

Clark, J. S. and Mcaulay, K. (2017) Total synthesis of 7-epi-pukalide and 7-acetylsinumaximol B. *Chemistry: A European Journal*, 23(41), pp. 9761-9765. There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

Clark, J. S. and Mcaulay, K. (2017) Total synthesis of 7-epi-pukalide and 7-acetylsinumaximol B. *Chemistry: A European Journal*, 23(41), pp. 9761-9765. (doi:[10.1002/chem.201702591](https://doi.org/10.1002/chem.201702591)) This article may be used for non-commercial purposes in accordance with [Wiley Terms and Conditions for Self-Archiving](#).

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Deposited on: 09 June 2017

Total Synthesis of 7-*epi*-Pukalide and 7-Acetylsinumaximol B

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Abstract: Convergent total syntheses of the furanocembranoids 7-*epi*-pukalide and 7-acetylsinumaximol B have been achieved using a one-pot Knoevenagel condensation and thioether-mediated furan-forming reaction. Furan formation proceeds via a sulfur ylide and results in rapid introduction of structural complexity during the coupling of two highly functionalised fragments. The targets have been prepared in 16 steps from (*R*)-perillyl alcohol.

The furanocembrane family of natural products comprises structurally diverse diterpenoids that have been isolated from several octocoral species (Figure 1).^[1–5] The first furanocembranoid to be fully characterised was pukalide, a compound that was first isolated from the alcyonacean octocoral *Sinularia abrupta* by Scheuer and co-workers in 1975^[6] and has been isolated from several other species of coral more recently.^[7]

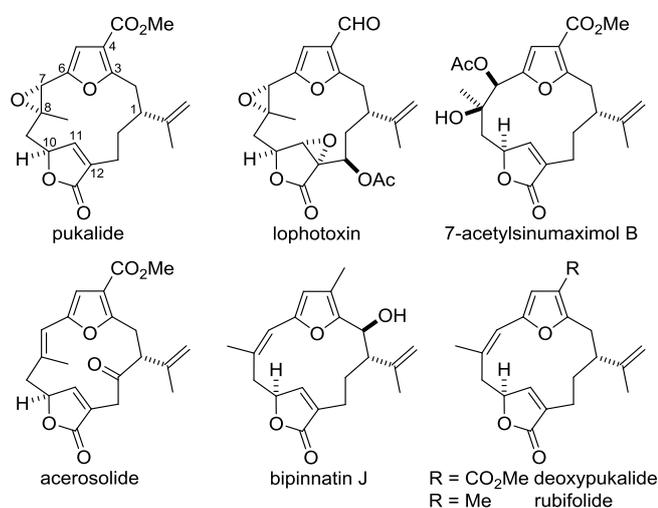


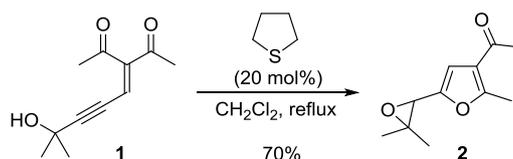
Figure 1. Selected furanocembranoid marine natural products.

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Pukalide and the other furanocembranoids possess a 14-membered carbocyclic skeleton that includes a bridging furan (C3–C6) and a five-membered lactone (C10–C12), and bears an isopropenyl substituent at C1 and a methyl substituent at C8 (Figure 1). Structural variation occurs at the C4 position, where an ester, aldehyde or methyl group can be present, and at the C7–C8 and C11–C12 positions, which can be unsaturated or bear an epoxide (Figure 1). Positions C2, C7, C8 and C13 can be substituted with hydroxyl or acetate groups in some cases.

Several furanocembranoids have been reported to possess significant biological activities. For example, lophotoxin is an irreversible antagonist of the nicotinic acetylcholine receptor^[8] and pukalide has emetic activity in fish (Figure 1).^[7d] As a consequence of their pharmacological activities and interesting molecular structures, the furanocembranoids have received considerable attention as synthetic targets.^[9–20] The first synthesis of a furanocembrane natural product – acerosolide (Figure 1) – was reported by Paquette and co-workers in 1993.^[10] Subsequent pioneering studies by the groups of Pattenden,^[11] Marshall^[12] and Trauner^[13] resulted in total syntheses of deoxypukalide, rubifolide and bipinnatin J (Figure 1). Total syntheses of furanocembranoids have also been reported by the groups of Donohoe (*Z*-deoxypukalide)^[14] and Rawal (bipinnatin J).^[15] In addition, the groups of Paterson^[16] and Wipf^[17] have made important contributions with regard to the synthesis of lophotoxin and pukalide, the groups of Bach^[18] and Honda^[19] have prepared advanced intermediates to bipinnatin J, and Mulzer and co-workers assembled the complete skeleton of providencin.^[20]

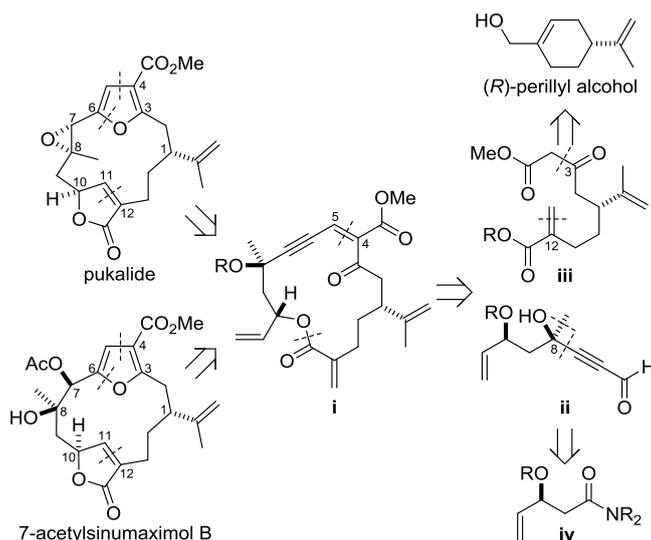
In spite of the considerable amount of work that has been devoted to the synthesis of furanocembrane natural products, they continue to be extremely challenging targets by virtue of their complex structures and reactive functionality. It is noteworthy that all of the previously reported total syntheses have been of family members possessing low levels of oxygenation.^[10–15] Introduction of the C7–C8 epoxide that is present in lophotoxin and pukalide, as well as many of the other furanocembranoids, has proved to be particularly challenging, but the work of Mulzer and co-workers concerning the total synthesis of providencin has demonstrated how this problem might be addressed.^[20]



Scheme 1. Tetrahydrothiophene-promoted formation of an epoxyfuran.

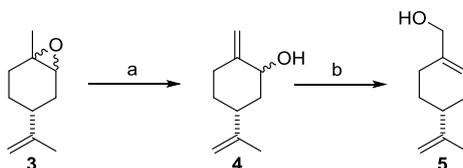
In 2012, we reported a new method for the synthesis of trisubstituted furans,^[21] including epoxyfurans, from ynenones that can be obtained by performing Knoevenagel condensation reactions on propargylic aldehydes.^[22] In the course of this work, the epoxyfuran **2** was prepared in good yield by treatment of the ynenone substrate **1** with a sub-stoichiometric amount of tetrahydrothiophene (THT) (Scheme 1). We became interested in exploring whether the transformation could be used as the furan-forming reaction in a total synthesis of pukalide, given that construction of the epoxyfuran unit present in many furanocembranoids has proved to be very challenging. Herein, we describe our efforts to prepare pukalide and the related natural product 7-acetylsinumaximol B.^[6,7,23]

The syntheses of pukalide and 7-acetylsinumaximol B were planned so that our THT-mediated reaction could be used to install the C7–C8 epoxide and the furan simultaneously, late in the synthesis. In the retrosynthetic analysis of both targets (Scheme 2), disconnection of the furan and butenolide leads to the macrolactone **i** as a late-stage intermediate. In the forward direction, it was anticipated that the butenolide would be formed by ring-closing metathesis (RCM) and the furan would be constructed using our organocatalytic reaction; a decision about the order in which these reactions would be performed was to be made late in the synthesis. Disconnection of the lactone and the ynenone (C4–C5) then reveals the propargylic aldehyde **ii** and the β -keto ester **iii** as the key fragments. In the forward direction, it was expected that formation of the ynenone would precede macrolactone construction. Disconnection of the methyl and alkyne groups of the tertiary alcohol (C8) in fragment **ii** leads to the amide **iv**. In the case of fragment **iii**, cleavage of the β -keto ester by retro-Claisen condensation, removal of the methylene group and reconnection of C3 to C12 reveals (*R*)-perillyl alcohol as the starting material.^[12,14]



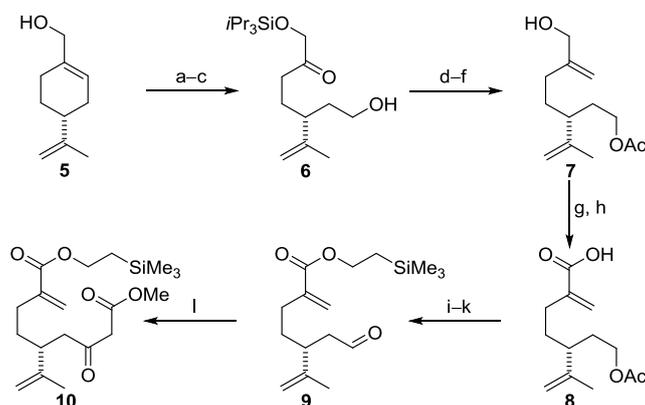
Scheme 2. Retrosynthetic analysis of 7-acetylsinumaximol B and pukalide.

The chiral pool compound (*R*)-perillyl alcohol was required for the synthesis of the β-keto ester fragment (compound **iii**, Scheme 1). Unlike its *S*-enantiomer, (*R*)-perillyl alcohol is not readily available from commercial suppliers and so a simple synthetic route to large quantities of this starting material had to be devised. Commercially available (+)-limonene oxide **3** was subjected to base mediated epoxide rearrangement to produce the allylic alcohol **4** as a mixture of diastereomers (Scheme 3).^[24] Treatment of the alcohols **4** with methanesulfonyl chloride delivered a mixture of the corresponding mesylates that underwent S_N2' rearrangement to afford (*R*)-perillyl alcohol (**5**) during aqueous work-up. As far as we are aware, the only other synthesis of (*R*)-perillyl alcohol that does not involve the use of a biocatalyst^[25] is that reported by Evans *et al.*, in which a palladium-mediated rearrangement reaction is employed.^[26]



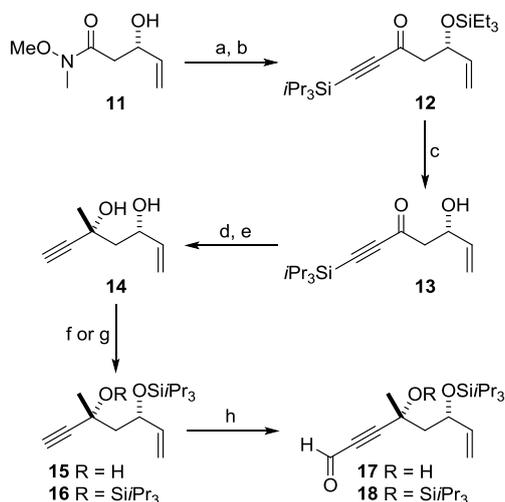
Scheme 3. Synthesis of (*R*)-(+)-perillyl alcohol from (+)-limonene oxide. a) LDA, Et₂O, -78 °C, 87%; b) MeSO₂Cl, Et₃N, CH₂Cl₂, rt then sat. aq. NaHCO₃, 61%.

(*R*)-Perillyl alcohol (**5**) was protected as its triisopropylsilyl (TIPS) ether and then subjected to selective ozonolysis, under conditions reported by Donohoe *et al.*^[14] (Scheme 4). The intermediate aldehyde was subjected to chemoselective reduction using sodium triacetoxyborohydride to afford hydroxyketone **6** in 41% yield over three steps.^[27] Wittig methylenation of the ketone gave an alkene that was then transformed into the allylic alcohol **7** by sequential acetylation and silyl ether cleavage. The carboxylic acid functionality was installed in a stepwise manner by formation of the aldehyde using Dess-Martin periodinane (DMP) and subsequent Pinnick oxidation. Protection of the resulting carboxylic acid **8** was necessary prior to the introduction of the β-keto ester and so it was subjected to DCC-mediated esterification with 2-(trimethylsilyl)ethanol. Acetate hydrolysis under basic conditions and oxidation of the resulting alcohol using DMP then gave aldehyde **9**. The synthesis of the β-keto ester **10** was completed by the tin(II) chloride mediated reaction of the aldehyde **9** with methyl diazoacetate, following the procedure described by Holmquist and Roskamp.^[28]



Scheme 4. Synthesis of the β -keto ester **10** required for the Knoevenagel condensation reaction. a) $i\text{Pr}_3\text{SiCl}$, imidazole, DMAP, CH_2Cl_2 , rt, 99%; b) O_3 , isoprene, pyridine, CH_2Cl_2 -MeOH, $-78\text{ }^\circ\text{C}$; c) $\text{NaBH}(\text{OAc})_3$, PhMe, rt, 41% (2 steps); d) $[\text{Ph}_3\text{PCH}_3]^+\text{Br}^-$, $n\text{BuLi}$, THF, $0\text{ }^\circ\text{C} \rightarrow \text{rt}$, 86%; e) Ac_2O , Et_3N , DMAP, CH_2Cl_2 , rt, 94%; f) $n\text{Bu}_4\text{NF}$, THF, rt, 99%; g) Dess-Martin periodinane, CH_2Cl_2 , rt; h) NaClO_2 , NaH_2PO_4 , $t\text{BuOH}$, H_2O , rt, 99% (2 steps); i) DCC, DMAP, $\text{Me}_3\text{Si}(\text{CH}_2)_2\text{OH}$, CH_2Cl_2 , rt, 87%; j) K_2CO_3 , MeOH, rt; k) Dess-Martin periodinane, CH_2Cl_2 , rt, 84% (2 steps); l) $\text{N}_2\text{CHCO}_2\text{Me}$, SnCl_2 , CH_2Cl_2 , rt, 67%.

The second fragment was prepared by the route shown in Scheme 5. The β -hydroxy amide **11** was prepared by the stereoselective titanium-mediated aldol condensation reaction between acrolein and an *N*-acetylthiazolidinethione and subsequent formation of a Weinreb amide as described by Venkatesham and Nagaiah.^[29] Protection of the hydroxyl group as a triethylsilyl ether followed by addition of lithiated triisopropylsilylacetylene afforded the propargylic ketone **12**. Cleavage of the silyl ether under acidic conditions afforded the β -hydroxyketone **13** in good yield. The requisite C8 methyl substituent was introduced stereoselectively by chelation-controlled addition of $\text{MeTi}(\text{O}i\text{Pr})_3$ to the ketone **13**; subsequent desilylation afforded the diol **14**. The *syn* diol was obtained as the major product with an excellent *dr*.^[30] Other reaction conditions were explored, but these resulted in formation of the diol with diminished *dr* and lower yield. Interestingly, addition of MeLi to the ketone **13** in the presence of ZnBr_2 resulted in a reversal of diastereoselectivity and delivered the *anti* 1,3-diol as the major product. Selective TIPS-protection of the secondary hydroxyl group of the diol **14** afforded the alcohol **15** and double TIPS-protection afforded the bis-silyl ether **16**. The alkynes **15** and **16** were formylated thereafter to give the propargylic aldehydes, **17** and **18**, required for the key one-pot fragment coupling and furan-forming reaction.



Scheme 5. Synthesis of the propargylic aldehydes **17** and **18** required for the Knoevenagel condensation reaction. a) Et_3SiCl , imidazole, CH_2Cl_2 , rt, 95%; b) $i\text{Pr}_3\text{SiCCH}$, $n\text{BuLi}$, THF, rt, 91%; c) PPTS, MeOH, THF, 99%; d) $(\text{PrO})_3\text{TiMe}$, Et_2O , $0\text{ }^\circ\text{C}$, 97% (9:1 *d.r.*); e) $n\text{Bu}_4\text{NF}$, THF, rt, 89%; f) NaH , $i\text{Pr}_3\text{SiCl}$ (1 equiv.), THF, rt, 98% (**15**); g) $i\text{Pr}_3\text{SiOSO}_2\text{CF}_3$ (2.1 equiv.), 2,6-lutidine, CH_2Cl_2 , $0\text{ }^\circ\text{C} \rightarrow \text{rt}$, 97% (**16**); h) $n\text{BuLi}$, DMF, THF, $-78\text{ }^\circ\text{C}$, 90% (**17**), 94% (**18**).

The development of robust routes to the β -keto ester **10** and to the aldehydes **17** and **18** meant that fragment coupling could be explored. The original synthetic plan (Scheme 1) had been devised with the expectation that the fragments would be coupled by use of a Knoevenagel condensation reaction and the resulting ynenone would be subjected to macrocyclisation prior to the furan formation. However, the ynenone was unstable and so it was necessary to perform furan formation prior to macrocyclisation. It transpired that Knoevenagel condensation and furan formation could be effected in a simple one-pot

process (Table 1). Reaction of the β -ketoester **10** with the aldehyde **17** in the presence of piperidine, acetic acid (0.6 equiv.) and tetrahydrothiophene (THT), produced the epoxy-furan **19** (1:1 mixture of diastereoisomers) in 30% yield and the acetate **20** (~3:2 mixture of diastereoisomers) in 32% yield (Entry 1, Table 1). It was found that the selectivity of the reaction could be tuned by altering the amount and type of carboxylic acid additive or by protecting the tertiary alcohol. When one equivalent of acetic acid was used in the one-pot Knoevenagel condensation and cyclisation reaction, the acetate **20** was obtained in 50% yield and the yield of the epoxy **19** was reduced to 16% (Entry 2, Table 1). The epoxy **19** was obtained exclusively in 62% yield from the reaction promoted by pivalic acid (Entry 3, Table 1), and the acetate **21** was obtained in 85% yield (3:2 mixture of diastereomers) when the bis-protected aldehyde **18** was used as a substrate and the reaction was performed in the presence 1.2 equivalents of acetic acid (Entry 4, Table 1).

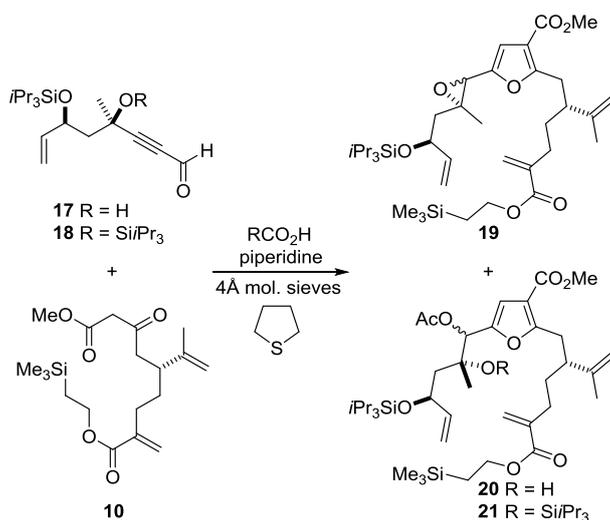
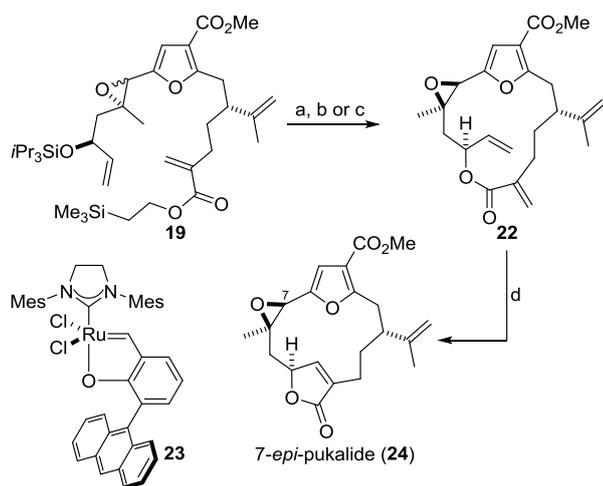


Table 1. One-pot Knoevenagel condensation and catalytic furan formation.

Entry	Aldehyde	RCO ₂ H	Equiv. RCO ₂ H	Yield 19 (%) ^a	Yield 20 (%) ^a	Yield 21 (%) ^a
1	17	MeCO ₂ H	0.6	30	32	–
2	17	MeCO ₂ H	1.0	16	50	–
3	17	<i>t</i> BuCO ₂ H	0.6	62	–	–
4	18	MeCO ₂ H	1.2	–	–	85

^a Isolated yield.

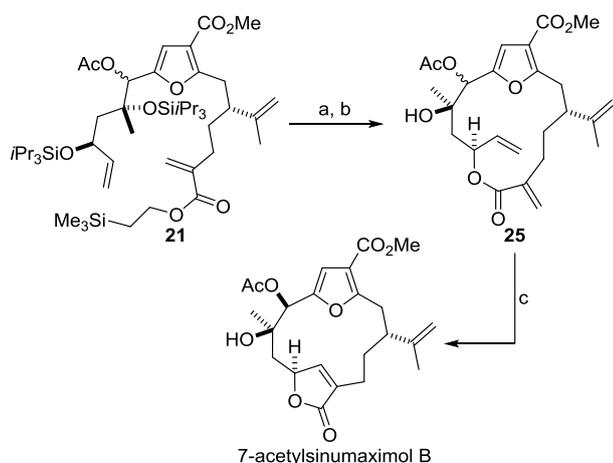
Cleavage of both the silyl ether and the ester was accomplished by treatment of epoxyfuran **19** with TBAF (Scheme 6). The resulting hydroxyacid was then subjected to Yamaguchi macrolactonisation conditions to afford the lactone **22** as a single isomer in 39% yield over two steps;³¹ the other diastereomer failed to undergo cyclisation under the reaction conditions (Scheme 6). Cyclisation of the hydroxyacid using the Corey-Nicolaou method delivered the lactone **22** in 46% yield as a single isomer and none of the diastereomeric lactone was isolated.³¹



Scheme 6. Completion of the total synthesis of 7-*epi*-pukalide (**24**). a) $n\text{Bu}_4\text{NF}$, THF, 10 °C; b) $\text{Cl}_3\text{C}_6\text{H}_2\text{COCl}$, $i\text{Pr}_2\text{NEt}$, DMAP, C_6H_6 , rt, 39% (2 steps); c) 2,2'-dipyridyl disulphide, PPh_3 , PhMe, rt then reflux 46% (2 steps); d) **23**, CH_2Cl_2 , 40 °C, 90%.

Attempts to construct the butenolide by transannular ring-closing metathesis (RCM) with either the Grubbs second generation catalyst or the Hoveyda-Grubbs second generation catalyst were unsuccessful. However, the very reactive modified Hoveyda-Grubbs second generation catalyst **23**, developed by Matsugi and co-workers,^[32] proved to be highly effective for the required RCM reaction and the butenolide was obtained in 90% yield (Scheme 6). The ^1H and ^{13}C NMR data obtained for the final compound were found to be inconsistent with the original data recorded for natural pukalide.^[33] Careful analysis of NOE data revealed that the final compound was the epoxide **24**, the C7-*epimer* of natural pukalide.^[34,35] This result leads to the conclusion that the isomer of epoxide **19** required for the synthesis of pukalide did not undergo macrolactonisation (Scheme 6). The finding that the hydroxyacid obtained from the *cis*-epoxide isomer of **19** undergoes cyclization whereas that obtained from the *trans*-epoxide isomer of **19** does not, is unsurprising. Mulzer and co-workers found that installation of an *E*-alkene at C7–C8 and its subsequent conversion into the requisite epoxide were both challenging transformations during the synthesis of 17-deoxyprovidencin.^[20]

The acetate product **21** was subjected to the same three-step sequence – deprotection, lactonisation and RCM – as the epoxide **19** to afford 7-acetylsinumaximol B (Scheme 7).^[23] In this case, although both diastereomeric hydroxyacids underwent Yamaguchi macrolactonisation, only one diastereomer of the resulting triene **25** underwent RCM to produce the butenolide. It transpired that the diastereomer that underwent cyclisation was the one required for preparation of the natural product. The ^1H and ^{13}C NMR data and other data for the final compound were identical to those reported for 7-acetylsinumaximol B that had been isolated from natural sources.^[23,36]



Scheme 7. Completion of the total synthesis of 7-acetylsinumaximol B. a) $n\text{Bu}_4\text{NF}$, THF, 10 °C; b) $\text{Cl}_3\text{C}_6\text{H}_2\text{COCl}$, $i\text{Pr}_2\text{NEt}$, DMAP, C_6H_6 , rt, 25% (2 steps); c) **23**, CH_2Cl_2 , 40 °C, 25% + 73% recovered **25**.

In conclusion, convergent total syntheses of both 7-*epi*-pukalide and 7-acetylsinumaximol B have been completed with longest linear sequences of just 16 steps from (*R*)-perillyl alcohol. The route

represents the first total synthesis of both compounds and demonstrates an effective strategy for the selective introduction of oxygen substituents (epoxide or diol) at C7 and C8. The key THT promoted reaction allowed the rapid and convergent assembly of the complete furan-containing skeleton and permitted completion of the syntheses by a parallel macrolactonisation and RCM sequence.

Acknowledgements

The authors acknowledge the award of a College of Science and Engineering Scholarship to KM from the University of Glasgow. We thank Professor W. Fenical (Scripps Institution of Oceanography, UC San Diego) for very kindly providing us with the original ^1H and ^{13}C NMR spectra recorded for natural pukalide.

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- [34] The configuration of the C7-C8 epoxide was confirmed by ¹H NMR analysis. NOEs were observed between the C7 proton and the protons of the C8 methyl substituent and between the C7 proton the furan proton (C5). For further details, see Supporting Information.
- [35] A reviewer queried whether the stereochemical integrity at the C8 position is maintained during the key cyclization reaction (**10** + **17** → **19**). The evidence that the configurational integrity of this position is maintained during the furan-forming reaction is as follows: i) in the literature, the integrity of related enantiomerically pure epoxides is maintained in the presence of carboxylic acids, even in cases where tethering of the epoxide to the carboxylic acid could promote intramolecular protonation and subsequent nucleophilic opening of the epoxide; ii) we have found that there is little stereocontrol at the stereogenic centre adjacent to the furan in cases where furan construction occurs with concomitant cyclic ether formation and so additional scrambling of the C8 stereocentre would be expected to deliver four diastereomers, but only two isomers of epoxide **19** are obtained from the reaction; iii) the ratio of the two diastereomers of the epoxide **19** does not vary during the course of the reaction; iv) compounds produced by external nucleophilic trapping of the C8 carbocation, arising from epoxide protonation and ring opening, are not obtained.
- [36] The specific rotation of our synthetic 7-acetylsumaximol is $[\alpha]_D^{27} -38$ (*c* = 0.080, CHCl₃) compared to a literature value of $[\alpha]_D^{25} -56.0$ (*c* = 0.6, CHCl₃) reported for natural material (ref. 23). The discrepancy can be accounted for by the low concentration of our synthetic sample and the difference in temperature during measurement.