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Novel Polyene Cyclisation Routes to the Acyl Tetronic Acid Ionophore Tetronasin (ICI M139603)

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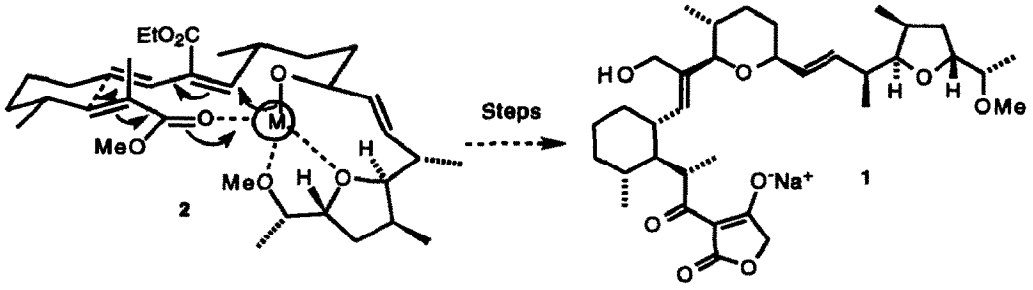
Abstract: An approach to the total synthesis of the ionophore antibiotic tetronasin (**1**) is reported, in which the key step is a novel base catalysed cascade cyslisation of an activated polyene (**2**). This establishes two rings and four stereogenic centres in one step. A related polyene (**16**) has been cyclised in a similar fashion, illustrating the generality of the procedure.

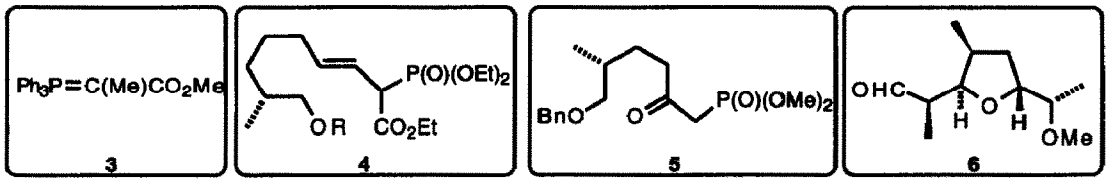
In addition to the biosynthetic studies reported in the preceeding series of papers, we have been studying the total synthesis of the novel ionophore antibiotic tetronasin (ICI M139603) (**1**). Previously we and others have described convergent approaches to (**1**) and related compounds.[1,2] Here we report on a new strategy towards these interesting molecules. The route is based upon the idea of using a metal-templated polyene cyclisation (Scheme 1) somewhat similar to the proposed biosynthetic pathway.[1] The synthetic polyene (**2**) was designed with an electron-deficient diene system to facilitate pyran ring formation *via* a conjugate addition, and the furan ring intact to enhance chelation. A subsequent intramolecular Michael cyclisation would result in the formation of the carbocyclic ring. In this way it would be possible to set up the formation of both six-membered rings and control four stereogenic centres in one operation. The success of this general concept is reported below.



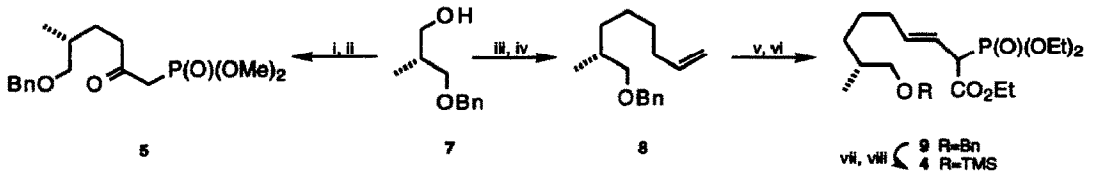
Scheme 1

For the synthesis of the C3-C26 polyene fragment (**2**) we envisaged a convergent approach involving the coupling of the substituted units (**3**), (**4**), (**5**), and (**6**). Compound (**3**) is well known[1] and compounds (**5**)

and (**6**) are readily available by chemistry reported in previous letters in this series. Therefore we only require a synthesis of the remaining C5-C12 unit (**4**) prior to investigating coupling studies.

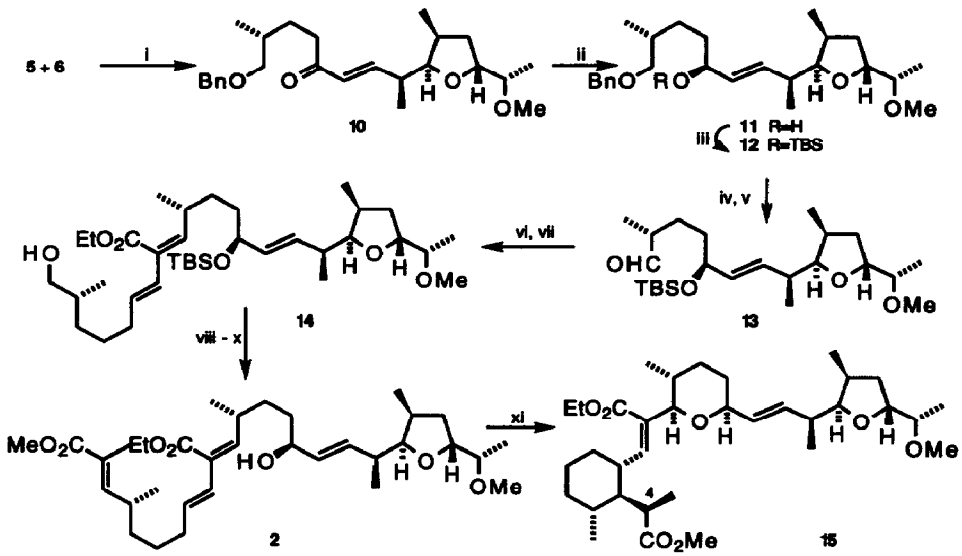


Compounds (**4**) and (**5**) share the same absolute stereochemistry and hence common starting materials could be used in their synthesis (Scheme 2). Thus, conversion of the alcohol (**7**) to its tosylate and subsequent Fouquet-Schlosser coupling[3] with pent-5-enyl magnesium bromide in the presence of Kochi's catalyst gave (**8**) in 83% yield[4]. Ozonolysis and Knoevenagel condensation with triethyl phosphonoacetate, N-methylmorpholine and $TiCl_4$[5] yielded the allylic phosphonate (**9**). This was transformed to the transiently protected coupling partner (**4**) using the standard procedure of sodium in ammonia, followed by trimethylsilyl chloride. Alternatively, the reaction of (**7**) with *N*-bromosuccinimide and triphenylphosphine gave a bromide intermediate which was used to quench kinetically the dianion derived from dimethyl (2-oxopropyl)phosphonate[6] at the γ-position, to give the ketophosphonate (**5**).



Scheme 2 (i) NBS, PPh_3, CH_2Cl_2, 0°C (87%). (ii) Dimethyl (2-oxopropyl)phosphonate, NaH, ^nBuLi, THF, -10°C (70%). (iii) TsCl, Pyridine (88%). (iv) CH_2=$CH(CH_2)_3MgBr$, Li_2CuCl_4, THF, -78°C to RT (83%). (v) O_3, CH_2Cl_2, -78°C; then Ph_3P (71%). (vi) $EtO_2CCH_2P(O)(OEt)_2$, $TiCl_4$, NMM, THF, 5°C (90%). (vii) Na, NH_3, -33°C (77%). (viii) TMSCl, Et_3N, CH_2Cl_2, 0°C (98%).

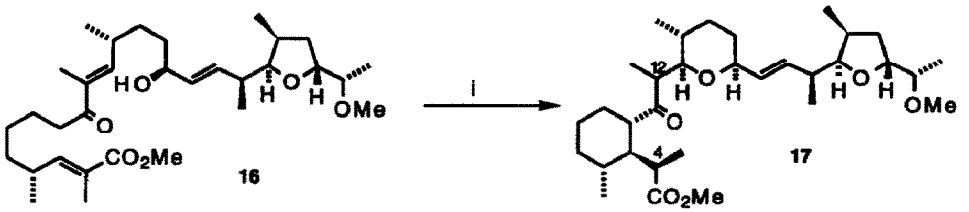
The next series of coupling reactions all proceeded smoothly to afford the desired tetraene (**2**). Coupling of (**5**) and (**6**) using the Masamune-Roush conditions[7] gave the enone (**10**). This was reduced with (*S*)-BINAL-H[8] at -100°C to give (**11**) with high diastereoselectivity. Compound (**11**) was protected as its *t*-butyldimethylsilyl ether (**12**) and converted to the aldehyde (**13**) by removal of the benzyl protecting group with sodium in ammonia followed by oxidation with tetra-*n*-propylammonium perruthenate (TPAP).[9] The coupling of (**13**) with the phosphonate ester (**4**) was achieved using lithium hexamethyldisilazide as the base, followed by treatment with a pH 3 acetate buffer to give (**14**). The use of other bases was much less satisfactory in giving poor yields of the required *E,Z*-geometry. The alcohol (**14**) was then oxidised with TPAP, coupled *via* a Wittig reaction with methyl 2-(triphenylphosphoranylidene)propanoate, and finally deprotected with Dowex in methanol to give (**2**) in 93% overall yield from (**13**) (Scheme 3).



Scheme 3 (i) LiCl, DIPEA, CH_3CN (71%). (ii) (*S*)-BINAL-H, THF, -100°C (84%; 9:1). (iii) TBSCl, imidazole, DMF (98%). (iv) Na, NH_3, -33°C (99%). (v) $^nPr_4NRuO_4$ (TPAP), NMO, 4Å Sieves, CH_2Cl_2 (93%). (vi) **4**, LHMDS, THF, -78°C (86%). (vii) NaOAc, AcOH, MeOH (pH 3) (100%). (viii) TPAP, NMO, 4Å Sieves, CH_3CN (95%). (ix) $Ph_3P{=}C(Me)CO_2Me$, $CHCl_3$, Δ (100%). (x) DOWEX-50W, MeOH (98%). (xi) KHMDS, PhMe, 0°C (86%).

Having synthesised the precursor, the key polyene cyclisation reaction could then be investigated. It was found that treatment of (**2**) with potassium hexamethyldisilazide, in toluene for 30 minutes at 0°C, gave an excellent yield of one main diastereomer (**15**)[10] in 67% yield (Scheme 3). From extensive nmr experiments and comparison with spectra of the natural product and derivatives it was determined that the structure was that of (**15**) in which the C4 methyl group has the wrong orientation for the natural product. Obviously (**15**) contains useful functionality for further elaboration to the natural product (**1**), and it should be possible to equilibrate the C4 centre at a later stage.

In an extension of these studies we also examined the double cyclisation of an enone (**16**) to give (**17**) (Scheme 4) which contains functionality that could potentially be readily modified to the natural product (**1**). The preparation of the necessary enone (**16**) utilizes standard precursors and chemistry similar to that used in the synthesis of (**2**) and will not be reported here. Exposure of (**2**) to potassium hexamethyldisilazide in THF/toluene at 0°C resulted in the desired double cyclisation, affording (**17**) in 67% yield. The use of other bases was much less satisfactory and gave substantial quantities of a monocyclic product. The structure of (**17**) was solved by performing extensive nmr experiments; although the stereochemistry of the C12 methyl group could not be definitively assigned the double cyclization reaction gives largely one diastereoisomeric product. Unfortunately, in terms of our total synthetic goal, the stereochemistry at C4 is again opposite to that required for tetronasin (**1**).



Scheme 4 (i) KHMDS, PhMe, 0°C 67%.

These examples serve to illustrate that the polyene cyclisation process is a powerful method for the construction of multiple ring systems and can potentially be adapted in a more general way to other synthetic targets.

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10. $[\alpha]_D$ = -22.5 (c = 0.92, $CHCl_3$). ^{1}H-nmr (500 MHz, $CDCl_3$): 0.74 (3H, d, *J* = 6.6 Hz, 12-Me); 0.75 d, *J* = 7.5 Hz, 4-Me); 0.92 (3H, d, *J* = 6.9 Hz, 20-Me); 0.93 (3H, d, *J* = 6.8 Hz, 18-Me); 1.07 (3H d, *J* = 6.9 Hz, 2-Me); 1.08 (3H, d, *J* = 6.3 Hz, 23 Me); 1.00 - 1.38 (6H, m, 4-H, 5-Hβ, 6-Hβ, 7-Hβ, 13-Hβ, 14-Hβ); 1.29 (3H, t, *J* = 7.1 Hz, $CO_2CH_2\underline{C}H_3$); 1.50 - 1.83 (8H, m, 3-H, 4-Hα, 6-Hα, 7-Hα, 12-H, 13-Hα, 14-Hα, 21-Hβ); 1.96 (1H, ddd, *J* = 12.4, 8.6, 6.8 Hz, 21-Hα); 2.23 (2H, m, 18-H, 20-H); 2.51 (1H, m, 2-H); 2.83 (1H, dtd, *J* = 10.9, 11.0, 3.5 Hz, 8-H); 3.34 (1H, dq, *J* = 6.3, 5.0 Hz, 23-H); 3.38 (3H, s, OMe); 3.50 (1H, dd, *J* = 9.5, 4.1 Hz, 19-H); 3.66 (3H, s, CO_2Me); 3.77 (1H, d, *J* = 9.8 Hz, 11-H); 3.82 (1H, m, 15-H); 3.95 (1H, ddd, *J* = 8.6, 7.0, 4.9 Hz, 22-H); 4.20 (2H, q, *J* = 7.1 Hz, $CO_2\underline{C}H_2CH_3$); 5.55 (1H, dd, *J* = 15.9, 5.7 Hz, 16-H); 5.76 (1H, dd, *J* = 15.9, 6.3 Hz, 17-H); 5.89 (1H, d, *J* = 10.5 Hz, 9-H). ^{13}C-nmr ($CDCl_3$, 126 MHz): 8.97 (2-Me); 13.51 (18- or 20-Me); 14.27 ($CO_2CH_2\underline{C}H_3$); 15.94 (23-Me); 16.44 (18- or 20-Me); 17.65 (12-Me); 19.78 (4-Me); 25.49 (C6); 32.44 (C5); 32.74 (C4); 32.94 (C13); 33.22 (C7); 35.23 (C18 or C20); 35.29 (C21); 35.82 (C14); 36.09 (C12); 36.60 (C18 or C20); 40.36 (C2); 40.79 (C8); 49.85 (C3); 51.49 ($CO_2\underline{Me}$); 57.42 (23-OMe); 60.13 ($CO_2\underline{C}H_2CH_3$); 78.40 (C15); 79.54 (C23); 80.23 (C22); 83.72 (C11); 85.91 (C19); 130.13 (C16); 133.62 (C10); 134.07 (C17); 145.41 (C9); 167.59 ($\underline{C}O_2Me$); 177.59 ($\underline{C}O_2Et$).

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