SYNTHESIS OF THE ENANTIOMERIC POLYETHER FRAGMENT OF TETRONOMYCIN

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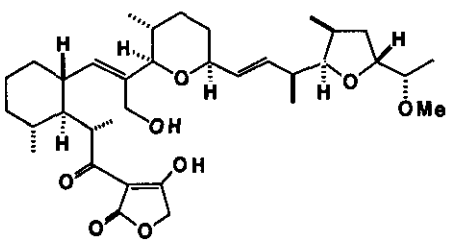
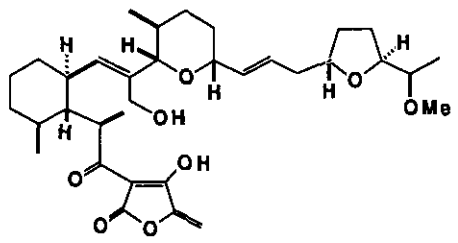
Abstract - The absolute stereochemistry of tetronomycin (2), a novel acyltetronic acid ionophore, was confirmed by comparison of the degradation product 3 with the synthetic enantiomer 9 derived from L-rhamnose. The enantiomer 18 of the polyether subunit of 2 was synthesized by coupling 9 with tetrahydropyran portion 15 prepared from D-glucose.

Tetronasin (ICI-139603)[1] (1) and tetronomycin[2] (2) reported early in the 1980s are structurally unique polyether antibiotics which contain α-acyl-β-tetronic acids as an acidic function. As seen from the absolute structures depicted below, which have been determined by X-ray crystallographic analyses, the two molecules share very similar constitution but tetronomycin has the opposite configurations at all ten chiral centers.[3] Furthermore, it should be noted that the tetronic acid of 2 bears additional methylene group at the γ-position. This paper describes confirmation of the absolute structure of tetronomycin via a chemical degradation study, and also synthesis of the enantiomer of the polyether subunit.

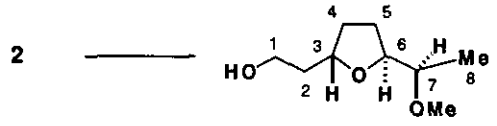
Ozonolysis of 2 in dichloromethane at low temperatures followed by reductive workup with sodium



Tetronasin (ICI-139603)
(1)



Tetronomycin
(2)



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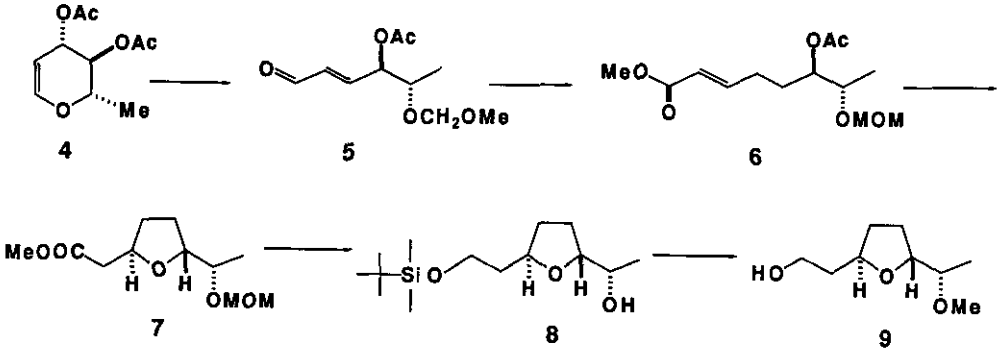
borohydride produced tetrahydrofuran fragment **3**,[4] $[\alpha]_D^{27}$ -11.9° (c 0.88, $CHCl_3$) in 74% yield. In order to determine the absolute stereochemistry of the degradation product **3**, we have prepared (3R,6R,7S) compound **9** for comparison by using L-rhamnal diacetate (**4**) as the starting material (Scheme 1). Thus, (4R)-acetoxy-(5S)-methoxymethoxy-2-hexenal (**5**) obtained from **4** in 80% yield via Perlin reaction[5] and O-methoxymethylation was subjected to catalytic hydrogenation (10% Pd-C, AcOEt) and then Wittig reaction with Ph_3P=CHCOOMe in refluxing MeCN. The resulting conjugated ester **6** (86% yield for the two steps) was treated with methanolic KOH to give an inseparable mixture of trans-tetrahydrofuran **7** and cis isomer (3.4:1 ratio by ^{1}H-nmr, 94% yield). The mixture was subjected to reduction with i-Bu_2AlH (Et_2O, -40 °C), removal of the MOM protecting group (1:40 HCl/THF, 40-45 °C), and selective O-silylation (t-$BuMe_2SiCl$, imidazole, -80 to 10 °C) to afford **8** as a homogeneous oil after chromatographic purification (34% overall yield from **6**). Finally, O-methylation of **8** (Me_2SO_4, NaH, THF) followed by desilylation (TsOH, aqueous acetone) afforded compound **9** (90% yield), $[\alpha]_D^{27}$ +12.6° (c 1.37, $CHCl_3$), which was indistinguishable from **3** in their ^{1}H-nmr spectra. Thus, the observed sign of $[\alpha]_D$ for **3**, opposite to that of **9**, supports the absolute stereochemistry previously assigned for **2**.

With tetrahydrofuran **9** at hands, we pursued synthesis of the enantiomeric polyether fragment (**18**) by joining **9** with tetrahydropyran aldehyde **15** (Scheme 2). The (6S) chirality of **15** was secured

Scheme 1.



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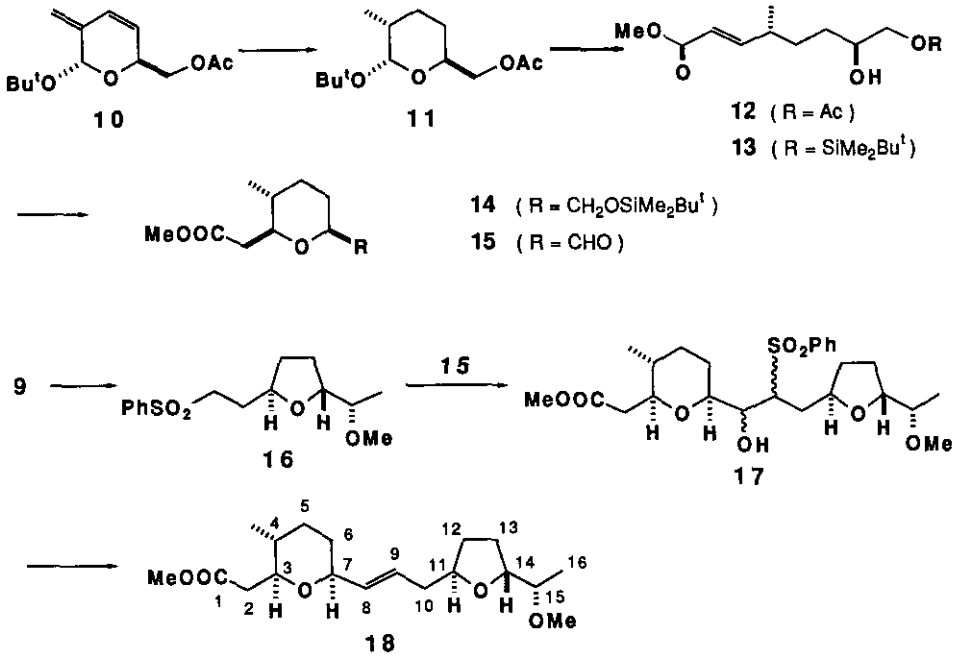
by employing unsaturated sugar **10** as the starting material, readily accessible from D-glucose.[6] Catalytic hydrogenation of **10** (*10% Pd-C, AcOEt*) *under medium* pressure produced a 5:1 mixture of **11** and its C-Me epimer.[6] The mixture was sequentially treated with toluene-p-sulfonic acid in refluxing aqueous acetone and with Ph_3P=*CHCOOMe in refluxing* MeCN to give **12** (homogeneous oil) in 79% yield after silica gel chromatography. The terminal acetoxy group in **12** was then replaced by t-butyldimethylsilyloxy group by hydrolysis *with 0.5% methanolic KOH followed* by selective silylation. The resulting compound **13** (71% yield) was now treated with 40% Triton B (1 equiv) in THF at 0 °C for 15 min and then with t-BuOK (0.2 equiv.) in *THF at room temperature* for 4 h, affording a 5:1 mixture of tetrahydropyran (**14**) and its C(2) epimer (68% yield) which are chromatographically separable. Compound **14** was converted to aldehyde **15** (*91% yield*) *by Swern oxidation*[7] after desilylation (TsOH, aq. acetone), and the aldehyde was employed for a Julia coupling[8] with sulfone **16** derived from **9** in two steps. (PhSSPh, n-Bu_3P, pyridine;[9] then *MCPBA*).

Thus, sulfone **16** was metallated with n-BuLi (1.1 equiv., THF, -78 °C) and, after addition of $MgBr_2$,[10] allowed to react with **15** to give hydroxysulfone **17** in 73% yield. *O-Benzoylation of this* intermediate (PhCOCl, Et_3N, 84% yield) followed by treatment with 5% Na-Hg (Na_2HPO_4, MeOH) afforded a 2:1 mixture of **18** and cis-olefin isomer (55% yield) which are separable by *HPLC*.[11]

Scheme 2.



Synthesis of the cyclohexane fragment as well as the enantiomer of **18** (correct polyether fragment) will be reported in near future.

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3. The absolute configuration of **1** has been proved by synthetic and degradation studies. A. M. Doherty and S. V. Ley, Tetrahedron Lett., 1986, **27**, 105.
4. ^{1}H-Nmr spectral data for **3** (270 MHz, $CDCl_3$): δ 1.12 (d, J = 6.2 Hz, 3H, Me-7), 1.58 (ddt, J = 11.8, 9.8, 8.2 Hz, 1H, H-4), 1.75 (q, J = 6.1 Hz, 2H, H-2), 1.80 (dddd, J = 14.9, 9.8, 8.1, 8.0 Hz, 1H, H-5), 1.99 (dddd, J = 14.9, 8.2, 6.8, 3.1 Hz, 1H, H-5), 2.07 (dddd, J = 11.8, 8.1, 6.1, 3.1 Hz, 1H, H-4), 2.93 (br t, J = 6.1 Hz, 1H, OH), 3.34 (qd, J = 6.2, 4.9 Hz, 1H, H-7), 3.38 (s, 3H, OMe), 3.78 (br q, J = 6.1 Hz, 2H, H-1), 3.93 (ddd, J = 8.0, 6.8, 4.9 Hz, 1H, H-6), 4.15 (dq, J = 8.2, 6.1 Hz, 1H, H-3).
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11. ^{1}H-Nmr spectral data for **18** (270 MHz, $CDCl_3$): δ 0.84 (d, J = 6.4 Hz, 3H, Me-4), 1.11 (d, J = 6.2 Hz, 3H, Me-15), 1.21-1.58 (m, 4H), 1.60-1.65 (m, 1H), 1.72-1.85 (m, 2H), 1.88-2.03 (m, 2H, H-12 and H-13), 2.14 (dt, J = 13.6, 7.0 Hz, 1H, H-10), 2.34 (dt, J = 13.6, 5.8 Hz, 1H, H-10). 2.43 (dd, J = 15.0, 9.0 Hz, 1H, H-2), 2.62 (dd, J = 15.0, 3.8 Hz, 1H, H-2), 3.33 (qd, J = 6.2, 4.6 Hz, 1H, H-15), 3.37 (s, 3H, OMe), 3.48 (td, J = 9.0, 3.8 Hz, 1H, H-3), 3.68 (s, 3H, OMe), 3.79 (ddd, J = 10.0, 5.1, 2.2 Hz, 1H, H-7), 3.89 (ddd, J = 7.8, 6.9, 4.6 Hz, 1H, H-14), 3.98 (ddt, J = 7.9, 7.0, 5.8 Hz, 1H, H-11), 5.53 (dd, J = 15.9, 5.1 Hz, 1H, H-8), 5.57 (ddd, J = 15.9, 7.0, 5.8 Hz, 1H, H-9).

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