Synthesis and Evaluation of a 2,11-Cembranoid-inspired Library

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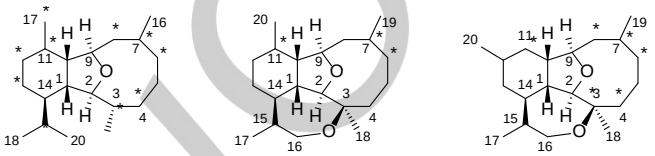
Abstract:

The 2,11-cembranoid family of natural products has been used as inspiration for the synthesis of a structurally simplified, functionally diverse library of octahydrobenzofuran based compounds designed to augment a typical medicinal chemistry library screen. Ring-closing metathesis, lactonisation and SmI_2 mediated methods were exemplified and applied to installation of a third ring to mimic the nine-membered ring of the 2,11-cembranoids. The library was assessed for aqueous solubility and permeability, with a chemical space analysis performed for comparison to the family of cembranoid natural products and a sample set of a screening library. Preliminary investigations in cancer cells showed that the simpler scaffolds could recapitulate the reported anti-migratory activity of the natural products.

Introduction

The 2,11-cembranoids are a structurally complex family of natural products isolated from the Octocorallia species, consisting of a polyoxygenated 2,11-cyclised diterpenoid core scaffold.[1] The structures are further subcategorised into cladiellins **1**, briarellins **2** and asbestinins **3** (Figure 1). Due to their structural complexity and broad ranging biological activities, the members of the structural class have been and continue to be attractive targets for total synthesis.[2-17] By necessity, such approaches require multi-step routes, with a particular challenge being introduction of the 9-membered cyclic ether ring and the installation of the specific complex substitution patterns associated with each natural product. Methods used to form such a ring include Nozaki-Hiyama-Kishi coupling,[7,8,11,14] Claisen ring expansion,[6] ring-closing metathesis (RCM),[4,9,13,15] diazo ketone cyclisations[10,16] and oxidative ring expansion.[17] A number of these total synthesis routes have been shown to afford access to more than one member of the natural product family[5,7,8,10,11,13,17] allowing the preparation of small libraries of the natural products. The broad ranging biological activities of the cembranoid family have been reviewed,[1] and have been found to encompass anticancer, anti-inflammatory, antiviral and antibacterial properties, amongst others.



Cladiellin **1** Briarellin **2** Asbestinin **3**

Figure 1. Cladiellin, Briarellin and Asbestinin core scaffolds. Carbons bearing an asterisk are commonly oxygenated or unsaturated within the class.

Natural products have been a great source of inspiration in drug discovery, being used either in their own right as drugs or as the starting point for drug discovery projects.[18] Libraries of natural products, natural product inspired or other structurally complex scaffolds have been shown to be a rich source of hits in phenotypic screens,[19] which probe phenotypes arising from biological manipulation with small molecules in cells or small organisms (for example, zebra fish embryos[20]). As biological assay screening tools they frequently occupy complementary chemical space to commercially available synthetic libraries, providing novelty from both a structural and intellectual property perspective.[21] Those natural products found to display interesting biological activities can, however, be stereochemically complex molecules, thus presenting significant synthetic challenges regarding analogue synthesis. Numerous approaches have been taken to overcome such challenges, in particular Diversity Oriented Synthesis (DOS),[19,22] Biological Oriented Synthesis (BIOS)[23] and Lead-oriented Synthesis.[24] A principal challenge is to retain structural features of the natural products that differentiate them from chemical space explored by traditional small molecule screening libraries, and may be associated with the bioactivities of the natural products, while simplifying the structures to give easier synthetic access and control of physicochemical properties.

Within the context of drug discovery, numerous metrics have been suggested as design aids in attempts to predict the likelihood of drugability,[25] one of the most prevalent being Lipinski's rule-of-five.[26] The central tenet of many of these metrics is to predict the ability of a compound to dissolve in aqueous media and to pass through a lipid membrane, both properties that may also be readily measured. To be useful for cell or organism-based biology, compounds must be sufficiently cell permeable and water soluble. It is therefore desirable to design new libraries around scaffolds where these properties are intrinsic.

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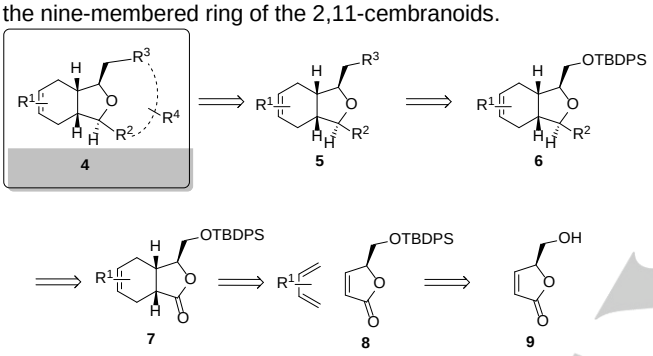
Here, we present the synthesis of a 2,11-cembranoid inspired small library of compounds, designed to retain the biological activities of the natural product class within structurally simplified library analogues, whilst displaying desirable lead-like properties. The cembranoid class of natural products have demonstrated multiple biological activities in cells and parasites,[1] making the core scaffold an ideal starting point to make libraries of cell permeable compounds. It was envisaged that the octahydrobenzofuran core, with and without the third fused medium ring from the 2,11-cembranoid motif, could be used as a privileged structure.[28] It was anticipated that the library of compounds produced from such a privileged core would be able to recapitulate some of the biological activities observed in the natural product class, whilst reducing the synthetic complexity. The main synthetic challenge, therefore, was to find quick and concise routes to introduce substituent variation around the chosen core and methods to install a third ring system to mimic the nine-membered ring of the 2,11-cembranoids.



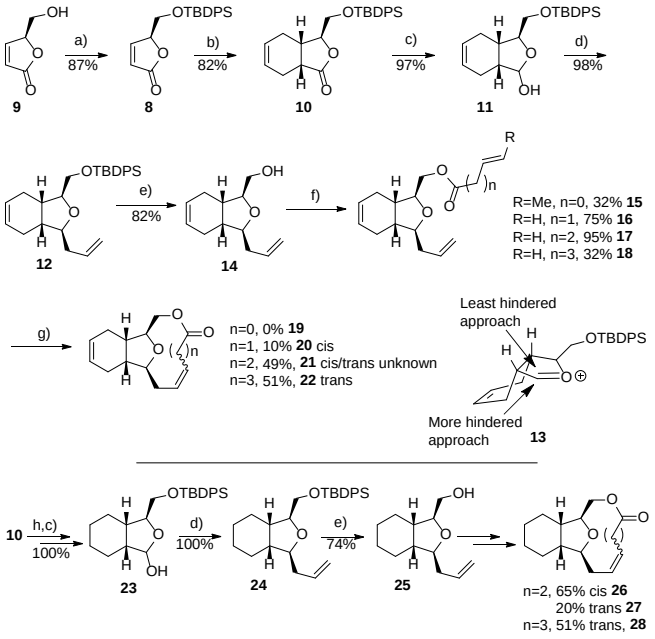
Scheme 1. Library design and retrosynthetic analysis

From the many successful synthetic strategies exemplified for the 2,11-cembranoid natural products, we chose to explore a Diels-Alder reaction to construct the [6,5]-bicyclic core of the library[6,7] We anticipated a rapid and flexible entry to the octahydrobenzofuran scaffold through Diels Alder cyclisation, with the potential to vary substituent patterns through choice of starting materials or manipulation of intermediates. Such an approach would provide a platform to investigate both functionalization of the bicycle as well as installation of a medium or larger ring equivalent to the nine-membered ring of the natural products. The retrosynthetic approach is as outlined in Scheme 1. From (*S*)-5-(hydroxymethyl)-2(5H)-one **9**, Diels Alder reaction with a range of dienes was envisaged to install the [6,5] core of **7**, which can be further manipulated to produce bicyclic analogues of general structure **5**, or further cyclised to tricyclics such as **4**. Following generation of the library, aqueous solubility, permeability and structural diversity in relation to in-house screening libraries were assessed. In addition, the ability to recapitulate some of the biological activity of the more complex natural products with simpler structures from the library was demonstrated.

Results and Discussion

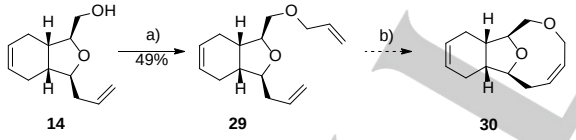
Protection of commercially available alcohol **9** with TBDPSCl gave lactone **8** in 87% yield; chiral HPLC confirmed the presence of a single enantiomer (Scheme 2). Reaction of silyl ether **8** with butadiene in the presence of $AlCl_3$ in dichloromethane at 55 ºC in a sealed tube for one week under literature conditions[29] gave bicyclic **10** in 40% yield. Although forming the desired product, yields were found to be highly variable. Screening of a number of Lewis Acids found $TfN(AlMeCl)_2$[30] to give a consistently high yield of around 70-80% after a two day reaction. Furthermore, it was found possible to use a solution of 30% butadiene in toluene as the diene source, avoiding the inconvenience and hazards associated with condensing gaseous butadiene. Reduction of lactone **10** with DIBAL-H gave lactol **11** in high yield, which in turn was reacted with allyltrimethylsilane[31,32] to give **12** as a single enantiomer. The exclusive cis selectivity from reaction of the bicyclic lactol **11** contrasts with literature examples of monocyclic lactols, where the trans isomer predominates from an intermolecular allyltrimethylsilane addition.[30] The observed difference can be rationalised by looking at a proposed conformation of oxonium intermediate **13**, where the least hindered approach from the nucleophile leads to the cis product **12**.

Deprotection of silyl ether **12** using TBAF gave alcohol **14** in 82% yield, which was esterified to form esters of various chain lengths **15**, **16**, **17** and **18**. Following considerable opimisation, ring closing metathesis (RCM) cyclisation using Grubbs II catalyst at high dilution in dichloromethane gave tricyclics **20**, **21** and **22**. Nine-membered lactone **19** could not be formed, whereas 10-membered lactone **20** was produced in low yield. The alkene conformation of **20** was presumed to be cis due to the strain of a trans double bond in such a 10-membered lactone. The larger, less strained 11- and 12-membered lactones were more readily constructed. The alkene conformation of **21** was undetermined due to overlapping NMR signals, whereas **22** was assigned trans by analogy to the crystal structure conformations of **40** and **42** (vide infra). By using a similar reaction sequence, but reducing the alkene of **10** earlier in the route, cyclohexane analogues **26**, **27** and **28** were also formed. The structure of **26** was confirmed by X-ray crystallography (see supplementary information).



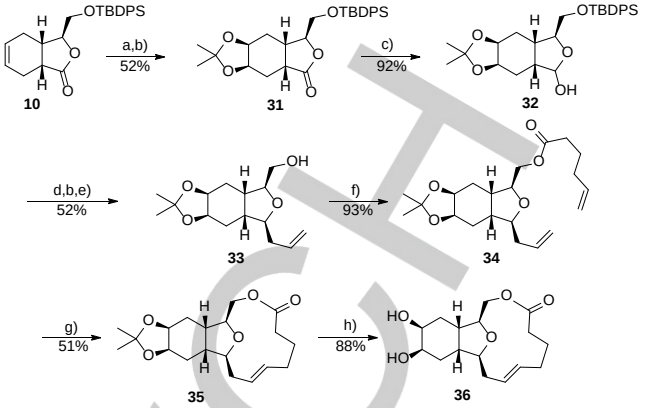
Scheme 2. *Reagents and Conditions*: a) TBDPSCl, imidazole, DMF, 0 ºC-rt, 2.5 h, b) butadiene, TfN(AlMeCl)$_2$, CH_2Cl_2, 60 ºC, c) DIBAL-H, CH_2Cl_2, -78 ºC, d) allylTMS,BF_3.OEt_2, -78 ºC, e) TBAF, 0 ºC, f) acid chloride, pyridine or Et_3N g) Grubbs II, 0.0005 M CH_2Cl_2, rt h) Pd/C (5 wt%), H_2, EtOAc, rt.

As lactone **19** could not be formed, speculated to be due to the transoid nature of the ester in **15** adding to the strain in forming a 9-membered ring, synthesis of the ether analogue **30** was attempted (Scheme 3). Alkylation of alcohol **14** with allyl bromide gave cyclisation precursor **29**. However, no RCM product could be observed under the above optimised conditions, highlighting the difficulty in forming the strained 9-membered ring. Previous RCM approaches to 9-membered ring formation in the context of 2,11-cembranoid synthesis have met with mixed success,[3,4,15,33] and appear highly substrate dependant.



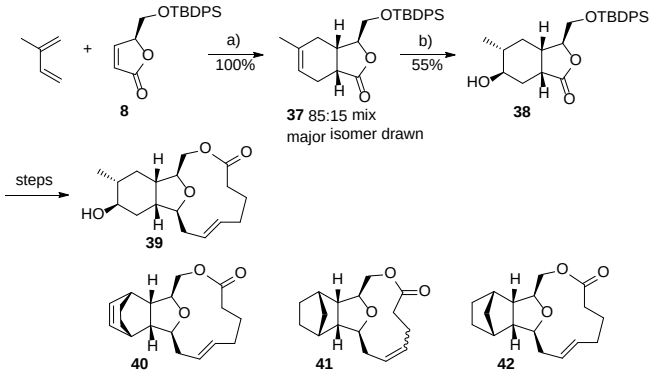
Scheme 3. *Reagents and Conditions:* a) NaH, allylbromide, b) Grubbs II, 0.0005 M, CH_2Cl_2, rt. 0%.

Using the alkene functionality of lactone **10** as a point of derivatisation, dihydroxylation of the alkene from the least sterically crowded face using catalytic osmium tetroxide followed by dimethylacetal protection gave tricyclic **31** in 52% yield over two steps (Scheme 4). Using a similar sequence to that shown in Scheme 2, lactone **31** was reduced to lactol **32**, reacted with allyltrimethylsilane in the presence of BF_3.OEt_2 and deprotected to alcohol **33**. Esterification, ring closing metathesis and acetal deprotection with acid gave diol **36**.



Scheme 4. *Reagents and Conditions*: a) OsEnCat (0.5 mol%), NMO b) 2,2-dimethoxypropane, PPTS, c) DIBAL-H, -78 ºC d) allylTMS, BF_3.OEt_2, -78 ºC e) TBAF, f) hex-5-enoyl chloride, py, CH_2Cl_2, g) Grubbs II, 0.0005 M CH_2Cl_2, h) HCl, THF.

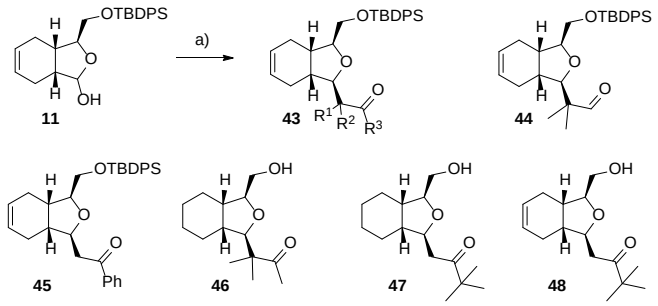
Analogue synthesis by changing the diene component was also demonstrated (Scheme 5). Using 2-methylbutadiene gave an 85:15 inseparable mix of methyl regioisomers (major isomer **37** shown). The major 5-methyl component was isolated following oxidative hydroborylation to give alcohol **38**. As above, alcohol **38** was in turn converted to lactone **39**. As further exemplification of diene variations in the Diels Alder reaction, cyclohexa-1,3-diene and cyclopentadiene were used to make tetracyclics **40**, **41** and **42**. Confirmation of the structure of **40** and **42** was achieved by X-ray crystallography (see supplementary information). During the synthesis of **42**, it was found necessary to reduce the alkene derived from the diene due to undesired ring opening occurring in the subsequent RCM reaction, presumably as a consequence of release of inherent ring strain in the embedded cyclopentene ring that was not present in the cyclohexene analogue.



Scheme 5. *Reagents and Conditions*: a) TfN(AlMeCl)$_2$, CH_2Cl_2, 60 ºC, 100% b) BH_3.THF, then H_2O_2, H_2O 55%.

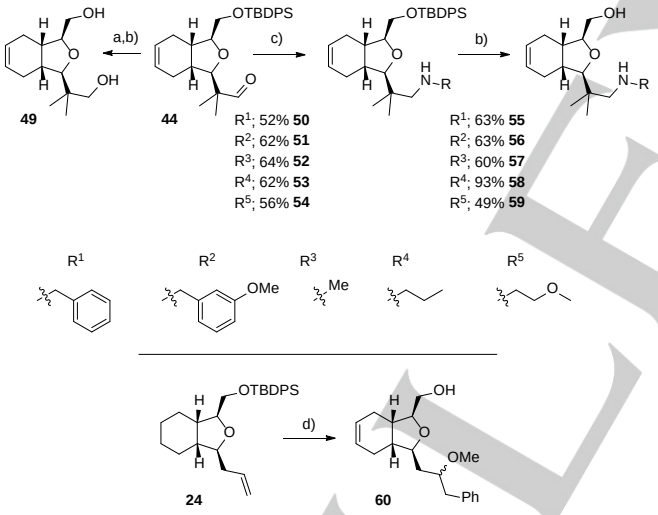
The Mukaiyama aldol reaction on lactol **11** provided a means of introducing further substitution and a handle for elaboration. To this end, adducts of general structure **43** were formed as single

enantiomers by reacting hemiacetal **11** with a range of silyl enol ethers. As in the example of allyltrimethylsilane addition above (Scheme 2), the cis products were observed exclusively or as the major component (85:15 in the formation of **48**). Silyl ethers **44**, and **45** were obtained, as well as alcohols **46, 47** and **48** following silyl deprotection (Scheme 6).



Scheme 6. *Reagents and Conditions*: a) Silyl enol ether, $BF_3.OEt_2$ (TMSOTf for **46**), CH_2Cl_2, -78 ºC 36-97%.

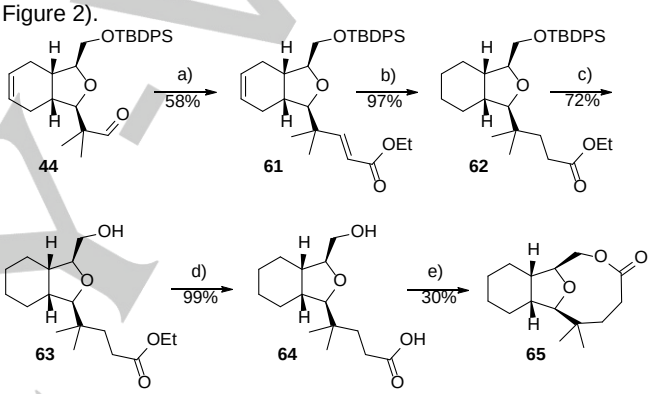
With aldehyde **44** in hand, derivation was exemplified either by reduction to diol **49**, or through reductive amination with the amines listed in Scheme 7. Deprotection of the amines **50**-**54** with TBAF provided alcohols **55**-**59** in good yield.



Scheme 7. *Reagents and Conditions*: a) $NaBH_4$, THF, MeOH 82% b) TBAF, THF, 41-93% c) amine, $NaBH(OAc)_3$, DCE, 52-64% d). $PhSiMe_3$, $AuCl(PPh_3)$, Selectfluor, MeOH, MeCN, then TBAF 29%.

Modification of the terminal olefin in **24** was also exemplified. Oxyarylation[34] using a gold (I) catalyst in the presence of Selectfluor with phenyltrimethylsilane gave ether **60** as an inseparable 4:1 mix of diastereomers (Scheme 7).

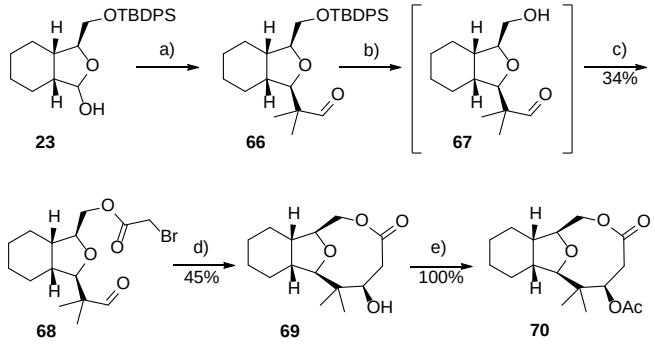
An alternative lactonisation approach to forming an oxygen containing nine-membered ring system and thus provide library members with closer correspondence to the [6,5,9]-tricyclic core of the natural product family was attempted from aldehyde **44**. A Horner-Wadsworth-Emmons reaction gave α,β-unsaturated ester **61** (Scheme 8). Reduction of both alkenes by hydrogenation over palladium gave ester **62**. Deprotection of the silyl group with TBAF followed by ester hydrolysis gave acid **64** in 71% over two steps. Lactonisation was initially attempted using the Yamaguchi protocol,[35] via the intermediate 2,4,6-trichlorobenzoyl anhydride. None of the desired lactone was observed in a number of attempts, with a dimeric species the only isolated product seen. A more successful approach used conditions developed by Shiina,[36] whereby a solution of acid **64** was added slowly by syringe pump over a 15 h period to a solution of 2-methyl-6-nitrobenzoic anhydride and DMAP in dichloromethane. Using these conditions, lactone **65** was isolated in 30% yield. Interestingly, an IR absorption for the carbonyl group was observed at 1730 cm^{-1}, suggesting the carbonyl group to be significantly twisted out of plane from the lowest energy lactone conformation (cf. crystal structure of **69**, Figure 2).



Scheme 8. *Reagents and Conditions*: a) triethylphosphonoacetate, NaH, THF, b) Pd/C, EtOAc, H_2 c) TBAF, THF, d) LiCl, H_2O, THF, e) 2-methyl-6-nitrobenzoic anhydride.

A SmI_2-mediated Reformatsky reaction approach was also found successful in the synthesis of a 9-membered lactone. The Reformatsky reaction has been shown previously to give high yields and controlled stereochemistry in the synthesis of a variety of natural product ring systems,[37] and more pertinently in medium ring synthesis.[38] Here, alcohol **23** was subjected to the Mukaiyama aldol/TBAF deprotection sequence used above to give unstable alcohol **67** (Scheme 9). Bromoacetyl bromide acylation followed by SmI_2 induced cyclisation gave alcohol **69** in 45% yield. In addition, alcohol **69** could be further derivatised if required, such as to acetate **70**. The structure and absolute stereochemistry of **69** was confirmed by crystallography (Figure 2). As with lactone **65**, an unusual IR carbonyl stretch of 1723 cm^{-1} was observed for **69** as a consequence of a 33° twist out of conjugation with the ester oxygen.

With synthetic routes to 9-membered lactones in hand, focus returned to accessing 9-membered ethers. Starting from alcohol **25**, synthesised as shown in Scheme 2, oxidation to aldehyde **71** and subsequent reaction with but-3-en-1-ylmagnesium



Scheme 9. *Reagents and Conditions*: a) $BF_3.OEt_2$, trimethyl((2-methylprop-1-en-1-yl)oxy)silane, CH_2Cl_2, -78 ºC-rt, b) TBAF, THF c) bromoacetyl bromide, Et_3N, CH_2Cl_2, 34% over three steps d) SmI_2, THF, e) Ac_2O, DMAP, rt.

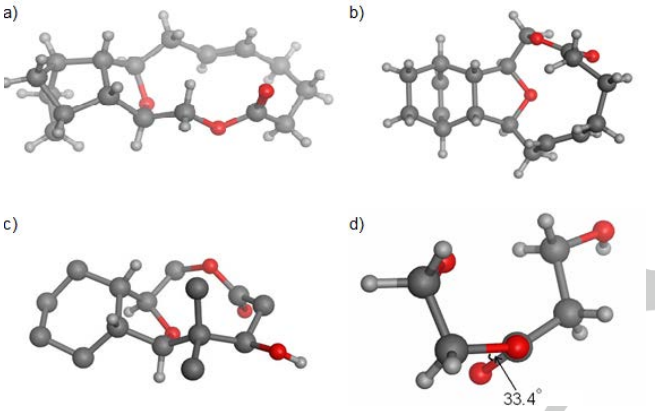
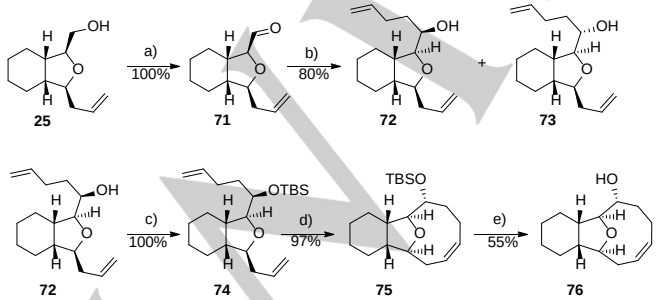


Figure 2. X-ray crystal structure of **42** (a), **40** (b), **69** (c) and a partial view of **69** (d) along the O-C lactone single bond.

bromide gave alcohols **72** and **73** as a 5:3 separable mixture of isomers (Scheme 10). Following TBS protection, only the major isomer **72** was found to cyclise in the RCM reaction, giving tricyclic **75** in 97% yield. A NOESY correlation between both [6,5] bridgehead hydrogens and the siloxy substituted C-H hydrogen in **75** as highlighted in Figure 3 was used to confirm the sterochemistry of Grignard addition. Deprotection with TBAF gave alcohol **76** in 55% yield.



Scheme 10. *Reagents and Conditions:* a) Dess Martin reagent, CH_2Cl_2 b) but-3-en-1-ylmagnesium bromide, THF c) TBSOTf, DIPEA, CH_2Cl_2, d) Grubbs II (10 mol%), CH_2Cl_2, reflux, e) HCl, EtOH, Et_2O.

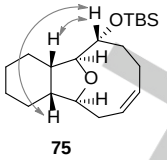


Figure 3. ^{1}H-^{1}H NOESY correlations in tricyclic **75**.

The 2,11-cembranoid based library of 44 compounds synthesised using the routes and methods outlined above is shown in full in Figure 4. As the compounds were intended for use in drug discovery screening programmes, an assessment of the library in terms of structural diversity, physicochemical properties and potential biological activity was undertaken. An analysis of the molecular properties of the compounds in Figure 4 is compiled in Table 1. For comparison, the properties of 183 cembranoid natural products taken from reviews[1,39] and a random sampling set of 358 compounds taken from a substantially larger 75000 screening library at The Institute of Cancer Research (ICR) are also listed for comparison. The ability of a random sampling set of a large screening library to represent the entirety has been demonstrated by Feher and Schmidt,[21] and has been applied here. The ICR screening library itself was chosen by typical criteria for lead-like/drug like libraries, including limits on predicted/calculated physicochemical parameters and choice of scaffolds, with a high frequency of heterocyclic aromatic and aliphatic scaffolds[26,27]. As a means of visually assessing the diversity between the groups, a principal component analysis (PCA)[41] was performed. PCA has been used widely in chemoinformatics[42] and particularly in the description of chemical space.[22,43] The analysis, carried out using SIMCA-P+[44] and visualised using Spotfire,[45] showed (Figure 5) that the ICR screening compounds (red) cover a wide range of chemical space as would be expected from a well designed screening deck; however, little overlap exists with the cembranoid natural products (blue) which occupied a discrete and well defined region defined by the PCA. By contrast, the cembranoid-inspired library as synthesised here (green) was found to occupy an area of chemical space between the natural products and the ICR screening collection, showing that the cembranoid-inspired library begins to effectively bridge the chemical space between classical drug discovery screening compounds and the natural products.

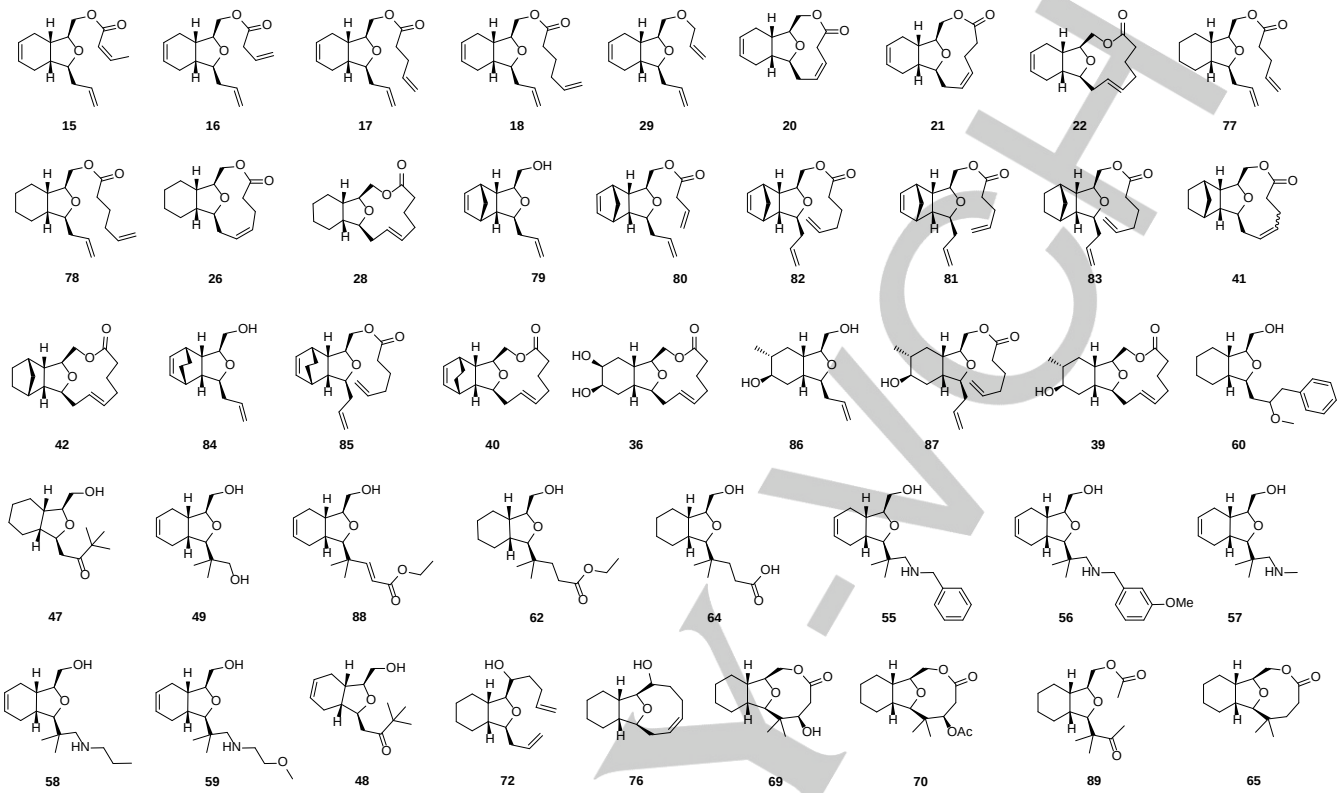


Figure 4. Cembranoid-like library

Table 1. Arithmetic mean and standard deviation of the molecular properties of the cembranoid-inspired library, 2,11-cyclised cembranoid natural products and a random sampling set from The Institute of Cancer Research screening collection.

	Cembranoid-inspired library	2,11-cyclised Cembranoids	ICR Screening Collection sample
No. of compounds	44	183	358
MW	275 (28)	441 (77)	332 (59)
AlogP	2.6 (0.8)	3.1 (1.1)	2.6 (1.1)
No. H acceptors	3.2 (0.7)	6.4 (2.0)	4.1 (1.4)
No. H donors	0.7 (0.8)	1.0 (0.9)	1.1 (0.8)
No. rings	2.6 (0.6)	3.4 (0.6)	2.9 (0.9)
No. aromatic rings	0.07 (0.26)	0 (0)	2.0 (1.0)
No. Oxygen atoms	3.1 (0.7)	6.4 (2.0)	2.4 (1.4)
No. hydrogen atoms	25 (2.9)	39 (5.9)	18 (5.3)
No. Stereoatoms	4.7 (0.9)	8.9 (1.5)	0.04 (0.33)
No. bonds	21 (2.2)	34 (5.4)	25 (4.7)
No. Aromatic bonds	0.43 (1.6)	0 (0)	11 (5.2)
No. rotatable bonds	4.8 (3.2)	5.9 (3.1)	4.5 (2.0)

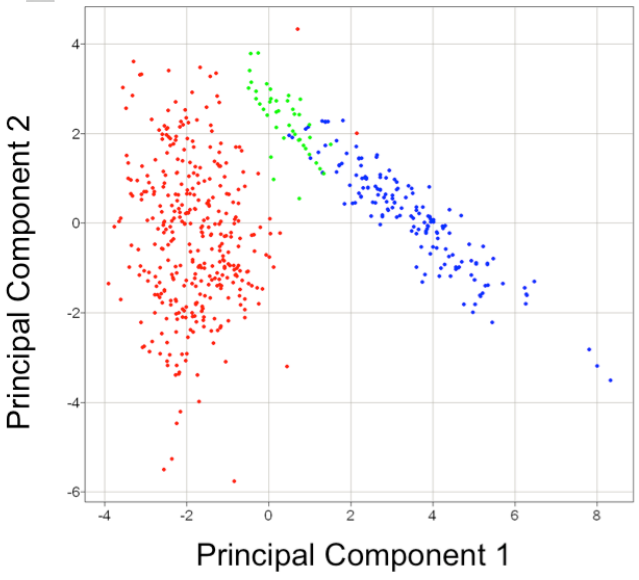


Figure 5. Principal component analysis (PCA) of the cembranoid-inspired library (green, 44 structures), 2,11-cyclised cembranoid natural products (blue, 183 structures) and the ICR screening sample (red, 358 structures). Performed using SIMCA-P+[44] and displayed using Spotfire.[45]

The library prepared was assessed for both solubility and permeability, with representative results shown in Table 2. Due to a lack of UV chromophore and/or poor mass spectrometry ionisation, nephelometry[46] was used to measure solubility. PAMPA (parallel artificial membrane permeability assay)[47] was used to assess permeability. Generally, the compounds were found to have high aqueous solubility and permeability. Of the 44 compounds in Figure 4, all were measured to have greater that 100 uM aqueous solubility, with 34 greater than 500 uM and 21 greater than 1000 uM. In regard to the 28 compounds that ionised sufficiently well to be detected in PAMPA, 25 were found to have high permeability, greater than $25x10^{-6}$ cms^{-1}. For the specific example of compound **28** in addition to good aqueous solubility and high PAMPA, the compound showed moderate permeability across a monolayer of Caco-2 human intestinal cancer cells,[48] ($16x10^{-6}$ cms^{-1}) with no evidence of transporter efflux.

Table 2. Solubility and permeability of selected representative compounds

	compounds			
	28	**15**	**65**	**76**
Sol (uM)	550	500	550	500
Permeability (Pe, $x10^{-6}$ cms^{-1})	52	25	>150	Not detected[a]

Solubility measured by nephelometry. Eqm indicates maximum permeability achieved within the assay timescale. n.d. not done. [a] indicates undetectable due to low ionisation.

A selection of 15 of the cembranoid inspired compounds were screened against a panel of 60 cancer cell lines at the National Cancer Institute screening panel (see supporting information).[49] This cell-based assay aims to discover compounds with a strong cytostatic or cytotoxic growth inhibition over 48 hours. Unfortunately, only low levels (up to 20%) of cell growth inhibition were seen when screened at a single concentration of 10 uM. Of these, compound **28** gave 17% inhibition of proliferation in the PC3 human prostate cancer cell line. A full dose response curve obtained for compound **28** (Figure 6) found a GI_{50} of 63 uM. It is important to note that the cembranoid family itself is not overtly cytotoxic, with most examples screened to date ranging from single figure micromolar IC_{50} to inactive in the cytotoxic assays used.[1] One obvious exception to this is sclerophytin A, with in vitro IC_{50} of 3 nM in L1210 mouse lymphocytic leukemia cells,[51] although the natural product showed no effect on proliferation in PC3 cells at 50 uM. Therefore, within this context, compound **28** displays typical cytotoxicity for the natural product family,[39] with reduced structural and synthetic complexity.

Whereas cembranoid natural products may not be inherently cytotoxic, an appreciable number do display an ability to inhibit the migratory and invasive properties of cancer cells.[50] The effect of compound **28** on a PC3 based migratory assay was therefore determined. Tricyclic **28** at 3- and 5-fold GI_{50} concentrations demonstrated a reduction to near basal levels of migration (Figure 6). Although less potent than a number of the 2,11-cembranoid natural products (most active being sclerophytin A, with 85% inhibition of migration at 50 uM),[50] it does demonstrate that the anti-migratory activity can be retained in a greatly simplified structural motif.

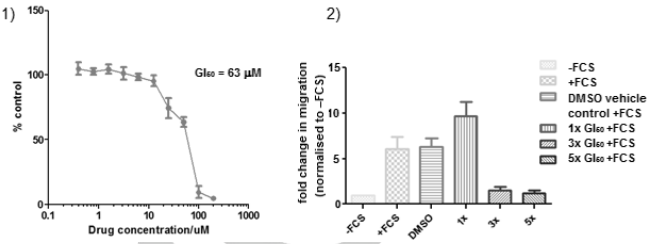


Figure 6. 1) Concentration-response curve for the antiproliferative effect of **28** on PC3 cells in vitro 96 h assay. 2) Compound **28** inhibiting the migration properties of PC3 TEM cancer cells. FCS- fetal calf serum. Y-axis shows fold-change in cell migration normalised to the absence of FCS.

Conclusions

The 2,11-cembranoid class of natural products has served as a rich source of inspiration from both a synthetic and biological perspective. Here, we have developed a number of synthetic approaches to produce a library of structurally simplified cembranoid inspired derivatives. An assessment of the molecular properties of the hexahydroisobenzofuran-based library found them to be complementary to both the cembranoid natural products as well as a sample set of an in-house medicinal chemistry screening collection, providing potential access to novel chemical space. A screen of physicochemical properties found the library to have desirable properties, namely aqueous solubility and cell membrane permeability, essential to be useful in both biochemical and cell based assays. The illustrative synthetic routes developed could readily be expanded to more densely populate the chemical space occupied by the small library and the natural products, or indeed to follow up any hits from future screening. A preliminary screen of a sample set of the library found compound **28** to weakly inhibit the growth of PC3 cells, as well as having an inhibitory effect when screened in a cell migration assay. These data suggest that some of the bioactivities observed in cancer cells for the structurally complex 2,11-cembranoid natural products can be recapitulated with much simpler scaffolds derived from the embedded hexahydroisobenzofuran core.

Experimental

All synthetic methods are included in the Supplementary section. Crystallographic data is available free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. CCDC numbers; **26** CCDC 1010197, **40** CCDC 1011320**, 42** CCDC 1435146**, 69** CCDC 1435148**.**

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The authors declare no competing financial interest.

Keywords: Medium-ring compounds • Oxygen heterocycles • Medicinal chemistry • Molecular diversity • Synthesis design

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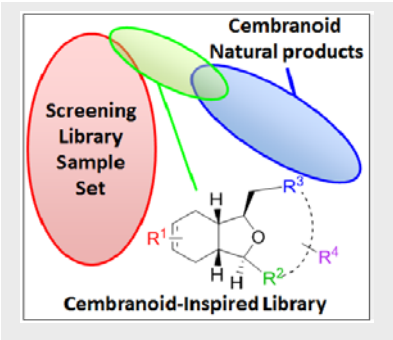

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Synthesis and Evaluation of a 2,11-Cembranoid-inspired Library