A Synthesis of 3-Hydroxymethyl-2-(6-methylheptanoyl)-4-butanolide (A-Factor)

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The A-Factor was conveniently synthesized from 3-furoic acid *via* the Birch reduction.

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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-furoic acid and 3-furoic acid (**1**) gave methyl 2,5-dihydro-2-furoate and methyl 2,3-dihydro-3-furoate (**2**), after esterification with diazomethane, respectively. Some naturally occurring compounds such as apiose [2], dihydrostreptose [3], pantolactone and its homologue [4] have been synthesized from this versatile synthetic intermediate **2**. In this paper we describe the convenient synthesis of the (±) A-factor (**7**), which is an autoregulator isolated from *Streptomycetes sp.* The synthesis of both racemic [5] and optically active A-factor [6] [7] [8] have been reported by two groups.

The methoxy acetal methyl ester **3** required for the synthesis of **7** was directly prepared in almost quantitative yield by the Birch reduction of 3-furoic acid followed by esterification and treatment with acetyl chloride in methanol, without isolation of the dihydro compound **2**. The acetal ester **3** was a mixture of *anti* and *syn* (2:1) isomers which were separable by column chromatography.

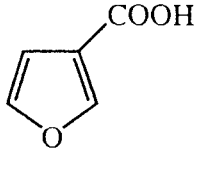
After lithium aluminium hydride reduction of **3** followed by oxidation using Grieco's method [9] lactone alcohol **5** was obtained in 71%, which was converted to the corresponding trimethylsilyl ether **6**. This is a key compound for the synthesis of many butanolide autoregulators. The lactone enolate generated by treating **6** with lithium diisopropylamide in tetrahydrofuran at −78° was acylated with 6-methylheptanoyl chloride to give the silyl ether of **7**. This was dissolved in aqueous ethanol and the solution was refluxed to remove the trimethylsilyl protective group. Subsequent workup followed by chromatographic purification afforded (±) A-factor **7** as a waxy solid. The ir, ms, ^{1}H nmr and ^{13}C nmr spectral data all were identical to that synthesized by Mori.

EXPERIMENTAL

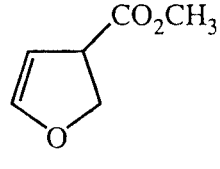
Column chromatography was performed with silica gel (Merck NO. 7734; 63-200 μm), and thin-layer chromatography (tlc) was performed on a glass plate coated with Kieselgel 60 GF_{254} (Merck), followed by heating with anisaldehyde-acetic acid-sulfuric acid (1:100:2). The ir spectra were taken on a JASCO A-102 IR spectrophotometer. The ^{1}H nmr spectra (400 MHz) were recorded with a JEOL JNM-GX 400 FT NMR spectrometer, and ^{1}H (100 MHz) and ^{13}C (25 MHz) nmr spectra were recorded with a JEOL FX-100 spectrometer for deuteriochloroform solution.

The Birch Reduction of 3-Furoic Acid [1]: Methyl 5-Methoxy-3-tetrahydrofuran-3-carboxylate **3**.

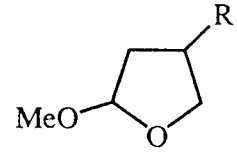
The Birch reduction of 3-furoic acid (22.4 g) was carried out by the method reported previously, in the presence of dry methanol as a proton source. After evaporation of liquid ammonia at room temperature methanol (600 ml) was added to the residue. To the ice-cold solution was slowly added acetyl chloride and adjusted to *p*H 1 with vigorous stirring, and the precipitated solid mass was removed by filtration. The filtrate was stirred at room tempera-



1

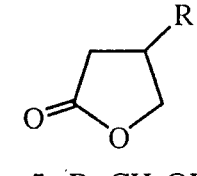


2



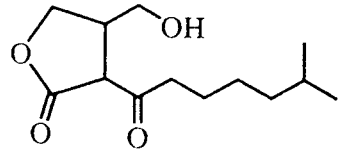
3 R=CO_2CH_3

4 R=CH_2OH



5 R=CH_2OH

6 R=CH_2OSiMe_3



7

ture for 12 hours. After neutralization by adding solid sodium hydrogen carbonate the reaction mixture was extracted with dichloromethane. The extract was distilled to give **3** (31.2 g, 98%), bp 90-92°/10 mm Hg, (lit [1] bp 90-92°/10 mm Hg).

Column chromatography of **3** was performed with a hexane-ethyl acetate (4:1) as eluant; Rf 0.44 (*anti*); ^{1}H nmr: (400 MHz) δ 2.08 (dd, 1H, J = 8.54 Hz, J = 12.81 Hz, H-4), 2.24 (dddd, 1H, J = 4.88 Hz, J = 8.54 Hz, J = 12.81 Hz, H-4), 3.21 (quint, 1H, J = 7.33 Hz, H-3), 3.28 (s, 3H, OMe), 3.66 (s, 3H, CO_2CH_3), 4.03 (d, 2H, J = 7.33 Hz, H-2), 5.04 (d, 1H, J = 4.88 Hz, H-5); ^{13}C nmr: δ 36.1 (C-4), 42.0 (C-3), 52.1 (CO_2CH_3), 54.6 (OMe), 68.7 (C-2), 105.1 (C-5), 174.2; Rf 0.33 (*syn*); ^{1}H nmr: (400 MHz) δ 2.24 (m, 2H, H-4), 3.05 (m, 1H, H-3), 3.29 (OMe), 3.68 (CO_2CH_3), 4.02 (t, 1H, J = 8.54 Hz, J = 11.6 Hz, H-2), 4.05 (t, 1H, J = 8.54 Hz, J = 11.6 Hz, H-2'), 5.00 (dd, 1H, J = 1.83 Hz, J = 4.88 Hz, H-5); ^{13}C nmr: δ 35.9 (C-4), 42.5 (C-3), 52.1 (CO_2CH_3), 54.7 (OMe), 67.7 (C-2), 104.9 (C-5), 173.1.

5-Methoxy-3-tetrahydrofuran-3-methanol (**4**).

To a stirred suspension of lithium aluminium hydride (2.4 g) in dry ether (200 ml) was added a solution of **3** (4.8 g, 30 mmoles) in dry ether (30 ml). After refluxing for 3 hours, a small amount of water was added to decompose excess lithium aluminium hydride and the precipitate was filtered off. The residue was distilled to give **4** as a colorless oil (3.64 g, 92%), bp 119-120°/25 mm Hg; ir (neat): 3400, 1200, 1090, 1040 cm^{-1}; ^{1}H nmr: δ 1.60-2.20 (m, 2H, H-4), 2.50 (m, 1H, H-3), 3.18 (br s, 1H, OH), 3.32 (s, 3H, OMe), 3.40-4.10 (m, 4H, H-2, CH_2OH), 5.02 (d, 1H, J = 5.12 Hz, H-5); ^{13}C nmr: δ 35.4 (C-4), 39.5 (C-3), 54.4 (OMe), 64.6 (CH_2OH), 68.9 (C-2), 105.0 (C-5).

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.41; H, 9.18.

3-Hydroxymethyl-4-butanolide **5**.

A solution of **4** (3.2 g, 24.2 mmoles) in dry dichloromethane (80 ml) containing catalytic amounts of boron trifluoride etherate (10 drops) was treated at room temperature with *m*-chloroperbenzoic acid (6.0 g, 34.3 mmoles). After 3 hours aqueous sodium thiosulfate and saturated sodium bicarbonate was added to the reaction mixture, and evaporated to dryness. Dichloromethane (50 ml) was added to the residue. After triturating well, the solid mass was filtered off and washed with dichlromethane. The filtrate was evaporated and the residue was chromatographed using (50:1) ethyl acetate-2-propanol, and then distilled to give **5** (2.0 g, 71%), bp 124-127°/3 mm Hg; (lit [6] bp 160°/8 mm Hg); ir (neat): 3450, 1775 cm^{-1}; ^{13}C nmr: δ 30.7 (C-3), 36.7 (C-4), 62.5 (CH_2OH), 70.8 (C-2), 178.1 (C-5).

3-Trimethylsilyloxymethyl-4-butanolide **6**.

To a stirred and ice-cooled solution of **5** (2.0 g, 17.3 mmoles) in dry pyridine (2.5 ml) was added hexamethyldisilazane (2.1 ml) and trimethylsilyl chloride (2.1 ml) and the mixture was kept at 0° for 3 hours. After dilution with benzene-pentane (1:1, 18 ml), the mixture was filtered through Celite to remove pyridine hydrochloride. The filtrate was concentrated *in vacuo*. The residue was distilled to give **6** (2.8 g, 87%), bp 155-158°/30 mm Hg, (lit [6] bp 140-144°/26 mm Hg); ^{13}C nmr: δ −0.7 ($SiMe_3$), 30.8 (C-3), 37.2 (C-4), 62.7 (CH_2OH), 70.5 (C-2) 155.5 (C-5).

3-Hydroxymethyl-2-(6-methylheptanoly)-4-butanolide (A-Factor) **7**.

The reaction was carried out using a modification of the procedure reported by Mori [6]. A solution of lithium diisopropylamide was prepared by the addition of *n*-butyllithium (1.6 *N* in *n*-hexane, 5.53 ml, 8.78 mmoles) to a stirred and cooled solution of diisopropylamine (834 mg, 8.23 mmoles) in dry tetrahydrofuran (7.0 ml) at −78° under nitrogen. To this was added with stirring and cooling at −78° a solution of **6** (629 mg, 3.35 mmoles) in dry tetrahydrofuran (4 ml). The solution was stirred at −78° for 30 minutes. Then 6-methylheptanoyl chloride (606 mg, 3.73 mmoles) in dry hexamethyl phosphorousamide (1.5 ml) was added dropwise during 5 minutes. After stirring for 1 hour at −78°, the mixture was quenched by the addition of saturated ammonium chloride and extracted with ether. The ether solution was washed with water and brine, dried with sodium sulfate, and concentrated *in vacuo* to give an oil. This was dissolved in ethanol-water (4:1; 12 ml), and the solution was heated at reflux for 15 minutes. After the removal of ethanol *in vacuo*, the product was extracted with ether. The ether solution was washed with water and brine, dried with sodium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel (100 g) with benzene-ethyl acetate (2:1) to give **7** (431 mg, 53%) of a waxy solid; ir (neat): 3460, 2960, 1765, 1720, 1640, 1470, 1380, 1215, 1170, 1025 cm^{-1}; ^{13}C nmr: δ 22.6 (q, C-12,13), 23.5 (t, C-10), 26.7 (t, C-9), 27.8 (d, C-11), 38.6 (t, C-8), 39.4 (d, C-3), 42.6 (t, C-7), 55.0 (d, C-2), 61.0 (t, C-5), 69.3 (t, C-4), 172.9 (s, C-1), 203.2 (s, C-6); ms: $M^{+\cdot}$ (m/z) 242 (3%), 224 (5%), 211 (37%), 158 (28%), 153 (21%), 143 (23%), 127 (52%), 116 (25%), 109 (100%, base peak), 102 (26%), 85 (70%), 82 (30%), 67 (14%), 57 (54%).

The ir, ms and nmr spectral data all were identical with those of the A-Factor synthesized and reported by Mori.

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