A Convenient Synthesis of Hypotensive (±)-Oudenone

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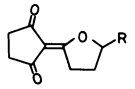
(Received September 22, 1986)

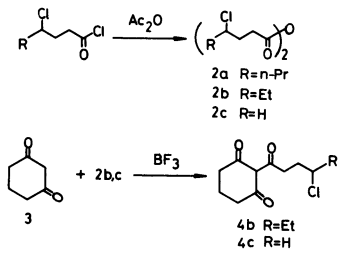
Synopsis. (±)-Oudenone, 2-(tetrahydro-5-propyl-2-furylidene)-1,3-cyclopentanedione, was conveniently synthesized by BF_3-catalyzed acylation of 1,3-cyclopentanedione with 4-chloroheptanoic anhydride and subsequent cyclization with triethylamine in a 36% overall yield.

Oudenone (**1a**) was isolated from a culture filtrate of *Oudemansiella radicata* by the group of Ohno and Umezawa[1] 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



1a R=n-Pr (Oudenone)
1b R=Et

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



2a R=n-Pr
2b R=Et
2c R=H

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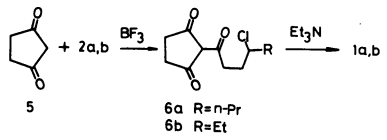
4b R=Et
4c R=H

Scheme 1.



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6a R=n-Pr
6b R=Et

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: $BF_3 \cdot OEt_2$, 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. Leucht[11] 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 chloride[12] 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 $BF_3 \cdot OEt_2$ (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 PF_{254}).

Typical Reaction for the Preparation of Anhydrides 2a—c. 4-Chloroheptanoic Anhydride (2a). A mixture of 4-chloroheptanoyl chloride[12] (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 (CCl_4) 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. ($C_{14}H_{24}O_3Cl_2$) C, H.

4-Chlorohexanoic Anhydride (2b): Yield 71%; bp 135—143 °C (2 mmHg); IR (neat) 1815, 1745, 1045 cm^{-1}; ^1H NMR (CCl_4) 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. ($C_{12}H_{20}O_3Cl_2$) C, H.

4-Chlorobutanoic Anhydride (2c): Yield 88%; bp 120—124 °C (1.5 mmHg); IR (neat) 1815, 1750, 1045 cm^{-1}; ^1H NMR (CCl_4) δ=2.16 (4H, m), 2.64 (4H, t, J=7 Hz), 3.60 (4H, t, J=7 Hz). Anal. ($C_8H_{12}O_3Cl_2$) C, H.

Typical Reactions for Acylation. 2-(4-Chlorobutanoyl)-1,3-cyclohexanedione (4c). a. With $BF_3 \cdot OEt_2$. To a mixture of **3** (275 mg, 2.45 mmol) and $BF_3 \cdot OEt_2$ (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 $MgSO_4$, 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 ($CDCl_3$) 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). ^{13}C NMR ($CDCl_3$) 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. ($C_{10}H_{13}O_3Cl$) C, H.

b. With BF_3 in Ethyl Acetate-Dichloromethane. BF_3 generated by using sodium tetrafluoroborate ($NaBF_4$) (60 g, 546 mmol), anhydrous diboron trioxide (B_2O_3) (10 g, 144 mmol), and concd sulfuric acid (60 ml)[13] 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 BF_3. To a cooled (0 °C) mixture of **3** (2.62 g, 23.4 mmol) and **2c** (11.2 g, 49.5 mmol), was introduced BF_3 generated from $NaBF_4$ (60 g, 546 mmol), anhydrous B_2O_3 (10 g, 144 mmol), and concd sulfuric acid (60 ml).[13] 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 ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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. ($C_{12}H_{17}O_3Cl$) 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 ($CDCl_3$) 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. ($C_{12}H_{17}O_3Cl$) 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 ($CDCl_3$) 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. ($C_{11}H_{15}O_3Cl$) 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 ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 ($CDCl_3$) 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. ($C_{11}H_{14}O_3$) C, H.

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