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Asymmetric Solid-Phase Synthesis of (3′*R*,4′*R*)-Di-*O*-*cis*-acyl 3-Carboxyl Khellactones†

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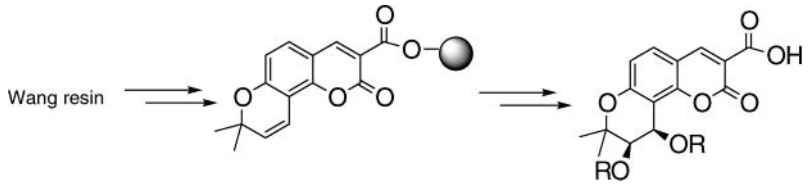
ABSTRACT



We describe a practical parallel synthesis of (3′*R*,4′*R*)-di-*O*-*cis*-acyl 3-carboxyl khellactones on a solid phase in high yield. The highlights of this synthesis include a Knoevenagel condensation, asymmetric dihydroxylation, catalyzed acylation, and product cleavage from the solid support.

Substituted khellactones exhibit a broad range of biological activities, including antifungal, antitumor, and antiviral effects.[1] In addition, our laboratory has discovered that (3′*R*,4′*R*)-di-*O*-(−)-camphanoyl-(+)-*cis*-khellactone (DCK) displayed extremely potent inhibitory activity against HIV-1 replication.[2] DCK was more potent than AZT as an anti-HIV agent in the same assay. Therefore, (3′*R*,4′*R*)-di-*O*-*cis*-substituted khellactones have proven to be crucial drug leads and have elicited considerable pharmaceutical interest. Thus, a general method of rapidly preparing analogues of khellactones would be advantageous and merits investigation for drug discovery. Meanwhile, solid-phase synthesis of small organic molecules has emerged as an important technology, enabling chemists to synthesize numerous pharmaceutically interesting compounds.[3] The relative ease of automation, along with a multiple parallel synthesis strategy, has greatly supported the growing needs for identifying novel biologically active lead compounds and accelerated structure−activity relationship studies in drug discovery. We report here the first asymmetric solid-phase synthetic route to (3′*R*,4′*R*)-di-*O*-*cis*-acyl 3-carboxyl khellactones.

The synthetic route is described in Scheme 1. The strategy we used is to attach a polystyrene resin to the khellactone ring skeleton through a C-3 carboxylate group. The linker group of the Wang resin could serve as a carboxyl protecting group, because a free carboxyl is not compatible with the asymmetric dihydroxylation (AD) or acylation reaction conditions. In addition, this linkage is cleaved under mild acidic conditions that are compatible with the desired compounds. We chose different supports, including low divinylbenzene-cross-linked polystyrene beads (ArgoPore), which are relatively hydrophobic matrices, and ArgoGel

† Anti-AIDS Agents. 40.

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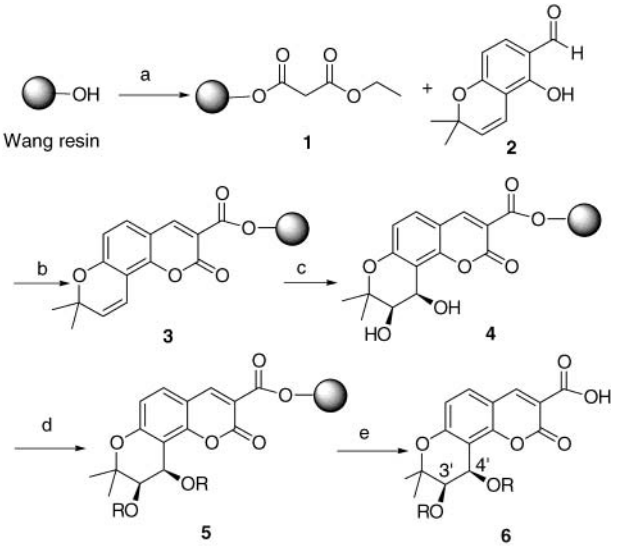
Scheme 1



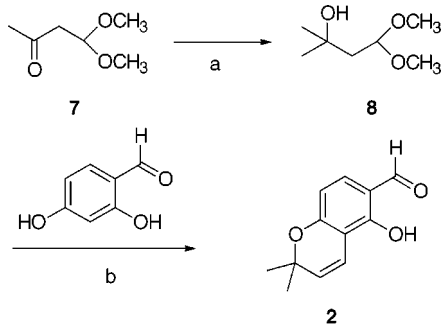
a) ethyl potassium malonate, rt;
b) pyridine, piperidine, rt;
c) $K_3[Fe(CN)_6]$, OsO_4, K_2CO_3, $(DHQ)_2$-PHAL, t-BuOH/H_2O, rt;
d) (1) R_2COOH, 1 equiv DIC; (2) DIEA, DMAP;
e) 50% TFA/CH_2Cl_2

resin, which is considered a relatively hydrophilic tentacle polymer with more "solution like" characteristics.[4] Because the solvents in the Sharpless AD reaction proposed in the following reaction are *t*-BuOH and water, ArgoGel resin was found more suitable for the reaction, as well as for better swelling.

The scaffold of the khellactone 3-carboxyl ring skeleton was prepared by a Knoevenagel condensation[5] between ethyl malonate bound to the Wang resin (**1**) and *o*-hydroxyarylaldehyde (**2**). In the previous solution-phase synthesis, we reacted 7-hydroxycoumarin with 3-chloro-3-methybut-1-yne followed by a Claisen rearrangement to generate the khellactone ring skeleton.[6] Although we obtained the highly regiospecific product in high yield, the reaction was carried out at high temperature. Therefore, we have adapted a Knoevenagel condensation, treating resin **1** with **2** at room temperature with a catalytic amount of piperidine to create the khellactone scaffold. The reaction condition is very mild, which is more amenable for solid-phase synthesis.

The synthesis of *o*-hydroxyarylaldehyde (**2**) is illustrated in Scheme 2. Grignard addition of acetyl acetaldehyde dimethyl acetal (**7**) with methylmagnesium bromide in diethyl ether afforded **8**. Nucleophilic substitution of 2,4-dihydroxybenzoylaldehyde, followed by regiospecific aromatic cyclization, gave **2**.[7]

Scheme 2



a) CH_3MgBr, ether; b) Pyridine, reflux

The next key step was asymmetric dihydroxylation of the khellactone. Sharpless asymmetric dihydroxylation (AD) reactions have been successfully and widely used in the solution phase, but AD reactions on solid phase have been reported only infrequently.[8] However, a high percent enantiomeric excess (% ee) value has not been accomplished for the AD reaction of a styrene-like olefin contained in a six-membered ring fused with benzene on a solid phase. Our asymmetric synthesis of (3′*R*,4′*R*)-*cis*-dihydroxykhellactone (**4**) was successful on a solid phase using $(DHQ)_2$-PHAL as ligand and catalytic OsO_4. The 3′,4′-dihydroxy 3-carboxyl khellactone **6** (R = H) was obtained by cleaving the resin **4** using 50% trifluoroacetic acid in DCM. The % ee of the AD reaction was 91%.[9] The acyl khellactones **5** were synthesized by acylation of the resin **4**. Symmetrical anhydrides were prepared from the desired carboxylic acid using 1 equiv of DIC in dichloromethane. Then, in an automated parallel synthesis using the Quest 210 Organic Synthesizer, excess anhydride was added to the resin **4** and the reaction proceeded for 8 h in the presence of DIEA and DMAP. After a second acylation, the resin was washed with DMF and DCM. The resins **5** then were treated with 50% trifluoroacetic acid in DCM for 2 h to cleave the target 3-carboxyl khellactones (**6a**−**f**).[10] The crude products cleaved from the resin showed excellent purity (>90%). Silica gel column chromatography then gave the pure compounds. Representative compounds are listed in Figure 1. Yields correspond to purified products and were calculated on the basis of the hydroxyl group of the Wang resin. The structure and identity of the products were compared to those produced via solution synthesis, and ^{1}H NMR and electrospray mass spectrometric data were satisfactory.

In conclusion, we have developed a novel, straightforward, easily automated solid-phase procedure for the synthesis of (3′*R*,4′*R*)-di-*O*-*cis*-acyl 3-carboxyl khellactones. The procedure is particularly useful because of its efficiency and ease

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(7) ^{1}H NMR (300 MHz, $CDCl_3$) data for **5-Hydroxy-2,2-dimethyl-2*H*-chromene-6-carbaldehyde (2)**: δ 1.38 (s, 6H, 2 × CH_3), 5.54 (d, J = 10.1 Hz, 1H, H-3), 6.36 (d, J = 8.4 Hz, 1H, H-8), 6.62 (d, J = 10.1 Hz, 1H, H-4), 7.21 (d, J = 8.4 Hz, 1H, H-7), 9.59 (s, 1H, aldehyde). Yield: 29.4%. Mp: 69−70 °C.
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(9) The percent enantiomeric excess was determined by ^{1}H NMR analysis of the bis-(−)-camphanic esters.

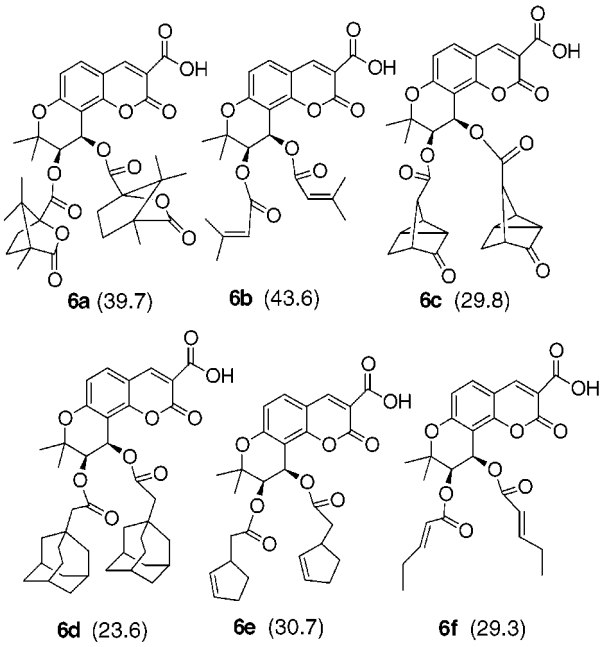

Figure 1. 3-Carboxyl khellactones **6a**−**f**. Yields in parentheses correspond to purified products and were calculated on the basis of the hydroxyl group of Wang resin.

of operation. It is well-suited to the preparation of analogues for SAR studies.

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Supporting Information Available: Procedures for the formation of 3′,4′-di-*O*-*cis*-acyl 3-carboxyl khellactones and characterization data for **6** and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) General procedure for the synthesis of 3′,4′-di-*O*-*cis*-acyl 3-carboxyl khellactones: ArgoGel Wang resin (1 equiv), purchased from Argonaut with a loading of 0.39 mmol/g, was washed with DMF (3×) and methylene chloride (3×) and dried in vacuo. Ethyl potassium malonate (10 equiv) was added followed by *N*-(3-dimethylaminopropyl)-*N*′-ethyl carbodiimide hydrochloride (10 equiv), and the reaction mixture was shaken at room temperature for 16 h. The resin was filtered and washed: 9/1 DMF/H_2O (3×), DMF (3×), methylene chloride (3×). Then, resin **1** was suspended in pyridine; compound **2** (10 equiv) and piperidine (40 μL) were added. The reaction mixture was shaken for 16 h at room temperature, and then the resin was filtered and washed with 9/1 DMF/H_2O (3×), DMF (3×), and methylene chloride (3×), 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 equiv) in t-BuOH (2.5% solution (wt %)) was added to a mixture of $(DHQ)_2$-PHAL (2.5 equiv), $K_3[Fe(CN)_6]$ (6 equiv), K_2CO_3 (3 equiv), and methanesulfonamide (1 equiv) in t-BuOH/water (4 mL, v/v 1/1) at room temperature. After the reaction mixture was stirred for 10 min, resin **3** (1 equiv) was added in one portion, and the mixture was 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 equiv), anhydrous CH_2Cl_2, and DIC (10 equiv) and the solution was stirred for 30 min. The resulting symmetrical anhydride was added to resin **5**, DIEA (20 equiv), and DMAP (10 equiv), and then the mixture was shaken for 2 h. The acylation procedure was repeated, and then the suspension was drained and washed and the products **6a**−**f** were cleaved from the resin by treatment with 50% TFA/CH_2Cl_2 for 2 h. All new compounds gave satisfactory analytical and spectroscopic data.