ASYMMETRIC SOLID PHASE SYNTHESIS OF 3'*R*,4'*R*-DI-*O*-*CIS*-ACYL 3-CARBOXYL KHELLACTONES

Supporting Information

Experimental Section

All the reagents used are available from commercial sources, and were used without further purification. Quest 210 Organic Synthesizer was purchased from Argonaut Technologies. ArgoGel Wang resin was purchased from Argonaut Technologies. NMR data were obtained using a Varian Gemini spectrometer (300 MHz).

General procedure for modified Wang resin 1

ArgoGel Wang resin (1.5 g, 1 eq), purchased from Argonaut with a loading of 0.39 mmol/g was placed into a FLEX-column® with a luer lock purchased from Kontes. The resin was washed with DMF (15 mL, 3x), and methylene chloride (15 mL, 3x) and dried in vacuo. Ethyl potassium malonate (995.7 mg, 10 eq) was added followed by N-(3-dimethylaminopropyl)-N'-ethyl carbodiimide hydrochloride (1.12 g, 10 eq) and the reaction was allowed to shake at RT for 16 h. The resin was filtered and washed: (9/1) DMF/H_2O (15 mL, 3x), DMF (15 mL, 3x), methylene chloride (15 mL, 3x) and used directly in the next reaction sequence.

General procedure for the synthesis of 3',4'-di-*O*-*cis*-acyl 3-carboxyl khellactones (6a-f)

Resin **1** (Scheme 1) was suspended in pyridine; compound **2** (10 eq) and piperidine (40 μL) were added. The reaction was allowed to shake for 16 h at RT, then the resin was filtered and washed: (9/1) DMF/H_2O (3x), DMF (3x), methylene chloride (3x); retreated with the reagents; and washed again as described to obtain resin **3**. For synthesis of resin **4**: A small aliquot of OsO_4 (0.1 eq) in t-BuOH (2.5% solution (wt%) was added to a mixture of $(DHQ)_2PHAL$ (2.5 eq), $K_3[Fe(CN)_6]$ (6 eq), K_2CO_3 (3 eq), and methanesulfonamide (1 eq) in t-BuOH/water (v/v 1/1) at room temperature. After the reaction mixture was stirred for 10 min, resin **3** (1 eq) was added in one portion, and the mixture further stirred for 36 h. Solid $Na_2S_2O_5$

was added; the mixture was stirred for an additional 20 min, filtered, and successively washed with acetone and dichloromethane. The resin was dried, and then acylated. First, to a dry flask under nitrogen was added the desired carboxylic acid (10 eq), anhydrous CH_2Cl_2 and DIC (10 eq) and the solution stirred for 30 min. The resulting symmetrical anhydride was added to resin **5**, DIEA (20 eq), and DMAP (10 eq) and then was shaken for 2 h. The acylation procedure was repeated, then the suspension was drained, washed, and the products **6a-f** were cleaved from the resin by treatment with 50% TFA/CH_2Cl_2 for 2h. The cleavage eluant was collected and the resin washed with 50% TFA/CH_2Cl_2 (2 x) and MeOH (3 x). The eluant and washes were combined and dried in vacuum. The compound was purified by column chromatography (Chloroform-methanol 9 : 1) to afford the desired product.

Compound 6: ^{1}H-NMR (300 MHz, DMSO-d_6) δ : 1.35 (s, 6 H, 2'-CH_3), 3.59 (d, J = 5.1 Hz, 1H, H-3'), 4.85 (d, J = 5.1, 1H, H-4'), 6.82 (d, J = 9.0 Hz, 1H, H-6), 7.76 (d, J = 9.0 Hz, 1H, H-5) 8.70 (s, 1H, H-4); HRMS *m/z* for $C_{15}H_{14}O_7$ calcd 306.0740, obsd 306.0743.

Compound 6a: ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 1.03, 1.05, 1.07, 1.08, 1.09, 1.19 (each s, 3 H, camphanoyl CH_3), 1.44, 1.48 (each s, 3 H, 2'-CH_3), 1.68, 1.92, 2.47, 2.51 (each m, 2 H, camphanoyl CH_2), 5.39 (d, J = 4.7 Hz, 1H, H-3'), 6.65 (d, J = 4.7, 1.2 Hz, 1H, H-4'), 6.84 (d, J = 8.8 Hz, 1H, H-6), 7.51 (d, J = 8.8 Hz, 1H, H-5), 7.44 (s, 1H, H-4),; HRMS *m/z* for $C_{35}H_{38}O_{13}$ calcd 666.2312, obsd 666.2310.