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Synthetic Approaches towards γ-Furylparaconic Acid Methyl Ester – An Important Intermediate for the Synthesis of *Pseudopterogorgia* Diterpenoids.

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ABSTRACT

A short synthesis of γ-furylparaconic acid methyl ester as valuable intermediate for the synthesis of the northeastern segment of biologically interesting complex *Pseudopterogorgia* diterpenoids was studied. Starting from furfural, the lactones were successfully prepared via hydride and yeast reductions of a beta-keto diester derivative. The structures of the newly synthesized compounds were identified on the basis of their IR, MS and NMR spectroscopic data. In addition, their stereochemistry was established using X-ray and CD spectroscopic measurements.

Keywords: -lactones, *Pseudopterogorgia* diterpenoids, reduction, bielschowskysin

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INTRODUCTION

The octocoral genus *Pseudopterogorgia* ("sea plumes") is well-known for the production of complex, highly oxidized diterpenoids that exhibit a wide array of biological activities including antibacterial, anti-inflammatory, antimalarial, and cytotoxic properties such as bielschowskysin (**1**), verillin (**2**) and bipinnatin K (**3**) [1-4]. The furanocembranoids and their derivatives are structurally variegated natural products that not only display a wide variety of oxidation patterns but also display a highly diverse carbon skeleton. Within the frame of our interest to provide strategies towards the stereocontrolled synthesis of the furan lactone backbone of furanocembranoids **1-3** from furan derivatives (ex. furfural, **4**), attention was further envisioned to synthesize a γ-furyllactone β-carboxy ester **5** by way of diastereoselective reduction of β-keto furylsuccinic diester **6** (Scheme 1). Lactone **5** is envisaged as a suitable synthetic intermediate to further study furan-oxidation, homologation and coupling reactions which may ultimately lead to the synthesis of the northeastern portion of diterpenoids **1-3**.

MATERIALS AND METHODS

NMR spectra were recorded on a Bruker Avance 300 (300.13 MHz) spectrometer using the solvent peak as internal reference ($CDCl_3$: δ H 7.26; δ C: 77.0). Multiplicities are indicated, s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet); coupling constants (*J*) are in Hertz (Hz). Mass spectra (MS ESI) were recorded with a Finnigan MAT 95 or Varian MAT 311A. All reactions were monitored by thin–layer chromatography (TLC) using Merck silica gel plates 60 F254; visualization was accomplished with UV light and/or staining with vanillin-sulfuric acid followed by heating. Infrared spectra were obtained using samples on a Biorad Excalibur FTS 3000 FT IR spectrometer equipped with a universal ATR sampling accessory (Specac Golden Gate Diamond Single Reflection ATR system). Optical rotations were measured with a 241 MC Perkin-Elmer polarimeter at a wavelength of 589 nm (Na-D) in a 1 dm. CD spectra were measured on a JASCO model J-710/720. Single crystal X-ray crystallographic analyses were carried out on Stoe Imaging Plate Diffraction System (IPDS) (Stoe & Cie GmbH, Darmstadt).

Synthesis of 2-(Furan-2-carbonyl)-succinic acid dimethyl ester (6)

To LDA (13.92 mmol, 1.1 equiv) in toluene (200 mL) were added dropwise successively the cyanohydrin **8** (3 g, 12.7 mmol, 1 equiv) in toluene (20 mL) and dimethyl maleate (1.91 g, 13.3 mmol, 1.05 equiv) in toluene (20 mL) at -78 °C under nitrogen atmosphere. The mixture was quenched by addition of aqueous AcOH (15%, 11 mL, 25.3 mmol). The organic layer was separated, and the aqueous layer was extracted with EtOAc (200 mL). The combined organic layer was washed with brine (100 mL) and dried ($MgSO_4$). After evaporation of the solvent, the residue was dissolved in THF (100 mL), and then AcOH (1.2 mL, 19 mmol) and TBAF (1.0 M in THF, 17 mL) were added to the solution at room temperature. After 30 min, the solution was washed with water (100 mL), 10% citric acid (100 mL), and brine (100 mL) and then dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by silica gel column chromatography using hexane/EtOAc (1:1) as an eluent to afford **6** as a brown syrup. Yield 1.86 g, 61%. ^{1}HMR spectrum (300 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.29 (m, 1H), 6.52 (m, 1H), 4.53 (m, 1H), 3.60 (dd, *J* = 8.6, 3.5 Hz, 6H), 2.96 (m, 2H). ^{13}C NMR spectrum (75 MHz, $CDCl_3$) 182.3, 171.4, 168.8, 151.5, 147.4, 119.2, 112.8, 52.8, 52.0, 49.4, 32.4. HR-EIMS: calcd for $C_{11}H_{12}O_6$ $[M]^+$: 240.0634, found: 240.0636. IR (KBr)**:** $\tilde{\nu}$ = 1738, 1677, 1466, 1262, 1165, 1016, 890 cm^{-1}.

Diastereoselective reduction of furan diester 6 with $NaBH_4$

To a suspension of $NaBH_4$ (190 mg, 5 mmol, 2 equiv) in methanol (20 mL) at 0 °C, was added **6** (2.45 mmol) in methanol (10 mL). The solution was allowed to warm to 0 °C and stirred for 2 h. The reaction was quenched with water and concentrated. The aqueous layer was extracted with EtOAc (3x10 mL) and concentrated. The residue was dissolved in 25 mL THF and catalytic PTSA was added. The solution was stirred further for 3 h and water was added (25 mL). The solution was extracted with 20 mL EtOAc (3x). The combined organic layers were washed with saturated $NaHCO_3$, brine and dried (Na_2SO_4). After concentration, the residue was chromatographed on silica gel using hexane-EtOAc (2:1) to afford lactone **5** in 79% yield (406 mg, 19:81 *trans/cis*).

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Diastereoselective reduction of furan diester 6 with $Zn(BH_4)_2$.

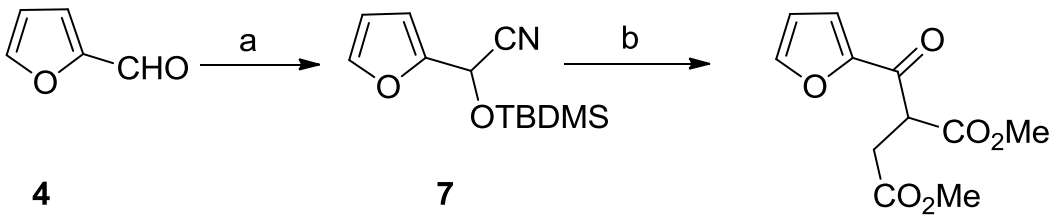
To a suspension of $NaBH_4$ (190 mg, 5 mmol, 2 equiv) in diethyl ether (3 mL) was added $ZnCl_2$ (1M in diethyl ether, 2.5 mL, 2.5 mmol, 1 equiv), at room temperature. The mixture was stirred for 5 h and the insoluble materials were filtered off. The filtrate was poured into a solution of **6** (2.45 mmol) in diethyl ether (50 mL) at -20 ^{o}C. The solution was allowed to warm to 0 ^{o}C and stirred for 2 h. The reaction was quenched by the addition of acetic acid (40 mmol). The mixture was washed with brine and dried and concentrated *in vacuo*. The residue was chromatographed on silica gel using hexane-EtOAc (2:1) to afford lactone **5** in 52% yield (267.5 mg, 86:14 *trans/cis*).

Enantioselective reduction of furan diester 6 with yeast

In a 1 L Erlenmeyer flask, 300 mg of furan succinate **6** in 5 mL ethanol and 100 mL water were added. Eight packs of Dr. Ötcker's yeast were added and the flask was shaken. Fermentation was signaled by the evolution of gas (CO_2) and the flask was set aside for 3 days. The yeast mixture was mixed with Celite 535 and filtered under vacuum and the residue was washed with some volumes of ethanol. The collected filtrate was concentrated *in vacuo* until ethanol was completely removed. The aqueous mixture was partitioned with diethyl ether (3x100 mL) and the combined organic layers were washed with brine (100 mL) and concentrated. The residue was chromatographed in silica using hexanes-EtOAc (4:1) to furnish *cis*-**5a** and *trans*-**5b** (75:25) in 25 % combined yield.

(2R,3S)-5-Oxo-2,3,4,5-tetrahydro-[2,2']bifuranyl-3-carboxylic acid methyl ester (cis-5a). Yield 49.1 mg. $[\alpha]_{20}^{D}$ -34.0 (*c* 0.12, MeOH). ^{1}H NMR spectrum (300 MHz, $CDCl_3$) □ 7.39 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.42 (d, *J* = 3.3 Hz, 1H), 6.32 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.59 (d, *J* = 6.3 Hz, 1H), 3.70 (s, 3H), 3.63 (m, 1H), 2.94 (m, 2H). ^{13}C NMR spectrum (75 MHz, $CDCl_3$) δ 173.98, 171.29, 144.21, 110.99, 110.73, 75.65, 53.21, 44.52, 32.30. HR-EIMS: calcd for $C_{10}H_{10}O_5$ $[M]^+$: 210.0528, found: 210.0526. IR spectrum (KBr)**:** $\tilde{\nu}$ = 2954, 1773, 1773, 1737, 1441, 1369, 1211, 1166, 1099, 945, 737 cm^{-1}. X-ray structural data has been deposited in the Cambridge Crystallographic Data Centre (CCDC 900032).

(2R,3R)-5-Oxo-2,3,4,5-tetrahydro-[2,2']bifuranyl-3-carboxylic acid methyl ester (trans-5b) . Yield 16.3 mg. $[\alpha]_{20}^{D}$ +56.0 (*c* 0.10, MeOH). ^{1}H NMR spectrum (300 MHz, $CDCl_3$) □ 7.35 (dd, *J* = 10.2, 9.2 Hz, 1H), 6.35 (d, *J* = 3.3 Hz, 1H), 6.29 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.67 (d, *J* = 8.5 Hz, 1H), 3.74 (m, 1H), 3.49 (s, 3H), 3.26 (dd, *J* = 17.7, 9.9 Hz, 1H), 2.69 (m, 1H). ^{13}C NMR spectrum (75 MHz, $CDCl_3$) δ 174.4, 169.1, 148.6, 143.6, 110.5, 110.1, 74.2, 52.4, 44.7, 30.2. HR-EIMS: calcd for $C_{10}H_{10}O_5$ $[M]^+$: 210.0528, found: 210.0527. IR spectrum (KBr)**:** $\tilde{\nu}$ = 1781, 1733, 1437, 1260, 1189, 1154, 984, 923, 885, 751 cm^{-1}.



Scheme 1: Synthesis of furan diester 6. Conditions: a) TBSCl, KCN, ZnI_2, MeCN, 12 h, rt (96%); b) (i) LDA, dimethylmaleate, THF, 1 h, -78 ^{o}C; (ii) TBAF, HAc, THF, rt, 4h (61%).

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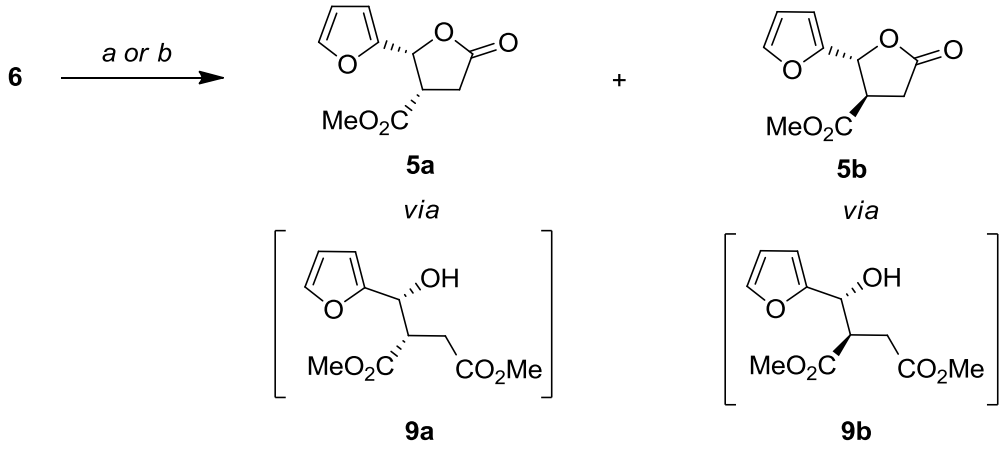

Scheme 2: Conditions: a) (i) $NaBH_4$, MeOH, 2h, 0 °C; (ii) PTSA (79%, (*cis:trans* = 81:19); b) (i) $Zn(BH_4)_2$, THF, 2 h, 0 °C; (ii) HAc (52%, *cis:trans* = 14:86).

RESULTS AND DISCUSSION

The synthesis of diester **6** started from furfural **4** [5]. Thus, treatment of **4** with TBSCl, KCN and ZnI_2 (catalyst) furnished the known siloxynitrile derivative **7** in excellent yield (96%). Umpolung manipulation of **7** via LDA assisted deprotonation at -78 °C provided a nucleophile intermediate which subsequently undergone Michael addition to dimethylmaleate to afford diester nitrile **8** (Scheme 1) [6]. TBAF accelerated removal of the TBS group followed by concurrent eviction of the nitrile group furnished **6** in moderate yield (61%).

Treatment of furylketosuccinyl diester **6** with $NaBH_4$ and $Zn(BH_4)_2$ followed by exposure in TFA afforded the *cis*- and *trans*-□-furylparaconic methyl esters **5a** and **5b**, respectively, with different degrees of selectivity. A high preference to form the *cis*- and *trans*-lactones was observed with $NaBH_4$ and $Zn(BH_4)_2$, respectively (Scheme 2) [6]. This partiality can be explained on the basis of Felkin-Ahn and Cram Chelate principles, respectively. Under the Felkin-Ahn control, the hydride is delivered at the least congested site to give *anti*-alcohol **9a** while the $Zn(BH_4)_2$ chelated, 1,3-stereocontrolled addition drives the hydride on the opposite side to furnish *syn*-alcohol **9b** (Figure 2). *Cis-lactone* **5a** and *trans*- lactones **5b** were generated under acidic conditions.

To examine the enantioselective reduction of **6**, the yeast reduction of □-substituted □-keto esters (a common dynamic kinetic resolution bioreaction) was carried-out next. In this transformation, the chiral substrates that undergo ready racemization passing through the enol form are converted to a series of important □-hydroxy esters. Although four stereoisomers are furnished in this reaction, the selection of appropriate conditions may result in a single product with high stereoselectivity [7]. Thus, bioreduction of furylsuccinate **6** with *Saccharomyces cerevisiae* (Dr. Ötcker baker's yeast) biomass furnished a 25% combined yield of 3:1 *cis*-lactone **5a** and *trans*-lactone **5b**. Plagued with difficulty of their separation in silica, the □-hydroxysuccinate intermediates were treated directly with PTSA. The low yield can be attributed to complications brought about by the high hydrolytic activity of *S. cerevisiae* enzymes and concomitant decarboxylation reactions occurring on many intermediates. The absolute stereochemistry of *cis*-lactone **5a** was established from its single crystal X-ray data (Figure 3). Thus, the C4 and C5 stereocenters were assigned the *4S,5R* configuration. *Trans*-lactone **5b** on the other hand, was given the *4R,5R* stereochemistry based on its negative Cotton effects around 210 nm (Figure 4) readily corroborated for n-□* transition of (*R*) γ-arylated-β-carboxylactones [8].

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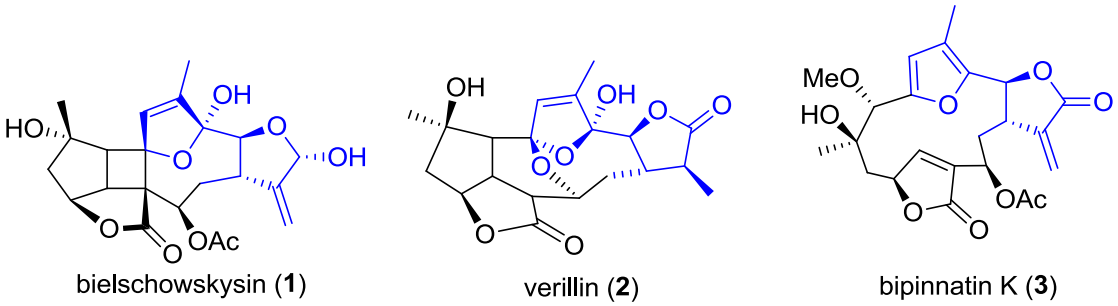

Figure 1: Structure of *Pseudopterogorgia* diterpenoids 1-3.

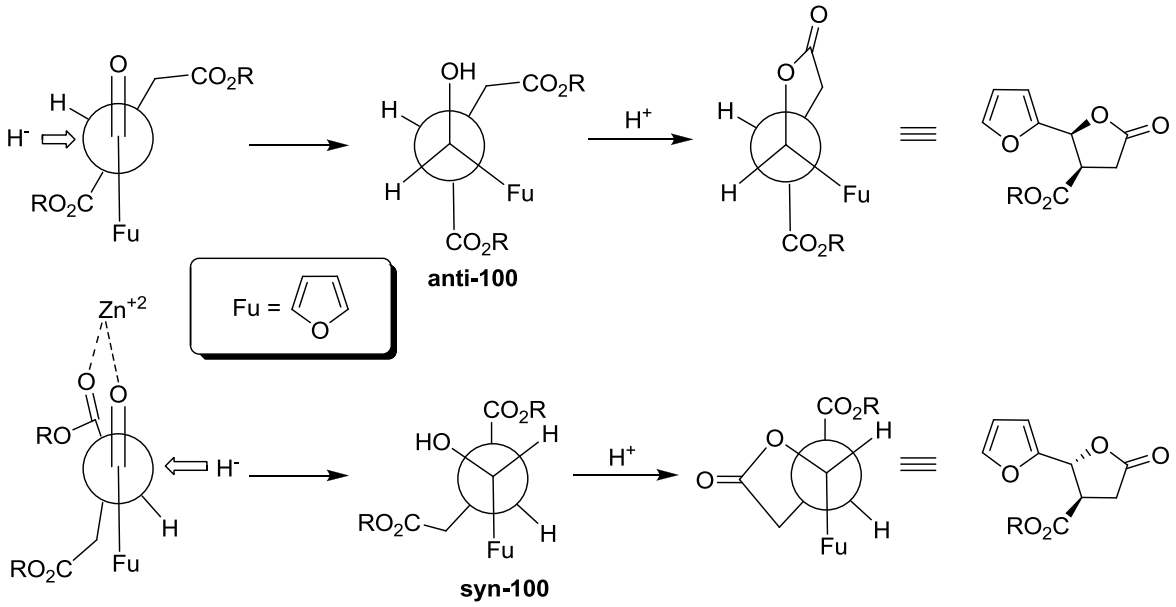

Figure 2: Addition of hydride in Felkin-Ahn and Chelate controlled conditions

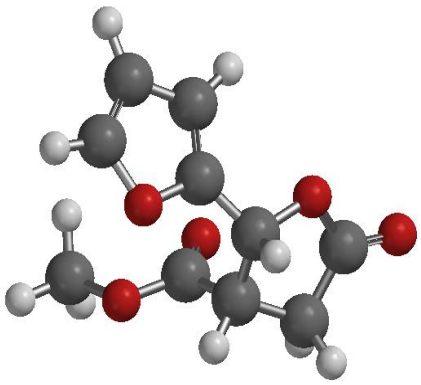

Figure 3: Single X-ray crystal structure of *cis*-γ-furyllactone β-carboxymethyl ester (-)-5a.

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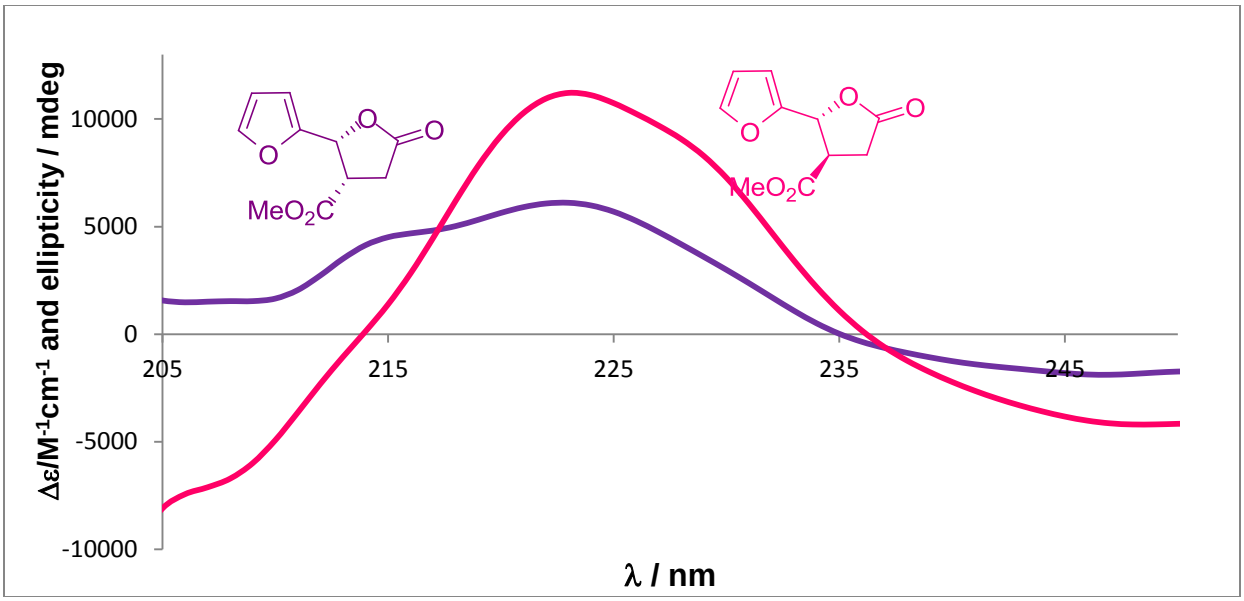

Figure 4: CD spectrum (MeOH) of *cis*-5 and *trans*-5.

CONCLUSION

Enantioselective reduction of a furylated β-keto succinate ester **6** was successfully carried out using yeast to furnish *cis*- and *trans*- lactones **5**. Thus, further investigations and optimizations on this aspect are still needed. The *trans* lactones prepared in this synthetic study can be a useful template for the synthesis *en route* the enantiomer of **1-3**.

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