Total Synthesis of the Furanocembrane *bis*-Deoxylophotoxin

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Received 8 October 2001

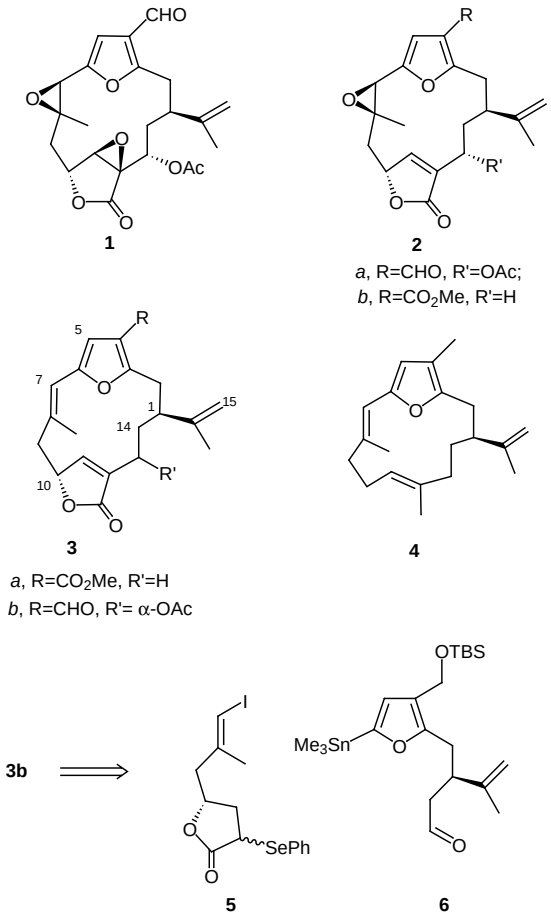
Abstract: A total synthesis of the *bis*-deoxylophotoxin **25a**, the probable biological precursor to the neurotoxin lophotoxin **1** is described. The synthesis uses a strategy based on sequential carbanion alkylation and Stille coupling between the chiral building blocks **5** and **6**, leading to the furanocembranolide **23**, following by functional group manipulation.

Key words: furanocembranes, lophotoxin, Stille macrocyclisation

Lophotoxin **1** is a unique furanocembrane isolated from species of the Pacific sea whip *Lophogorgia*.[1] The compound is a potent neurotoxin that binds selectively and irreversibly to acetylcholine recognition sites in nicotinic acetylcholine receptors, leading to paralysis and asphyxiation.[2] Lophotoxin co-occurs with the deoxylophotoxin **2a** in *L. chilensis*, and both metabolites share a structural resemblance to the natural products pukalide **2b** and to deoxypukalide **3a** found in *L. alba*.[2,3] Circumstantial evidence would suggest that the metabolites **1**–**3** share a common biosynthetic origin involving elaboration of the furanocembrane carbon framework **4** followed by sequential oxidation, to **3a/3b** and then epoxidation to **2a/2b** en route to **1**. With its unusual juxtapositioned and diverse oxygen functionality, embedded in a reactive macrocyclic furan-based framework, lophotoxin **1** is a deceptively challenging synthetic target.[4] In earlier synthetic work we outlined an approach to the core hydrocarbon furanocembrane macrocyclic system **4** in lophotoxin based on a novel acyl radical macrocyclisation strategy.[5] However, attempts to extend this strategy to the macrocyclisation of oxygen-functionalised acyl radical precursors met with failure, and competing cyclisation processes became dominant.[6] Building on our investigations of the scope for intramolecular sp^2-sp^2 coupling reactions in macrocyclic constructions,[7] we now describe a total synthesis of the *bis*-deoxylophotoxin **3b** using a stratagem based on sequential carbanion alkylation and Stille coupling between the chiral building blocks **5** and **6** (Figure).[8]

The substituted phenylseleno lactone **5** was synthesised from commercially available (*R*)-(–)-epichlorohydrin as shown in Scheme 1. Thus, treatment of the epoxide **7** with the lithium salt derived from trimethylsilylacetylene at –78 °C, under Yamaguchi conditions,[9] first gave the corresponding chlorohydrin **8a** which was then deprotected leading to the monosubstituted acetylene **8b**. Carbometalation-iodination of **8b**,[10] next gave the *E*-vinyl iodide **9**, which was converted into the epoxide **10** in the presence of NaOH. When the chiral epoxide **10** was treated with the lithium salt derived from 1-ethoxyacetylene, and then with *p*-toluenesulphonic acid, work up and chromatography gave the (+)-lactone **11**, in 60% overall yield.[11] Deprotonation of **11**, using LiHMDS, followed by quenching the resulting anion with phenylselenenyl bromide at –78 °C finally gave a 2:1 mixture of diastereomers of the α-phenylselenolactone intermediate **5**, as a viscous oil.[12]

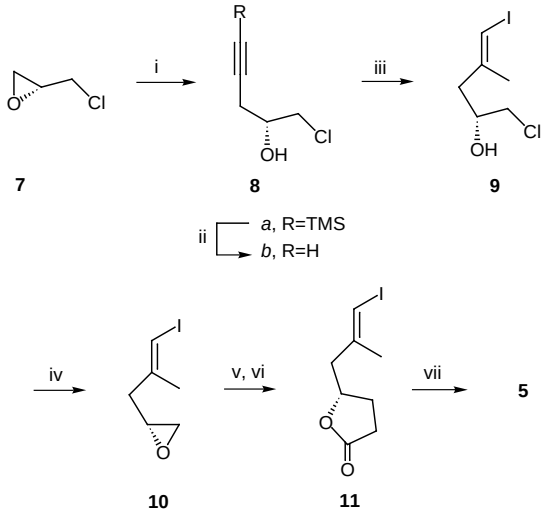
The furylstannane building block **6** was prepared starting with the oxazolidinone **13** derived from 3-methylbuten-2-oyl chloride and the lithium salt of the Evans' auxiliary **12**[13]. Thus, deprotonation of the oxazolidine **13** with NaHMDS in THF at –78 °C, followed by addition of ethyl 2-



Figure

Synlett 2001, No. 12, 30 11 2001. Article Identifier:
1437-2096,E;2001,0,12,1869,1872,ftx,en;D21201ST.pdf.

ISSN 0936-5214

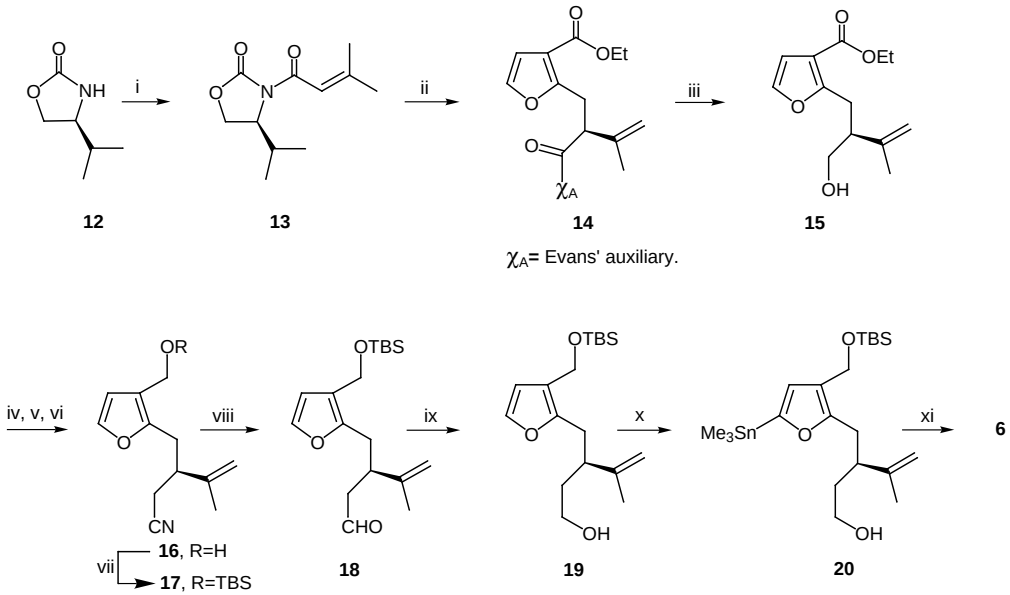


Scheme 1 *Reagents:* (i) TMSCCH, *n*-BuLi, BF_3, –78 °C; (ii) TBAF, HCl, THF, r.t., 42% over 2 steps; (iii) Me_3Al, Cp_2ZrCl_2, CH_2Cl_2, r.t., 3 days, then I_2/THF, –30 °C to r.t., 2 h, 62%; (iv) NaOH, Et_2O, r.t., 14 h; (v) 1-ethoxyacetylene, *n*-BuLi, BF_3, 2 h; (vi) *p*-TsOH, EtOH, 2 h, then $CHCl_3$, reflux, 14 h, 60% overall from **9**; (vii) LiHMDS, THF, 5 min, then PhSeBr, 40 min., –78 °C, 75%

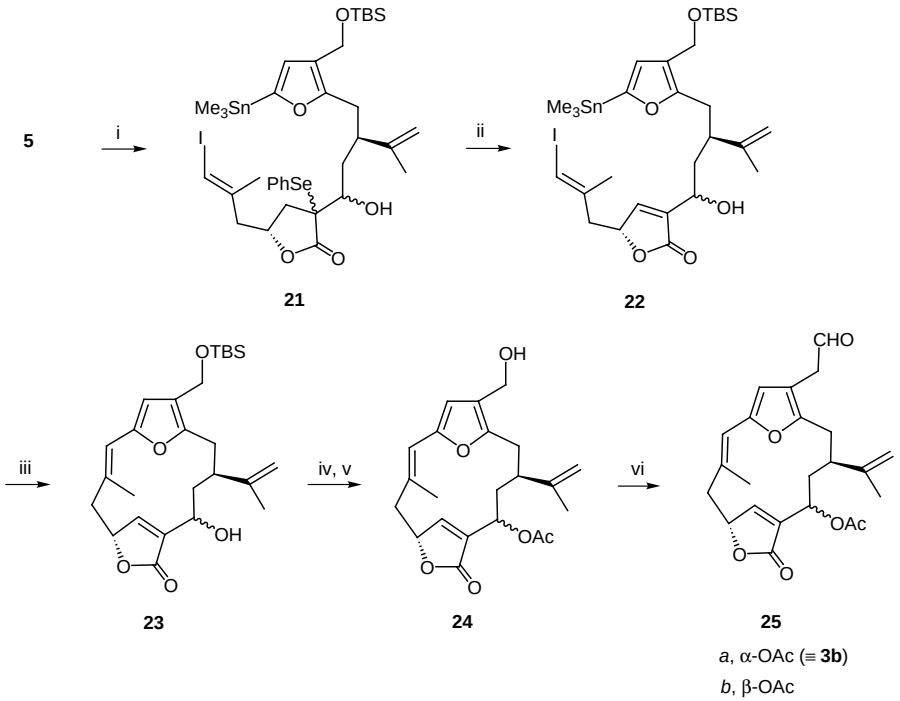
bromomethyl-3-furoate[14] first led to the product **14**, resulting from deconjugative alkylation.[15] The absolute stereochemistry of **14**, melting point 59–61 °C, was established from X-ray crystal measurements.[16] Reduction of **14** with Super Hydride next produced the alcohol **15** which was then converted into the nitrile **17** by sequential tosylation, reduction, cyanide displacement (to **16**) and, finally, alcohol group protection. The nitrile group in **17** was reduced with Dibal-H leading to the aldehyde **18** which, on further reduction with $NaBH_4$, gave the alcohol **19**. Deprotonation of the 2,3-disubstituted furan **19**, using *n*-BuLi, next gave the corresponding 5-lithiofuran which was quenched with Me_3SnCl at 0 °C to produce the 5-trimethylstannylfuran **20**. Finally, oxidation of the substituted alcohol **20** using TPAP gave the key furylstannane aldehyde intermediate **6** (Scheme 2).[17]

Deprotonation of the phenylselenolactone **5** using LiHMDS in THF at –78 °C, followed by addition of the aldehyde **6** gave a satisfying 75% yield of the secondary alcohol **21** which was isolated as a mixture of diastereomers.[18] Oxidation of the selenide **21** using hydrogen peroxide[19] was accompanied by in situ dehydroselenenylation producing the unsaturated lactone **22**.[20] An intramolecular Stille reaction with **22** under the conditions described by Farina et al[21] (Pd_2dba_3, $AsPh_3$, NMP) at 40 °C, then led to the macrocycle **23** which was obtained as an oily mixture of two diastereomers in 20% yield over three steps from **21**. Acetylation of the macrocyclic alcohol **23**, followed by deprotection of the *t*-butyldimethylsilyl ether group next produced the primary alcohol **24** as a mixture of epimeric acetates which could be separated by chromatography. Finally, oxidation of each of the epimeric acetates led to the α-**25a** and to the β-**25b** epimers of the *bis*-deoxylophotoxin **3b** (Scheme 3).[22]

Preliminary investigations of the regio- and stereo-selective epoxidations of the *bis*-deoxylophotoxin diastereomers **25** have been carried out, but the dearth of material has not allowed us to assign unambiguous structures and stereochemistries to the epoxide products resulting from these studies. Further studies are now in progress and will be reported in future publications.



Scheme 2 *Reagents:* (i) *n*-BuLi, –78 °C, 20 min, then 3-methylbuten-2-oyl chloride, from –78 °C to r.t., 30 min,75%; (ii) NaHMDS, 1 h, –78 °C, THF; then, 1.2 equiv of ethyl 2-bromomethyl-3-furoate, 65%; (iii) Super Hydride, toluene, –78 °C, 20 min, 80%; (iv) TsCl, Et_3N, DMAP, r.t., 75%; (v) Dibal-H, CH_2Cl_2, –78 °C, 95%; (vi) *n*-Bu_4NCN, 3equiv, DMSO, 60 °C, 90%; (vii) TBDMSiCl, Et_3N, DMAP, r.t., 91%; (viii) Dibal-H, 1.1 equiv, toluene, –78 °C to r.t., 85%; (ix) $NaBH_4$, MeOH, 0 °C, 70%; (x) *n*-BuLi, 20 min, then TMEDA for 6 h and *n*-BuLi for 20 min, r.t.; then Me_3SnCl, 0 °C to r.t. 16 h, 80%; (xi) TPAP, NMO, MS 4, CH_2Cl_2, 1 h, 75%



Scheme 3 *Reagents:* (i) LiHMDS, –78 °C, 20 min, then **6**, 50 min, 75%; (ii) H_2O_2, CH_2Cl_2/pyridine, 1 h, 0 °C; (iii) $AsPh_3$, Pd_2dba_3, 40 °C, 14 h, 20% from **21**; (iv) Ac_2O, Et_3N, DMAP, r.t., 4 h, 40%; (v) CSA, MeOH:CH_2Cl_2, 3 h, 0 °C; (vi) Dess–Martin periodinane, pyridine, CH_2Cl_2, 3 h, 0 °C, 80% over two steps

Acknowledgement

We thank the EPSRC for support of this work via a Fellowship (to MC), and AstraZeneca for financial provision.

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(12) All new compounds showed satisfactory spectroscopic data together with microanalytical and/or mass spectrometry data. Compound **11** showed: ν_{max}/cm^{-1}: 1758; ^{1}H NMR (360 MHz): δ = 6.11–6.10 (br m, 1 H, =C*H*I), 4.67–4.59 (m, 1 H, C*H*–O), 2.67 (dd, 1 H, *J* = 7.4, 14.2, CH*H*–C=C), 2.57–2.48 (m, 3 H, CH_2–C=O and CH*H*–C=C), 2.37–2.28 (m, 1 H, CH*H*–CH$_2$–C=O), 1.94–1.83 (m, 4 H, C=C–CH_3, CH*H*–CH$_2$–C=O); ^{13}C NMR (90 MHz): δ = 176.5 (C), 142.6 (C), 78.5 (CH), 78.2 (CH), 44.8 (CH_2), 28.4 (CH_2), 27.5 (CH_2), 24.3 (CH_3); $[\alpha]^{20}_D$ +41.8 (c = 3.5, CH_2Cl_2); HRMS: 265.98081 ($C_8H_{11}O_2I$ requires: 265.98038). Compound **6** showed: ν_{max}/cm^{-1}: 1722; ^{1}H NMR (360 MHz): δ = 9.51 (t, 1 H, *J* = 2.2, C*H*O), 6.47 (m, 1 H, =C*H*), 4.79 (br s, 1 H, C=C*H*H), 4.76 (s, 1 H, C=C*H*H), 4.48 (s, 2 H, CH_2-OTBS), 3.11–3.01 (m, 1 H, C*H*–C=C), 2.84 (dd, 1 H, *J* = 14.7 and 6.1, CH*H*-furan), 2.71 (dd, 1 H, *J* = 14.7 and 8.7, CH*H*-furan), 2.45 (dd, 2 H, *J* = 7.3 and 2.2, CH_2–CHO), 1.73 (s, 3 H, =C–CH_3), 0.92 (s, 9 H, Si(CH_3)$_3$), 0.38–0.13 (m, 9 H, Sn(CH_3)$_3$), 0.10 (s, 6 H, (Si(CH_3)$_2$); ^{13}C NMR (90 MHz): δ = 201.9 (CH), 158.6 (C), 154.2 (C), 146.2 (C), 122.3 (CH), 120.7 (C), 112.0 (CH_2), 57.2 (CH_2), 46.6 (CH_2), 41.0 (CH), 31.1 (CH_2), 26.5 (CH_3), 20.0 (CH_3), 18.5 (C), 1.1 (CH_3), –5.1 (CH_3), –9.2 (CH_3); $[\alpha]^{20}_D$ +2.7 (c = 1.6, CH_2Cl_2).
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(16) We thank Dr A. J. Blake of this School for this crystal structure determination, which will be published elsewhere.
(17) Both of the furylstannanes **20** and **6** could be purified by flash chromatography using Woelm basic alumina without significant destannylation being observed.
(18) A Stille coupling reaction between **5** and **20** under the conditions of Farina[21] (Pd_2dba_3, $AsPh_3$, NMP, 40 °C) gave the corresponding *E*-furylalkene, but attempts to carry out a subsequent intramolecular alkylation reaction, via deprotonation, were unsuccessful.
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(22) Main epimer: Cembrane ring numbering: ^{1}H NMR (400 MHz, 318K): δ = 9.86 (s, 1 H, C*H*O), 7.31 (br s, 1 H, *H-11*), 6.44 (s, 1 H, *H-5*), 5.95 (br s, 1 H, *H-7*), 5.77 (br m, 1 H, *H-13*), 5.27 (br s, 1 H, *H-10*), 4.91 (s, 1 H, *H-15a*), 4.88 (s, 1 H, *H-15b*), 2.92 (dd, 1 H, *J* = 13.6 and 3.3, *H-9a*), 2.80–2.00 (br m, 6 H, *H-1*, *H-2*, *H-9b*, *H-14*), 1.95 (s, 3 H, COCH_3), 1.85 (s, 3 H, CH_3), 1.74 (s, 3 H, CH_3); MS (ES): *m/z* = 407.1444 ($C_{22}H_{24}O_6Na$ requires: 407.1470); Minor epimer: ^{1}H NMR (400 MHz, 318K): δ = 9.86 (s, 1 H, C*H*O), 7.16 (s, 1 H, *H-11*), 6.44 (s, 1 H, *H-5*), 6.01 (br s, 1 H, *H-7*), 5.45 (br d, 1 H, *J* = 9.7, *H-13*), 5.27 (br s, 1 H, *H-10*), 5.21 (s, 1 H, *H-15a*), 5.02 (s, 1 H, *H-15b*), 3.03 (dd, 1 H, *J* = 13.6 and 3.6, *H-9a*), 2.80–2.00 (br m, 6 H, *H-1*, *H-2*, *H-9b*, *H-14*), 2.03 (s, 3 H), 1.84 (s, 3 H), 1.71(s, 3 H); MS (ES): m/z = 407.1441 ($C_{22}H_{24}O_6Na$ requires: 407.1470).