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Enantioselective Synthesis of the C3-C11 Hydrocarbon Fragment of the Ionophore Antibiotic Tetronasin (ICI 139603).

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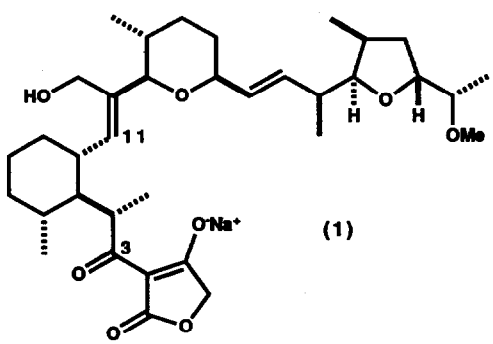
Summary: *The enantioselective synthesis of the C3-C11 fragment (2) of the novel ionophore tetronasin (1) has been completed via an intermediate enamine-enal cyclisation of the dialdehyde (8) when treated with morpholine. The high degree of stereocontrol and asymmetric induction observed in this reaction provided the aminal (10) in excellent yield after hydrogenation which then possessed all four stereocentres required for the C3-C11 fragment of (1).*

In view of the recent reports directed towards the synthesis of the novel ionophore antibiotic tetronasin (1) (ICI 139603) and related compounds[1-6], we wish to describe some of our studies in this area[7, 8]. Here we report the construction of the C3-C11 hydrocarbon fragment (2) of tetronasin (1).

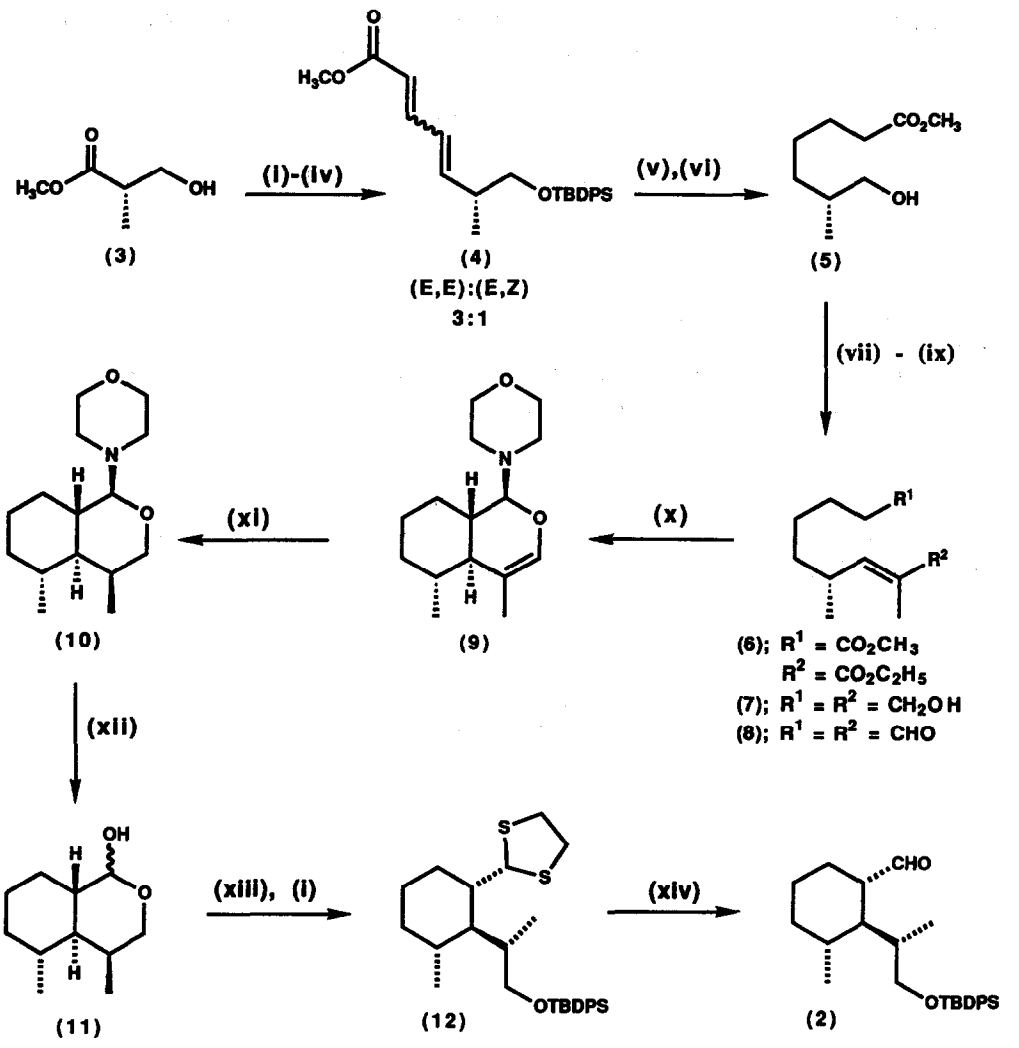


(1)

As illustrated in Scheme 1, the initial steps of the synthesis were straightforward and involved conversion of (S)-(+)-methyl 3-hydroxy-2-methylpropionate (3) into the corresponding hydroxy-*t*-butyldiphenylsilyl ether by protection of the hydroxyl group followed by DIBAL-H reduction of the ester. Oxidation with tetra-n-propylammonium perruthenate (TPAP)[9] and phosphonate ylide coupling using modified Wadsworth-Emmons conditions with trimethylphosphoranocrotonate[10], gave the diene esters (4) in 85% overall yield.[11] Hydrogenation of the diene mixture (4) followed by deprotection of the *t*-butyldiphenylsilyl ether in 3% HCl / CH_3OH gave (5) in 70% yield. The diester (6) was prepared from (5) using a one-pot oxidation / stabilized ylide Wittig olefination procedure developed by Ireland.[12] Reduction of (6) with lithium aluminium hydride followed by TPAP oxidation provided the important key dialdehyde (8)[13] in 82% yield in optically pure form (Scheme 1).

In a similar fashion to the method recently developed by Schreiber for the diastereoselective synthesis of five-membered carbocycles[14], an etheral solution of (8) in the presence of activated 4Å molecular sieves was treated

Scheme 1



(i) TBDPSCl, Et_3N, DMAP, DCM, 0°C. (ii) DIBAL-H, $PhCH_3$, -78°C. (iii) TPAP, NMO, 4Å ground sieves, CH_3CN. (iv) ^nBuLi, HMDS, THF, -78°C, trimethylphosphoranocrotonate. (v) H_2, Pd/C, MeOH. (vi) 3% HCl/MeOH. (vii) $(COCl)_2$, DMSO, Et_3N, DCM, -78°C, then $Ph_3PCCH_3CO_2Et$, reflux. (viii) $LiAlH_4$, Et_2O, -0°C. (ix) TPAP, NMO, 4Å ground sieves, CH_3CN. (x) morpholine, Et_2O, 4Å sieves, 1 h, 25°C. (xi) H_2, PtO_2, EtOAc. (xii) *p*-TsOH, THF/H_2O. (xiii) $(CH_2SH)_2$, $TiCl_4$, DCM. (xiv) MeI, CH_3CN/H_20, $CaCO_3$, reflux.

with morpholine. The intramolecular enamine-enal cyclisation which ensued proceeded extremely well to afford the unsaturated bicyclic aminal (9) as the major diastereoisomer. Owing to the lability of (9) towards chromatography the unsaturated aminal was not isolated but rather the crude products were directly subjected to catalytic hydrogenation over Adams catalyst. This afforded the saturated aminal (10)[15], as the only product as predicted from molecular modelling studies[16], in 72% overall yield from (8). The minor diastereoisomer(s) in the crude cyclisation mixture did not readily undergo hydrogenation and were therefore easily separated from (10) at this stage by flash chromatography. The cyclisation reaction used to form the six-membered carbocyclic ring (9) proceeded in excellent yield (92%) in a highly stereoselective fashion. The one asymmetric carbon atom present in (8) induced the desired stereochemistry at all four of the stereocentres required for the hydrocarbon fragment after hydrogenation of the aminal (9). As the structure determination of (10) was crucial to these studies, in addition to the detailed nmr investigation, the structure of (10) was determined by X-ray crystallography which unequivocally confirmed the stereochemical outcome of the reaction sequence.[16]

Following this efficient stereoselective synthesis of the aminal (10) which contained all the desired stereocentres of the cyclohexyl unit found in (1), hydrolysis to the lactol (11) was achieved by heating (10) in aqueous THF (1:1) in the presence of *p*-toluenesulphonic acid. The lactol (11) was converted into the desired trisubstituted cyclohexyl fragment (2) by treatment with 1,2-ethanedithiol and $TiCl_4$[17] followed by protection as the *t*-butyldiphenylsilyl ether (12). Removal of the dithiolane group provided the trisubstituted cyclohexyl aldehyde (2)[18] in 79% overall yield in optically pure form.

The cyclohexyl aldehyde (2) is believed to be a key synthetic intermediate for the total synthesis of tetronasin (1). The coupling of the hydrocarbon fragment (2) with the polyether fragment C12 - C26[8], has now become the pivotal step in this total synthesis. A variety of methods are currently under investigation for the stereoselective coupling of the hydrocarbon fragment (2) with funtionalised polyether derivatives to generate the *E*-trisubstituted carbon-carbon double bond (C11 - C12) of (1). The labile tetronic acid group will be coupled in the final stages of the total synthesis of (1) to the completed hydrocarbon-polyether fragment C3 - C26 using chemistry previously developed in these laboratories.[7,19] The results of these studies will be reported in due course.

Acknowledgements

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13. (8); $[\alpha]_D^{25}$ = -13.6° (c 8.67,CHCl3); ν_{max} (film, NaCl) 2930, 2858, 2715, 1721, 1684, 1639, 1457, 1408, 1016, 828 cm^{-1}; m/z 182 (M^+), 167 (M^+-Me) and 153 (M^+-CHO); δ (500 MHz, $CDCl_3$) 1.06 (3H, d, 6.8 Hz, 4-Me), 1.30 (2H, m), 1.37 (1H, m), 1.47 (1H, m), 1.62 (2H, m), 1.74 (3H, d, 1.2 Hz, 2-Me), 2.43 (2H, dt, 7.2 and 1.6 Hz, 8-H_2), 2.70 (1H, m, 4-H), 6.23 (1H, dd, 10.0 and 1.2 Hz, 3-H), 9.39 (1H, s, 1-CHO), 9.76 (1H, t, 1.6 Hz, 9-CHO).
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18. (2); $[\alpha]_D^{25}$ = + 0.51° (c 1.96, $CHCl_3$); ν_{max} (film, NaCl), 3070, 3048, 2928, 2856, 2707, 1721, 1589, 1468, 1112, 1085, 823, 740 and 703 cm^{-1}; δ (500 MHz, $CDCl_3$) 0.76 (3H, d, 7.2 Hz, β-Me), 0.93 (3H, d, 6.5 Hz, 6-Me), 1.02 (1H, m, 5-H_{ax}), 1.06 (9H, s, t-Bu), 1.26 -1.42 (3H, m), 1.57 (1H, m), 1.68 - 1.78 (3H, m), 1.75 (1H, tt, 9.8 and 3.8 Hz, 2-H), 2.09 (1H, dq, 7.0 and 2.0 Hz, 4-H_{eq}), 2.24 (1H, m, β-H), 3.38 (1H, dd, 10.7 and 8.9 Hz, α-H), 3.47 (1H, dd, 10.7 and 6.8 Hz, α-H), 7.36 - 7.44 (6H, m, Ph), 7.62 - 7.68 (4H, m, Ph), 9.42 (1H, 5.1 Hz, CHO); Exact mass calcd. for $C_{23}H_{29}O_2Si$: 365.1939. Found: 365.1945.
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