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Studies Towards the Synthesis of Lophotoxin and Pukalide: Synthesis of the 14-Membered Macrocyclic Core and Some Acyclic Structural Analogues.

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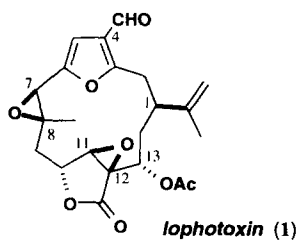
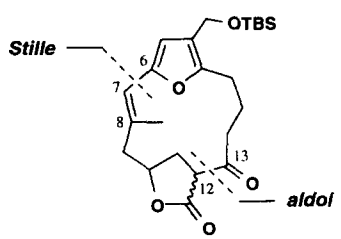
Abstract: The 14-membered macrocycle **3**, an advanced intermediate in a synthetic approach to lophotoxin, was prepared from stannane **20** using an intramolecular Stille coupling. The acyclic structural analogues **6** and **7** were obtained by analogous intermolecular coupling reactions.

Lophotoxin (**1**), isolated from several species of the Pacific sea whip *Lophogorgia*, is a potent neurotoxin that irreversibly blocks nicotinic acetylcholinergic neurotransmission in autonomic ganglia causing paralysis and asphyxiation.[1] Lophotoxin is structurally unique among neuromuscular toxins, since it lacks the cationic quaternary ammonium functional group of acetylcholine and displays highly specific inactivation. As such, it offers considerable potential as a selective neuropharmacological probe for the characterisation of the nicotinic acetylcholine receptor involved in synaptic transmission.[2,3] The furanocembranolide class of natural products, based on a 14-membered macrocycle with an associated C_7–C_8 epoxide and α,β-epoxy-γ-lactone, has been the focus of SAR studies. Abramson *et al.*[3] have postulated that the mode of lophotoxin's neuroinhibition involves covalent attachment of a tyrosine residue in the receptor to the epoxide C_7 position and that the γ-lactone is important for recognition. In line with this proposal, deoxypukalide (**2**) is one of a number of structurally related natural products[4] that are found to be inactive. The C_{11}–C_{12} epoxide and the substitution at C_1 and C_4 were found to be inessential,[3] suggesting that simplified structural analogues of lophotoxin may be designed which retain activity.



lophotoxin (1)



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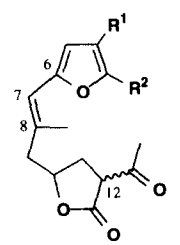
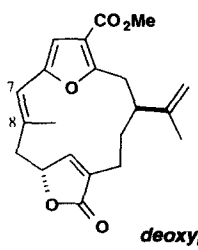
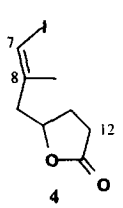


6: $R^1 = R^2 = H$

7: $R^1 = CH_2OTBS$, $R^2 = Me$



deoxypukalide (2)



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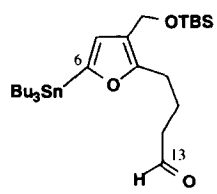

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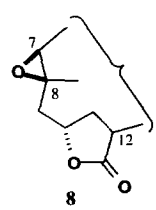

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As part of efforts towards the synthesis[5,6] of lophotoxin and pukalide, we now report the preparation of the common macrocyclic core **3** from the iodide **4** and stannane **5**, making use of a Stille cross-coupling reaction at C_6–C_7 as the key step for closing the 14-membered ring. We also describe the synthesis of the

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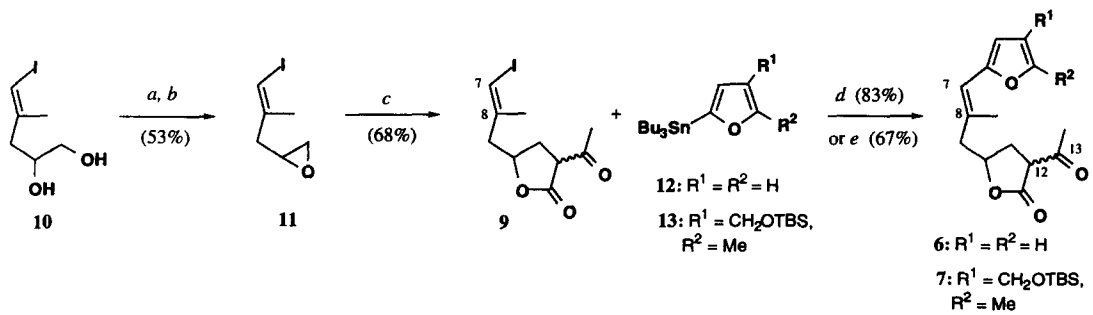
alkenyl furans **6** and **7**, which were designed from the Abramson pharmacophore model (*cf.* **8**) to possess, after epoxidation, the neuroinhibitory properties of lophotoxin.

As shown in **Scheme 1**,[7] the γ-lactone **9** containing an (*E*)-alkenyl iodide terminus was selected initially as a suitable intermediate for the generation of a series of acyclic structural analogues of lophotoxin and deoxypukalide. Following our earlier work,[5] a Stille coupling[8] was chosen for formation of the C_6–C_7 bond attached to the furan moiety. Selective tosylation of the diol **10**,[5] followed by treatment with base, gave the epoxide **11** (53%), which was opened by the sodium enolate of methyl acetoacetate to provide the required γ-lactone **9** in 68% yield (as a 1:1 mixture of diastereomers). A Stille coupling between vinyl iodide **9** and stannane **12**, under conditions developed in model studies ($Pd(PPh_3)_4$, CuI, DMF), then gave the 2-alkenyl furan **6** in 83% yield. For the more elaborate stannane **13**,[9] the use of $Pd_2(dba)_3$ and Ph_3P in NMP was found to be preferable for promoting the cross-coupling reaction with **9**, leading to a 67% yield of the trisubstituted furan **7**.



Scheme 1 (*a*) TsCl, py, 3 °C, 48 h; (*b*) K_2CO_3, MeOH, 90 min; (*c*) $MeCOCH_2CO_2Me$, NaOMe, MeOH, 55 °C, 16 h; AcOH; (*d*) **12**, $Pd(PPh_3)_4$, CuI, DMF, 4 h; (*e*) **13**, $Pd_2(dba)_3$, PPh_3, NMP, 20 h.

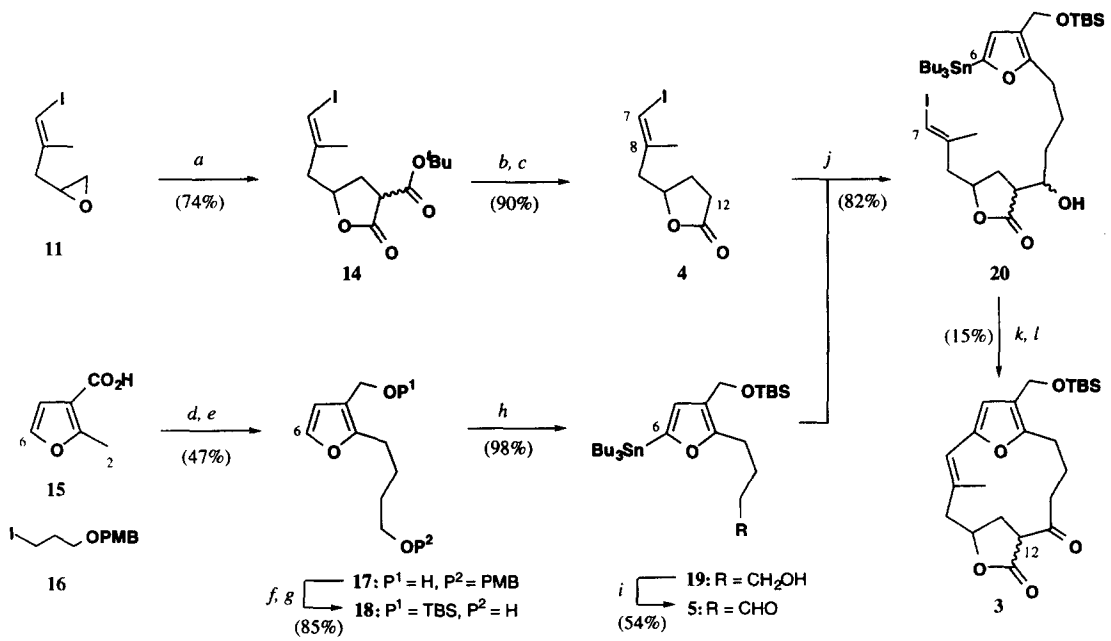
Following these preliminary model studies on acyclic analogues, it was decided next to pursue the synthesis of the macrocyclic core **3** in which rotation about the C_6–C_7 bond is constrained, thereby reducing epoxide destabilisation.[10] In our approach to **3**, we planned to install the C_{12}–C_{13} bond by a suitable aldol coupling between the subunits **4** and **5**, then carry out macrocyclisation *via* a Stille coupling at C_6–C_7 in an analogous fashion to that already used for the preparation of **7** (*cf.* **Scheme 1**).

As outlined in **Scheme 2**, the synthesis of the vinyl iodide **4** started out with a sequential alkylation-lactonisation reaction between the previously prepared epoxide **11** and di-*tert*-butylmalonate, giving the γ-lactone **14** (74%). Ester hydrolysis of **14** using TFA gave the acid, which was decarboxylated in the presence of Et_3N to give subunit **4** in 90% yield. The corresponding aldehyde subunit **5**, containing a tributylstannyl group at C_6, was obtained from the furan carboxylic acid **15**. The dianion of **15**, generated using LDA in THF, was alkylated at the C_2 position by reaction with iodide **16**. An *in situ* reduction using $LiAlH_4$ served to simplify the isolation and thereby increase the yield of the alkylation product **17**. Silyl protection followed by reductive removal of the PMB group (Li, NH_3) then gave the alcohol **18**. Double deprotonation of **18** using ^{n}BuLi (Et_2O, 20 °C) and subsequent treatment with Bu_3SnCl led to the formation of the furyl stannane **19** in 98% yield. Finally, mild oxidation using TPAP[11] led to isolation of the required aldehyde subunit **5** (54%), where the acid-sensitive tributylstannyl group was retained.

A directed aldol reaction between the two subunits was now required without compromising the tributylstannyl group on the furan. By employing LiHMDS as the base, the aldol coupling between the γ-lactone **4** and aldehyde **5** proceeded in 82% yield to give **20** (as a mixture of 3 diastereomers) without any destannylation at C_6. Initial attempts to oxidise the C_{13} position in **20** to generate the corresponding β-keto

lactone, which would simplify the isomer mixture, proved unrewarding.[12] As a result, it was decided first to explore the intramolecular Stille coupling of **20** and then attempt oxidation at C_{13} on the resulting macrocycle.

The acyclic systems already studied in **Scheme 1** indicated that $Pd_2(dba)_3/PPh_3$ was the catalyst system of choice for performing intermolecular Stille coupling reactions on highly substituted furans. The macrocycle precursor **20** was therefore subjected initially to these conditions in NMP at 60 °C. After 3–6 h, the starting material had been consumed and 3 new products appeared by TLC.[13] The crude product mixture, after work-up and chromatography to remove Sn and Pd residues, could be carefully[14] oxidised by Dess Martin periodinane[15] to give the desired macrocycle **3**[7] (as a 1:1 mixture of diastereomers[16]). By switching to the softer Ph_3As ligand in the Stille coupling step,[17] a modest 15% yield was achieved for this demanding two-step macrocyclisation-oxidation sequence.



Scheme 2 (*a*) $CH_2(CO^tBu)_2$, ^{t}BuONa, ^{t}BuOH, 50 °C, 19 h; AcOH; (*b*) TFA, CH_2Cl_2, 0 → 20 °C, 3 h; (*c*) Et_3N, THF, 60 °C, 90 min; (*d*) LDA, THF, -78 → 0 °C; **16**, 18 h; (*e*) $LiAlH_4$, 0 °C, 2 h; (*f*) TBSCl, Et_3N, DMAP, CH_2Cl_2, 15 h; (*g*) Li, NH_3, THF, -78 °C, 2 min; (*h*) ^{n}BuLi, TMEDA, Et_2O, 20 °C; Bu_3SnCl, -78 → 20 °C, 15 h; (*i*) TPAP, NMO, 4Å MS, CH_2Cl_2, 30 min; (*j*) LiHMDS, THF, -78 °C, 5 min; **5**, 30 min; (*k*) $Pd_2(dba)_3$, $AsPh_3$, NMP, 40 °C, 24 h; (*l*) DMP, CH_2Cl_2, 40 min.

In conclusion, the 14-membered macrocycle **3**, which represents an advanced intermediate in the synthesis of lophotoxin and related furanocembranolides, has been prepared in 8 steps from diol **10**. The late stage fragment coupling should allow the route to be adapted readily to incorporate further substituents (*e.g.* the isopropenyl group at C_1). Efforts to optimise the crucial Stille macrocyclisation step[18] and further work towards the synthesis of lophotoxin and structural analogues are underway.

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References and Notes

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7. All new compounds gave spectroscopic data in agreement with the assigned structures. Macrocycle **3** (isomers **A** and **B**) had: ^{1}H NMR δ (500 MHz, gCOSY, $CDCl_3$) 6.25 (1H, s, $\underline{H}_5$ A), 6.24 (1H, s, $\underline{H}_5$ B), 6.15 (1H, s, $\underline{H}_7$ B), 6.14 (1H, s, $\underline{H}_7$ A), 5.16 (1H, dd, J = 13.6, 7.6 Hz, $\underline{H}_{12}$ A), 5.06 (1H, dd, J = 13.6, 8.0 Hz, $\underline{H}_{12}$ B), 4.93 (1H, dt, J = 7.8, 3.1 Hz, $\underline{H}_{10}$ B), 4.84 (1H, dt, J = 8.1, 3.1 Hz, $\underline{H}_{10}$ A), 4.51 (2H, s, $C_4C\underline{H}_2OSi$ A), 4.51 (2H, s, $C_4C\underline{H}_2OSi$ B), 2.94-1.89 (20H, m, $\underline{H}_{9a,b}$, $\underline{H}_{11a,b}$, $\underline{H}_{14a,b}$, $\underline{H}_{1a,b}$, $\underline{H}_{2a,b}$ A and B), 2.17 (3H, s, $C_8\underline{Me}$ B), 2.08 (3H, s, $C_8\underline{Me}$ A), 0.91 (18H, s, $SiC\underline{Me}_3$ A and B), 0.09 (12H, s, $Si\underline{Me}_2$ A and B); ^{13}C NMR δ (100 MHz) 205.3, 203.3, 173.9, 173.2, 150.2, 149.7, 149.6, 149.1, 137.9, 132.9, 123.8, 123.5, 120.2, 118.6, 112.4, 111.3, 79.2, 76.4, 57.1, 56.9, 48.3, 48.1, 44.3, 43.9, 43.1, 40.2, 30.8, 29.7, 28.1, 27.8, 26.8, 26.4, 25.9, 25.9, 23.8, 22.6, 28.4 (2C), -5.2 (2C); HRMS (+EI) $[M]^+$ found 418.2158, $C_{23}H_{34}O_5Si$ requires 418.2175.
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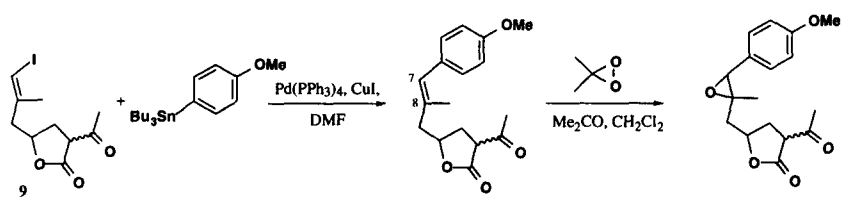
9. The stannane **13** was prepared from methyl 2-methyl-3-furan carboxylate (Aldrich) in 82% yield by the sequence: (a) $LiAlH_4$, Et_2O, 1 h; (b) TBSCl, DMAP, Et_3N, CH_2Cl_2, 6 h; (c) ^{t}BuLi, THF, -78°C; Bu_3SnCl, -78 → 20 °C, 1.5 h.
10. Reaction of alkenes **6** and **7** with either dimethyldioxirane or *m*CPBA was attempted but, in each case, no epoxide could be isolated. Notably, the electron-rich furan ring is not only susceptible to oxidation itself but also destabilises any intermediate epoxide formed at the desired C_7–C_8 position. On replacement of the furan with a methoxyphenyl group, epoxidation was successful, as in the following example:



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11. Ley, S. V.; Norman, J.; Griffith, W. F.; Marsden, S. P. *Synthesis* **1994**, 639.
12. TPAP oxidation failed and Dess-Martin, Swern and Parikh-Doering protocols all led to destannylation at a rate comparable to oxidation.
13. Attempts to chromatographically separate the Stille coupling products were unsuccessful. Prolonged silica chromatography, HPLC and preparative TLC all led to decomposition and poor mass recovery.
14. The Dess Martin oxidation suffered from over-oxidation at C_{12}, which was minimised by using short reaction times and recycling unreacted starting material.
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16. Despite the strained geometry of the 14-membered ring, it appears that the diastereomers are in dynamic equilibrium at room temperature and 1:1 represents the thermodynamic ratio.
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18. Recently, Smith and Ott have demonstrated a dramatic yield improvement in Stille cross-couplings on switching from tributyl to trimethyl stannanes. Smith, A. B., III.; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935.