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Biosynthesis of Tetronasin: Part 3 Preparation of Deuterium Labelled Tri- and Tetraketides as Putative Biosynthetic Precursors of Tetronasin

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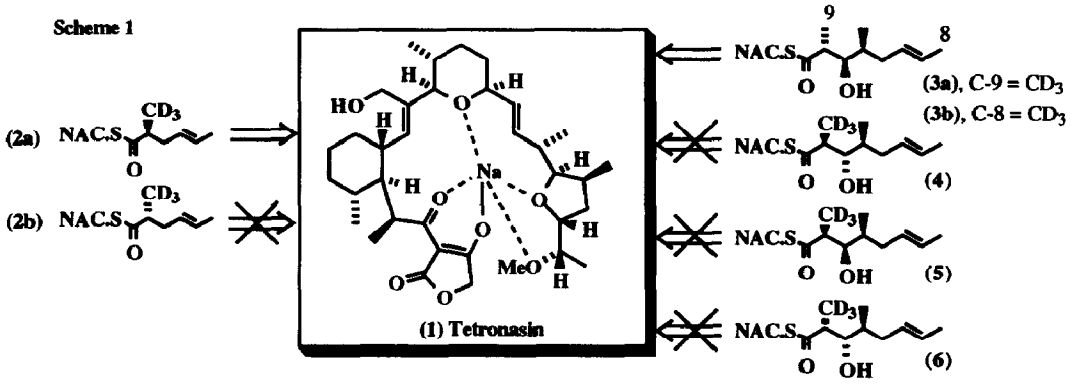
Abstract: *The preparation of seven deuterium labelled N-acetyl cysteamine thioesters (2a), (2b), (3a), (3b), (4), (5) and (6) as putative biosynthetic precursors of the acyl tetronic acid ionophore tetronasin is described.*

In the preceding two Letters we have discussed incorporation experiments, with proposed tri- and tetraketide precursors in the biosynthesis of the ionophore antibiotic tetronasin (**1**), the results of which are shown in Scheme 1.[1] Here we report the synthetic routes used to prepare the deuterium labelled compounds (**2a**), (**2b**), (**3a**), (**3b**), (**4**), (**5**) and (**6**) that were required for our studies.

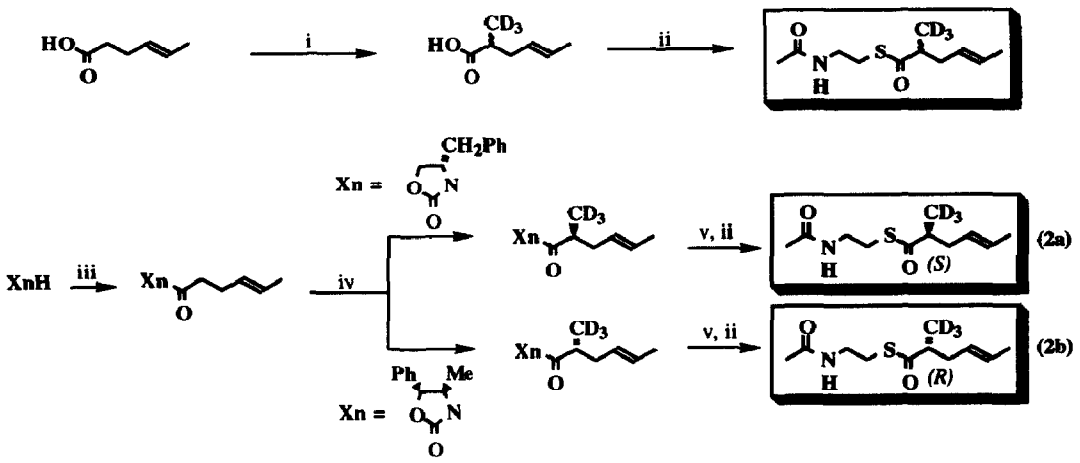
Scheme 1



The routes to these *N*-acetyl cysteamine thioester derivatives were designed to be flexible in order to access the maximum number of compounds. Those compounds labelled at the C-2 methyl group (*i.e.* all except (**3b**)) were produced *via* a linked synthetic route and their preparation shall be dealt with together. The C-8 labelled analogue (**3b**) was produced *via* a different route and will be dealt with independently of the others.

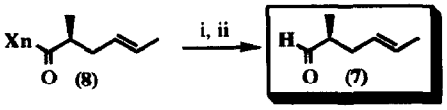
Synthesis of the tri- and tetraketide analogues (2a), (2b), (3a), (4), (5) and (6).

Scheme 2 shows synthetic routes leading to the triketide analogues. The racemic form of the acyl residue was produced by methylation of the di-anion of (4*E*)-hexenoic acid.[2] The homochiral forms were prepared using Evans chiral oxazolidinones[3] to direct the addition of the CD_3 group followed by cleavage of the auxiliary under standard conditions.[4] All three acids were coupled with *N*-acetyl cysteamine[5] using DCC-DMAP.[6]



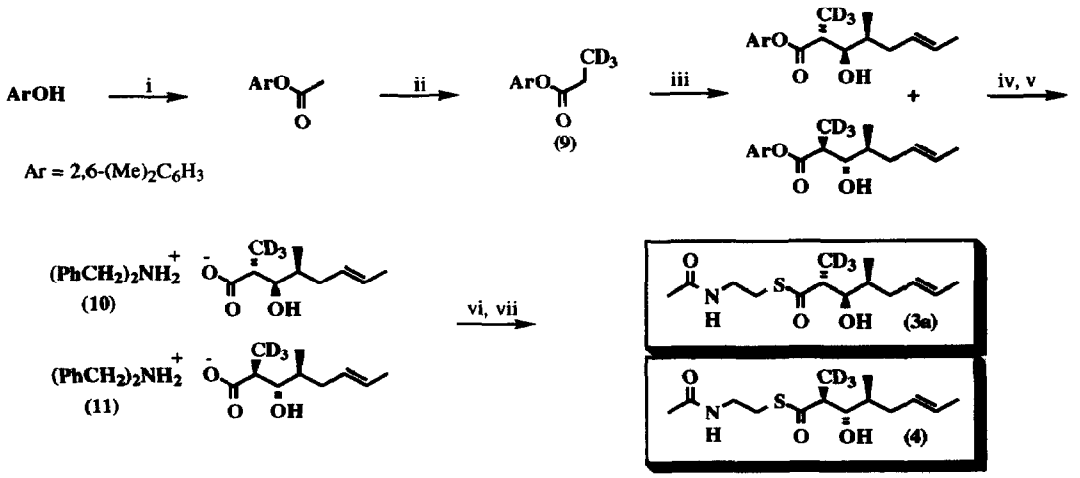
Scheme 2: (i) LDA 2 equiv., THF, 0°C; 5 equiv. CD_3I (78%). (ii) *N*-acetyl cysteamine, DCC, DMAP, CH_2Cl_2 (70%). (iii) nBuLi, THF; then add to mixed anhydride formed from (4*E*)-hexenoic acid, Et_3N, Me_3COCl, THF (91%). (iv) $NaN(SiMe_3)_2$, THF, -78°C; 5 equiv CD_3I (65%). (v) LiOH, H_2O_2, THF-H_2O 3-1 (95%).

The four diastereoisomers of the tetraketide were synthesised by complementary routes employing an aldol reaction of different propionate derivatives with the common aldehyde (**7**). This was produced from the intermediate (**8**), itself prepared by a method analogous to that shown above in Scheme 2.



(i) $LiAlH_4$, Et_2O, 0°C (70%). (ii) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; then Et_3N, -30°C (87%).

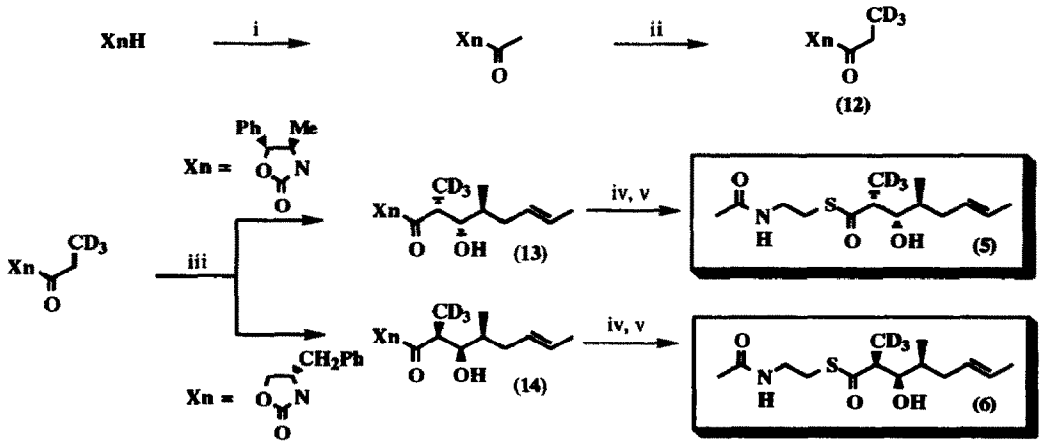
The tetraketide precursors (**3a**) and (**4**) having an *anti* relationship between the C-2 and C-3 centres were produced by employing a Heathcock *anti* aldol condensation[7], between 2',6'-dimethylphenyl-[3-$^2H_3$]-propionate (**9**) and the aldehyde (**7**) as shown in Scheme 3.



Scheme 3: (i) nBuLi, THF, 0°C; then acetyl chloride (100%). (ii) $NaN(SiMe_3)_2$, THF, -78°C; 5 equiv. CD_3I (67%). (iii) LDA, -78°C, 45 min; then -118°C and add (**7**) and warm to -78°C (53% overall). (iv) KOH 5 equiv, dioxan-H_2O 30-1. (v) $(PhCH_2)_2NH$ 1.05 equiv, recrystallise from Et_2O/hexanes (87% overall over two steps ; 55% of (**10**), 32% of (**11**)). (vi) Dowex 50-H^+ (99%). (vii) *N*-acetyl cysteamine, DCC, DMAP, CH_2Cl_2 (54%).

The reaction produced a mixture of two diastereoisomers that were separated by conversion to the dibenyzlammonium salts (*via* the acids), followed by recrystallisation from ether/hexane to give the pure diastereomeric salts (**10**) and (**11**).[8] These salts were reconverted to the acids by treatment with Dowex-50 (H^+ form) and coupled to *N*-acetyl cysteamine as before to give (**3a**) and (**4**).[5,6]

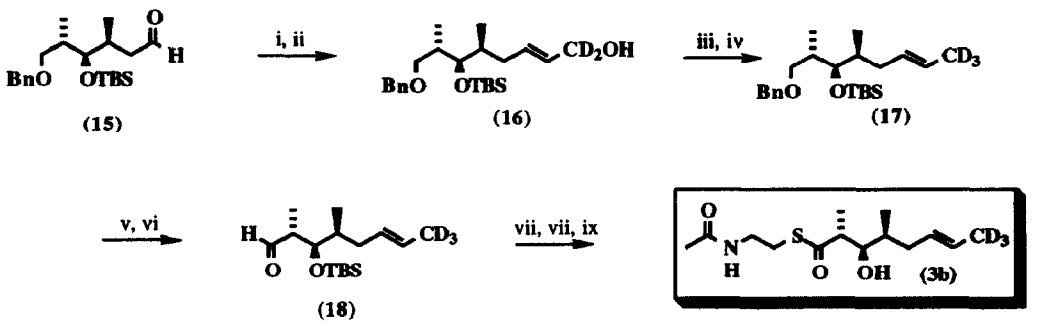
The two isomers (**5**) and (**6**) having a *syn* relationship between the C-2 and C-3 centres were prepared using Evans' *syn* aldol methodology[9] as shown in Scheme 4. Thus condensation of the boron enolates of the CD_3-propionate oxazolidinones (**12**) with the aldehyde (**7**) under standard conditions[9] gave the diastereomerically pure products (**13**) and (**14**).[8] Hydrolysis of the auxiliary under standard conditions[4] followed by coupling of the resulting acids to *N*-acetyl cysteamine gave the derivatives (**5**) and (**6**) as shown.



Scheme 4: (i) nBuLi, THF, 0°C; then acetyl chloride (99%). (ii) $NaN(SiMe_3)_2$, DMPU 10 equiv., THF, -78°C; 5 equiv.CD_3I (74%). (iii) Bu_2BOTf, iPr_2EtN, CH_2Cl_2, 0°C; then -78°C and add (7) (65%). (iv) LiOH, H_2O_2, THF-H_2O 3-1, 0°C (95%). (v) *N*-acetyl cysteamine, DCC, DMAP, CH_2Cl_2 (57%).

Synthesis of the tetraketide analogues (3b).

The synthesis of (**3b**), the precursor that was required to complete our biosynthetic studies,[1b] was achieved as shown in Scheme 5. The preparation of the initial building block (**15**) is reported in a subsequent paper in this series, since it is also a precursor for the C19-C26 tetrahydrofuran fragment required for the total synthesis studies.[10] Compound (**15**) was reacted with triethyl phosphonoacetate, using the Masamune-Roush conditions,[11] to give an intermediate homologated ester which upon reduction with DIBAL-D[12] gave the deuteriated allylic alcohol (**16**). This was further reduced *via* conversion to the corresponding chloride, using tosyl chloride in CH_2Cl_2 containing DMAP[13] and treatment with lithium triethyl borodeuteride (Super-Deuteride®) to give the trideuterio derivative (**17**) in excellent overall yield. Deprotection of (**17**) with lithium in ammonia at -78°C,[14] and oxidation with tetra-*n*-propylammonium perruthenate (TPAP)[15] under catalytic conditions gave the aldehyde (**18**) also in excellent yield. The last steps toward (**3b**) were then straightforward. Oxidation of (**18**) with sodium chlorite, using 2-methyl-2-butene as a chlorine scavenger,[16] gave an acid which was converted to the (**3b**) on coupling with *N*-acetyl cysteamine using DCC/DMAP, and subsequent deprotection with HF/pyridine.



Scheme 5 (i) $EtO_2CH_2P(O)(OEt)_2$, LiCl, DIPEA, CH_3CN (93%). (ii) DIBAL-D, THF, -78°C (85%). (iii) TsCl, DMAP, CH_2Cl_2 (90%). (iv) $LiEt_3BD$, THF, -78°C (85%). (v) Li/NH_3, Et_2O, -78°C (97%). (vi) $^nPr_4NRuO_4$, NMO, 4Å powdered sieves, CH_2Cl_2 (95%). (vii) $NaClO_2$, 2-methyl-2-butene, KH_2PO_4, $^tBuOH/H_2O$ (99%). (viii) *N*-acetylcysteamine, DCC, DMAP, CH_2Cl_2 (80%). (ix) HF, pyridine, MeCN (80%).

Acknowledgements: We thank the SERC and Ciba-Geigy PLC for financial support.

References and Notes

1. (a) See one of the proceeding papers in this series: *Biosynthesis of Tetronasin: Part 1*, (b) See preceding paper *Biosynthesis of Tetronasin: Part 2* and references therein.
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