# A Total Synthesis of Nonactin

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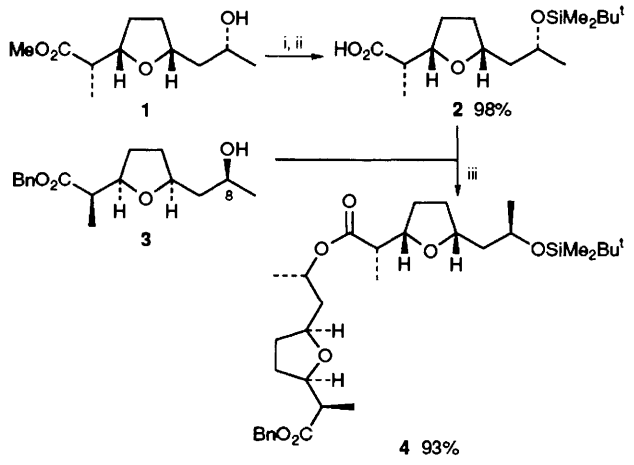
With appropriate protecting group manipulation, the nonactate esters **1** and **3**, one from each enantiomeric series, are joined together in an alternating sequence to give the hydroxyacid **7**, which is lactonised to give nonactin **8** in 59% overall yield.

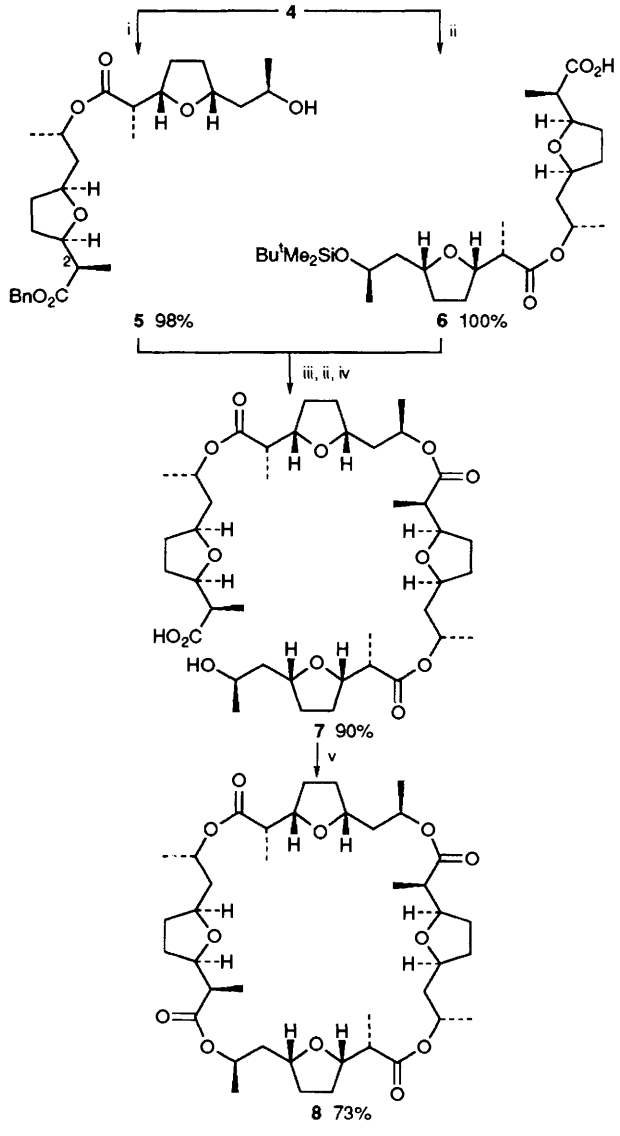
In contrast to its subunit nonactic acid, which has been synthesised many times,[1–3] nonactin **8** has been synthesised by only three groups, successively those of Gerlach,[2] Schmidt,[3] and Bartlett.[4] The overall yield from the nonactic acid esters was low in all of these syntheses, with Bartlett's, the best and most recent, being 10%. We now report a synthesis of nonactin in much better yield, using the nonactate esters **1** and **3**, one in each enantiomeric series, synthesised by the highly controlled methods reported in the preceding communication.[5]

Silylation of the free hydroxy group of the methyl ester **1** and hydrolysis of the ester group gave the carboxylic acid **2**, which we coupled to the free hydroxy group of the benzyl ester **3** to give the protected ester **4** (Scheme 1). Removing the silyl protecting group from half of this ester gave the alcohol **5**, and removing the benzyl group from the other half gave the acid **6** (Scheme 2). We coupled these two compounds, using Yamaguchi's mixed anhydride method,[6] and removed the remaining protecting groups to give the hydroxyacid **7**. Yamaguchi macrolactonisation gave nonactin **8**, in 73% yield, after recrystallisation, mp 146–147 °C, with mp and $^1H$ and $^{13}C$ NMR data matching those reported by Bartlett.[4] We repeated the macrolactonisation in the presence of potassium fluoroborate (nonactin chelates potassium exceptionally well), in the hope that chelation might raise the yield even more, but it had no effect. The overall yield of nonactin from the esters **1** and **3** was 59%.

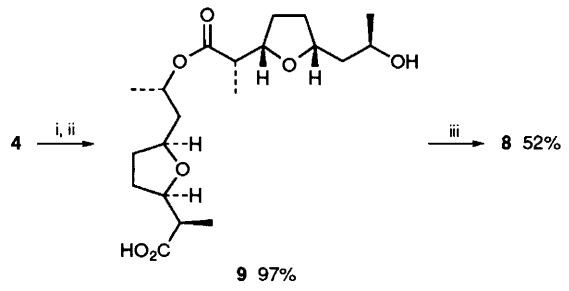
The yield in the macrolactonisation step is remarkably high given the number of stereogenic centres among which errors could have accumulated during the synthesis. That we achieve this high yield can probably be credited principally to Yamaguchi's method, but it must also mean that we had components **1** and **3** of high enantiomeric and diastereoisomeric purity, even though we had not been able to recrystallise any of the intermediates in the homochiral series—only the meso compounds, our starting material (**1** in the preceding paper) and nonactin were usefully crystalline. (There were actually two crystalline intermediates—the alcohol obtained by silyl-to-hydroxy conversion of **12** in the preceding paper and the *tert*-butyldimethylsilyl ether of **16** in the preceding paper—but both were too soluble in organic solvents for effective recrystallisation.) However, we had the advantage in our sequence that we did not have to invert the configuration at C-8 in preparing the 'dimer' **4**, as both Schmidt and Bartlett did using displacements of tosylate and mesylate groups, respectively. Their operations, if inversion of configuration is not total, are inherently more likely to give mixtures of diastereoisomers than our method leaving the




**Scheme 1** *Reagents and condition*: i, $Bu^tMe_2SiCl$, DMF, imidazole, room temp., 15 h; ii, KOH, MeOH, $H_2O$, THF, room temp., 15 h; iii, DCC, DMAP, $CH_2Cl_2$, room temp., 15 h




**Scheme 2** *Reagents and conditions*: i, TsOH, AcOH, $H_2O$, room temp., 30 min; ii, $H_2$, Pd/C, THF, room temp., 10 h; iii, 2,4,6-trichlorobenzoyl chloride, DMAP, $CH_2Cl_2$, room temp., 12 h; iv, TsOH, AcOH, $H_2O$, room temp., 1 h; v, 2,4,6-trichlorobenzoyl chloride, DMAP, $CH_2Cl_2$, 4 Å sieves, room temp., 12 h




**Scheme 3** *Reagents and conditions*: i, TsOH, AcOH, $H_2O$, room temp., 30 min; ii, $H_2$, Pd/C, THF, room temp., 10 h; iii, 2,4,6-trichlorobenzoyl chloride, DMAP, $CH_2Cl_2$, 4 Å sieves, room temp., 12 h

configuration at this centre undisturbed. We were also able to use the hydrogenolysis of a benzyl ester twice in this sequence, having taken to heart Bartlett's observation that base- or nucelophile-induced ester cleavage caused 20% or more epimerisation at C-2 in the methyl ester corresponding to our intermediate **5**.

We also tried the shorter route using 2 + 2 coupling (Scheme 3). We removed both protecting groups from the intermediate **4**, to give the hydroxyacid **9** having $^1H$ and $^{13}C$ NMR spectra essentially identical with those reported by Bartlett.[4] Using Yamaguchi's conditions again, we carried out the coupling and macrolactonisation in one operation to give nonactin **8** directly, in 52% yield after recrystallisation. As Bartlett found using different macrolactonisation conditions, this sequence detectably gave the lactone of the 'dimer' and probably higher oligomeric lactones too, which must account for the lower yield.

Although we used dilute solutions for the macrolactonisation (97 mg of **7** in 45 $cm^3$ of dichloromethane, and 37 mg of **9** in 25 $cm^3$), they were not exceptionally dilute. We conclude that there is no inherent difficulty in closing the macrocyclic ring of nonactin.

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