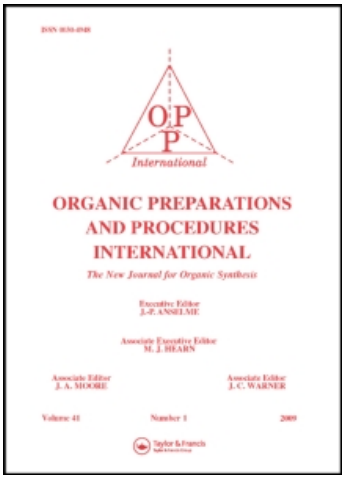

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DIMERIZATION OF LITHOCHOLATE UNSATURATED ESTERS USING THE 'SECOND GENERATION' GRUBBS' REAGENT

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DIMERIZATION OF LITHOCHOLATE UNSATURATED ESTERS USING THE 'SECOND GENERATION' GRUBBS' REAGENT

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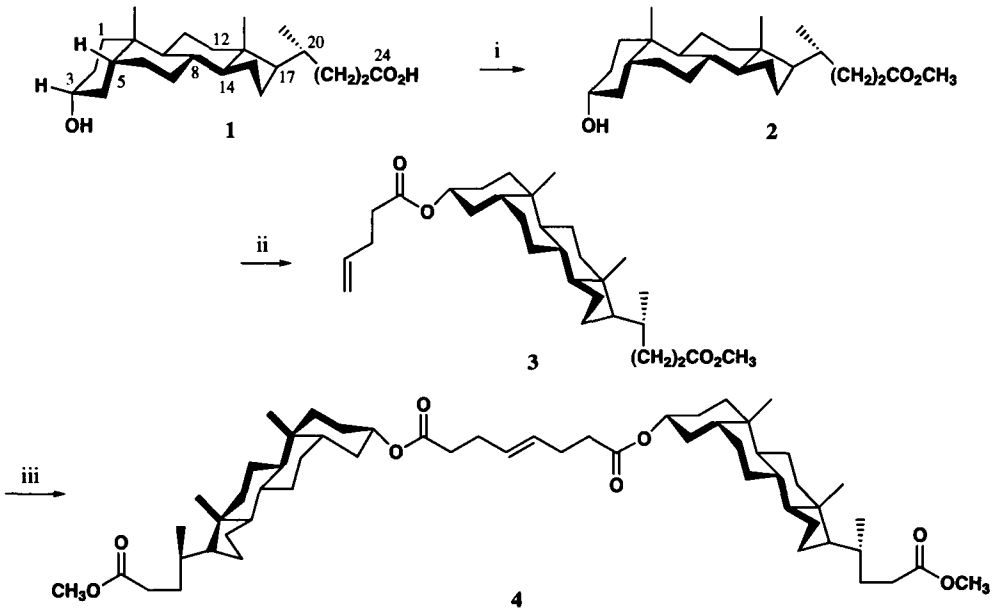
A taylor-made linear dimer was synthesized starting from lithocholic acid, an inexpensive steroid bile acid. The presented route uses the Yamaguchi reaction for attaching an unsaturated acid to the methyl lithocholate ester. Linking of two lithocholate ester derivatives was performed *via* the Grubbs' ruthenium catalyzed olefin cross-metathesis. Possible applications of this coupling strategy include development of bile acid based polymers for use as biocompatible prosthetic devices and drug delivery systems. Examples of oligomers having these potential applications can be found in the recent literature.[1]

The bile acids, such as lithocholic acid (**1**), are known to have a rigid-concave oriented skeleton with multiple chiral centers capable of being diversely functionalized. The unique features of chirality, rigid framework, and chemically different hydroxyl groups have made them ideal components for supramolecular chemistry.[2] The generation of supramolecular systems constructed with biomolecular components represents an important strategy directed toward a better understanding of the role these molecules play in many cellular pathways as well as providing new targets for drug development.[3] With the recently gained prominence of olefin metathesis in synthetic organic chemistry using the ruthenium-based Grubbs' catalyst,[4] we decided to investigate potential applications of cross-metathesis in the construction of cholic acid dimers. Herein, we present the first report of cross-metathesis between terminal olefins to generate a steroid-based linear bile acid dimer (head to head).

Our studies began with the production of methyl lithocholate (**2**) from lithocholic acid (**1**). To produce the methyl 3-tiglyl-, 3-acryloyl-, and the 3-(4-pentenoyl)-lithocholate esters (**3**), the Yamaguchi method was used.

Esterification by reaction with a combination of *N N'*-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) was less successful.[5] The Yamaguchi method, which uses 2,6-dichlorobenzoyl chloride as a coupling agent along with DMAP as a catalyst in tetrahydrofuran (THF) produced overall yields of 95%. During the reaction, triethylamine was added in order to neutralize the HCl formed as a by-product and produced a white crystalline salt (Et_3N•HCl). Since it does not react with any of the reactants or products, the salt was removed *via* column chromatography only at the end of the synthetic sequence.

Our attempt to perform Grubbs' coupling of methyl 3-tiglyllithocholate was unsuccessful. Coupling the less sterically hindered methyl 3-acryllithocholate was also unsuccessful.



i) AcCl/MeOH; ii) 4-pentenoic acid, 2,6-dichlorobenzoyl chloride, Et_3N, THF, reflux, 24 h; iii) Five mol % of 1,3-*bis*(2,4,6-trimethylphenyl)-2-imidazolidinylidene)(dichlorophenylmethylene)(tricyclohexylphosphene) ruthenium(IV) under nitrogen, CH_2Cl_2, reflux 6 h

Second generation Grubbs' coupling of the less sterically hindered and non-conjugated 4-pentenoate ester **3** was successful and gave the desired dimer **4**. The changes between the ^{13}C NMR spectra of 4-pentenoate ester moiety in **3** and of the 4-octendioate moiety in **4** are informative. The peak at δ 115.6 in **3** for the 5-methylene carbon disappeared and the peak at 137 for the 4-methine carbon shifts to 129 in the spectrum of **4**.

In summary, lithocholate ester **3** was synthesized and successfully dimerized to **4** using the Grubbs' second generation catalyst, 1,3-*bis*-(2,4,6-trimethyphenyl)- 2-(imidazolidinylidene)(dichlorophenylmethylene)(tricyclohexylphosphine)ruthenium. While the TLC of **4** showed only one spot, the ^1H NMR showed a small peak (hump) at δ 5.56 next to the δ 5.46 peak, which suggests that the product may be a mixture of *cis*- and *trans*-isomers (≈ 4:1). The methyl 3-acryloyllithocholate ester did not produce a dimer in the presence of the ruthenium catalyst. This is believed to be a result from the conjugation of the double bond with the carbonyl group. The methyl 3-tiglyllithocholate did not produce a dimer because of both steric and conjugation factors. Interestingly, in the attempt to dimerize the methyl 3-tiglyllithocholate, the catalyst appeared to instead isomerize the tiglic ester moiety as the TLC showed a change in R_f from 0.53 to 0.62 in a 3:1 mixture of hexanes in ethyl acetate while the ^1H NMR spectra remained unchanged.

EXPERIMENTAL SECTION

All air-sensitive reactions were carried out under nitrogen. Proton magnetic resonance (^{1}H NMR) and carbon magnetic resonance (^{13}C NMR) spectra were recorded at 250 MHz and 63 MHz, respectively, in chloroform-*d* (7.27 and 77.0 ppm, respectively) as solvent and with TMS as internal standard. Chemical shifts are reported in ppm on δ scale. The following abbreviations indicate signal multiplicity, s = singlet, d = doublet, q = quartet, m = multiplet. All ^{13}C NMR assignments are based on both comparison with a previous extensive compilation[5] and Chem-Draw Ultra 8.0 NMR Estimation. Flash chromatography (FC) was carried out using 230-400 mesh silica gel. Thin layer chromatography (TLC) was carried out on pre-coated glass plates silica. Spots were visualized by spraying cerium (IV) sulfate solution and charring on a hot plate. Melting points (mp) were determined on a Fisher-Johns melting point apparatus and are uncorrected. The second generation Grubbs' catalyst was supplied by Aldrich. The FAB mass spectra were determined by the Nebraska Center for Mass Spectrometry at the University of Nebraska – Lincoln, and the C/H analyses were performed by Galbraith Laboratories. The experimental and spectra of methyl 3-tiglyl- and 3-acryloyllithocholate esters are available upon request from the authors.

Methyl 3α-Hydroxy-5β-cholan-24-oate (2).- Acetyl chloride (1.0 mL, 17.7 mmol) was added dropwise to methanol (10 mL) cooling in an ice bath under constant stirring. Lithocholic acid (1.0 g, 2.7 mmol) was then added to the stirred solution and the reaction mixture was quenched by addition of ice water (approx 50 mL) after 12 h. The solution was evaporated to dryness to produce 1.0 g (99%) of a foamy white solid (**2**), mp 90-93°C (Merck Index *mp* 126-127°C). ^{1}H NMR ($CDCl_3$): δ 0.64 (s, 3H, 18-H_3); 0.91 (d, 3H, 21-H_3); 0.92 (s, 3H, 19-H_3); 1.98 (s, 1H, 3α-OH); 3.66 (s, 3H, OCH_3); 4.75 (peak, 1H, 3β-H). ^{13}C NMR ($CDCl_3$): δ 35.00 (C-1), 30.10 (C-2), 71.00 (C-3), 36.00 (C-4), 41.80 (C-5), 26.90 (C-6), 26.20 (C-7), 35.50 (C-8), 40.10 (C-9), 34.20 (C-10), 20.50 (C-11), 39.90 (C-12), 42.40 (C-13), 56.20 (C-14), 23.90 (C-15), 27.80 (C-16), 55.60 (C-17), 11.70 (C-18), 23.10 (C-19), 35.10 (C-20), 17.90 (C-21), 30.70 (C-22), 30.70 (C-23), 174.20 (C-24), 51.10 (OCH_3).[6]

Methyl 3α-(4-Pentenoyloxy)-5β-cholan-24-oate (3).- A mixture of 4-pentenoic acid (300 mg, 3.0 mmol), 2,6-dichlorobenzoyl chloride (628 mg, 3.0 mmol) and triethylamine (303 mg, 3.0 mmol) was refluxed for 3 h in THF (15 mL). Methyl 3α-hydroxy-5β-cholan-24-oate (**2**) (390 mg, 1.0 mmol) and DMAP (122 mg, 1.0 mmol) were then added to the cooled solution and refluxed for 24 h. FC (10% ethyl acetate in hexanes) of this mixture afforded 440 mg (95%) of **3**. *mp* 100-105°C. ^{1}H NMR ($CDCl_3$): δ 0.65 (s, 3H, 18-H_3); 0.91(d, 3H, 21-H_3); 0.92 (s, 3H, 19-H_3); 2.3 (m, 2H, 23-H_2); 2.4 (m, 4H, CHH=CH$\underline{CH_2}CH_2CO_2$ & CHH=CHCH$_2\underline{CH_2}CO_2$); 3.67 (s, 3H, OCH_3), 4.73 (peak, 1H, 3β-H); 4.98, 5.02, 5.09 (crude t, 2H, C$\underline{HH}$=CHCH$_2CH_2CO_2$); 5.8 (hump, 1H, CHH=$\underline{CH}CH_2CH_2CO_2$). ^{13}C NMR ($CDCl_3$): δ 35.21 (C-1), 26.52 (C-2), 74.1 (C-3), 32.45 (C-4), 42.08 (C-5), 27.18 (C-6), 26.85 (C-7), 36.00 (C-8), 40.61 (C-9), 34.78 (C-10), 21.01 (C-11), 40.29 (C-12), 42.93 (C-13), 56.68 (C-14), 24.38 (C-15), 28.38 (C-16), 56.17 (C-17), 12.23 (C-18), 23.52 (C-19), 35.56 (C-20), 18.44 (C-21), 31.21 (C-22), 31.21 (C-23), 174.99 (C-

24), 51.9 (OCH_3), 29.20 (CHH=CH$\underline{C}H_2CH_2CO_2$), 34.10 (CHH=CHCH$_2\underline{C}H_2CO_2$), 115.58 ($\underline{C}$HH=CHCH$_2$CH$_2$CO$_2$), 137.0 (CHH=$\underline{C}$HCH$_2$CH$_2$CO$_2$), 172.79 (CHH=CHCH$_2$CH$_2\underline{C}O_2$). MS (LRFAB) 479.2 $[M+Li]^+$, 613.1 $[M+Li_2I]^+$. MS (HRFAB) 479.3725 [M+Li = $C_{30}H_{48}O_4Li]^+$.

Anal. Calcd for $C_{30}H_{48}O_4$: C, 76.23; H, 10.24. Found: C, 76.15; H, 10.15.

Dimerization of Methyl 3α-(4-pentenoyloxy)-5β-cholan-24-oate (4).- Methyl 3α-(4-penten oyloxy)-5β-cholan-24-oate (150 mg, 0.32 mmol) was added *via* a syringe to a stirred solution of the catalyst (13 mg, 5 mol%) in methylene chloride (3 mL). The solution was refluxed under nitrogen for 6 h. flash chromatography (15% ethyl acetate in hexanes) of this mixture afforded 139 mg (95%) of **4** as colorless glassy solid. ^{1}H NMR ($CDCl_3$): δ 0.64 (s, 3H, 18-H_3); 0.91 (d, 3H, 21-H_3); 0.92 (s, 3H, 19-H_3), 2.3 (m, 2H, 23-H_2,), 2.4 (m, 4H, =CH$\underline{CH_2}$CH$_2$CO$_2$ and =CHCH$_2\underline{CH_2}$CO$_2$), 3.66 (s, 3H, OCH_3), 4.73 (peak, 1H, 3β-H), 5.46 (br s, 1H, =$\underline{CH}$CH$_2$CH$_2$CO$_2$). ^{13}C NMR ($CDCl_3$): δ 35.19 (C-1), 26.46 (C-2), 74.2 (C-3), 32.44 (C-4), 42.02 (C-5), 27.20 (C-6), 26.81 (C-7), 35.93 (C-8), 40.55 (C-9), 34.69 (C-10), 20.99 (C-11), 40.24 (C-12), 42.88 (C-13), 56.62 (C-14), 24.32 (C-15), 28.36 (C-16), 56.11 (C-17), 12.17 (C-18), 23.47 (C-19), 35.46 (C-20), 18.34 (C-21), 31.19 (C-22), 31.19 (C-23), 174.97 (C-24), 52.0 (OCH_3), 28.13 (=CH$\underline{C}H_2$CH$_2$CO$_2$), 34.69 (=CHCH$_2\underline{C}H_2$CO$_2$), 129.0 (=$\underline{C}$HCH$_2$CH$_2$CO$_2$), 172.79 (=CHCH$_2$CH$_2\underline{C}O_2$). MS (LRFAB): 917.3$[M+H]^+$. MS (HRFAB) 923.6965 [M+Li = $C_{58}H_{92}O_8Li]^+$.

Anal. Calcd for $C_{58}H_{92}O_8$: C, 75.94; H, 10.11. Found: C, 75.74; H, 9.81.

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