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# Biosynthesis of Tetronasin: Part 7. Preparation of Structural Analogues of the Tetraketide Biosynthetic Precursor to Tetronasin

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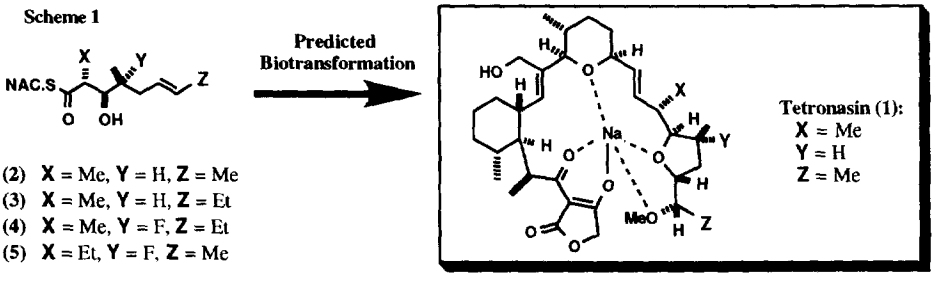
***Abstract:*** *The preparation of three structural analogues of the putative tetraketide biosynthetic precursor (2) of the acyl tetronic acid ionophore tetronasin, as N-acetylcysteamine thioesters (3), (4) and (5) is described. Two examples are $^{19}$F-labelled.* Copyright © 1996 Elsevier Science Ltd

In a 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 *N*-acetylcysteamine thioesters, the three analogues (**3**), (**4**) and (**5**) of the proposed tetraketide precursor (**2**) that were required for our studies, as their *N*-acetylcysteamine thioesters. The syntheses of the diketide and triketide analogues are described elsewhere.[3]

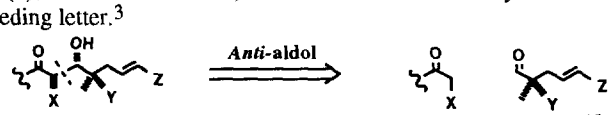
**Scheme 1**




(**2**) **X** = Me, **Y** = H, **Z** = Me
(**3**) **X** = Me, **Y** = H, **Z** = Et
(**4**) **X** = Me, **Y** = F, **Z** = Et
(**5**) **X** = Et, **Y** = F, **Z** = Me

The retrosynthetic analysis, shown in Scheme 2, required a π-facially selective *anti*-aldol reaction to create the absolute stereochemistry at centres C-2 and C-3. Aldehydes corresponding to synthon (**6**) were accessible from intermediates (**7**), (**8**) and (**9**), shown in Scheme 3, each of which lies on the synthetic route to a triketide analogue, described in the preceding letter.[3]

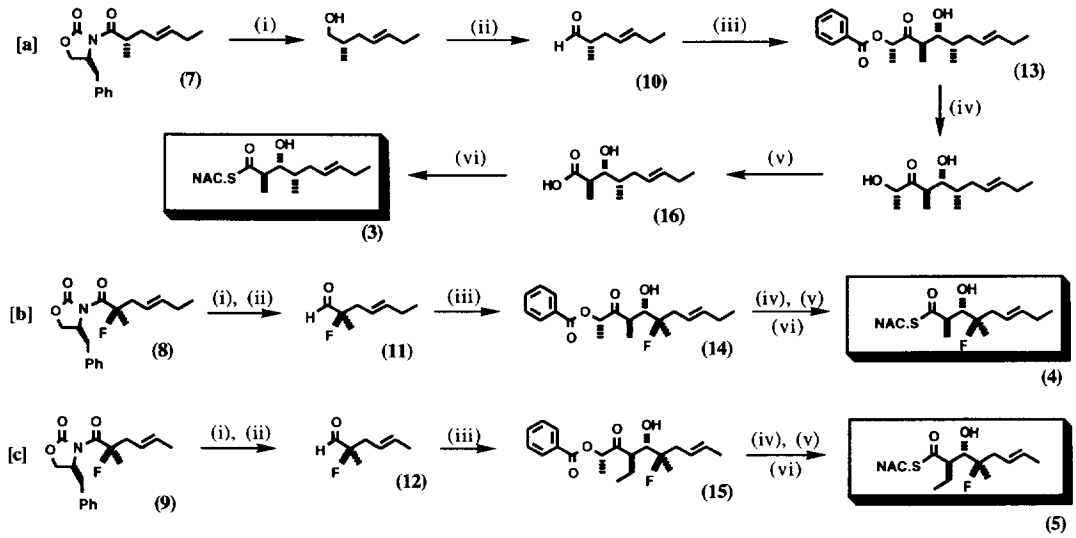
**Scheme 2: Retrosynthetic analysis of tetraketide analogues**



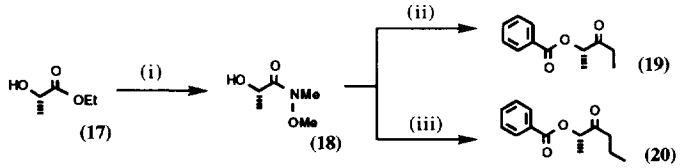

(**6**)

The aldehydes (**10**), (**11**) and (**12**)[4] were obtained *via* reductive cleavage of oxazolidinone from compounds (**7**), (**8**) and (**9**) respectively, to give the corresponding alcohols, followed by oxidation using the Dess-Martin periodinane.[5] Paterson's aldol methodology[6] was employed in the preparation of the *anti*-aldol adducts (**13**), (**14**) and (**15**). This involved reacting the chiral boron *E*-enolates of the α'-benzoyloxy ketones (**19**) and (**20**), shown in Scheme 4, with the requisite aldehydes. Ketones (**19**) and (**20**) were prepared from (*S*)-ethyl lactate (**17**) *via* the appropriate Grignard attack on the derived Weinreb amide (**18**),[7] immediately followed by addition of benzoic anhydride. On reaction with dicyclohexylboron chloride[8] and dimethylethylamine, the presence of the benzoyl protecting group ensured formation of *E*-enol dicyclohexyl borinates. The *anti*-aldol products (**13**), (**14**) and (**15**) were formed with complete π-face selectivity (by $^1$H n.m.r), and any Felkin-Ahn type influence from the chiral aldehyde helped to reinforce this selectivity. Subsequent steps in the synthesis involved hydrolysis of the benzoyl ester, then 1, 2-hydroxy ketone cleavage

by periodate[9] to give the carboxylic acids (*e.g.* **16**), and finally coupling with *N*-acetylcysteamine using DCC-DMAP,[10] to give the target analogues (**3**), (**4**) and (**5**).




**Scheme 3:** [a] (i) $LiAlH_4$, $Et_2O$, 0°C (59%). (ii) 2 eq. Dess-Martin periodinane, $CH_2Cl_2$ (90%). (iii) added to -78°C boron enolate formed from (2*S*)-*O*-benzoyl-3-pentanone (**19**), dicyclohexylboron chloride, dimethylethylamine, $Et_2O$, 0°C (50%). (iv) $K_2CO_3$, MeOH-$H_2O$ 5:1 (67%). (v) 6 eq. sodium periodate, MeOH-$H_2O$ 2:1 (72%). (vi) *N*-acetylcysteamine, DCC, DMAP, $CH_2Cl_2$ (66%). [b] *conditions as [a]* (i) (66%). (ii) (77%). (iii) (35%). (iv) (63%). (v) (96%). (vi) (80%). [c] *conditions as [a] unless otherwise stated* (i) (57%). (iii) (2*S*)-*O*-benzoyl-3-hexanone (**20**), dicyclohexylboron chloride, dimethylethylamine, $Et_2O$, 0°C (4%, over 2 steps). (iv) (36%). (v) (77%). (vi) (92%).




**Scheme 4:** (i) 2 eq. *N,O*-dimethylhydroxylamine.hydrochloride, 2 eq. $AlMe_3$, $CH_2Cl_2$, -10°C to 20°C (74%). (ii) 4 eq. EtMgCl, THF, 0°C, 2 h; then added to 8 eq. benzoic anhydride, 10 eq. diisopropylethylamine, 2 eq. DMAP, $CH_2Cl_2$, 0°C to 20°C, 48 h (61%). (iii) 3 eq. *n*-PrMgCl, THF, 0°C, 2 h; then added to 6 eq. benzoic anhydride, 7 eq. diisopropylethylamine, 2 eq. DMAP, $CH_2Cl_2$, 0°C to 20°C, 18 h (28%).

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### *References and Notes*

1. See a proceeding paper in this journal and references therein: *Biosynthesis of Tetronasin: Part 5. Novel Fluorinated and Non-fluorinated Analogues of Tetronasin via Intact Incorporation of Di-, Tri- and Tetraketide Analogue Precursors.*
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3. See the proceeding paper in this journal: *Biosynthesis of Tetronasin: Part 6. Preparation of Structural Analogues of the Diketide and Triketide Biosynthetic Precursors to Tetronasin.*
4. All new compounds gave spectroscopic data in agreement with the assigned structures.
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