Synthesis of (±)-Methylenolactocin and (±)-*trans* Cognac Lactone

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The title compounds were efficeintly synthesized from 3-fuancarboxylic acid *via* the Birch recuction-elimination.

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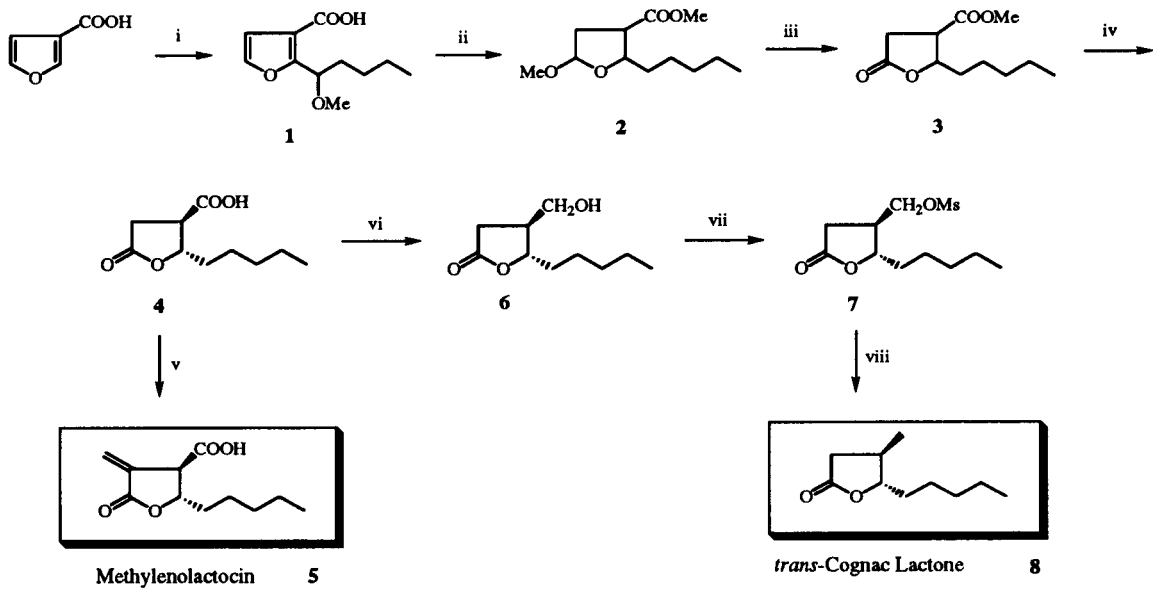
In the course of studying the metal ammonia reduction of heterocyclic compounds, we found [1] that the Birch reduction of 2-(1-alkoxyalkyl)-3-furancarboxylic acids produced 2-alkyl-3-furancarboxylic acids in excellent isolated yield with loss of the alkoxyl group. In this paper we describe a successful application of this reaction to the synthesis of the antitumor antibiotic (±)-methylenolactocin **5** [2], isolated from the culture filtrate of *penicillium sp.*, and the flavor component (±)-*trans*-cognac lactone **8** [3], extracted by alcoholic beverages like whisky or brandy from oak barrels in which they were kept for maturing.

Scheme 1

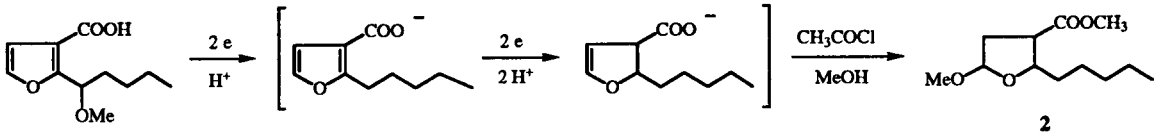


Reaction conditions and reagents: i) ref 1 ii) a) 5 equivalents Na, NH_3, MeOH, b) MeCOCl, MeOH, 89% (2 steps) iii) CrO_3, H_2SO_4, acetone, 93% iv) KOH, H_2O-dioxane, 93% v) Stiles reagent, Me_2NH, HCHO, 45% vi) BH_3, tetrahydrofuran, 60% vii) mesyl chloride, Et_3N, CH_2Cl_2, 81%, viii) Zn, NaI, 1,2-dimethoxyethane, 67%

The Birch reduction of **1** with 5 equivalent atoms of sodium in liquid ammonia, followed by treatment with acetyl chloride in methanol [4], afforded the methoxy acetal methyl ester **2** in 89% yield without isolation of the 2-pentyl-3-furancarboxylic acid and 2-pentyl-2,3-dihydro-3-furancarboxylic acid (Schemes 1 and 2). The acetal ester **2** was an isomeric mixture which could not be separated. Jones oxidation of **2** in acetone gave a mixture (*trans/cis*, 11:1) of lactone ester **3** which, without separation, was subjected to alkaline hydrolysis to give only *trans*-lactone acid **4** in 93% yield. This is a common compound for the synthesis of both (±)-methylenolactocin and (±)-*trans*-cognac lactone. Conversion of **4** to (±)-methylenolactocin was carried out according to the procedure reported by Stiles [5]. The ^1H and ^{13}C nmr spectra data of the syntetic **5** all matched those reported [2] for the natural compound.

On the other hand, the selective reduction of the carboxyl group in lactone acid **4** was performed with diborane in tetrahydrofuran to give a hydroxy lactone **6**, which was converted to the corresponding mesylate **7** in 50% yield (2 steps). The direct conversion of **7** to *trans*-cognac lactone was carried out according to the procedure reported by Fujimoto [6] in 67% yield. A colorless oil was obtained after separation and purification by column chromatography on silica gel of the residue from the reaction mixture. The resulting compound was identical with the natural product by comparing its hrms, ^1H and ^{13}C nmr spectra with those reported [2e].

Scheme 2



1 2

EXPERIMENTAL

Column chromatography was performed with silica gel (Merck NO. 7734; 63-200 μm), and thin layer chromatography (tlc) was performed on a glass plate coated with Kieselgel 60 GF_{254} (Merck). The ir spectra were taken on a JASCO A-102 IR spectrophotometer. The ^1H and ^{13}C nmr (deuteriochloroform), and mass spectra were recorded on JEOL LA-300 (300 MHz) and JEOL AX-500 spectrometers, respectively.

2-Methoxy-4-methoxycarbonyl-5-pentyltetrahydrofuran **2**.

This compound was prepared according to the procedure described previously [4]. To a stirred solution of **1** (4.2 g, 0.02 mole) and dry methanol (8 ml) in liquid ammonia (100 ml) was added sodium metal (2.3 g, 5 equivalents) little by little at - 33°, and the solution was stirred for 1 hour. After evaporation of ammonia at room temperature dry methanol (120 ml) was added to the residue. To the ice-cold solution was slowly added acetyl chloride and the solution was adjusted to *p*H 1 with vigorous stirring. Then the precipitated solid mass was removed by filtration. The filtrate was stirred at room temperature for 12 hours. After neutralization by adding solid sodium hydrogen carbonate the reaction mixture was extracted with dichloromethane. The extract was chromatographed to give **2** as an inseparable isomeric mixture , 4.55 g (89%); ^1H nmr: δ 0.89 (t, 3H, J = 7.0 Hz), 1.30-1.65 (m, 8H), 2.23-2.90 (m, 3H), 3.32 (s, 3H), 3.70 (s, 3H), 4.20 (m, 1H), 5.00 (m, 1H).

4-Methoxycarbonyl-5-pentyl-4,5-dihydro-2(3*H*)-furanone **3**.

To a cold stirred solution of **2** (1.65 g, 7.1 *l* mmoles) in acetone (20 ml) at 0° was dropwise added Jones reagent (8 ml) over 1 hour, and the solution was stirred overnight at room temperature. The usual work-up afforded **3** as an isomeric mixture (*trans*:*cis* = 11:1 by nmr), 1.43 g (93%). Chromatographic separation (hexane-ethyl acetate, 4:1) gave the *trans* form (1.1 g); ^1H nmr: δ 0.89 (t, 3H, J = 6.7 Hz), 1.33-1.51 (m, 6H), 1.71 (m, 2H), 2.82 (dd, 1H, J = 9.5 Hz, J = 17.8 Hz), 2.85 (dd, 1H, J = 8.6 Hz, J = 17.8 Hz), 3.07 (ddd, 1H, J = 7.3 Hz, J = 8.6 Hz, J = 9.5 Hz), 3.76 (s, 3H), 4.56 (dt, 1H, J = 4.9 Hz, J = 7.3 Hz) and the *cis* form (87 mg); ^1H nmr: δ 0.89 (t, 3H, J = 6.9 Hz), 1.26-1.50 (m, 6H), 1.53 (m, 2H), 2.68 (dd, 1H, J = 8.6 Hz, J = 17.6 Hz), 2.86 (ddd, 1H, J = 5.4 Hz, J = 7.5 Hz, J = 17.6 Hz), 3.45 (ddd, 1H, J = 5.3 Hz, J = 7.5 Hz, J = 8.4 Hz), 3.75 (s, 3H), 4.63 (ddd, 1H, J = 3.3 Hz, J = 7.3 Hz, J = 7.5 Hz).

trans-4-Carboxy-5-pentyl-4,5-dihydro-2(3*H*)-furanone **4**.

The isomeric mixture of **3** (2.0 g, 9.35 mmoles) was hydrolyzed with potassium hydroxide (730 mg, 18.7 mmoles) in dioxane-water (20 ml, 10 ml) at room temperature for 2 hours to give *trans*-**4** as a single product (1.74 g, 93%), mp 84-85° (recrystallizaion from cyclohexane), lit [2b] mp 105-107° for the (-)-form. ^1H nmr: δ 0.91 (t, 3H, J = 6.0 Hz), 1.30 (m, 6H), 1.83 (m, 2H), 2.82 (dd, 1H, J = 9.8 Hz, J = 17.7 Hz), 2.95 (dd, 1H, J = 8.5 Hz, J = 17.7 Hz), 3.09 (ddd, 1H, J = 7.3 Hz, J = 8.5 Hz, J = 9.8 Hz), 4.63 (dt, 1H, J = 4.8 Hz, J = 7.4 Hz); ^{13}C nmr: δ 13.9 (q), 22.4 (t), 24.9 (t), 31.3 (t), 31.9 (t), 35.4 (t), 45.4 (d), 81.8 (d), 174.2 (s), 175.7 (s).

(±)-Methylenolactocin **5**.

This compound was synthesized in 45% yield from **4** according to the procedure reported by Stiles [5], mp 82-83°; lit [2a] mp 82-84° for the (-)-form; ^1H nmr: δ 0.91 (t, 3H, J = 6.0 Hz), 1.31 (m, 6H), 1.73 (m, 2H), 3.61 (dt, 1H, J = 2.9 Hz, J = 5.6 Hz), 4.81 (dd, 1H, J = 5.9 Hz, J = 6.0 Hz), 6.02 (d, 1H, J = 2.9 Hz), 6.46 (d, 1H, J = 2.9 Hz); ^{13}C nmr: δ 13.9 (q), 22.4 (t), 24.4 (t), 31.4 (t), 35.7 (t), 49.6 (d), 78.9 (d), 125.8 (t), 132.5 (s), 168.4 (s), 174.7 (s).

trans-4-Hydroxymetthyl-5-pentyl-4,5-dihydro-2(3*H*)-furanone **6**.

To a stirred solution of **4** (457 mg, 2.3 mmoles) in dry tetrahydrofuran (5 ml) was dropwise added diborane (1 *M* in tetrahydrofuran, 4.7 ml, 4.7 mmoles) over 30 minutes below 0° under nitrogen. After stirring 20 hours at room temperature the reaction mixture was quenched by adding water (5 ml) and solid potassium carbonate (600 mg), and extracted with ether. The residue was chromatographed to give **6** (253 mg, 60%) as an oil; ir (neat): 3500, 1740 cm^{-1}; ^1H nmr: δ 0.81 (t, 3H, J = 6.8 Hz), 1.33-1.61 (m, 8H), 2.25 (m, 1H), 2.44 (dd, 1H, J = 6.8 Hz, J = 17.8 Hz), 2.57 (dd, 1H, J = 9.0 Hz, J = 17.8 Hz), 3.11 (bs, 1H), 3.58 (d, 2H, J = 5.4 Hz), 4.31 (dt, 1H, J = 5.4 Hz); ^{13}C nmr: δ 13.4 (q), 22.3 (t), 24.9 (t), 31.3 (t), 31.4 (t), 35.0 (t), 42.4 (d), 62.4 (t), 83.2 (d), 177.3 (s).

The *p*-Nitrobenzoate of **6** had mp 66-67°; ir (nujol): 1760, 1715 cm^{-1}; ^1H nmr: δ 0.89 (t, 3H, J = 6.7 Hz), 1.25-1.75 (m, 8H), 2.51 (dd, 1H, J = 6.0 Hz, J = 17.0 Hz), 2.70 (m, 1H), 2.84 (dd, 1H, J = 9.0 Hz, J = 17.0 Hz), 4.42 (m, 1H), 4.44 (d, 2H, J = 4.2 Hz), 8.16 (d, 2H, J = 8.6 Hz), 8.32 (d, 2H, J = 8.6 Hz); ^{13}C nmr: δ 13.9 (q), 22.4 (t), 25.0 (t), 31.4 (t), 31.7 (t), 35.1 (t), 39.6 (d), 66.1 (t), 82.7 (d), 123.7 (d), 130.8 (d), 134.7 (s), 150.8 (s), 164.3 (s), 175.1 (s).

Anal. Calcd. for $C_{17}H_{21}NO_6$. C, 60.89; H, 6.31; N, 4.18. Found: C, 60.84; H, 6.34; N, 4.15.

trans-4-Methanesulfonyloxymethyl-5-pentyl-4,5-dihydo-2(3*H*)-furanone **7**.

This compound was prepared in 81% yield from **6** (183 mg, 0.98 mmole) on treatment with mesyl chloride (0.1 ml, 1.28 mmoles) in dichloromethane (3 ml) and triethylamine (3 ml) at room temperature for 20 hours; ir (neat): 1760, 1345, 1165 cm^{-1}; ^1H nmr: δ 0.90 (t, 3H, J = 6.6 Hz), 1.26-1.72 (m, 8H), 2.49 (dd, 1H, J = 6.6 Hz, J = 17.2 Hz), 2.60 (m, 1H), 2.75 (dd, 1H, J = 9.0 Hz, J = 17.2 Hz), 3.07 (s, 3H), 4.25 (d, 2H, J = 5.7 Hz), 4.33 (dt,

1H, J = 5.7 Hz, J = 5.9 Hz); ^{13}C nmr: δ 13.9 (q), 22.4 (t), 24.9 (t), 31.2 (t), 31.3 (t), 34.9 (t), 37.6 (q), 40.1 (d), 68.2 (t), 81.9 (d), 175.1 (s); hrms: Calcd. for $C_{11}H_{21}O_5S$: $(M+H)^+$ 265.1109. Found: m/z 265.1112.

trans-Cognac Lactone **8**.

To a stirred solution of 7 (118 mg, 0.45 mmole) in dimethoxyethane (8 ml) were added sodium iodide (336 mg) and freshly activated zinc powder (293 mg) at room temperature for 1 hour. After stirring at 83° for 2.5 hours the reaction mixture was filtered, and extracted with ether. The residue was chromatographed (hexane-ethyl acetate, 4:1) to give the *trans*-cognac lactone **8** (51mg, 67%), bp 122°/128 mm Hg (Kugelrohr), lit [2e] bp 80°/6 mm Hg; ^1H nmr (500 MHz): δ 0.89 (t, 3H, J=7.0 Hz), 1.13 (d, 3H, J=6.5 Hz), 1.26-1.70 (m, 8H), 2.15-2.24 (m, 2H), 2.63-2.70 (m, 1H), 4.01 (dt, 1H, J=4.1 Hz, J=7.9 Hz); ^{13}C nmr: δ 14.2, 17.6, 22.58 , 22.64, 31.7, 34.1, 36.2, 37.3, 87.7, 176.9; hrms: Calcd. for $C_{10}H_{18}O_2$: M^+ 170.1307. Found: m/z 170.1287.

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