Novel method for the synthesis of α- and β-halogenonaphthalenes by regioselective benzannulation of aryl(*gem*-dihalogenocyclopropyl)methanols: application to the total synthesis of the lignan lactones, justicidin E and taiwanin C[1]

Yoo Tanabe,*[a] Shinzo Seko,[b] Yoshinori Nishii,[a] Taichi Yoshida,[a] Naoka Utsumi[b] and Gohfu Suzukamo[b]

[a] *School of Science, Kwansei Gakuin University, 1-1-155 Uegahara, Nishinomiya, Hyogo 662, Japan*

[b] *Synthetic Organic Research Laboratory, Sumitomo Chemical Co., Ltd., 2-10-1 Tsukahara, Takatsuki, Osaka 569, Japan*

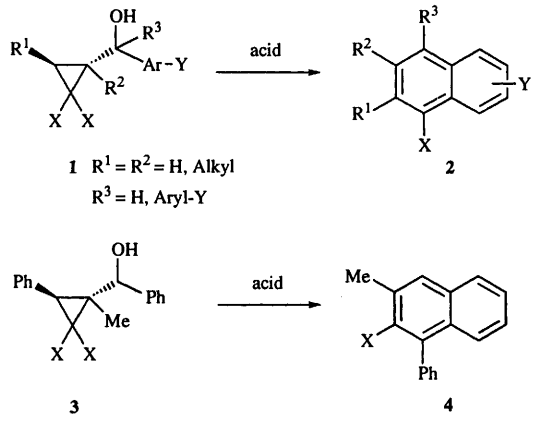
Acid treatment of two types of aryl(*gem*-dihalogenocyclopropyl)methanols (ADCMs) 1 and 3 gives α- and β-halogenonaphthalenes in good yields with excellent selectivity. These alternative annulations involve two distinctive types of highly regioselective acid-induced cyclopropane ring cleavage, wherein the preferential formation of more stable cationic intermediates determines the selectivity. The stereochemical mode of both the preparation and the annulation between diastereoisomers of an ADCM has been checked. As a demonstration of this annulation, a total synthesis of each of the natural lignan lactones, justicidin E 19 and taiwanin C 20, has also been performed. Since these 4-arylnaphthalenes are expected to exhibit biological activity, the anti-platelet activating factor (anti-PAF) activity of justicidin E has been assayed.

Reactions utilizing the characteristic properties of cyclopropanes have allowed the development of several unique and useful syntheses.[2] The relief of the inherent ring strain provides a variety of thermal, oxidative and reductive, electrophilic and nucleophilic ring-opening reactions. Of the functionalized cyclopropanes, *gem*-dihalogenocyclopropanes possess the following significant features: (1) constituents of useful biologically active compounds, themselves;[3] (2) easy preparation by the dihalogenocarbene addition to olefins;[4] (3) a precursor of halogenocyclopropanes or cyclopropanes by reductive dehalogenation using tributyltin hydride, metal hydrides, and other reagents;[5] (4) worthwhile intermediates for transformations such as the Nazarov-type cyclopentannulation[6] and the vinylcyclopropylidene rearrangement;[7] and (5) favourite synthons for cyclopropane derivatives by inter- and intra-molecular stereocontrolled C–C bond formation through both anionic[8] and radical type methods.[9]

Along with our interest in new and useful reactions and in compounds utilizing *gem*-dihalogenocyclopropanes,[9,10] we have already communicated a novel method for the synthesis of 1- and 2-halogenonaphthalenes by using annulation of aryl(*gem*-dihalogenocyclopropyl)methanols (abbreviated ADCM **1** and **3**) with suitable acid catalysts, wherein two distinctive types of highly regioselective acid-induced cyclopropane ring cleavage are involved.[1] Application of this benzannulation† to a total synthesis of natural lignan lactones, justicidin E **17**[11] and taiwanin C **18**,[12] was also performed. In this context, we describe the full details of these results. Since 4-arylnaphthalenes are attracting attention as the basic skeleton of several biologically active natural products and pharmaceuticals, these compounds and their synthetic isosteres have been one of the synthetic targets.[13] In connection with our studies on the anti-platelet activating factor (anti-PAF) active drug,[14] we also assayed justicidin E, since lignan-type compounds are reported to exhibit significant anti-PAF activity.[15]

Results and discussion

Transformation of cyclopropylmethanols to homoallyl halides and halogenocyclobutanes are representative examples. As for *gem*-dihalogenocyclopropylmethanols, however, little attention has been paid to them except for the Nazarov-type cyclopentannulation,[6] although *gem*-dihalogenocyclopropylmethanols are readily available by dihalogenocarbene addition to allyl alcohols and related compounds. Taking this information into account, we started to investigate the new reaction of ADCMs **1** and **3**. First, we found that the reaction of ADCM **1a** ($R^1 = R^3 = Y = H$, $R^2 = Me$) with 1.0 equiv. of $BF_3{\cdot}Et_2O$ at room temperature gave 1-chloro-3-methylnaphthalene **2a** (62%) as the main product. Lewis acids such as $SnCl_4$ and $TiCl_4$ were also applicable, although the yields were somewhat poorer. CF_3CO_2H used as a solvent gave a better yield. Encouraged by these results, we next tried the reaction with other ADCMs **1b–j**. Table 1 lists these results.

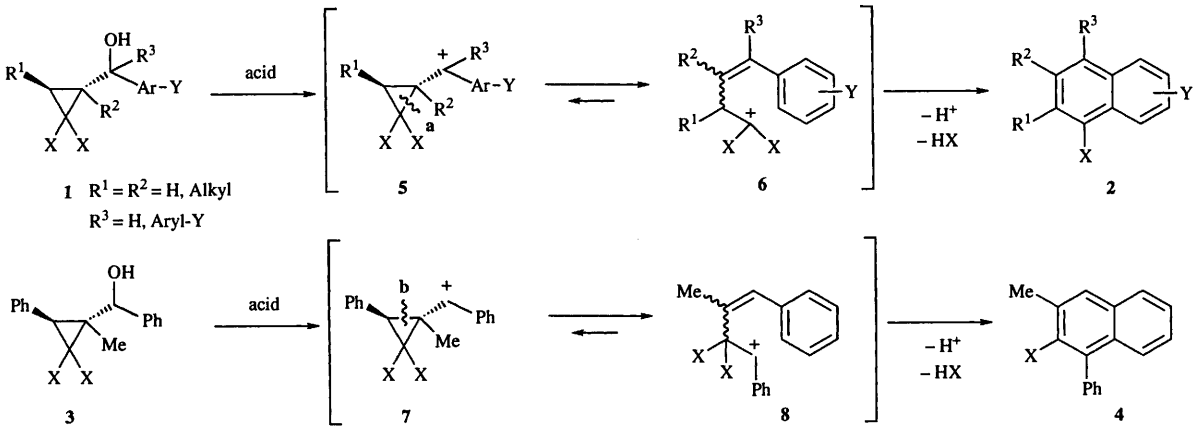


† The term 'benzannulation' is used, for example, in M. F. Semmelhack, S. Ho, D. Cohen, M. Steigerwald, M. C. Lee, G. Lee, A. M. Gilbert, W. D. Wulff and R. G. Ball, *J. Am. Chem. Soc.*, 1994, **116**, 7108.

Table 1 Synthesis of 1- and 2-halogenonaphthalenes **2** and **4** from aryl(*gem*-dihalogenocyclopropyl)methanols (ADCMs) **1** and **3**[a]

								1- and 2-Halogenonaphthalene			
Entry	ADCM	X	R^1	R^2	R^3	Y	Acid	**2**	(%)	**4**	(%)
1	**1a**	Cl	H	Me	H	H	BF_3·OEt_2	**2a**	62		0
2	**1a**	Cl	H	Me	H	H	$SnCl_4$	**2a**	55		0
3	**1a**	Cl	H	Me	H	H	$TiCl_4$	**2a**	35		0
4	**1a**	Cl	H	Me	H	H	CF_3CO_2H[b]	**2a**	77		0
5	**1b**	Cl	H	Me	Ph	H	BF_3·OEt_2	**2b**	100		0
6	**1c**	Cl	H	H	Ph	H	CF_3CO_2H[b]	**2c**	40		0
7	**1d**	Cl	Et	Me	Ph	H	BF_3·OEt_2	**2d**	86		0
8	**1d**	Cl	Et	Me	Ph	H	CF_3CO_2H[b]	**2d**	58		0
9[c]	**1e**	Cl	H	Me	Ph	*p*-MeO	BF_3·OEt_2	**2e**	43[d]		0
10[c]	**1e**	Cl	H	Me	Ph	*p*-MeO	CF_3CO_2H[b]	**2e**	28[d]		0
11[c]	**1e**	Cl	H	Me	Ph	*p*-MeO	$SnCl_4$	**2e**	62[d]		0
12[c]	**1f**	Cl	H	Me	Ph	*o*-MeO	BF_3·OEt_2	**2f**	66[e]		0
13[c]	**1g**	Cl	H	Me	Ph	*p*-Me	$SnCl_4$	**2g**	65[e]		0
14[c]	**1h**	Cl	H	Me	Ph	*p*-Cl	$SnCl_4$	**2h**	27[d]		0
15[c]	**1i**	Cl	H	Me	Ph	*p*-NHAc	$SnCl_4$	**2i**	39[d]		0
16[c]	**1j**	Br	H	Me	H	*p*-Me	$SnCl_4$	**2j**	62[d]		0
17	**3a**	Cl	Ph	Me	H	H	CF_3CO_2H[b]		0	**4a**	78
18	**3b**	Br	Ph	Me	H	H	CF_3CO_2H[b]		0	**4b**	64

[a] These reactions were carried out using equimolar amounts of Lewis acids in 1,2-dichloroethane at room temp. for 1–24 h unless noted otherwise. [b] Used as solvent. [c] Dilute conditions (about 1×10^{-2} M) in the presence of molecular sieves 4 Å. [d] 1-Halogeno-3-methyl-7-substituted (Y) naphthalenes were obtained as the sole regioisomer. [e] 1-Chloro-3-methyl-5-methoxynaphthalene was obtained as the sole regioisomer.



Scheme 1

A plausible reaction pathway for the present benzannulation is illustrated in Scheme 1. The initially formed benzyl cation **5** rearranges into the homoallyl cation **6** through regioselective bond **a** cleavage in accord with the reported study on the regioselectivity of *gem*-dichlorocyclopropylmethanols.[16] The *Z*-form of the cation of **6** undergoes an intramolecular Friedel–Crafts reaction with the aryl group and subsequent elimination of HX to afford the corresponding 1-halogenonaphthalenes **2**. Although the *E*-form of **6** may be predominantly formed for steric reasons, it is postulated to isomerize rapidly into the *Z*-form *via* the benzyl cation **5** by equilibrium.

In the case of the ADCM **1b** (R^1 = Y = H, R^2 = Me, R^3 = Ph), the annulation spontaneously took place (reaction time within 5 min) to give quantitatively 4-chloro-2-methyl-1-phenylnaphthalene **2b**, since this homoallyl cation intermediate **6** should orientate itself toward the phenyl group (Table 1, entry 5). X-Ray crystallographic analysis of **2b** confirmed the unambiguous structure and conformation of the compound (Fig. 1). However, the reaction of ADCM **1c** (R^1 = R^2 = Y = H, R^3 = Ph) was a little sluggish so that the desired 1-chloro-4-phenylnaphthalene **2c** (40%) was accompanied by 1,1,1-trichloro-4,4-diphenylbut-3-ene (20%) (entry 6). We presently think the reason for this different result between ADCMs **1b** and **1c** is as follows.‡ The benzyl cation **5** derived from ADCM **1b** would be more reactive than that derived from ADCM **1c**, and, therefore, the desired benzannulation proceeds more rapidly in the case of **1b**. On the other hand, Cl^- produced during the benzannulation attacks the C-2 position on the less reactive intermediate **5** derived from **1c** to give, partially, 1,1,1-trichloro-4,4-diphenylbut-3-ene as a by-product.

$SnCl_4$ and BF_3·Et_2O worked as effective catalysts for ADCMs **1e–j** bearing substituents on the benzene ring (Table 1, entries 9–16). These reactions needed to be carried out in dilute solution (*ca.* 1×10^2 M) with the addition of molecular sieves 4 Å, a technique which would circumvent the undesirable intermolecular oligomerization of cationic intermediates and the formation of (*E*)-4-aryl-1,1,1-trichlorobut-3-enes.

In clear contrast, the reaction of (1*R**,3*S**)-2,2-dihalogeno-1-methyl-3-phenylcyclopropyl(phenyl)methanols **3a** (X = Cl) and **3b** (X = Br) in CF_3CO_2H as solvent gave the corresponding 2-halogeno-3-methyl-1-phenylnaphthalenes **4** by regioselective cleavage of bond **b** (Scheme 1). Obviously, the benzyl cation intermediate **8** rather than **6** was predominantly formed due to the higher stability of the benzyl cation compared with the dihalogenomethylinium cation (Table 1, entries 17 and 18).

‡ Recently, we found a similar phenomenon in the related benzannulation of 2-chlorocyclopropyl(diaryl)methanols. These results will be reported in the future.

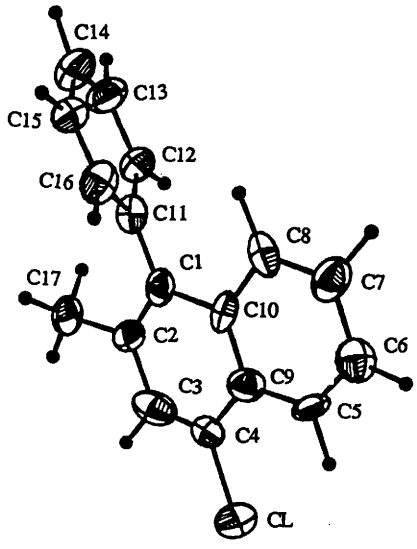


Fig. 1 X-Ray structure of **2b**. There are two crystallographically independent molecules (A or B). An ORTEP drawing of molecule A is shown. All atoms are represented by 50% thermal ellipsoids.

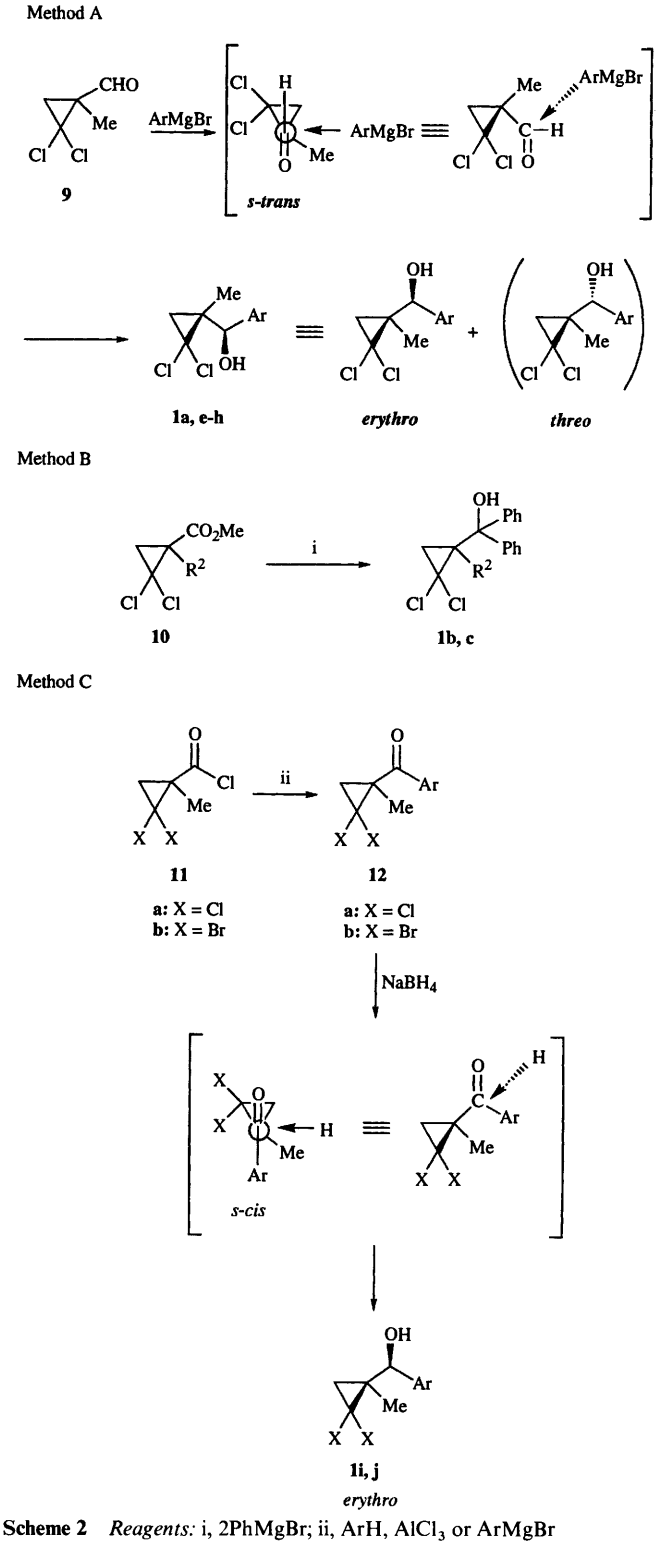
Table 2 Preparation of aryl(*gem*-dihalogenocyclopropyl)methanols (ADCMs) **1** and **3**

Entry	Method[a]	ADCM	Yield (%)
1	A	**1a**	65[b]
2	B	**1a**	41[c]
3	B	**1b**	71
4	B	**1c**	56
5	A	**1d**	65[c]
6	A	**1e**	73[c]
7	A	**1f**	55[c]
8	A	**1g**	52[c]
9	A	**1h**	66[c]
10	C	**1i**	65[c]
11	C	**1j**	65[c]
12	D	**3a**	94[d]
13	D	**3b**	34[e]

[a] Described in the text. [b] *erythro* and *threo* (7:1) mixtures. [c] *erythro* (>98%) isomers after purification. [d] Based on the corresponding ketone. [e] Based on the corresponding acyl chloride.

ADCMs **1** were prepared in three ways as shown in Scheme 2 (Table 2). Method A: Grignard reaction of ArMgBr with 2,2-dichloro-1-methylcyclopropanecarbaldehydes **9** with moderate stereoselectivity (for example: Ar = Ph; **1a**, *erythro*:*threo* = 7:1). Method B: Addition of 2 equiv. of ArMgBr or ArLi to methyl 2,2-dichlorocyclopropanecarboxylates **10**. Method C: Highly stereoselective $NaBH_4$ reduction (for example: Ar = Ph; **1a**, *erythro*:*threo* = 98:2) of ketones **12a** (X = Cl) and **12b** (X = Br), which were produced by Friedel–Crafts acylation of **11a** with ArH or by the controlled Grignard reaction of ArMgBr with cyclopropanecarbonyl chlorides **11b**, respectively. It should be noted that the 2,2-dibromo analogue **1j** was prepared by a Grignard coupling reaction with the acyl chloride **11b**, because the related esters and even aldehydes were of such low reactivity as to cause significant undesirable reductive removal of the bromine atom.

The proposed mechanism which takes the bisected conformational intermediates[1a] into account explains the stereochemical course of these reactions. ArMgBr attacks the less hindered face of the s-*trans* conformer of aldehyde **9** to form preferentially the diastereoisomers **1a** and **1e–h**. Similarly, the hydride of $NaBH_4$ adds to the less hindered face of the s-*cis* conformer of **12** to form the diastereoisomer **1i** or **1j** with high selectivity. This explanation is supported by Shuto's study on the reaction of substituted cyclopropyl ketones and by the



Scheme 2 *Reagents:* i, 2PhMgBr; ii, ArH, $AlCl_3$ or ArMgBr

so-called Cieplak theory.[17] The configuration of the *erythro* diastereoisomer of **1** was unambiguously determined by X-ray crystallography of **1g** (Fig. 2).

ADCMs **3** were prepared as follows. Method D: Grignard coupling of PhMgBr with the known (1*R**,3*S**)-2,2-dihalogeno-1-methyl-3-phenylcyclopropanecarbonyl chlorides giving the corresponding ketones,[10c] followed by $NaBH_4$ reduction.

The present benzannulation using both *erythro* and *threo* diastereoisomers of **1a** proceeded in almost the same yields, 62% and 60%, respectively. This result indicates that the same cationic intermediate **5** is equally formed from both these diastereoisomers.

Following the demonstration of the utility of this new

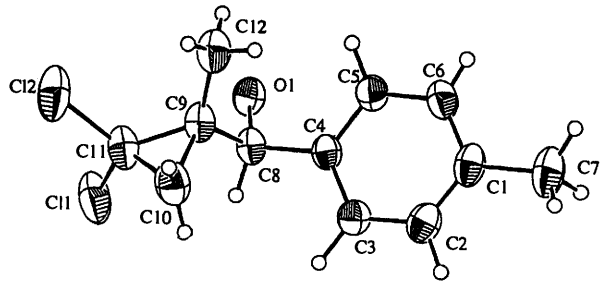
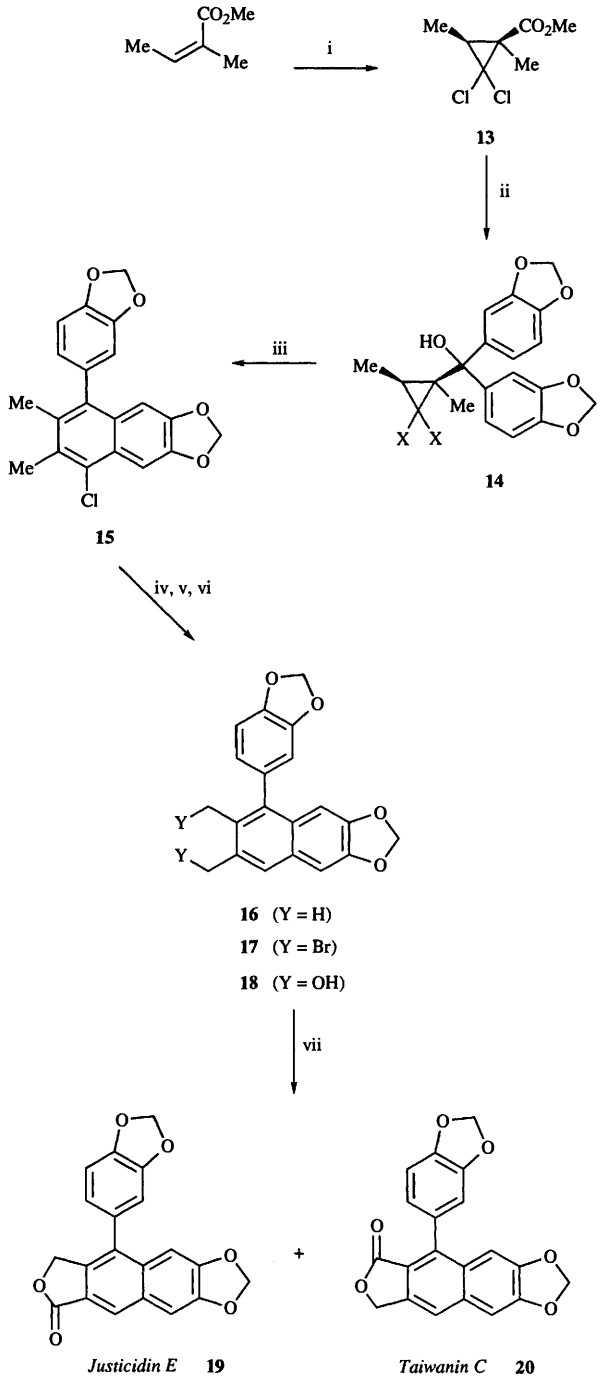


Fig. 2 X-Ray structure of *erythro*-**1g**. There are two crystallographically independent molecules (A or B). An ORTEP drawing of molecule A is shown. All atoms are represented by 30% thermal ellipsoids.

method, we described a total synthesis of the two lignan lactones, justicidin E **17**[11] and taiwanin C **18**,[12] wherein the construction of the 4-aryl-1-chloro-2,3-dimethylnaphthalene skeleton is involved as the key step (Scheme 3). Dichlorocarbene addition of the starting methyl angelate [methyl (*Z*)-2-methylbut-2-enoate] gave the *gem*-dichlorocyclopropyl ester **13**, which was converted into ADCM **14** by the treatment with 2 molar equiv. of 3,4-methylenedioxyphenyllithium, in 68% overall yield. Treatment of ADCM **14** with $SnCl_4$ (0.1 equiv.) and molecular sieves 4 Å in 1,2-dichloroethane at room temperature for 30 min successfully afforded the desired 1-chloro-2,3-dimethyl-4-(3,4-methylenedioxyphenyl)-6,7-methylenedioxynaphthelene **15** in 83% yield; a 0.1 molar catalytic amount of $SnCl_4$ was sufficient to complete the reaction in this case. $LiAlH_4$–$TiCl_4$ removal[18] of the chlorine atom in 1-chloronaphthalene **15** gave the naphthalene **16**, whose vicinal methyl groups were brominated by *N*-bromosuccinimide to give the dibromide **17**. The dibromide **17** was converted into the diol **18** upon treatment with $AgNO_3$ in 10% aqueous NaOH, in 32% overall yield from **15**. Finally, the reported oxidation of **18** by $AgCO_3$–Celite (Fetizon's reagent)[19] followed by separation gave justicidin E **19** and taiwanin C **20** (**17**/**18** = 5:1), respectively, in 17% overall yield from methyl angelate.

Finally, we tested the anti-platelet activating factor (anti-PAF) activity of justicidin E, since these kinds of lignan-type compounds are expected to show anti-PAF activity as already mentioned.[15] As a result, a significant, but relatively weak activity (IC_{50} value = 100–150 μM) was observed for justicidin E.§

In conclusion, a novel benzannulation of aryl(*gem*-dihalogenocyclopropyl)methanols to give 1- and 2-halogenonaphthalenes has been developed, the use of which has been demonstrated by application to the total synthesis of the lignan lactones, justicidin E and taiwanin C. Further extension of this benzannulation is now in progress.



Scheme 3 *Reagents:* i, $CHCl_3$, 50% aq. NaOH, cat. $PhCH_2N^+Et_3Cl^-$; ii, 3,4-(–OCH_2O–)C_6H_3Li; iii, $SnCl_4$ (0.1 equiv.), MS 4 Å; iv, $LiAlH_4$–$TiCl_4$; v, 2NBS; vi, $AgNO_3$, aq. NaOH; vii, Fetizon's reagent

Experimental

Melting points were determined on a hot-stage microscope apparatus (Yanagimoto) and are uncorrected. ^1H NMR spectra were recorded on a JEOL EX-90 (90 MHz) and/or JEOL α (400 MHz) spectrometer in $CDCl_3$ using a TMS internal standard; *J* values given in Hz. IR spectra were recorded on a Hitachi 270–30 spectrophotometer. Mass spectra were obtained with a Hitachi GC/MS M-80 instrument (70 eV). All of the reagents and solvents were purified prior to use. Silica gel column chromatography was performed on a Merck Art. 7734 and 9385. 2,2-Dichloro-1-methylcyclopropanecarboxylic acid and methyl 2,2-dichloro-1-methylcyclopropanecarboxylate were commercially available. Ether refers to diethyl ether.

§ Other biological activity for this type of lignan lactone has been described; for example, in S. Yamamura, *J. Synth. Org. Chem. Jpn.*, 1985, **43**, 583.

2,2-Dichloro-1-methylcyclopropanecarbaldehyde 9

Methyl 2,2-dichloro-1-methylcyclopropanecarboxylate (9.25 g, 50.5 mmol) in THF (50 cm^3) was added to a stirred suspension of $LiAlH_4$ (1.13 g, 28.3 mmol) in THF (15 cm^3) at 0–5 °C. The mixture was stirred at room temp. for 5 h after which it was treated with saturated aqueous Na_2SO_4, with cooling, and then diluted with ether and filtered through Celite using ether. Concentration of the mixture and distillation of the crude oil gave 2,2-dichloro-1-methylcyclopropylmethanol[20] (7.12 g, 91%) as a colourless liquid, bp 83–86 °C/17 mmHg; ν_{max}(neat)/cm^{-1} 3356 and 2968; δ(90 MHz) 1.25 (1 H, d, J_{gem} 7.1), 1.42 (1 H, d, J_{gem} 7.1), 1.45 (3 H, s), 2.10 (1 H, s, OH), 3.62

(1 H, d, J_{gem} 12.2) and 3.84 (1 H, d, J_{gem} 12.2). Pyridinium chlorochromate (PCC reagent) (17.9 g, 83.3 mmol) was added portionwise during 1 h to a stirred solution of 2,2-dichloro-1-methylcyclopropylmethanol (8.61 g, 55.5 mmol) in CH_2Cl_2 (50 cm^3) at room temp. under a N_2 atmosphere. The mixture was stirred at room temp. for 20 h after which it was diluted with ether, filtered through Celite using ether and concentrated. The crude oil was subjected to flash column chromatography on Florisil using C_6H_{14}–AcOEt (8:1) as eluent, followed by distillation to give the *product* **9** (7.56 g, 89%) as a colourless liquid; bp 80–82 °C/60 mmHg (Found: C, 38.91; H, 3.77. $C_5H_6Cl_2O$ requires C, 39.25; H, 3.95%); ν_{max}(neat)/cm^{-1} 1722, 1452 and 1053; δ_H(90 MHz) 1.51 (3 H, s), 1.68 (1 H, d, J_{gem} 7.6), 2.26 (1 H, d, J_{gem} 7.6) and 9.30 (1 H, s). Compared with PCC reagent, the use of pyridinium dichromate (PDC) gave significantly slower conversion of 2,2-dichloro-1-methylcyclopropylmethanol.

2,2-Dichloro-1-methylcyclopropanecarbonyl chloride 11a

Thionyl chloride (6.55 g, 0.055 mol) was added to a stirred solution of 2,2-dichloro-1-methylcyclopropanecarboxylic acid (8.45 g, 50.0 mmol) and a small amount of DMF (*ca.* 20 mg) in toluene (50 cm^3) at room temp. The mixture was refluxed for 2 h and then, after being cooled to room temp., was evaporated and distilled to give the *product* **11a** (8.53 g, 91%) as a pale yellow liquid; bp 68–70 °C/18 mmHg (Found: C, 31.83; H, 2.47. $C_5H_5Cl_3O$ requires C, 32.04; H, 2.69%); ν_{max}(neat)/cm^{-1} 2942, 1784 and 1454; δ_H(90 MHz) 1.65 (1 H, d, J_{gem} 7.0), 1.75 (3 H, s) and 2.40 (1 H, d, J_{gem} 7.0).

2,2-Dibromo-1-methylcyclopropanecarbonyl chloride 11b[20a]

Jones oxidation of 2,2-dibromo-1-methylcyclopropylmethanol[21] in a similar manner to that described earlier[10c] gave 2,2-dibromo-1-methylcyclopropanecarboxylic acid[20] (82%) as a light brown liquid. In a manner similar to that described for the preparation of the acid chloride **11a**, the reaction of 2,2-dibromo-1-methylcyclopropanecarboxylic acid gave the *product* **11b** (83%) as a light brown liquid; bp 88–90 °C/4 mmHg (lit.,[20a] 82–84 °C/2 mmHg); ν_{max}(neat)/cm^{-1} 2942, 1780 and 1452; δ_H(90 MHz) 1.60 (1 H, d, J_{gem} 8.1), 1.76 (3 H, s) and 1.78 (1 H, d, J_{gem} 7.0).

Methyl (1*R**,3*R**)-2,2-dichloro-1,3-dimethylcyclopropanecarboxylate 13

50% aqueous NaOH (70.0 g) was added to a vigorously stirred mixture of methyl angelate [methyl (*Z*)-2-methylbut-2-enoate; 10.0 g, 88 mmol], benzyl(triethyl)ammonium chloride (1.00 g, 4.4 mmol) and $CHCl_3$ (47.8 g) at 35–40 °C. The mixture was then stirred for 16 h at the same temperature after which it was diluted with water and extracted with CH_2Cl_2 (50 cm^3 × 2). The combined extracts were washed with water and brine, dried (Na_2SO_4) and distilled to give the *product* **13** (14.0 g, 81%) as a pale yellow liquid; bp 90–93 °C/18 mmHg (Found: C, 42.44; H, 9.96. $C_7H_{10}Cl_2O_2$ requires C, 42.67; H, 5.11%); ν_{max}(neat)/cm^{-1} 2938, 1742 and 1155; δ_H(90 MHz) 1.33–1.66 (1 H, m), 1.41 (3 H, d, *J* 9.5), 1.59 (3 H, s) and 3.72 (3 H, s).

2,2-Dichloro-1-methylcyclopropyl(phenyl)methanol 1a

Method A. 2,2-Dichloro-1-methylcyclopropanecarbaldehyde **9** (1.53 g, 10 mmol) in THF (10 cm^3) was added to a stirred solution of PhMgBr (1 M THF solution; 12 cm^3, 12 mmol) at 0–5 °C under a N_2 atmosphere. The mixture was stirred at room temp. for 5 h after which it was diluted with saturated aqueous NH_4Cl and extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated to leave a crude oil. This was subjected to flash column chromatography on SiO_2 using C_6H_{14}–AcOEt (10:1) as eluent to give the *product* **1a** (1.50 g, 65%; a mixture of diastereoisomers; *erythro*/*threo* = 7:1); *erythro* isomer: colourless liquid (Found: C, 57.23; H, 5.43. $C_{11}H_{12}Cl_2O$ requires C, 57.17; H, 5.23%); ν_{max}(neat)/cm^{-1} 3449, 3032, 2939 and 1037; δ_H(90 MHz) 1.20 (3 H, s), 1.35 (1 H, d, J_{gem} 7.6), 1.75 (1 H, d, J_{gem} 7.6), 2.35 (1 H, d, *J* 5.0, OH), 4.75 (1 H, d, *J* 5.0) and 7.30–7.45 (5 H, m); *threo* isomer: colourless liquid; δ_H(90 MHz) 1.16 (3 H, s), 1.42 (1 H, d, J_{gem} 7.6), 1.71 (1 H, d, J_{gem} 7.6), 2.15 (1 H, d, *J* 4.1, OH), 4.81 (1 H, d, *J* 4.1) and 7.05–7.69 (5 H, m).

Method C. PhMgBr (1 M THF solution; 7.2 cm^3, 7.2 mmol) was added to a stirred solution of 2,2-dichloro-1-methylcyclopropanecarbonyl chloride **11a** (2.69 g, 14.4 mmol) in THF (15 cm^3) at 0–5 °C. The mixture was stirred at room temp. for 10 h after which a similar work-up to that described for method A gave 2,2-dichloro-1-methylcyclopropyl(phenyl)methanone **12a** (1.48 g, 45% based on **11a**; 90% based on PhMgBr) as a colourless liquid (Found: C, 57.43; H, 4.17. $C_{11}H_{10}Cl_2O$ requires C, 57.67; H, 4.40%); δ_H(90 MHz) 1.45 (1 H, d, J_{gem} 7.0), 1.65 (3 H, s), 2.35 (1 H, d, J_{gem} 7.0), 7.40–8.10 (5 H, m). $NaBH_4$ (0.15 g, 3.97 mmol) was added to the ketone **12a** (1.83 g, 8.03 mmol) in MeOH (7.0 cm^3) at room temp. and the mixture was stirred at room temp. for 5 h. Aqueous 1 M HCl was added to the mixture, which was then extracted with ether. The organic phase was washed with water and brine, dried (Na_2SO_4) and concentrated to give a crude oil. This was subjected to flash column chromatography on SiO_2 using C_6H_{14}–AcOEt (10:1) as eluent to give the diastereoisomer product **1a** (1.67 g, 90%; *erythro*/*threo* = 98:2 determined by 400 MHz ^1H NMR measurement).

2,2-Dichloro-1-methylcyclopropyl(diphenyl)methanol 1b

Method B. Methyl 2,2-dichloro-1-methylcyclopropanecarboxylate (3.66 g, 20 mmol) in THF (20 cm^3) was added to a stirred solution of PhMgBr (1 M THF solution; 50 cm^3, 50 mmol) at 0–5 °C after which the mixture was stirred at 40–45 °C for 24 h. Sat. aqueous NH_4Cl (100 cm^3) was added to the mixture, which was then extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated. The crude crystals were washed with hexane (20 cm^3) and dried to give the desired *product* **1b** (4.36 g, 71%) as colourless crystals; mp 87.0–88.5 °C (Found: C, 66.16; H, 5.26. $C_{17}H_{16}Cl_2O$ requires C, 66.46; H, 5.25%); ν_{max}(neat)/cm^{-1} 3569, 3059, 1491 and 1445; δ_H(90 MHz) 1.20 (3 H, s), 1.30 (1 H, d, J_{gem} 7.0), 2.55 (1 H, d, J_{gem} 7.0), 2.80 (1 H, s, OH) and 7.10–7.60 (10 H, m).

2,2-Dichlorocyclopropyl(diphenyl)methanol 1c

Method B. In a manner similar to that described for the preparation of the alcohol **1b**, the reaction of methyl 2,2-dichlorocyclopropanecarboxylate[22] gave the *product* **1c** (56%) as colourless crystals; mp 62–65 °C (Found: C, 65.85; H, 4.97. $C_{16}H_{14}Cl_2O$ requires C, 65.55; H, 4.81%); ν_{max}(KBr disk)/cm^{-1} 3571, 1493 and 1449; δ_H(400 MHz) 1.69 (1 H, dd, *J* 11.0, *J* 7.1), 2.08 (1 H, dd, *J* 8.5, *J* 7.1), 2.45 (1 H, dd, *J* 11.0, *J* 8.5), 2.54 (1 H, br s, OH), 7.20–7.50 (8 H, m) and 7.60–7.65 (2 H, m).

(1*R**,3*S**)-3-Ethyl-2,2-dichloro-1-methylcyclopropyl(diphenyl)methanol 1d

Method B. Methyl (1*R**,3*S**)-2,2-dichloro-3-ethyl-1-methylcyclopropanecarboxylate was prepared in a procedure similar to that described for the preparation of **13** (72%) as a pale yellow liquid; bp 97–99 °C/17 mmHg (Found: C, 45.12; H, 5.58. $C_8H_{12}Cl_2O_2$ requires C, 45.52; H, 5.73%); ν_{max}(neat)/cm^{-1} 2943, 1742 and 1147; δ_H(90 MHz) 0.99–1.70 (5 H, m), 1.60 (3 H, s) 2.25 (1 H, dd, *J* 11.0, *J* 9.0) and 3.70 (3 H, s). In a manner similar to that described for the preparation of the alcohol **1b**, the reaction of methyl (1*R**,3*S**)-2,2-dichloro-3-ethyl-1-methylcyclopropanecarboxylate gave the *product* **1d** (65%) as colourless crystals; mp 109–112 °C (Found: C, 67.80; H, 6.05. $C_{19}H_{20}Cl_2O$ requires C, 68.07; H, 6.01%); ν_{max}(KBr disk)/cm^{-1} 3561, 2965 and 1447; δ_H(90 MHz) 1.00 (3 H, s), 1.05 (3 H, t, *J* 7.0), 1.20–1.80 (2 H, m), 2.65 (1 H, dd, *J* 9.0, *J* 7.0), 2.80 (1 H, s, OH) and 7.10–7.60 (10 H, m).

2,2-Dichloro-1-methylcyclopropyl(4-methoxyphenyl)methanol 1e

Method A. In a manner similar to that described for the preparation of the alcohol **1a**, the reaction of 4-methoxyphenylmagnesium bromide with the aldehyde **9** gave the erythro-*product* **1e** (73%) as colourless crystals; mp 49.0–50.0 °C (Found: C, 54.82; H, 5.55. $C_{12}H_{14}Cl_2O_2$ requires C, 55.19; H, 5.40%); ν_{max}(neat)/cm^{-1} 3570, 2937, 2837 and 1032; δ_H(90 MHz) 1.23 (3 H, s), 1.32 (1 H, d, J_{gem} 7.1), 1.72 (1 H, d, J_{gem} 7.1), 1.89–2.42 (1 H, br, OH), 3.81 (3 H, s), 4.72 (1 H, s), 6.89 (2 H, d, *J* 9.7) and 7.32 (2 H, d, *J* 9.7).

2,2-Dichloro-1-methylcyclopropyl(2-methoxyphenyl)methanol 1f

Method A. In a manner similar to that described for the preparation of the alcohol **1a**, the reaction of 2-methoxyphenylmagnesium bromide with the aldehyde **9** gave erythro-*product* **1f** (55%) as colourless crystals; mp 50.5–51.5 °C (Found: C, 54.92; H, 5.57. $C_{12}H_{14}Cl_2O_2$ requires C, 55.19; H, 5.40%); ν_{max}(neat)/cm^{-1} 3460, 2939, 2837 and 1032; δ_H(90 MHz) 1.21 (1 H, d, J_{gem} 7.1), 1.26 (3 H, s), 1.94 (1 H, d, J_{gem} 7.1), 2.07–2.63 (1 H, br, OH), 3.81 (3 H, s), 5.12 (1 H, s), 6.79–7.41 (3 H, m) and 7.50–7.68 (1 H, m).

2,2-Dichloro-1-methylcyclopropyl(*p*-tolyl)methanol 1g

Method A. In a manner similar to that described for the preparation of the alcohol **1a**, the reaction of *p*-tolylmagnesium bromide with the aldehyde **9** gave the erythro-*product* (52%) as colourless crystals; mp 53.5–54.5 °C (Found: C, 58.63; H, 5.90. $C_{12}H_{14}Cl_2O$ requires C, 58.79; H, 5.76%); ν_{max}(neat)/cm^{-1} 3423, 2922, 2854 and 1041; δ_H(90 MHz) 1.22 (3 H, s), 1.32 (1 H, d, J_{gem} 6.1), 1.73 (1 H, d, J_{gem} 6.1), 2.15–2.42 (1 H, br, OH), 2.38 (3 H, s), 4.68–4.82 (1 H, br) and 7.08–7.44 (4 H, m).

X-Ray analysis of 1g

Intensity data were collected on a Rigaku AFC7R diffractometer using graphite-monochromated Cu-Kα radiation (λ = 1.541 78 Å). Crystal data are as follows: $C_{12}H_{11}OCl_2$, *M* 245.15, triclinic, space group ($P\bar{1}$2), a = 11.012(3), b = 11.956(2), c = 10.538(2) Å, α = 95.32(2)°, β = 104.14(2)°, γ = 65.44(1)°, V = 1223.4(4) Å^3, Z = 4, F(000) = 512.00, D_x = 1.331 g cm^{-3}, μ(Cu-Kα) = 45.36 cm^{-1}. A total of 4388 reflections with θ < 65° were collected by the ω–2θ scan technique. The structure was solved by direct methods and refined by full-matrix least-squares. Non-hydrogen atoms were refined with anisotropic thermal parameters. The final R and R_w factors were 0.056 and 0.077, respectively, for 2768 observed reflections [$I > 3\sigma(I)$]. There are two crystallographically independent molecules in the asymmetric unit. The conformations of the two molecules are almost identical except for those torsion angles corresponding to C(5), C(4), C(8), C(9) (molecule A, −86.7°; molecule B −105.5°). All calculations were carried out on a micro VAX II using SDP package. All the structural parameters for this determination (coordinates, bond lengths and bond angles, thermal parameters) and that described later for compound **2b** have been deposited with the Cambridge Crystallographic Data Centre (see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1). Any request to the CCDC for this information should include the full bibliographic citation together with the reference no. 207/33.

2,2-Dichloro-1-methylcyclopropyl(4-chlorophenyl)methanol 1h

Method A. In a manner similar to that described for the preparation of the alcohol **1a**, the reaction of 4-chlorophenylmagnesium bromide with the aldehyde **9** gave the erythro-*product* **1h** (66%) as colourless crystals; mp 72–72.5 °C (Found: C, 49.48; H, 4.37. $C_{11}H_{11}Cl_3O$ requires C, 49.75; H, 4.17%); ν_{max}(neat)/cm^{-1} 3387, 2928, 2854 and 1041; δ_H(90 MHz) 1.18 (3 H, s), 1.34 (1 H, d, J_{gem} 6.5), 1.73 (1 H, d, J_{gem} 6.5), 2.38 (1 H, d, *J* 3.3, OH), 4.75 (1 H, d, *J* 3.3) and 7.33 (4 H, br s).

2,2-Dichloro-1-methylcyclopropyl(4-acetamidophenyl)methanol 1i

Method C. Phenylacetamide (1.35 g, 10.0 mmol) was added to a stirred suspension of 2,2-dichloro-1-methylcyclopropanecarbonyl chloride (1.88 g, 10.0 mmol) and $AlCl_3$ (1.46 g, 10.0 mmol) in CS_2 (20 cm^3) at room temp. The mixture was stirred at room temp. for 10 h and then quenched with 1 M aqueous HCl. The mixture was extracted with ether and the extract washed with water and brine, dried (Na_2SO_4) and concentrated. The resulting crude oil was subjected to flash column chromatography on SiO_2 using C_6H_{14}–AcOEt (50:1) as eluent to give the desired intermediary ketone (0.33 g, 18%) as a colourless liquid. $NaBH_4$ (77 mg, 2.03 mmol) was added to a stirred solution of the ketone (291 mg, 1.02 mmol) in MeOH (2 cm^3) at room temp. after which the mixture was stirred at room temp. for 10 h. It was then diluted with water and extracted with ethyl acetate. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated. The resulting crude oil was subjected to flash column chromatography on SiO_2 using C_6H_{14}–AcOEt (5:1) as eluent to give the *product* (192 mg, 65%) as colourless crystals; mp 50.5–51.5 °C (Found: C, 53.85; H, 5.01; N, 4.66. $C_{13}H_{15}Cl_2NO_2$ requires C, 54.18; H, 5.25; N, 4.86%); ν_{max}(KBr disk)/cm^{-1} 3424, 2363, 1512 and 1042; δ_H(90 MHz) 1.15 (3 H, s), 1.33 (1 H, d, J_{gem} 6.0), 1.78 (1 H, d, J_{gem} 6.0), 2.15 (3 H, s), 4.70 (1 H, s) and 7.10–7.35 (4 H, m).

2,2-Dibromo-1-methylcyclopropyl(*p*-tolyl)methanol 1j

Method C. $AlCl_3$ (1.34 g, 10.0 mmol) was added to a stirred solution of 2,2-dibromo-1-methylcyclopropanecarbonyl chloride **11b** (2.77 g, 10.0 mmol) in toluene (30 cm^3) at 0–5 °C after which the mixture was stirred at 0–5 °C for 1h. The mixture was then diluted with water and extracted with ether. The organic phase was washed with water and brine, dried (Na_2SO_4) and concentrated. The resulting crude oil was subjected to flash column chromatography on SiO_2 using C_6H_{14}–AcOEt (20:1) as eluent to give the desired intermediary *ketone* (2.15 g, 65%) as a colourless liquid (Found: C, 43.21; H, 3.49. $C_{12}H_{12}Br_2O$ requires C, 43.41; H, 3.64%); ν_{max}(neat)/cm^{-1} 2930, 1684, 1607 and 1316; δ_H(90 MHz) 1.65 (1 H, d, J_{gem} 7.0), 1.67 (3 H, s), 2.45 (1 H, d, J_{gem} 7.0) and 7.36 (2 H, d, *J* 10.0) and 7.90 (2 H, d, *J* 10.0). In a manner similar to that described for the reduction of method C, the reaction using the ketone gave the *product* **1j** (81%) as colourless crystals; mp 56.5–60.0 °C (Found: C, 43.26; H, 4.39. $C_{12}H_{14}Br_2O$ requires C, 43.51; H, 4.22%); ν_{max}(KBr)/cm^{-1} 3387, 2920, 1514 and 1047; δ_H(90 MHz) 1.35 (3 H, s), 1.50 (1 H, d, J_{gem} 7.0), 1.95 (1 H, d, J_{gem} 7.0), 2.35 (3 H, s), 2.40 (1 H, br d, *J* 2.0, OH), 4.75 (1 H, d, *J* 2.0) and 7.05–7.40 (4 H, m).

(1*R,3*S**)-2,2-Dichloro-1-methyl-3-phenylcyclopropyl(phenyl)-methanol 3a**

Method D. $NaBH_4$ (32.5 mg, 0.85 mmol) was added to a stirred solution of (1*R**,3*S**)-2,2-dichloro-1-methyl-3-phenylcyclopropyl(phenyl)methanone[10c] (255 mg, 0.85 mmol) in MeOH (2.0 cm^3) at room temp. and the mixture was stirred at room temp. for 5 h. After this, the mixture was treated with 1 M aqueous HCl and extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated. The resulting crude oil was subjected to flash column chromatography on SiO_2 using C_6H_{14}–AcOEt (10:1) as eluent to give the *product* **3a** (245 mg, 94%) as colourless crystals; mp 129–131 °C (Found: C, 66.17; H, 5.01. $C_{17}H_{16}Cl_2O$ requires C, 66.46; H, 5.25%); ν_{max}(KBr)/cm^{-1} 3588, 2926, 1449 and 1040; δ_H(400 MHz) 0.91 (3 H × 2/100, s), 1.01 (3 H × 98/100, s), 2.98 (1 H × 2/100, s), 3.03 (1 H × 98/100, s), 4.97 (1 H × 2/100, s), 5.01 (1 H × 98/100, s), 6.95–7.05 (2 H, m), 7.20–7.34 (3 H, m), 7.34–7.45 (3 H, m) and 7.45–7.54 (2 H, m).

2,2-Dibromo-1-methyl-3-phenylcyclopropyl(phenyl)methanol 3b

Method D. In a manner similar to that described for the preparation of the alcohol **3a**, a reaction using (1*R**,3*S**)-2,2-dibromo-1-methyl-3-phenylcyclopropanecarbonyl chloride[10c] gave the *product* **3b** (34%) as brown crystals; mp 95–98 °C (Found: C, 51.38; H, 3.87. $C_{17}H_{16}Br_2O$ requires C, 51.55; H, 4.07%); ν_{max}(KBr)/cm^{-1} 3575, 2918 and 1453; δ_H(400 MHz) 0.94 (3 H × 2/100, s), 0.99 (3 H × 98/100, s), 2.77 (1 H × 2/100, s), 3.01 (1 H × 98/100, s), 4.95 (1 H × 2/100, s), 4.98 (1 H × 98/100, s) and 6.95–7.54 (10 H, m).

4-Chloro-2-methyl-1-phenylnaphthalene 2b

BF_3·OEt_2 (142 mg, 1.0 mmol) was added to a stirred solution of 2,2-dichloro-1-methylcyclopropyl(diphenyl)methanol (ADCM) **1b** (307 mg, 1.0 mmol) in 1,2-dichloromethane (2.0 cm^3) at room temp. after which the mixture was stored at room temp. for 1 h. It was then diluted with water and extracted with ether. The organic phase was washed with water and brine, dried (Na_2SO_4) and concentrated. The resulting crude oil was subjected to flash column chromatography on SiO_2 using C_6H_{14}–AcOEt (50:1) as eluent to give the *product* **2a** (252 mg, 100%) as colourless crystals; mp 87–87.5 °C (Found: C, 80.64; H, 4.92. $C_{17}H_{13}Cl$ requires C, 80.79; H, 5.18%); ν_{max}(neat)/cm^{-1} 2919, 1579 and 1375; δ_H(90 MHz) 2.20 (3 H, s), 7.00–7.60 (9 H, m) and 8.15–8.35 (1 H, m); *m*/*z* 252 (M^+, 100%).

X-Ray analysis of 2b

Intensity data were collected on an Enraf-Nonius CAD4 diffractometer using graphite-monochromated Cu-Kα radiation (λ = 1.5418 Å). Crystal data are as follows: $C_{17}H_{13}Cl$, *M* 252.74, monoclinic, space group $P2_1$, a = 11.798(1), b = 12.269(1), c = 8.903(1) Å, β = 99.47(1)°, V = 1271.2 Å^3, Z = 4, F(000) = 528, D_x = 1.321 g cm^{-3}, μ(Cu-Kα) = 24.76 cm^{-1}. A total of 2543 reflections with θ < 70° were collected by ω–2θ scan technique. The structure was solved by direct methods using MULTAN and refined by full-matrix least-squares. Non-hydrogen atoms were refined with anisotropic thermal parameters. The final R and R_w factors were 0.040 and 0.058, respectively, for 1686 observed reflections [$I > 3\sigma(I)$]. There are two crystallographically independent molecules in the asymmetric unit. The conformations of the two molecules are almost identical. All calculations were carried out on a micro VAX II using SDP package.

1-Chloro-3-methylnaphthalene 2a

In a manner similar to that described for the preparation of the naphthalene **2b**, the reaction of ADCM **1a** with BF_3·OEt_2 gave the *product* **2b** (62%) as a colourless liquid (Found: C, 74.95; H, 4.87. $C_{11}H_9Cl$ requires C, 74.79; H, 5.14%); ν_{max}(neat)/cm^{-1} 3053, 2920, 1599 and 1500; δ_H(90 MHz) 2.49 (3 H, s), 7.31–7.77 (5 H, m) and 8.08–8.34 (1 H, m); *m*/*z* 176 (M^+, 100%).

1-Chloro-4-phenylnaphthalene 2c

In a manner similar to that described for the preparation of the naphthalene **2b**, the reaction of ADCM **1c** with BF_3·OEt_2 gave the *product* (40%) as colourless crystals; mp 63–65 °C (lit.,[23] 66–68 °C); ν_{max}(neat)/cm^{-1} 3055, 1491, 1444 and 1381; δ_H(90 MHz) 7.14–7.74 (9 H, m), 7.92 (1 H, d, *J* 9.0) and 8.38 (1 H, d, *J* 9.0); *m*/*z* 252 (M^+, 100). 1,1,1-Trichloro-4,4-diphenylbut-3-ene was obtained as a by-product (20%); ν_{max}(neat)/cm^{-1} 3052, 1488 and 1357; δ_H(90 MHz) 3.32 (1 H, dd, *J* 9.0, *J* 9.0), 3.50 (1 H, dd, *J* 12.0, *J* 9.0), 6.15–6.45 (1 H, m) and 7.18–7.7 (10 H, m); *m*/*z* (20 eV) 310 (M^+, 45) and 193 ($M^+ - CCl_3$, 100); *m*/*z* 193 ($M^+ - CCl_3$, 100).

1-Chloro-2-ethyl-3-methyl-4-phenylnaphthalene 2d

In a manner similar to that described for the preparation of the naphthalene **2b**, the reaction of ADCM **1d** with BF_3·OEt_2 or with CF_3CO_2H gave the *product* **2d** (86% or 58%) as a colourless liquid (Found: C, 81.01; H, 5.88. $C_{19}H_{17}Cl$ requires C, 81.27; H, 6.10%); ν_{max}(neat)/cm^{-1} 3043, 1485 and 1391; δ_H(90 MHz) 1.30 (3 H, t, *J* 7.0), 2.20 (3 H, s), 3.10 (2 H, q, *J* 7.0), 7.10–7.70 (8 H, m) and 8.25–8.40 (1 H, m); *m*/*z* 280 (M^+, 100%).

1,7-Dichloro-3-methylnaphthalene 2h

BF_3·OEt_2 (152 mg, 1.07 mmol) was added to a stirred solution of ADCM **1h** (246 mg, 1.07 mmol) and molecular sieves 4 Å (1.0 g) in 1,2-dichloromethane (110 cm^3) at room temp. after which the mixture was stirred at room temp. for 1 h. The mixture was then diluted with water and extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated. The resulting crude oil was subjected to flash column chromatography on SiO_2 using C_6H_{14}–AcOEt (50:1) as eluent to give the *product* **2h** (27%) as colourless crystals; mp 30.0–31.0 °C (Found: C, 62.21; H, 3.97. $C_{11}H_8Cl_2$ requires C, 62.59; H, 3.82%); ν_{max}(neat)/cm^{-1} 2953, 2854, 1593 and 1489; δ_H(90 MHz) 2.44 (3 H, s), 7.17–7.81 (4 H, m) and 7.92–8.24 (1 H, m).

1-Chloro-7-methoxy-3-methylnaphthalene 2e

In a manner similar to that described for the preparation of the naphthalene **2h**, the reaction of ADCM **1e** with $SnCl_4$ gave the *product* **2f** (62%) as a colourless oil (Found: C, 69.44; H, 5.08. $C_{12}H_{11}ClO$ requires C, 69.74; H, 5.36%); ν_{max}(neat)/cm^{-1} 2957, 2837, 1630 and 1506; δ_H(90 MHz) 2.43 (3 H, s), 2.90 (3 H, s), 6.90–7.46 (4 H, m) and 8.06 (1 H, d, *J* 7.0); *m*/*z* 206 (M^+, 100%).

1-Chloro-5-methoxy-3-methylnaphthalene 2f

In a manner similar to that described for the preparation of the naphthalene **2h**, the reaction of ADCM **1f** with BF_3·OEt_2 gave the *product* **2g** (66%) as colourless crystals; mp 60–61 °C (Found: C, 69.40; H, 5.43. $C_{12}H_{11}ClO$ requires C, 69.74; H, 5.36%); ν_{max}(neat)/cm^{-1} 2957, 2934, 2837, 1630 and 1506; δ_H(90 MHz) 2.43 (3 H, s), 2.90 (3 H, s), 6.90–7.46 (4 H, m) and 8.06 (1 H, d, *J* 7.0); *m*/*z* 206 (M^+, 100%).

1-Chloro-3,7-dimethylnaphthalene 2g

In a manner similar to that described for the preparation of the naphthalene **2h**, the reaction of ADCM **1g** with $SnCl_4$ gave the *product* **2h** (65%) as a colourless oil (Found: C, 75.87; H, 6.05. $C_{12}H_{11}Cl$ requires C, 75.59; H, 5.81%); ν_{max}(neat)/cm^{-1} 2924, 2854, 1599 and 1498; δ_H(90 MHz) 2.46 (3 H, s), 2.51 (3 H, s), 7.16–7.86 (4 H, m) and 7.92–8.21 (1 H, m).

1-Bromo-3,7-dimethylnaphthalene 2j

In a manner similar to that described for the preparation of the naphthalene **2h**, the reaction of ADCM **1j** with $SnCl_4$ gave the *product* **2j** (62%) as a colourless oil (Found: C, 61.07; H, 4.55. $C_{12}H_{11}Br$ requires C, 61.30; H, 4.72%); ν_{max}(neat)/cm^{-1} 2919, 2361 and 1610; δ_H(90 MHz) 2.46 (3 H, s), 2.51 (3 H, s), 7.20–7.85 (4 H, m) and 8.05 (1 H, d, *J* 10).

1-Phenyl-2-chloro-3-methylnaphthalene 4a

A solution of (1*R**,3*S**)-2,2-dichloro-1-methyl-3-phenylcyclopropyl(phenyl)methanol **3a** (100 mg, 0.33 mmol) in trifluoroacetic acid (1 cm^3) was stirred at room temp. for 1 h after which the mixture was evaporated to give a crude oil. This was subjected to flash column chromatography on SiO_2 using C_6H_{14}–AcOEt (50:1) as eluent to give the *product* **4a** (65 mg, 78%) as colourless crystals; mp 112–115 °C (Found: C, 80.66; H, 5.09. $C_{17}H_{13}Cl$ requires C, 80.79; H, 5.18%); ν_{max}(KBr disk)/cm^{-1} 2954, 1475 and 1378; δ_H(90 MHz) 2.25 (3 H, s), 7.00–7.80 (9 H, m) and 7.90 (1 H, br s); *m*/*z* 252 (M^+, 100%).

2-Bromo-3-methyl-1-phenylnaphthalene 4b

In a manner similar to that described for the preparation of the naphthalene **4a**, the reaction of ADCM **3b** gave the *product* **4b** (64%) as colourless crystals; mp 66–67 °C (Found: C, 68.45; H, 4.19. $C_{17}H_{13}Br$ requires C, 68.70; H, 4.41%); ν_{max}(KBr disk)/cm^{-1} 3054, 2363, 1487 and 747; δ_H(90 MHz) 2.35 (3 H, s), 7.00–7.85 (9 H, m) and 8.05 (1 H, br s).

(1*R,3*R**)-2,2-Dichloro-1,3-dimethylcyclopropylbis(3,4-methylenedioxyphenyl)methanol 14**

BuLi (1.6 M THF solution; 34 cm^3, 55 mmol) was added to a stirred solution of 1-bromo-3,4-methylenedioxybenzene (10.1 g, 50 mmol) in THF (50 cm^3) at −60 °C, and the mixture was stirred at −60 °C for 30 min. Then, methyl (1*R**,3*R**)-2,2-dichloro-1,3-dimethyl-2,2-dichlorocyclopropanecarboxylate **13** (0.99 g, 25 mmol) in THF (10 cm^3) was added to the mixture over 10 min, after which the latter was stirred for 1 h. After this it was poured into ice–water and extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated to give a crude oil. This was subjected to flash column chromatography on SiO_2 using C_6H_{14}–AcOEt (5:1) as eluent to give the *product* **14** (7.26 g, 71%) as a colourless amorphous solid (Found: C, 58.43; H, 4.21. $C_{20}H_{18}Cl_2O_5$ requires C, 58.70; H, 4.43%); ν_{max}(neat)/cm^{-1} 3451, 2924, 1487 and 1237; δ_H(90 MHz) 1.20 (3 H, s), 1.20–1.80 (4 H, m), 2.70 (1 H, br s, OH), 6.00 (2 H, s), 6.05 (2 H, s) and 6.60–7.30 (6 H, m).

1-Chloro-2,3-dimethyl-4-(3,4-methylenedioxyphenyl)-6,7-(methylenedioxy)naphthalene 15

$SnCl_4$ (0.56 g, 2.15 mmol) was added to a stirred suspension of 2,2-dichloro-1,3-dimethylcyclopropylbis(3,4-methylenedioxyphenyl)methanol **14** (8.70 g, 21.3 mmol) and molecular sieves 4 Å (5.0 g) in 1,2-dichloroethane (10^3 cm^3) at room temp. Work-up similar to that described for the preparation of **2e** gave the *product* **15** (6.27 g, 83%) as colourless crystals; mp 185–186.5 °C (Found: C, 67.51; H, 4.38. $C_{20}H_{15}ClO_4$ requires C, 67.71; H, 4.26%); ν_{max}(KBr disk)/cm^{-1} 2913, 2884, 1483, 1460 and 945; δ_H(90 MHz) 2.09 (3 H, s), 2.41 (3 H, s), 5.92 (2 H, s), 6.03 (2 H, s) and 6.50–7.60 (5 H, m); *m/z* 354 (M^+, 100%).

2,3-Dimethyl-1-(3,4-methylenedioxyphenyl)-(6,7-methylenedioxy)naphthalene 16

$TiCl_4$ (9.64 g, 51 mmol) was added to THF (250 cm^3) at room temp. with stirring. To the stirred suspension were successively added $LiAlH_4$ (1 M THF solution; 102 cm^3, 0.102 mol) and the chloronaphthalene **15** (6.00 g, 16.9 mmol) in THF (50 cm^3), at room temp. The reaction mixture was refluxed for 4 h, cooled to room temp., and carefully poured into ice–water. The mixture was filtered through Celite using ether and the residue was extracted with ether. The organic phase was washed with water and brine, dried (Mg_2SO_4) and concentrated. The resulting crude residue was subjected to flash column chromatography on SiO_2 using C_6H_{14}–AcOEt (10:1) as eluent to give the *product* **16** (4.72 g, 87%) as colourless crystals; mp 150–152 °C (Found: C, 74.15; H, 5.09. $C_{20}H_{16}O_4$ requires C, 74.99; H, 5.03%); ν_{max}(KBr disk)/cm^{-1} 2905, 1460, 1238, 1042 and 947; δ_H(90 MHz) 2.09 (3 H, s), 2.41 (3 H, s), 5.92 (2 H, s), 6.03 (2 H, s) and 6.50–7.60 (6 H, m); *m/z* 320 (M^+, 100%).

2,3-Bis(bromomethyl)-1-(3,4-methylenedioxyphenyl)-(6,7-methylenedioxy)naphthalene 17

A mixture of 2,3-dimethylnaphthalene **16** (2.67 g, 8.34 mmol), *N*-bromosuccinimide (3.13 g, 17.6 mmol), and dibenzoyl peroxide (121 mg, 0.5 mmol) in CCl_4 (30 cm^3) was refluxed for 5.5 h. After cooling to room temp., the mixture was concentrated. The crude residue was subjected to flash column chromatography on SiO_2 using C_6H_{14}–AcOEt (10:1) as eluent to give the *product* **17** (2.31 g, 58%) as colourless crystals; mp 162–164 °C (Found: C, 50.48; H, 3.25. $C_{20}H_{14}Br_2O_4$ requires C, 50.24; H, 2.95%); ν_{max}(KBr disk)/cm^{-1} 2895, 1460, 1244, 1205 and 937; δ_H(90 MHz) 4.64 (2 H, s), 4.88 (2 H, s), 5.98 (2 H, s), 6.06 (2 H, s) and 6.67–7.80 (6 H, m); *m/z* 476 (M^+, 100%).

1-(3,4-Methylenedioxyphenyl)-(6,7-methylenedioxy)-naphthalene-2,3-diyldimethanol 18

A mixture of 2,3-bis(bromomethyl)naphthalene **17** (635 mg, 1.33 mmol) and $AgNO_3$ (1.36 g, 8.00 mmol) in acetone–H_2O (v/v 1:1; 60 cm^3) was stirred at room temp. for 2 h. The mixture was filtered through Celite using ether and the residue was extracted with ether. The organic phase was dried (Mg_2SO_4) and concentrated to give a crude residue which was subjected to flash column chromatography on SiO_2 using C_6H_{14}–AcOEt (10:1) as eluent. This afforded the *product* **18** (294 mg, 63%) as colourless crystals; mp 194–195 °C (lit.,[13b] 199–201 °C) (Found: C, 67.84; H, 4.68. $C_{20}H_{16}O_6$ requires C, 68.18; H, 4.58%); ν_{max}(KBr disk)/cm^{-1} 3358, 2901, 1460, 1238 and 1040; δ_H(90 MHz) 2.60–3.32 (2 H, br s), 4.60 (2 H, s), 4.85 (2 H, s), 6.00 (2 H, s), 6.04 (2 H, s) and 6.60–7.80 (6 H, m).

Justicidin E 19 and taiwanin C 20

According to a reported procedure,[13b] a stirred suspension of the diol **18** (290 mg, 0.82 mmol) and Fetizon's reagent (7.25 g) in benzene (160 cm^3) were refluxed for 1.5 h with azeotropic removal of water using a Dean–Stark apparatus. After cooling, the mixture was concentrated. The residue was filtered off and washed with hot benzene to give a 5:1 mixture of justicidin E **19** and Taiwanin C **20** (270 mg, 94%). Recrystallization of this twice from $CHCl_3$ gave **19** (120 mg) as colourless crystals; mp 265–267 °C (lit.,[13b] 271–272 °C); ν_{max}(KBr disk)/cm^{-1} 3350, 1761 and 1230; δ_H(400 MHz) 5.18 (1 H, d, J_{gem} 15.0), 5.23 (1 H, d, J_{gem} 15.0), 6.03–6.10 (4 H, m), 6.80 (1 H, d, *J* 8.0), 6.82 (1 H, s), 6.98 (1 H, d, *J* 8.0), 7.10 (1 H, s), 7.31 (1 H, s) and 8.28 (1 H, s). The mother liquor was concentrated to provide a crude residue which was subjected to flash column chromatography on SiO_2 using C_6H_{14}–AcOEt (1:1) as eluent to give **20** (40 mg) as colourless crystals; mp 264–267 °C (lit.,[13b] 272–276.5 °C); ν_{max}(KBr disk)/cm^{-1} 3355, 1765 and 1230; δ_H(400 MHz) 5.38 (2 H, s), 6.09 (4 H, s), 6.80 (1 H, d, *J* 8.0), 6.82 (1 H, s), 6.96 (1 H, d, *J* 8.0), 7.12 (1 H, s), 7.20 (1 H, s) and 7.69 (1 H, s). These spectral data **19** and **20** are identical with reported values.

Assay of anti-PAF activity of justicidin E

A ^{1}H-C16-PAF binding assay was carried out according to the reported procedure.[14a] The IC_{50} value of justicidin E was 100–150 μM (activity: 28%/30 μM, 45%/100 μM), when thiazolidin-4-one type anti-PAF SM-10661[14a] (IC_{50} = *ca.* 3.2 μM) was selected as a reference drug.

Acknowledgements

We thank Dr Tadatoshi Aratani for helpful discussions, and Dr Kazunori Yanagi and Dr Hitoshi Miura for the X-ray crystallographic measurements. We also thank the Sumitomo Pharmaceutical Co., Ltd., for measurement of the anti-PAF activity of justicidin E. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture (Japan).

References

1 Part of this work appeared in a preliminary communication: S. Seko, Y. Tanabe and G. Suzukamo, *Tetrahedron Lett.*, 1990, **31**, 6883.
2 (*a*) H. N. C. Wong, M.-Y. Hon, C.-Y. Tse, Y.-C. Yip, J. Tanko and T. Hudlicky, *Chem. Rev.*, 1989, **89**, 165; (*b*) U.-H. Reißig, *Top. Curr. Chem.*, 1988, **144**, 73.
3 (*a*) D. Cartwrite, P. Langcake, R. J. Pryce, D. P. Leworthy and J. P. Ride, *Nature*, 1977, **267**, 511; (*b*) G. Holan, D. F. O'Keefe, C. Vergona and R. Walser, *Nature*, 1978, **272**, 734; (*c*) Y. Kurahashi, S. Kagabu, N. Matsumoto, T. Yamada, K. Wada and T. Kondo, Jap P 54 349/1988 (*Chem. Abstr.*, 1988, **109**, 190038h).
4 (*a*) W. E. Paham and E. E. Schweizer, *Organic Reactions*, Wiley, New York, 1963, vol. 13, p. 55; (*b*) C. M. Starks and C. Liotta, *Phase Transfer Catalysis*, Academic Press, New York, 1978, p. 224.
5 (*a*) D. Seyferth, H. Yamazaki and D. L. Alleston, *J. Org. Chem.*, 1963, **28**, 703; (*b*) T. Ando, H. Yamanaka, F. Namigata and W. Funasaka, *J. Am. Chem. Soc.*, 1967, **89**, 5719; (*c*) R. M. Blankenship, K. A. Burdett and J. S. Swenton, *J. Am. Chem. Soc.*, 1974, **39**, 2300; (*d*) L. K. Sydnes and L. Skattebøl, *Tetrahedron Lett.*, 1974, 3703; (*e*) T. Hirao, T. Masunaga, Y. Ohshiro and T. Agawa, *J. Org. Chem.*, 1981, **46**, 3745; (*f*) A. Osuka, K. Takeuchi and

H. Suzuki, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 303; (*g*) K. Miura, Y. Ichinose, K. Fugami, K. Oshima and K. Utimoto, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 143; (*h*) T. Hirao, K. Hirano, T. Hasegawa, Y. Ohshiro and I. Ikeda, *J. Org. Chem.*, 1993, **58**, 6529; (*i*) Y. Apeloig and M. Nakash, *J. Am. Chem. Soc.*, 1994, **116**, 10084.

6 T. Hiyama, M. Tsukanaka and H. Nozaki, *J. Am. Chem. Soc.*, 1974, **96**, 3713. For recent study of transformation of *gem*-dihalogenocyclopropane: (*a*) M. Mitani, Y. Kobayashi and K. Koyama, *J. Chem. Soc., Perkin Trans. 1*, 1995, 653; (*b*) S. Kagabu, C. Ando and J. Ando, *J. Chem. Soc., Perkin Trans. 1*, 1996, 739; (*c*) M. Mitani, Y. Kobayashi and K. Koyama, *J. Chem. Soc., Perkin Trans. 1*, 1995, 653; (*d*) J. R. A. Dulayymi and M. S. Baird, *Tetrahedron Lett.*, 1995, **36**, 3393; (*e*) A. R. A. Dulayymi, J. R. A. Dulayymi, M. S. Baird and L. Rajaram, *Tetrahedron*, 1995, 8371.

7 (*a*) K. H. Holm and L. Skattebøl, *Tetrahedron Lett.*, 1977, 2347; (*b*) K. H. Holm and L. Skattebøl, *J. Am. Chem. Soc.*, 1977, **99**, 5480; (*c*) K. H. Holm, E. A. Mohamed and L. Skattebøl, *Acta Chem. Scand.*, 1993, **47**, 500.

8 (*a*) K. Kitatani, T. Hiyama and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 1600; (*b*) T. Harada, T. Katsuhira, K. Hattori and A. Oku, *J. Org. Chem.*, 1993, **58**, 2958; (*c*) T. Harada, T. Katsuhira, K. Hattori and A. Oku, *Tetrahedron*, 1994, **50**, 7987.

9 (*a*) Y. Tanabe, Y. Nishii and K. Wakimura, *Chem. Lett.*, 1994, 1757; (*b*) Y. Tanabe, K. Wakimura and Y. Nishii, *Tetrahedron Lett.*, 1996, **37**, 1837.

10 (*a*) Y. Nishii and Y. Tanabe, *Tetrahedron Lett.*, 1995, **36**, 8803; (*b*) Y. Nishii, H. Matsumura, Y. Muroya, T. Tsuchiya and Y. Tanabe, *Biosci. Biotech. Biochem.*, 1995, **59**, 1355; (*c*) Y. Tanabe, K. Wakimura, Y. Nishii and Y. Muroya, *Synthesis*, 1996, 388; (*d*) Y. Nishii, K. Wakimura, T. Tsuchiya, S. Nakamura and Y. Tanabe, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1243.

11 K. Wada and K. Munakata, *Tetrahedron Lett.*, 1970, 2017.

12 Y.-T. Lin, T.-B. Lo, K. T. Wang and B. Weinstein, *Tetrahedron Lett.*, 1967, 849.

13 Previous syntheses: (*a*) T. L. Holmes and R. Stevenson, *J. Chem. Soc. C*, 1971, 2091; (*b*) T. L. Holmes and R. Stevenson, *J. Org. Chem.*, 1971, **36**, 3450; (*c*) E. Block and R. Stevenson, *J. Org. Chem.*, 1971, **36**, 3450; (*d*) B. J. Arnold, S. M. Mellows and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1266; (*e*) Z. Horii, M. Tujiuchi, K. Kanai and T. Momose, *Chem. Pharm. Bull.*, 25, 1977, 1803. For recent syntheses: (*f*) T. Hattori, H. Tanaka, Y. Okaishi and S. Miyano, *J. Chem. Soc., Perkin Trans. 1*, 1995, 235; (*g*) J. E. Cochran and A. Padwa, *J. Org. Chem.*, 1995, **60**, 3938; (*h*) T. Ogiku, S. Yoshida, H. Ohmizu and T. Iwasaki, *J. Org. Chem.*, 1995, **60**, 4585; (*i*) K. Kobayashi, J. Tokimatsu, K. Maeda, O. Morikawa and H. Konishi, *J. Chem. Soc., Perkin Trans. 1*, 1995, 3013.

14 (*a*) Y. Tanabe, G. Suzukamo, Y. Komuro, N. Imanishi, S. Morooka, M. Enomoto, A. Kojima, Y. Sanemitsu and M. Mizutani, *Tetrahedron Lett.*, 1991, **32**, 379; (*b*) Y. Tanabe, Y. Kubota, Y. Sanemitsu, N. Itaya and G. Suzukamo, *Tetrahedron Lett.*, 1991, **32**, 383; (*c*) Y. Tanabe, H. Yamamoto, M. Murakami, K. Yanagi, Y. Kubota, H. Okumura, Y. Sanemitsu and G. Suzukamo, *J. Chem. Soc., Perkin Trans. 1*, 1995, 935; (*d*) Y. Tanabe, H. Okumura, M. Nagaosa and M. Murakami, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 1467.

15 (*a*) D. J. Hanahan, *Ann. Rev. Biochem.*, 1986, **55**, 483; (*b*) M. N. Chang, *Drugs of the Future*, 1986, **11**, 869; (*c*) M. Shiraiwa, K. Fujita, H. Yoshiwara, S. Kobayashi and M. Ohno, *J. Synth. Org. Chem. Jpn.*, 1987, **45**, 369; (*d*) M. Koltai and P. G. Braquet, *Clinical Reviews in Allergy*, 1994, **12**, 361.

16 (*a*) F. T. DeWeese, D. E. Minter, J. T. Nosovitch and M. G. Rudel, *Tetrahedron*, 1986, **42**, 4195; (*b*) C. S-Rouvier, *Tetrahedron*, 1981, **37**, 4195.

17 (*a*) S. Shuto, S. Ono, Y. Hase, N. Kamiyama, H. Takada, K. Yamashita and A. Matsuda, *J. Org. Chem.*, 1996, **61**, 915; (*b*) A. S. Cieplak, *J. Am. Chem. Soc.*, 1981, **103**, 4540; (*c*) A. S. Cieplak, B. D. Tait and C. R. Johnson, *J. Am. Chem. Soc.*, 1989, **111**, 8447.

18 T. Mukaiyama, M. Hayashi and K. Narasaka, *Chem. Lett.*, 1973, 291.

19 M. Fetizon, M. Golfier and J.-M. Louis, *J. Chem. Soc., Chem. Commun.*, 1969, 1102 and 1118.

20 (*a*) British Drug Houses Ltd., Neth. Appl. 6506881, 1965 (*Chem. Abstr.*, 1966, **64**, p. 17445e); (*b*) I. A. D'yakonov and L. P. Denilkina, *Zh. Obshch. Khim.*, 1964, **34**, 38 (*Chem. Abstr.*, 1964, **60**, 15745c).

21 K. Kleveland, L. Skattebøl and L. K. Sydnes, *Acta Chem. Scand., Ser. B*, 1977, **31**, 463.

22 D. Seyferth, J. M. Burlitch, R. J. Minasz, J. V.-P. Mui, H. D. Simmons, Jr., A. J. H. Treiber and S. R. Dowd, *J. Am. Chem. Soc.*, 1965, **87**, 4259.

23 K. R. Bedford, G. W. Burton, M. Dela, B. D. Peter and H. Suzuki, *J. Chem. Soc., Perkin Trans. 2*, 1974, 459.

Paper 6/01885H
Received 19*th March* 1996
Accepted 30*th April* 1996