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Stereoselective total synthesis of (+)-cardiobutanolide and (+)-3-*epi*-cardiobutanolide from diacetone D-glucose☆

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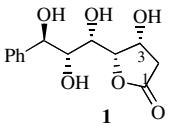
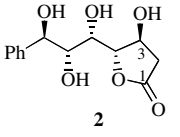
Abstract—A chiron approach starting with 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose utilizing a Grignard reaction, Mitsunobu stereoinversion, ethyl diazoacetate addition, and selective reduction of the ketone is employed as a key step for the total synthesis of (+)-cardiobutanolide described; a similar strategy is also reported for the first total synthesis of (+)-3-*epi*-cardiobutanolide.

The annonaceae plant family has been under extensive investigation by natural product chemists due to the diverse and potent polyketide constituents it offers.[1] Amongst this family, the most interesting is the genus *Goniothalamus* since a wide range of compounds with varied properties were isolated from it. Of the many natural products isolated, (+)-goniofufurone and its stereoisomers[2] have been extensively studied synthetic targets not only because of their interesting biological properties[3] but also due to their exquisite bicyclic core skeleton. (+)-Cardiobutanolide **1**,[4] a structurally dissimilar natural product was isolated recently from *Goniothalamus cardiopetalus* along with various styryl-lactones.



1

(+)-cardiobutanolide



2

3-*epi*-cardiobutanolide

An earlier synthesis[5] of **1** relied on the *anti* boron aldol reaction and asymmetric allylboration of the chiral starting material for generating the additional stereogenic centers. While this manuscript was in preparation, a stereocontrolled asymmetric synthesis of **1** appeared using D-glucuronolactone as the starting material.[6] The reported strategy derives stereogenic centers at C(3), C(4), and C(5) from D-glucuronolactone translating as those of C(3), C(4), and C(5) of **1**. As a part of our interest in the synthesis of the butenolide and valerolactone skeleton-containing bioactive natural products,[7] herein a chiron approach is reported for the synthesis of **1** from an inexpensive starting material, diacetone D-glucose (DAG). The first synthesis of 3-*epi*-cardiobutanolide **2**, a nonnatural product, is also reported wherein ethyl acetate addition resulted in an exclusive isomer, later identified as the C(3)-epimer of **1**, with the remainder of the chiral centers derived from a common intermediate **5** employed for the synthesis of **1**.

Thus, the synthesis (Scheme 1) was begun following the literature procedure.[8] For instance, the known[9] 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose, obtained from diacetone-D-glucose, on exposure to PhMgBr in THF resulted in 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*C*-phenyl-α-L-*ido*-pentofuranose **6** as the major product and the desired C(5) epimer **7** as the minor product (78%, 85:15 ratio, respectively). The diastereomers were separated by column chromatography and the major product was subjected to Mitsunobu reaction (p-$NO_2C_6H_4COOH$/DEAD/TPP/THF) followed by methanolysis (K_2CO_3/MeOH/rt) of the benzoate formed to invert the chiral center, as a simple means of enhancing the chemical yield of **7** (85% over two steps). The *gluco* configuration at C(5) in **7** was confirmed by comparison with reported data.[8] Next the C(5) hydroxyl group in **7** was protected as its benzyl

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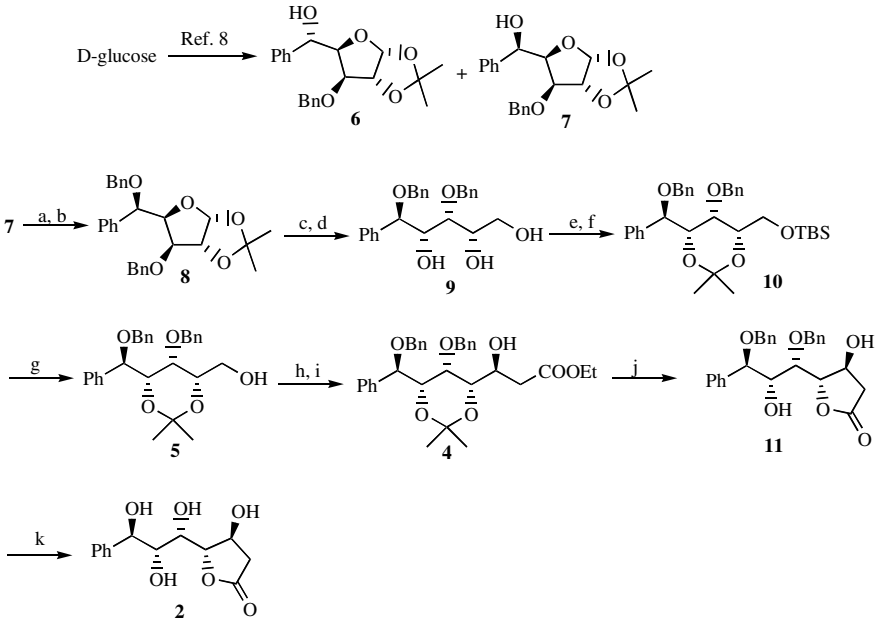
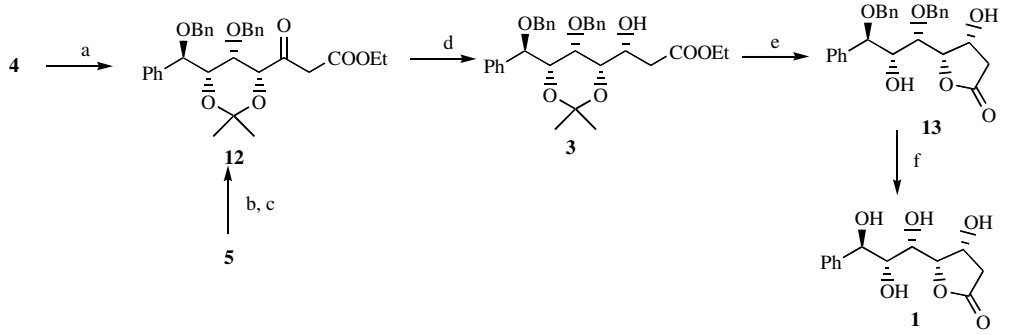


Scheme 1. Reagents and conditions: (a) (i) *p*-NO_2–C_6H_4COOH, DEAD, TPP, THF, 0 °C–rt, 6 h; (ii) K_2CO_3, MeOH, rt, 1 h (85% over two steps); (b) BnBr, NaG, THF, 0 °C–rt, 1 h (80%); (c) 30% aq AcOH, reflux, 6 h (70%); (d) $LiAlH_4$, THF, 2 h 0 °C–rt (65%); (e) TBSCl, imidazole, CH_2Cl_2 (85%); (f) 2,2′-DMP, PPTS, CH_2Cl_2, rt (85%); (g) TBAF, THF, rt (90%); (h, i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; EtOAc, LiHMDS, THF, −78 °C, 1 h (60% over two steps); (j) 80% aq AcOH, 6 h (70%); (k) 10% Pd–C/H_2, MeOH (80%).

ether with BnBr in the presence of NaH in DMF to afford **8** (80%). Cleavage of the 1,2-*O*-isopropylidene group of **8** in refluxing 30% aq AcOH (70%) followed by reduction with $LiAlH_4$ in THF provided triol **9** (65%). The primary alcohol group of **9** was protected as its TBS ether with TBSCl and imidazole (85%) and the two secondary 1,3-hydroxy groups were protected as the acetonide under conventional reaction conditions using 2,2′-DMP in CH_2Cl_2 catalyzed by PPTS affording **10** (85%). Subsequent desilylation with TBAF in THF gave **5** in 90% yield.

With alcohol **5** in hand, our next task was the two-carbon chain elongation preferably with a terminal ester functional group for later conversion into the lactone functionality. Thus **5** was subjected to Swern oxidation and an EtOAc addition reaction on the resulting aldehyde (EtOAc/LiHMDS/THF/−78 °C) to afford product **4** (60%) as a single isomer. To determine the configuration of the newly formed stereogenic center unambiguously, the remainder of the synthesis was continued as planned. β-Hydroxy ester **4** was treated with 80% AcOH to afford a five-membered lactone **11** in 70% yield, which on debenzylation (H_2/Pd–C/MeOH/rt) afforded the final target compound (80%). However, the ^1H NMR, physical data and $[\alpha]_D^{25}$ values did not match with the reported values of the natural product. The ^1H NMR spectrum revealed that two of the protons were more shielded in comparison to those of the natural product (δ 3.82 instead of δ 4.40 and δ 4.53 instead of δ 4.62). Hence it may be assumed that the EtOAc addition gave exclusively the *anti* product, since the other chiral centers remained untouched. Formation of **4** can be explained by presuming a metal chelated six-membered



Scheme 2. Reagents and conditions: (a) PDC, CH_2Cl_2, 4 Å MS, reflux, 8 h (30%); (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (c) ethyl diazoacetate, $BF_3{\cdot}OEt_2$, 4 Å MS, 0 °C–rt (70% for two steps); (d) $LiEt_3BH$, THF, −78 °C (85%); (e) 80% aq AcOH, 8 h (80%); (f) H_2/Pd–C, MeOH (80%).

transition state leading to *anti* addition.[10] Consequently, (+)-3-*epi*-cardiobutanolide **2** was synthesized instead of **1**.

Exposure of **4** to PDC in refluxing CH_2Cl_2 gave β-keto-ester **12** albeit in a low 30% yield (Scheme 2). In order to increase the chemical yield, **5** was subjected to Swern oxidation and then treated with ethyl diazoacetate in the presence of $BF_3{\cdot}OEt_2$ and 4 Å MS in CH_2Cl_2 at 0 °C to afford **12** in 70% yield. Stereoselective reduction of **12** with $LiEt_3BH$[11] in THF at −78 °C gave an easily separable mixture of **3** and **4** in a 95:5 ratio. The spectral data of the minor isomer **4** matched with that of the earlier sample (Scheme 1). Next, **3** was treated with 80% AcOH to give lactone **13** (80%) and finally debenzylation (H_2/Pd–C/MeOH/rt) afforded the natural product **1**, $[\alpha]_D^{25}$ +8.5 (*c* 0.4, MeOH) {natural **1**; $[\alpha]_D^{25}$ +6.4 (*c* 0.28, MeOH)[4] and synthetic **1**, $[\alpha]_D^{25}$ +5.5 (*c* 0.28, MeOH),[5] $[\alpha]_D^{25}$ +9.2 (*c* 1.00, MeOH)[6]} in 80% yield. The physical and spectroscopic data of the synthetic sample **1** were identical to those of the reported natural and synthetic products.

In conclusion, stereoselective syntheses of (+)-cardiobutanolide and (+)-3-*epi*-cardiobutanolide were accomplished by means of a versatile strategy.[12] A combination of a Mitsunobu stereoinversion reaction, ethyl diazoacetate addition and selective 1,2-*syn* reduction was used as the key step to prepare **1**. The synthesis of **2** was accomplished from a common intermediate **5** wherein ethyl acetate addition resulted in an exclusive *anti* product that was further elaborated to the target compound by a comparable reaction sequence.

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12. Spectral data of selected compounds. Compound **11**: White solid, mp: 118–120 °C; $[\alpha]_D^{25}$ −84.14 (*c* 0.75, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$); δ 7.41–7.21 (m, 15H), 4.75 (d, 1H, $J = 11.3$ Hz), 4.50 (d, 1H, $J = 10.5$ Hz), 4.45–4.33 (m, 4H), 4.12 (d, 1H, $J = 11.3$ Hz), 4.05 (dd, 1H, $J = 2.2$, 6.9 Hz), 3.81 (dd, 1H, $J = 1.51$, 8.3 Hz), 2.79 (dd, 1H, $J = 7.5$, 18.1 Hz), 2.41 (dd, 1H, $J = 6.0$, 17.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$); 174.41, 138.18, 137.46, 137.34, 128.53, 128.35, 128.29, 128.24, 128.00, 127.89, 127.74, 87.59, 80.53, 76.34, 74.21, 73.19, 70.31, 68.01, 37.15; IR (KBr), 3443, 3064, 3030, 2924, 2863, 1753, 1497, 1079 cm^{-1}; ESIMS; 471 $(M+Na)^+$, 466 $(M+NH_4)^+$, 449 $(M+H)^+$. Anal. Calcd for $C_{27}H_{28}O_6$: C, 72.30; H, 6.29. Found: C, 72.28; H, 6.32. Compound **2**: Thick syrup; $[\alpha]_D^{25}$ +26.5 (*c* 0.7, MeOH); ^1H NMR (200 MHz, acetone-d_6): 7.44 (d, 2H, $J = 8.2$ Hz), 7.22–7.36 (m, 3H), 4.75 (d, 1H, $J = 8.2$ Hz), 4.53 (d, 2H, $J = 2.7$ Hz), 3.96 (t, 1H, $J = 3.2$ Hz), 3.82 (dd, 1H, $J = 4.1$, 6.8 Hz), 2.84 (m, 1H, overlapped by residual water), 2.29 (dd, 1H, $J = 2.7$, 17.8 Hz); ^{13}C NMR (50 MHz, acetone-d_6): 177.3, 144.8, 129.6, 129.0, 128.9, 90.3, 76.6, 75.5, 72.6, 71.0, 39.5; IR (thin film): 3381, 2925, 1766, 1494, 1194 cm^{-1}; HRMS: calcd *m*/*z* 291.0844 ($C_{13}H_{16}O_6Na$). Found *m*/*z* 291.0833, ppm error −3.9788. Compound **13**: White solid, mp: 138–140 °C; $[\alpha]_D^{25}$ −58.6 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$); δ 7.35–7.17 (m, 15H), 4.85 (d, 1H, $J = 11.3$ Hz), 4.44 (d, 1H, $J = 11.3$ Hz), 4.20–4.36 (m, 4H), 4.10 (d, 1H, $J = 8.0$ Hz), 3.97 (d, 1H, $J = 11.3$ Hz), 3.70 (d, 1H, $J = 8.0$ Hz), 2.55 (dd, 1H, $J = 4.0$, 16.9 Hz), 2.39 (d, 1H, $J = 17.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$); 175.45, 138.10, 137.75, 137.08, 128.58, 128.49, 128.44, 128.26, 128.06, 127.94, 85.44, 81.13, 75.46, 74.59, 72.38, 70.46, 68.96, 38.86; IR (KBr), 3412, 3061, 3030, 2925, 2862, 1777, 1453, 1093 cm^{-1}; ESIMS; 471 $(M+Na)^+$, 466 $(M+NH_4)^+$, 449 $(M+H)^+$. Anal. Calcd for $C_{27}H_{28}O_6$: C, 72.30; H, 6.29. Found: C, 72.38; H, 6.21. Compound **1**: White crystalline solid; mp: 191–192 °C; $[\alpha]_D^{25}$ +8.5 (*c* 0.4, MeOH); ^1H NMR (300 MHz, acetone-d_6): δ 7.44 (d, 1H, $J = 6.7$ Hz), 7.22–

7.33 (m, 4H), 4.80 (d, 1H, $J = 7.5$ Hz), 4.62 (br s, 1H), 4.55 (dd, 1H, $J = 3.0$, 6.7 Hz), 4.40 (d, 1H, $J = 7.5$ Hz), 3.96 (d, 1H, $J = 6.0$ Hz), 2.84 (m, 1H, overlapped by residual water), 2.38 (d, 1H, $J = 16.6$ Hz); ^{13}C NMR (75 MHz, acetone-d_6): 176.0, 144.0, 129.8, 128.0, 127.0, 88.5, 76.0, 75.3, 71.6, 70.7, 39.0; IR (KBr): 3512, 3476, 2930, 2853, 1760, 1447, 1207 cm^{-1}; HRMS: calcd m/z 291.0844 ($C_{13}H_{16}O_6Na$). Found m/z 291.0834, ppm error −3.6353.