COMMUNICATION

Synthetic approaches to pseudopterosin G aglycone dimethyl ether

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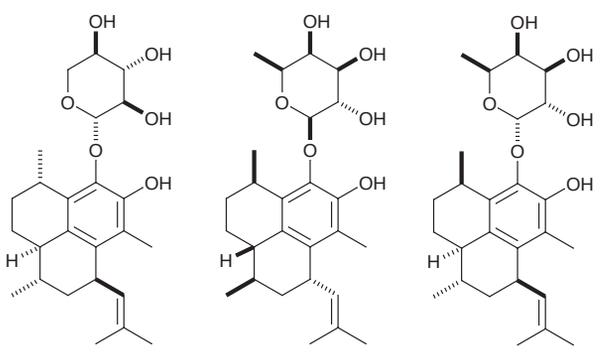
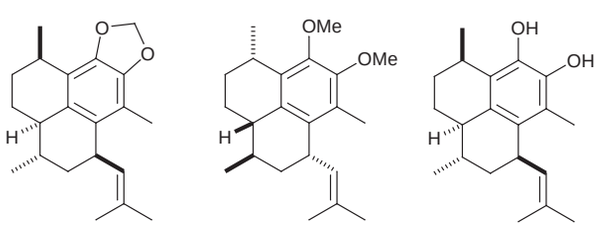
Three successive reactions of a dimethoxy arene with allylic cation equivalents were used to convert 2,3-dimethoxy-4-methyl-1-iodobenzene to the hexahydro-1*H*-phenalene system of the potent marine antiinflammatory pseudopterosins G–J.

The pseudopterosins are a group of 12 diterpene glycosides of the sea whip *Pseudopterogorgia elisabethae* which inhibit leukotriene synthesis and therefore are of potential use as anti-inflammatory agents.[1] The family can be divided into three groups having diastereoisomeric hexahydro-1*H*-phenalene ring systems. The stereochemical relationships are exemplified by pseudopterosins A (**1a**) and L (**1b**) which have enantiomeric



1a **1b** **1c**



2 **3** **4**

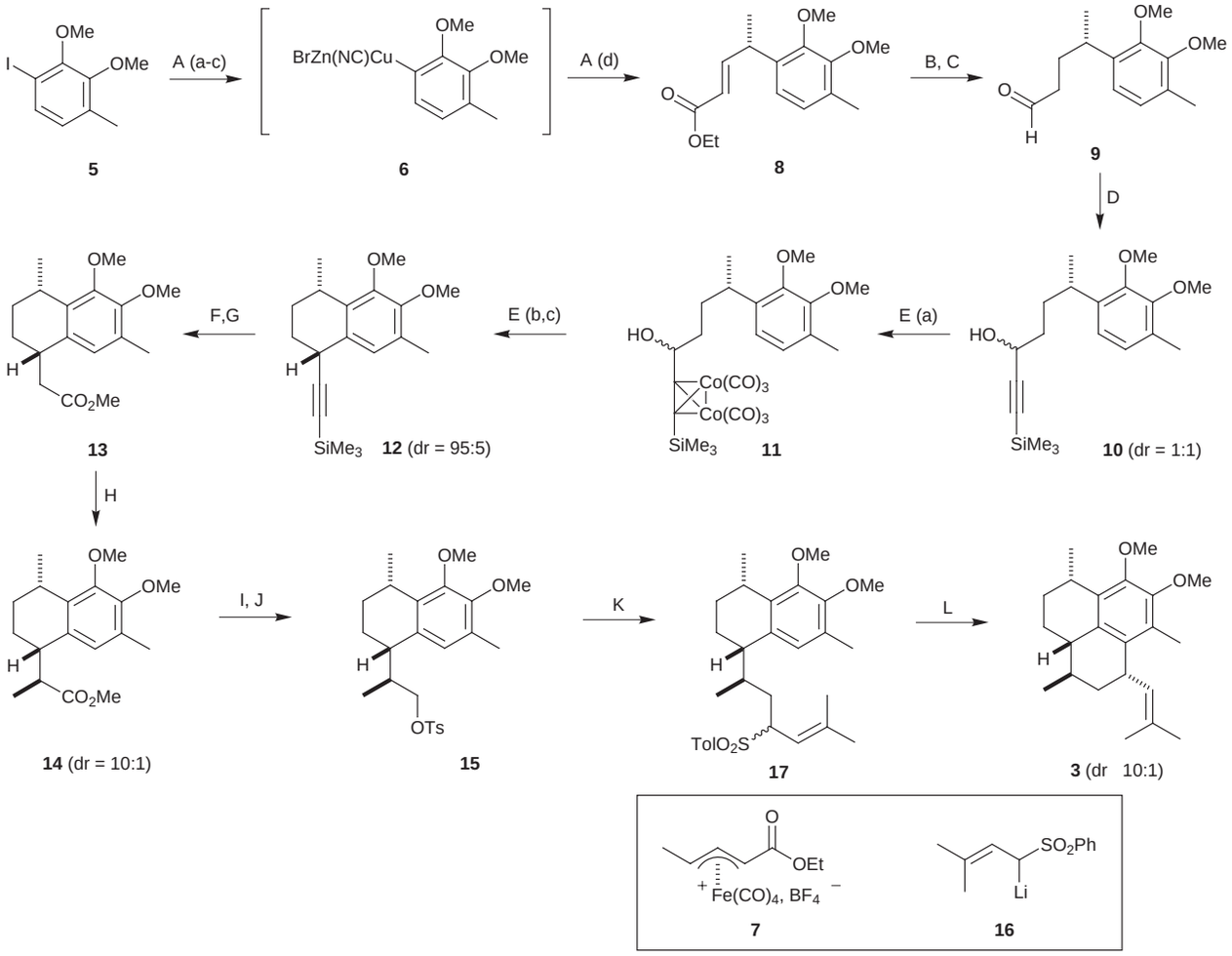
hexahydro-1*H*-phenalene systems whereas pseudopterosin G (**1c**) differs from A only at C6. Helioporin E (**2**) a bioactive metabolite isolated from the blue coral *Heliopora coerulea*, is stereochemically related to pseudopterosin G.[2] Most of the synthetic effort to date[3] has been invested in the pseudopterosin A ring system **1a** and we recently reported[4] a synthesis of the aglycone corresponding to **1b**. An approach to a pseudopterosin G model using chiral η^6-arene-$Cr(CO)_3$ complexes appeared in 1994.[5,6] We now report a synthesis of the hexahydro-1*H*-phenalene **3** which bears an enantiomeric relationship to pseudopterosin G and helioporin E. Our approach features three stereoselective arene alkylations involving allylic cation equivalents as electrophiles.

The first stereogenic centre at C6 (1*H*-phenalene numbering) was established by regio- and enantiofacially-selective addition of the zinc-cuprate reagent **6** to the homochiral (*E*)-[(2,3,4-η^3)-1-ethoxy-1-oxopent-3-enyl]tricarbonyliron(1−) tetrafluoroborate complex **7**[7] to give the adduct **8** in 60% yield and er ⩾ 95:5 according to ^{1}H NMR spectroscopy in the presence of europium tris[3-heptafluoropropylhydroxymethylene)-(+)-camphorate [Eu(hfc)$_3$] (Scheme 1). *Trans* addition of the nucleophile to η^3-allyl complex **7** leading to the (6*S*) stereochemistry in **8** was expected from the extensive studies of Enders and Jackson, respectively.[8,9] Conjugate reduction of the enoate ester in **8** using magnesium in methanol followed by reduction of the ester function with DIBAL-H returned the saturated aldehyde **9** in good yield. Addition of (trimethylsilyl)ethynylmagnesium bromide then led to an inseparable 1:1 mixture of diastereoisomeric propargylic alcohols **10**.

For the construction of the second ring we employed an intramolecular Nicholas reaction[10] involving electrophilic aromatic substitution using a cobalt-stabilised propargylic cation equivalent as an electrophile. We prepared the complex **11** in the usual way and reacted it with $BF_3{\cdot}OEt_2$ at −20 °C to induce cation formation and ring closure. After decomplexation with ferric nitrate, tetrahydronaphthalene **12** was obtained in 65% yield. NMR spectroscopy revealed good diastereoselectivity (dr = 95:5) but confirmation of the stereochemistry had to await the final step. Hydroboration–oxidation of the silylalkyne gave a crystalline carboxylic acid (mp 78–80 °C) which was esterified using tetramethylguanidine and iodomethane to give the methyl ester **13** in 95% yield. The next step in the sequence, the α-alkylation of ester **13** using LDA and iodomethane, proceeded with good diastereocontrol giving the ester **14** in 85% yield (dr = 10:1). The toluene-*p*-sulfonate ester **15**, prepared in two standard steps, was obtained as a single diastereoisomer after crystallisation from diethyl ether–pentane (mp 102–104 °C).

For the creation of the third ring and the introduction of the stereogenic centre at C-1, we returned to the Lewis acid mediated electrophilic cyclisation of an allylic sulfone[11] which had been a prominent feature in our earlier synthesis of pseudopterosin K aglycone.[4] Thus treatment of the diastereoisomeric mixture of sulfones **16** with ethylaluminium dichloride gave **3** with good stereoselectivity (dr ⩾ 10:1) in 90% yield. The structure and relative stereochemistry of the product (Fig. 1) was established by X-ray analysis† of a pure sample obtained by crystallisation from MeOH (mp 107–109 °C). Solid **3** contains

† Crystal structure of **3**. $C_{22}H_{32}O_2$, M = 328.48, triclinic, space group, $P-1$, a = 10.173(1), b = 10.400(1), c = 18.532(1) Å, α = 93.98(1), β = 93.70(1), γ = 91.70(1)°, V = 1950.7(2) Å^3, Z = 4, D_{calc} = 1.118 Mg m^{-3}, μ = 0.069 mm^{-1}, $F(000)$ = 720. Intensities of 12 825 reflections with $2 \leqslant \theta$(Mo-Kα) $\leqslant 30°$ were measured at 20 °C on an Enraf-Nonius CAD4 diffractometer with Mo-Kα X-rays, λ = 0.710 73 Å. Refinement on F^2 of 447 parameters using all 11 370 unique reflections [R_{int} = 0.011] converged at R_1 = 0.054, wR_2 = 0.16 for 8345 reflections with $I > 2\sigma(I)$ and R_1 = 0.076, wR_2 = 0.17 for all data, $|\Delta\rho| < 0.41$ e Å^{-3}. Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/235.



Scheme 1 *Reagents and Conditions*:

A	60%	(a) BuLi, THF–Et_2O (5:1), −100 °C; (b) $ZnBr_2$, −100 ⟶ −70 °C
	↓	(c) CuCN·2LiCl, −70 °C; (d) **7**, −70 °C ⟶ 0 °C
B	90%	Mg (6 equiv.), MeOH, 5 °C, 3 h
C	87%	DIBALH (1.05 equiv.), CH_2Cl_2, −80 °C, 1 h
D	89%	$Me_3SiC{\equiv}C{-}MgBr$ (1.3 equiv.), 0 °C, 15 min
E	86%	(a) $Co_2(CO)_8$ (1.3 equiv.), CH_2Cl_2, 20 °C, 1 h;
	↓	(b) $BF_3{\cdot}OEt_2$ (2 equiv.), −20 °C, 3 h;
	↓	(c) $Fe(NO_3)_3{\cdot}9H_2O$ (10 equiv.), MeOH, 20 °C, 3 h
F	65%	(a) $(C_6H_{11})_2BH$ (2 equiv.), THF, 5 °C, 1 h;
	↓	(b) H_2O_2, NaOH, MeOH, 30–50 °C, 1 h
G	95%	tetramethylguanidine (2 equiv.), MeI, PhMe, 20 °C
H	85%	(a) LDA (1.5 equiv.), THF, −40 °C; (b) MeI (2 equiv.)
I	92%	$LiAlH_4$ (0.75 equiv.), THF, 0 °C
J	86%	TsCl (1.5 equiv.), DMAP, NEt_3, CH_2Cl_2
K	75%	**16** (2 equiv.), THF, 3 h
L	90%	$EtAlCl_2$ (2 equiv.), CH_2Cl_2, −30 °C, 3 h

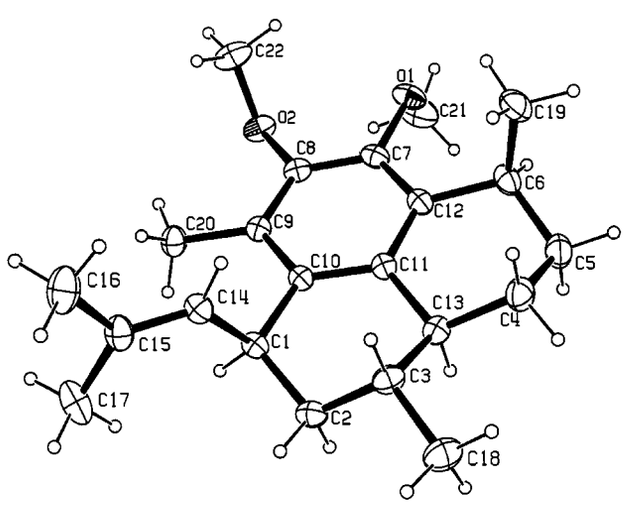
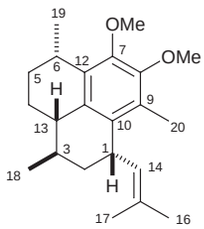


Fig. 1 A view of one of the two independent molecules of **3** showing the atom numbering scheme and 20% probability ellipsoids

two crystallographically independent but structurally indistinguishable molecules. The saturated six-membered rings adopt similar distorted half-chair conformations, with axial substitution at C1 and C6 and an equatorial methyl group at C3. A comparison of the high field ^1H and ^{13}C NMR data for compound **3** (Table 1) with those reported [1,2] for pseudopterosin G (**1c**) and its aglycone **4** are very similar with the exception of the signals for carbons 3 and 4. Compound **3** gives signals at δ 29.7 (C-3) and 22.6 (C-4) whereas the corresponding signals for pseudopterosin G appear at δ 34.2 and 27.6 and for the aglycone at δ 34.1 and 27.8 respectively. These data suggest that **1c** and **4** adopt a conformation different from **3** or their stereochemistry may need revision.

In conclusion, we have prepared the enantiomeric hexahydro-1*H*-phenalene core with the relative configuration ascribed to pseudopterosin G in just 12 steps (4.5% overall) from readily available starting materials. Noteworthy features of our approach are (a) creation of the (6*S*) stereochemistry by regio- and enantiofacially-selective nucleophilic addition of an arylmetal to an η^3-allyl cationic complex and (b) control of the 3 subsequent stereogenic centres by stereorelay [*i.e.*, (6*S*) ⇒ (13*S*) ⇒ (3*R*) ⇒ (1*S*)]. A fortuitous bonus was the stereoconvergence observed in the two cyclisation reactions (**11** ⟶ **12** and **17** ⟶ **3**) thereby removing the need to control the stereochemistry of the precursors **11** and **17**.

Table 1 ^{1}H and ^{13}C NMR data for compound **3**[a]



3

Position	δ_C [b,c]	δ_H [b,c]
1	36.2	3.63 (br d, *J* 9.3)
2	41.0	*ca*. 1.7 (m)
3	29.7	*ca*. 1.7 (m)
4	22.6	1.97 (dq, *J* 12.6, 3.3) eq
		1.45 (dq, *J* 2.7, 12.6) ax
5	31.0	1.84 (ddt, *J* 5.8, 2.8, 13.2) ax
		1.75 (dm, *J* 13.2) eq
6	28.3	3.24 (quintet, *J* 6.5)
7	149.1	
8	149.3	
9	128.5[d]	
10	134.2[d]	
11	131.5	
12	133.3	
13	46.3	2.05 (m)
14	131.0	5.13 (br d, *J* 9.3)
15	129.3	
16	25.8	1.68 (br s)
17	17.8	1.74 (br s)
18	20.9	1.01 (br d, *J* 5.2)
19	24.0	1.20 (d, *J* 7.2)
20	11.0	2.04 (br s)
7-OMe	60.5	3.88
8-OMe	60.5	3.77

[a] Recorded in $CDCl_3$ on a Bruker 400 MHz spectrometer. [b] Chemical shifts are reported in ppm relative to residual $CHCl_3$ at δ 7.27 (^{1}H) and δ 77.2 (^{13}C) with coupling constants (*J*) quoted in Hz. [c] Assignments are based on COSY, NOE, HMBC and HMQC experiments. [d] These assignments may be reversed.

Acknowledgements

We thank Glaxo Wellcome for financial support and Dr Krzysztof Jarowicki for extensive NMR experiments.

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Paper 8/03888K
Received 22*nd May* 1998
Accepted 25*th June* 1998