Convergent Syntheses of Luteoreticulin and Didemethylluteoreticulin

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Convergent syntheses of luteoreticulin (**1a**) and didemethylluteoreticulin (**1c**) are described which are ammenable to structural variation in both the pyran and phenyl rings.

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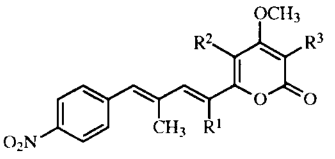
Luteoreticulin (**1a**) was first isolated by Koyama *et al.* [1,2] from *Streptomyces luteoreticuli*. They indicated that it was a "toxic metabolite" but did not disclose the spectrum of activity. Recently, a close structural analog of luteoreticulin, griseulin (**1b**), was reported to have activity against nematodes (*P. redivivus*, *C. elegans*, and *H. glycines*) and mosquito (*A. eagypti*) [3]. In order to investigate the potential insecticidal activity of luteoreticulin and its relationship to griseulin, we initiated a synthesis program.



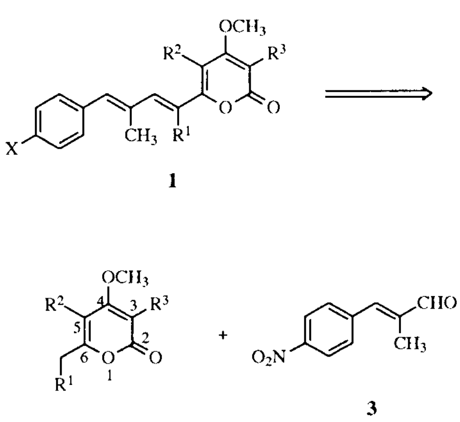
1a: R^1, $R^3 = CH_3$; $R^2 = H$
1b: $R^1 = H$; R^2, $R^3 = CH_3$
1c: R^1, R^2, $R^3 = H$

In the only reported synthesis of luteoreticulin [4], the carbon framework of the pyrone ring was constructed by the successive addition of a propionate and an acetate unit onto 4-nitro-α-methylcinnamaldehyde followed by ring closure. Since our goal was to prepare compounds varying both the aromatic nitro group and methyl substitution in the pyrone ring, we desired a more convergent route. Retrosynthetic analysis, shown in Scheme 1, suggested pyrone **2** and the nitrocinnamaldehyde **3** to be reasonable starting materials. We selected the readily available pyrone **2a** [5] for a model system.

Aldol condensation between **2a** and aromatic aldehydes in the presence of magnesium methoxide is known to occur at C-6 but the reaction generally suffers from low yields [6]. Lithiation of **2a** with lithium diisopropylamide or *n*-butyllithium occurs readily, but the reaction with aldehydes gives the undesired product of condensation at C-3 [7]. This regiospecificity was reversed, in a closely related pyrone **2b**, by the addition of hexamethylphosphoramide to the reaction mixture [8,9]. Due to the structural similarity of pyrones **2a** and **2b**, we believed that the desired C-6 condensation product could be obtained using this method.

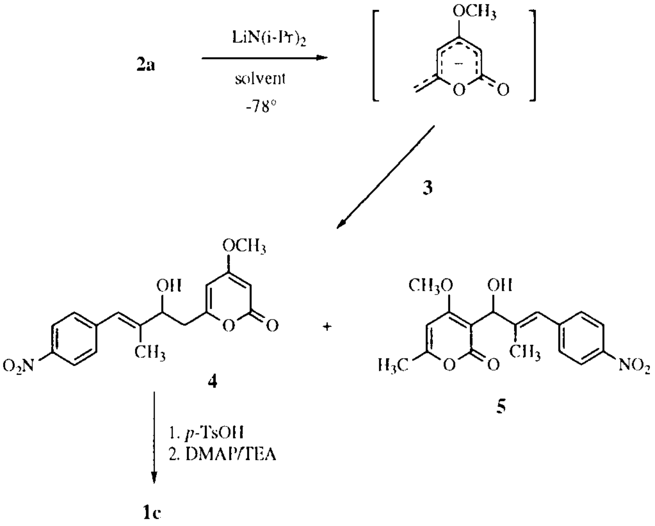
Deprotonation of **2a** with lithium diisopropylamide in tetrahydrofuran followed by quenching with **3** afforded the C-3 condensed product **5** as expected [7]. The addition of 1 equivalent of hexamethylphosphoramide to the reaction resulted in a 1:1 mixture of the C-6 condensed product **4** and the C-3 product **5**. Adding more hexamethylphosphor-

Scheme 1



2a: R^1, R^2, $R^3 = H$
2b: R^1, $R^3 = H$; $R^2 = CH_3$
2c: R^1, $R^3 = CH_3$; $R^2 = H$

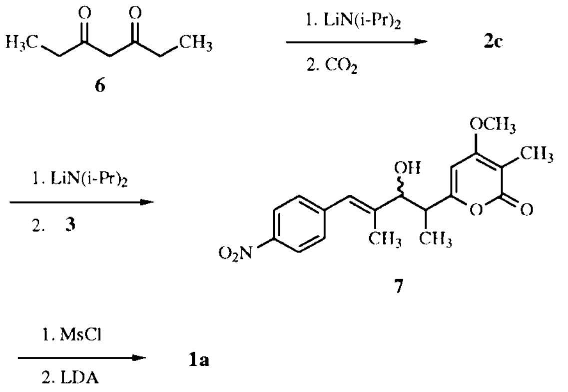
Scheme 2



amide did not change the **4**/**5** ratio. We were able to convert **4** to didemethylluteoreticulin (**1c**) in good yield by tosylation of the alcohol followed by elimination to the diene.

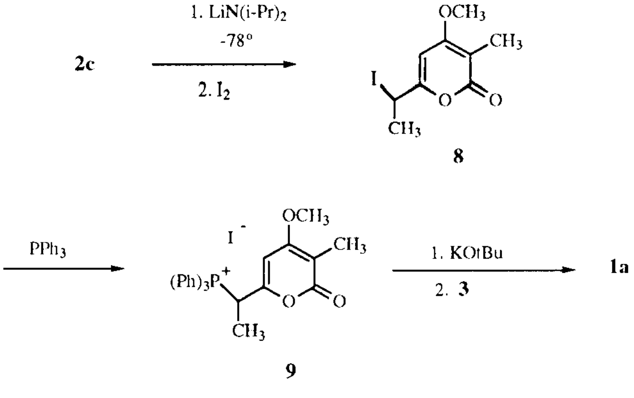
With the success of the model study, we applied this strategy to the synthesis of luteoreticulin (**1a**). The required pyrone **2c** was easily prepared from 2,4-heptadione (**6**) adapting a literature procedure [10]. Deprotonation of **2c** with lithium diisopropylamide in tetrahydrofuran/hexamethylphosphoramide, followed by the reaction with **3** afforded a mixture of diastereomeric vinyl alcohols **7**. No C-3 substituted products were isolated even without the addition of hexamethylphosphoramide. Unfortunately, conversion of **7** into **1a** was achieved but only in poor yield. Since we were unable to overcome this problem, we decided to convert **2c** into a phosphonium ylide and use a Wittig approach for the construction of the diene.

Scheme 3



The iodopyrone **8** was prepared by adding the lithiated **2c** to a solution of iodine in tetrahydrofuran. Conversion of **8** to the phosphonium salt **9** was done at room temperature in sulfolane in good yield. The ylide, prepared *in situ* from **9** and potassium *t*-butoxide in dichloromethane, was reacted with **3** to give **1a** in a recrystallized yield of 44%.

Scheme 4



In summary, convergent syntheses of luteoreticulin and didemethylluteoreticulin were developed ammenable to structural variations in both the phenyl and pyrone rings.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^{1}H (300 MHz) and ^{13}C (75.5 MHz) nmr spectra were recorded in deuteriochloroform, unless otherwise indicated, on a General Electric QE300 spectrometer. Chemical shifts are expressed in parts per million downfield from internal tetramethysilane and deuteriochloroform respectively. Elemental analyses were determined at FMC Corporation, Analytical Services Department. Chromatography was performed using EM Silica Gel 60 (0.040-0.063 mm). Solvents and reagents were used as purchased from Aldrich Chemical Co., EM Science, and J. T. Baker Inc.

Synthesis of [*R,S*] 3-Hydroxy-4-(4-methoxy-2*H*-pyran-2-on-6-yl)-2-methyl-1-(4-nitrophenyl)-1-butene (**4**) and [*R,S*] 1-Hydroxy-1-(4-methoxy-6-methyl-2*H*-pyran-2-on-3-yl)-2-methyl-3-(4-nitrophenyl)-2-propene (**5**).

To a solution of 2 g (14.3 mmoles) of **2a**, 2.6 ml of hexamethylphosphoramide, and 50 ml of dry tetrahydrofuran at -78° was added 7.8 ml of 2*M* lithium diisopropylamide. After 10 minutes stirring at -78°, a solution of 2.8 g (14.6 mmoles) of **3** [11] and 25 ml of dry tetrahydrofuran was added. After 10 minutes, the mixture was warmed to -25° and then poured into ice (100 g) and 5% aqueous hydrochloric acid (100 ml) and then extracted with ethyl ether (2 x 250 ml). After drying with magnesium sulfate, the ether was evaporated *in vacuo* to an oil which was chromatographed (ethyl acetate/heptane, 2:1) to afford **4** and **5**.

Compound **4** (higher Rf) was a yellow solid, 0.95 g (21%), mp 148-150°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.87 (3H, d, J = 1 Hz), 2.66 (2H, dq), 3.76 (3H, s), 4.37 (1H, m), 5.45 (1H, bs), 5.51 (1H, d, J = 2 Hz), 6.09 (1H, d, J = 2 Hz), 6.57 (1H, s), 7.51 (2H, d, J = 9 Hz), 8.17 (2H, d, J = 9 Hz).

Anal. Calcd for $C_{17}H_{17}NO_6$: C, 61.63; H, 5.17; N, 4.23. Found: C, 61.64; H, 5.33; N, 4.05.

Compound **5** (lower Rf) was a yellow solid, 1.1 g (24%), mp 135-137° (lit mp 138-142° [7]); ^{1}H nmr: δ 1.87 (3H, s), 2.32 (3H, s), 3.95 (3H, s), 4.85 (1H, d, J = 11 Hz), 5.38 (1H, d, J = 11 Hz), 6.13 (1H, s), 6.67 (1H, s), 7.39 (2H, d, J = 9 Hz), 8.17 (2H, d, J = 9 Hz).

Synthesis of 4-(4-Methoxy-2*H*-pyran-2-on-6-yl)-2-methyl-1-(4-nitrophenyl)-1,3-butadiene (**1c**).

A solution of 0.9 g (2.7 mmoles) of **4** in 50 ml of dichloromethane was stirred at rt as 0.57 g (3 mmoles) of *p*-toluenesulfonyl chloride, 0.36 g (3 mmoles) of *N,N*-dimethylaminopyridine, and 0.42 ml (3 mmoles) of triethylamine were added. The mixture was stirred at rt for 18 hours and then washed with 10% aqueous hydrochloric acid (25 ml), saturated sodium bicarbonate (25 ml), dried over magnesium sulfate and then concentrated *in vacuo* to afford 0.8 g (94%) of a yellow solid which was recrystalized from ethyl acetate, mp 205-206°; ^{1}H nmr: δ 2.07 (3H, d, J = 1 Hz), 3.83 (3H, s), 5.50 (1H, d, J = 2 Hz), 5.94 (1H, d, J = 2 Hz), 6.23 (1H, d, J = 15 Hz), 6.81 (1H, s), 7.34 (1H, d, J = 15 Hz), 7.48 (2H, d, J = 9 Hz), 8.23 (2H, d, J = 9 Hz).

Anal. Calcd. for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 65.10; H, 5.05; N, 4.61.

Synthesis of 6-Ethyl-4-methoxy-3-methyl-2*H*-pyran-2-one (**2c**).

A solution of 12.7 g (99 mmoles) of 3,5-heptanedione and 20 ml of dry tetrahydrofuran was added dropwise to 100 ml of 2 *M* lithium diisopropylamide at -10° under nitrogen. After stirring at -10° for 30 minutes the solution was poured onto 100 g of powdered solid carbon dioxide in a 2 l beaker. The slurry was mixed well and then 400 ml of ice cold 5 *N* hydrochloric acid was cautiously added. The mixture was extracted with ethyl ether (3 x 200 ml), dried over magnesium sulfate, and then concentrated *in vacuo* to an amber oil. Acetic anhydride (25 ml) was added and the solution was let stand for 2 hours and then dilluted with 50 ml of 9:1 (v/v) petroleum ether/ethyl ether. The precipitated solid was filtered and washed with 50 ml of 9:1 (v/v) petroleum ether/ethylether to yield 9.2 g (65%) of a white solid, mp 179-181°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.07 (3H, t), 1.71 (3H, s), 2.40 (2H, q), 5.94 (1H, s), 11.07 (1H, s).

A mixture of 8.6 g (56 mmoles) of the above solid, 500 ml of acetone, 7.6 g (56 mmoles) of potassium carbonate, and 5.3 ml (56 mmoles) dimethyl sulfate was heated at reflux temperature for 1 hour and then stirred at room temperature for 16 hours. The acetone was removed *in vacuo* and the residue was dilluted with 200 ml of water, acidified with 10% aqueous hydrochloric acid, extracted with 250 ml of ethyl ether, and then concentrated *in vacuo* to an oil which was triturated with cold petroleum ether to yield 7.1 g (76%) of **2c** as a white solid, mp 69-70°; ^{1}H nmr (detuteriodimethyl sulfoxide): δ 1.12 (3H, t), 1.72 (3H, s), 2.48 (2H, q), 3.86 (3H, s), 6.41 (1H, s).

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 63.98; H, 7.40.

Synthesis of [*R*,*S*] 3-Hydroxy-4-(4-methoxy-2-methyl-2*H*-pyran-2-on-6-yl)-2,4-dimethyl-1-(4-nitrophenyl)-1-butene (**7**).

To a solution of 2 g (12 mmoles) of **2c**, 2 ml of hexamethylphosphoramide, and 50 ml of tetrahydrofuran at -78° was added 6 ml (12 mmoles) of lithium diisopropylamide. After 10 minutes stirring at -78°, a solution of 2.6 g (13.6 mmoles) of **3** and 10 ml of tetrahydrofuran was added. Work-up as in **4** afforded 2.1 g (49%) of an oily solid after chromatography (7:3, ethyl acetate/heptane) which was a mixture of diasteromers.

Crystallization from ethyl acetate/ethanol afforded 1.4 g of a yellow solid, mp 179-181°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.19 (3H, d J = 7 Hz, 1.70 (3H, s), 1.84 (3H, s), 2.86 (1H, m), 3.84 (3H, s), 4.21 (1H, t), 5.45 (1H, d, J = 4 Hz), 6.45 (1H, s), 6.46 (1H, s), 7.41 (2H, d, J = 9 Hz), 8.17 (2H, d, J = 9 Hz).

Anal. Calcd. for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.80; H, 6.10; N, 3.95.

Evaporation of the mother liquor left 0.70 g of a yellow foam; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.03 (3H, d, J = 6 Hz), 1.74 (3H, s), 1.86 (3H, s), 2.82 (1H, m), 3.87 (3H, s), 4.18 (1H, m), 5.31 (1H, d, J = 4 Hz), 6.51 (1H, s), 6.60 (1H, s), 7.56 (2H, d, J = 9 Hz), 8.19 (2H, d, J = 9 Hz).

Anal. Calcd. for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.53; H, 6.03; N, 3.79.

Synthesis of 4-(4-Methoxy-2-methyl-2*H*-pyron-2-on-6-yl)-2,4-dimethyl-1-(4-nitrophenyl)-1,3-butadiene (**1a**) from **7**.

A solution of 0.6 g (1.7 mmoles) of **7** in 10 ml of tetrahydrofuran was stirred at 10° as 0.5 ml of triethylamine was added followed by the dropwise addition of 0.13 ml (1.7 mmoles) of methanesulfonyl chloride. After 30 minutes, the mixture was poured into water (25 ml) and extracted with ethyl acetate (50 ml). The organic layer was washed with brine (25 ml), dried over magnesium sulfate, and concentrated *in vacuo* to yield 0.8 g of a crude oil; ^{1}H nmr: δ 1.24 (3H, d), 1.91 (3H, s), 1.97 (3H, s), 2.87 (3H, s, SO_2CH_3), 3.04 (1H, m), 3.92 (3H, s), 5.22 (1H, d, J = 10 Hz), 6.22 (1H, s), 6.75 (1H, s), 7.45 (2H, d, J = 9 Hz), 8.22 (2H, d, J = 9 Hz).

The crude oil, dissolved in tetrahydrofuran (10 ml) and cooled to -78°, was treated with 1 ml of 2 *M* lithium diisopropylamide. After 10 minutes, the solution was warmed to room temperature and then poured into saturated aqueous ammonium chloride (25 ml) and ethyl acetate (50 ml). The organic phase was washed with brine (25 ml), dried over magnesium sulfate, and then concentrated *in vacuo* to an oil which was chromatographed on preparative thin layer chromatography plates with 1:1 (v:v) ethyl acetate/heptane to yield 80 mg (14%) of a light yellow solid, mp 185-186° (lit mp 184-185° [4]); ^{1}H nmr: δ 1.96 (3H, s), 2.12 (3H, d, J = 1.5 Hz), 2.15 (3H, d, J = 1.5 Hz), 3.97 (3H, s), 6.29 (1H, s), 6.61 (1H, s), 7.18 (1H, s), 7.49 (2H, d, J = 9.5 Hz), 8.23 (2H, d, J = 9.5 Hz).

Synthesis of 6-(1-Iodoethyl)-4-methoxy-3-methyl-2*H*-pyran-2-one (**8**).

To a solution of 7.3 g (43 mmoles) of **2c** in 150 ml of tetrahydrofuran at -78° was added 22 ml of 2*M* lithium diisopropylamide over 15 minutes. The resulting orange-red solution was stirred for 15 minutes and then cannulated into a solution of 10.9 g (43 mmoles) of iodine and 200 ml of tetrahydrofuran at -78°. After stirring for 30 minutes at -78°, the dark red solution was warmed to -20° and then poured into ice and water (400 ml) and extracted with ethyl ether (3 x 200 ml). The ether was washed with 10% aqueous sodium thiosulfate (100 ml), brine (100 ml), dried over magnesium sulfate and then concentrated *in vacuo* to an oil. The crude oil was chromatographed (1:1, ethyl acetate/heptane) to yield 4.2 g (34%) of a yellow oil which was used directly; ^{1}H nmr: δ 1.87 (3H, s), 2.09 (3H, d, J = 7 Hz), 3.88 (3H, s), 4.97 (1H, q), 6.26 (1H, s).

Synthesis of 1-(4-Methoxy-3-methyl-2*H*-pyran-2-on-6-yl) Ethyltriphenylphosphonium Iodide (**9**).

A solution of 4.2 g (14.2 mmoles) of **8** and 7 ml of sulfolane was stirred as 3.7 g (14.2 mmoles) of triphenylphosphine was added. The mixture was warmed to 60° for 30 minutes then stirred at room temperature for 64 hours. The amber solution was dissolved in 10 ml of dichloromethane and then added dropwise to 800 ml of ethyl ether with stirring. The resulting light yellow solid was filtered and dried to yield 6.8 g (77%), mp 137° dec; ^{1}H nmr: δ 1.69 (3H, dd), 1.78 (3H, s), 3.95 (3H, s), 6.75 (1H, m), 7.71-7.97 (15H, m), 7.79 (1H, m).

Anal. Calcd. for $C_{27}H_{26}IO_3P$: C, 58.29; H, 4.71. Found: C, 57.99; H, 5.00.

Synthesis of 4-(4-Methoxy-2-methyl-2*H*-pyran-2-on-6-yl)-2,4-dimethyl-1-(4-nitrophenyl)-1,3-butadiene (**1a**) from **9**.

To a solution of 1.2 g (2.1 mmoles) of **9** and 25 ml of dichloromethane was added a solution of 0.24 g (2.1 mmoles) of potassium *t*-butoxide in 3 ml of *t*-butyl alcohol. The mixture was stirred for 30 minutes at room temperature then a solution of 0.4 g (2.1 mmoles) of **3** in 5 ml of dichloromethane was added.

After stirring for 16 hours, the solvents were removed *in vacuo* and the residue was partitioned between ethyl ether (50 ml) and 10% aqueous ammonium chloride (25 ml). The ether layer was washed with brine (25 ml), dried over magnesium sulfate, and then concentrated *in vacuo* to afford 1.1 g of crude yellow solid. Recrystallization from ethyl acetate yielded 0.32 g (44%) of a light yellow solid, identical to **1a** obtained from **7**.

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