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PREPARATION OF O-METHYL 3-ACYL TETRONIC ACIDS BY THE DIRECT ACYLATION OF STANNYL TETRONATES

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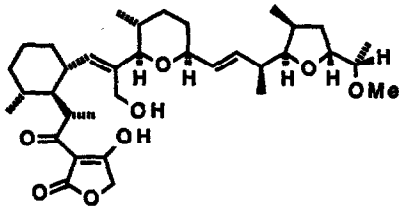
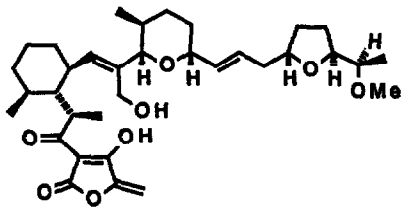
Summary: *Formation of the 5-unsubstituted, O-methyl acyl tetronic acid nucleus found in tetronasin (1) has been achieved by the direct acylation of a 3-stannyl tetronate with a variety of acid chlorides in the presence of a palladium catalyst. Further functionalization of the tin tetronate at C-5 prior to acylation leads to the synthesis of the mould metabolite (±) dimethyl carolinic acid (12) and the 5-methylene tetronate nucleus found in tetronomycin (2).*

Tetronasin (1)[1] and tetronomycin (2)[2] are structurally-related polyether ionophore antibiotics recently isolated from the fermentation of two closely-related *Streptomyces* species.

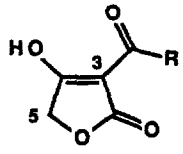


tetronasin **1**



tetronomycin **2**

As part of a synthetic programme towards (1) we required a method for the preparation of 5-unsubstituted, 3-acyl tetronic acids (3). Although there have been several reported approaches to this system involving the cyclization of α-substituted derivatives of ethyl glycollate[3], the simplest approach to (3) employs the direct C-3 acylation of a suitable tetronic acid derivative. Several methods have been devised to address this problem[4], however they all suffer from harsh reaction conditions, lack of generality or poor yields. The direct acylation of O-methyl tetronic acids lithiated at C-3 has been accomplished[5] but C-5 unsubstituted substrates undergo preferential deprotonation[6] and our attempts to acylate the dianion (4) led to a mixture of products.



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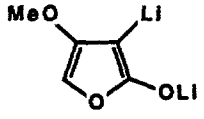

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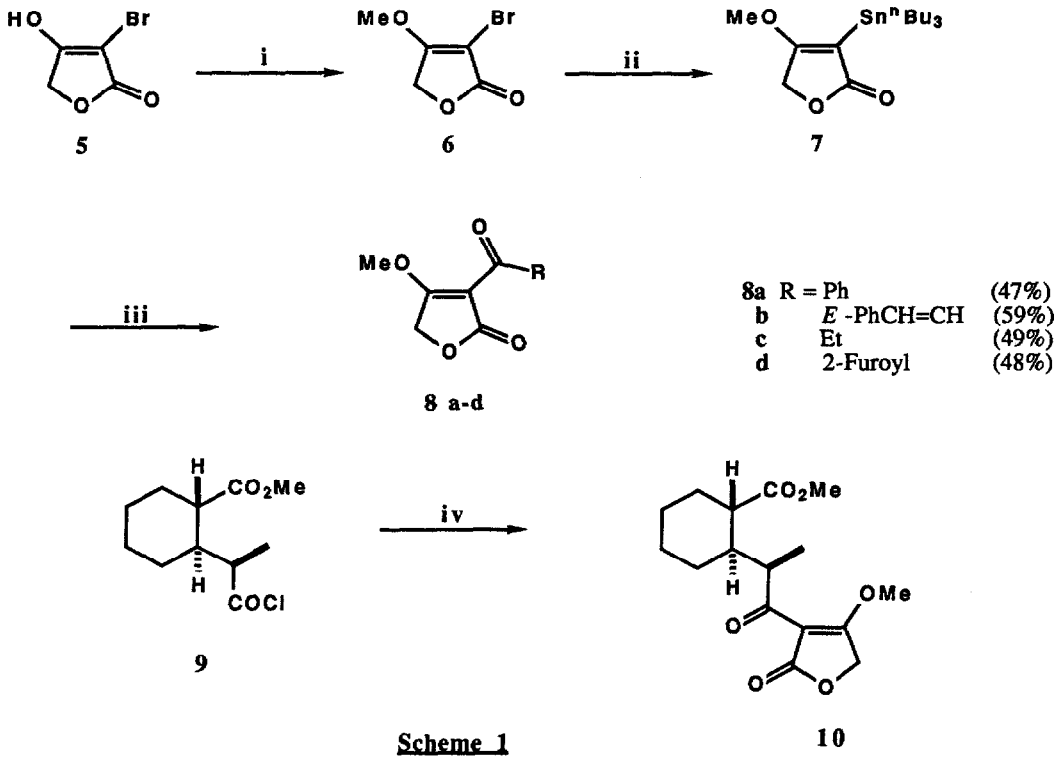
The acylation of organotin compounds in the presence of a palladium catalyst has been extensively investigated in recent years[7]. The reactions are usually high-yielding and tolerant of a high degree of functionality. In an attempt to prepare a 3-stannylated tetronate the known 3-bromo tetronic acid (**5**)[8] was first alkylated with diazomethane; but the resulting O-methyl 3-bromo tetronic acid (**6**) did not undergo metal-halogen exchange upon treatment with *t*-butyl lithium owing to preferential C-5 deprotonation. However treatment of (**6**) with sodium naphthalenide in THF at -78°C followed by addition of *n*-Bu_3SnCl afforded the key O-methyl 3-(tri-*n*-butylstannyl) tetronate (**7**)[9] in 69% yield. Direct acylation of (**7**) with a variety of acid chlorides in the presence of a palladium catalyst occurred cleanly and in reasonable yield furnishing the O-methyl 3-acyl tetronic acids (**8a-d**). Significantly the more highly functionalized acid chloride (**9**)[10] also underwent substitution to afford (**10**), a close model of the tetronasin CD ring system. (**Scheme 1**).



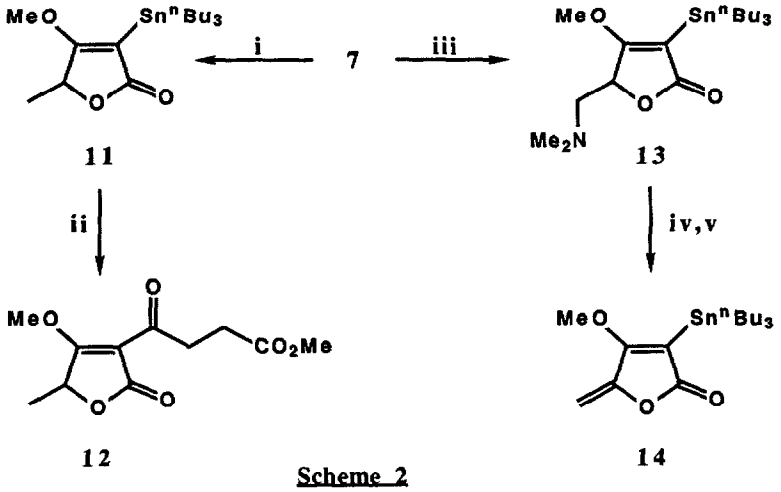
Scheme 1

(i) CH_2N_2, MeOH, r.t., 44%. (ii) $Na^+[nap]^{\cdot-}$, nBu_3SnCl, THF, -78°C to r.t., 69%. (iii) RCOCl, *t*-$PhCH_2(Cl)Pd(PPh_3)_2$ (cat.),$CHCl_3$, CO, 65°C, 16 hrs, 47-59% (as above). (iv) (**7**), *t*-$PhCH_2(Cl)Pd(PPh_3)_2$ (cat.) , $CHCl_3$, 65°C, 16 hrs, 40%.

There has been some confusion in the literature relating to the regioselectivity of alkylation of tetronic acids[11]. The structure of (**8d**) was unambiguously assigned by X-ray crystallography. (**Figure 1**).

In a typical acylation experiment (**7**) (5.2 mmol), the acid chloride (5.0 mmol) and *trans*-benzyl(chloro)-bistriphenylphosphine palladium (II) (0.02 x 10^{-2}mmol) were heated to 65°C in chloroform for 16h, under an atmosphere of CO. The reaction was complete upon precipitation of black metallic palladium. The products were purified by crystallization or column chromatography on silica gel in the usual way.

The carbon-tin bond in (**7**) is relatively stable towards cleavage and permits further elaboration at C-5 should this be required. Thus treatment of (**7**) with LDA followed by quenching with MeI afforded the 5-methyl stannyl tetronate (**11**). C-3 acylation of (**11**) with methyl succinoyl chloride furnished (±) dimethyl carolinic acid (**12**), one of several tetronic acids isolated from the mould *Penicillium charlesii* G.Smith[12]. Some de-stannylated tetronate (20%) was also recovered in this reaction. Additionally quenching of 5-lithio (**7**) with Eschenmoser's salt[13] yielded the dimethyl amine (**13**) which, after quaternization with MeI and elimination with base, gave the 5-methylene tetronyl tin compound (**14**) which is an obvious precursor to the tetronomycin (**2**) series. (**Scheme 2**).



Scheme 2

(i) LDA, MeI, THF, -78°C, 77%. (ii) $ClOCCH_2CH_2CO_2Me$, *t*-$PhCH_2(Cl)Pd(PPh_3)_2$ (cat.), $CHCl_3$, CO, 65°C, 56%. (iii) LDA, $CH_2NMe_2^+.I^-$, THF, -78°C to r.t., 55%. (iv) MeI, MeOH, r.t., 24hrs. (v) NaOH, H_2O, r.t., 40% overall.

Clearly the O-methyl 3-(tri-*n*-butylstannyl) tetronic acid (**7**) is an important and versatile reagent for the formation of 3-acyl tetronates. The opportunity to be able to functionalize (**7**) at the 5-position allows access to a number of interesting systems. Although in the above examples final hydrolysis of O-methyl derivatives to the parent tetronic acid was not attempted, we have previously demonstrated the viability of this process in other examples[14]. We are currently examining the synthetic utility of (**7**) in the formation of a variety of tetronate systems.

Figure 1 X-ray structure of **8d**

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9. ^{1}H-nmr, (270 MHz), $CDCl_3$; δ 0.89 (9H, t, J = 6.94 Hz), δ 1.05-1.50 (18H, m), δ 3.84 (3H, s), δ 4.74 (2H, s).
   ν_{max} (cm^{-1}), thin film; 2956, 2954, 2854, 1733, 1603, 1461, 1366, 1296, 1058.
   microanalysis; found C 50.77%, H 8.03% (calculated for $C_{17}H_{32}O_3Sn$; C 50.66%, H 7.95%).
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