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PAPER

Synthesis of novel molecular probes inspired by harringtonolide†

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A novel harringtonolide-inspired scaffold containing a cycloheptatriene ring and two fused cyclopentane rings has been synthesised from simple starting materials. The scaffold, containing a similar substitution pattern and relative stereochemistry to the complex diterpenoid, has been enumerated into a small library of derivatives. One of these library members has been converted into a sub-library of substituted triazoles using copper-catalysed azide-alkyne cycloaddition (click) chemistry. The scaffold may be useful in drug discovery or in the preparation of additional molecular probes for chemical biology.

Introduction

Small molecules are critical tools for understanding important cellular events and biological pathways involved in health and disease. The identification of new structural classes is one of the many drivers *en route* to understanding biological systems and developing innovative, safer therapeutics with novel modes of action. This is a truly daunting task given there are in excess of an estimated 10^{62} drug-like molecules with a molecular weight below 500 Da comprised of the atoms that make up current small molecule therapies.[1] Indeed, it would be impossible to synthesize even one molecule of each member from this set considering there is estimated to be 'only' 10^{50} atoms on Earth.[2] Various strategies that attempt to address the relationship between chemistry and biology space have been developed in an effort to meet this challenge.

One popular approach, particularly within the pharmaceutical industry, has been to exploit 'privileged' structures with known drug-like properties.[3] The term was originally introduced to describe motifs that could be elaborated into libraries of drug-like molecules (ligands) in which different members could selectively and potently interact with a variety of unrelated biological targets.[4,5]

Harringtonolide **1** was first isolated from the seeds of the yew species *Cephalotaxus harringtonia* (Taxaceae) and shown to inhibit plant growth in tobacco and beans.[6] Soon after, **1** was independently discovered in the bark of the related Chinese species, *Cephalotaxus hainanensis*, and found to be active against Lewis lung carcinoma, Walker carcinoma, Sarcoma-180 and L-1210, L-615 and P-388 leukemias.[7] It has also exhibited *in vitro* activity against influenza type A, Newcastle disease, Japanese B encephalitis and vaccinia viruses.[8] The breadth of biological activity that spans plant and human health attributed to **1** suggests that it may contain a privileged substructure.

Interestingly, homoharringtonine **2**, which is currently in phase II/III trials for chronic myeloid leukemia,[9] is produced by the same species while Taxol® **3**, an FDA approved drug for various cancers,[10] was originally isolated from another member of the Taxaceae family, *Taxus brevifolia* (Fig. 1).[11]

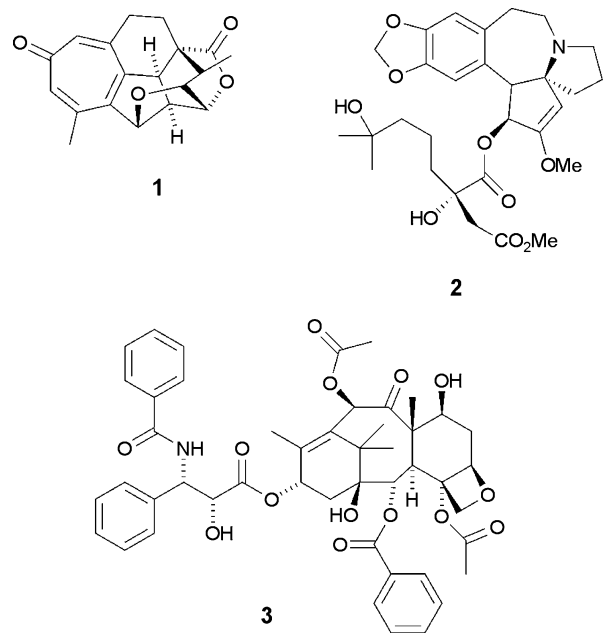

Fig. 1 Bioactive molecules isolated from the Taxaceae family.

Results and discussion

Scaffolds **4** and **5** (Fig. 2) were initially selected for synthesis (Scheme 1) because of the unusual 5-6-7 fused tricyclic substructure embedded in harringtonolide. Scaffold **4** incorporates

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† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of all previously unreported compounds, *i.e.* **15**, **16**, **17**, **20a–b**, **21a–f**, **23a–c**. See DOI: 10.1039/c1ob05299c

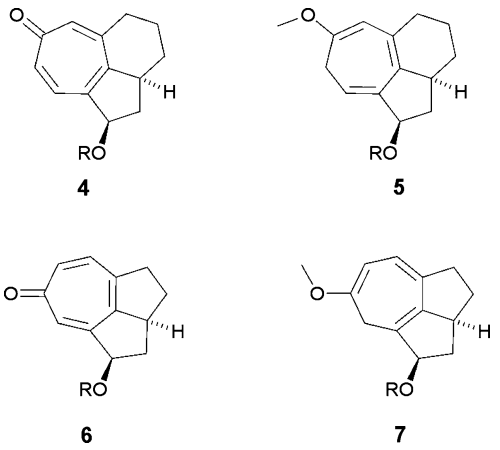


Fig. 2 Scaffolds **4** and **5** incorporating the 5-6-7 tricycle of harringtonolide and scaffolds **6** and **7** containing a 5-5-7 motif inspired by the natural product.

the tropone moiety of **1** while **5** is the methoxycycloheptatriene analogue. We also saw tactical value in preparing a second scaffold *inspired* by the natural product that could afford a library of closely related structural analogues. Ideally, such a motif would be novel, derived from readily available starting materials and synthesized *via* the same reaction sequence as that of **4** and **5**.

The 5-5-7 fused tricyclic framework in **6** and **7** has not previously been reported, which was somewhat surprising given that fused seven-member ring systems are found in an increasing number of natural products of interest to the biological and pharmaceutical communities.[12,13] For example, it has recently been proposed that the 5-7-5 lactone ring system found in helenalin, parthenin and chinensiolide B should be regarded as a privileged scaffold due to the diverse biological activity exhibited by these compounds.[14] We therefore pursued the synthesis of the 5-5-7 tricycle on account of the novel carbon skeleton containing a highly desirable 5-7 fused ring system.

Positioning of the methoxy group *gamma* to the carbonyl and use of a 5-membered ring in the starting material (Scheme 2) was also reasoned to provide sufficient variation in the key intermediate and related downstream products so as to ameliorate any potential stability issues that may be encountered with the series based on the natural product.[15]

The methoxycycloheptatriene motif in **5** and **7** would clearly have a different electron density to the tropone substructure of **4** and **6**. Thus, libraries based on **5** and **7** would not be expected to mimic binding of the tropone moiety in the natural product. However, we considered the synthesis of **5** and **7** to nevertheless be important from the perspective of being able to generate novel probe libraries that may afford valuable SAR insights. In this sense, our objective was not necessarily to produce scaffolds derived directly from the natural product but rather explore the chemistry of similarly substituted analogues based on, or inspired by, the unusual carbon framework of **1**.

An overlay of the most dissimilar scaffolds, **4** and **7** (R = CH_3), as shown in Fig. 3 reveals that the 5-5-7 system inspired by the natural product closely approximates the 5-6-7 assembly in terms of placement of the oxygen atoms relative to each other. Additionally, Scitegic® EPFP4 fingerprints generated from Bennis and Murko molecular framework representations were compared using the Tanimoto coefficient (Tc).[16] The calculated Tc of 0.74 between scaffolds **4** and **7** (R = H) indicates that the 5-6-7 and 5-5-7 scaffolds are within the commonly used heuristic (≥ 0.7) for clustering similar chemical structures.[17]

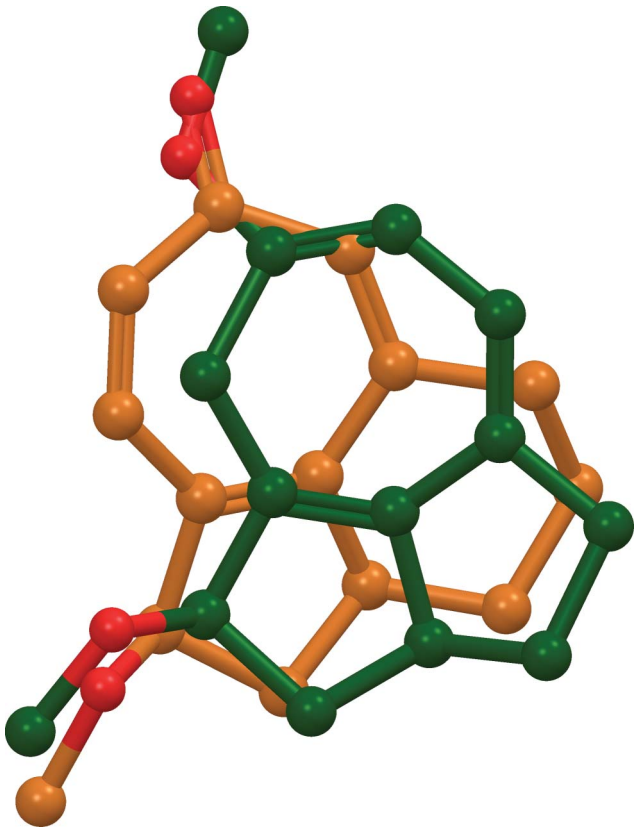
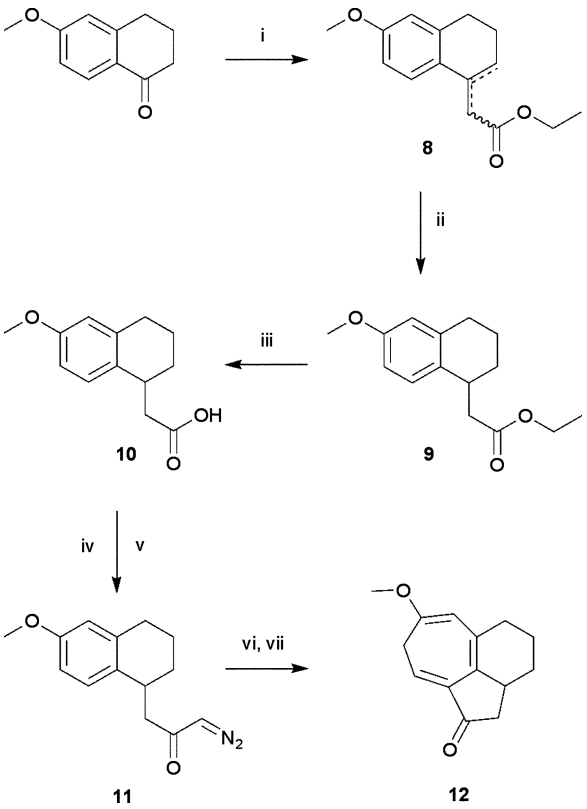


Fig. 3 Overlay of the natural product 5-6-7 substructure, **4**, shown in orange and the 5-5-7 series scaffold of **7** shown in green.

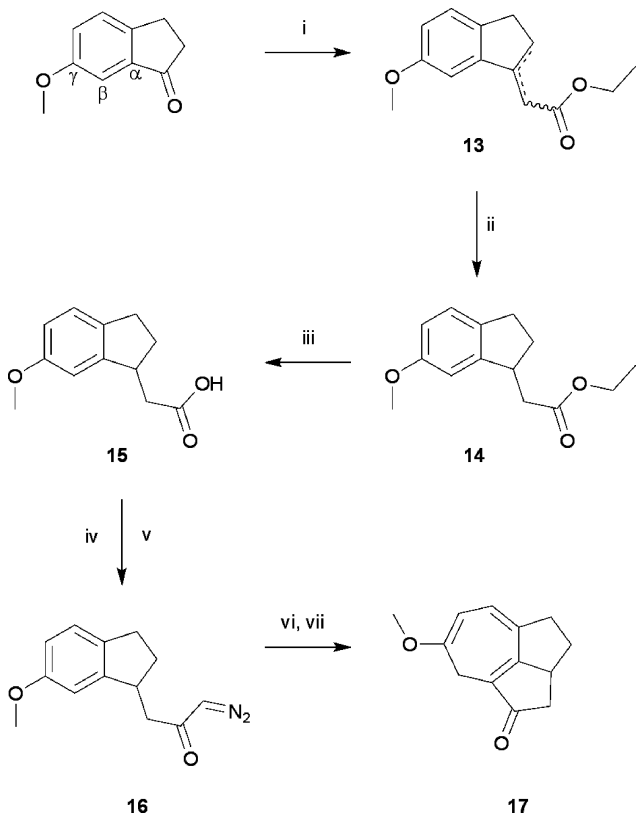
Our synthetic strategy for the preparation of scaffolds **4–7** was guided by model studies involving intramolecular cyclopropanation of a benzenoid synthon described by Mander and co-workers *en route* towards the first total synthesis of **1**.[18,19] Scheme 1 outlines the synthesis of intermediates **8–12** to construct the 5-6-7 framework found in the natural product while Scheme 2 summarises the synthesis of analogues **13–17** leading to the 5-5-7 tricycle.

Generally, more care or longer reaction times were necessary for the 5-6-7 series but, overall, production of **12** and **17** proceeded smoothly in fair to excellent yield (Table 1). Rhodium acetate was also investigated in the critical reaction to install the cycloheptatriene ring in an effort to improve yields. However, product formation for both series was typically 10% lower than with the copper catalyst in our hands.

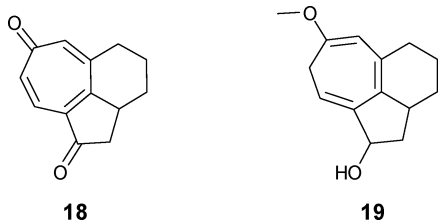
Mander's report[15] that the tropone derived directly from the key intermediate **12**, *i.e.* **18**, was unstable influenced the planning of the next stage of our synthesis. Library enumeration would proceed *via* the scaffolds **19** and **20a** derived from reduction of the carbonyl group on the key ketocycloheptatriene intermediates, **12** and **17** respectively, and not from reduction of the same group *via* the tropones.



Scheme 1 Synthesis of the key intermediate **12** for scaffolds based on the 5-6-7 ring system embedded in harringtonolide.



Scheme 2 Synthesis of the key intermediate **17** for scaffolds based on the 5-5-7 inspired by harringtonolide.



Unfortunately, in the case of the 5-6-7 series, any further manipulation of **12** proved futile as the ensuing products were unstable and either decomposed upon standing or further reaction immediately following purification. Indeed, while **12** could be obtained as a white powder following chromatography, it gradually turned grey over 2–3 days despite being stored in the dark at 4 °C. Attempted reduction of the ketone functionality with $NaBH_4$ yielded the unstable alcohol **19** which decomposed completely following reaction of freshly purified material with different benzyl bromides.

In an effort to retrieve this series, we converted **12** to **18** despite reservations about proceeding *via* the tropone. While the crude tropone was produced in reasonable yield, it decomposed during purification on silica or upon storage in the dark at 4 °C thus obviating reduction of the ketone on the five-membered ring to afford **4** (R = H) and effectively extinguishing this route for subsequent enumeration.

It was therefore heartening to observe that the closely related **17** was not only obtained in improved yield following the crucial cyclopropanation step but was also considerably more stable than **12**. The ketocycloheptatriene **17** could readily be converted to a mixture of *syn* and *anti* alcohols, **20a** and **20b**, in a diastereomeric ratio of 95 : 5 respectively, and near quantitative yield using $NaBH_4$. Both alcohols are stable at room temperature, unlike the corresponding analogues in the 5-6-7 series.

Table 1 Reaction conditions and yields *en route* to the key intermediates **12** and **17**

		yield (%)	
step	conditions	5-6-7 series	5-5-7 series
i	Triethyl phosphonoacetate, NaH, toluene, reflux	64[20]	72[21]
ii	Pd/C, H_2, ethanol, 50 °C, 5 h	91[20]	98[21]
iii	1 M NaOH, aq. MeOH, 20 °C	98	98
iv	Oxalyl chloride, DMF, –20 °C, 2 h[a]		
v	Diazomethane, ether, 0 °C	90[b]	85[b]
vi	Copper(II) ethylacetoacetate		
vii	DBU	52[b]	75[b]

[a] A temperature of –10 °C was used for the 5-5-7 series. [b] Overall yield when combined with previous step.

The relative stereochemistry of each isomer was established by ROESY NMR spectroscopy. A through-space interaction was observed between the C1 and C2a protons in $CDCl_3$ of the major product (Fig. 4) but not the minor adduct. Unfortunately, the hydroxyl proton signal for both the *syn* and *anti* adducts was not apparent in $CDCl_3$ so that any additional correlations supporting the relative stereochemistry of each isomer was not possible. However, changing the solvent to acetone-D_6 allowed the hydroxyl proton signals for the *syn* and *anti* isomers to

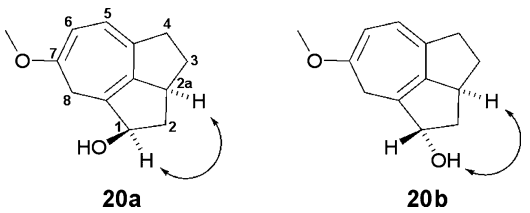


Fig. 4 *syn* (**20a**) and *anti* (**20b**) Adducts obtained following reaction of **17** with $NaBH_4$. ROESY correlations specific to each isomer are shown.

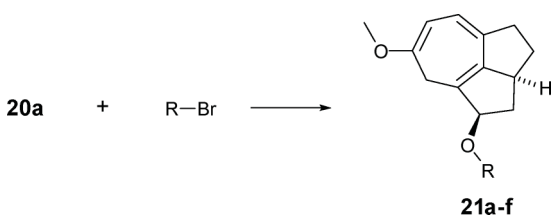
be observed as doublets at δ_H 3.91 and 3.66 ppm respectively. This facilitated detection of a through-space interaction between the H atoms attached to the hydroxyl oxygen and C2a in the case of the minor *anti* isomer **20b** only. Importantly, the ROESY NMR experiments established that the major product had the same relative stereochemistry as harringtonolide's fused 5-7 substructure.

The *syn* adduct is presumably favored because of steric approach control. This occurs when delivery of hydride takes place from the same face as the hydrogen atom on C2a. The *syn* isomers were not resolved into their enantiomers as we considered the racemic compound adequate for the purposes of a probe/lead generation library.

Having successfully generated scaffold **20a**, we next set about converting it into a library of probe molecules. Thus, **20a** was reacted further with a selection of benzyl-, alkyl-, and propargyl bromides to afford the corresponding ethers **21a–f** in moderate to good yields (Table 2).

The propargyl ether **21f** was subsequently converted into a sub-library of substituted triazoles using copper-catalysed azide-alkyne cycloaddition (click) chemistry. Thus, reaction of benzylazide **22**, derived from the reaction of benzyl bromide with NaN_3, under standard click chemistry reaction conditions afforded the triazole **23a** in good yield with the expected regioselectivity[22] (Scheme 3, Table 3). Preparation of the corresponding alkyl azides from n-butyl and i-pentyl bromides was more problematic, most likely due to their low boiling points which hampered isolation, and necessitated use of a modified method to prepare the triazoles. Employing a one-pot, three-component microwave-assisted procedure directly afforded **23b–c** with exclusive formation of the

Table 2 Reaction conditions and yields of ethers **21a–f**



21	R	conditions	yield (%)
a	$CH_2C_6H_5$	NaH, THF, 25 °C, 40 h	72
b	$CH_2(4\text{-}ClC_6H_4)$	NaH, THF, 25 °C, 40 h	89
c	$CH_2(4\text{-}FC_6H_4)$	NaH, THF, 25 °C, 40 h	73
d	$CH_2CH_2CH_2CH_3$	NaH, DMF, microwave, 110 °C, 45 min	55
e	$CH_2CH_2CH(CH_3)_2$	NaH, DMF, microwave, 115 °C, 45 min	52
f	$CH_2C{\equiv}CH$	NaH, THF, 60 °C, 48 h	55

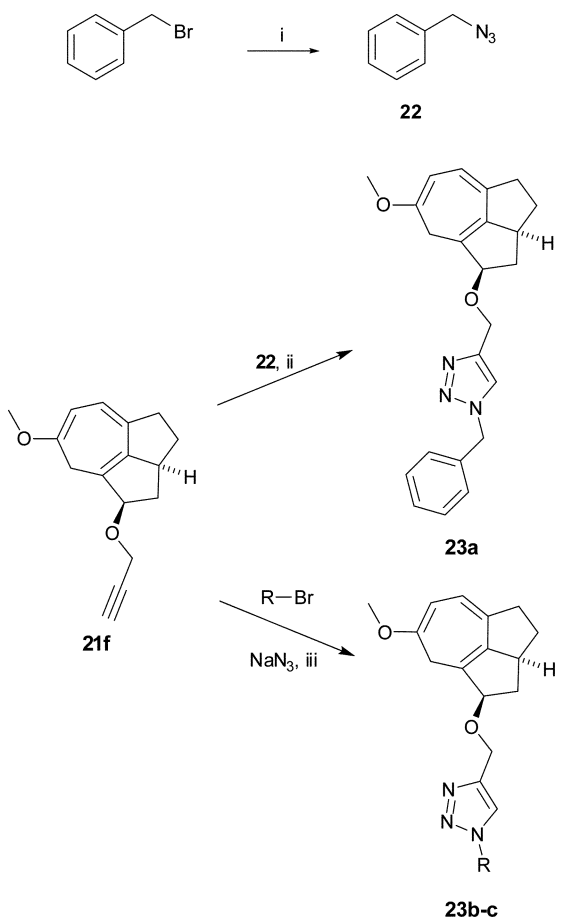
Table 3 Reaction conditions and yields of triazoles **23a–c**

23	R	conditions	yield (%)
a	$CH_2C_6H_5$	(i) NaN_3, DMF, 25 °C, 12 h (ii) *t*-BuOH/H_2O, $CuSO_4$, sodium ascorbate, 25 °C, 16 h	85[a] 60
b	$CH_2CH_2CH_2CH_3$	(iii) *t*-BuOH/H_2O, Cu/$CuSO_4$, microwave, 110 °C, 20 min	52[b]
c	$CH_2CH_2CH(CH_3)_2$	(iii) *t*-BuOH/H_2O, Cu/$CuSO_4$, microwave, 110 °C, 20 min	45[b]

[a] Two step procedure showing yield of individual reactions. [b] Overall yield for the one pot cycloaddition-alkylation procedure performed in a sealed microwave reactor.

1,4-disubstituted regioisomer in reasonable yield (Scheme 3, Table 3).[23]

Production of the tropones from the corresponding methyl ethers remains elusive. Nucleophilic displacement reactions employing **21a** as the model system and NaI or thiolate anions in DMSO or TMSI in CH_3CN did not afford the desired product. Starting material was recovered in all cases. Use of Lewis acids such as BBr_3 or $Hg(NO_3)_2$, not unexpectedly, cleaved both ethers of **21a** and afforded a complex mixture of products. Mass spectrometric analysis of the crude reaction mixtures indicated that **4** (R = H)



Scheme 3 Synthesis of triazoles **23a–c** from benzyl-, n-butyl- and i-pentyl bromide starting materials and **21f** using two-step (**23a**) and one-pot three-component procedure (**23b–c**).

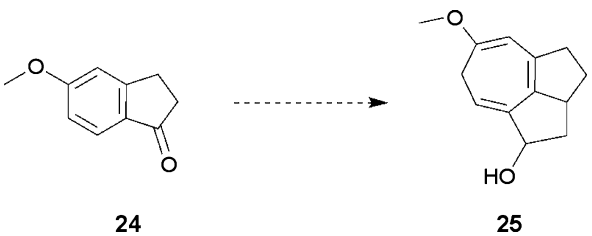
was present but all attempts to isolate the compound using silica gel chromatography failed.

Conclusions

The work described here represents the first attempt to incorporate structural elements of an unusual and highly complex diterpenoid, harringtonolide, into a library of simpler probe molecules. The novel 5-5-7 ring system inspired by the natural product was synthesized from readily available, inexpensive starting materials. Key intermediates were easily isolated, purified and stored to facilitate production of the scaffold **20a** and enumeration into libraries **21a–f** and **23a–c** containing a fused cycloheptatriene moiety.

Although the final tropone substructure was not obtained, the resulting library is nevertheless based on a scaffold that incorporates a fused 5-7 ring with appropriate substitution and stereochemistry at positions that closely resemble that of the natural product.

This preliminary study suggests that use of 5-methoxyindanone **24** as the starting material may afford a library based on the 5-5-7 scaffold **25** (Scheme 4) in which the positioning of the two oxygen functionalities more closely resembles templates based on the natural product, *e.g.* **19**. The synthesis of **25** will shed light on whether it is the replacement of the 6-membered ring by a 5-membered ring or the different substitution pattern between oxygen functionalities in **20** that confers greater stability.



24 **25**

Scheme 4 Production of a second 5-5-7 series based on 5-methoxyindanone.

Finally, while our motivation is defined by a continuing quest to identify new privileged structures and scaffolds embedded within natural products for drug discovery,[24,25] screening the cycloheptatriene probe library also has potential to provide additional insights into the already rich biological activity of harringtonolide itself. In this respect, our approach complements the ongoing efforts of others[26,27] to find accessible routes to the synthesis of **1** and closely related analogues such as hainanolidol for screening and drug discovery.

Experimental

General

Starting materials and reagents used in reactions and purification were obtained from commercial suppliers and used without further purification unless otherwise stated. Silica chromatography was conducted using Merck Kieselgel 60 silica as the adsorbant. IR spectra were recorded on a Bruker Tensor 27 spectrometer. Proton and carbon-13 nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded on a Varian Unity INOVA 500 MHz spectrometer. The ^{1}H NMR chemical shifts were referenced to the residual $CHCl_3$ peak at 7.26 ppm in $CDCl_3$ or CH_3COCH_3 resonance at 2.09 ppm in acetone-D_6. The ^{13}C NMR chemical shifts were referenced to the central peak of $CDCl_3$ at 77.16 ppm.[28] ^{1}H NMR and ^{13}C NMR assignments were made with the aid of COSY, ROESY, HMBC and HSQC experiments. Low resolution ESI mass spectra (LRESIMS) were recorded on a Waters ZQ mass spectrometer. High resolution ESI mass spectra (HRESIMS) were measured on a Bruker Daltonics Apex III 4.7e Fourier transform mass spectrometer, fitted with an Apollo API source. Melting points (mp) were recorded on a Cole-Parmer hot stage and are uncorrected. Schrödinger's Macromodel 9.8 and Maestro 9.1 were used to minimise and superimpose the 5-5-7 and 5-6-7 scaffolds respectively. Accelrys' Pipeline Pilot Student Edition 6.1.5 was used to calculate Tanimoto similarity coefficients.

Cheminformatics

The 5-6-7 and 5-5-7 ring scaffolds **4** (R = H) and **20a**, respectively, were minimised using the MMFFs force-field with default settings (H_2O solvation, PRCG gradient optimization) on Macromodel (MacroModel, version 9.8, Schrödinger, LLC, New York, NY, 2010). The minimised structures were overlaid by manual manipulation into the same plane followed by rigid superposition in Maestro (Maestro, version 9.1, Schrödinger, LLC, New York, NY, 2010) by defining the corresponding oxygen atom pairs.

As described by Shelat and Guy,[17] the MurkoAssemblies option of Pipeline Pilot's *Generate Fragments* component (Pipeline Pilot Student Edition, version 6.1.5, Accelrys Software Inc., San Diego, CA, 2007) was used to transform compounds **4** (R = H) and **20a** into their respective scaffolds while retaining exocyclic double bonds and excluding α attachment atoms. The Tanimoto similarity coefficient (Tc) was calculated from the generated scaffolds using SciTegic® path-based fingerprints with Daylight-like atom types and a 4-atom maximum depth (EPFP_4). Identical results were obtained using SciTegic® Extended Connectivity fingerprints (ECFP4).

Ethyl 6′-methoxy-1′,2′,3′,4′-tetrahydro-1′-naphthylacetate (9)

Triethyl phosphonoacetate (10.54 g, 47.0 mmol) was added dropwise over 25 min to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 1.88 g, 47.0 mmol) in dry toluene (30 mL) at 0 °C. The clear reaction mixture was stirred at room temperature for a further 15 min and then cooled to 0 °C. A solution of 6-methoxy-1-tetralone (4.0 g, 22.7 mmol) in toluene (45 mL) was then added over 10 min after which time the reaction mixture was heated to reflux for 14 h. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (50 mL) and washed with brine (2 × 50 mL). The aqueous layer was extracted with ethyl acetate (2 × 30 mL) and the combined organic extracts washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure. The crude product was purified on silica (hexane : ethyl acetate, 98 : 2) to afford 3.59 g (64.2%) of **8** as an oil containing a mixture of *endo*- and (*E*, *Z*) *exo*-double bond isomers. The adducts were dissolved in ethanol (35 mL) without further purification and stirred in the presence of 10% Pd–C (110 mg) under a hydrogen atmosphere at 50 °C for 5 h. After this time, the reaction mixture was filtered through Celite® and concentrated at reduced pressure.

The crude product was purified on a silica column (hexane : ethyl acetate, 98 : 2) to afford 3.31 g (91%, 58.5% overall yield) of the title compound as a colourless oil with the same ^{1}H NMR spectrum and molecular ion as previously reported:[20] δ_H (500 MHz, $CDCl_3$) 7.07 (d, J = 8.5 Hz, 1H, H-8′), 6.70 (dd, J = 2.5, 8.5 Hz, 1H, H-7′), 6.60 (d, J = 2.5 Hz, 1H, H-5′), 4.17 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.76 (s, 3H, OCH_3), 3.29 (m, 1H, H-1′), 2.75 (m, 2H, $CHCH_2CO$), 2.66 (dd, J = 5.0, 10.0 Hz, 1H, H-4′), 2.48 (dd, J = 10.0, 14.75 Hz, 1H, H′-4′), 1.92–1.65 (m, 4H, H-2′, H′-2′, H-3′, H′-3′), 1.27 (t, J = 7.2 Hz, 3H, $COCH_2CH_3$); δ_C (125 MHz, $CDCl_3$) 173.02 (CO), 157.83 (C6′), 138.48 (C4′a), 131.69 (C8′a), 129.36 (C8′), 113.83 (C5′), 112.31 (C7′), 60.46 (CH_2CH_3), 55.34 (OCH_3), 42.34 (CH_2CO), 34.09 (C1′), 30.04 (C4′), 28.56 (C2′), 19.72 (C3′), 14.42 (CH_2CH_3); (+) LRESIMS m/z 271 $[M + Na]^+$.

6′-Methoxy-1′,2′,3′,4′-tetrahydro-1′-naphthylacetic acid (10)

The ester **9** (2.73 g, 11.0 mmol) was dissolved in 1 M NaOH (90% methanol in water, 60 mL) and stirred at room temperature for 3 h. The reaction mixture was concentrated, dissolved in water (50 mL), acidified with 5 M HCl (12 mL) and extracted with ethyl acetate (3 × 40 mL). The organic extract was washed with brine (2 × 40 mL), dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure to afford the crude product which was purified on a silica column (hexane : ethyl acetate, 85 : 15) to yield the title compound[29] as a white solid (2.37 g, 97.8%): mp 80–82 °C; δ_H (500 MHz, $CDCl_3$) 7.10 (d, J = 8.5 Hz, 1H, H-8′), 6.72 (dd, J = 2.5, 7.7 Hz, 1H, H-7′), 6.62 (d, J = 2.0 Hz, 1H, H-5′), 3.77 (s, 3H, OCH_3), 3.32 (m, 1H, H-1′), 2.81–2.70 (m, 3H, CH_2CO, H-4′), 2.56 (dd, J = 10.0, 15.5 Hz, 1H, H′-4′), 1.98–1.92 (m, 1H, H-2′), 1.87–1.71 (m, 3H, H′-2′, H-3′, H′-3′); δ_C (125 MHz, $CDCl_3$) 178.82 (CO), 157.92 (C6′), 138.53 (C4′a), 131.30 (C8′a), 129.30 (C8′), 113.91 (C5′), 112.43 (C7′), 55.35 (OCH_3), 41.93 (CH_2CO), 33.89 (C1′), 29.99 (C4′), 28.43 (C2′), 19.66 (C3′); (+)-LRESIMS m/z 243 $[M + Na]^+$; (+)-HRESIMS m/z 243.0992, $C_{13}H_{16}O_3$ $[M + Na]^+$ requires 243.0992.

3-(6′-Methoxy-1′,2′,3′,4′-tetrahydro-1′-naphthyl)-1-diazo-propane-2-one (11)

The title compound was prepared according to the method reported by Mander *et al.*[15] as a yellow solid: mp 82–84 °C (lit.[15] 84–86 °C); δ_H (500 MHz, $CDCl_3$) 7.05 (d, J = 9.0 Hz, 1H, H-8′), 6.69 (dd, J = 2.5, 8.5 Hz, 1H, H-7′), 6.60 (d, J = 2.0 Hz, 1H, H-5′), 5.20 (br s, 1H, $CH{=}N$), 3.76 (s, 3H, OCH_3), 3.36 (m, 1H, H-1′), 2.78–2.51 (m, 4H), 1.93–1.87 (m, 1H), 1.82–1.64 (m, 3H); δ_C (125 MHz, $CDCl_3$) 194.25 (CO), 157.84 (C6′), 138.48 (C4′a), 131.76 (C8′a), 129.41 (C8′), 113.87 (C5′), 112.33 (C7′), 55.33 (OCH_3), 55.25($CH{=}N_2$), 48.69 (C1′), 33.80 (CH_2CO), 30.01 (C4′), 28.53 (C2′), 19.76 (C3′); (+)-LRESIMS m/z 267 $[M + Na]^+$; (+)-HRESIMS m/z 267.1099, $C_{14}H_{16}N_2O_2$ $[M + Na]^+$ requires 267.1104.

7-Methoxy-1,2,2a,3,4,5-hexahydro-(8*H*)-benz[cd]azulen-1-one (12)

The title compound was prepared according to the method reported by Mander *et al.*[15] and obtained as an unstable white solid that gradually turned grey: δ_H (500 MHz, $CDCl_3$) 5.99 (dd, J = 6.0, 8.0 Hz, 1H, H-9), 5.28 (s, 1H, H-6), 3.60 (s, 3H, OCH_3), 3.19 (m, 1H, H-8), 2.95–2.80 (m, 1H, H-2a), 2.73 (dd, J = 8.0, 18.2 Hz, 1H, H-2), 2.51–2.48 (m, 2H, H-5, H′-5), 2.22–2.17 (m, 2H, H′-8, H-3), 2.05 (dd, J = 9.0, 15.7 Hz, 1H, H′-2), 2.03–1.97 (m, 1H, H-4), 1.76–1.67 (m, 1H, H′-4), 1.28–1.20 (m, 1H, H′-3); δ_C (125 MHz, $CDCl_3$) 206.00 (C1), 146.99 (C7), 139.09, 136.13, 134.57 (C5a, C9a, C9b), 115.44 (C9), 101.36 (C6), 56.29 (OCH_3), 46.05 (C2a), 36.05, 32.76 (C2, C8), 31.00, 29.86 (C3, C5), 22.68 (C4); (+)-LRESIMS m/z 217 $[M + H]^+$.

7-Methoxy-1,2,2a,3,4,5-hexahydro-(8*H*)-benz[cd]azulen-1-ol (19)

The title compound was prepared according to the method reported by Mander *et al.*[15] and obtained as an unstable white solid that gradually turned grey: δ_H (500 MHz, $CDCl_3$) 5.35 (t, J = 6.5 Hz, H-9), 5.08 (s, 1H, H-6), 4.65 (m, 1H, H-1), 3.57 (s, 3H, OCH_3), 2.92 (m, 1H, H-2), 2.52 (m, 2H, H-2a, H-5), 2.43 (dd, J = 5.0, 14.0 Hz, 1H, H′-2), 2.34 (m, 2H, H-8, H-8′), 2.05 (m, 1H, H-3), 1.87 (dt, J = 3.5, 13.0 Hz, 1H, H-4), 1.62–1.46 (m, 1H, H-4′), 1.22–1.06 (m, 2H, H-5′, H-3′); δ_C (125 MHz, $CDCl_3$) 149.01 (C7), 146.32 (C9a), 134.97, 132.18 (C5a, C9b), 110.70 (C9), 99.83 (C6), 73.29 (C1), 55.78 (OCH_3), 44.60 (C5), 38.56 (C2a), 32.50 (C2), 31.60 (C8), 29.90 (C3), 22.85 (C4); (+)-LRESIMS m/z 219 $[M + H]^+$, 231 $[M + Na]^+$.

Ethyl 2-(6′-methoxy-2′,3′-dihydro-1′*H*-inden-1′-yl)acetate (14)

Triethyl phosphonoacetate (4.15 g, 18.5 mmol) was added dropwise over 20 min to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 0.74 g, 18.5 mmol) in dry THF (40 mL) at 0 °C under argon. Upon complete addition, the clear reaction mixture was stirred at room temperature for 30 min and cooled to 0 °C. A solution of 6-methoxy-1-indanone (2.5 g, 15.4 mmol) in THF (10 mL) was then added over 5 min and the resulting mixture stirred at room temperature for 1 h and heated to reflux for a further 15 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (50 mL) and washed with brine (2 × 40 mL). The aqueous layer was extracted with ethyl acetate (2 × 30 mL) and the combined organic extracts washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure. The crude product was purified on silica (hexane : ethyl acetate, 98 : 2) to yield 2.59 g (72.3%) of **13** as a colourless oil containing a mixture of *endo*- and (*E*, *Z*) *exo*-double bond isomers. The adducts were dissolved in ethanol (45 mL) without further purification and stirred in the presence of 10% Pd–C (200 mg) under a hydrogen atmosphere at 50 °C for 8 h. After this time, the reaction mixture was filtered through Celite® and concentrated at reduced pressure. The crude product was purified on a silica column (hexane : ethyl acetate, 98 : 2) to afford 2.56 g (98%, 70.9% overall yield) of the title compound as a colourless oil with the same ^{1}H NMR spectrum as previously reported:[21] δ_H (500 MHz, $CDCl_3$) 7.11 (d, J = 8.0 Hz, 1H, H-4′), 6.74–6.71 (m, 2H, H-7, H-5′), 4.18 (q, J = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 3.77 (s, 3H, OCH_3), 3.55 (pent, J = 7.3 Hz, 1H, H-1′), 2.89–2.72 (m, 3H, $CHCH_2CO$, H-3′), 2.45-2.35 (m, 2H, H′-3′, H-2′), 1.76 (m, 1H, H′-2′), 1.28 (t, J = 7.0 Hz, 3H, $COCH_2CH_3$); (+)-LRESIMS m/z 257 $[M + Na]^+$.

2-(6′-Methoxy-2′,3′-dihydro-1′*H*-inden-1′-yl)acetic acid (15)

The ester **14** (2.55 g, 10.89 mmol) was dissolved in 1 M NaOH (90% methanol in water, 60 mL) and stirred at room temperature

for 3 h. The reaction mixture was concentrated, dissolved in water (50 mL), acidified with 5 M HCl (13 mL) and extracted with ethyl acetate (3 × 40 mL). The ethyl acetate extract was washed with brine (2 × 40 mL), dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure to afford the crude product which was purified on silica gel (hexane : ethyl acetate, 85 : 15) to yield the title compound as a white solid (2.37 g, 97.6%): mp 65–68 °C; ν_{max} (cm^{-1}) 3300–2500 (COOH), 3005 (ArH), 2835 (CH), 1710 (C═O), 1240 ($ArOCH_3$); δ_H (500 MHz, $CDCl_3$) 7.13 (d, J = 8.0 Hz, 1H, H-4′), 6.77 (s, 1H, H-7′), 6.74 (d, J = 8.0 Hz, H-5′), 3.79 (s, 3H, OCH_3), 3.57 (5, J = 7.2 Hz, 1H, H-1′), 2.91–2.81 (m, 3H, $COCH_2$, H-3′), 2.52–2.40 (m, 2H, H′-3′, H-2′), 1.79 (sext, J = 7.2 Hz, 1H, H′-2′); δ_C (125 MHz, $CDCl_3$) 179.06 (*C*O), 159.15 (C6′), 147.24 (C7′a), 136.13 (C3′a), 125.41 (C4′), 112.97 (C5′), 109.58 (C7′), 55.82 (OCH_3), 41.63 (CH_2CO), 39.90 (C1′), 33.25 (C3′), 30.64 (C2′); (+)-LRESIMS m/z 229 $[M + Na]^+$; (+)-HRESIMS m/z 229.0825, $C_{12}H_{14}O_3$ $[M + Na]^+$ requires 229.0835.

1-Diazo-3-(6′-methoxy-2′,3′-dihydro-1′*H*-inden-1′-yl)propan-2-one (16)

A solution of the acid **13** (1.29 g, 6.26 mmol) in DCM (20 mL) was carefully added to a mixture of oxalyl chloride (1.6 g, 12.53 mmol) and DMF (0.2 mL) at −5 °C dropwise over 10 min all the while ensuring the temperature did not rise above 0 °C. The reaction mixture was then stirred at 0–5 °C for 1 h and ambient temperature for an additional 1 h and the mixture was concentrated at reduced pressure to afford a thick yellow oil. The residue was taken up in toluene (10 mL) and added dropwise to a solution of freshly prepared diazomethane in diethyl ether (25 mL) at 0 °C (CARE). The reaction mixture stirred at 0–5 °C for 2 h and then overnight at 25 °C. Excess diazomethane and diethyl ether was removed by bubbling nitrogen gas into the reaction mixture. The crude yellow product was purified on silica gel (hexane : ethyl acetate, 95 : 5 → 90 : 10) to yield 1.22 g (84.5%) of the title compound as a bright yellow solid: mp 45–46 °C; ν_{max} (cm^{-1}) 3090 (ArH), 2940 (CH), 2102 (CHN_2), 1640 (C═O), 1490 (CH_2), 1240 ($ArOCH_3$); δ_H (500 MHz, $CDCl_3$) δ 7.11 (d, J = 7.5 Hz, 1H, H-4′), 6.72 (m, 2H, H-7′, H-5′), 5.24 (br s, 1H, $CH{=}N_2$), 3.78 (s, 3H, OCH_3), 3.61 (pent, 1H, J = 7.1 Hz, H-1′), 2.88–2.74 (m, 3H, $COCH_2$, H-3′), 2.44–2.34 (m, 2H, H′-3′, H-2′), 1.74 (sext, J = 7.1 Hz, 1H, H′-2′); δ_C (125 MHz, $CDCl_3$) 193.91 (*C*O), 158.90 (C6′), 147.52 (C7′a), 135.89 (C3′a), 125.16 (C4′), 112.64 (C5′), 109.40 (C7′), 55.60 (OCH_3), 55.04 (CHN_2), 46.49 (CH_2CO), 41.73 (C1′), 32.94 (C3′), 30.47 (C2′); (+)-LRESIMS m/z 253 $[M + Na]^+$; (+)-HRESIMS m/z 253.0943, $C_{13}H_{14}N_2O_2$ $[M + Na]^+$ requires 253.0947.

7-Methoxy-2,2a,3,4-tetrahydro-(8*H*)-cyclopenta[cd]azulen-1-one (17)

A solution of the diazoketone **16** (252 mg, 1.1 mmol) in dry DCE (25 mL) was added slowly (25 μL min^{-1}) *via* a syringe pump fitted with fine Teflon® tubing into a solution of copper(II) ethylacetoacetate (22 mg, 6 mol%) in dry DCE (25 mL) at mild reflux under an inert argon atmosphere. The reaction mixture was heated to reflux for 15 min and cooled to room temperature. DBU (0.25 mL) was added dropwise under argon and the mixture stirred for a further 10 min. After this time, the reaction mixture was diluted with DCM (50 mL) and washed with 1 M HCl (40 mL) followed by brine (2 × 50 mL). The organic layer was decanted and dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure to afford the reddish brown crude product which was purified on silica gel (hexane : ethyl acetate, 98 : 2) to afford 165 mg of the title compound as a white solid (74.5%): mp 82–84 °C; ν_{max} (cm^{-1}) 3010 (ArH), 1710 (C═O), 1485 (CH_2), 1250 (OCH_3); δ_H (500 MHz, $CDCl_3$) 7.10 (d, J = 8.0 Hz, 1H, H-5), 6.69 (d, J = 8.0 Hz, 1H, H-6), 3.81 (s, 3H, OCH_3), 3.60 (d, J = 22.0 Hz, 1H, H-2), 3.36–3.26 (m, 2H, H-2a, H′-2), 2.97–2.83 (m, 3H, H-8, H′-8, H-4), 2.49 (pent, J = 6.3 Hz, 1H, H-3), 2.21 (m, 1H, H′-4), 1.72 (m, 1H, H′-3); δ_C (125 MHz, $CDCl_3$) 210.91 (C1), 155.58 (C7), 144.63 (C8b), 134.42 (C4a), 123.06 (C8a), 119.08 (C5), 109.16 (C6), 55.97 (OCH_3), 47.00 (C4), 40.44 (2a), 37.27 (C2), 35.89 (C3), 31.81 (C8); (+)-LRESIMS m/z 225 $[M + Na]^+$; (+)-HRESIMS m/z 225.0888, $C_{13}H_{14}O_2$ $[M + Na]^+$ requires 225.0886.

7-Methoxy-1,2,2a,3,4,8-hexahydrocyclopenta[cd]azulen-1-ol (20)

To a stirred and cooled (0 °C) solution of the cycloheptatriene **17** (140 mg, 0.69 mmol) in dry methanol (15 mL) was added sodium borohydride (52 mg, 1.37 mmol). The resulting mixture was stirred for 30 min at 0–5 °C. 0.1 M HCl in brine (25 mL) was slowly added to the reaction mixture until evolution of hydrogen gas had ceased at which time a voluminous white suspension was observed. The product was extracted with ethyl acetate (4 × 20 mL) and the organic extract washed with brine (2 × 25 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated at reduced pressure to obtain the crude product (a 95 : 5 mixture of *syn* and *anti* isomers **20a** and **20b** respectively). The crude products were washed with hexane to obtain the pure *cis* adduct (96 mg). After concentrating the hexane washes at reduced pressure, the two isomers were separated on a silica gel column (hexane : ethyl acetate, 92 : 8 → 90 : 10) to obtain a further 35 mg of **20a** as a white solid (131 mg overall, 92.7%) and 6 mg (4.2%) of **20b** as a white solid.

20a: mp 130–134 °C; ν_{max} (cm^{-1}) 3500 (OH); 3010 (ArH), 2935 (CH), 1485 (CH_2), 1245 (OCH_3), 1110 (C-OH); δ_H (500 MHz, $CDCl_3$) 7.01 (d, J = 8.0 Hz, 1H, H-5), 6.10 (d, J = 8.0 Hz, 1H, H-6), 4.19 (m, 1H, H-1), 3.80 (s, 3H, OCH_3), 3.22 (dd, J = 6.5, 17.0 Hz, 1H, H-2), 2.99 (hept, J = 5.7 Hz, 1H, H-2a), 2.88–2.81 (m, 1H, H-4), 2.73 (dd, J = 7.5, 14.7 Hz, 1H, H′-4), 2.39 (dd, J = 10.0, 17.0 Hz, H′-2), 2.33–2.28 (m, 2H, H-8, H-3), 1.66–1.60 (m, 1H, H′-3), 1.37 (q, J = 11.6 Hz, 1H, H′-8); δ_C (125 MHz, $CDCl_3$) 155.79 (C7), 145.22 (C8b), 134.59 (C4a), 122.02 (C5), 120.71 (C8a), 108.18 (C6), 69.74 (C1), 55.69 (OCH_3), 41.75 (C2a), 38.87 (C8), 35.31 (C3), 32.66 (C2), 31.71 (C4); (+)-LRESIMS m/z 227 $[M + Na]^+$; (+)-HRESIMS m/z 227.1052, $C_{13}H_{16}O_2$ $[M + Na]^+$ requires 227.1043.

20b: ν_{max} (cm^{-1}) 3500 (OH); 3010 (ArH), 2920 (CH), 1485 (CH_2), 1245 (OCH_3), 1090 (C-OH); δ_H (500 MHz, $CDCl_3$) 7.04 (d, J = 8.0 Hz, 1H, H-5), 6.62 (d, J = 8.0 Hz, 1H, H-6), 4.52 (br s, 1H, H-1), 3.80 (s, 3H, OCH_3), 3.20 (hept, J = 5.8 Hz, 1H, H-2a), 2.89–2.81 (m, 3H, H-8, H-4, H′-4), 2.77– 2.71 (m, 1H, H′-8), 2.34 (m, 1H, H-2), 2.28 (m, 1H, H-3), 1.62 (m, 1H, H′-2), 1.33 (m, 1H, H′-3); δ_C (125 MHz, $CDCl_3$) 156.39 (C7), 145.50 (C8b), 135.23 (C4a), 121.97 (C5), 119.98 (C8a), 108.18 (C6), 66.67 (C1), 55.84 (OCH_3), 35.77 (C2), 35.67 (C3), 35.34 (C2a), 31.48, 31.47 (C4, C8); (+)-LRESIMS m/z 227 $[M + Na]^+$; (+)-HRESIMS m/z 227.1045, $C_{13}H_{16}O_2$ $[M + Na]^+$ requires 227.1043.

General procedure for the synthesis of compounds 21a–c

Alcohol **20a** (24 mg, 0.12 mmol) in dry THF (0.6 mL) was slowly added to a stirred and cooled suspension of sodium hydride (60% dispersion in mineral oil, 14 mg, 0.35 mmol) in dry THF (1.0 mL). Following complete addition, the reaction mixture was stirred at ambient temperature for 1 h under argon. The appropriate benzyl bromide (0.176 mmol) was then added and the mixture stirred for an additional 40 h under argon. The reaction mixture was quenched with brine (3 mL) and extracted with ethyl acetate (4 × 2 mL). The organic extract was washed with brine (3 mL), dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure. The crude oil was purified on silica gel (hexane : ethyl acetate, 98 : 2) to obtain the desired compounds in yields ranging from 72–89%.

1-(Benzyloxy)-7-methoxy-1,2,2a,3,4,8-hexahydrocyclopenta[cd]-azulene (21a)

Colourless oil; 24.9 mg (72.0%); ν_{max} (cm^{-1}) 3010 (ArH), 2835 (CH_2), 1485 (CH_2), 1245 (OCH_3); δ_H (500 MHz, $CDCl_3$) 7.41 (d, J = 7.5 Hz, 2H, PhH), 7.35 (t, J = 7.5 Hz, 2H, PhH), 7.29 (d, J = 7.0 Hz, 1H, PhH), 7.01 (d, J = 8.0 Hz, 1H, H-5), 6.61 (d, J = 8.0 Hz, 1H, H-6), 4.70 (q, J = 12.3 Hz, 2H, OCH_2), 3.92 (m, 1H, H-1) 3.81 (s, 3H, OCH_3), 3.29 (dd, J = 6.5, 8.5 Hz, 1H, H-2), 2.93 (m, 1H, H-2a), 2.84 (m, 1H, H-8), 2.72 (dd, J = 8.0, 15.0 Hz, H′-8), 2.51 (dd, J = 9.5 Hz, 16.7 Hz, 1H, H′-2), 2.45 (dt, J = 3.7, 11.5 Hz, 1H, H-4), 2.30 (pent, J = 6.0 Hz, 1H, H′-4), 1.62 (m, 1H, H-3), 1.38 (q, J = 11.6 Hz, 1H, H′-3); δ_C (125 MHz, $CDCl_3$) 156.08 (C7), 145.74 (C8b), 139.28 (C4a), 134.79 (C1′), 128.72 (C3′), 127.98 (C4′), 127.81 (C2′), 122.12 (C5), 121.08 (C8a), 108.35 (C6), 76.50 (C1), 70.71 (OCH_2), 55.91 (OCH_3), 41.82 (C2a), 35.72 (C4), 35.57 (C3), 31.87 (C8), 29.90 (C2); (+)-LRESIMS m/z 317 $[M + Na]^+$; (+)-HRESIMS m/z 317.1511, $C_{20}H_{22}O_2$ $[M + Na]^+$ requires 317.1512.

1-(4′-Chlorobenzyloxy)-7-methoxy-1,2,2a,3,4,8-hexahydrocyclo-penta[cd]azulene (21b)

White solid; 34.4 mg (89.1%); mp 78–80 °C; ν_{max} (cm^{-1}) 3010 (ArH), 2835 (CH_2), 1485 (CH_2), 1245 (OCH_3); δ_H (500 MHz, $CDCl_3$) 7.35 (m, 4H, PhH), 7.02 (d, J = 8.0 Hz, 1H, H-5), 6.62 (d, J = 8.0 Hz, 1H, H-5), 4.66 (q, J = 12.5 Hz, 2H, OCH_2), 3.91 (m, 1H, H-1), 3.82 (s, 3H, OCH_3), 3.27 (dd, J = 6.0, 17.0 Hz, 1H, H-2), 2.94 (m, 1H, H-2a), 2.84 (m, 1H, H-8), 2.73 (dd, J = 8.5, 15.2 Hz, 1H, H′-8), 2.49 (dd, J = 9.5, 17.5 Hz, 1H, H′-2), 2.44 (dt, J = 3.7, 11.0 Hz, 1H, H-4), 2.31 (pent, J = 6.0 Hz, 1H, H′-4), 1.64 (m, 1H, H-3), 1.38 (q, J = 7.6 Hz, 1H, H′-3); δ_C (125 MHz, $CDCl_3$) 156.06 (C7), 145.66 (C8b), 137.83 (C4a), 134.79 (C1′), 133.54 (C4′), 129.23 (C2′), 128.87 (C3′), 122.18 (C5), 120.88 (C8a), 108.37 (C6), 76.55 (C1), 69.95 (OCH_2), 55.90 (OCH_3), 41.77 (C2a), 35.71 (C4), 35.56 (C3), 31.87 (C8), 29.88 (C2); (+)-LRESIMS m/z 351 $[M + Na]^+$; (+)-HRESIMS m/z 351.1110, $C_{20}H_{21}ClO_2$ $[M + Na]^+$ requires 351.1123.

1-(4′-Fluorobenzyloxy)-7-methoxy-1,2,2a,3,4,8-hexahydrocyclo-penta[cd]azulene (21c)

White solid, 26.9 mg (73.2%); mp 47–50 °C; ν_{max} (cm^{-1}) 3010 (ArH), 2835 (CH_2), 1485 (CH_2), 1245 (OCH_3); δ_H (500 MHz, $CDCl_3$) 7.38 (m, 2H, PhH), 7.03 (m, 3H, PhH, H-5), 6.63 (d, J = 8.0 Hz, H-6), 4.66 (q, J = 12.5 Hz, 2H, OCH_2), 3.92 (m, 1H, H-1), 3.82 (s, 3H, OCH_3), 3.29 (dd, J = 6.5, 17.0 Hz, 1H, H-2), 2.94 (m, 1H, H-2a), 2.85 (m, 1H, H-8), 2.74 (dd, J = 8.0 Hz, 15.0 Hz, H′-8), 2.51 (dd, J = 9.5, 17.0 Hz, H′-2), 2.43 (dt, J = 4.0, 11.5 Hz, H-4), 2.31 (pent, J = 6.1 Hz, 1H, H′-4), 1.63 (m, 1H, H-3), 1.39 (q, J = 11.6 Hz, 1H, H′-3); δ_C (125 MHz, $CDCl_3$) 163.51 and 161.56 (C4′), 155.96 (C7), 145.57 (C8b), 134.90 (C4a), 134.93 and 134.68 (C1′), 129.58 and 129.52 (C2′), 122.07 (C5), 120.83 (C8a), 115.53 and 115.36 (C3′), 108.25 (C6), 76.52 (C1), 69.93 (OCH_2), 55.70 (OCH_3), 41.69 (C2a), 35.62 (C4), 35.29 (C3), 31.76 (C8), 29.79 (C2); (+)-LRESIMS m/z 335 $[M + Na]^+$; (+)-HRESIMS m/z 335.1408, $C_{20}H_{21}FO_2$ $[M + Na]^+$ requires 335.1418.

General procedure for the synthesis of compounds 21d–e

A solution of **20a** (25 mg, 0.12 mmol) in dry DMF (0.5 mL) was added slowly to a 2 mL microwave process vial equipped with a stirrer bar and containing a cooled suspension of sodium hydride (60% dispersion in oil, 15 mg, 0.36 mmol) in dry DMF (1.0 mL). Following complete addition, the reaction mixture was stirred at ambient temperature for 1 h under argon prior to addition of alkyl bromide (0.25 mmol). The mixture was subsequently heated in a microwave reactor at 110–115 °C for 45 min. The reaction mixture was quenched with brine (3 mL) and extracted with ethyl acetate (4 × 2 mL). The organic extracts were washed with brine (3 mL), dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure. The crude oil was purified on silica gel (hexane : ethyl acetate, 98 : 2 → 99 : 1) to obtain the desired ethers as colourless oils in yields ranging from 52–55%.

1-Butoxy-7-methoxy-1,2,2a,3,4,8-hexahydrocyclopenta[cd]azulene (21d)

Colourless oil; 17.6 mg (55%); ν_{max} (cm^{-1}) 3010 (ArH), 2940 (CH), 1620 (C=C), 1485 (CH_2), 1245 (OCH_3); δ_H (500 MHz, $CDCl_3$) 7.01 (d, J = 8.0 Hz, 1H, H-5), 6.61 (d, J = 8.0 Hz, 1H, H-6), 3.81–3.75 (m, 4H, OCH_3, H-1), 3.61 (m, 2H, OCH_2), 3.23 (dd, J = 6.5, 19.0 Hz, 1H, H-2), 2.94 (m, 1H, H-2a), 2.84 (m, 1H, H-8), 2.72 (dd, J = 7.5, 14.7 Hz, H′-8), 2.39 (m, 2H, H-4, H′-2), 2.30 (pent, J = 6.1 Hz, 1H, H′-4), 1.61 (m, 3H, OCH_2CH_2, H-3), 1.42 (m, 2H, CH_2CH_3), 1.30 (q, J = 11.6 Hz, 1H, H′-3), 0.95 (t, J = 7.2 Hz, 3H, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 155.90 (C7), 145.60 (C8b), 134.58 (C4a), 121.83 (C5), 121.06 (C8a), 108.31 (C6), 76.86 (C1), 68.55 (OCH_2), 55.70 (OCH_3), 41.70 (C2a), 35.66 (C4), 35.37 (C3), 32.45 (OCH_2CH_2), 31.66 (C8), 29.73 (C2), 19.60 (CH_2CH_3), 14.10 (CH_2CH_3); (+)-LRESIMS m/z 283 $[M + Na]^+$; (+)-HRESIMS m/z 283.1663, $C_{17}H_{24}O_2$ $[M + Na]^+$ requires 283.1668.

1-(Isopentyloxy)-7-methoxy-1,2,2a,3,4,8-hexahydrocyclo-penta[cd]azulene (21e)

Colourless oil; 17.5 mg (52.2%); ν_{max} (cm^{-1}) 3010 (ArH), 2950 (CH), 1620 (C=C), 1485 (CH_2), 1245 (OCH_3); δ_H (500 MHz, $CDCl_3$) 7.01 (d, J = 8.0 Hz, 1H, H-5), 6.60 (d, J = 8.0 Hz, 1H, H-6), 3.81 (m, 4H, OCH_3, H-1), 3.61 (m, 2H, OCH_2), 3.23 (dd, J = 6.5, 17.0 Hz, H-2), 2.94 (m, 1H, H-2a), 2.84 (m, 1H, H-8), 2.72 (dd, J = 7.5, 15.0 Hz, H′-8), 2.38 (m, 2H, H-4, H′-2), 2.30 (pent, J = 6.0 Hz, 1H, H′-4), 1.75 (m, 1H, $CH(CH_3)_2$), 1.63 (m, 1H, H-3), 1.52 (q, J = 6.8 Hz, 2H, OCH_2CH_2), 1.30 (q, J = 11.6 Hz, 1H, H′-3),

0.93 (d, J = 6.5 Hz, 6H, CH(CH_3)$_2$); δ_C (125 MHz, $CDCl_3$) 155.90 (C7), 145 (C8b), 134.58 (4a), 121.84 (C5), 121.07 (C8a), 108.13 (C6), 76.89 (C1), 67.17 (OCH_2), 55.70 (OCH_3), 41.70 (C2a), 39.19 (OCH$_2$$CH_2$), 35.65 (C4), 35.37 (C3), 31.67 (C8), 29.74 (C2), 25.33 (CH), 22.85 (CH(CH_3)$_2$); (+)-LRESIMS m/z 297 [M + Na]$^+$; (+)-HRESIMS m/z 297.1824, $C_{18}H_{26}O_2$ [M + Na]$^+$ requires 297.1825.

1-(Prop-2′-ynyloxy)-7-methoxy-1,2,2a,3,4,8-hexahydrocyclopenta[cd]azulene (21f)

A solution of **20a** (100 mg, 0.12 mmol) in dry THF (1.0 mL) was added slowly to a stirred and cooled suspension sodium hydride (60% dispersion in oil, 79 mg, 1.96 mmol) in dry THF (1.2 mL). Upon complete addition, the reaction mixture was stirred at ambient temperature for 1 h under argon. Propargyl bromide (233 mg, 1.96 mmol) was then added and the mixture stirred for an additional 40 h at 55 °C under argon. The reaction mixture was quenched with brine (3 mL) and extracted with ethyl acetate (4 × 2 mL). The organic extract was washed with brine (3 mL), dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure. The crude oil was purified on silica gel (hexane : ethyl acetate, 98 : 2) to obtain the title compound as a yellow oil (62 mg, 65% after recovery of 20 mg of unreacted starting material): ν_{max} (cm^{-1}) 3285 (CC-H), 3010 (ArH), 2940 (CH), 1620 (C═C), 1485 (CH_2), 1245 (OCH$_3$), 670 (CC-H); δ_H (500 MHz, $CDCl_3$) 7.02 (d, J = 8.0 Hz, 1H, H-5), 6.61 (d, J = 8.0 Hz, 1H, H-6), 4.37–4.30 (m, 2H, OCH_2), 4.06 (m, 1H, H-1), 3.80 (s, 3H, OCH_3), 3.26 (dd, J = 6.5, 17.0 Hz, 1H, H-2), 2.97 (hept, J = 5.6 Hz, 1H, H-2a), 2.85 (m, 1H, H-8), 2.73 (dd, J = 7.5, 15.2 Hz, 1H, H′-8), 2.45–2.39 (m, 3H, CH_2CCH, H′-2, H-4), 2.32 (pent, J = 6.1 Hz, H′-4), 1.63 (m, 1H, H-3), 1.33 (q, J = 8.7 Hz, 1H, H′-3); δ_C (125 MHz, $CDCl_3$) 155.85 (C7), 145.37 (C8b), 134.54 (4a), 121.99 (C5), 120 (C8a), 108.17 (C6), 80.40 (CH_2CCH), 75.94 (C1), 74.11 (CH_2CCH), 55.77 (OCH_2), 55.69 (OCH_3), 41.49 (C2a), 35.34 (C4), 35.21 (C3), 31.66 (C8), 29.31 (C2); (+)-LRESIMS m/z 265 [M + Na]$^+$; (+)-HRESIMS m/z 265.1195, $C_{16}H_{18}O_2$ [M + Na]$^+$ requires 265.1199.

1′-Benzyl-4′-((-7-methoxy-1,2,2a,3,4,8-hexahydrocyclopenta[cd]azulen-1-yloxy)methyl)-1*H*-1′,2′,3′-triazole (23a)

To a stirred suspension of **21f** (40 mg, 0.17 mmol), benzyl azide (26.4 mg, 0.2 mmol) and sodium ascorbate (20 mol%) in a solution of *t*-butanol (0.5 mL), water (0.5 mL) and ethanol (0.5 mL) was added copper sulfate pentahydrate (5 mol%). The reaction mixture was stirred at room temperature for 16 h then diluted with brine (3 mL) and extracted with ethyl acetate (4 × 3 mL). The organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure to afford the crude product. Silica gel chromatography (hexane : ethyl acetate, 85 : 15 → 80 : 20) afforded the title compound as a white solid (37 mg, 60%): mp 78–82 °C; ν_{max} (cm^{-1}) 2940 (CH), 1615 (N═N), 1485 (CH_2), 1245 (OCH$_3$); δ_H (500 MHz, $CDCl_3$) 7.48 (s, 1H, H-5′), 7.40–7.34 (m, 3H, PhH), 7.28 (d, J = 7.0 Hz, 2H, PhH), 7.00 (d, J = 8.0 Hz, 1H, H5), 6.59 (d, J = 8.0 Hz, 1H, H6), 5.52 (s, 2H, N-CH_2), 4.82–4.76 (m, 2H, OCH_2), 3.95 (m, 1H, H-1), 3.79 (s, 3H, OCH_3), 3.24 (dd, J = 6.0, 17.2 Hz, H-2), 2.92 (m, 1H, H-2a), 2.82 (m, 1H, H-8), 2.71 (dd, J = 8.0, 15.0 Hz, 1H, H′-8), 2.46 (m, 2H, H′-2, H-4), 2.29 (5, J = 6.1 Hz, 1H, H′-4), 1.60 (m, 1H, H-3), 1.30 (q, J = 13.5 Hz, 1H, H′-3); δ_C (125 MHz, $CDCl_3$) 155.82 (C7), 145.41 (C8b), 134.78 (C4a), 134.54 (C1″), 129.25 (C4″), 128.88 (C3″), 128.29 (C2″), 122.35 (C5′), 121.94 (C5), 120.63 (C8a), 108.14 (C6), 77.41 (C4′), 76.86 (C1), 62.40 (OCH_2), 55.67 (OCH_3), 54.34 (*N*-CH_2), 41.48 (C2a), 35.31 (C4), 35.31 (C3), 31.64 (C8), 29.66 (C2); (+)-LRESIMS m/z 398 [M + Na]$^+$; (+)-HRESIMS m/z 398.1825, $C_{23}H_{25}N_3O_2$ [M + Na]$^+$ requires 398.1838.

General procedure for the synthesis of compounds 23b–c

Copper sulfate solution (1 M, 0.5 mL) was added to a 2 mL microwave process vial equipped with stirrer bar and containing **21f** (35.0 mg, 0.14 mmol), alkyl bromide, sodium azide (10.4 mg, 0.16 mmol) and copper powder (8 mg) in *t*-butanol (0.8 mL). The reaction vessel was sealed and the mixture was heated in a microwave reactor at 110 °C for 20 min. The reaction mixture was quenched with brine (3 mL) and extracted with ethyl acetate (4 × 3 mL). The organic solvent was washed with brine (4 mL), dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure to afford an oil. The crude product was purified on silica gel (hexane : ethyl acetate, 85 : 15 → 80 : 20) to obtain the title compounds as white solids in 42–45% yield.

1′-Butyl-4′-((-7-methoxy-1,2,2a,3,4,8-hexahydrocyclopenta[cd]azulen-1-yloxy)methyl)-1*H*-1′,2′,3′-triazole (23b)

White solid; 20.9 mg (44.8%); 90–92 °C; ν_{max} (cm^{-1}) 2940 (CH), 1615 (N═N), 1485 (CH_2), 1245 (OCH$_3$); δ_H (500 MHz, $CDCl_3$) 7.5 (s, 1H, H-5′); 7.01 (d, J = 8.0 Hz, 1H, H-5), 6.60 (d, J = 8.0 Hz, 1H, H-6), 4.81 (q, J = 10.0 Hz, 2H, N-CH_2), 4.35 (*t*, J = 7.2 Hz, 2H, OCH_2), 3.95 (m, 1H, H-1), 3.80 (s, 3H, OCH_3), 3.26 (dd, J = 6.0, 17.0 Hz, 1H, H-2), 2.94 (m, 1H, H-2a), 2.84 (m, 1H, H-8), 2.72 (dd, J = 8.0, 14.7 Hz, 1H, H′-8), 2.45 (m, 2H, H′-2, H-4), 2.30 (5, J = 6.2 Hz, 1H, H′-4), 1.90 (m, 2H, NCH$_2$CH_2), 1.61 (m, 1H, H-3), 1.36 (m, 3H, CH_2CH$_3$, H′-3), 0.96 (t, J = 7.2 Hz, 3H, CH$_2$CH_3); δ_C (125 MHz, $CDCl_3$) 155.86 (C7), 146.10 (C4′), 145.47 (C8b), 134.59 (C4a), 122.20 (C5′), 121.97 (C5), 120.70 (C8a), 108.17 (C6), 76.79 (C1), 62.49 (OCH_2), 55.71 (OCH_3), 50.21 (NCH_2), 41.53 (C2a), 35.37 (C4), 35.32 (C3), 32.43 (NCH$_2$$CH_2$), 31.68 (C8), 29.73 (C2), 19.90 (CH_2CH_3), 13.60 (CH_2CH_3); (+)-LRESIMS m/z 364 [M + Na]$^+$; (+)-HRESIMS m/z 364.1997, $C_{20}H_{27}N_3O_2$ [M + Na]$^+$ requires 364.1995.

1′-Isopentyl-4′-((-7-methoxy-1,2,2a,3,4,8-hexahydrocyclopenta[cd]azulen-1-yloxy)methyl)-1*H*-1′,2′,3′-triazole (23c)

White solid: 23.1 mg (42.4%); mp 88–90 °C; ν_{max} (cm^{-1}) 2950 (CH), 1615 (N═N), 1485 (CH_2), 1245 (OCH$_3$); δ_H (500 MHz, $CDCl_3$) 7.55 (s, 1H, H-5′), 7.01–6.99 (d, J = 8.0 Hz, 1H, H-5), 6.61 (d, J = 8.0 Hz, 1H, H-6), 4.42 (q, J = 10.0 Hz, 2H, N-CH_2), 4.37 (t, J = 7.7 Hz, 2H, OCH_2), 3.96 (m, 1H, H-1), 3.80 (s, 3H, OCH_3), 3.26 (dd, J = 6.0, 17.0 Hz, 1H, H-2), 2.94 (m, 1H, H-2a), 2.83 (m, 1H, H-8), 2.72 (dd, J = 8.0, 15.0 Hz, 1H, H′-8), 2.44 (m, 2H, H′-2, H-4), 2.30 (5, J = 6.1 Hz, 1H, H′-4), 1.81 (m, 2H, CH_2CH_2CH), 1.62 (m, 2H, CH_2CH, H-3), 1.33 (q, J = 11.6 Hz, 1H, H′-3); δ_C (125 MHz, $CDCl_3$) 155.84 (C7), 146.11 (C4′), 145.45 (C8b), 134.57 (C4a), 122.11 (C5′), 121.95 (C5), 120.68 (C8a), 108.15 (C6), 76.76 (C1), 62.46 (OCH_2), 55.69 (OCH_3), 48.81 (*N*-CH_2), 41.51 (C2a), 39.21 (CH_2CH), 35.34 (C4), 35.32 (C3), 31.66 (C8), 29.71 (C2), 25.69 (CH_2CH), 22.34 (CH_3)$_2$; (+)-LRESIMS m/z 378 [M + Na]$^+$,

356 $[M + H]^+$; (+)-HRESIMS *m/z* 378.2136, $C_{21}H_{29}N_3O_2$ $[M + Na]^+$ requires 378.2152.

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