C; $[\alpha]_D^{25}$ −60.00 (c 0.80, $CHCl_3$); IR (thin film, cm^{-1}) 3025, 1240; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.26 (s, 3H), 1.40 (s, 3H), 4.23 (m, 2H), 4.36 (m, 2H), 4.59 (m, 2H), 4.72 (m, 2H), 5.85 (d, J=3.7 Hz, 1H), 7.20–7.46 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.3, 26.7, 53.4, 70.3, 72.4, 78.2, 81.8, 82.1, 82.9, 105.0, 111.5, 127.5, 127.6, 127.8, 128.1, 128.3, 128.4, 137.7, 138.2, 139.3. MS (FAB) 447 (M^++1). Anal. Calcd for $C_{28}H_{30}O_5$: C, 75.31; H, 6.77; found: C, 75.23; H, 6.85.

2.1.4. (2*S*,3*R*,4*R*)-2,4-Bis-(benzyloxy)-3-formyloxy-4-phenyl-1-butanal (8). A solution of the acetonide **7** (9.0 g, 20.17 mmol) in dioxane (60.0 mL) was treated with 0.4% H_2SO_4 (21.0 mL) at 100 °C for 20 h. The reaction mixture was quenched with solid Na_2CO_3 and concentrated. The residue was dissolved in ethyl acetate, washed with water and brine, and dried over Na_2SO_4. The organic layer was concentrated and chromatographed over silica gel to give (6.55 g, 80%) hemiacetal as a white solid. The hemiacetal (4.3 g, 10.6 mmol) was dissolved in MeOH (305.0 mL) and treated with 0.6 N $NaIO_4$ aqueous solution (308.0 mL). The reaction mixture was stirred at room temperature for 1 h and then concentrated on rotavapor. The residue was diluted with water and extracted with DCM. The combined organic layers were washed with brine and dried over *anhydrous* Na_2SO_4. The solvent was removed in vacuo and the residue was chromatographed over silica gel to give formido aldehyde **8** (4.2 g, 98%) as an oily liquid; $[\alpha]_D^{25}$ −8.52 (c 0.68, $CHCl_3$); IR (thin film, cm^{-1}) 3040, 1720; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.11 (d, J=10.9 Hz, 1H), 4.38 (d, J=11.2 Hz, 1H), 4.47 (d, J=2.7 Hz, 1H), 4.62 (ABq, J=11.7 Hz, $\Delta\nu$=84.6 Hz, 2H), 4.65 (d, J=9.0 Hz, 1H), 5.55 (dd, J=9.0, 2.5 Hz, 1H), 7.17–7.40 (m, 15H), 7.62 (s, 1H), 9.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 53.4, 70.5, 73.2, 73.7, 77.9, 82.1, 127.9, 128.0, 128.1, 128.33, 128.39, 128.4, 128.5, 128.6, 128.8, 137.2, 158.9, 199.8. MS (FAB) 405 (M^++1). Anal. Calcd for $C_{25}H_{24}O_5$: C, 74.24; H, 5.98; found: C, 74.31; H, 5.92.

2.1.5. (4*R*,5*R*,6*R*)-Ethyl-4,6-bis-(benzyloxy)-5-(formidohydroxy)-5-phenyl-(2*E*/*Z*)-hexenoate (9). To a solution of formido aldehyde **8** (203.0 mg, 0.5 mmol) in dry DCM (3.0 mL), ethoxycarbonylmethylenetriphenylphosphorane (348 g, 1.0 mmol) was added and stirred at room temperature for 2 h. The reaction mixture was quenched with water and extracted with DCM. The organic layer was washed with water and brine and dried over *anhydrous* Na_2SO_4. The solvent was removed under vacuo and purified over silica gel to give an inseparable mixture (*E*/*Z* 3:1) of *trans*- and *cis*-enoate **9** (238 mg, 98%). IR (thin film, cm^{-1}) 3048, 1645; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.24 (t, J=7.3 Hz, 0.75H), 1.27 (t, J=7.3 Hz, 2.75H), 4.09 (d, J=11.2 Hz, 1H), 4.14–4.21 (m, 2H), 4.35 (dd, J=11.5, 2.7 Hz, 2H), 4.55–4.73 (m, 3H), 5.30 (dd, J=8.8, 1.5 Hz, 0.75H), 5.44 (dd, J=9.0, 1.7 Hz, 0.25H), 5.68 (d, J=8.6 Hz, 0.25H), 5.91 (dd, J=11.7, 1.2 Hz, 0.25H), 6.11 (dd, J=15.8, 1.4 Hz, 0.75H), 6.79 (dd, J=15.8, 5.8 Hz, 0.75H), 7.15–7.14 (m, 15H), 7.65 (d, J=2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 53.4, 60.6, 70.6, 72.1, 75.2, 75.9, 78.4, 123.9, 127.7, 127.8, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 137.2, 137.5, 143.7, 159.0, 165.6. MS (FAB) 475 (M^++1). Anal. Calcd for $C_{29}H_{30}O_6$: C, 73.40; H, 6.37; found: C, 73.35; H, 6.47.

2.1.6. (4*R*,5*R*,6*R*)-Ethyl-4,6-bis-(benzyloxy)-5-(hydroxy)-5-phenyl-(2*E*)-hexenoate (10a) and (5*R*,6*R*,7*R*)-4-ethoxy-5,7-bis-(benzyloxy)-6-(1-phenylmethyl)-3,4,5,6-tetrahydro-4*H*-pyran-2-one (10b). The mixture of α,β-unsaturated

ester **9** (6.8 g, 14.3 mmol) was dissolved in EtOH (45.0 mL) and cooled to 0 °C. To this cooled solution, K_2CO_3 (2.96 g, 21.42 mmol) was added and stirred at room temperature for 1 h. The reaction mixture was quenched with 2 N HCl at 0 °C and stirred for 2 h. The aqueous layer was extracted with ethyl acetate, washed with brine, and placed over *anhydrous* Na_2SO_4. The solvent was removed under vacuo and chromatographed to give the *trans*-ester **10a** (4.78 g, 72%) and the corresponding lactone **10b** (1.51 g, 23%). Compound **10a**: $[\alpha]_D^{25}$ +56.18 (*c* 2.62, $CHCl_3$); IR (thin film, cm^{-1}) 3452, 1740; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.28 (t, *J*=7.1 Hz, 3H), 3.71 (dd, *J*=8.3, 2.2 Hz, 1H), 4.08 (d, *J*=11.2 Hz, 1H), 4.19 (q, *J*=7.1 Hz, 2H), 4.33 (dd, *J*=15.1, 11.2 Hz, 2H), 4.41 (d, *J*=8.3 Hz, 1H), 4.46 (dd, *J*=6.4, 1.2 Hz, 1H), 4.63 (d, *J*=11.5 Hz, 1H), 6.09 (dd, *J*=15.9, 1.2 Hz, 1H), 6.97 (dd, *J*=15.8, 6.6 Hz, 1H), 7.17 (d, *J*=7.3 Hz, 1H), 7.23–7.39 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.2, 60.5, 70.4, 71.7, 76.2, 76.8, 80.9, 123.5, 127.7, 127.91, 127.96, 128.0, 128.2, 128.3, 128.4, 128.5, 137.5, 137.8, 138.8, 145.4, 165.9. MS (FAB) 447 (M^++1). Anal. Calcd for $C_{28}H_{30}O_5$: C, 75.31; H, 6.77; found: C, 75.25; H, 6.84. Compound **10b**: $[\alpha]_D^{25}$ −8.00 (*c* 0.60, $CHCl_3$); IR (thin film, cm^{-1}) 3455, 1758; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.14 (t, *J*=6.8 Hz, 3H), 2.56 (dd, *J*=17.8, 2.4 Hz, 1H), 2.84 (dd, *J*=17.8, 4.9 Hz, 1H), 3.40–3.50 (m, 2H), 3.77 (ABq, *J*=4.9 Hz, $\Delta\nu$=6.6 Hz, 1H), 4.19 (d, *J*=4.4 Hz, 1H), 4.71 (d, *J*=8.6 Hz, 1H), 4.42 (d, *J*=11.2 Hz, 1H), 4.60–4.73 (m, 4H), 7.24–7.48 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.2, 32.6, 60.2, 64.5, 70.2, 71.3, 71.7, 72.6, 78.0, 80.2, 126.8, 127.5, 127.6, 127.7, 127.8, 128.1, 128.2, 128.3, 128.4, 137.6, 137.7, 138.2, 168.8. MS (FAB) 447 (M^++1). Anal. Calcd for $C_{28}H_{30}O_5$: C, 75.31; H, 6.77; found: C, 75.42; H, 6.65.

2.1.7. (4*R*,5*R*,6*R*)-Ethyl-4,6-bis(benzyloxy)-2,3-dihydroxy-6-phenyl-5-(triisopropylsilyloxy)-hexanoate (11). To a solution of alcohol **10a** (564 mg, 1.14 mmol) in dry DCM (5.0 mL), 2,6-lutidine (400 μL, 3.43 mmol) was added at 0 °C. The solution was stirred for 30 min, and then TIPSOTf was added and was further stirred for 12 h at room temperature. The reaction mixture was quenched with water and diluted with DCM. The organic layer was washed with water and brine and dried over *anhydrous* Na_2SO_4. The organic layer was concentrated in vacuo. The residue was chromatographed on silica gel to give the TIPS ether (695 mg, 98%). After that to a 1:1 solution of *t*-BuOH and H_2O (10.0 mL), AD-mix β (4.12 g) was added and stirred for 5 min. To this stirred solution $(DHQD)_2PHAL$ (103.0 mg) and $MeSO_2NH_2$ (172.0 mg) was added at room temperature. The reaction mixture was cooled to 0 °C, TIPS ether (1.03 g, 1.93 mmol) was added, and was further stirred at same temperature for 24 h. The reaction mixture was quenched with Na_2SO_3. After 30 min EtOAc was added and organic phase was separated. The combined organic layer was washed twice with 1 M $KHSO_4$ solution, 5% $NaHCO_3$, brine and dried over *anhydrous* Na_2SO_4. The organic layer was evaporated in vacuo and residue was purified on silica gel to give a inseparable mixture of diol **11** (1.12 g, 92%). ^1H NMR ($CDCl_3$, 400 MHz): δ 0.91 (m, 3H), 1.01 (m, 18H), 1.22 (t, *J*=17.3 Hz, 3H), 2.96 (d, *J*=8.5 Hz, 1H), 3.32 (d, *J*=2.9 Hz, 1H), 3.87 (dd, *J*=9.8, 3.4 Hz, 1H), 4.17–4.34 (m, 4H), 4.51 (m, 3H), 4.73 (d, *J*=4.6 Hz, 1H), 7.09–7.47 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.6, 12.8, 14.1, 18.0, 18.1, 61.5, 70.1, 70.8, 73.0, 73.1, 76.0, 76.7, 82.7, 127.5, 127.6, 127.8, 127.9, 128.0, 128.1, 128.2, 128.7, 138.1, 138.2, 138.5, 173.8. MS (FAB) 638 (M^++1). Anal. Calcd for $C_{37}H_{52}O_7Si$: C, 69.78; H, 8.23; found: C, 69.69; H, 8.33.

2.1.8. (4*S*,5*R*)-Ethyl-5-((1*R*,2*R*,3*R*)-1,3-bis(benzyloxy)-3-phenyl-2-(triisopropylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (12). To the solution of diol **11** (2.34 g, 3.58 mmol) in DCM (12.0 mL), 2,2-dimethoxy propane (4.4 mL, 35.78 mmol) and catalytic amount of CSA were added at 0 °C. The reaction mixture was stirred at room temperature for 2 h under nitrogen atmosphere, quenched with water, and extracted with DCM. The combined organic layer was washed with brine, dried over *anhydrous* Na_2SO_4, and concentrated in vacuo. The residue was purified on column chromatography to give ester **12** (2.26 g, 91%) as a separable mixture in a ratio of 4:1. $[\alpha]_D^{25}$ −25.61 (*c* 2.15, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 0.77 (m, 3H), 0.97 (d, *J*=7.3 Hz, 18H), 1.08 (m, 3H), 1.47 (d, *J*=9.1 Hz, 6H), 3.96 (m, 2H), 4.14 (m, 2H), 4.34 (m, 2H), 4.50 (m, 3H), 4.68 (s, 2H), 7.27–7.44 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.4, 13.8, 18.1, 18.3, 25.9, 27.1, 61.2, 70.3, 73.4, 75.8, 76.7, 78.1, 78.2, 79.8, 87.8, 111.4, 126.7, 126.9, 127.4, 127.8, 127.9, 128.1, 128.7, 138.2, 139.1, 139.3, 171.2. MS (FAB) 678 (M^++1). Anal. Calcd for $C_{40}H_{56}O_7Si$: C, 70.97; H, 8.34; found: C, 70.87; H, 8.43.

2.1.9. 1-[5-(1,3-Bis-benzyloxy-3-phenyl-2-triisopropylsilanyloxy-propyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-2-diazo-ethanone (13). To a ice cooled solution of **12** (300 mg, 0.43 mmol) in methanol/water (5.0 mL, 4:1) was added lithium hydroxide monohydrate (108.7 mg, 2.59 mmol) at 0 °C. The mixture was brought to 25 °C and was further stirred for 2 h. The pH of the solution was adjusted to 7.0 by addition of aqueous NH_4Cl, the solvent was evaporated and the residue so obtained was extracted with chloroform to give an acid. To this acid (730.0 mg, 1.09 mmol) in THF (8.0 mL) at 0 °C, triethylamine (451.0 μL, 3.29 mmol) and ethylchloroformate (204.3 μL, 2.18 mmol) were added one after the other. After 15 min, the reaction mixture was brought to room temperature for 30 min and was filtered over Celite. To this filtrate a freshly prepared solution of diazomethane in diethyl ether [(prepared from *N*-nitrosomethyl urea (1.10 g) and KOH (2.0 g)] was added dropwise over a period of 30 min. The mixture was stirred for 1.5 h at room temperature. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography to give **13** (453.7 mg, 60%). $[\alpha]_D^{25}$ −21.96 (*c* 2.85, $CHCl_3$); IR (thin film, cm^{-1}) 3371, 3031, 2107, 1637, 1071; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.77 (m, 3H), 0.93 (d, *J*=7.3 Hz, 18H), 1.26 (d, *J*=10.9 Hz, 6H), 3.83 (m, 1H), 4.19 (m, 1H), 4.35 (m, 3H), 4.51 (m, 2H), 4.67 (ABq, *J*=11.7 Hz, $\Delta\nu$=41.0 Hz, 2H), 7.18–7.41 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.3, 18.1, 18.3, 26.0, 26.9, 53.1, 70.5, 73.7, 75.4, 78.0, 79.9, 81.3, 83.1, 110.7, 127.1, 127.2, 127.3, 127.6, 127.8, 128.0, 128.09, 128.13, 128.6, 138.3, 138.9, 139.2, 193.8. MS (FAB) 674 (M^++1). Anal. Calcd for $C_{39}H_{52}N_2O_6Si$: C, 69.61; H, 7.79; found: C, 69.72; H, 7.65.

2.1.10. Methyl 2-((4*R*,5*S*)-5-((1*R*,2*R*,3*R*)-1,3-bis(benzyloxy)-3-phenyl-2-(triisopropylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acetate (14). To a solution of α-diazoketone **13** (316.0 mg, 0.45 mmol) in anhydrous MeOH (6.0 mL) was added, dropwise, a solution of silver benzoate (38.0 mg, 0.14 mmol) in triethylamine (731 μL) under dry N_2 at −10 °C. The reaction mixture was further stirred for 1.5 h. The solvent was evaporated and the residue was purified by column chromatography to give **14** (217 mg, 68%) as a syrupy liquid. $[\alpha]_D^{25}$ −2.79 (*c* 3.25, $CHCl_3$); IR (thin film, cm^{-1}) 3030, 2928, 1743, 1071; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.72 (m, 3H), 0.96 (d, *J*=7.3 Hz, 18H), 1.29 (m, 6H), 2.41 (dd, *J*=15.8, 9.5 Hz, 1H), 2.72 (dd, *J*=15.8, 2.2 Hz, 1H), 3.62 (s, 3H), 3.80 (t, *J*=9.0 Hz, 1H), 3.95 (dd, *J*=9.3, 1.5 Hz, 1H), 4.15 (d, *J*=11.5 Hz, 1H), 4.31 (m, 3H), 4.45 (d, *J*=7.3 Hz, 1H), 4.60 (ABq, *J*=11.9 Hz, Δν=20.6 Hz, 2H), 7.24–7.43 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.4, 13.8, 18.1, 18.3, 25.9, 27.1, 61.2, 70.3, 73.4, 75.8, 76.7, 78.1, 78.2, 79.8, 87.8, 111.4, 126.7, 126.9, 127.4, 127.8, 127.9, 128.1, 128.7, 138.2, 139.1, 139.3, 171.2. MS (FAB) 678 (M^++1). Anal. Calcd for $C_{40}H_{56}O_7Si$: C, 70.97; H, 8.34; found: C, 70.92; H, 8.41.

2.1.11. 5-(1,3-Bis-benzyloxy-2-hydroxy-3-phenyl-propyl)-4-hydroxy-dihydro-furan-2-one (15). To a stirred solution of **14** (103 mg, 0.15 mmol) in CH_2Cl_2 (2.0 mL) was added a mixture of water (1.0 mL) and TFA (0.1 mL). The reaction mixture was stirred for 24 h. The reaction mixture was quenched with solid $NaHCO_3$, extracted with DCM, washed with brine, and placed over *anhydrous* $NaSO_4$, evaporated under reduced pressure to provide the lactonized product **15** (69 mg, 98%) as a solid. Mp 136–138 °C; $[\alpha]_D^{25}$ −49.5 (*c* 1.2, $CHCl_3$); IR (thin film, cm^{-1}) 3397, 3030, 2924, 1767, 1060; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.50 (d, *J*=17.3 Hz, 1H), 2.64 (dd, *J*=17.6, 4.9 Hz, 1H), 3.88 (dd, *J*=8.6, 1.5 Hz, 1H), 4.13 (d, *J*=8.5 Hz, 1H), 4.40–4.45 (m, 3H), 4.55–4.60 (m, 3H), 4.81 (d, *J*=11.2 Hz, 1H), 7.24–7.44 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 39.4, 69.7, 70.4, 74.3, 75.1, 75.5, 80.9, 83.1, 127.9, 128.1, 128.2, 128.4, 128.6, 128.8, 137.4, 137.5, 138.3, 175.2. MS (FAB) 450 (M^++1). Anal. Calcd for $C_{27}H_{28}O_6$: C, 72.30; H, 6.29; found: C, 72.38; H, 6.22.

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