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Biosynthesis of Tetronasin: Part 6. Preparation of Structural Analogues of the Diketide and Triketide Biosynthetic Precursors to Tetronasin.

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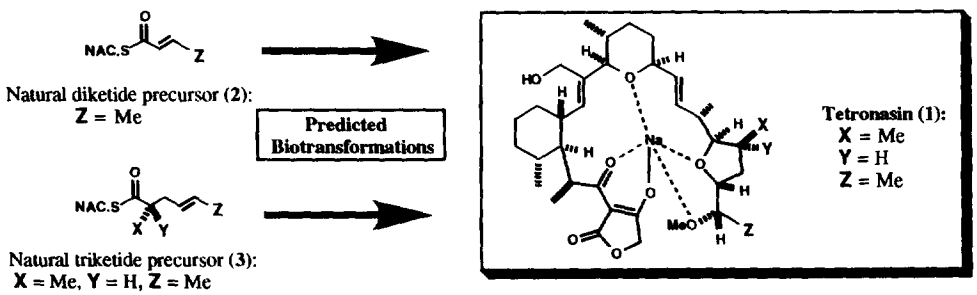
Abstract: *The preparation of three analogues of the putative diketide biosynthetic precursor (2) and eight analogues of the putative triketide biosynthetic precursor (3) of the acyl tetronic acid ionophore tetronasin, as N-acetylcysteamine thioesters (4), (5), (6), (12), (13), (14), (15), (22), (23), (24) and (25) is described. Five examples are ^{19}F-labelled; a new, enantiospecific method for the creation of a fluorinated quaternary α-centre is presented.*

In the preceding letter[1] we discussed incorporation experiments which involved structural analogues of the proposed di-, tri- and tetraketide intermediates on the biosynthetic route to the ionophore antibiotic tetronasin (**1**).[2] These experiments probed the substrate specificity of the polyketide synthase by attempting to produce tetronasin analogue metabolites, shown in Scheme 1. Here we report the synthetic routes used to prepare, as their *N*-acetylcysteamine thioesters, the three diketide analogues (**4**), (**5**) and (**6**) and the eight triketide analogues (**12**), (**13**), (**14**), (**15**), (**22**), (**23**), (**24**) and (**25**) which were required for our studies. The syntheses of the tetraketide analogues are published elsewhere.[3]



Unnatural moieties introduced in precursor analogues:

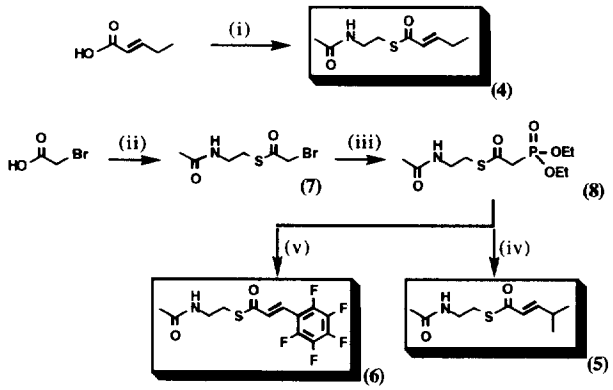
X = Et, Bn, CD_3
Y = F
Z = Et, ^{i}Pr, F_5-Ph

Scheme 1

Synthesis of the diketide analogues (4), (5) and (6).

The preparation of the first diketide analogue (**4**) was straightforward, requiring the coupling of commercially available pent-2-enoic acid with *N*-acetylcysteamine, using DCC-DMAP.[4, 5] For the others, a general approach, based on the Horner-Wadsworth-Emmons reaction,[6] was devised to access as many analogues as possible. Initially bromoacetic acid was coupled with *N*-acetylcysteamine and the product (**7**) converted, *via* the Arbuszov reaction,[7] to the phosphono derivative (**8**). Subsequent formation of the ylid and its reaction with various aldehydes yielded diketide analogues such as (**5**) and (**6**), shown in Scheme 2. This

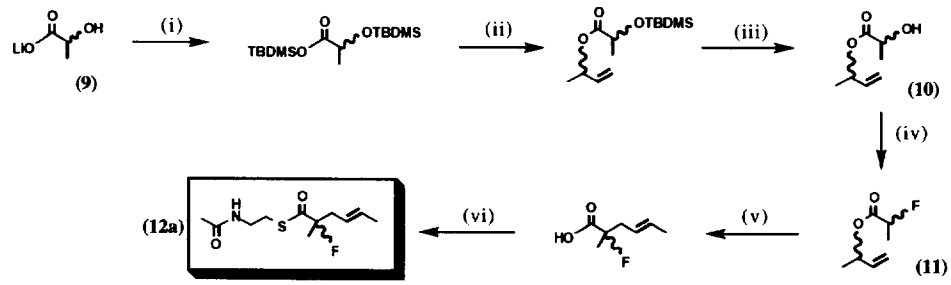
route was favoured over the use of the Wittig's triphenylphosphonium ylid[8] since it proved difficult to separate triphenylphosphine oxide from the reaction product.



Scheme 2: (i) *N*-acetylcysteamine, DCC, DMAP, CH_2Cl_2 (58%). (ii) *N*-acetylcysteamine, DCC, DMAP, CH_2Cl_2 (64%). (iii) Triethylphosphite, toluene, reflux, 48 h (60%). (iv) LiBr, Et_3N, CH_2Cl_2, then *iso*-butyraldehyde (50%). (v) LiBr, Et_3N, CH_2Cl_2; then pentafluorobenzaldehyde (63%).

Synthesis of the racemic α-fluoro triketide analogue (12a).

The first triketide analogue to be synthesised possessed the structure of the natural triketide precursor, but with the α-hydrogen replaced by fluorine. Scheme 3 shows its preparation, as a racemic mixture, *via* the Claisen rearrangement of the allyl α-fluoropropionate (**11**).[9] The initial steps involved double protection of the lithium salt of lactic acid (**9**), conversion to the acid chloride,[10] then attack on this by (±)-but-3-en-1-ol and deprotection to give the hydroxy ester (**10**).[11] Use of diethylaminosulphurtrifluoride (DAST) facilitated fluoride attack on the hydroxyl group to give (**11**).[12] Following the Claisen rearrangement, the final step in this and all the syntheses of the triketide precursor analogues was coupling with *N*-acetylcysteamine.

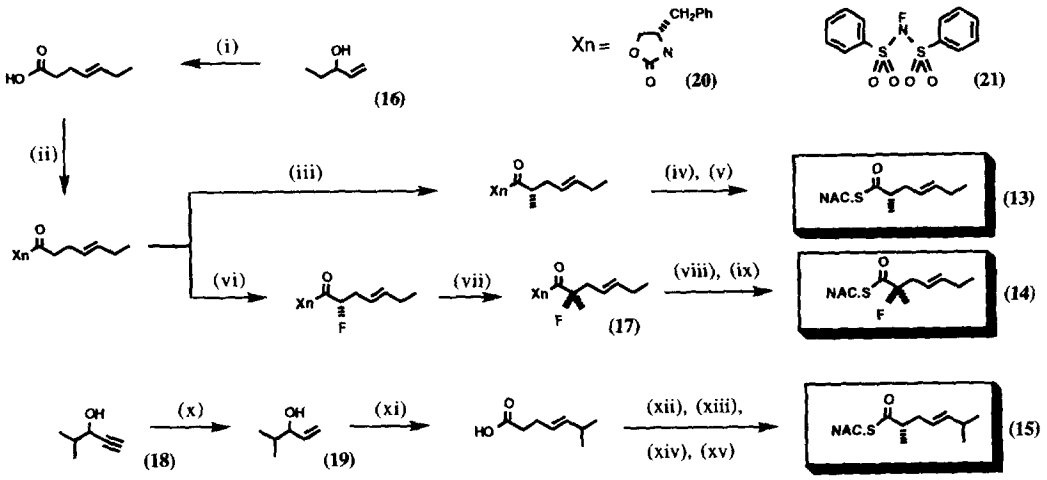


Scheme 3: (i) 2 Eq. TBDMSCl, 4 eq. imidazole, DMF, 30°C (91%). (ii) oxalyl chloride, DMF, CH_2Cl_2, 0°C to 20°C; then (±)-but-3-en-2-ol, pyridine (88%). (iii) 50% aq. HF, acetonitrile, 0°C to 20°C (86%). (iv) 3 eq. DAST, CH_2Cl_2, -78°C to 20°C, 24 h (47%). (v) 3 eq. LDA, THF, -100°C; then 3 eq. TMSCl, -100°C to 40°C (63%). (vi) *N*-acetylcysteamine, DCC, DMAP, CH_2Cl_2 (70%).

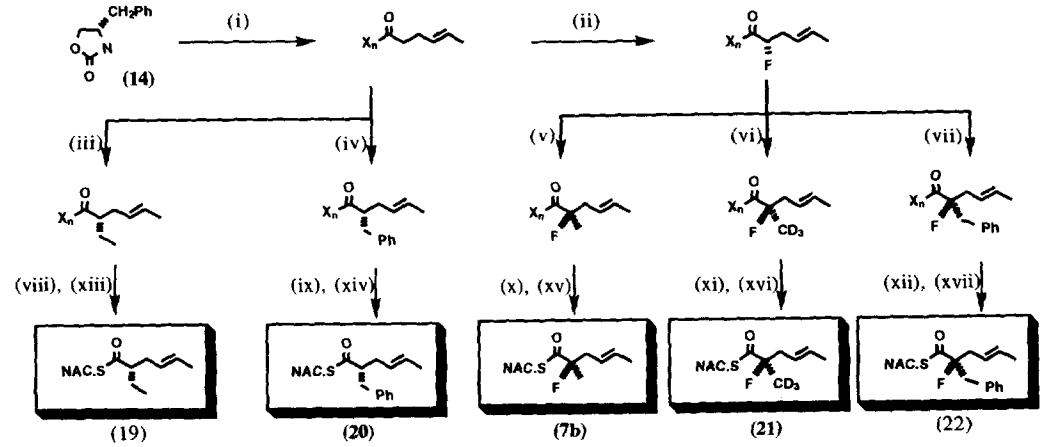
Homochiral syntheses of the triketide analogues (12b), (13), (14), (15), (22), (23), (24) and (25).

The synthetic routes to these analogues were flexible to allow a range of unnatural groups to be introduced at the chain terminus and α-positions. Scheme 4 shows synthetic routes leading to the class of triketide analogues whose structures differ from the natural precursor at the chain terminus. The backbone of each molecule, with its *trans* double bond, was constructed *via* a Claisen rearrangement,[13] such that each different terminal group originated from a particular allylic alcohol, e.g. (**16**). In the synthesis of analogue (**13**) the starting allylic alcohol (**19**) was obtained *via* Lindlar reduction[14] of the commercially available acetylenic

alcohol (**18**). In subsequent steps, Evans' chiral oxazolidinone (**20**)[15] was used to direct the addition of the α-methyl group and the auxiliary was removed under standard conditions.[16]



Scheme 4: (i) 7 Eq. triethyl orthoacetate, propionic acid, 90°C, 48 h; then 2M NaOH, MeOH, 18 h (89%). (ii) Et_3N, Me_3COCl, THF, -78°C to 0°C ; then lithiated oxazolidinone (**20**), -78°C to 0°C (77%). (iii) $NaN(SiMe_3)_2$, THF, -78°C, 30 min.; then 5 eq. MeI, -78°C (84%). (iv) LiOH, H_2O_2, THF-H_20 3:1 (70%). (v) *N*-acetylcysteamine, DCC, DMAP, CH_2Cl_2 (80%). (vi) $LiN(SiMe_3)_2$, THF, -78°C; then 1.2 eq. *N*-fluorobenzenesulphonimide (**21**) (78%, >98% d.e.). (vii) 2 eq. $LiN(SiMe_3)_2$, THF, -55°C, 1 h; then 7 eq. MeI , -25°C (73%, >98% d.e.). (viii) *as (iv)* (95%). (ix) *as (v)* (94%). (x) Lindlar cat., 1 atm. H_2, quinoline, pentane (56%). (xi) *as (i)* (78%). (xii) *as (ii)* (75%). (xiii) *as (iii)* (86%). (xiv) *as (iv)* (82%). (xv) *as (v)* (63%).



Scheme 5: (i) *n*-BuLi, THF; then add to mixed anhydride formed *in situ* from (4*E*)-hexenoic acid, Et_3N, Me_3COCl, THF (79%). (ii) $LiN(SiMe_3)_2$, THF, -78°C; then 1.2 eq. *N*-fluorobenzenesulphonimide (**21**) (60%, 92% d.e.). (iii) $LiN(SiMe_3)_2$, THF, -78°C, 30 min.; then 5 eq. EtI , -5°C (32%). (iv) $LiN(SiMe_3)_2$, THF, -78°C, 30 min.; then 5 eq. benzyl bromide, -25°C (90%). (v) 2 eq. $LiN(SiMe_3)_2$, THF, -55°C, 30 min.; then 8 eq. MeI , -25°C (35%, 75% d.e.). (vi) 2 eq. $LiN(SiMe_3)_2$, THF, -55°C, 1 h; then 6 eq. CD_3I, -25°C (32%, 75% d.e.). (vii) 2 eq. $LiN(SiMe_3)_2$, THF, -55°C, 1 h ; then 7 eq. benzyl bromide , -25°C (17%, >98% d.e.). (viii) LiOH, H_2O_2, THF-H_20 3:1 (93%). (ix) *as (viii)* (98%). (x) *as (viii)* (47%). (xi) *as (viii)* (91%). (xii) *as (viii)* (68%). (xiii) *N*-acetylcysteamine, DCC, DMAP, CH_2Cl_2 (82%). (xiv) *as (xiii)* (90%). (xv) *as (xiii)* (30%). (xvi) *as (xiii)* (90%). (xvii) *as (xiii)* (86%).

The fluorinated analogue (**14**) was prepared *via* attack on the Evans' enolate by an electrophilic fluorinating reagent, *N*-fluorobenzenesulphonimide (**20**),[17] with complete diastereoselectivity (>98% d.e.).[18] This reagent has therefore proved to be a commercially available alternative to *N*-fluoro-*o*-benzenesulphonimide, previously reported as diastereoselectively fluorinating chiral imide enolates.[19] During the course of this work, similar results from the use of *N*-fluorobenzenesulphonimide were published.[20] In order to set up the asymmetric quaternary α-centre in (**17**), the α-fluoro enolate was first formed, at -55°C. The chiral auxiliary then directed methyl addition (the reaction temperature at -25°C was critical) again with complete diastereoselectivity (>98% d.e.). There is considerable current interest in the development of efficient methodology for the asymmetric synthesis of organofluorine compounds,[21] particularly of α-fluoro carbonyl compounds, as these have found important applications in the study of enzyme mechanisms and as synthons in the synthesis of other organofluorine compounds.[22] This is the first enantiospecific introduction of a quaternary fluorinated α-centre using Evans' chiral oxazolidinone.

The triketide analogues modified at C-2, (**12b**), (**22**), (**23**), (**24**) and (**25**), were produced *via* a linked synthetic route, starting with commercially available (4*E*)-hexenoic acid. Their preparation is shown together, in Scheme 5. As before, Evans' chiral oxazolidinone directed the alkylations, with each different C-2 substituent being derived from the corresponding alkyl halide.

In summary, the asymmetric syntheses of eight triketide precursor analogues have been achieved. Asymmetric fluorinated quaternary α-centres have been introduced into four of the analogues *via* the use of an Evans' chiral auxiliary and the fluorinating reagent, *N*-fluorobenzenesulphonimide.

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References and Notes

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