SYNTHESES OF THE TETRAHYDROFURAN SUBUNITS OF TETRONASIN AND TETRONOMYCIN

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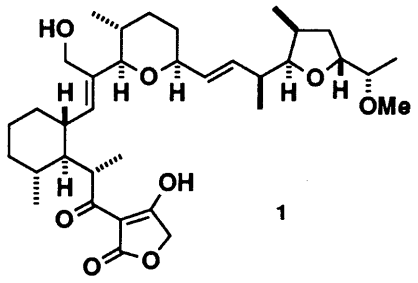
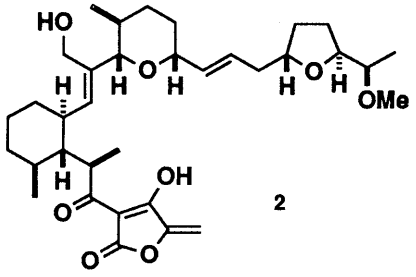
L-Rhamnal has been transformed into the tetrahydrofuran subunits (**14** and **21**) of tetronasin (ICI-139603) (**1**) and tetronomycin (**2**), in which the three chiral centers at the 2- and 5-positions and the methoxy-bearing carbon are of mirror image.

KEYWORDS ionophore antibiotic; tetronasin; tetronomycin; synthesis; L-rhamnal; aldol reaction

Tetronasin (**1**)[1] and tetronomycin (**2**),[2] which had been discovered in the early 1980s, are structurally novel ionophore antibiotics containing α-acyl-β-tetronic acid groups. Total synthesis of the two molecules has been of considerable interest in recent years owing to the unusual cyclohexyl group attached to the terminal tetronic acids, a structural feature not observed with other ionophore antibiotics. In their efforts to synthesize **1**, S.V. Ley and his coworkers[3] have synthesized the cyclohexyl, tetrahydropyranyl, and tetrahydrofuranyl portions. Our group's effort in this field of investigation[4] has been rewarded with the synthesis of the acyltetronic acid and enantiomeric polyether fragments of **2**. Here we describe easy access to both tetrahydrofuran subunits (**14** and **21**) in **1** and **2**, using L-rhamnal as the common starting material.[5]



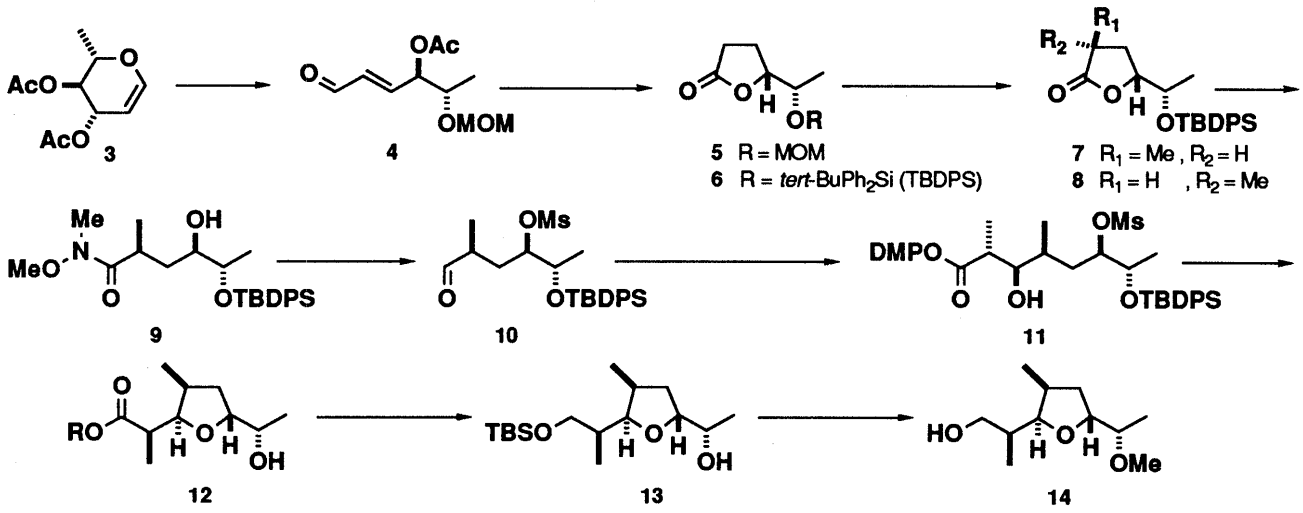
1



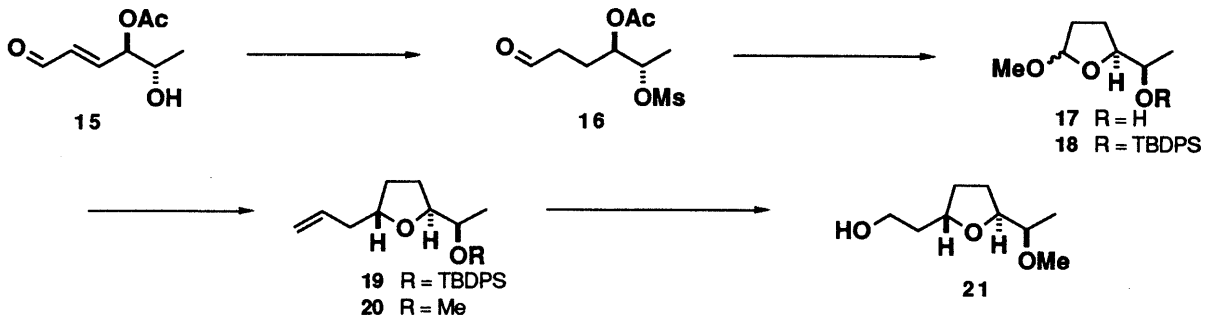
2

The hexenal derivative **4**,[4b] readily obtainable *via* a Perlin hydrolysis of L-rhamnal diacetate (**3**) in a high yield,[6] was converted to γ-lactone **5** in three steps: catalytic hydrogenation (H_2, 10% Pd-C, EtOH); γ-lactol formation by alkaline hydrolysis of the acetate group (1 eq KOH in aq. MeOH); and oxidation with pyridinium chlorochromate (PCC)[7] (62 % overall yield). The *O*-methoxymethyl (MOM) protecting group in **5** was then replaced with *tert*-butyldiphenylsilyl (TBDPS) group by an acid-catalyzed hydrolysis (35% HCl/H_2O/THF = 1:2:18, 50 °C) followed by *O*-silylation of the resulting hydroxy compound with TBDPS-Cl in the usual manner, affording **6** in 87% yield. Enolate methylation[8] of **6** (1.2 eq. lithium diisopropylamide, THF, -70 °C; then 1.1 eq MeI, -90 °C, 2.5 h) provided α-methylated lactone **7**[9] in 74% yield. The stereochemistry of **7** as depicted was confirmed by differential NOE experiments performed with **7** and its epimer **8**, which were produced in an isolated ratio of 50:1. Aminolysis of **7** with MeNHOMe•HCl / Me_3Al (2 eq each)[10] in benzene at room temperature furnished amide **9** in 90% yield. It was subjected to *O*-mesylation (1.1 eq $MeSO_2Cl$, 0.25 eq 4-dimethylaminopyridine, 5 eq pyridine, CH_2Cl_2), then to reduction with 1.5 eq diisobutylaluminum hydride (DIBAL) in tetrahydrofuran (THF), affording aldehyde **10** in 72% yield. Aldol reaction of **10** with the lithium enolate of 2,6-dimethylphenyl (DMP) propionate (Heathcock's protocol)[11]

produced the *anti*/*syn* adduct **11**[9] in 54% yield.[12] Desilylation of **11** (HF in aq. MeCN) followed by treatment of the resulting diol with methanolic KOH (2.5 eq) afforded in 85% yield the tetrahydrofuran **12** (a mixture of Me and DMP esters) *via* 6,7-epoxide formation and ring closure. Reduction of the ester **12** with 3.5 eq DIBAL in ether followed by selective silylation with 1.1 eq *tert*-butyldimethylsilyl (TBS) chloride in the presence of imidazole gave **13**[9] in 47% yield,[13] which on *O*-methylation (8 eq NaH, 4 eq Me_2SO_4, THF) and subsequent desilylation (toluene-*p*-sulfonic acid, aq. acetone) provided **14** in 96% yield, $[\alpha]_D^{27}$ +46.4° (*c*=1.41, $CHCl_3$) (lit. $[\alpha]_D^{25}$ +38.8° (*c*=5.0, $CHCl_3$)).[3a] The ^{1}H-NMR spectral data of **14** were in accord with those published.[3a]



Synthesis of the tetrahydrofuran fragment **21** of tetronomycin (**2**) began with *O*-mesylation of **15**[6] and subsequent catalytic hydrogenation to give **16** (74% overall yield from L-rhamnal). Treatment of **16** with 1.2 eq methanolic MeONa at 5 °C gave lactol ether **17** *via* 4,5-epoxide formation, and it was then converted to *O*-TBDPS derivative **18**[9] in 69% yield from **16**. A Lewis acid-catalyzed allylation of **18** with allyltrimethylsilane (1 eq BF_3-Et_2O, CH_2Cl_2, -70 °C) proceeded in highly stereoselective manner to give **19** in 98% yield. It was converted to *O*-methyl ether **20** by desilylation (HF in aq. MeCN) followed by *O*-methylation (Me_2SO_4, NaH, THF). Finally, compound **20** was subjected to ozonolysis (reductive work-up with $NaBH_4$) to furnish **21**,[14] $[\alpha]_D^{26}$ -12.4° (*c*=0.52, $CHCl_3$). The stereochemistry of **21** was confirmed by comparison of the optical rotation and ^{1}H-NMR spectrum with those of the sample obtained by degradation of tetronomycin (**2**).[4b]



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9) ^{1}H-NMR spectral data (270 MHz, $CDCl_3$).

7: δ 0.97 (3H, d, *J*=6.4 Hz, CH(Me)OTBDPS), 1.04 (9H, s, ^{t}Bu), 1.26 (3H, d, *J*=7.1 Hz, Me-3), 1.85 (1H, dt, *J*=12.7, 8.2 Hz, H-4), 2.54 (1H, ddd, *J*=12.7, 9.5, 3.9 Hz, H-4), 2.67 (1H, ddq, *J*=9.5, 8.2, 7.1 Hz, H-3), 4.05 (1H, qd, *J*=6.4, 3.9 Hz, CH(Me)OTBDPS), 4.28 (1H, dt, *J*=8.2, 3.9 Hz, H-5), 7.26-7.47 (6H, m, Ar-H), 7.65-7.71 (4H, m, Ar-H).

11: δ 0.91 (3H, d, *J*=6.8 Hz, Me-4), 1.09 (9H, s, ^{t}Bu), 1.12 (3H, d, *J*=6.4 Hz, Me-7), 1.35 (3H, d, *J*=7.3 Hz, Me-2), 1.53 (1H, ddd, *J*=14.6, 10.1, 4.1 Hz, H-5), 1.70 (1H, ddd, *J*=14.6, 9.8, 2.1 Hz, H-5), 1.93 (1H, dqdd, *J*=9.8, 6.8, 4.1, 2.2 Hz, H-4), 2.17 (6H, s, Ar-Me), 2.45 (1H, d, *J*=5.0 Hz, OH), 2.88 (1H, dq, *J*=9.5, 7.3 Hz, H-2), 3.04 (3H, s, OMs), 3.85 (1H, ddd, *J*=9.5, 5.0, 2.2 Hz, H-3), 3.92 (1H, qd, *J*=6.4, 2.1 Hz, H-7), 4.79 (1H, dt, *J*=10.1, 2.1 Hz, H-6), 7.07 (3H, s, Ar-H), 7.36-7.47 (6H, m, Ar-H), 7.66-7.72 (4H, m, Ar-H).

13: δ 0.04 (3H, s, SiMe), 0.05 (3H, s, SiMe), 0.89 (3H, d, *J*=6.6 Hz, Me-3), 0.89 (9H, s, ^{t}Bu), 0.92 (3H, d, *J*=7.1 Hz, CH(Me)OH), 1.09 (3H, d, *J*=6.4 Hz, CH(Me)CH_2OTBS), 1.56 (1H, dd, *J*=12.0, 6.1 Hz, H-4), 1.67 (1H, dqdd, *J*=9.6, 6.4, 6.4, 3.2 Hz, CH(Me)CH_2OTBS), 1.96 (1H, br.s, OH), 2.05 (1H, ddd, *J*=12.0, 9.6, 6.6 Hz, H-4), 2.27 (1H, qdd, *J*=6.6, 6.6, 4.0 Hz, H-3), 3.62 (1H, dd, *J*=9.4, 6.4 Hz, CHHOTBS), 3.64 (1H, dd, *J*=9.6, 4.0 Hz, H-2), 3.72 (1H, dd, *J*=9.4, 3.2 Hz, CHHOTBS), 3.92-4.13 (2H, m, H-5, CH(Me)OH).

18: β-OMe: δ 0.99 (3H, d, *J*=6.1 Hz, CH(Me)OTBDPS), 1.05 (9H, s, ^{t}Bu), 1.76-2.00 (4H, m, H-3, H-4), 3.32 (3H, s, OMe), 3.87-3.98 (2H, m, H-5, CH(Me)OTBDPS), 4.95 (1H, d, *J*=4.4 Hz, H-2), 7.33-7.45 (6H, m, Ar-H), 7.67-7.73 (4H, m, Ar-H).

α-OMe: δ 1.05 (9H, s, ^{t}Bu), 1.10 (3H, d, *J*=6.1 Hz, CH(Me)OTBDPS), 1.78-2.02 (4H, m, H-3, H-4), 3.21 (3H, s, OMe), 3.73 (1H, quint., *J*=6.1 Hz, CH(Me)OTBDPS), 3.89 (1H, m, H-5), 4.91 (1H, m, H-2), 7.33-7.45 (6H, m, Ar-H), 7.67-7.73 (4H, m, Ar-H).

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12) An inseparable mixture of three diastereomers (*ca.* 10:1.5:1 ratio by ^{1}H-NMR spectral analysis) was also obtained in 33% yield. Stereochemistries of these by-products have not been determined.

13) This unexpectedly low overall yield is presumably due to the volatility of the diol intermediate.

14) The overall yield of **21** from **19** is presently *ca.* 20%. The major losses occur in isolation of the volatile intermediates.

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