

SYNTHESIS OF THE ENANTIOMERIC POLYETHER FRAGMENT OF TETRONOMYCIN

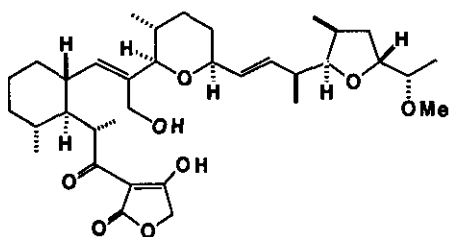
Kozo Hori, Keiichi Nomura, and Eiichi Yoshii*

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Toyama 930-01, Japan

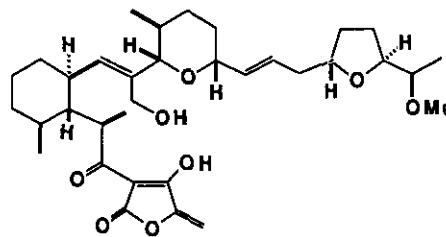
Abstract - The absolute stereochemistry of tetronomycin (2), a novel acyl-tetronic acid ionophore, was confirmed by comparison of the degradation product 3 with the synthetic enantiomer 9 derived from L-rhamnose. The enantiomer 18 of the polyether subunit of 2 was synthesized by coupling 9 with tetrahydropyran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

Tetronasin (ICI-139603)¹ (1) and tetronomycin² (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.

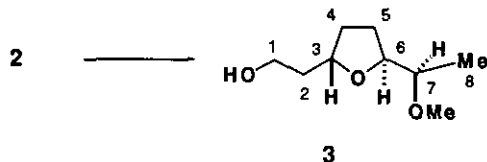
Ozonolysis of 2 in dichloromethane at low temperatures followed by reductive workup with sodium



Tetronasin (ICI-139603)
(1)



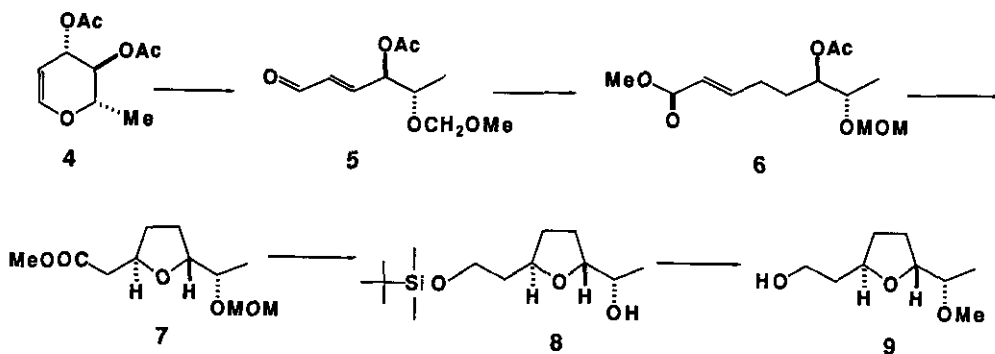
Tetronomycin
(2)



borohydride produced tetrahydrofuran fragment 3,⁴ $[\alpha]_D^{27} -11.9^\circ$ (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-rhamnaldiacetate (4) as the starting material (Scheme 1). Thus, (4R)-acetoxy-(5S)-methoxymethoxy-2-hexenal (5) obtained from 4 in 80% yield via Perlin reaction⁵ and O-methoxymethylation was subjected to catalytic hydrogenation (10% Pd-C, AcOEt) and then Wittig reaction with $\text{Ph}_3\text{P}=\text{CHCOOMe}$ 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 ¹H-nmr, 94% yield). The mixture was subjected to reduction with *i*-Bu₂AlH (Et_2O , -40°C), removal of the MOM protecting group (1:40 HCl/THF, $40-45^\circ\text{C}$), and selective O-silylation (*t*-BuMe₂SiCl, 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), $[\alpha]_D^{27} +12.6^\circ$ (c 1.37, CHCl_3), which was indistinguishable from 3 in their ¹H-nmr spectra. Thus, the observed sign of $[\alpha]_D$ for 3, opposite to that of 9, supports the absolute stereochemistry previously assigned for 2.

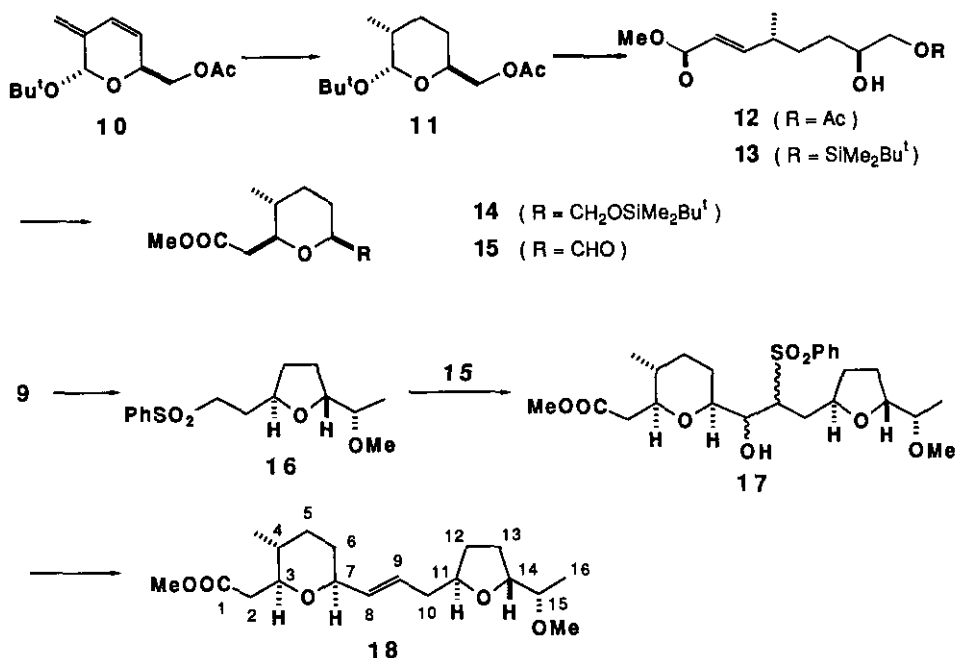
With tetrahydrofuran 9 at hands, we pursued synthesis of the enantiomeric polyether fragment (18) by joining 9 with tetrahydropyran aldehyde 15 (Scheme 2). The (6S) chirality of 15 was secured

Scheme 1.



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 $\text{Ph}_3\text{P}=\text{CHCOOMe}$ 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 oxidation⁷ after desilylation (TsOH, aq. acetone), and the aldehyde was employed for a Julia coupling⁸ with sulfone **16** derived from **9** in two steps. (PhSSPh, n-Bu₃P, pyridine;⁹ then MCPBA). Thus, sulfone **16** was metallated with n-BuLi (1.1 equiv., THF, -78 °C) and, after addition of MgBr₂,¹⁰ allowed to react with **15** to give hydroxysulfone **17** in 73% yield. o-Benzoylation of this intermediate (PhCOCl, Et₃N, 84% yield) followed by treatment with 5% Na-Hg (Na₂HPO₄, MeOH) afforded a 2:1 mixture of **18** and cis-olefin isomer (55% yield) which are separable by HPLC.¹¹

Scheme 2.



received, 16th December, 1988

11. ¹H-NMR spectral data for **18** (270 MHz, CDCl₃): δ 0.84 (d, \bar{J} = 6.4 Hz, 3H, Me-4), 1.11 (d, \bar{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, \bar{J} = 13.6, 7.0 Hz, 1H, H-10), 2.34 (dt, \bar{J} = 13.6, 5.8 Hz, 1H, H-10), 2.43 (dd, \bar{J} = 15.0, 9.0 Hz, 1H, H-2), 2.62 (dd, \bar{J} = 15.0, 3.8 Hz, 1H, H-2), 3.33 (qd, \bar{J} = 6.2, 4.6 Hz, 1H, H-15), 3.37 (s, 3H, OMe), 3.48 (td, \bar{J} = 9.0, 3.8 Hz, 1H, H-3), 3.68 (s, 3H, OMe), 3.79 (ddd, \bar{J} = 10.0, 5.1, 2.2 Hz, 1H, H-7), 3.89 (ddd, \bar{J} = 7.8, 6.9, 4.6 Hz, 1H, H-14), 3.98 (ddt, \bar{J} = 7.9, 7.0, 5.8 Hz, 1H, H-11), 5.53 (dd, \bar{J} = 15.9, 5.1 Hz, 1H, H-8), 5.57 (ddd, \bar{J} = 15.9, 7.0, 5.8 Hz, 1H, H-9).

1. D. H. Davies, E. W. Snape, P. J. Suter, T. J. King, and C. P. Falshaw, *J. Chem. Soc., Chem. Commun.*, 1981, 1073.

2. C. Keller-Justen, H. D. King, M. Kuhn, H.-R. Looß, W. Pache, T. J. Petcher, H. P. Weber, and A. von Wartburg, *J. Antibiot.*, 1982, 35, 142.

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. ¹H-NMR spectral data for **3** (270 MHz, CDCl₃): δ 1.12 (d, \bar{J} = 6.2 Hz, 3H, Me-7), 1.58 (ddt, \bar{J} = 11.8, 9.8, 8.2 Hz, 1H, H-4), 1.75 (q, \bar{J} = 6.1 Hz, 2H, H-2), 1.80 (dddd, \bar{J} = 14.9, 9.8, 8.1, 8.0 Hz, 1H, H-5), 1.99 (dddd, \bar{J} = 14.9, 8.2, 6.8, 3.1 Hz, 1H, H-5), 2.07 (dddd, \bar{J} = 11.8, 8.1, 6.1, 3.1 Hz, 1H, H-4), 2.93 (br t, \bar{J} = 6.1 Hz, 1H, OH), 3.34 (qd, \bar{J} = 6.2, 4.9 Hz, 1H, H-7), 3.38 (s, 3H, OMe), 3.78 (br q, \bar{J} = 6.1 Hz, 2H, H-1), 3.93 (ddd, \bar{J} = 8.0, 6.8, 4.9 Hz, 1H, H-6), 4.15 (dq, \bar{J} = 8.2, 6.1 Hz, 1H, H-3).

5. J. D. White, E. G. Nolen, Jr., and C. H. Miller, Jr., *J. Org. Chem.*, 1986, 51, 1150.

6. S. Hanessian, G. Demally, Y. Chapleur, and S. Leger, *J. Chem. Soc., Chem. Commun.*, 1981, 1125; S. Hanessian, P. C. Tyler, G. Demally, and Y. Chapleur, *J. Am. Chem. Soc.*, 1981, 103, 6243.

7. K. Omura, A. K. Sharma, and D. Swern, *J. Org. Chem.*, 1976, 41, 957; S. L. Huang, K. Omura, and D. Swern, *ibid.*, 1976, 41, 3329.

8. P. J. Kocienski and B. Lythgoe, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1409.

9. I. Nakagawa and T. Hata, *Tetrahedron Lett.*, 1975, 1409.

10. S. J. Danishefsky, H. G. Selnick, M. P. DeNinno, and R. E. Zelle, *J. Am. Chem. Soc.*, 1987, 109, 1572.

11. ¹H-NMR spectral data for **18** (270 MHz, CDCl₃): δ 0.84 (d, \bar{J} = 6.4 Hz, 3H, Me-4), 1.11 (d, \bar{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, \bar{J} = 13.6, 7.0 Hz, 1H, H-10), 2.34 (dt, \bar{J} = 13.6, 5.8 Hz, 1H, H-10), 2.43 (dd, \bar{J} = 15.0, 9.0 Hz, 1H, H-2), 2.62 (dd, \bar{J} = 15.0, 3.8 Hz, 1H, H-2), 3.33 (qd, \bar{J} = 6.2, 4.6 Hz, 1H, H-15), 3.37 (s, 3H, OMe), 3.48 (td, \bar{J} = 9.0, 3.8 Hz, 1H, H-3), 3.68 (s, 3H, OMe), 3.79 (ddd, \bar{J} = 10.0, 5.1, 2.2 Hz, 1H, H-7), 3.89 (ddd, \bar{J} = 7.8, 6.9, 4.6 Hz, 1H, H-14), 3.98 (ddt, \bar{J} = 7.9, 7.0, 5.8 Hz, 1H, H-11), 5.53 (dd, \bar{J} = 15.9, 5.1 Hz, 1H, H-8), 5.57 (ddd, \bar{J} = 15.9, 7.0, 5.8 Hz, 1H, H-9).

REFERENCES AND NOTES

assistance.

us with a sample of tetromycin. We also thank Misses M. Takemura and M. Fujii for technical

ACKNOWLEDGEMENT: We are grateful to Dr. Roland Wenger at Sandoz Ltd., Switzerland, for providing

ment) will be reported in near future.

Synthesis of the cyclohexane fragment as well as the enantiomer of **18** (correct polyether frag-