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Total synthesis of (+)-*Z*-deoxypukalide, a furanobutenolide-based cembranoid isolated from the pacific octocoral *Leptogorgia* spp.

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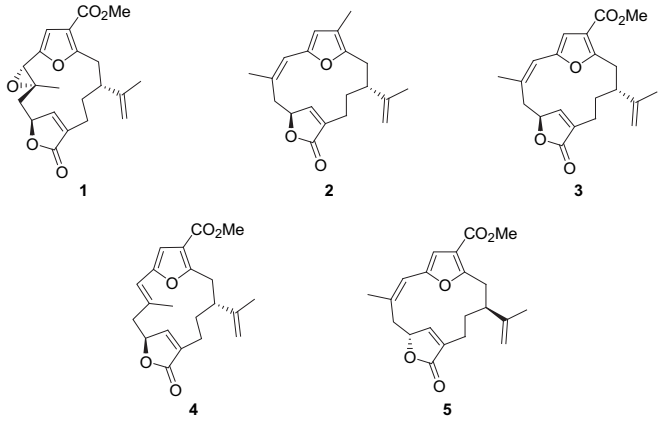
ABSTRACT

A total synthesis of (+)-*Z*-deoxypukalide **3** using a combination of Stille and Nozaki–Hiyama–Kishi(NHK) coupling reactions as key steps, is described. During this study a new practical synthesis of the substituted butenolide intermediate **10**, based on a combination of RCM and CM reactions from the cyclobutene ester **21** in the presence of 2-methylpropenol was also developed. Attempts to apply the intramolecular NHK reaction to the substrates **8a** and **8b** containing an ester group adjacent to the reacting aldehyde functionality gave disappointing low yields (<6%) of the corresponding coupled products **9**. The synthetic (+)-*Z*-deoxypukalide **3** was correlated with naturally derived material, and also with pukalide **1**, the first member of the furanobutenolide-based cembranoids to be isolated from corals.

1. Introduction

The furanobutenolide-based cembranoid pukalide **1** occupies a special place in natural product chemistry, since it was the first member of this burgeoning family of secondary metabolites to be described, in 1975, from corals, i.e. *Sinularia abrupta*.[1] Since then pukalide has been isolated from many other coral species,[2] and has also been found in the dendronoid nudibranch *Tochuina tetraquetra*, together with rubifolide **2**.[3] (+)-*Z*-Deoxypukalide **3** was reported only recently alongside the corresponding *E*-isomer **4** from the Pacific coral *Leptogorgia* spp.[4] The enantiomer **5** of natural *Z*-deoxypukalide **3** was synthesised by Marshall and van Devender[5] in 2001, and was correlated with the (+)-enantiomer produced by reducing natural pukalide **1** with zinc in ethanol. A synthesis of the same non-natural, (−)-*Z*-deoxypukalide **5** was also achieved recently by Donohoe et al.[6] We now report our own studies directed towards the pukalides **1**–**3**, which have culminated in a concise synthesis of natural (+)-*Z*-deoxypukalide **3** for the first time.



2. Results and discussion

2.1. Synthetic plan

A variety of synthetic methods have been developed for elaborating the macrocyclic cores in furanobutenolide cembranoids.[7] Many of these methods have been based on the intramolecular Nozaki–Hiyama–Kishi (NHK) reaction,[8] intrannular furan and butenolide ring synthesis,[9] the intramolecular Stille reaction,[10] radical macrocyclisations,[11] ring closure metathesis (RCM),[12] Wittig rearrangements and intramolecular Wadsworth–Emmons olefination.[7] Indeed, many of these approaches have subsequently been applied in the synthesis of naturally occurring furanobutenolides.[5,6,10a,13]

Our own research group has developed synthetic routes to both deoxylophotoxin **6**[10] and to bipinnatin J (**7**)[14] using methods which have featured intramolecular Stille and NHK reactions, respectively, as key steps. Our experience suggested that the most practical route to the *Z*- and *E*-deoxypukalides **3** and **4** would be via intramolecular NHK reactions from appropriate *Z*- and

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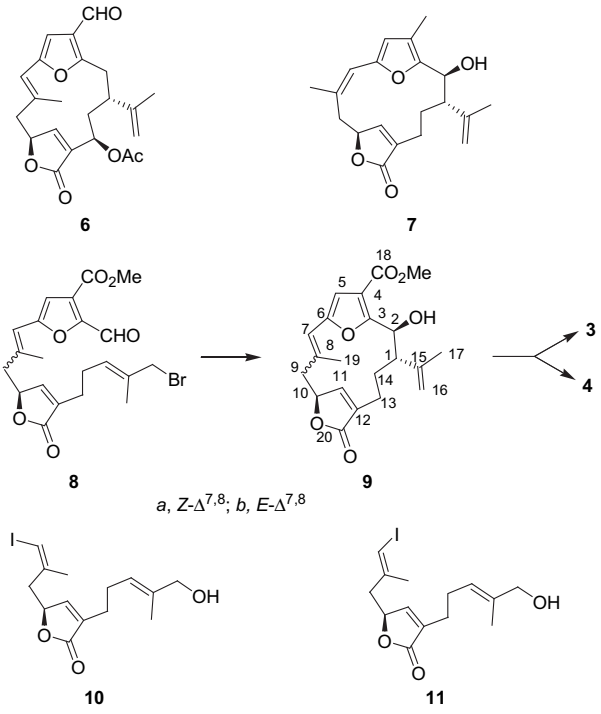
E-$\Delta^{7,8}$-alkene isomers of the bromoaldehyde precursor **8**, leading to **9**, as the key step. This synthetic approach had the added benefit that we had already developed a concise synthesis of the enantiomerically pure *Z*-vinyl iodide **10** during our total synthesis of (−)-bipinnatin J (**7**).[14] This same synthetic approach to **10** could easily be adapted to a synthesis of the corresponding *E*-vinyl iodide **11**.

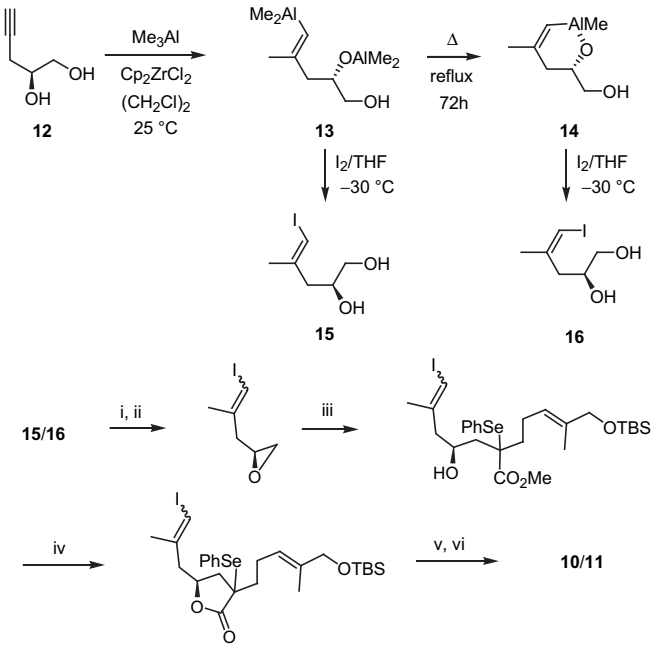


2.2. Synthesis of the *Z*- and *E*-alkenyl iodides 10 and 11

In our synthesis of **10**, the *Z*-alkenyl iodide moiety was generated from the corresponding homopropargylic alcohol **12**, using an *anti*-carbometalation protocol described by Negishi and Ma.[15] In this sequence, the first-formed *syn*-carbometalation product **13** derived from the alcohol **12** is heated under reflux for 72 h resulting in a chelation-controlled thermodynamic *E*- to *Z*- isomerisation producing **14**, which is then quenched by iodine leading to **16**. When the same carbometalation of **12** was instead carried out at room temperature, iodination of the intermediate **13** gave the anticipated *E*-alkenyl iodide isomer **15**. Each of the isomeric alkenyl iodides **15** and **16** were then converted into the corresponding enantiomerically pure substituted **10** and **11**, respectively, using the published synthetic sequence summarised in Scheme 1.[14]

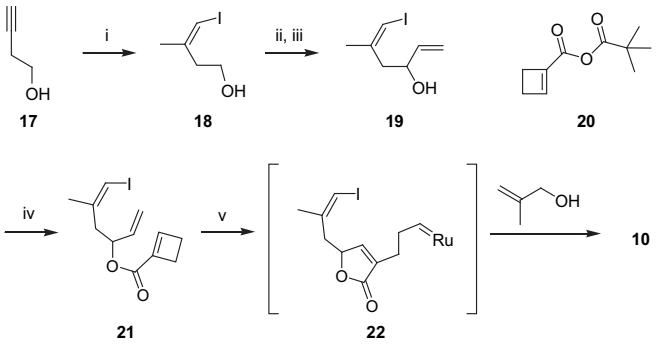
The isomeric substituted butenolides **10** and **11** gave closely similar ^{1}H and ^{13}C NMR spectra. They were distinguished however by the appearance of the diastereotopic methylene protons adjacent to the butenolide as double doublets at δ 2.66 (*J* 13.6 and 6.1 Hz) and δ 2.54 (*J* 13.6 and 7.4 Hz) in the ^{1}H NMR spectrum of the *Z*-isomer **10**, which appeared as an unresolved multiplet at δ 2.54–2.57 ppm in the ^{1}H NMR spectrum of the corresponding *E*-isomer **11**. In addition, the same CH_2 in the *Z*-isomer, together with the adjacent CH were shielded relative to the same carbon centres in the ^{13}C NMR spectra of the isomers, i.e. δ 42.4 and 78.5 ppm for **10**, and δ 42.8 and 79.0 ppm for **11**.

In contemporaneous studies three other research groups described alternative synthetic routes to the *Z*-alkenyl iodide **10**.[16–18]



Scheme 1. Reagents and conditions: (i) TsCl, Py, 4 °C, 28 h; (ii) K_2CO_3, MeOH, rt, 1.5 h, 73%; (iii) NaHMDS, $MeO_2CCH(SePh)CH_2CH_2CH{=}C(Me)CH_2OTBS$, THF, −78 °C, 0.5 h, then epoxide, $BF_3{\cdot}Et_2O$, −78 °C to rt overnight, 72%; (iv) PTSA (0.1 equiv), DCM, rt, 3 h; (v) H_2O_2, THF, 0 °C to rt, 2 h; (vi) PPTS (0.2 equiv), DCM/MeOH(1:1), rt, 24 h, 62% for three steps.

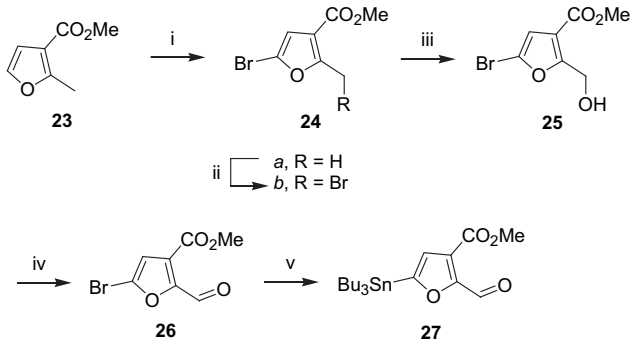
More recently we developed a new and practical five-step synthetic route to the substituted butenolide **10** starting from 3-butynol, which featured a combination of RCM and cross-metathesis (CM) reactions involving the cyclobutene ester intermediate **21** and 2-methylpropenol. Thus, a Negishi *anti*-carbometalation iodination sequence from the butynol **17** first gave the known *Z*-alkenyl iodide **18**,[19] which, in two steps was next converted into the racemic allylic alcohol **19** (Scheme 2). Treatment of **19** with the mixed anhydride **20** derived from cyclobutene carboxylic acid and pivalic acid then gave the cyclobutene derivative **21**. Finally, when a refluxing solution of the cyclobutene ester **21** in dichloromethane was reacted with Grubbs' catalyst in the presence of 2-methylpropenol, it underwent RCM leading to **22** presumably followed by CM with the propenol leading to the substituted racemic butenolide **10** in 57% overall yield; NMR data established that <5% of the *Z*-allylic alcohol corresponding to **10** was produced concurrently.[20]



Scheme 2. Reagents and conditions: (i) $AlMe_3$, Cp_2ZrCl_2, DCM, reflux 72 h, then I_2, THF, −30 °C–0 °C, 1 h, 81%; (ii) DMP, DCM, $NaHCO_3$, 25 °C, 15 min; (iii) vinylmagnesium bromide, THF, −78 °C, 1 h, 40% over two steps; (iv) LiHMDS, THF, −78 °C, 20 min, reflux, then **20**, THF, 1.5 h, 65%; (v) Grubbs' second generation catalyst, DCM reflux 2 h, 2-methylpropenol, 57%.

2.3. Elaboration of 10 and 11 to the isomeric 2-alkenylfurans 28 and 29, respectively, using Stille coupling reactions

With the enantiomerically pure iodoalkenes **10** and **11** to hand, we next planned to couple them, separately, to the substituted stannylfuran **27** in the presence of Pd(0) leading to the furanobutenolides **8a**/**8b** en route to the targets **3** and **4**. The substituted stannylfuran **27** was prepared in five steps starting from methyl 2-methyl-3-furanoate **23** (Scheme 3). Thus, bromination of **23** using NBS in DMF first gave the bromofuran **24a**, which on further treatment with NBS in the presence of AIBN was converted into the corresponding furanmethyl bromide **24b**. Hydrolysis of **24b**, using aqueous K_2CO_3 in DMF and THF at 50 °C next gave the furanmethanol **25**, which was then oxidised to the corresponding furan aldehyde **26** using MnO_2 in CH_2Cl_2. When a solution of the bromofuran **26** in NMP was reacted with hexabutyldistannane in the presence of $Pd_2(dba)_3$–Ph_3 As, work up and chromatography gave the stannyfuran **27** as a colourless oil.

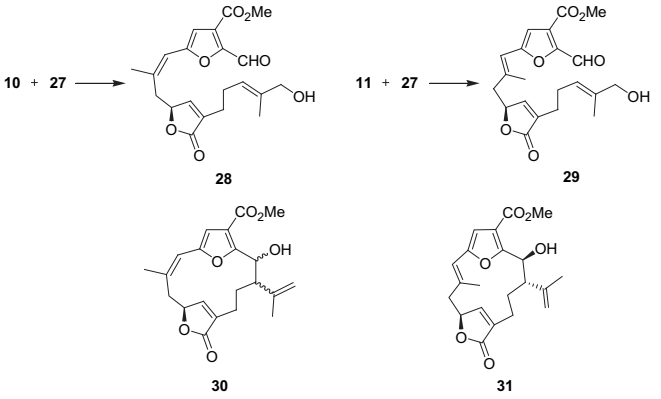


Scheme 3. Reagents and conditions: (i) NBS, DMF, 25–50 °C, 0.5 h, 91%; (ii) NBS, AIBN, CCl_4, 24 h, 98%; (iii) aqueous K_2CO_3, DMF, THF, 50 °C, 24 h, 38%; (iv) MnO_2, DCM, 25 °C, 2 h, 96%; (v) $Pd_2(dba)_3$, Ph_3As, NMP, Bu_6Sn_2, 21%.

Separate Stille coupling reactions between the stannylfuran **27** and the *Z*- and *E*-alkenyl iodides **10** and **11**, using $Pd(PPh_3)_4$—CuI and CsF in DMF, next led to the isomeric 2-alkenylfurans **28** and **29**, respectively, in 60–65% yields. The allyl alcohol groups in **28** and **29** were then brominated, using NBS—PPh_3, leading to the corresponding allyl bromides **8a** and **8b**, which we now planned to cyclise to the macrocyclic homoallylic alcohols **9a** and **9b**, under NHK conditions. The isomeric alkenylfurans **28**/**29** and **8a**/**8b** were distinguished in their NMR spectroscopic data where the *Z*-isomers showed characteristic signals at δ 3.26 ppm (dd, *J* 13.9 and 3.1 Hz) for H-9α in the proton spectrum for **28**; the corresponding proton resonance in the *E*-isomer **29** appeared as a multiplet, δ 2.50–2.65 ppm. In addition, the ^{13}C resonances for C19 Me in the *E*-isomer **8b** and for C9 CH_2 in the *Z*-isomer **8a** were significantly shielded, i.e. δ 19.1 and 38.3 ppm, in comparison with the corresponding resonances in the isomeric pairs, i.e. 26.8 and 44.7 ppm, respectively.

2.4. Inefficient intramolecular NHK coupling reactions leading to the macrocycles 30 and 31

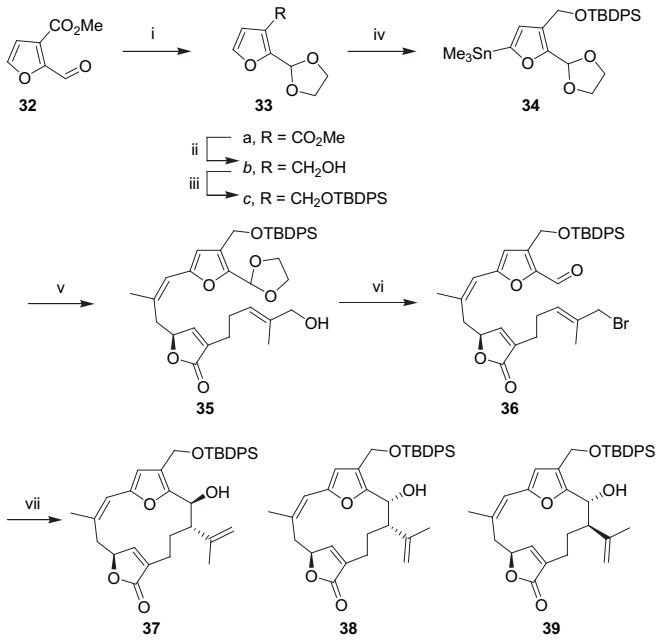
The intramolecular NHK reaction with a substrate identical to **8** but accommodating a methyl group instead of a methoxycarbonyl residue on the furan ring, had previously been used successfully by us, and others, in a total synthesis of bipinnatin J (**7**).[14,16,17] It was much to our chagrin therefore to find that when **8a** was subjected to the same NHK cyclisation conditions, i.e. $CrCl_2$ in the presence of 4 Å molecular sieves, the macrocycle **30** was produced in very low yields (<5%), and as a complex mixture of diastereoisomers. Likewise, the *E*-isomer **8b**, corresponding to **8a**, underwent a similar disappointing macrocyclisation under NHK conditions from which the *anti*-diastereoisomer **31** could be separated in only approximately 6% yield. Although we had expected that the macrocyclisation of the *E*-isomer **8b** would be more problematic than the *Z*-isomer, taking into account the distance between the reacting centres, we were particularly surprised by the poor yield and lack of specificity in the intramolecular NHK cyclisation with **8a**. It seems probable that in this instance the methoxycarbonyl and the aldehyde functionalities in **8a** conspire to deactivate the substrate in the presence of $CrCl_2$, and thus inhibit a facile NHK cyclisation.



2.5. Efficient intramolecular NHK coupling reaction of the bromoaldehyde 36 leading to the macrocyclic homoallylic alcohol 37

The poor yield and disappointing diastereoselectivity of **30** resulting from the NHK cyclisation of **8a** did not provide us with sufficient material to investigate its conversion into (+)-*Z*-deoxypukalide **3**. We therefore decided to synthesise the furanmethanol derivative **36** corresponding to the furanoate **8a** and examine its conversion into **37** under NHK conditions, anticipating that this cyclisation would be relatively facile. A series of functional group interconversions with **37** should then provide access to (+)-*Z*-deoxypukalide **3**. Thus, protection of the known furan aldehyde **32**[21] as its dioxolan **33a**, followed by reduction of the ester group in **33a** and protection of the resulting alcohol **33b** first gave the furanmethanol TBDPS ether **33c**. Deprotonation of **33c**, using *n*-BuLi at −40 °C followed by treatment of the resulting furyllithium species with Me_3SnCl next gave the stannylfuran **34** (Scheme 4). A Stille reaction between **34** and the vinyl iodide **10**, using $Pd(PPh_3)_4$ and CuI in DMF in the presence of Et_3N then led to the adduct **35** in a pleasing 90% yield. Treatment of the adduct **35** with PPh_3-NBS at −78 °C resulted in simultaneous bromination of the allyl alcohol group and deprotection of the dioxolane giving the bromide–aldehyde **36**. When a solution of **36** in THF was stirred in the presence of $CrCl_2$ and 4 Å molecular sieves at room temperature for 16 h, work up and chromatography gave a 63% yield of the *anti*-diastereoisomer **37** of the anticipated macrocyclic homoallylic alcohol, together with smaller amounts of the *syn*-diastereoisomer **38** (9%) and the isomeric *anti*-diastereoisomer **39** (6%).

The relative stereochemistries of the macrocyclic homoallylic alcohols **37**–**39** were determined by the magnitude of the vicinal coupling constants between their H-atoms at C1 and C2 (cembrane ring numbering; Structure **9**), i.e. *J*(H1-H2)>10 Hz(*anti*) and <2 Hz(*syn*) and by comparison of these data with corresponding data recorded for bipinnatin J (**7**)[14,22] (for diastereoisomer **37**) and other bipinnatins.[23]



Scheme 4. Reagents and conditions: (i) L-tartaric acid, $MgSO_4$, ethylene glycol, benzene, reflux, 48 h, 97%; (ii) $LiAlH_4$, Et_2O, rt, 1 h, 89%; (iii) TBDPSCl, imi, DMF, 0 °C, 10 min, rt, 20 min, 74%; (iv) *n*-BuLi, THF, −40 °C, 50 min, Me_3SnCl, −40–0 °C, 1.25 h, 86%; (v) **10**, $Pd(PPh_3)_4$, CuI, Et_3N, DMF, rt, 2 h, 90%; (vi) Ph_3P, NBS, −78 °C, 45 min, 67%; (vii) $CrCl_2$, 4 Å MS, THF, rt, 16 h, 63%.

Table 1
NMR Spectroscopic data for synthetic and natural (+)-*Z*-Deoxypukalide **3**

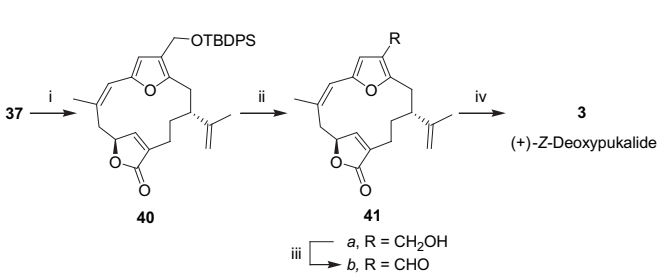
Position	Synthetic deoxypukalide		Natural deoxypukalide	
	^{1}H NMR	^{13}C NMR	^{1}H NMR	^{13}C NMR
1	2.49–2.39, m	42.6, d	2.41, dd (3.5, 14.4)	42.6, d
2α	3.51, dd (13.0, 16.7)	32.3, t	3.48, dd (12.9, 16.7)	32.3, t
2β	2.68, dd (3.6, 16.7)		2.67, dd (3.6, 16.7)	
3		160.7, s		160.7, s
4		115.9, s		115.9, s
5	6.44, s	110.7, d	6.42, s	110.7, d
6		150.6, s		150.6, s
7	6.11, br s	116.8, d	6.10, s	116.8, d
8		130.1, s		130.1, s
9α	3.15, app t (11.8)	39.9, t	3.13, dd (11.8, 11.8)	39.9, t
9β	2.76, dd (4.2, 11.8)		2.75, dd (4.2, 11.9)	
10	5.02 ddt (11.8, 4.0, 1.6)	78.5, d	5.0, dd (4.2, 11.8)	78.5, d
11	6.96, app. t (~1.6)	151.5, d	6.94, s	151.5, d
12		133.3, s		133.3, s
13α	2.16–2.09, m	20.0, t	2.10, m	19.9, t
13β	2.49–2.39, m		2.45, m	
14α	1.81–1.71, m	32.0, t	1.76, m	32.0, t
14β	1.15, ddt (3.6, 1.0, 14.0)		1.12, ddd (3.6, 13.9, 16.9)	
15		144.7, s		144.8, s
16α	4.90, br s	113.5, t	4.89, s	113.5, t
16β	4.95–4.92, m		4.92, dd (1.5, 1.5)	
17	1.76, br s	19.1, q	1.75, s	19.1, q
18		164.1, s		164.1, s
19	2.03, d (1.0)	25.8, q	2.01, s	25.8, q
20		174.2, s		174.2, s
OMe	3.83, s	51.5, q	3.78, s	51.4, q

2.6. Completion of the synthesis of (+)-*Z*-deoxypukalide 3

To complete a synthesis of (+)-*Z*-deoxypukalide **3** from the macrocycle **37**, all that was needed was to reduce the secondary alcohol group in **37** and then oxidise the remaining protected furanmethanol group to the corresponding methoxycarbonyl functionality. Thus, the secondary alcohol group was first reduced using TFA–Et_3SiH in DCM at 0 °C, leading to the deoxy compound **40** in 82% yield (Scheme 5). Deprotection of the TBDPS protecting group in **40** next led to the furanmethanol **41a**, which was then oxidised, using MnO_2 in DCM, to the corresponding aldehyde **41b**. Finally, the aldehyde group in **41b** was converted into the corresponding methoxycarbonyl group, and hence *Z*-(+)-deoxypukalide **3**, using Corey's protocol.[24] The synthetic deoxypukalide was obtained as a colourless powder, mp 133–136 °C, $[\alpha]_D^{27}$ +15.5 (*c* 0.38, $CHCl_3$) Lit.[4] $[\alpha]_D^{20}$ +11.0 (*c* 0.4, $CHCl_3$) whose ^{1}H and ^{13}C NMR spectroscopic data were identical to those reported for the natural product (Table 1).

3. Summary

A concise total synthesis of (+)-*Z*-deoxypukalide **3** isolated recently from the Pacific coral *Leptogorgia* spp. has been achieved. The synthesis features a combination of RCM and CM to prepare the substituted butenolide **10**, and of intermolecular Stille, and intramolecular NHK, coupling reactions to elaborate the advanced intermediate **37**. The synthetic study also highlights a limitation to the use of the intramolecular NHK reaction in instances where an ester function is proximal to the reacting aldehyde group, i.e. substrates **8a** and **8b**.



Scheme 5. Reagents and conditions: (i) TFA, Et_3SiH, DCM, 0 °C, 2.5 h, 82%; (ii) TBAF, THF, 0 °C, 1.5 h, 51%; (iii) MnO_2, DCM, rt, 2 h, 97%; (iv) HOAc, NaCN, MeOH, rt, 1 h, then MnO_2, 21 h, 65%.

4. Experimental

4.1. General

For general experimental details see Ref. 14.

4.2. *Z*-6-Iodo-5-methylhexa-1,5-dien-3-ol (19)

Dess–Martin periodinane (7.50 g, 17.7 mmol) was added in one portion to a stirred solution of (*Z*)-4-iodo-3-methyl-but-3-en-1-ol **18**[15] (2.50 g, 11.8 mmol) and $NaHCO_3$ (4.95 g, 59.0 mmol) in DCM (60 ml) at room temperature, and the mixture was then stirred for 45 min. Saturated aqueous $Na_2S_2O_3$ (15 ml), water (15 ml) and saturated aqueous $NaHCO_3$ (15 ml) were added, and the resulting biphasic mixture was then stirred vigorously for 45 min. The separated aqueous phase was extracted with DCM (3×60 ml) and the combined organic extracts were then dried ($MgSO_4$) and concentrated in vacuo to leave the corresponding aldehyde as colourless oil, which was used without further purification. Vinylmagnesium bromide (35.4 ml, 35.4 mmol, 1.0 M in THF) was added dropwise over 15 min to a stirred solution of the aldehyde in THF (150 ml) at −78 °C under a nitrogen atmosphere, and the mixture was then stirred for 1 h. Water (60 ml) and diethyl ether (60 ml) were added, and the mixture was then warmed to room temperature. The separated aqueous phase was extracted with diethyl ether (3×60 ml) and the combined organic extracts were then dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with a gradient of 20–30% diethyl ether in petroleum ether (product eluted at 30%), to give the

allylic alcohol (1.27 g, 45%) as a colourless oil. ν_{max} ($CHCl_3$ cm^{-1}): 3605, 2945, 2915, 1645, 1614; δ_H (360 MHz; $CDCl_3$): 6.00 (q, 1H, *J* 1.4, IC*H*=C(Me)CH_2), 5.92 (ddd, 1H, *J* 17.1, 10.4 and 6.1, C*H*=CH_2), 5.27 (ddd, 1H, *J* 17.1, 1.3 and 1.3, CH=C*H*H), 5.12 (dd, 1H, *J* 10.4 and 1.3, CH=CH*H*), 4.39–4.31 (m, 1H, C*H*(OH)CH), 2.52 (dd, 1H, *J* 13.5 and 8.2, C=C(Me)C*H*H), 2.42 (dd, 1H, *J* 13.5 and 5.6, C=C(Me)CH*H*), 1.95 (d, 3H, *J* 1.4, ICH=C(*Me*)CH_2), 1.93 (br s, 1H, CH(O*H*)CH); δ_C (90 MHz; $CDCl_3$): 144.3 (s), 140.2 (d), 114.9 (t), 76.9 (d), 71.2 (d), 45.8 (t), 24.5 (q); HRMS (ESI) 209.9520 ($M^+-C_2H_4$, C_5H_7OI requires 209.9542).

4.3. Cyclobut-1-enecarboxylic acid (*Z*)-4-iodo-3-methyl-1-vinyl-but-3-enyl ester (21)

Triethylamine (2.12 ml, 15.2 mmol) was added dropwise over 2 min to a stirred solution of 1-cyclobutene-1-carboxylic acid[25] (1.49 g, 15.2 mmol) and pivaloyl chloride (1.87 ml, 15.2 mmol) in THF (30 ml) at room temperature under a nitrogen atmosphere, and the mixture was then stirred for 30 min. Meanwhile, a solution of LiHMDS (7.61 ml, 7.61 mol, 1.0 M in THF) was added dropwise over 2 min to a stirred solution of the allylic alcohol **19** (1.51 g, 6.34 mmol) in THF (75 ml) at −78 °C under a nitrogen atmosphere, and the mixture was then stirred at −78 °C for 20 min. The solution of the mixed anhydride was filtered quickly and then added dropwise over 15 min to the stirred solution of the allylic alcohol anion at −78 °C under a nitrogen atmosphere. The mixture was stirred at −78 °C for 90 min, and then water (50 ml), saturated aqueous $NaHCO_3$ (50 ml) and diethyl ether (50 ml) were added sequentially, and the mixture was then warmed to room temperature. The separated aqueous phase was extracted with diethyl ether (3×75 ml) and the combined organic extracts were then dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with a gradient of 100% petroleum ether, 5–10% diethyl ether in petroleum ether (product eluted at 10%) to give the *cyclobutene ester* (1.32 g, 65%) as a light yellow oil. ν_{max}/cm^{-1} ($CHCl_3$ solution): 2928, 2852, 2254, 1712, 1647, 1610; δ_H (400 MHz; $CDCl_3$): 6.82 (1H, t, *J* 1.2, C=C*H*CH_2), 6.02 (1H, q, *J* 1.4, IC*H*=C(Me)CH_2), 5.88 (1H, ddd, *J* 17.2, 10.5 and 6.3, C*H*=CH_2), 5.57–5.50 (1H, m, C*H*(O)CH), 5.32 (1H, ddd, *J* 17.2, 1.2 and 1.2, CH=C*H*H), 5.20 (1H, ddd, *J* 10.5, 1.2 and 1.2, CH=CH*H*), 2.77–2.66 (3H, m, C$H_2$$CH_2$CH=C and ICH=C(Me)C*H*H), 2.54–2.45 (3H, m, CH_2CH_2CH=C and ICH=C(Me)CH*H*), 1.94 (3H, d, *J* 1.4, ICH=C(*Me*)CH_2); δ_C (100 MHz; $CDCl_3$): 161.2 (s), 147.0 (d), 143.2 (s), 138.5 (s), 135.7 (d), 117.0 (t), 77.5 (d), 72.1 (d), 43.2 (t), 29.1 (t), 27.1 (t), 24.2 (q); *m*/*z* (ESI) found 341.0017 ($M+Na^+$, $C_{12}H_{15}O_2INa$ requires 341.0009).

4.4. (±)-3-((*Z*)-5-Hydroxy-4-methyl-(*E*)-pent-3-enyl)-5-((*Z*)-3-iodo-2-methyl-allyl)-5*H*-furan-2-one (10)

A solution of Grubbs' second generation catalyst (467 mg, 0.55 mmol) in DCM (10 ml), and a solution of the (±)-cyclobutene ester **21** (1.75 g, 5.50 mmol) and 2-methyl-2-propen-1-ol (0.93 ml, 11.0 mmol) in DCM (10 ml) were added simultaneously over 8 h to a refluxing solution of DCM (1.75 l) under a nitrogen atmosphere. 2-Methyl-2-propen-1-ol (3.70 ml, 44.0 mmol) was added dropwise over 1 h, and the mixture was then stirred under reflux for 12 h. The mixture was cooled to room temperature and then concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with 50% ethyl acetate in petroleum ether, to give a 7:1 mixture of *E*/*Z*-isomers of the known allylic alcohol[14,16] (1.13 g, 57%) as a yellow oil. δ_H (400 MHz; $CDCl_3$): (*E*-isomer) 7.11 (1H, q, *J* 1.4, C*H*=CCH_2), 6.11 (1H, q, *J* 1.4, IC*H*=C(Me)CH_2), 5.44–5.34 (1H, m, C*H*=C(Me)CH_2), 5.05 (1H, ddd, *J* 7.4, 6.1 and 1.4, C*H*(O)CH), 3.99 (2H, br s, CH_2OH), 2.66 (1H, dd, *J* 13.6 and 6.1, ICH=C(Me)C*H*H), 2.54 (1H, dd, *J* 13.6 and 7.4, ICH=C(Me)CH*H*), 2.41–2.25 (4H, m, CH_2CH=C and C$H_2$$CH_2$CH=C), 1.98 (3H, d, *J* 1.4, ICH=C(*Me*)CH_2), 1.77 (1H, br s, CH_2O*H*), 1.66 (3H, br s, CH=C(*Me*)CH_2); δ_C (100 MHz): 173.4 (s), 147.8 (d), 142.3 (s), 136.2 (s), 133.9 (s), 123.8 (d), 79.4 (d), 78.5 (d), 68.4 (t), 42.4 (t), 25.3 (t), 25.0 (t), 24.8 (q), 13.7 (q). HRMS (ESI) 385.0274 ($M+Na^+$, $C_{14}H_{19}IO_3Na$ requires 385.0276).

4.5. (*S*)-3-((*E*)-5-Hydroxy-4-methyl-pent-3-enyl)-5-((*E*)-3-iodo-2-methylallyl)-5*H*-furan-2-one (11)

The furanone was prepared starting from *S*-pent-4-yne-1, 2-diol **12**, and proceeded via the *E*-iodoalkene **15**, using the same sequence of reactions that have been published for the synthesis of the corresponding *Z*-iodoalkene-substituted furanone **10**[14]; $[\alpha]_D^{25}$ +26.5 (*c* 0.8, $CHCl_3$); ν_{max} (film)/cm^{-1} 1753; δ_H (360 MHz; $CDCl_3$) 7.02 (1H, q, *J* 1.5, CHC*H*=), 6.11 (1H, q, *J* 1.5, IC*H*=), 5.36–5.39 (1H, m, =C*H*CH_2), 5.0–5.03 (1H, m, C*H*CH=), 4.0 (2H, CH_2O), 2.54–2.57 (2H, m), 2.3–2.55 (4H, m), 2.0 (1H, O*H*), 1.91 (3H, ICH=C*Me*), 1.65 (3H, =C*Me*); δ_C (90 MHz; $CDCl_3$) 173.3 (s), 147.6 (d), 142.0 (s), 136.3 (s), 134.2 (s), 123.5 (d), 79.2 (d), 79.0 (d), 68.2 (t), 42.8 (t), 25.4 (t), 25.0 (t), 24.5 (q), 13.7 (q). HRMS (ESI) 385.0284 ($M+Na^+$, $C_{14}H_{19}IO_3Na$ requires 385.0276).

4.6. Methyl 5-bromo-2-hydroxymethyl-3-furanoate (25)

N-Bromosuccinimide (4.9 g, 27.5 mmol) was added to a solution of methyl 2-methyl-3-furancarboxylate **23** (3.5 g, 25 mmol) in DMF (7 ml) at 0 °C, and the mixture was then stirred at 0 °C for 10 min under a nitrogen atmosphere. The mixture was warmed to 25 °C over 20 min, and then heated at 50 °C for 30 min. The cooled mixture was quenched with diethyl ether and water, and the separated aqueous layer was then extracted with diethyl ether. The combined ether extracts were evaporated in vacuo and the residue was purified by chromatography on silica, eluting with petroleum ether–ethyl acetate (20:1), to give methyl 5-bromo-2-methyl-3-furancarboxylate **24a** (5 g, 91%) as a pale yellow oil, δ_H (400 MHz; $CDCl_3$) 6.56 (1H, s, =C*H*), 3.80 (3H, s, O*Me*), 2.58 (3H, s, Me), which was used immediately. A stirred solution of the 5-bromofuran (5 g) in carbon tetrachloride (80 ml) containing *N*-bromosuccinimide (4.5 g) and AIBN (190 mg) was heated at 50 °C overnight and then cooled to room temperature. The mixture was filtered and the filtrate was washed with water (3×10 ml), dried (Na_2SO_4) and evaporated in vacuo to leave the furanmethyl bromide **24b** (98%), δ_H (400 MHz; $CDCl_3$) 6.66 (1H, s, =C*H*), 4.80 (2H, s, CH_2Br), 3.91 (3H, s, O*Me*), as a pale yellow oil. A mixture of **24b** (6 g, 20.1 mmol) and saturated aqueous K_2CO_3 (33 ml) in THF (17 ml) and DMF (33 ml) was heated at 50 °C overnight, then cooled to room temperature and extracted with ethyl acetate (3×70 ml). The combined organic extracts were dried ($MgSO_4$) and then evaporated in vacuo. The residue was purified by chromatography on silica, eluting with petroleum ether–ethyl acetate (5:1), to give the *furanmethanol* (2.0 g, 42%) as a colourless oil, δ_H (360 MHz; $CDCl_3$) 6.60 (1H, s, =C*H*), 4.76 (2H, d, *J* 7.1, CH_2OH), 3.86 (3H, s, O*Me*), 3.54 (1H, br t, *J* ~7, CH_2O*H*); δ_C (100 MHz; $CDCl_3$) 163.7 (s), 162.4 (s), 121.8 (s), 117.2 (s), 112.1 (d), 56.9 (t), 52.2 (q); HRMS (ESI) 256.9416 ($M+Na^+$, $C_7H_7BrO_4Na$ requires 256.9425).

4.7. Methyl 5-(tri-*n*-butylstannyl)-2-formyl-3-furanoate (27)

Manganese dioxide (2.5 g, 28.8 mmol) was added to a solution of the furanmethanol **25** (0.5 g, 2.1 mmol) in dry dichloromethane (30 ml) and the mixture was stirred at room temperature for 2 h, and then filtered through Celite. The filtrate was evaporated in vacuo to leave the corresponding furan aldehyde **26** (0.48 g, 96%) as a viscous oil, δ_H (360 MHz; $CDCl_3$) 10.10 (1H, s, C*H*O), 6.85 (1H, s,

=C*H*), 3.96 (3H, s, O*Me*); δ_C (100 MHz; $CDCl_3$) 178.0 (d), 161.5 (s), 153.0 (s), 132.2 (s), 127.5 (s), 125.0 (d), 53.0 (q); HRMS (ESI) 254.9257 ($M+Na^+$, $C_7H_5BrO_4Na$ requires 254.9269), which was used immediately. $Pd_2(dba)_3$ (94 mg, 5% equiv) and Ph_3As (110 mg) were added to a solution of **26** (0.48 g, 2.1 mmol) in NMP (10 ml), which had been degassed with argon three times. The mixture was again degassed with argon three times, and then hexabutyldistannane (1.43 g, 2.1 mmol) was added via syringe under an argon atmosphere. The mixture was heated at 80 °C for 1 h, then cooled and filtered through Celite using petroleum ether–diethyl ether (5:1) as eluent. The filtrate was washed with water, then dried (K_2CO_3) and evaporated. The residue was purified by chromatography on Florisil, eluting with petroleum ether–diethyl ether (10:1) to give the *stannylfuran* (0.2 g, 21%) as a colourless oil, ν_{max} (film)/cm^{-1} 1727, 1681, 1577; δ_H (500 MHz; $CDCl_3$) 10.2 (1H, s, C*H*O), 7.0 (1H, s, =C*H*), 3.9 (3H, s, O*Me*), 1.7–1.5 (6H, m), 1.4–1.3 (6H, m), 1.2–1.15 (6H, m), 0.9 (9H, t, *J* 7, *Me*); δ_C (100 MHz; $CDCl_3$) 178.6 (d), 170.9 (s), 162.8 (s), 157.1 (s), 126.2 (s), 123.8 (d), 52.4 (q), 28.8 (t), 27.3 (t), 13.6 (t), 10.5 (q).

4.8. 2-Formyl-5-{(*Z*)-3-[(*S*)-4-((*E*)-5-hydroxy-4-methyl-pent-3-enyl)-5-oxo-2,5-dihydro-furan-2-yl]-2-methyl-propenyl}-furan-3-carboxylic acid methyl ester (28)

A solution of the enantiomerically pure vinyl iodide **10**[14] (100 mg, 0.28 mmol) and the furanylstannane **27** (184 mg, 0.41 mmol) in DMF (2 ml) was degassed with argon for 30 min and then added via cannula to a stirred mixture of $Pd(PPh_3)_4$ (13 mg, 0.011 mmol), CuI (4.2 mg, 0.022 mmol) and CsF (84 mg, 0.56 mmol) at room temperature. The resulting yellow mixture was stirred at room temperature for 20 min, whereupon the colour of the mixture changed to brown, first, then dark green. The mixture was poured into a mixture of a saturated solution of aqueous NH_4Cl (6 ml) and Et_2O (6 ml), and the separated aqueous layer was then extracted with Et_2O (3×6 ml). The combined organic extracts were washed with brine (2 ml), then dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography on silica, eluting with petroleum ether–ethyl acetate (1:1), to give the *alkenylfuran* (67 mg, 63%) as a viscous orange oil, δ_H (360 MHz; $CDCl_3$) 10.13 (1H, s, C*H*O), 7.36 (1H, q, *J* 1.3, H-11), 6.62 (1H, s, H-5), 6.23 (1H, br s, H-7), 5.45–5.41 (1H, m, H-1), 5.16–5.11 (1H, m, H-10), 4.02 (2H, d, *J* 6.3, H-16), 3.95 (3H, s, O*Me*), 3.26 (1H, dd, *J* 3.1 and 13.9, H-9α), 2.44–2.30 (5H, m, H-9β, H-13 and H-14), 2.08 (3H, d, *J* 1.4, Me-19), 1.78 (1H, t, *J* 6.3, O*H*), 1.68 (3H, s, Me-17); δ_C (90 MHz, $CDCl_3$) 178.2 (d), 173.7 (s), 161.8 (s), 156.5 (s), 150.5 (s), 148.8 (d), 143.4 (s), 136.4 (s), 133.6 (s), 127.6 (s), 123.8 (d), 114.7 (d), 110.8 (d), 81.3 (d), 68.5 (t), 52.5 (q), 38.3 (t), 26.8 (q), 25.3 (t), 24.8 (t), 13.7 (q); HRMS (ESI) 411.1415 ($M+Na^+$, $C_{21}H_{24}O_7Na$ requires 411.1419).

4.9. Methyl 2-formyl-5-((*E*)-3-((*S*)-4-((*E*)-5-hydroxy-4-methylpent-3-enyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-methylprop-1-enyl)furan-3-carboxylate (29)

The alkenylfuran was prepared using a Stille coupling reaction between the *E*-$\Delta^{7,8}$ vinyl iodide **11** and the furanylstannane **27**, using the same reaction conditions that had been used to synthesise the corresponding *Z*-$\Delta^{7,8}$–alkenylfuran **28**; ν_{max} (film)/cm^{-1} 1753, 1728, 1670; δ_H (500 MHz; $CDCl_3$) 10.13 (1H, s, C*H*O), 7.06 (1H, s, H-11), 6.69 (1H, s, H-5), 6.22 (1H, br s, H-7), 5.35–5.37 (1H, m, H-1), 5.06–5.08 (1H, m, H-10), 3.94 (2H, d, *J* 6, H-16), 3.92 (3H, s, O*Me*) 2.50–2.65 (2H, m, H-9), 2.28–2.34 (4H, m), 2.30 (3H, s, Me-19), 1.62 (3H, s, Me-17); δ_C (100 MHz; $CDCl_3$) 178.2 (d), 173.2 (s), 162.0 (s), 156.3 (s), 150.1 (s), 147.5 (d), 140.8 (s), 136.3 (s), 134.4 (s), 127.6 (s), 123.4 (d), 116.3 (d), 111.0 (d), 79.2 (d), 68.2 (t), 52.5 (q), 44.7 (t), 25.3 (t), 25.0 (t), 17.8 (q), 13.7 (q).

4.10. 5-{(*Z*)-3-[(*S*)-4-((*E*)-5-Bromo-4-methyl-pent-3-enyl)-5-oxo-2,5-dihydro-furan-2-yl]-2-methyl-propenyl}-2-formyl-furan-3-carboxylic acid methyl ester (8a)

Triphenylphosphine (50 mg, 0.19 mmol) and *N*-bromosuccinimide (34 mg, 0.19 mmol) were added to a stirred solution of the allylic alcohol **28** (67 mg, 0.17 mmol) in DCM (3.7 ml) at 0 °C, and the mixture was stirred at 0 °C for 20 min, and then poured into water (1.5 ml). The separated aqueous layer was extracted with DCM (2×5 ml), and the combined organic extracts were then dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography on silica, eluting with petroleum ether–ethyl acetate (4:1), to give the corresponding *allyl bromide* (52 mg, 67%) as a pale yellow oil. ν_{max} (film)/cm^{-1} 1756, 1727, 1670; δ_H (360 MHz; $CDCl_3$) 10.15 (1H, s, C*H*O), 7.32 (1H, q, *J* 1.4, H-11), 6.62 (1H, s, H-5), 6.24 (1H, br s, H-7), 5.58 (1H, t, *J* 6.5, H-1), 5.16–5.11 (1H, m, H-10), 3.96 (2H, s, H-16), 3.95 (3H, s, O*Me*), 3.23 (1H, dd, *J* 3.5 and 14.0, H-9α), 2.49 (1H, dd, *J* 8.7 and 14.0, H-9β), 2.42–2.27 (4H, m, H-13 and H-14), 2.09 (3H, d, *J* 1.3, Me-19), 1.76 (3H, s, Me-17); δ_C (90 MHZ; $CDCl_3$) 178.0 (d), 173.5(s), 161.9 (s), 156.3 (s), 150.6 (s), 148.9 (d), 143.0 (s), 133.6 (s), 133.3 (s), 129.3 (d), 127.4 (s), 114.8 (d), 110.7 (d), 81.2 (d), 52.5 (q), 41.1 (t), 38.3 (t), 26.8 (q), 26.0 (t), 24.6 (t), 14.7 (q); HRMS (ESI) 473.0571 ($M+Na^+$, $C_{21}H_{23}BrO_6Na$ requires 473.0575).

4.11. Methyl 5-((*E*)-3-((*S*)-4-((*E*)-5-bromo-4-methylpent-3-enyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-methylprop-1-enyl)-2-formylfuran-3-carboxylate (8b)

The *E*-$\Delta^{7,8}$-isomer was prepared from **29** using the same reagents and reaction conditions as those used to convert **28** into the corresponding *Z*-$\Delta^{7,8}$–isomer (**8a**); ν_{max} (film)/cm^{-1} 1755, 1730, 1672; δ_H (360 MHz; $CDCl_3$) 10.13 (1H, s, C*H*O), 7.02–7.05 (1H, s, H-11), 6.65–6.67 (1H, s, H-5), 6.23 (1H, br s, H-7), 5.50–5.60 (1H, m, H-1), 5.05–5.09 (1H, m, H-10), 3.90 (2H, s, H-16), 3.93 (3H, s, O*Me*), 2.50–2.62 (2H, m, H-9), 2.20–2.50 (4H, m, H-13, H-14), 2.16 (3H, s, Me-19), 1.74 (3H, s, Me-17); δ_C (90 MHz; $CDCl_3$) 178.2 (d), 172.9 (s), 161.9 (s), 156.3 (s), 150.2 (s), 147.7 (d), 140.8 (s), 133.8 (s), 133.7 (s), 129.1 (d), 127.5 (s), 116.2 (d), 111.0 (d), 79.2 (d), 52.5 (q), 44.7 (t), 41.0 (t), 25.8 (t), 24.6 (t), 19.1 (q), 14.7 (q).

4.12. (*E*)-(5*S*,11*S*,12*S*)-12-Hydroxy-11-isopropenyl-3-methyl-7-oxo-6,16-dioxa-tricyclo[11.2.1.1^{5,8}]heptadeca-1(15),2,8(17),13-tetraene-14-carboxylic acid methyl ester (31)

A solution of the bromoaldehyde (**8b**) (136 mg) in THF was treated with $CrCl_2$-4 Å MS, under the same conditions as those used to convert **36** into **37**. Work up and chromatography on Florisil, eluting with petroleum ether–ethyl acetate (3:2), gave the *E*-$\Delta^{7,8}$-alkene **31** (7 mg, 6%) as a pale yellow oil ν_{max} (film/cm^{-1}) 1756; δ_H (500 MHz; $CDCl_3$) 7.05 (1H, t, *J* 1.5, H-11), 6.42 (1H, s, H-5), 6.02 (1H, br s, H-7), 5.2 (1H, br, H-10), 5.05 (1H, m, H-16α), 5.0 (1H, br s, H-16β), 4.9 (1H, dd, *J* 10 and 3, H-2), 3.88 (3H, s, OMe), 3.05 (1H, dd, *J* 12 and 4, H-9α), 2.83 (1H, t, *J* 12, H-9β), 2.4–2.0 (2H, m, H-13α and H-1), 2.15–2.10 (1H, m, H-13β), 1.91 (3H, s, Me-19), 1.87 (3H, s, Me-17), 1.75–1.70 (1H, m, H-14α), 0.98–0.85 (1H, m, H-14β); δ_C (125 MHz, $CDCl_3$) 173.4 (s), 164.5 (s), 159.7 (s), 149.7 (d), 145.4 (s), 144.0 (s), 137.4 (s), 135.3 (s), 117.8 (d), 117.3 (s), 115.6 (t), 108.3 (d), 78.6 (d), 66.1 (d), 51.8 (q), 50.5 (d), 40.7 (t), 25.7 (t), 23.9 (q), 23.6 (t), 17.3 (q); HRMS (ESI) 395.1468 ($M+Na^+$, $C_{21}H_{24}O_6Na$ requires 395.1465).

4.13. 2-[1,3]Dioxolan-2-yl-furan-3-carboxylic acid methyl ester (33a)

Following the procedure developed by Lu et al.,[26] ethylene glycol (3.47 g, 55.9 mmol) was added dropwise, over 10 min, to

a vigorously stirred solution of the furfural **32**[21] (2.15 g, 14.0 mmol), L-tartaric acid (52 mg, 0.35 mmol) and anhydrous $MgSO_4$ (3.35 g, 27.9 mmol) in benzene (49 ml) in a 100 ml flash, equipped with a Dean and Stark adaptor and a condenser. The mixture was heated under reflux for 44 h and the progress of the reaction was monitored by ^{1}H NMR spectroscopy. Further amounts of L-tartaric acid (26 mg, 0.18 mmol), anhydrous $MgSO_4$ (1.68 g, 14.0 mmol) and ethylene glycol (1.74 g, 28.0 mmol) were added, and the mixture was heated under reflux for a further 4 h. The mixture was cooled to room temperature. Solid $NaHCO_3$ (44 mg) was added, and the resulting mixture was stirred for 30 min before it was filtered through a thin layer of $NaHCO_3$, and washed with DCM (150 ml). The filtrate was evaporated in vacuo to leave the *dioxolane* (2.69 g, 97%) as an oil. ν_{max} (film)/cm^{-1} 1723; δ_H (400 MHz; $CDCl_3$) 7.38 (1H, d, *J* 1.9, C*H*=CHCCO$_2$Me), 6.70 (1H, d, *J* 1.9, CH=C*H*CCO$_2$Me), 6.55 (1H, s, OC*H*O), 4.26–4.18 (2H, m, CH_2), 4.10–4.03 (2H, m, CH_2), 3.85 (3H, s, O*Me*); δ_C (100 MHZ; $CDCl_3$) 163.1 (s), 155.5 (s), 142.4 (d), 117.2 (s), 110.9 (d), 95.6 (d), 65.6 (2×t), 51.8 (q); HRMS (ESI) 221.0421 (M+Na$^+$, $C_9H_{10}O_5Na$ requires 221.0426).

4.14. (2-[1,3]Dioxolan-2-yl-furan-3-yl)-methanol (33b)

A solution of the ester **33a** (2.69 g, 13.6 mmol) in anhydrous diethyl ether (27 ml) was added dropwise, over 10 min, to maintain a steady reflux, to a stirred suspension of lithium aluminium hydride (671 mg, 17.7 mmol) in anhydrous diethyl ether (44 ml) under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h, and then quenched carefully with water (0.67 ml), followed by aqueous NaOH (20% w/w, 0.67 ml) and water (3×0.67 ml). The mixture was stirred at room temperature for a further 1 h and then filtered. The filtrate was dried (Na_2SO_4) and concentrated in vacuo to leave the *alcohol* (2.05 g, 89%) as a yellow oil. ν_{max} (film)/cm^{-1} 3385; δ_H (400 MHz; $CDCl_3$) 7.36 (1H, br s, C*H*=CHCCH$_2$OH), 6.40 (1H, br s, CH=C*H*CCH$_2$OH), 5.96 (1H, s, OC*H*O), 4.56 (2H, br s, CH_2OH), 4.19–4.11 (2H, m, CH_2), 4.06–3.97 (2H, m, CH_2), 2.46 (1H, br s, O*H*); δ_C (90 MHZ; $CDCl_3$) 146.2 (s), 142.5 (d), 124.2 (s), 111.5 (d), 97.3 (d), 65.2 (2×t), 55.8 (t); HRMS (ESI) 193.0482 (M+Na$^+$, $C_8H_{10}O_4Na$ requires 193.0477).

4.15. *tert*-Butyl-(2-[1,3]dioxolan-2-yl-furan-3-ylmethoxy)-diphenyl-silane (33c)

tert-Butyldiphenylsilyl chloride (10.0 g, 36.4 mmol) and imidazole (2.70 g, 39.7 mmol) were added to a stirred solution of the alcohol **33b** (5.62 g, 33.1 mmol) in DMF (11 ml) at 0 °C. The mixture was stirred at 0 °C for 10 min and then at room temperature for 20 min before it was diluted with diethyl ether (10 ml). The mixture was then evaporated with silica (ca. 10.0 g) before it was purified by chromatography on silica, eluting with petroleum ether–diethyl ether (9:1), to give the *silyl ether* (10.0 g, 74%) as a colourless solid, mp 64–68 °C. (Found: C, 70.6; H, 7.2. $C_{24}H_{28}O_4Si$ requires C, 70.5; H, 6.9%); ν_{max} (film)/cm^{-1} 3071, 2998, 1428, 703; δ_H (360 MHz; $CDCl_3$) 7.73–7.71 (4H, m, TBDPS), 7.48–7.38 (7H, m, TBDPS, OC*H*=CH), 6.43 (1H, d, *J* 1.8, OCH=C*H*), 5.91 (1H, s, O–C*H*–O), 4.71 (2H, s, CH_2OTBDPS), 4.09–4.02 (2H, m, CH_2), 3.95–3.91 (2H, m, CH_2), 1.09 (9H, s, TBDPS); δ_C (90 MHZ; $CDCl_3$) 145.1 (s), 142.4 (d), 135.5 (4×d), 133.3 (2×s), 129.7 (2×d), 127.7 (4×d), 124.4 (s), 111.0 (d), 96.9 (d), 65.1 (2×t), 57.4 (t), 26.7 (3×q), 19.2 (s); HRMS (ESI) 431.1634 (M+Na$^+$, $C_{24}H_{28}O_4SiNa$ requires 431.1655).

4.16. *tert*-Butyl-(2-[1,3]dioxolan-2-yl-5-trimethylstannanyl-furan-3-ylmethoxy)-diphenyl-silane (34)

A solution of *n*-BuLi (2.5 M) in hexane (2.64 ml, 6.60 mmol) was added dropwise over 3 min to a stirred solution of the furan **33c** (1.79 g, 4.40 mmol) in anhydrous THF (52 ml) at −40 °C under a nitrogen atmosphere. The resulting suspension was stirred at −40 °C for 50 min and then a solution of trimethyltin chloride (1.05 g, 5.28 mmol) in anhydrous THF (20 ml) was added dropwise over 10 min. The mixture was warmed to 0 °C over 1.25 h and then a saturated solution of aqueous NH_4Cl (30 ml) was added. The separated aqueous extract was extracted with diethyl ether (70 ml) and the combined organic extracts were then dried (Na_2SO_4) and concentrated in vacuo. The oily residue of the *stannylfuran* (2.17 g, 86%) was left under high vacuum for 48 h to remove residual Me_3SnCl, and then used without further purification. ν_{max} (film)/cm^{-1} 3071, 2930, 1472, 1428, 703; (360 MHz; $CDCl_3$) 7.74–7.69 (4H, m, TBDPS), 7.44–7.37 (6H, m, TBDPS), 6.53 (1H, s, OC=C*H*), 5.94 (1H, s, O–C*H*–O), 4.68 (2H, s, CH_2OTBDPS), 4.07–4.01 (2H, m, CH_2), 3.97–3.90 (2H, m, CH_2), 1.07 (9H, s, TBDPS), 0.33 (9H, s, Sn*Me*$_3$); δ_C (90 MHZ; $CDCl_3$) 161.1 (s), 149.9 (s), 135.6 (4×d), 134.8 (s), 133.5 (s), 129.6 (2×d), 127.7 (4×d), 124.0 (s), 122.4 (d), 97.3 (d), 65.1 (2×t), 57.5 (t), 26.8 (3×q), 19.2 (s), −9.02 (3×q); HRMS (ESI) 595.1289 (M+Na$^+$, $C_{27}H_{36}O_4SiSnNa$ requires 595.1302).

4.17. (*S*)-5-{(*Z*)-3-[4-(*tert*-Butyl-diphenyl-silanyloxymethyl)-5-[1,3]dioxolan-2-yl-furan-2-yl]-2-methyl-allyl}-3-((*E*)-5-hydroxy-4-methyl-pent-3-enyl)-5*H*-furan-2-one (35)

A solution of the (+)-vinyl iodide **10** (865 mg, 2.39 mmol) and the furanylstannane **34** (2.73 g, 4.78 mmol) in anhydrous DMF (12 ml) was degassed with nitrogen for 30 min and then added via cannula to a stirred mixture of $Pd(PPh_3)_4$ (276 mg, 0.24 mmol), CuI (91 mg, 0.48 mmol), Et_3N (241 mg, 0.33 ml, 2.39 mmol) was added dropwise via a syringe over 2 min and the resulting mixture was stirred at room temperature for 2 h. The mixture was poured into a saturated solution of aqueous NH_4Cl (50 ml) and diethyl ether (50 ml). The separated aqueous layer was then extracted with diethyl ether (50 ml) and the combined organic extracts were dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography on silica, neutralised with 3% Et_3N in petroleum ether (300 ml), eluting with petroleum ether–ethyl acetate (2:1), to give the *allylic alcohol–aldehyde* (1.38 g, 90%) as a viscous oil. $[\alpha]_D^{25}$ +52.1 (*c* 1.41, $CHCl_3$); ν_{max} (film)/cm^{-1} 3483, 1756; δ_H (400 MHz; $CDCl_3$) 7.70–7.68 (4H, m, Ph), 7.47–7.37 (6H, m, Ph), 7.05 (1H, br s, H-11), 6.18 (1H, s, H-5), 6.15 (1H, br s, H-7), 5.87 (1H, s, C*H*(OCH$_2$CH$_2$O)), 5.38–5.35 (1H, m, H-1), 5.17–5.13 (1H, m, H-10), 4.65 (2H, s, H-18), 4.07–3.99 (2H, m, OCH_2CH$_2$O), 3.95 (2H, br s, H-16), 3.97–3.91 (2H, m, OCH$_2$CH_2O), 2.88 (1H, dd, *J*, 13.5 and 7.0, H-9α), 2.82 (1H, dd, *J* 13.5 and 6.9, H-9β), 2.37–2.33 (2H, m, H-13), 2.29–2.24 (2H, m, H-14), 1.97 (3H, d, *J* 1.2, Me-19), 1.78–1.66 (1H, m, OH), 1.63 (3H, s, Me-17), 1.07 (9H, s, TBDPS); δ_C (100 MHZ; $CDCl_3$) 173.7 (s), 152.1 (s), 148.5 (d), 144.1 (s), 136.2 (s), 135.5 (4×d), 133.7 (s), 133.3 (2×s), 133.0 (s), 129.8 (2×d), 127.8 (4×d), 125.9 (s), 124.0 (s), 117.0 (d), 110.0 (d), 96.9 (d), 80.7 (d), 68.5 (t), 65.3 (2×t), 57.4 (t), 37.8 (t), 26.8 (3×q), 26.3 (q), 25.4 (t), 25.2 (t), 19.2 (s), 13.7 (q); HRMS (ESI) 665.2889 (M+Na$^+$, $C_{38}H_{46}O_7SiNa$ requires 665.2910).

4.18. 5-{(*Z*)-3-[(*S*)-4-((*E*)-5-Bromo-4-methyl-pent-3-enyl)-5-oxo-2,5-dihydro-furan-2-yl]-2-methyl-propenyl}-3-(*tert*-butyl-diphenyl-silanyloxymethyl)-furan-2-carbaldehyde (36)

Triphenylphosphine (1.07 g, 4.07 mmol) and *N*-bromosuccinimide (725 mg, 4.07 mmol) were added to a stirred solution of the (+)-alcohol **35** (1.19 g, 1.85 mmol) in DCM (110 ml) at −78 °C. The mixture was stirred at −78 °C for 45 min, then poured into water (30 ml), and allowed to warm to 0 °C. The separated aqueous layer was extracted with DCM (2×100 ml), and the combined organic extracts were then dried (Na_2SO_4) and concentrated in vacuo. The

residue was purified by flash chromatography on silica, eluting with petroleum ether–ethyl acetate (5:1), to give the *allyl bromide* (818 mg, 67%) as a yellow viscous oil. $[\alpha]_D^{29}$ +31.5 (*c* 1.1 $CHCl_3$); ν_{max} (film)/cm^{-1} 1757; δ_H (400 MHz; $CDCl_3$) 9.65 (1H, s, C*H*O), 7.68–7.66 (4H, m, Ph), 7.48–7.38 (6H, m, Ph), 7.27 (1H, s, H-11), 6.37 (1H, s, H-5), 6.22 (1H, br s, H-7), 5.57 (1H, t, *J* 6.7, H-1), 5.16–5.13 (1H, m, H-10), 4.90 (2H, s, H-18), 3.95 (2H, s, H-16), 3.21 (1H, dd, *J* 4.1 and 13.9, H-9a), 2.53 (1H, dd, *J* 8.4 and 13.9, H-9β), 2.40–2.28 (4H, m, H-13 and H-14), 2.07 (3H, d, *J* 1.2, Me-19), 1.75 (3H, s, Me-17), 1.09 (9H, s, TBDPS); δ_C (100 MHZ; $CDCl_3$) 176.9 (d), 173.5 (s), 156.7 (s), 149.0 (d), 146.3 (s), 141.3 (s), 139.4 (s), 135.4 (4×d), 133.6 (s), 133.2 (s), 132.6 (2×s), 130.0 (2×d), 129.3 (d), 127.9 (4×d), 115.7 (d), 111.2 (d), 81.3 (d), 58.2 (t), 41.1 (t), 38.2 (t), 26.7 (q), 26.7 (3×q), 26.0 (t), 24.7 (t), 19.2 (s), 14.8 (q); HRMS (ESI) 683.1795 ($M+Na^+$, $C_{36}H_{41}BrO_5SiNa$ requires 683.1804).

4.19. (*Z*)-(5S,11S,12S)-14-(*tert*-Butyl-diphenyl-silanyloxymethyl)-12-hydroxy-11-isopropenyl-3-methyl-6,16-dioxa-tricyclo[11.2.1.1^{5,8}]heptadeca-1(15),2,8(17),13-tetraen-7-one (37)

A solution of the (+)-bromoaldehyde **36** (409 mg, 0.62 mmol) in anhydrous THF (453 ml) was degassed with nitrogen for 1 h at room temperature, and then added via a cannula to a mixture of 4 Å MS (activated powder, 2.93 g) and anhydrous $CrCl_2$ (1.53 g, 12.4 mmol) at room temperature under an argon atmosphere. The resulting green coloured mixture was stirred at 25 °C for 16 h and then filtered through Celite. The filtrate was concentrated in vacuo and the residue was diluted with diethyl ether (260 ml), and then washed with water (2×35 ml) and brine (17 ml). The separated organic extract was dried (Na_2SO_4) and concentrated in vacuo to leave a residue, which was purified by chromatography on silica, eluting with petroleum ether–ethyl acetate (10:1), to give (i) the *C*-2β-*hydroxy epimer* **37** (227 mg, 63%) as a foaming oil. $[\alpha]_D^{27}$ −54.0 (*c* 0.8, $CHCl_3$); ν_{max} (film)/cm^{-1} 3457, 1756; δ_H (400 MHz; $CDCl_3$) 7.72–7.68 (4H, m, Ph), 7.49–7.38 (6H, m, Ph), 6.88 (1H, t, *J* 1.5, H-11), 6.18 (1H, s, H-5), 6.16 (1H, br s, H-7), 5.13–5.12 (1H, m, H-16β), 5.02 (1H, br s, H-16α), 5.03–4.99 (1H, m, H-10), 4.62 (2H, s, H-18), 4.50 (1H, d, *J* 11.0, H-2), 3.20 (1H, t, *J* 11.8, H-9β), 2.75 (1H, dd, *J* 4.3 and 11.8, H-9α), 2.44–2.35 (2H, m, H-13β and H-1), 2.10–2.05 (1H, m, H-13α), 2.03 (3H, d, *J* 1.0, Me-19), 1.83 (1H, br s, O*H*), 1.72 (3H, s, Me-17), 1.57 (1H, tdd, *J* 3.3, 11.1 and 14.1, H-14β), 1.07 (9H, s, TBDPS), 0.91 (1H, m, H-14α); δ_C (100 MHz; $CDCl_3$) 174.2 (s), 152.2 (d), 151.2 (s), 149.9 (s), 142.1 (s), 135.6 (4×d), 133.2 (s), 133.1 (s), 132.6 (s), 129.9 (d), 129.8 (d), 129.4 (s), 127.8 (2×d), 127.7 (2×d), 125.4 (s), 118.3 (t), 117.4 (d), 111.9 (d), 78.6 (d), 65.3 (d), 57.6 (t), 50.5 (d), 39.8 (t), 30.1 (t), 26.8 (3×q), 25.8 (q), 19.6 (t), 19.1 (s), 17.6 (q); HRMS (ESI) 605.2712 ($M+Na^+$, $C_{36}H_{42}O_5SiNa$ requires 605.2699); (ii) the *C*-2α-*hydroxy epimer* **38** (33 mg, 9%): δ_H (400 MHz; $CDCl_3$) 7.69–7.66 (4H, m, Ph), 7.47–7.36 (6H, m, Ph), 6.98 (1H, t, *J* 1.6, H-11), 6.10 (1H, br s, H-7), 6.04 (1H, s, H-5), 5.09–5.06 (1H, m, H-16β), 5.05–4.99 (1H, m, H-10), 4.91 (1H, br s, H-16α), 4.93 (1H, br s, H-2), 4.75 (1H, d, *J* 12.8, H-18α), 4.71 (1H, d, *J* 12.8, H-18β), 3.37 (1H, d, *J* 4.7, O*H*), 3.06 (1H, t, *J* 11.8, H-9β), 2.74 (1H, dd, *J* 4.4 and 11.8, H-9α), 2.44–2.33 (2H, m, H-13β, H-1), 2.23–2.16 (1H, m, H-13α), 2.00 (3H, br s, Me-19), 1.86 (3H, s, Me-17), 2.02–1.97 (1H, m, H-14α), 1.23–1.13 (1H, m, H-14β), 1.06 (9H, s, TBDPS); (iii) the *diastereoisomer* **39** (20 mg, 6%): δ_H (400 MHz; $CDCl_3$) 7.71–7.66 (4H, m, Ph), 7.47–7.37 (6H, m, Ph), 7.18 (1H, br s, H-11), 6.07 (1H, br s, H-7), 5.99 (1H, s, H-5), 5.12 (1H, t, *J* 8.7, H-10), 5.06 (1H, br s, H-16β), 4.97 (1H, br s, H-16α), 4.63–4.52 (3H, m, H-2 and H-18), 3.64 (1H, br s, OH), 2.76 (1H, t, *J* 10.2, H-1), 2.43–2.37 (2H, m, H-9β and H-13β), 2.15–2.02 (2H, m, H-9α and H-13α), 1.99 (3H, br s, Me-19), 1.77 (3H, s, Me-17), 1.58–1.50 (1H, m, H-14α), 1.08–1.21 (1H, m, H-14β), 1.06 (9H, s, TBDPS).

4.20. (*Z*)-(5S,11*R*)-14-(*tert*-Butyl-diphenyl-silanyloxymethyl)-11-isopropenyl-3-methyl-6,16-dioxa-tricyclo[11.2.1.1^{5,8}]-heptadeca-1(15),2,8(17),13-tetraen-7-one (40)

Trifluoroacetic acid (13.4 mg, 8.8 μl, 0.12 mmol) was added to a stirred solution of the secondary alcohol **37** (62 mg, 0.11 mmol) and triethylsilane (27 mg, 37 μl, 0.23 mmol) in anhydrous DCM (8 ml) at 0 °C under an atmosphere of nitrogen. The mixture was stirred at 0 °C for 2.5 h, and then it was quenched with a saturated solution of aqueous $NaHCO_3$ (2.6 ml). The separated aqueous layer was extracted with DCM (10 ml). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography on silica, eluting with petroleum ether–ethyl acetate (10:1), to give the *furanobutenolide* (51 mg, 82%) as a colourless foam. $[\alpha]_D^{26}$ +31.1 (*c* 0.44, $CHCl_3$); ν_{max} (film)/cm^{-1} 1757, 822, 702; δ_H (400 MHz; $CDCl_3$) 7.71–7.68 (4H, m, Ph), 7.47–7.38 (6H, m, Ph), 6.93 (1H, t, *J* 1.5, H-11), 6.17 (1H, s, H-5), 6.12 (1H, br s, H-7), 5.01–4.96 (1H, m, H-10), 4.89 (1H, d, *J* 1.7, H-16α), 4.84 (1H, br s, H-16β), 4.52 (1H, d, *J* 12.4, H-18α), 4.48 (1H, d, *J* 12.4, H-18β), 3.22 (1H, app. t, *J* 11.8, H-9β), 2.72 (1H, dd, *J* 4.2 and 11.8, H-9α), 2.53–2.28 (4H, m, H-13β, H-1 and H-2), 2.09–2.04 (1H, m, H-13α), 2.01 (3H, br s, Me-19), 1.66 (3H, br s, Me-17), 1.55 (1H, tdd, *J* 3.3, 10.8 and 13.9, H-14β), 1.15–1.09 (1H, m, H-14α), 1.07 (9H, s, TBDPS); δ_C (90 MHz; $CDCl_3$) 174.5 (s), 152.1 (d), 150.3 (s), 150.1 (s), 145.3 (s), 135.6 (4×d), 133.5 (s), 133.4 (s), 132.9 (s), 129.7 (2×d), 127.7 (4×d), 127.5 (s), 122.2 (s), 117.5 (d), 113.1 (t), 112.1 (d), 78.7 (d), 57.6 (t), 43.1 (d), 39.6 (t), 31.3 (t), 30.9 (t), 26.8 (3×q), 25.8 (q), 20.0 (t), 19.2 (s), 19.2 (q); HRMS (ESI) 589.2769 ($M+Na^+$, $C_{36}H_{42}O_4SiNa$ requires 589.2744).

4.21. (*Z*)-(5S,11*R*)-14-Hydroxymethyl-11-isopropenyl-3-methyl-6,16-dioxa-tricyclo[11.2.1.1^{5,8}]heptadeca-1(15),2,8(17),13-tetraen-7-one (41a)

Tetrabutylammonium fluoride (24 mg, 0.09 mmol) was added in portions to a stirred solution of the TBDPS ether **40** (51 mg, 0.09 mmol) in THF (8 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h, and then another portion of tetrabutylammonium fluoride (24 mg, 0.09 mmol) was added. The mixture was stirred for a further 30 min, and then concentrated in vacuo in the presence of silica (ca. 10 mg). The residue was purified by flash chromatography on silica, eluting with petroleum ether–ethyl acetate (2:1), to give the *alcohol* (15 mg, 51%) as a colourless powder, mp 174–176 °C. $[\alpha]_D^{23}$ +36.9 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3514, 1751; δ_H (500 MHz; $CDCl_3$) 6.92 (1H, t, *J* 1.6, H-11), 6.20 (1H, s, H-5), 6.11 (1H, br s, H-7), 5.00–4.96 (1H, m, H-10), 4.93–4.92 (1H, m, H-16β), 4.90–4.89 (1H, m, H-16α), 4.49 (1H, dd, *J* 12.4 and 5.4, H-18α), 4.45 (1H, dd, *J* 12.4 and 5.4, H-18β), 3.22 (1H, app. t, *J* 11.8, H-9β), 2.73 (1H, dd, *J* 4.2 and 11.8, H-9α), 2.69 (1H, dd, *J* 15.5 and 12.7, H-2α), 2.59 (1H, dd, *J* 15.5 and 4.0, H-2β), 2.47–2.37 (2H, m, H-13β and H-1), 2.14–2.08 (1H, m, H-13α), 2.01 (3H, d, *J* 1.0, Me-19), 1.74 (3H, dd, *J* 1.3 and 0.7, Me-17), 1.68 (1H, tdd, *J* 3.4, 3.4, 13.9 and 10.9, H-14β), 1.40 (1H, app. t, *J* 5.4, O*H*), 1.18 (1H, ddt, *J* 1.1, 3.6, 13.9 and 13.9, H-14α); δ_C (125 MHz; $CHCl_3$) 174.4 (s), 152.0 (d), 151.0 (s), 150.8 (s), 145.1 (s), 133.0 (s), 128.3 (s), 122.1 (s), 117.3 (d), 113.3 (t), 111.6 (d), 78.7 (d), 56.2 (t), 43.1 (d), 39.7 (t), 31.4 (t), 30.8 (t), 25.8 (q), 20.0 (t), 19.2 (q); HRMS (ESI) 351.1582 ($M+Na^+$, $C_{20}H_{24}O_4Na$ requires 351.1566).

4.22. (*Z*)-(5S,11*R*)-11-Isopropenyl-3-methyl-7-oxo-6,16-dioxa-tricyclo[11.2.1.1^{5,8}]heptadeca-1(15),2,8(17),13-tetraene-14-carbaldehyde (41b)

Manganese dioxide (100 mg, 1.15 mmol) was added to a solution of the alcohol **41a** (15 mg, 46 μmol) in anhydrous DCM (7 ml) and the mixture was stirred at room temperature for 2 h and then

filtered through a short pad of Celite. The filtrate was washed with DCM (15 ml), and the combined organic extracts were concentrated in vacuo to leave the *aldehyde* (14.6 mg, 97%) as a colourless foam. $[\alpha]_D^{26}$ +44.7 (*c* 0.73, $CHCl_3$); ν_{max} (film)/cm^{-1} 1755, 1679; δ_H (360 MHz; $CDCl_3$) 9.93 (1H, s, C*H*O), 6.95 (1H, t, *J* 1.5, H-11), 6.47 (1H, s, H-5), 6.16 (1H, br s, H-7), 5.06–5.00 (1H, m, H-10), 4.96–4.98 (1H, m, H-16β), 4.93 (1H, br s, H-16α), 3.24–3.12 (2H, m, H-9α and H-2α), 2.85–2.76 (2H, m, H-9β and H-2β), 2.52–2.41 (2H, m, H-13β and H-1), 2.15 (1H, m, H-13α), 2.04 (3H, d, *J* 1.0, Me-19), 1.78 (3H, dd, *J* 1.3 and 0.8, Me-17), 1.85–1.75 (1H, m, H-14β), 1.18 (1H, ddt, *J* 1.1, 3.7, 13.8 and 13.8, H-14α); δ_C (90 MHz; $CHCl_3$) 184.4 (d), 174.1 (s), 163.1 (s), 152.1 (s), 151.5 (d), 144.1 (s), 133.3 (s), 131.4 (s), 125.0 (s), 116.6 (d), 114.0 (t), 107.8 (d), 78.5 (d), 42.6 (d), 40.0 (t), 31.9 (t), 31.6 (t), 25.9 (q), 20.0 (t), 19.2 (q); HRMS (ESI) 349.1418 ($M+Na^+$, $C_{20}H_{22}O_4Na$ requires 349.1410).

4.23. (+)-*Z*-Deoxypukalide (3)

Acetic acid (6.7 mg, 6.5 μl, 0.11 mmol) and NaCN (11 mg, 0.22 mmol) were added to a stirred solution of the aldehyde **41b** (14.6 mg, 0.045 mmol) in anhydrous methanol (0.5 ml) at room temperature. The mixture was stirred at room temperature for 1 h, and then MnO_2 (78 mg, 0.90 mmol) was added in one portion. The mixture was left to stir at room temperature for 21 h, then filtered through a short pad of Celite, and the filtrates was washed with ethyl acetate (5 ml). The combined filtrates were evaporated in vacuo to remove methanol, and the residue was then dissolved in ethyl acetate (10 ml), washed with water (2 ml), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography on silica, eluting with petroleum ether–ethyl acetate (5:1), to give (+)-deoxypukalide (10.4 mg, 65%) as a colourless powder, mp 133–136 °C. $[\alpha]_D^{27}$ +15.5 (*c* 0.38, $CHCl_3$); ν_{max} (film)/cm^{-1} 1753, 1723; δ_H (360 MHz; $CDCl_3$) 6.96 (1H, app t, $J \sim 1.6$, H-11), 6.44 (1H, s, H-5), 6.11 (1H, br s, H-7), 5.05–4.90 (1H, ddt, *J* 11.8, 4.0, 1.6, H-10), 4.95–4.92 (1H, m, H-16β), 4.90 (1H, br s, H-16α), 3.83 (3H, s, O*Me*), 3.51 (1H, dd, *J* 16.7 and 13.0, H-2α), 3.15 (1H, app t, *J* 11.8, H-9α), 2.76 (1H, dd, *J* 11.8 and 4.2, H-9β), 2.68 (1H, dd, *J* 16.7 and 3.6, H-2β), 2.49–2.39 (2H, m, H-13β and H-1), 2.16–2.09 (1H, m, H-13α), 2.03 (3H, d, *J* 1.0, Me-19), 1.76 (3H, br s, Me-17), 1.81–1.71 (1H, m, H-14α), 1.15 (1H, ddt, *J* 3.6, 1.0, 14.0, H-14β); δ_C (90 MHz; $CHCl_3$) 174.2 (s), 164.1 (s), 160.7 (s), 151.5 (d), 150.6 (s), 144.7 (s), 133.3 (s), 130.1 (s), 116.8 (d), 115.9 (s), 113.5 (t), 110.7 (d), 78.5 (d), 51.5 (q), 42.6 (d), 39.9 (t), 32.3 (t), 32.0 (t), 25.8 (q), 20.0 (t), 19.1 (q); HRMS (ESI) 379.1531 ($M+Na^+$, $C_{21}H_{24}O_5Na$ requires 379.1521). The ^1H and ^{13}C NMR spectroscopic data were identical to those reported for the natural product.[4]

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