Synthesis and Chemistry of the Ionophore Antibiotic Tetronasin

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Studies towards the synthesis and biosynthesis of tetronasin, an acyltetronic acid ionophore are described, together with an account of some novel methodology which is more widely applicable for the synthesis of other acyltetronic acids.

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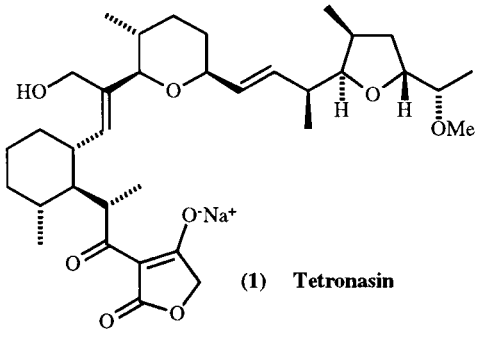
Introduction.

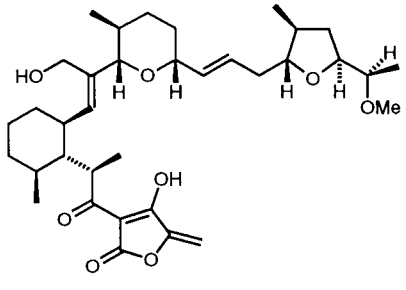
Tetronasin (ICI 139603) (**1**), an acyltetronic acid ionophore produced by *Streptomyces longisporoflavus* (1), is of commercial interest owing to its biological activity as an antibiotic, antiparasitic and growth promotion agent in ruminants (2).



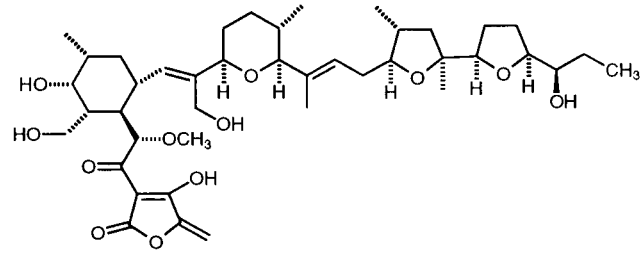
(1) Tetronasin

Several groups have reported on its structure (1), properties (3), biosynthesis (4) and synthesis (5, 6), and it is in these latter two areas that we have become especially involved in recent years. The highly functionalised tetronasin molecule is a challenging synthetic target not only due to the presence of three heterocyclic systems within its structure, but also due to the large number of stereogenic centres. Further challenge is derived from the fact that there are relatively few methods of synthesis of the biosynthetically rare acyltetronic acid unit. This paper will provide a review of our work in a number of areas including:

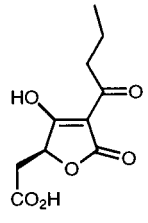
- New methodology for the synthesis of acyl tetronic acids.
- Work towards a total synthesis of tetronasin.
- Biosynthetic studies involving tetronasin.



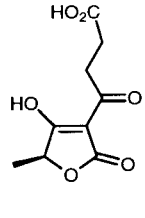
Tetronomycin



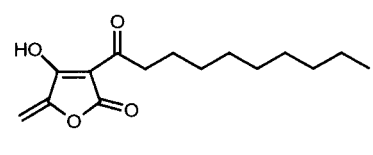
A80577



Carlosic acid



Carolinic Acid

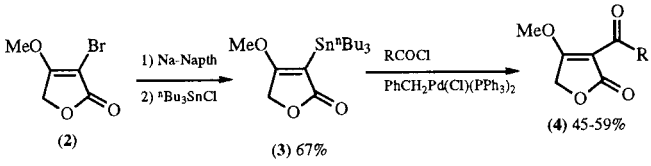


Agglomerin A

Methodology for the Synthesis of Acyl Tetronic Acids (7).

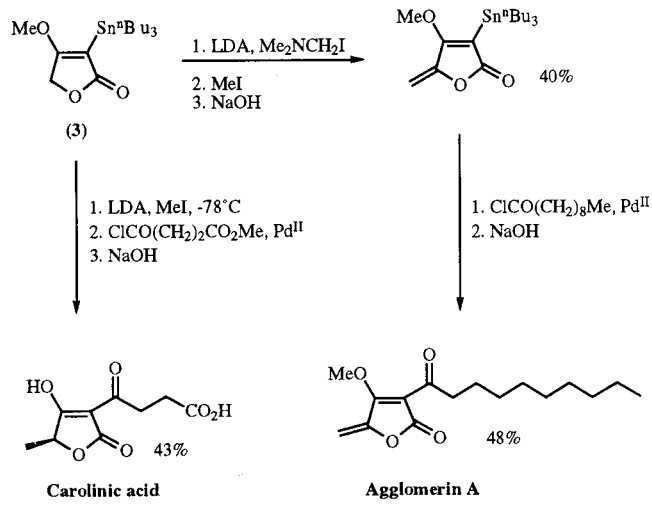
The acyl tetronic acid moiety of tetronasin is an important structural motif which is incorporated within many other natural products. For example, it can be found within the structurally related ionophores tetronomycin and A80577, as well as the more diverse structures of carlosic acid, carolinic acid and agglomerin A.

Whilst developing a synthesis of tetronasin, we investigated new methods for the synthesis of acyl tetronic acids. This work has demonstrated that the readily prepared stannyl tetronate (7) (**3**) is particularly useful for palladium catalysed coupling reactions with acid chlorides which thus allows facile entry to acyl tetronic acids (Scheme 1).



Scheme 1

For example tetronate (**3**) has been efficiently synthesised from bromo tetronate (**2**), by using sodium naphthalenide, and has been shown to subsequently couple with a range of acid chlorides under Pd^{II} catalysis to furnish tetronates (**4**) in good yield. The application of this methodology to the synthesis of carolinic acid and agglomerin A is shown in Scheme 2.

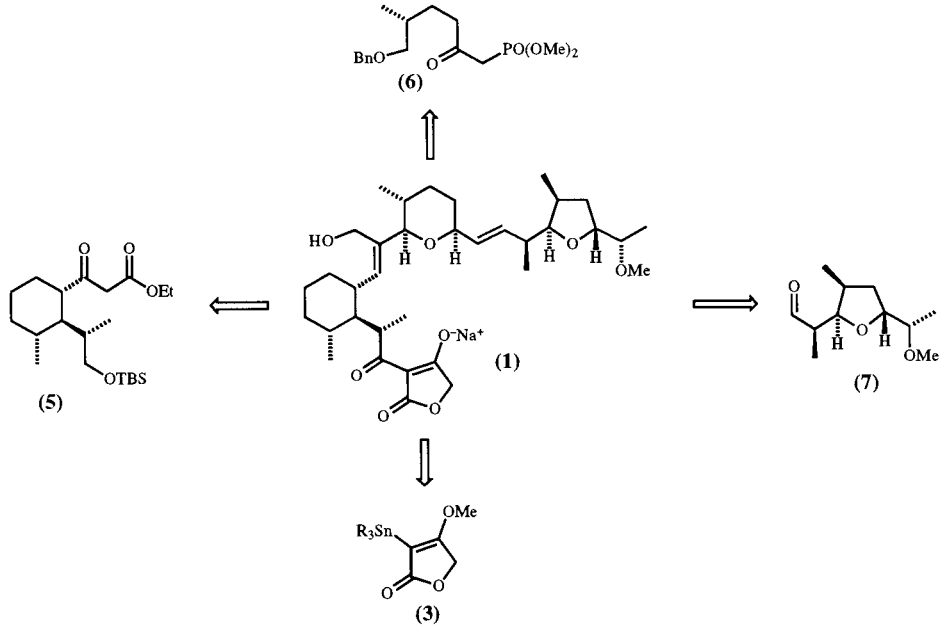


Scheme 2

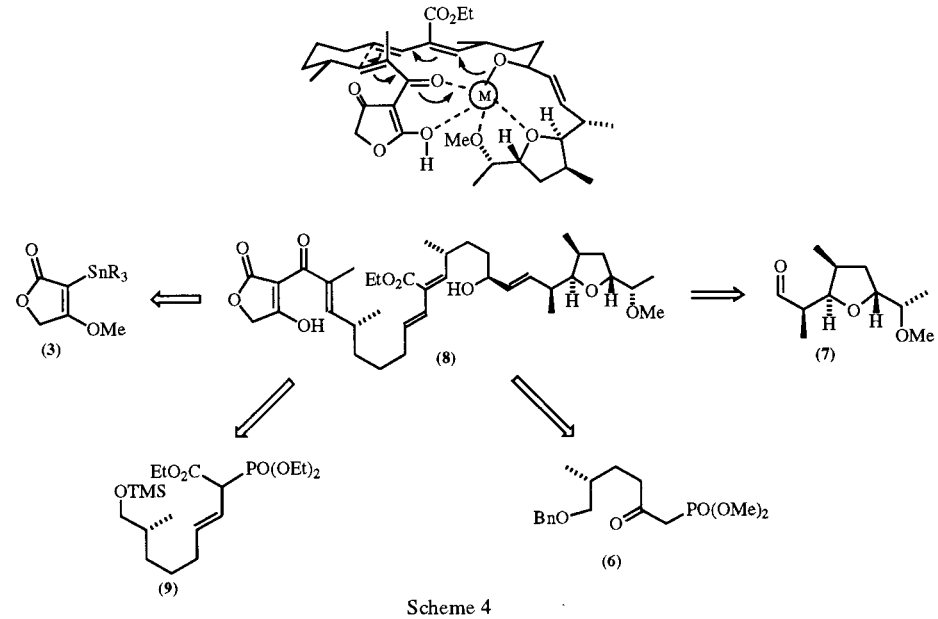
This methodology has not only allowed efficient access into a range of natural products, but has also established a plausible method for the introduction of the acyl tetronic acid fragment in a total synthesis of tetronasin.

Work towards a Total Synthesis of Tetronasin.

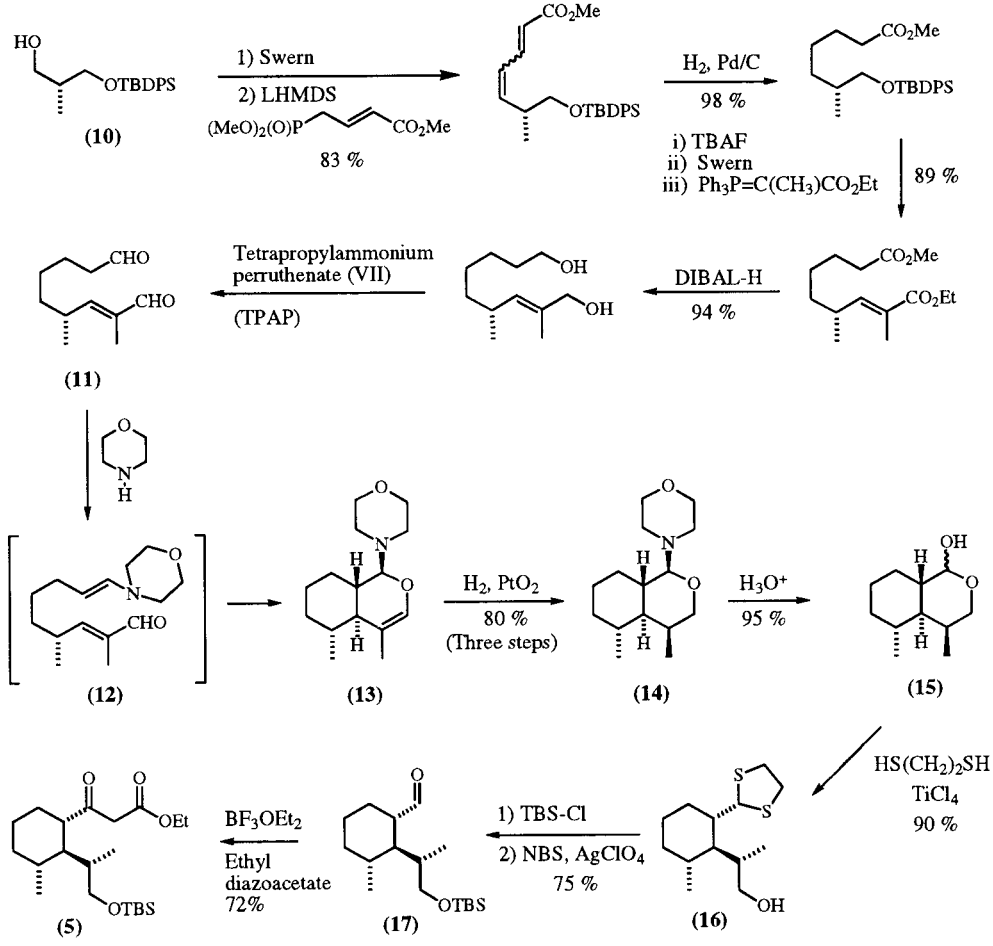
Two complementary approaches towards the synthesis of tetronasin are currently underway within our laboratory. The retrosynthetic analyses for the two pathways are shown below, with Scheme 3 representing a highly convergent approach, whilst Scheme 4 outlines a more linear but conceptually more interesting approach. It can be seen



Scheme 3



Scheme 4



Scheme 5

that coupling fragments that are ***common*** to both synthetic pathways have been deliberately selected so as to maximise the overall efficiency of our two routes.

The success of the approach depicted in Scheme 4 will rely upon the linear polyene (**8**) undergoing a metal-templated cyclisation to afford the tetrahydropyran and cyclohexyl rings of the target in a single operation. This key cyclisation is similar to that proposed in nature (4f) and it was hoped that the inherent stereochemical bias of the cyclisation would result in a single product containing all new chiral centres in the natural configuration.

1) Convergent Approach.

Prior to investigating the convergent synthesis shown in Scheme 3, the preparation of the coupling units (**3**), (**5**), (**6**) and (**7**) was required. Tetronate (**3**) was prepared from bromo alkene (**2**) as described before (Scheme 1).

i) Synthesis of Cyclohexyl Fragment (**5**).

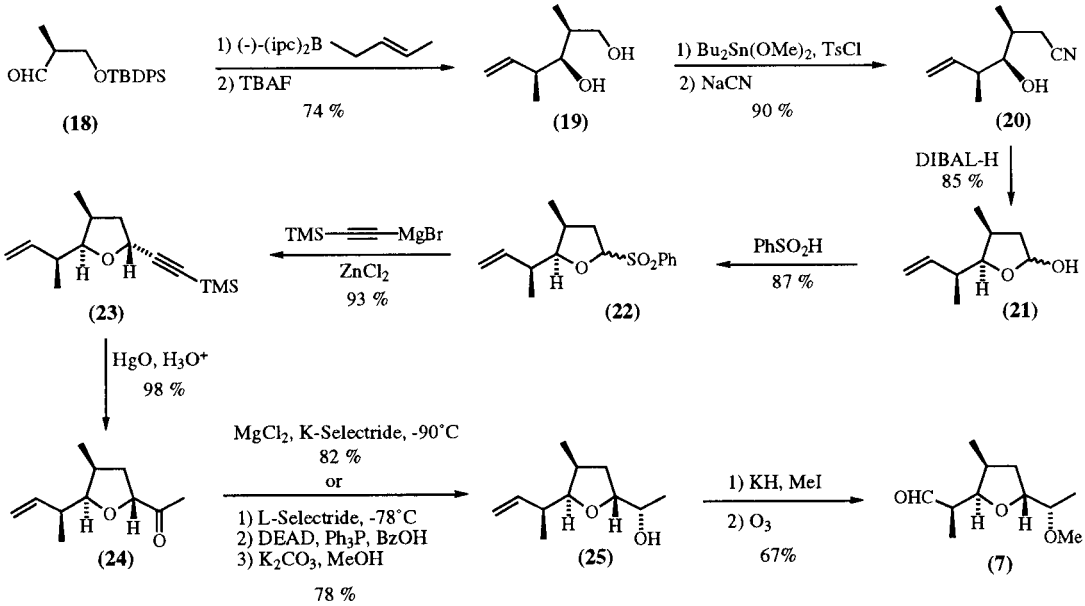
The synthesis of the cyclohexyl fragment (**5**) (5c) from the monoprotected diol (**10**) (8) is shown in Scheme 5.

The key step of this synthesis involves an enamimeenal cyclisation reaction (9) in which three new stereocentres of the product aminal (**13**) were controlled by the single stereogenic centre of the starting material (**12**). Hydrogenation of the sensitive enol ether moiety subsequently occurred with excellent stereoselectivity from the least hindered face to afford the desired compound (**14**) as almost exclusively one diastereomer. After acidic hydrolysis to the lactol (**15**), the aldehyde functionality was protected as the corresponding dithiolane (**16**), freeing the terminal alcohol group for protection as its TBS ether. Subsequent NBS/$AgClO_4$ mediated hydrolysis of the dithiolane to the aldehyde (**17**) was then achieved in 75%. One final reaction involving treatment of aldehyde (**17**) with ethyldiazoacetate in the presence of boron trifluoride etherate as Lewis acid (10) then gave the required fragment (**5**) in excellent yield.

ii) Synthesis of Tetrahydrofuran Fragment (**7**).

Our synthesis of the tetrahydrofuran fragment (**7**) utilises some methodology (11) which we have established within our group for the preparation of substituted tetrahydro-pyrans and -furans using anomeric sulfones (Scheme 6).

The key intermediate sulfone (**22**) was prepared as outlined in Scheme 6. Brown's asymmetric crotylation methodology (12) was applied to establish two of the three chiral centres of the target alcohol (**19**), with the third being derived from the known aldehyde (**18**) (8). The primary hydroxyl group of the diol (**19**) was selectively tosylated (13) and then displaced with cyanide to afford nitrile (**20**). Reduction of the nitrile (**20**) to the aldehyde with DIBAL-H proceeded with concommitant formation of the lactol (**21**) which was transformed to the sulfone (**22**) on treatment with benzenesulfinic acid. Treatment of (**22**) with the Grignard derived from trimethylsilylacetylene in the presence of zinc chloride afforded the alkyne (**23**) in excellent yield. The stereoselectivity of this reaction results from the nucleophile approaching an intermediate oxonium ion from the least hindered site. Treatment of the resulting alkyne with acidic mercury (II) then effected both deprotection of the silyl ether and hydrolysis of the alkyne moiety to yield

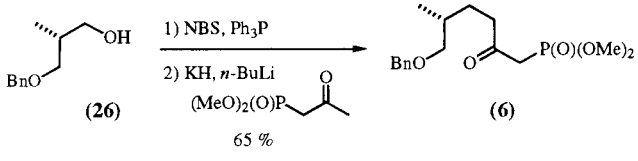


Scheme 6

methyl ketone (**24**). Stereoselective reduction of ketone (**24**) was next achieved *via* a pre-chelation controlled K-Selectride reduction, and the resulting alcohol was readily transformed to ether (**7**) *via* methylation and ozonolysis.

iii) Synthesis of the C13-C18 Fragment (**6**).

Phosphate (**6**) was readily obtained from the known alcohol (**26**) by simple conversion of the alochol (**26**) to the corresponding bromide and then using this compound to alkylate the dianion generated from dimethyl 2-oxopropylphosphonate (14) (Scheme 7). This method thus allowed entry to phosphonate (**6**) in an overall yield of 65%.

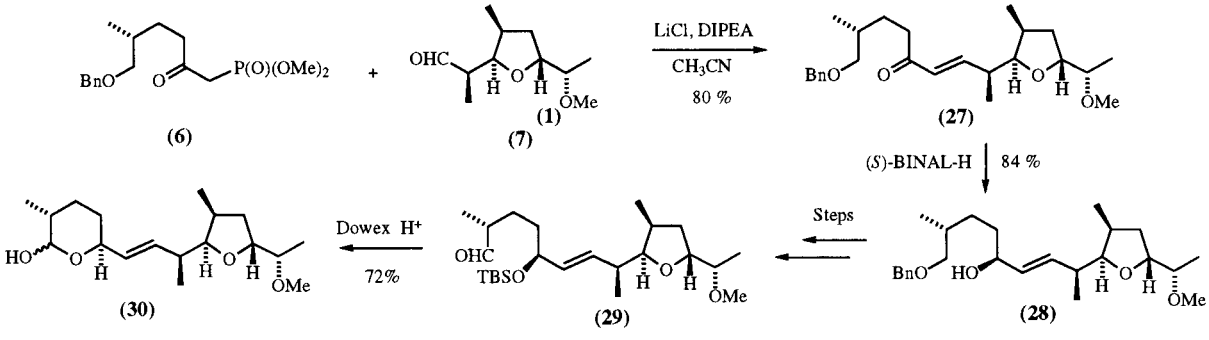


Scheme 7

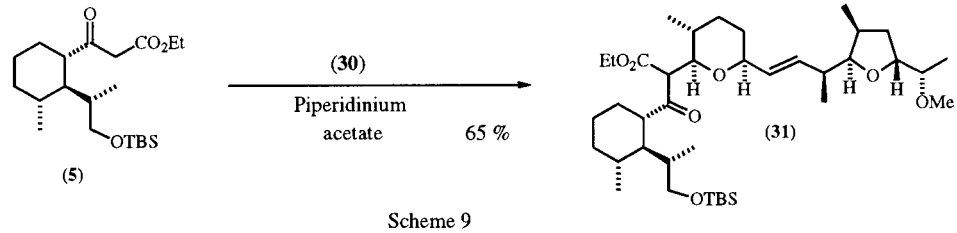
With the synthesis of all three fragments complete, coupling reactions to assemble the tetronasin framework could be investigated. Firstly, coupling of the aldehyde (**7**) with the phosphonate (**6**) (Scheme 8) was carried out under Masamune-Roush conditions (15), to afford the enone (**27**) with no appreciable racemisation of the sensitive centre adjacent to the aldehyde.

Reduction of the enone (**27**) with Noyori's (*S*)-BINAL-H reagent (16) proceeded well to create the new stereogenic centre of the allylic alcohol (**28**) with good control. The minor, unwanted, diastereomer was readily inverted using the Mitsunobu procedure (17). Protection, deprotection and oxidation then afforded aldehyde (**29**) which could be readily converted to lactol (**30**) under acidic deprotection conditions. The coupling reaction of lactol (**30**) with ketoester (**5**) could then be investigated (Scheme 9).

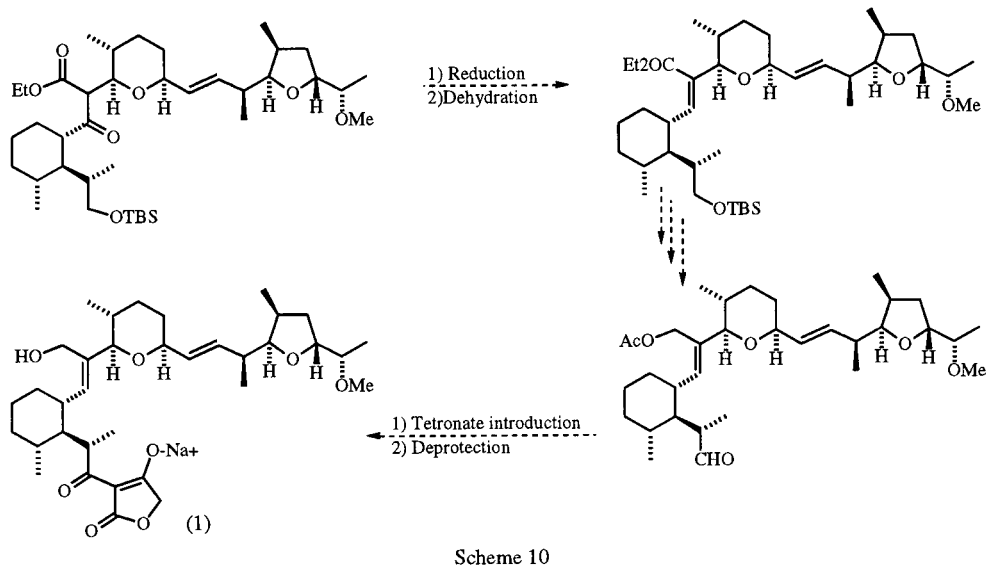
A Knoevenagel reaction was chosen to effect this coupling, and pleasingly conditions were discovered which gave the required product. Thus heating the lactol (**30**) and ketoester (**5**) in toluene under Dean Stark conditions with piperidinium acetate as acid catalyst allowed coupling to occur to yield (**31**) in 65% yield (18). The remaining synthetic transformations which are necessary for conversion of (**31**) to tetronasin are highlighted in Scheme 10. These are now being investigated within our laboratory.



Scheme8



Scheme 9



Scheme 10

2) Linear Polyene Cyclisation Approach (5b).

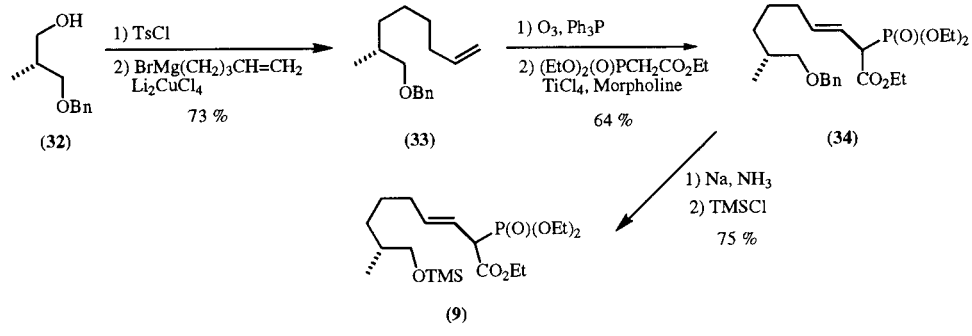
To ascertain whether the metal templated cyclisation approach would indeed realise tetronasin, the synthesis of the linear polyene (**8**) was investigated. This proved particularly facile since three of the four desired coupling fragments were identical to that used in the convergant approach previously described. The synthetic approach to the remaining fragment (**9**) is outlined below.

i) Synthesis of the Phosphonate Fragment (**9**).

Phosphonate (**9**), containing only one stereogenic centre, could be derived from alcohol (**32**) (Scheme 11).

to afford olefin (**33**). Ozonolysis of the olefin and Knoevenagel condensation of the resulting aldehyde with triethyl phosphonoacetate afforded (**34**), in which the double bond had moved out of conjugation with the ester and phosphonate groups. Finally, protecting group exchange afforded the silyl protected phosphonate (**9**).

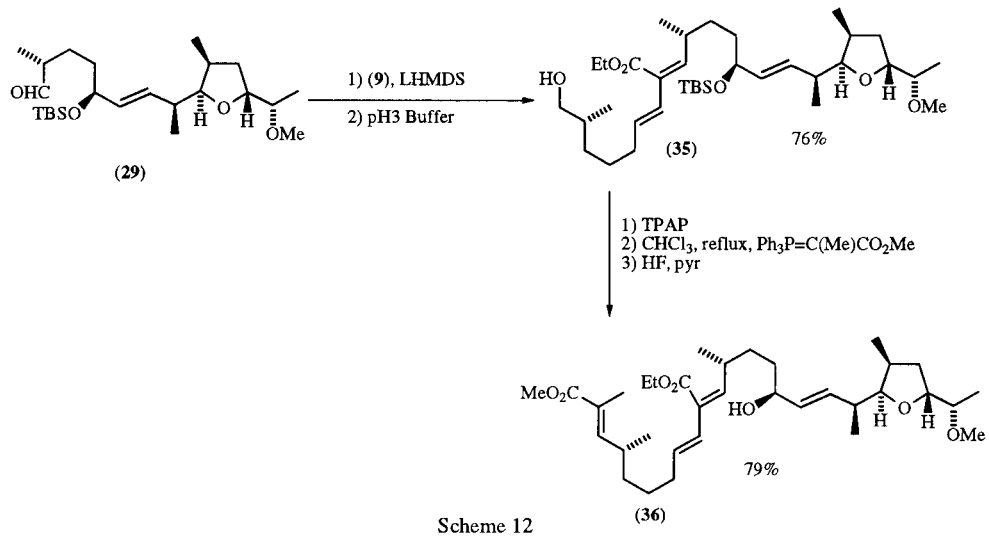
With both the phosphonate (**9**) and the aldehyde (**29**) in hand (for preparation of aldehyde (**29**) see scheme 8), coupling was achieved with LHMDS to afford the unsaturated ester (**35**) in 86% (Scheme 12). This was subsequently transformed to the cyclisation precursor (**36**) *via* simple deprotection, oxidation and homologation steps.



Scheme 11

The hydroxyl group of alcohol (**32**) was converted to the corresponding tosylate which underwent Fouquet-Schlosser coupling (19) with the Grignard reagent derived from 5-bromo-1-pentene, in the presence of Kochi's catalyst,

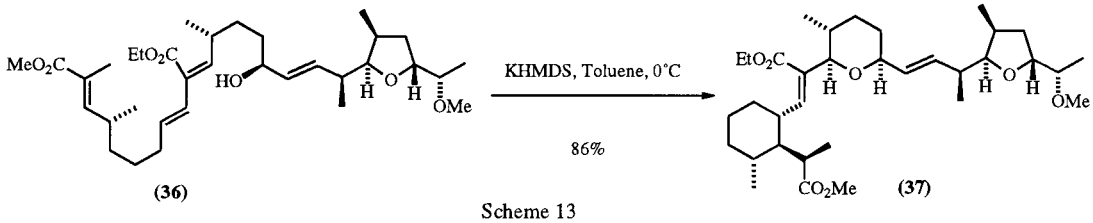
The challenging cascade cyclisation reaction was next attempted, with the aim of creating the two rings and four new chiral centres of the cyclised product (**37**) in a controlled fashion. In a very rewarding manner, conditions



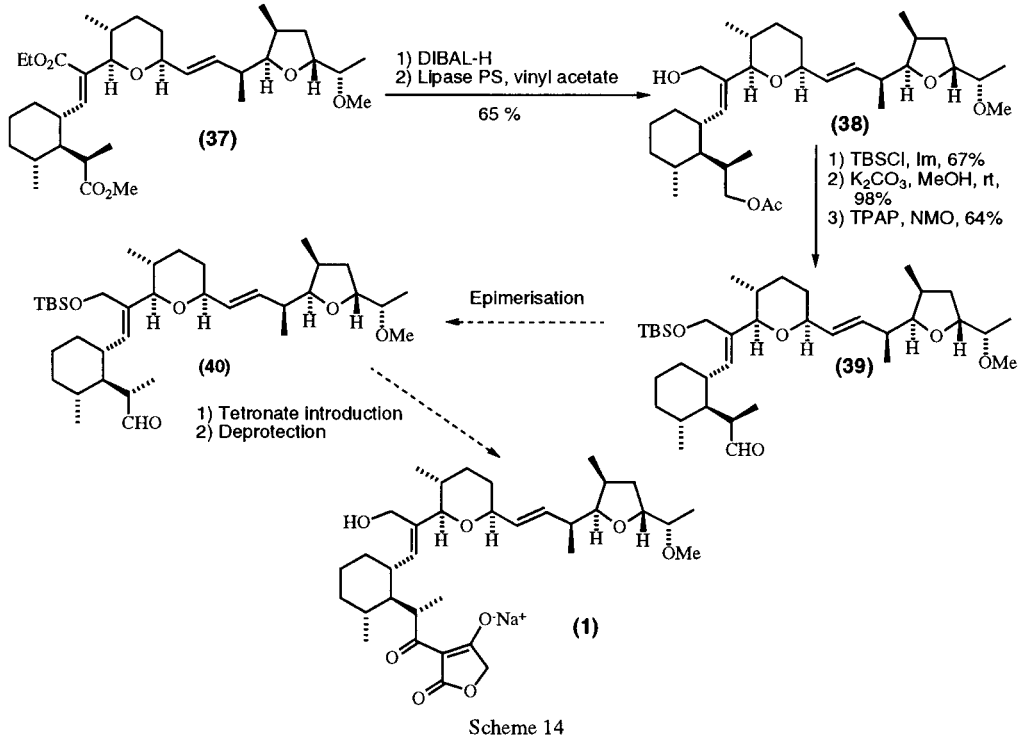
Scheme 12

have been established whereby the required cyclisation occurs smoothly to yield a single diastereomer of the cyclised product in excellent yield (5b) (Scheme 13).

Extensive nmr analysis of (**37**) has confirmed that three of the four new stereocentres are formed with the configuration desired for the natural product. The fourth centre,



Scheme 13

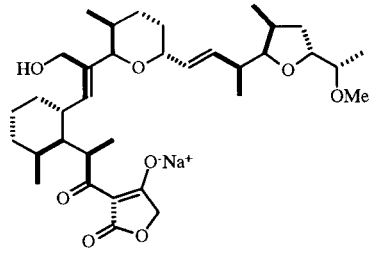


Scheme 14

the methyl group adjacent to the terminal methyl ester, possesses the opposite configuration to that required, but as this centre is activated to deprotonation it should prove possible to epimerise at a late stage of the synthesis. Further elaboration of the cyclised product (**37**) to potentially yield tetronasin is outlined in Scheme 14. Thus reduction of both esters using DIBAL-H afforded a diol, the less hindered, terminal alcohol of which could be selectively acetylated to provide (**38**) using Lipase PS (20) in vinyl acetate. Protecting group manipulation and oxidation then afforded aldehyde (**39**) (21) which we consider to be a suitable substrate for examining the required methyl group epimerisation. These studies are now in progress and their successful completion will afford (**40**) which has been converted to tetronasin by other workers (6a).

Biosynthesis.

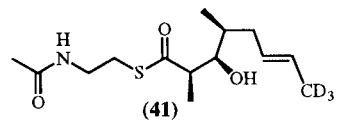
The biosynthesis of tetronasin (**1**) has been extensively investigated by Staunton and co-workers (4), and is found to be typical of the polyketide-derived natural products; the backbone of the molecule is comprised of acetate and propionate units at varying levels of oxidation (4g,h).



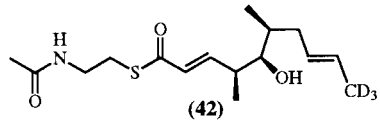
Tetronasin showing incorporation of acetate (""") and propionate (——) units.

It has been proposed that a suitably functionalised linear array of these units is assembled on a series of polyketide synthase (PKS) enzyme complexes (4f), and that following complete assembly of the chain, cyclisation steps occur to afford the natural product, either before or after release from the assembling enzyme complex. In order to test this theory, we embarked a collaboration with Dr. Staunton on the syntheses of a number of polyketide fragments that would represent intermediate polyketides of the growing chain, in the hope that feeding these compounds to cultures of the producing micro-organism would result in their incorporation into the natural product (4a,d). We selected the four targets (**41-44**) representing tetra-, penta-, octa- and dodeca-ketides respectively, and designed syntheses which would allow for the presence of deuterium labels in these molecules in order to be able to detect any incorporation into tetronasin using ^{2}H-nmr. The target molecules (**41-44**) were prepared as their *N*-acylcysteamine thioester derivatives (NAC-thioesters) as this unit has been shown to aid in incorporation in other studies (7).

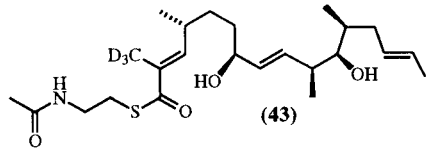
The tetra- and penta-ketides (**41** and **42**) were prepared from the readily available aldehyde (**45**) (8) as outlined in Scheme 15; this work has been described in detail elsewhere (4a). The two remaining chiral centres required were introduced using Brown's (*Z*)-crotyl-(+)-diisopinocampheylborane reagent (12) with subsequent oxidative work-up to give (**46**). Following a number of straightforward manipulations the unsaturated ester (**47**) was reduced with DIBAL-D (22) to incorporate two of the desired three deuterium labels into the alcohol (**48**). The final deuterium atom of the trideuteriomethyl group present in (**49**) was easily introduced by Super-Deuteride® reduction of the corresponding chloride. Conversion of (**49**) to the aldehyde (**50**) was easily accomplished; this compound was a key intermediate in



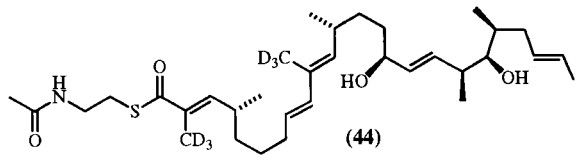
(**41**)



(**42**)



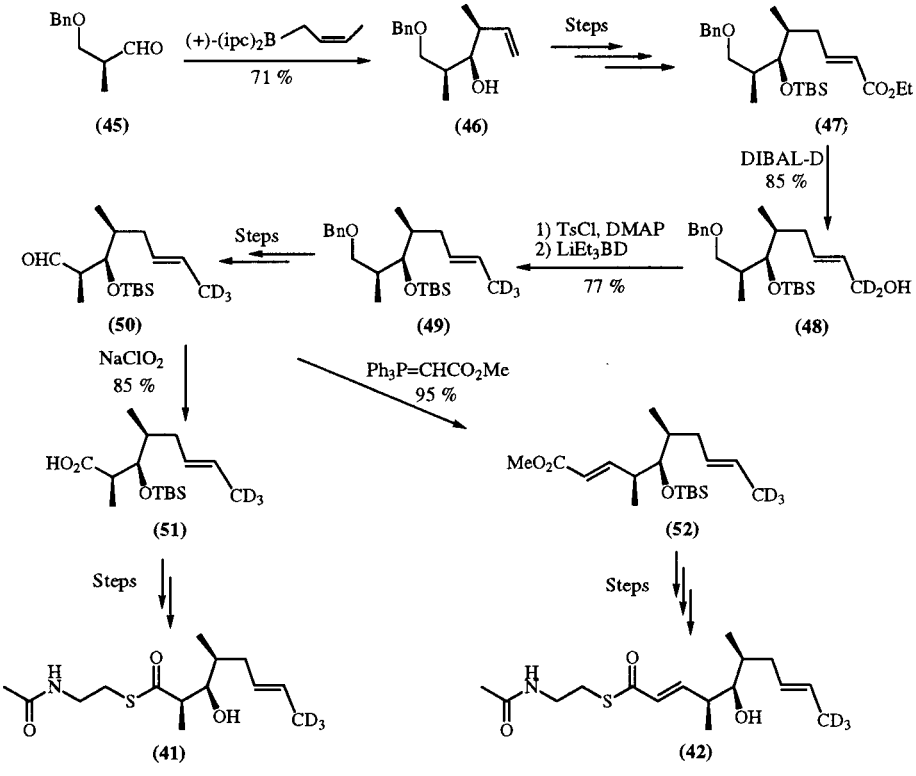
(**43**)



(**44**)

the synthesis of both the tetraketide (**41**) and the pentaketide (**42**). Oxidation to the corresponding acid (**51**), formation of the NAC-thioester and deprotection easly afforded (**41**), whilst homologation to the unsaturated ester (**52**), saponification, formation of the NAC-thioester and deprotection produced (**42**).

Thus the known alcohol (**55**) (8) was easily converted to the bromide (**56**) which was used to alkylate the dianion of the trideuteromethyl-substituted phosphonate (**57**), affording (**58**) in reasonable yield. Protecting group exchange then afforded the desired methylthiomethyl-protected (MTM) (24) compound (**54**).

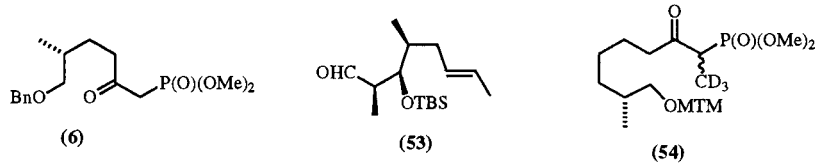


Scheme 15

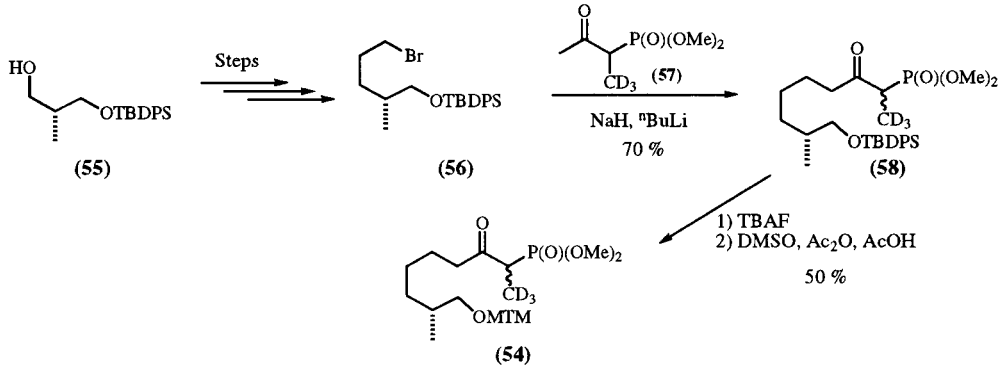
The two smallest polyketides (**41**) and (**42**) have been used in feeding studies with *S. longisporoflavus* and have been found to be successfully incorporated into tetronasin (4c, 23) thus proving the processive pathway to tetronasin.

The precursors to the remaining acyclic targets (**43**) and (**44**) were fragments (**6**), (**53**) and (**54**). The phosphonate fragment (**6**) was prepared as described before (Scheme 7), and aldehyde (**53**) was prepared in an anaologous route to that used for the synthesis of aldehyde (**50**) (Scheme 15) but using non-deuterated reagents (5a).

With the desired intermediates (**6**), (**53**) and (**54**) in hand, the syntheses of (**43**) and (**44**) were realised as shown in Scheme 17. The aldehyde (**53**) was reacted with phosphonate (**6**) under the mild conditions of Masamune and Roush (15), in order to avoid epimerisation of the sensitive centre adjacent to the aldehyde, affording the enone (**59**) in good yield. Asymmetric reduction of this compound was carried out with Noyori's (*S*)-BINAL-H reagent (16), affording the allylic alcohol (**60**) in good yield and with excellent stereoselectivity. Protecting group manipulation and oxidation then provided the key

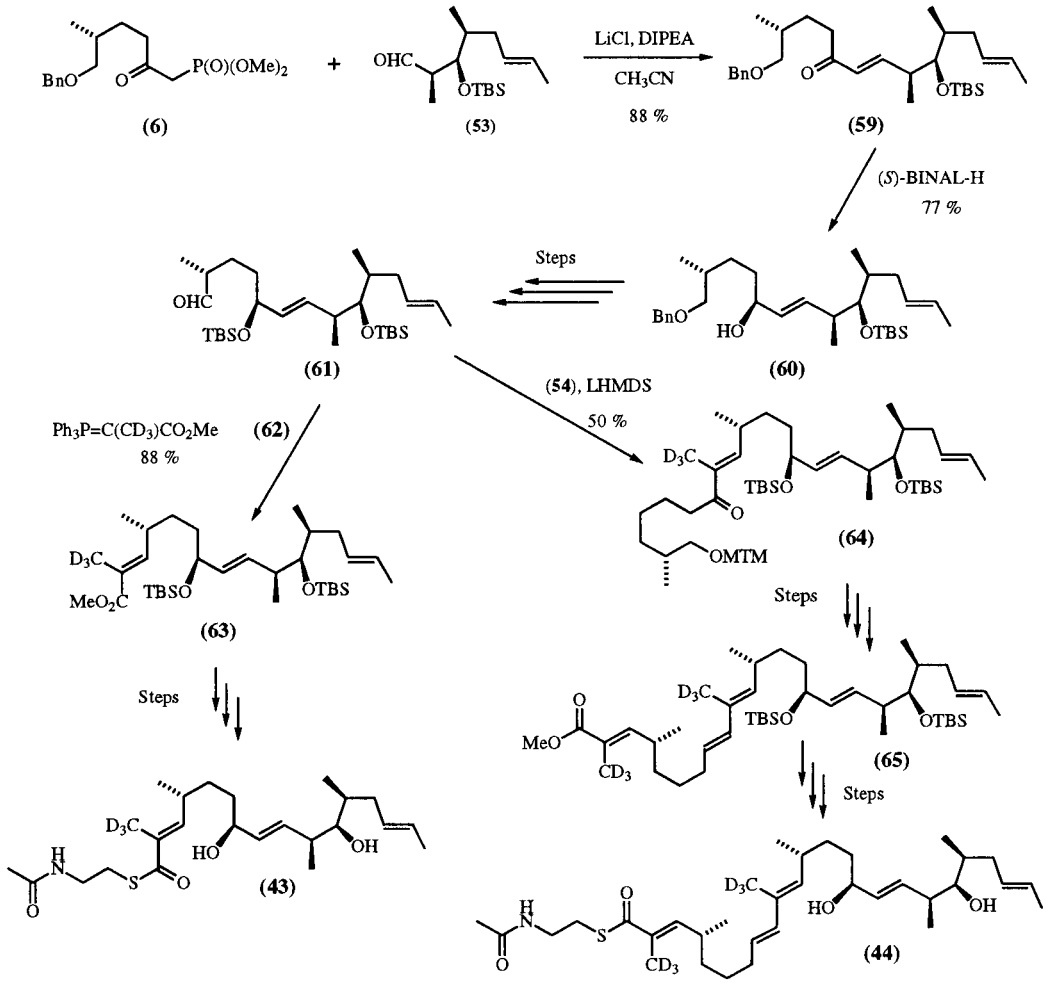


Phosphonate (**54**) was prepared as shown in Scheme 16.



Scheme 16

intermediate aldehyde (**61**). Reaction of (**61**) with the deuterated phosphorane (**62**) allowed incorporation of the necessary label; conversion of the ester (**63**) to the target NAC-thioester (**43**) was straightforward. Alternatively, (**61**) could be reacted with the phosphonate (**54**) in the presence of LHMDS to afford a moderate yield of the desired (*E*)-enone (**64**) as well as an almost equal amount of the undesired (*Z*)-isomer; these compounds were readily separable and only the (*E*)-isomer (**64**) was carried through the synthesis. Functional group manipulation and



Scheme 17

a final Wittig reaction with the deuterated phosphorane (**62**) afforded (**65**), this time incorporating *two* trideuteromethyl groups. In this way, any observed deuterium incorporation within tetronasin would be directly derived from the feeding unit (**44**), rather than from degradation, or partial degradation, to acetate and labelled propionate units.

Finally, the ester (**65**) was converted to the target (**44**) by replacement of the methyl ester with the NAC-thioester group and subsequent deprotection. To date, neither (**43**) nor (**44**) have been used in feeding experiments with *S. longisporoflavus* because we consider that they are too large to penetrate the cell wall of the intact organism and will be more likely to be degraded to acetate and propionate. Experiments with these two compounds will be performed when the tetronasin-producing PKS complex has been isolated and suitably purified from any degredative enzymes.

Conclusion.

In this paper we have descibed two routes towards a total synthesis of tetronasin. Both of these routes have successfully allowed the construction of the highly functionalised skeleton of the target molecule, and the elaboration of the molecules so produced is now being investigated to complete the total synthesis of tetronasin. We have achieved the synthesis of four labelled polyketide fragments for biosynthesis studies, and have shown that the two smallest fragments are successfully incorporated into tetronasin. Feeding studies with the remaining larger fragments will be performed when the tetronasin-producing PKS complex has been isolated and purified from any degradative enzymes.

Acknowledgements.

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