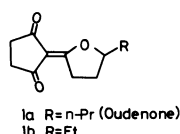


A Convenient Synthesis of Hypotensive (±)-Oudenone

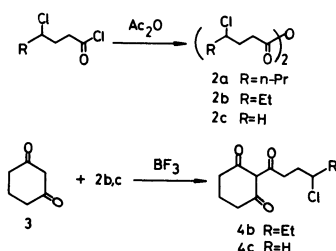
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Synopsis. (±)-Oudenone, 2-(tetrahydro-5-propyl-2-furylidene)-1,3-cyclopentanedione, was conveniently synthesized by BF_3 -catalyzed acylation of 1,3-cyclopentanedione with 4-chloroheptanoic anhydride and subsequent cyclization with triethylamine in a 36% overall yield.

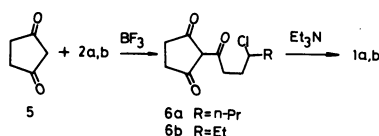
Oudenone (**1a**) was isolated from a culture filtrate of *Oudemansiella radicata* by the group of Ohno and Umezawa¹⁾ and found to exhibit significant hypotensive effect against spontaneously hypertensive rats due to inhibition of tyrosine hydroxylase.²⁾ Since it was synthesized initially in relation with the structural



elucidation,³⁾ several synthetic methods^{4–6)} have been reported. Recently, Bates et al.⁷⁾ have reported a new route to (±)-**1a** which involves the acid-catalyzed C-alkylation of 1,3-cyclopentanedione (**5**) with 5-propyltetrahydro-2-furanol to give dihydrooudenone



Scheme 1.



Scheme 2.

Table 1. Acylation of 1,3-Cyclohexanedione (**3**) with Anhydrides **2b, c**

Entry	Anhydride (R)	Method ^{a)}	Conditions °C/h	Product (Yield/%)
1	2c (H)	A	110/12	4c (24)
2	2c (H)	B	90/12	4c (34)
3	2c (H)	C	95/12	4c (46)
4	2b (Et)	B	110/12	4b (17)
5	2b (Et)	C	95/12	4b (36)

a) A: $\text{BF}_3 \cdot \text{OEt}_2$, B: BF_3 in CH_2Cl_2 -AcOEt, C: BF_3 .

and subsequent introduction of C–C double bond via phenylselenenylation.

We report here a convenient two-step synthesis of (±)-**1a** which is characterized by boron trifluoride (BF_3)-catalyzed acylation of **5** with 4-chloroheptanoic anhydride (**2a**) to give 2-(4-chloroheptanoyl)-1,3-cyclopentanedione (**6a**). Subsequent cyclization of **6a** by triethylamine gave (±)-**1a** in a 36% overall yield (Scheme 2). While the acylation of **5** would be effective not only for the straightforward synthesis of (±)-**1a** but also for the synthesis of other biologically active compounds,⁸⁾ the reaction has not been well established.⁹⁾

Manvik et al.¹⁰⁾ reported that BF_3 was effective for the acylation of carbon atom α to carbonyl group with acid anhydride. Leucht¹¹⁾ used the procedure for the C-acylation of 3-alkyl-1,2,4-cyclopentanetrione. We applied the method to the present synthesis. In the first place, we examined the reaction conditions for the BF_3 -catalyzed acylation of readily available 1,3-cyclohexanedione (**3**) with 4-chloroalkanoic anhydrides **2b, c** as shown in Scheme 1. Anhydrides **2a–c** were easily prepared by heating the corresponding acid chloride¹²⁾ in acetic anhydride. As shown in Table 1, the acylation of **3** with **2c** was examined as a typical example by using three conditions: a) use of $\text{BF}_3 \cdot \text{OEt}_2$ (Entry 1); b) addition of a mixture of **3** and **2c** to CH_2Cl_2 -AcOEt after saturation with BF_3 ¹¹⁾ (Entry 2), and c) introduction of BF_3 to a mixture of **3** and **2c**,¹¹⁾ which gave the best result (Entry 3). The use of **2b** slightly decreased the yield of **4b** (Entries 4 and 5).

The BF_3 -catalyzed acylation of **5** with **2a** was carried out by using the conditions C of Table 1 to give **6a** in a 74% yield (Scheme 2). Fortunately, the yield was approximately doubled as compared with that of **4b**. Compound **6a** was readily cyclized to (±)-**1a** by the treatment with triethylamine at 0 °C in a 49% yield after recrystallization. In a similar way, oudenone homolog (±)-**1b**^{5b)} was synthesized via **6b** in a 31% overall yield.

Experimental

Melting points were determined by a Yamato Model MP-21 apparatus and uncorrected. Infrared spectra were taken on a JASCO A-102 spectrometer. ^1H NMR spectra (60 MHz) were measured with a Hitachi R-24 spectrometer. ^{13}C NMR (25 MHz) spectra were taken on a JEOL FX-100 spectrometer. Column chromatography was performed through silica gel (Wakogel C-200). Preparative TLC was done on silica gel (Kieselgel 60 PF₂₅₄).

Typical Reaction for the Preparation of Anhydrides 2a–c. 4-Chloroheptanoic Anhydride (**2a**). A mixture of 4-chloroheptanoyl chloride¹²⁾ (4.89 g, 26.7 mmol) and acetic anhydride (9 ml, 95.2 mmol) was placed in a reaction vessel

connected with a distillation apparatus and heated at 95 °C for 3 h, removing the resulting acetyl chloride continuously. The reaction mixture was then distilled to give **2a** (2.69 g, 65% yield): bp 120–156 °C (1.0 mmHg) (1 mmHg=133.322 Pa); IR (neat) 1820, 1753, 1045 cm⁻¹; ¹H NMR (CCl₄) δ=0.97 (6H, t, *J*=8 Hz), 1.20–2.50 (12H, m), 2.65 (4H, t, *J*=8 Hz), 3.88 (2H, m). Anal. (C₁₄H₂₄O₃Cl₂) C, H.

4-Chlorohexanoic Anhydride (2b): Yield 71%; bp 135–143 °C (2 mmHg); IR (neat) 1815, 1745, 1045 cm⁻¹; ¹H NMR (CCl₄) δ=1.07 (6H, t, *J*=8 Hz), 1.35–2.45 (8H, m), 2.65 (4H, t, *J*=8 Hz), 3.83 (m, 2H). Anal. (C₁₂H₂₀O₃Cl₂) C, H.

4-Chlorobutanoic Anhydride (2c): Yield 88%; bp 120–124 °C (1.5 mmHg); IR (neat) 1815, 1750, 1045 cm⁻¹; ¹H NMR (CCl₄) δ=2.16 (4H, m), 2.64 (4H, t, *J*=7 Hz), 3.60 (4H, t, *J*=7 Hz). Anal. (C₈H₁₂O₃Cl₂) C, H.

Typical Reactions for Acylation. **2-(4-Chlorobutanoyl)-1,3-cyclohexanedione (4c).** a. With BF₃·OEt₂. To a mixture of **3** (275 mg, 2.45 mmol) and BF₃·OEt₂ (2.55 g, 17.7 mmol) was added 4-chlorobutanoic anhydride (**2c**) (640 mg, 2.82 mmol) at room temperature. The mixture was stirred for 12 h at 110 °C. After cooling the mixture, it was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over MgSO₄, and concentrated under vacuum. Purification of the residue by preparative TLC (hexane–ethyl acetate, 1:1, *R*_f=0.68) gave **4c** (112 mg, 23% yield): IR (neat) 3400 (enol OH), 1660, 1550 cm⁻¹; ¹H NMR (CDCl₃) δ=1.70–2.90 (8H, m), 3.16 (2H, t, *J*=7 Hz), 3.58 (2H, t, *J*=7 Hz), 17.9 (1H, s, enol OH). ¹³C NMR (CDCl₃) δ=19.0 (t), 27.2 (t), 32.8 (t), 38.1 (t), 38.6 (t), 44.3 (t), 112.9 (s), 194.9 (s), 197.5 (s), 204.5 (s). These spectral data implies that **4c** is present in enol form. Anal. (C₁₀H₁₃O₃Cl) C, H.

b. With BF₃ in Ethyl Acetate–Dichloromethane. BF₃ generated by using sodium tetrafluoroborate (NaBF₄) (60 g, 546 mmol), anhydrous diboron trioxide (B₂O₃) (10 g, 144 mmol), and concd sulfuric acid (60 ml)¹⁹ was introduced into a mixed solvent of ethyl acetate (5 ml) and dichloromethane (8 ml). After cooling the solution in an ice bath, a mixture of **3** (2.2 g, 20 mmol) and **2c** (9.05 g, 40 mmol) was added dropwise. It was stirred for 30 min at 0 °C and for additional 12 h at 90 °C. The mixture was treated in a similar manner to give **4c** (1.46 g, 34% yield) after purification by column chromatography (hexane–ethyl acetate, 5:1).

c. With BF₃. To a cooled (0 °C) mixture of **3** (2.62 g, 23.4 mmol) and **2c** (11.2 g, 49.5 mmol), was introduced BF₃ generated from NaBF₄ (60 g, 546 mmol), anhydrous B₂O₃ (10 g, 144 mmol), and concd sulfuric acid (60 ml).¹⁹ The introduction was completed within 15 min. The darkened mixture was stirred for 30 min at 0 °C, for 30 min at room temperature, and for additional 12 h at 95 °C. The reaction mixture was treated in a manner similar to the foregoing experiment to give **4c** (2.31 g, 46% yield).

2-(4-Chlorohexanoyl)-1,3-cyclohexanedione (4b): IR (neat) 3400 (enol OH), 1730, 1662, 1560 cm⁻¹; ¹H NMR (CDCl₃) δ=1.04 (3H, t, *J*=8 Hz), 1.60–2.84 (10H, m), 3.22 (2H, t, *J*=8 Hz), 3.90 (1H, m), 17.91 (1H, br s, enol OH); ¹³C NMR (CDCl₃) δ=11.0 (q), 19.2 (t), 31.6 (t), 32.5 (t), 32.9 (t), 38.1 (t), 38.8 (t), 64.9 (d), 113.1 (s), 195.3 (s), 197.9 (s), 205.3 (s). Anal. (C₁₂H₁₇O₃Cl) C, H.

2-(4-Chloroheptanoyl)-1,3-cyclopentanedione (6a): Yield 74% after purification by column chromatography (hexane–acetone, 8:1); IR (neat) 3420 (enol OH), 1710, 1630, 1585 cm⁻¹; ¹H NMR (CDCl₃) δ=0.95 (3H, t, *J*=7 Hz), 1.20–2.35 (6H, m), 2.35–2.90 (4H, m), 3.15 (2H, t, *J*=9 Hz), 4.05 (1H, m), 10.90 (1H, br s, enol OH). Anal. (C₁₂H₁₇O₃Cl) C, H.

2-(4-Chlorohexanoyl)-1,3-cyclopentanedione (6b): Yield 69% after purification by column chromatography (hexane–acetone, 8:1); IR (neat) 3450 (enol OH), 1710, 1625, 1580 cm⁻¹; ¹H NMR (CDCl₃) δ=0.92 (3H, t, *J*=8 Hz), 1.30–2.20 (4H, m), 2.20–2.80 (4H, m), 3.05 (2H, t, *J*=9 Hz), 3.86 (1H, m), 11.40 (1H, s, enol OH). Anal. (C₁₁H₁₅O₃Cl) C, H.

2-(5-Propyltetrahydro-2-furylidene)-1,3-cyclopentanedione (Oudenone) ((±)-1a). Triethylamine (2 ml) was added to **6a** (90 mg, 0.37 mmol) at 0 °C. After being stirred for 4.5 h at 0 °C, triethylamine unreacted was removed under reduced pressure. The residual oil was extracted with acetone, and purified by column chromatography (hexane–acetone, 1:1) followed by recrystallization from hexane to give (±)-**1a** (37 mg, 49% yield): Mp 81–82 °C (lit.^{3a} 77–78 °C); IR (KBr) 3440, 1712, 1660, 1560 cm⁻¹; ¹H NMR (CDCl₃) δ=0.92 (3H, t, *J*=7 Hz), 1.08–1.96 (4H, m), 2.54 (4H, br s), 2.84–3.76 (4H, m), 4.90 (1H, m); ¹³C NMR (CDCl₃) δ=13.9 (q), 18.7 (t), 26.9 (t), 33.8 (t), 34.6 (t), 35.0 (t), 36.8 (t), 90.5 (d), 109.3 (s), 184.6 (s), 200.8 (s), 204.8 (s). These spectral data were consistent with those reported.^{3a,7}

2-(5-Ethyltetrahydro-2-furylidene)-1,3-cyclopentanedione ((±)-1b)^{5b}: Yield 42%; mp 106–107 °C (hexane–benzene, 2:1); IR (KBr) 3375, 1712, 1660, 1560 cm⁻¹; ¹H NMR (CDCl₃) δ=0.97 (3H, t, *J*=7 Hz), 1.6–2.0 (2H, m), 2.56 (4H, s), 2.92–3.72 (4H, m), 4.84 (1H, m). Anal. (C₁₁H₁₄O₃) C, H.

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