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Recent developments in natural product synthesis

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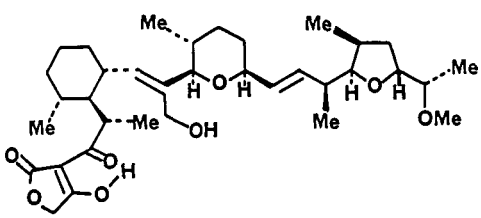
Abstract During work on the total synthesis of the novel ionophore antibiotic tetronasin, new methodology for the preparation of acyltetronic acids and β-ketomacrolides and diolides has been developed using t-butylacetothioacetate as a key building block. Further chemistry established a new route to β-ketoamides which in turn were used as precursors for acyltetramic acid preparation including a total synthesis of the plasmodial pigment fuligorubin A.

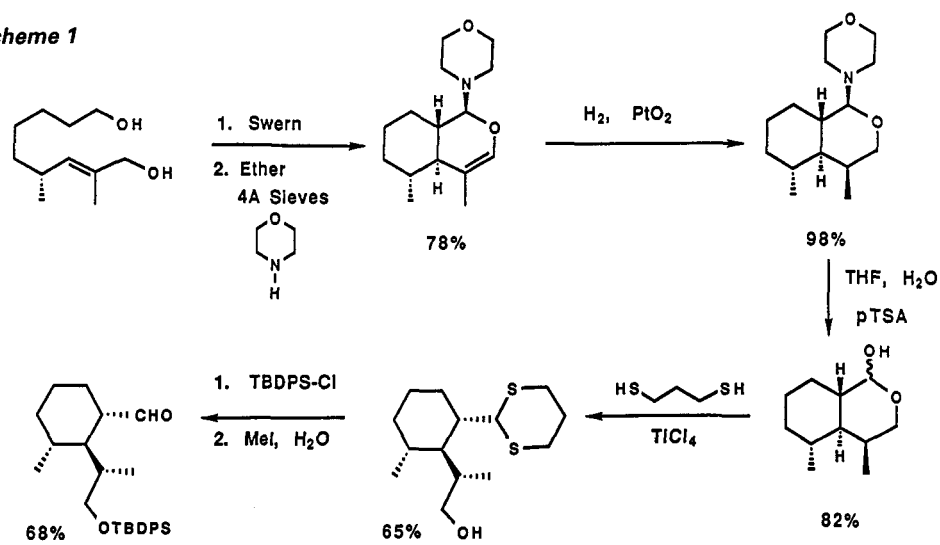
Tetronasin (ICI M139603) is a structurally novel acyl tetronic acid ionophore antibiotic discovered in 1981 and is presently being developed as a ruminant growth promotion agent. We became interested in the synthesis of tetronasin owing to the unusual cyclohexyl group and the terminal acyltetronic acid which had not been previously observed in other ionophore antibiotics. Tetronasin presents an interesting synthetic challenge as it contains 12 chiral centres isolated in five separate regions of the molecule.



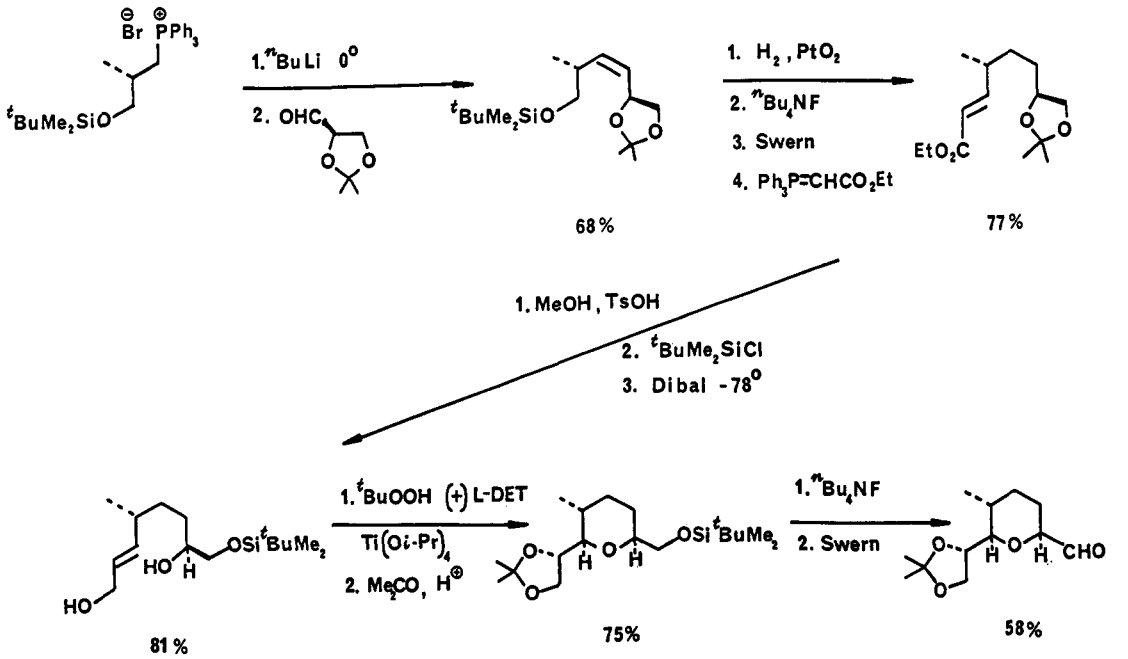
Tetronasin

In a convergent approach to tetronasin we have synthesised various cyclohexyl, central hydropyranyl and terminal hydrofuranyl fragments suitable for later coupling reactions (Schemes 1,2 and 3). Of note is the extremely efficient cyclisation reaction of an intermediate enamino enal to afford the required cyclohexyl unit with excellent stereochemical control (Scheme 1). This chemistry is based upon a related five ring cyclisation reaction reported by Schreiber.[2] In schemes 2 and 3 we have exploited a new modification of the Sharpless asymmetric epoxidation procedure whereby concommitant cyclisation to tetrahydropyrans and furans may be achieved using Lewis Acid catalysis.[3] Additionally the selenenylation reaction, using ultrasonic methods,[4] (Scheme 3) is a practically useful procedure for introduction of this group which we believe should be applicable in many other systems. Successful coupling reactions of these various structural fragments have also been investigated.

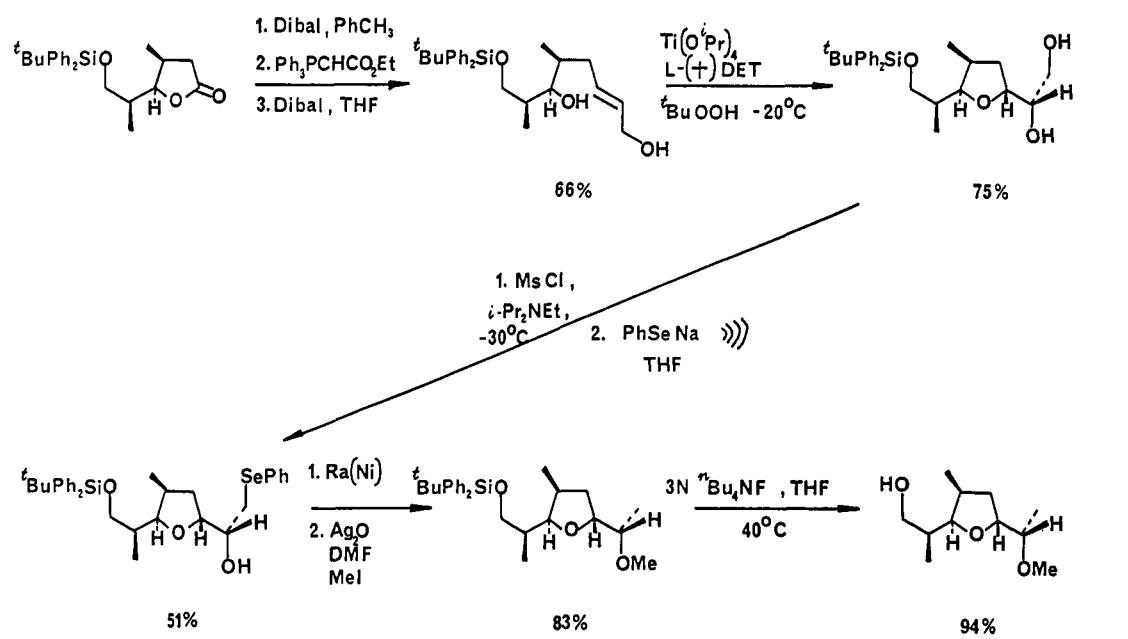
Scheme 1



Scheme 2

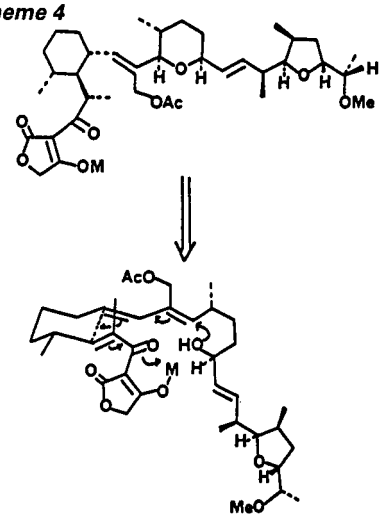


Scheme 3

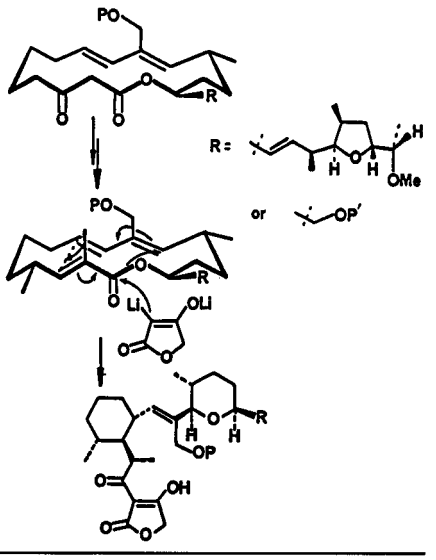


An alternative, and conceptually more interesting approach to tetronasin relies upon the possibility of employing a metal templated polyene cyclisation reaction[4] (Scheme 4). More ambitious may be the utilisation of a β-ketomacrolide via remote asymmetric macrocyclic stereocontrol to achieve similar results (Scheme 5). In an effort to access this chemistry we have developed t-butylacetothioacetate as a novel precursor for both tetronic acid[5] (e.g. Scheme 6 and 7) and β-ketomacrolide[6] synthesis (Scheme 8).

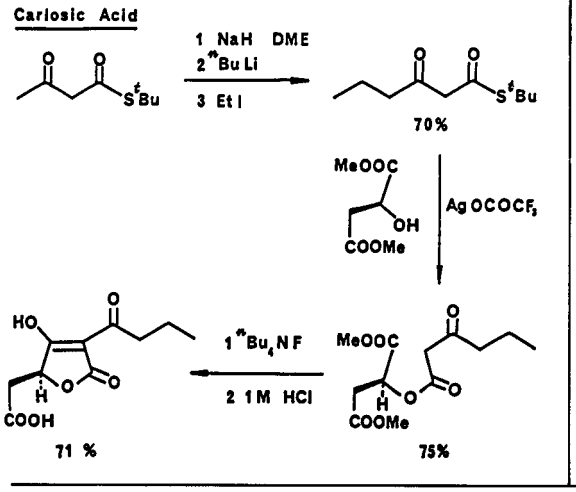
Scheme 4



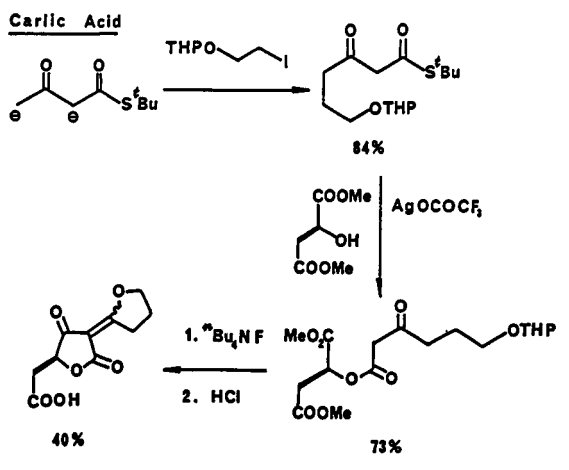
Scheme 5



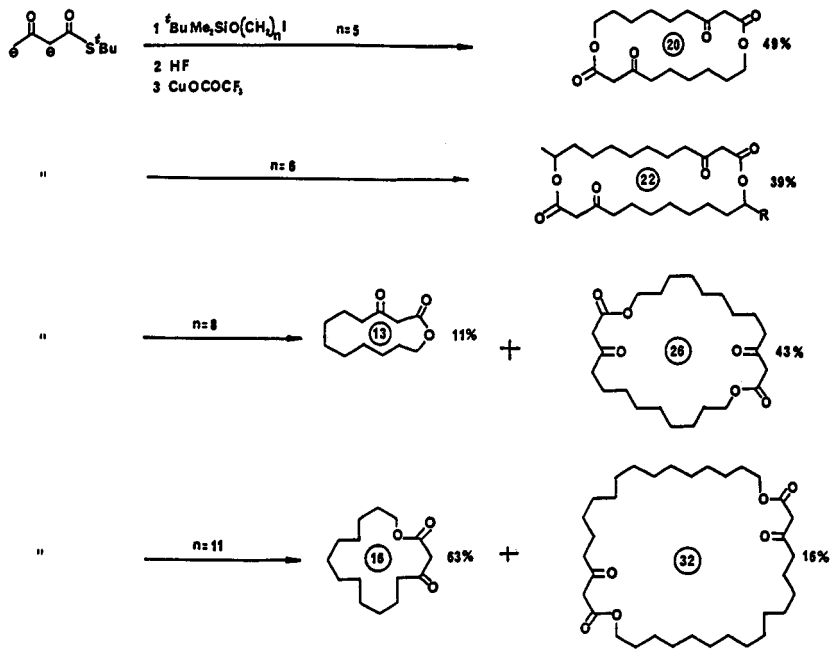
Scheme 6



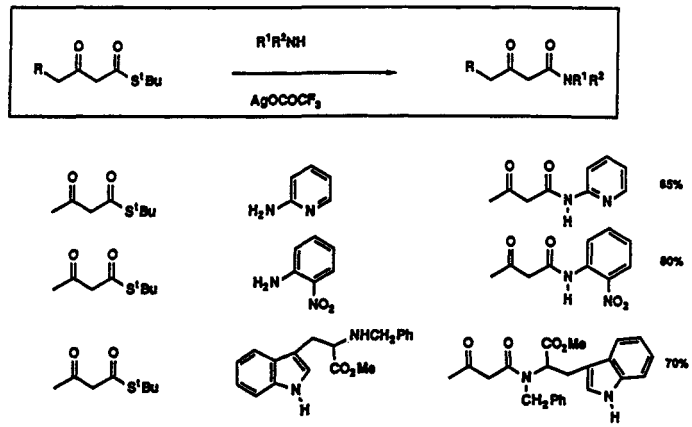
Scheme 7



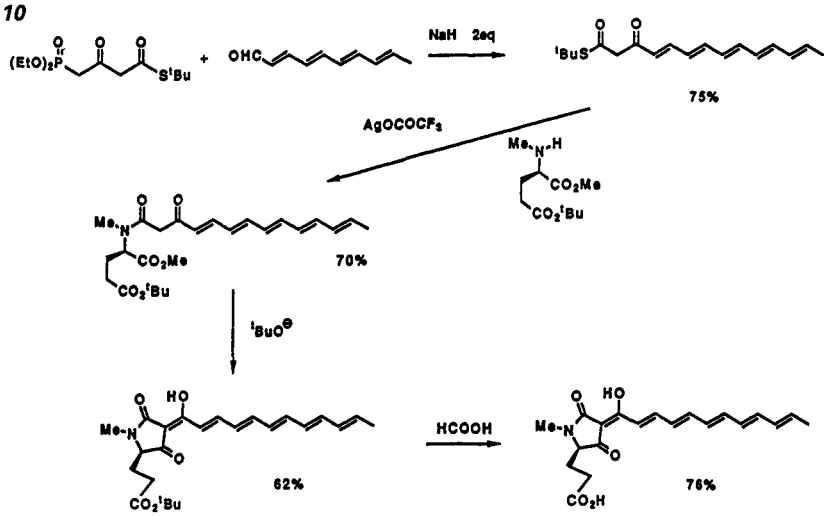
Scheme 8



Scheme 9



Scheme 10



This chemistry may be further elaborated using t-butyl 4-diethylphosphono-3-oxobutanethioate[7] for the synthesis of unsaturated β-ketomacrolides and diolides. The starting phosphonate derivative is readily available from diketene or Meldrum's acid.

The versatility of the t-butylthio substituent has also been demonstrated in the preparation of β-ketoamides, especially in examples where poorly nucleophilic amines are used.[8] The procedure is very mild and allows preparation of systems which contain readily racemised asymmetric centres (Scheme 9).

Some of the β-ketoamides prepared by this procedure are also precursors for acyltetramic acids.

The use of these methods for synthesis are illustrated by a highly efficient preparation of the plasmodial pigment fuligorubin A[9] (Scheme 10).

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