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Two New Routes to the C19-C26 Tetrahydrofuran Fragment of the Acyl Tetronic Acid Ionophore Tetronasin (ICI M139603)

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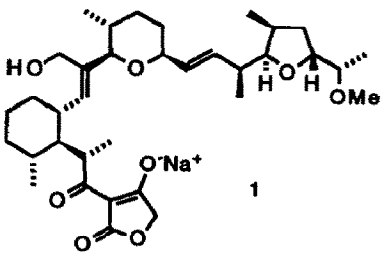
Abstract: Two highly efficient and complementary synthetic routes to the C19-C26 tetrahydrofuran fragment (2) of the novel acyltetronic acid ionophore antibiotic tetronasin (ICI 139603) (1) are described to provide multigramme quantities of the required product.

The ionophore antibiotic tetronasin (ICI M139603) (1)[1] is a structurally novel compound which has stimulated considerable interest in its synthesis,[2,3] structure and properties,[4] and its biosynthesis.[5]



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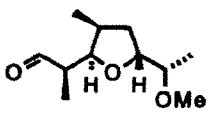

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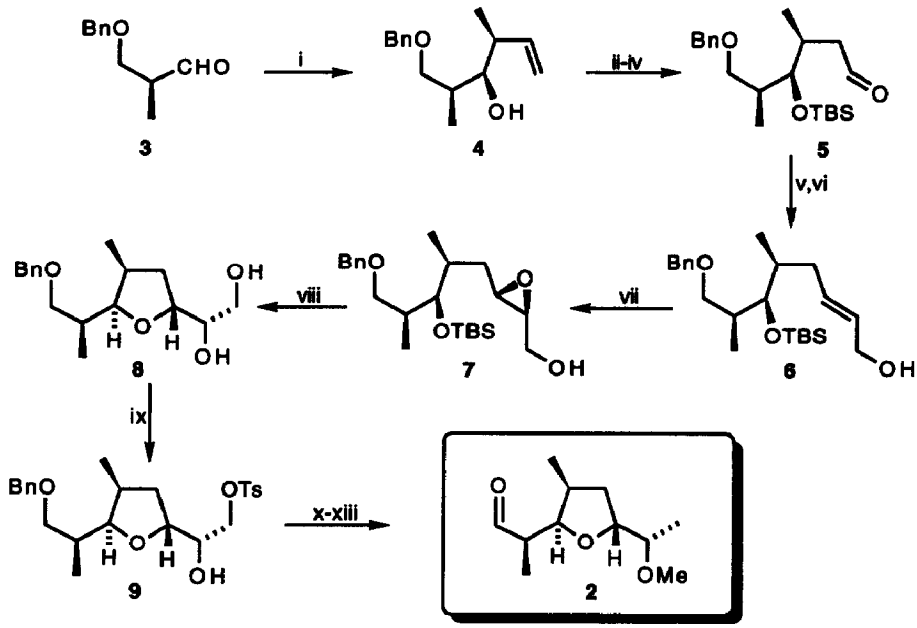
We have already reported on the synthesis of various fragments of this compound,[2] however in light of recent publications[3e,g] we wish to describe two new routes to the tetrahydrofuran unit (2) since this group will play an essential role in our total synthesis studies. Moreover, our previous preparation of (2)[2a,b] was unsuitable for scaleup and owing to limited supplies of the natural product for degradation studies, we required to develop a multigramme procedure. Here we describe the results of these efforts.

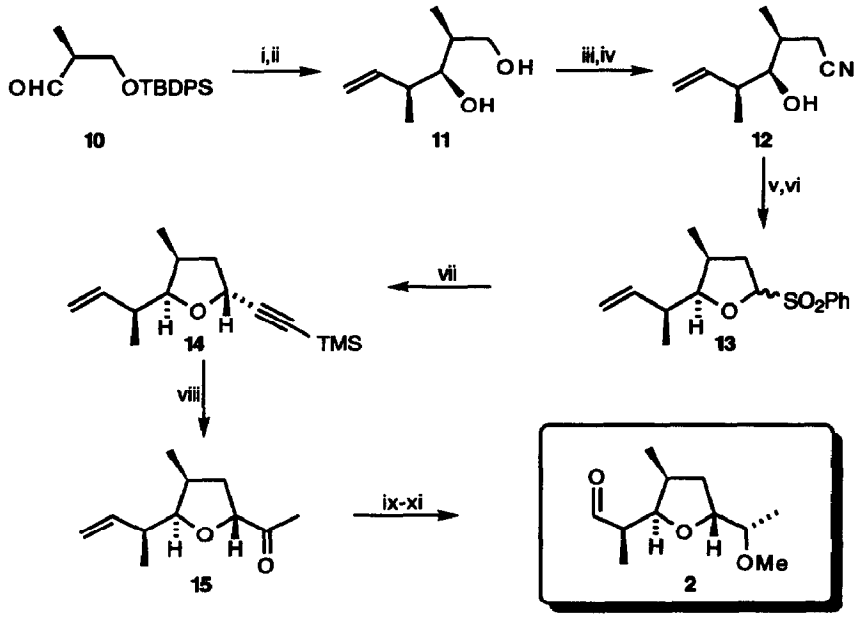
In the first route (Scheme 1) we have developed an extremely efficient process allowing conversion of the aldehyde (3)[6] to the C19-C26 fragment (2) in 37% overall yield. The route may also be intercepted to provide materials necessary for our biosynthetic studies and is consequently very versatile. Reaction of (3) with (*Z*)-crotyl-(+)-diisopinocampheylborane[7] and oxidative workup gave the protected diol (4)[8,9] in which three of the required stereogenic centres are now in place, in essentially one step. Compound (4) was transformed to the aldehyde (5) by standard procedures involving protection with *t*-butyldimethylsilyl triflate, hydroboration with 9-BBN and oxidative workup followed finally by Swern oxidation.[10] This was homologated to the allylic alcohol



Scheme 1 (i) (+)-$(IPC)_2B$-(*Z*)-$CH_2CH{=}CHCH_3$, Et_2O/THF, -100°C; then NaOH, H_2O_2, Δ (73%). (ii) TBDMSOTf, Et_3N, CH_2Cl_2, -30°C (100%). (iii) 9-BBN, THF; then NaOH, H_2O_2, Δ (95%). (iv) $(COCl)_2$, DMSO, CH_2Cl_2, -60°C; then Et_3N, RT (98%). (v) $EtO_2CCH_2P(O)(OEt)_2$, LiCl, DIPEA, CH_3CN (93%). (vi) DIBAL-H, THF, -78°C (97%). (vii) $Ti(O^iPr)_4$, ^{t}BuOOH, (+)-DET, 4Å Sieves, CH_2Cl_2 -20°C (87%). (viii) ^{n}Bu_4NF, THF, 60°C (93%). (ix) Bu_2SnO, MeOH, Δ; then TsCl, Et_3N (94%). (x) $LiEt_3BH$, THF (92%). (xi) MeI, NaH, THF, 0°C (91%). (xii) H_2, Pd/C, MeOH (98%). (xiii) ^{n}Pr_4NRuO_4, NMO, 4Å Sieves, CH_2Cl_2 (93%).

(**6**) by reaction with triethyl phosphonoacetate under the Masamune-Roush conditions[11] and subsequent reduction with DIBAL-H in THF (Scheme 1). The alcohol (**6**) is now set up for the introduction of the remaining stereocentres using the Sharpless asymmetric epoxidation procedure. Thus, reaction of (**6**) with titanium (IV) isopropoxide, *t*-butyl peroxide and (+)-diethyl tartrate as the chiral auxiliary gave (**7**).[12] Deprotection with tetra-*n*-butylammonium fluoride (TBAF) at 60°C resulted in concomitant intramolecular epoxide ring opening to provide the tetrahydrofuran diol (**8**) in an excellent 93% yield. The remaining steps in the synthesis of (**2**) were relatively straightforward and also proceeded in excellent yields. The selective tosylation of (**8**) was achieved by reaction with dibutyltin oxide[13] followed by tosyl chloride and triethylamine to provide (**9**). This was then readily transformed to (**2**) by a series of reactions involving tosylate reduction with Super-Hydride® ($LiEt_3BH$), methylation of the secondary hydroxyl group with iodomethane and potassium hydride, deprotection with palladium on charcoal as catalyst, followed by final oxidation with tetra-*n*-propylammonium perruthenate[14] (TPAP) at room temperature (Scheme 1). Compound (**2**) was identical in all respects to previously synthesised material[2a,b] and to that obtained by natural product degradation.[2a]

In the second route to (**2**) (Scheme 2) we sought to exploit synthetic methodology developed in these laboratories for the formation of carbon-carbon bonds adjacent to oxygen in cyclic ethers, using 2-phenyl-



Scheme 2 (i) (-)-$(IPC)_2B$-(E)-$CH_2CH{=}CHCH_3$, THF/Et_2O, -100°C; then NaOH, H_2O_2,Δ (74%). (ii) $^nBu_4NF$, THF (100%). (iii) 2-mesitylenesulphonyl chloride, Et_3N, CH_2Cl_2 (94%). (iv) NaCN, DMSO, 60°C (97%). (v) DIBAL-H, PhMe, -78°C; then 2N HCl, H_2O, 0°C (94%). (vi) $PhSO_2H$, $CaCl_2$, CH_2Cl_2 (93%). (vii) TMSC≡CMgBr, $ZnCl_2$, THF (93%). (viii) HgO, H_2SO_4, $(CH_3)_2CO$, H_2O, 60°C (98%). (ix) $MgBr_2$, Et_2O, 0°C; then K-Selectride (82%). (x) MeI, KH, THF, 0°C (98%). (xi) O_3, $MeOH/CH_2Cl_2$, -78°C; then Ph_3P (84%).

sulphonyl derivatives.[15] Accordingly, the chiral aldehyde (**10**)[8] was reacted with (*E*)-crotyl-(-)-diisopinocampheylborane,[7] and after deprotection with TBAF gave the diol (**11**) in which three out of five of the stereogenic centres of the final product were in place. Compound (**11**) was converted to the nitrile (**12**) by selective 2-mesitylenesulphonylation of the primary hydroxyl group, and displacement with sodium cyanide in 69% overall yield for the four steps. The cyano- group of (**12**) was reduced with DIBAL-H, and the lactol intermediate reacted with phenylsulphinic acid using our previously established protocol[15] to give the sulphone (**13**) also in good yield. Compound (**13**) was subsequently reacted with (trimethylsilyl)ethynyl magnesium bromide in the presence of zinc chloride at room temperature to afford stereoselectively the *trans*-substituted tetrahydrofuran (**14**). This was then hydrolysed with mercuric oxide and sulphuric acid to the acetyl derivative (**15**) in 91% overall yield from (**13**). Lastly, the carbonyl in (**15**) was prechelated with magnesium bromide at 0°C and selectively reduced with K-Selectride® to give the required product (9:1) which after methylation and ozonolysis again afforded the same C19-C26 furan fragment (**2**) prepared earlier (Scheme 2). This second route is complementary to the first sequence and also provides multigramme quantities of product in a relatively short sequence of reactions, in which the key process employs methodology developed in our group.

In summary, these two new routes to the furan aldehyde (**2**) provide essential material for further elaboration to the natural product (**1**).

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