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Synthesis of the C12-C26 Fragment of the Acyltetronic Acid Ionophore Antibiotic Tetronasin (ICI 139603)

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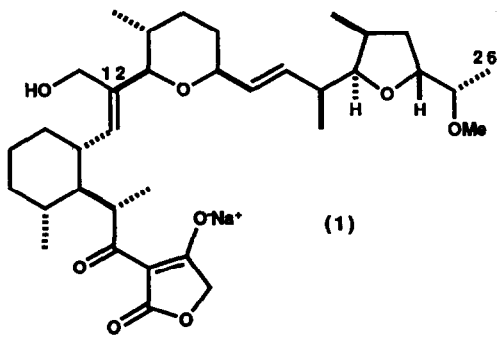
Summary: *Preparation of a central tetrahydropyran portion (2) of the antibiotic tetronasin (1) was achieved using an all-in-one epoxidation / cyclization modification of the Sharpless reaction. Further manipulation and coupling reactions afforded the C12-C26 fragment of tetronasin which was identical to that obtained by natural product degradation studies.*

Current interest in the synthesis[1-6], biosynthesis[7] and properties[8] of the unusual acyltetronic acid ionophore tetronasin (1) (ICI 139603)[9] is noticeably increasing. Here we report on the preparation the central tetrahydropyran unit (2) and its coupling *via* sulphone stabilized anion chemistry with the furan (3) to afford the C12-C26 fragment (4). Further manipulation of which gave the C-12 carbonyl portion (5). In turn this same compound was derived by natural product degradation and coupling reactions.

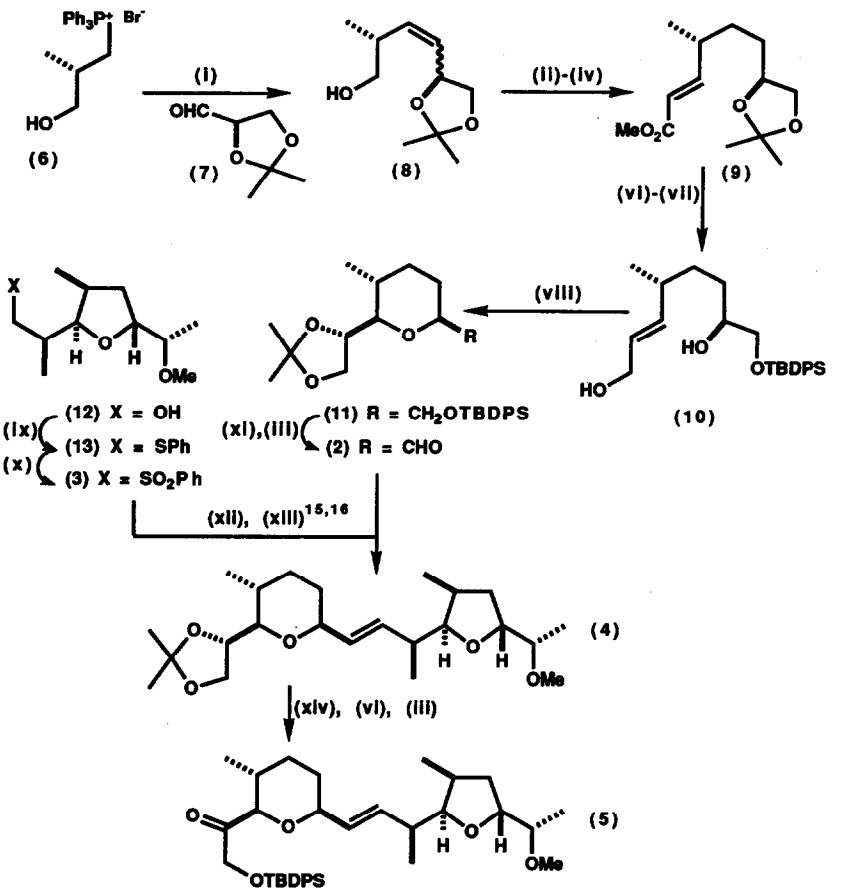


(1)

The dianion from the commercially available phosphonium salt (6) was reacted with freshly prepared aldehyde (7)[10] to give the olefin (8)[11] (70%) as a mixture of double bond isomers. Hydrogenation in the presence of platinum oxide, subsequent oxidation and stabilized Wittig coupling afforded the α,β-unsaturated ester (9) in 84% yield. Cleavage of the acetonide with methanol and pyridinium tosylate followed by selective protection of the primary hydroxyl group with *t*-butyldiphenylsilyl chloride and DIBAL-H reduction at -78°C in toluene gave the allylic alcohol (10) (81% overall). Direct one pot conversion to the hydropyran acetonide (11) was accomplished by a modification of the Sharpless asymmetric epoxidation reaction.[12] Thus treatment of (10) with (+)-diethyl tartrate (2.1 equiv.) and titanium IV isopropoxide (2 equiv.) in dry dichloromethane at -20°C for 20h followed by stirring with acetone and a catalytic amount of camphorsulphonic acid afforded (11) in 75% yield (Scheme 1). Previously we have used this modification of the Sharpless reaction using an excess of the Lewis acid to encourage intramolecular cyclization of the intermediate chiral epoxide during the preparation of the synthetic tetrahydrofuran fragment (12).[1] Additional deprotection and oxidation of the pyran (11) then furnished, in 79% yield, the key aldehyde unit (2).

Conversion of the synthetic alcohol (12) to the sulphone (3) required for the coupling reaction was acheived *via* the sulphide (13) using diphenyldisulphide / triphenylphosphine followed by Oxone® oxidation (77% yield).[13,14] The coupling was accomplished by deprotonation of (3) with *t*-butyllithium in toluene / THF (1:1) at -78°C followed by syringe pump addition of the aldehyde (2) over 1h. The resulting hydroxyphenylsulphones were immediately benzoylated and reductively eliminated with potassium dihydrogen phosphate buffered sodium amalgam[15, 16] to afford the *E*-olefin (4) in 52% isolated yield[17]. Further elaboration of (4) by deprotection with dimethylboron bromide, selective silylation of the primary alcohol and oxidation gave the protected C12-C26 fragment (5) in 44% yield (Scheme 1).[18]

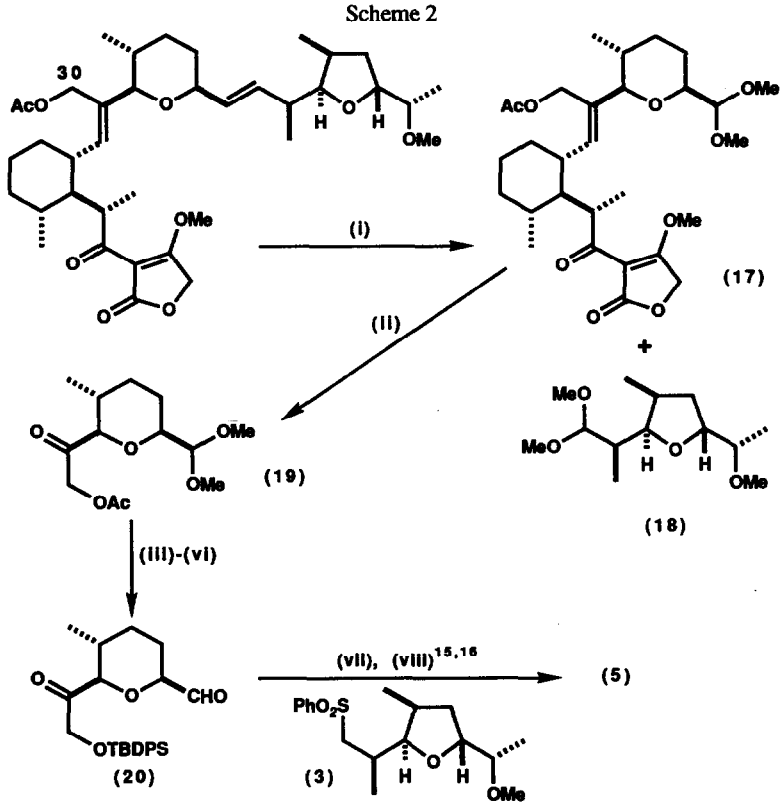
Scheme 1



(i) ^{n}BuLi, THF, then TMSCl, then (7) all at -78°C. (ii) PtO_2 / H_2. (iii) $(COCl)_2$, DMSO, Et_3N, DCM, -78°C. (iv) ^{n}BuLi, HMDS, THF, -78°C, methyl trimethylphosphoranocrotonate. (v) MeOH, PPTs, (vi) TBDPSCl, Im, DMF. (vii) DIBAL-H, PhMe, -78°C. (viii) (+)-diethyl tatrate, $Ti(O^{i}Pr)_4$, DCM, -20°C, then Me_2CO, CSA. (ix) Ph_2S_2, PPh_3, THF. (x) Oxone®. (xi) TBAF, THF. (xii) ^{t}BuLi, PhMe, THF, then (2) (1hr *via* syringe pump), then BzCl, all at -78°C. (xiii) Na / Hg, KH_2PO_4, MeOH, -40°C. (xiv) Me_2BBr, DCM, -78°C.

The stereochemical integrity of the above fragment was confirmed by the following natural product degradation reactions. Ozonolysis of methyl 30-*O*-acetyltetronasin[1] at -78°C followed by work-up with trimethylorthoformate gave the two acetals (17) and (18) in 80 and 89% yields respectively. Subsequent ozonolysis of (17) at -29°C then afforded the keto-tetrahydropyran derivative (19) (80% yield). This was transformed into the keto-aldehyde (20) in 54% yield *via* a straightforward lithium aluminiumhydride reduction, selective *t*-butyldiphenylsilylation, oxidation and dimethylboron bromide deacetalation procedure.[19] Then in a similar manner to above, condensation of the aldehyde (20) with the sulphone (3) derived from the natural product fragment (18) *via* (12)[1] furnished the C12-C26 fragment (5) (18% yield) identical in all respects to the previously prepared synthetic sample (Scheme 2).

Scheme 2



(I) O_3, DCM, -78°C, then $(MeO)_3CH$, CSA. (II) O_3, DCM, -29°C. (III) $LiAlH_4$, THF. (IV) TBDPSCl, Im, DMF. (V) $(COCl)_2$, DMSO, Et_3N, DCM, -78°C. (VI) Me_2BBr, DCM, -78°C. (VII) (3), ^tBuLi, PhMe, THF, then (20) (1hr *via* syringe pump), then BzCl, all at -78°C. (VIII) Na / Hg, KH_2PO_4, MeOH, -40°C.

The above studies, together with the accompanying paper, illustrate the preparation of synthetic fragments of the ionophore tetronasin (1). We are presently investigating final coupling reactions and exploring routes to novel unnatural ionophore species.

Acknowledgements

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References and Footnotes

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17. δ (500 MHz, $CDCl_3$) 0.92 (3H, d, 7.3 Hz), 0.93 (3H, d, 7.1 Hz), 0.95 (3H, d, 6.6 Hz), 1.09 (3H, d, 6.3 Hz), 1.24 (1H, dq, 12.2, 3.3 Hz), 1.30-1.40 (2H, m), 1.36 (3H, s), 1.41 (3H, s), 1.64 (1H, m), 1.66 (1H, ddd, 12.4, 7.0, 1.8 Hz), 1.77 (1H, dq, 12.7, 3.3 Hz), 1.96 (1H, ddd, 12.4, 8.5, 6.7 Hz), 2.20-2.27 (2H, m), 3.11 (1H, dd, 9.7, 5.6 Hz), 3.33 (1H, dt, 11.4, 6.3 Hz), 3.38 (3H, s), 3.51 (1H, dd, 9.3, 4.2 Hz), 3.77 (1H, dd, 11, 5.3 Hz), 3.95 (1H, ddd, 12.1, 7.1, 5.0 Hz), 3.97 (1H, t, 7.9 Hz), 4.02 (1H, dd, 8.2, 6.4 Hz), 4.13 (1H, dt, 7.2, 6.0 Hz), 5.51 (1H, ddd, 15.9, 5.3, 1.1 Hz), 5.74 (1H, ddd, 15.9, 6.6, 1.3 Hz); νmax(film) 2970, 2930, 1457, 1380, 1254, 1220, 1156, 1066, 909, 862, 648 cm^{-1}; $[\alpha]_D^{20}$ -41.5° (c 3.08, $CHCl_3$); m/z 396 (M^+), 381, 337, 295, 253, 143, 101; $C_{23}H_{40}O_5$ requires: C, 69.66; H, 10.17. Found: C, 69.56; H, 10.30.
18. δ (500 MHz, $CDCl_3$) 0.70 (3H, d, 6.5 Hz), 0.91 (6H, d, 6.8 Hz), 1.05 (3H, d, 6.3 Hz), 1.09 (9H, s), 1.20 (1H, m), 1.28-1.36 (2H, m), 1.57 (1H, dq, 13.7, 2.7 Hz), 1.65 (1H, ddd, 12.4, 7.0, 1.3 Hz), 1.77 (1H, dq, 13.1, 3.3 Hz), 1.96 (1H, ddd, 12.4, 8.6, 6.7 Hz), 2.19-2.28 (2H, m), 3.29 (1H, dd, 6.3, 5.1 Hz), 3.34 (3H, s), 3.48 (1H, dd, 9.4, 4.1 Hz), 3.51 (1H, d, 10.3 Hz), 3.70 (1H, dd, 10.8, 5.6 Hz), 3.93 (1H, ddd, 8.6, 7.0, 5.0 Hz), 4.52 (1H, d, 18.8 Hz), 4.64 (1H, d, 18.8 Hz), 5.46 (1H, ddd, 15.9, 5.7, 1.1 Hz), 5.68 (1H, ddd, 15.9, 6.5, 1.1 Hz), 7.35-7.69 (10H, m); νmax(film) 2964, 2858, 1734, 1675, 1603, 1457, 1381, 1113, 1012, 920, 756, 747, 719, 707 cm-1; $[\alpha]_D^{20}$ +24.5° (c 1.08, $CHCl_3$); m/z 592 (M^+), 517, 503, 485, 199, 143, 111; $C_{36}H_{52}O_5Si$ requires: C, 72.92; H, 8.84. Found: C, 73.25; H, 9.02;
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