Full Paper

CSIRO PUBLISHING

Aust. J. Chem. **2008**, *61*, 506–520

www.publish.csiro.au/journals/ajc

Synthesis and Biological Evaluation of Some Enantiomerically Pure C8c–C15 Monoseco Analogues of the Phenanthroquinolizidine-Type Alkaloids Cryptopleurine and Julandine*

Magne O. Sydnes,[A] *Anna Bezos,*[B] *Christopher Burns,*[C] *Irma Kruszelnicki,*[C] *Christopher R. Parish,*[B] *Stephen Su,*[C] *A. David Rae,*[A] *Anthony C. Willis,*[A] *and Martin G. Banwell*[A,D]

[A]Research School of Chemistry, Institute of Advanced Studies, Australian National University, Canberra, ACT 0200, Australia.

[B]John Curtin School of Medical Research, Institute of Advanced Studies, Australian National University, Canberra, ACT 0200, Australia.

[C]Cytopia Pty Ltd, 576 Swan Street, Richmond, VIC 3121, Australia.

[D]Corresponding author. Email: mgb@rsc.anu.edu.au

A series of enantiomerically pure C8c–C15 monoseco analogues, **23**–**30**, of the alkaloids cryptopleurine (**1**) and julandine (**2**) have been prepared using cinnamyl chloride **37** and (*S*)- or (*R*)-2-methylpiperidine as key building blocks. Two related compounds, **31** and **32**, have also been synthesized. Each of these analogues has been subjected to various biological evaluations and most of them show dramatically reduced cytotoxicity compared with parent system **1**. Nevertheless, they are potent anti-angiogenic agents. The formation and single-crystal X-ray analysis of the spirocyclic dienone **54**, a by-product arising from attempts to prepare analogue **32**, is also described.

Manuscript received: 5 May 2008.
Final version: 26 May 2008.

Introduction

The plant-derived natural product cryptopleurine (**1**,[1] Fig. 1) possesses significant anti-cancer, anti-fungal, anti-microbial, and anti-viral activity as well as being a powerful vesicant.[2,3] As a result numerous efforts have been directed towards the synthesis of this natural product[3] and the related alkaloid julandine (**2**),[4] which displays a similar biological profile.[5]

Some work has also been carried out on the preparation of simpler analogues of these compounds on the basis that they might display equivalent or even improved biological properties.[6,7] Thus, a Spanish group described the synthesis of a piperidine analogue, **3** (Fig. 2), of julandine although they also reported that it showed no activity against protein synthesis in yeast ribosomes.[6a] Further work from the same group resulted in the synthesis of the cryptopleurine analogues **4**–**10**[6b,6c] and the first of these was shown to possess the desired activity.[6b] Foldeak has detailed the preparation of analogues **11**–**14** together with several variations thereof.[7] Such pentacyclic systems were screened for anti-fungal activity and compound **11** was found to display an IC_{50} of 0.05 $\mu g\,mL^{-1}$, a value that compares favourably with that reported[7] for **1** itself (0.04 $\mu g\,mL^{-1}$). Three other analogues were also found to possess some anti-fungal activity.

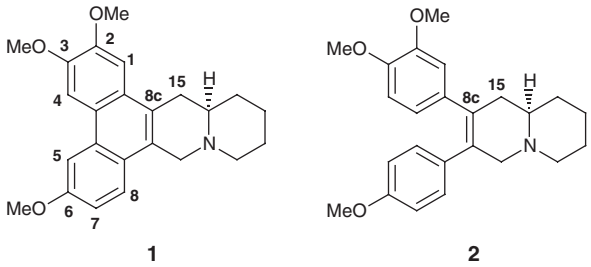


Fig. 1. Structures of the alkaloids cryptopleurine (**1**) and juladine (**2**).

Anand et al. reported the synthesis of the naphthoquinolizidine salts **15**–**22** (Fig. 3) as analogues of cryptopleurine and stated that none of these showed any significant anti-cancer activity.[6g] In a separate study, Bargar and coworkers[6f] found compound **22** to be a rather potent in vitro inhibitor of HeLa cell colonies (IC_{50} 0.6 $\mu g\,mL^{-1}$). Interestingly, this tetracyclic system did not exhibit significant in vivo activity in a P-388 pre-screen, thus implying that the compound has some cytoselective properties. Recently, Lee et al. reported that 7-methoxycryptopleurine possesses potent anti-inflammatory activity, both in vitro and in vivo, as well as cytotoxic activity

*Aspects of this work have been reported in preliminary form: M. G. Banwell, A. Bezos, C. Burns, I. Kruszelnicki, C. R. Parish, S. Su, M. O. Sydnes, *Bioorg. Med. Chem. Lett*. **2006**, *16*, 181.

10.1071/CH08190 0004-9425/08/070506

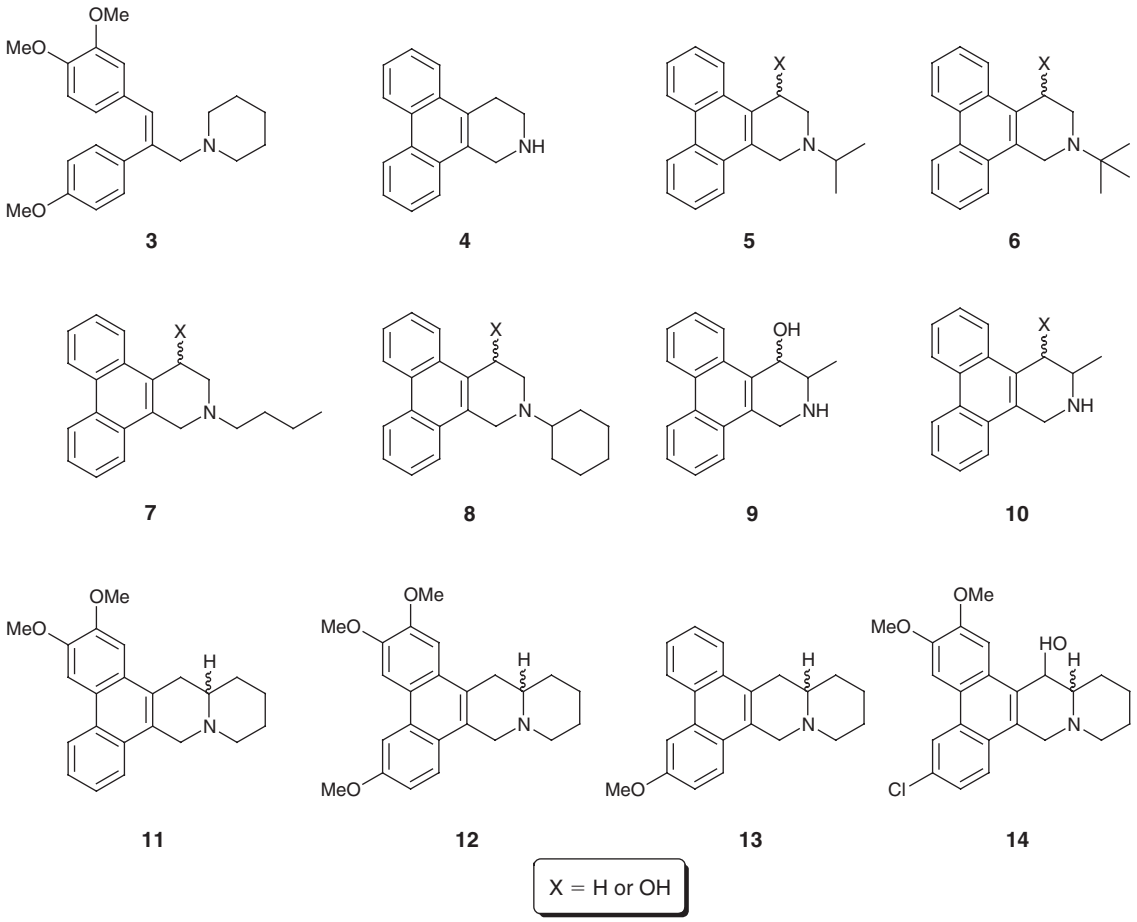


Fig. 2. Structures of compounds **3**–**14**.

against certain cancer cell lines, particularly gastric carcinoma (NUGC-3) and nasopharyngeal carcinoma (HONE-1).[6j]

As a consequence of the situation described above and our recent development of a relevant synthetic strategy,[8] we prepared, and now report on the C8c–C15 monoseco analogues **23**–**26** (Fig. 4) of julandine (**2**) as well as the corresponding phenanthrene-type systems **27**–**30**, which represent the equivalent analogues of cryptopleurine (**1**). The simpler analogues **31** and **32** were also considered to be relevant in establishing the structure–activity relationship (SAR) profile of such compounds. The fact that these seco-analogues bear significant structural resemblances to combretastatin A4 (**33**), a potent cell growth, tubulin polymerization, and angiogenesis inhibitor,[9] provided a further motivation for the work reported here.

Results and Discussion

Synthetic Studies

As suggested above, the first eight and previously unreported target compounds **23**–**30** were considered likely to be accessible using protocols we had described earlier.[8] The required and enantiomerically pure samples of (*S*)- and (*R*)-2-methylpiperidine were obtained following a procedure described by Aggarwal and coworkers[10] (Scheme 1). Thus, treatment of the commercially available racemate **34** with (*S*)-(+)-mandelic acid afforded, after fractional crystallization, the optically pure (+)-2-methylpiperidine mandelate salt **35** in 28% yield. The corresponding (−)-(2)-methylpiperidine mandelate salt **36** could be acquired by treatment of amine **34** with (*R*)-(−)-mandelic acid. The optical rotations of the salts obtained by such means were in full agreement with the values reported in the literature.[10] The free amines, (*S*)-**33** and (*R*)-**33**, could be generated by treating the respective precursor salts with aqueous sodium hydroxide. After extensive extraction with diethyl ether the free amines were isolated in 80–90% yield.

Independent treatment of each of the amines (*S*)-**34** and (*R*)-**34** with chloride **37**[8] and triethylamine in *N*,*N*-dimethylformamide (DMF) at 60°C for 4 h (Scheme 2) gave the expected styrenes **38** and **39**, respectively, in excellent yields (∼98%). The spectroscopic data obtained for compound **39** matched those obtained for enantiomer **38**. In keeping with expectations, the optical rotation of each compound was of the same magnitude but opposite sign. Using the optimized conditions established during our previous work,[8] both substrates **38** and **39** could be readily engaged in Suzuki–Miyaura cross-coupling with the known boronate **40**.[8] By such means products **23** and **24** were obtained in 73 and 74% yield, respectively. The ^{1}H and ^{13}C NMR spectra of the former compound indicated that the second aryl group had been installed, thus producing the required stilbene unit. The *Z*-configuration about the double bond within compound **23** was confirmed using nuclear overhauser effect correlation spectroscopy (NOESY) techniques. In particular, a strong interaction between the alkenyl proton and its methylenic counterparts was observed. The analogous NMR spectra of its enantiomer **24** were also in full agreement with the assigned structure.

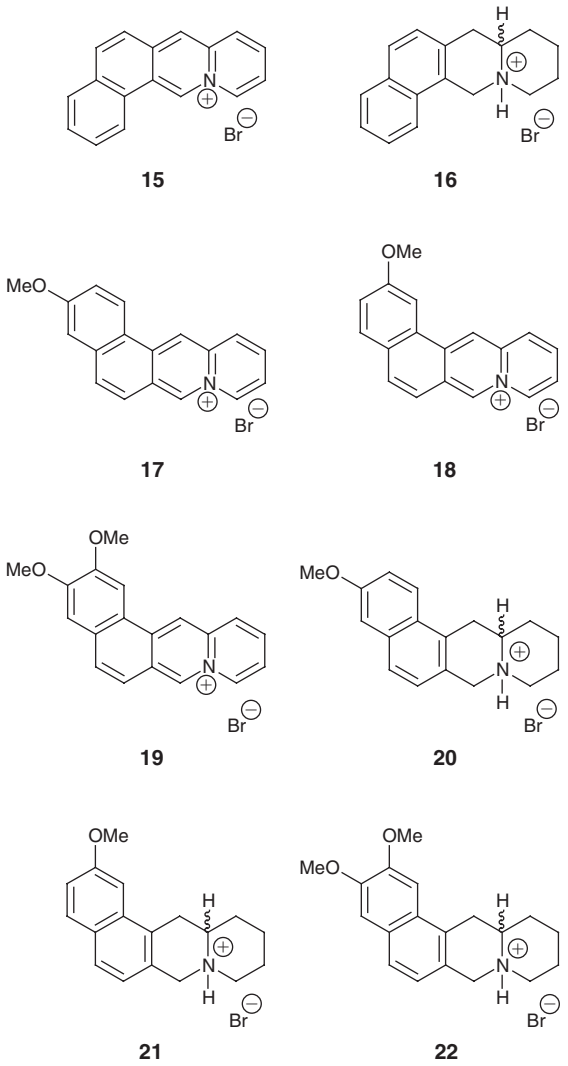


Fig. 3. Structures of compounds **15**–**22**.

Compounds **23** and **24** were each converted into the corresponding phenanthrenes, **27** and **28** respectively, by a Liepa-type oxidation[11] that involved their treatment with vanadium(v) oxytrifluoride (VOF_3) in dichloromethane at 0°C for 0.25 h. Subsequent addition of trifluoroacetic acid (TFA), stirring the reaction mixture at 0°C for a further 0.25 h, and then quenching it with 10% aqueous sodium hydroxide solution allowed for a straightforward workup. By such means, and after flash chromatography, enantiomers **27** and **28** were isolated in 48 and 63% yield, respectively. The spectroscopic data obtained for each compound were in full agreement with the assigned structures.

With the four trimethoxylated target compounds **23**, **24**, **27**, and **28** to hand, efforts were then directed toward the synthesis of those congeners, **25**, **26**, **29**, and **30**, which incorporated a free phenolic moiety in the lower aryl ring. Initial attempts (Scheme 3) to synthesize compound **25** directly by a Suzuki–Miyaura cross-coupling of alkenyl bromide **38** and boronate **41** gave only traces of the desired product. As a consequence the OH group within coupling partner **41** was protected as the corresponding *tert*-butyldiphenylsilyl (TBDPS) ether **42** (67%). Cross-coupling of the latter compound under Suzuki–Miyaura conditions with either alkenyl bromide **38** or enantiomer **39**, afforded compounds **43** (69%) and **44** (73%), respectively. Treatment of these product stilbenes with tetra-*n*-butylammonium fluoride (TBAF) in tetrahydrofuran (THF) at room temperature for 0.5 h gave, after flash chromatography, compounds **25** and **26** in 87 and 85% yield, respectively. The appearance of an OH-stretching band in the infrared spectrum of each of these products confirmed the presence of the free phenolic residue within them. Incorporation of the second aryl group was also confirmed by ^1H and ^{13}C NMR spectroscopies. Thus, the ^1H NMR spectra revealed the expected coupling patterns associated with the second aryl-group, while the *Z*-configuration about the double bond incorporated within the latter product was confirmed using NOESY techniques. The optical rotation for each of the two enantiomers was of the same order of magnitude but opposite sign. Upon treatment with Liepa's reagent (VOF_3),[11] compounds **43** and **44** could each be converted into phenanthrenes **45** and **46** which were obtained in 58 and 68% yield, respectively. Treatment of ethers **45** and **46** with TBAF efficiently converted each into the corresponding phenols **29** (82%) and **30** (93%). The optical rotation of each was as expected, that is, it was of the same order of magnitude but opposite sign.

cis-Stilbene **49** (Scheme 4) was considered to be a suitable intermediate for the synthesis of the last two analogues required in the present study, namely compounds **31** and **32**. Compound **49** itself was prepared in 45% yield by condensing aldehyde **47** with acid **48** under conditions defined by Oishi and Kurosawa.[12] Treatment of product **49** with oxalyl chloride followed by in situ reaction of the ensuing acid chloride with dimethylamine afforded amide **50** in 68% yield. The carbonyl moiety within the latter compound was then reduced, with $LiAlH_4$ in THF, to the corresponding tertiary amine **51** (74%). Treatment of product **51** with Liepa's reagent following the same procedure as used previously (see below) gave the corresponding phenanthrene **31** in 56% yield. The physical and spectroscopic data obtained for this compound were in full agreement with those reported in the literature.[13]

The last remaining target compound, phenanthrene **32**, was thought likely to be available in two steps from *cis*-stilbene **49** through an initial VOF_3-promoted oxidation reaction followed by decarboxylation of the anticipated product **52** (Scheme 5). However, despite numerous attempts, phenanthrene **52** failed to form when *cis*-stilbene **49** was subjected to the usual oxidative cyclization conditions. Such attempts only resulted in the recovery of starting material. Accordingly, efforts were made to effect a photochemically induced cyclization of compound **49** using conditions defined by Castedo and coworkers.[14] Unfortunately, these efforts were also in vain, with only starting material being recovered.

The lack of reactivity of the *cis*-stilbene **49** under the specified conditions was puzzling. However, a consideration of some earlier work by two different groups[12,15] prompted the conversion of acid **49** into methyl ester **53** (Scheme 5) on the basis that the latter compound should undergo the desired oxidative cyclization reaction. In the event, treatment of compound **53** with Liepa's reagent under the usual conditions failed to give the corresponding phenanthrene. Once again, only starting material was recovered. In contrast, when substrate **53** was subjected to the related conditions described by Halton et al.[15] a reaction did take place although still none of the hoped-for phenanthrene was obtained. The only isolable product of this reaction was subjected to detailed spectroscopic analysis, including a single-crystal X-ray study (see Fig. 5 and Experimental section), and by such means it was shown to possess the spirocyclic structure

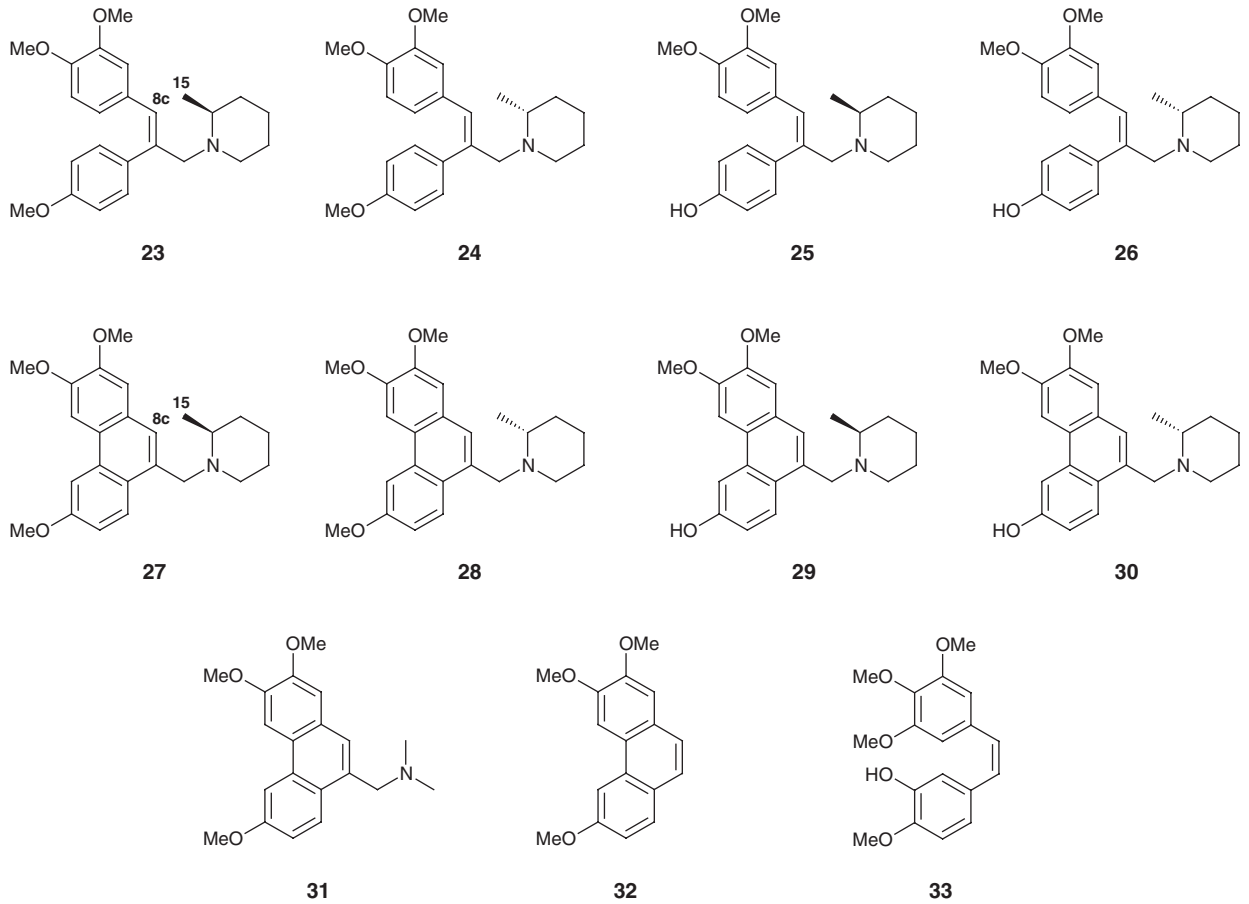
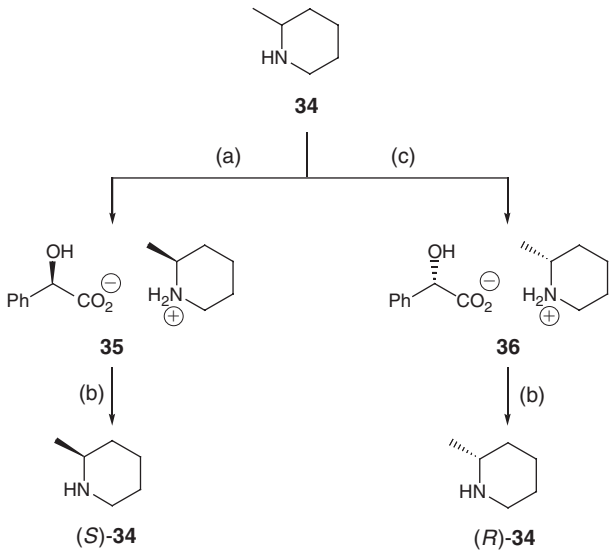
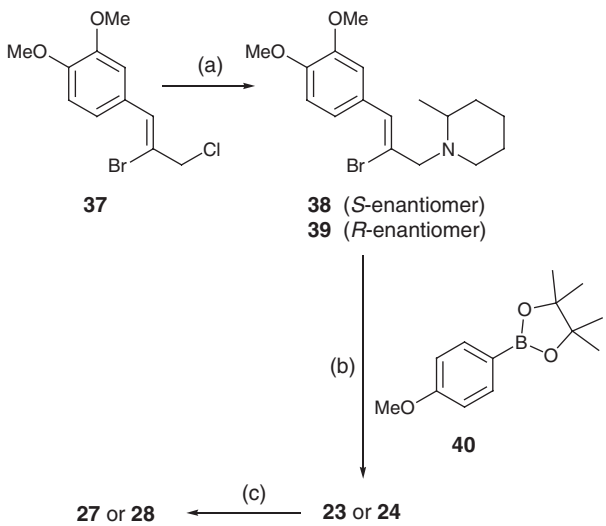


Fig. 4. Structures of analogues **23**–**32** and the structure of combretastatin A-4 (**33**).

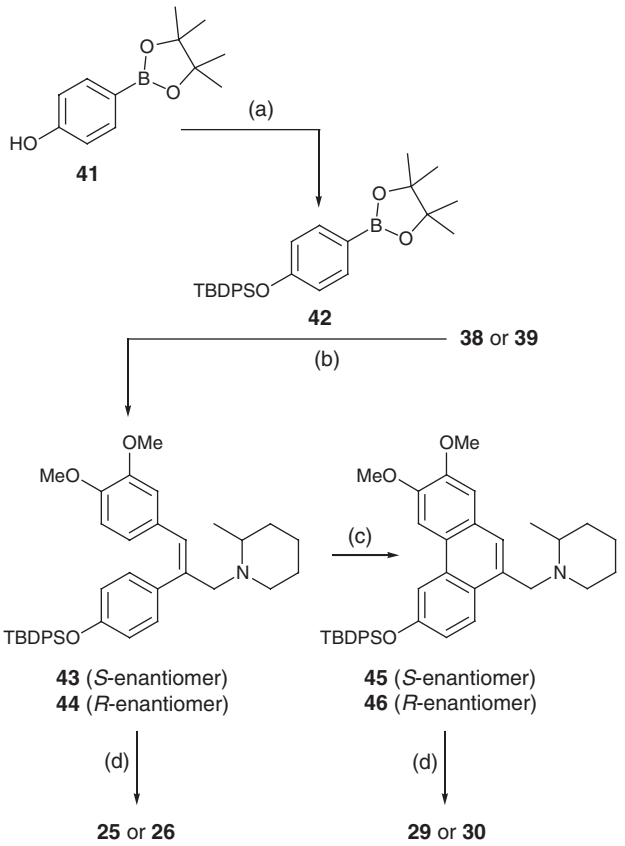


Scheme 1. *Reagents and conditions*: (a) (*S*)-(+)-mandelic acid (0.95 mol equiv.), methanol/ether, 0°C; (b) aqueous NaOH, 18°C, and then extraction with ether; (c) (*R*)-(−)-mandelic acid (0.97 mol equiv.), methanol/ether, 0°C.

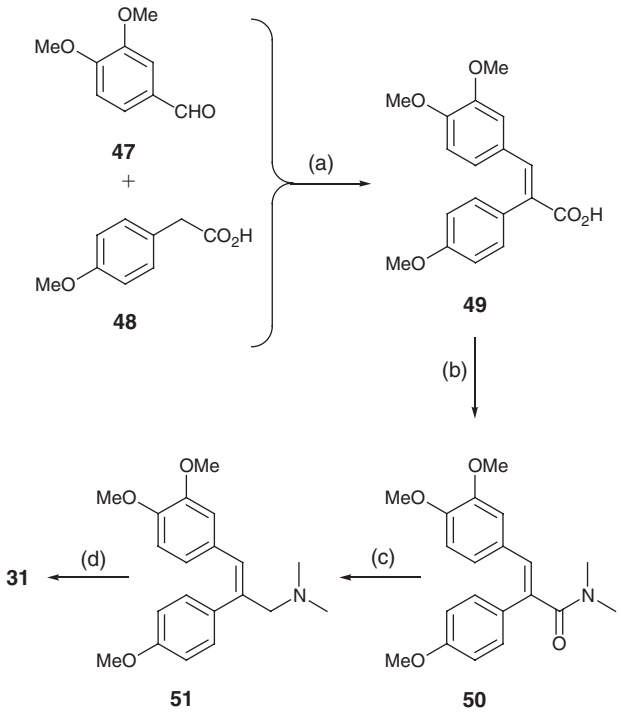


Scheme 2. *Reagents and conditions*: (a) (*S*)-(+)-**34** (1.05 mol equiv.) or (*R*)-(−)-**34** (1.05 mol equiv.), Et_3N, DMF, 60°C, 4 h; (b) compound **40** (2.1 mol equiv.), $PdCl_2$(dppf) (~7 mol %), 1:7 v/v ethanol/benzene, Na_2CO_3 (2 M aqueous solution), reflux, 6–7 h; (c) VOF_3 (4.4 mol equiv.), CH_2Cl_2, 0°C, 0.25 h then TFA (12 mol equiv.), 0°C, 0.25 h.

54 (16%). When *cis*-stilbene **53** was stirred in a solution of TFA and dichloromethane at 0°C for 1 h and then treated with VOF_3 a 27% yield of product **54** was obtained. However, the dominant product (66%) was now a bis-phenanthrene tentatively assigned structure **55**. The unsymmetrical nature of this dimeric species follows from, among other things, an analysis of the coupling patterns observed in the aromatic region of the ^{1}H NMR spectrum which revealed two mutually coupled (*J* 9.5 Hz) one-proton doublets at δ 7.42 and 9.00. The chemical



Scheme 3. *Reagents and conditions*: (a) *tert*-butyldiphenylsilyl chloride (TBDPS-Cl) (1.2 mol equiv.), imidazole (1.4 mol equiv.), DMF, −30 to 18°C, 16 h; (b) compound **42** (2 mol equiv.), $PdCl_2$(dppf) (17 mol %), 1:9 v/v ethanol/benzene, Na_2CO_3 (2 M aqueous solution), reflux, 6 h; (c) VOF_3 (5.2 mol equiv.), CH_2Cl_2, 0°C, 0.25 h and then TFA (13 mol equiv.), 0°C, 0.25 h; (d) tetra-*n*-butylammonium fluoride (TBAF) (1.4 mol equiv.), THF, 18°C, 0.5 h.



Scheme 4. *Reagents and conditions*: (a) compound **47** (1 mol equiv.), compound **48** (1 mol equiv.), 2:1 v/v acetic anhydride/Et_3N, reflux, 2.5 h; (b) oxalyl chloride (3 mol equiv.), THF, 18°C, reflux, 0.66 h and then dimethylamine (21 mol equiv.), THF, 18°C, 16 h; (c) $LiAlH_4$ (5.9 mol equiv.), THF, 18°C, 2 h; (d) VOF_3 (4.4 mol equiv.), CH_2Cl_2, 0°C, 0.25 h and then TFA (13 mol equiv.), 0°C, 0.25 h.

shift of the latter resonance is attributed to the deshielding effects of an adjacent carbomethoxy group. Eight one-proton singlets also appeared in the aromatic region of the same spectrum. The appearance of a methoxymethyl singlet at δ 2.74 presumably arises from the shielding effects of the adjacent phenanthrene residue. The EI mass spectrum of compound **55** showed a molecular ion at *m*/*z* 650 and an accurate mass measurement on this species established that it possessed the molecular formula $C_{38}H_{34}O_{10}$. Resonances attributable to all 38 carbons embodied within substrate **55** could be detected in the ^{13}C NMR spectrum.

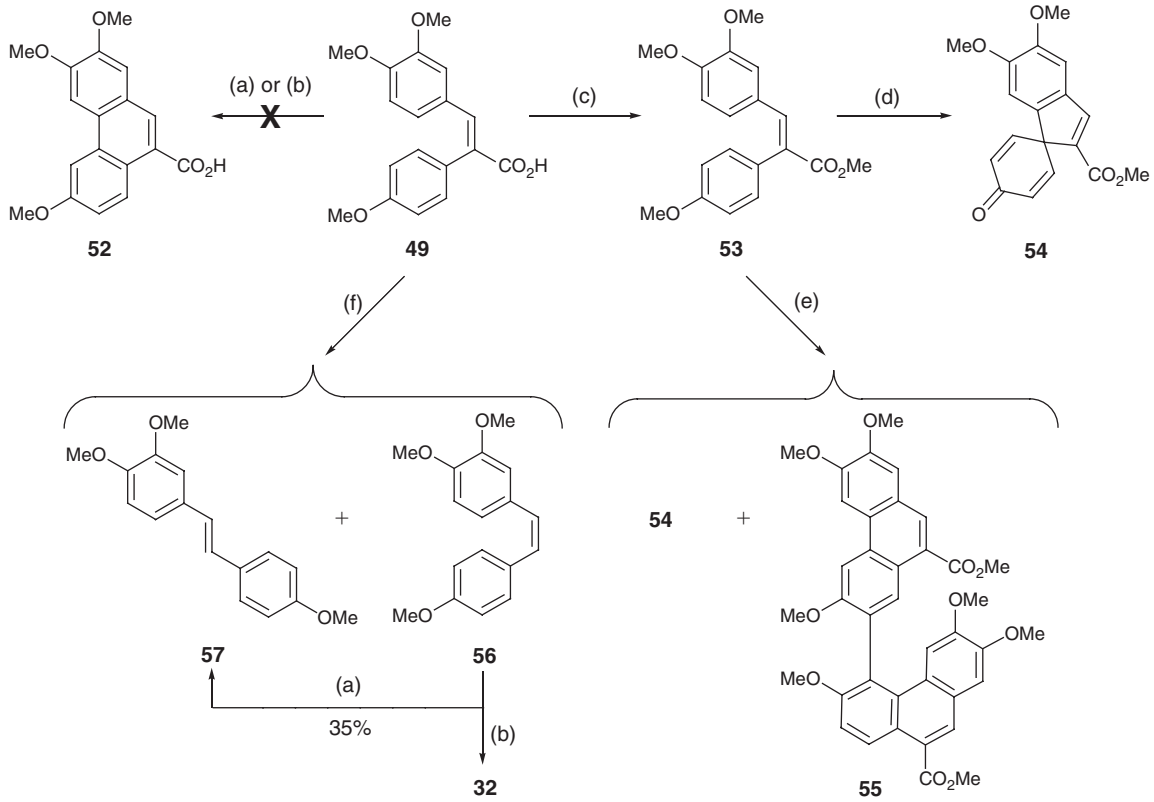
A synthesis of the required phenanthrene **32** was finally established by treating, in the first step of the reaction sequence, acid **49** with dry $CuSO_4$ in refluxing quinoline[16] (Scheme 5). In this manner the required decarboxylation reaction took place and so generated *cis*-stilbene **56** (70%) together with small amounts (5%) of the chromatographically separable *trans*-isomer **57**. Initial attempts to convert substrate **56** into phenathrene **32** by treating it, under the conditions detailed above, that is with VOF_3 in CH_2Cl_2 followed by treatment with TFA, only resulted in the isolation of *trans*-stilbene **57** (35%). As demonstrated by conducting the relevant control experiment, the conversion of **56** into **57** is a simple TFA-catalyzed process. In contrast, when a solution of *cis*-stilbene **56** in 35:1 v/v ether/dichloromethane that contained catalytic amounts of iodine was irradiated with light from a medium pressure Hg vapour lamp the by now long-sought-after phenanthrene **32** could be generated in 51% yield. The physical and spectroscopic data derived from this product were in full accord with those reported in the literature.[17]

A reaction pathway that accounts for the observed conversion **53** → **54** (Scheme 5) is shown in Fig. 6 and is based on arguments advanced by others to explain the outcomes of related processes that lead to similar products.[18] Thus, a one-electron oxidation of substrate **53** by VOF_3 would be expected to deliver the radical cation **58** that then engages in the relevant spirocyclization process. After a second one-electron oxidation and proton loss the oxonium ion **59** would be formed. Hydrolysis of the last species would then be expected to produce the observed spirocyclic dienone **54**. The formation of the unsymmetrical dimer **55** from precursor **53** under the conditions indicated in Scheme 5 is a rare example of a VOF_3-promoted version of such a process.[19] The significant selectivity associated with this oxidative dimerization process is notable but, at the present time, we cannot offer any satisfactory explanation for this particular outcome.

Biological Assays

Cytotoxicity Testing

Each of compounds **23**–**32** was screened, at eight different concentrations, against a panel of 19 human and other cancer cell lines as listed in Table 1. An authentic sample of natural product **1** was also tested against the same panel. As a consequence it became clear that the monoseco analogues, **27**–**30**, of cryptopleurine (**1**) are approx. three orders of magnitude less cytotoxic than the parent compound whereas the related *cis*-stilbenes show essentially no toxicity whatsoever. Furthermore, the configuration (*R* versus *S*) at the single stereogenic centre within these analogues has essentially no impact on activity. Clearly, then,



Scheme 5. *Reagents and conditions*: (a) see text; (b) air, I_2 (cat.), 1:35 v/v CH_2Cl_2/diethyl ether, hν, 2 h; (c) oxalyl chloride (3 mol equiv.), THF, 18°C to reflux, 0.66 h and then methanol, 18°C, 16 h; (d) 3:2 v/v TFA/CH_2Cl_2 then VOF_3 (3.4 mol equiv.) in 3:1 v/v TFA/EtOAc, 0°C, 1 h; (e) 2:1 v/v TFA/CH_2Cl_2, 0°C, 1 h and then VOF_3 (3.4 mol equiv.) in 3:1 v/v TFA/EtOAc, 0°C, 0.33 h; (f) $CuSO_4$ (2.2 mol equiv.), quinoline, reflux, 1 h.

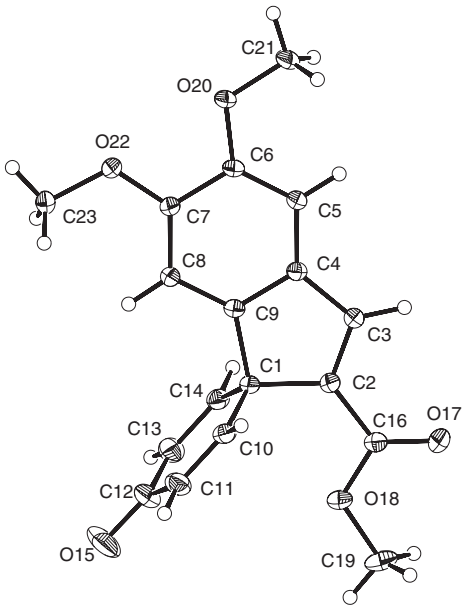


Fig. 5. Molecular structure of compound **54** ($C_{18}H_{16}O_5$) with labelling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

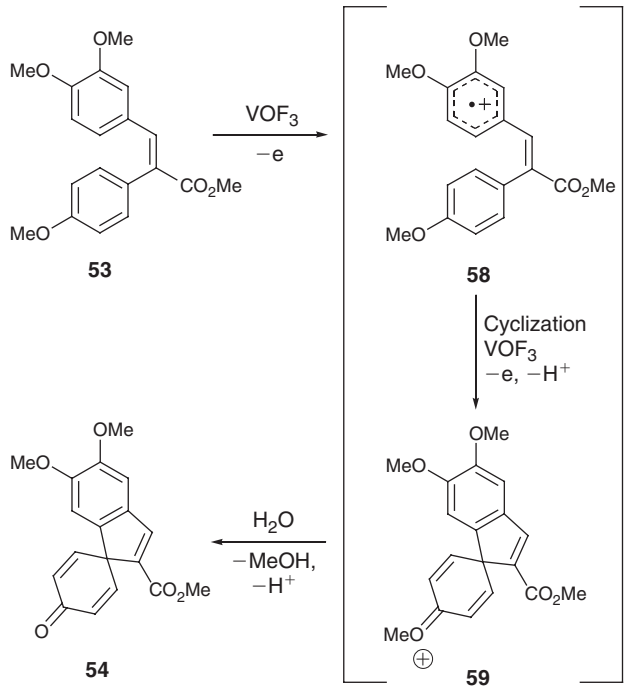


Fig. 6. Possible pathway for the conversion of stilbene **53** into spirocycle **54**.

the scission of the C8c–C15 bond within the title natural products leads to derivatives with dramatically reduced cytotoxicity profiles. The phenanthrenes **31** and **32** also proved to be only weakly cytotoxic.

Anti-angiogenic Testing

The anti-angiogenic properties of compounds **23**–**32** were determined in an in vitro assay using rat aorta blood vessel fragments.[20] Unfortunately, solubility problems prevented

Table 1. IC_{50} values ($\times 10^{-6}$ M) determined for compounds 1 and 23–32 in cytotoxicity testing against a range of cancer cell lines[A]

TFI, human erythroleukaemia; CTLL2, murine cytotoxic T-cells; BT20, human breast carcinoma; MatLyLu, rat prostate carcinoma; KHOS-NP, human osteosarcoma; A431, human epidermoid carcinoma; A375, human melanoma; A549, human lung carcinoma; HCT-15, human colon carcinoma; HT1376, human bladder carcinoma; PA-1, human ovarian teratocarcinoma; HEPG2, human hepatoma; HEK293, human embryonic kidney cells; BUD-8, human fibroblast; RAMOS, Burkitt lymphoma; DAUDI, Burkitt lymphoma; MES-SA, human uterine sarcoma; MES-SA-Dx5, human uterine sarcoma derived from MES-SA; MCF-7, human breast carcinoma

Cell line	Compound										
	(−)-**1**[B]	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**
TFI	—[C]	>20	>20	>20	>20	7.20	7.65	9.80	8.40	6.75	>20
CTLL2	—[C]	>20	>20	>20	>20	7.61	8.10	9.09	8.10	3.39	17.50
BT20	0.003	>20	>20	>20	>20	10.24	10.89	13.73	11.57	7.38	>20
MatLyLu	0.003	>20	>20	>20	>20	~15	~15	>20	>20	17.34	>20
KHOS-NP	0.010	>20	>20	>20	>20	12.28	13.99	15.43	13.42	17.14	>20
A431	0.003	>20	>20	>20	>20	8.12	8.09	13.77	20.00	5.37	>20
A375	0.003	>20	>20	>20	>20	8.96	10.05	11.25	9.38	7.10	>20
A549	0.003	>20	>20	>20	>20	11.25	12.02	16.55	15.18	17.03	>20
HCT-15	0.003	>20	>20	>20	>20	7.82	8.33	8.41	7.97	8.27	>20
HT1376	0.004	>20	>20	>20	>20	9.68	9.51	8.31	6.04	7.88	>20
PA-1	0.002	>20	>20	>20	>20	7.38	7.27	~8	—[C]	4.16	>20
HEPG2	—[C]	>20	>20	>20	>20	8.12	7.27	8.33	—[C]	—[C]	—[C]
HEK293	—[C]	>20	>20	>20	>20	15.50	17.08	14.83	—[C]	—[C]	—[C]
BUD-8	0.006	>20	>20	>20	>20	>20	>20	18.24	—[C]	>20	>20
RAMOS	0.003	>20	>20	>20	>20	>20	15.50	18.16	—[C]	16.65	>20
DAUDI	0.002	>20	>20	>20	>20	9.08	12.04	13.50	—[C]	15.71	>20
MES-SA	0.003	>20	>20	>20	>20	10.07	9.04	14.12	—[C]	9.10	>20
MES-SA-Dx5	0.003	>20	>20	>20	>20	11.73	8.46	11.79	—[C]	16.78	>20
MCF-7	0.003	—[C]	—[C]	—[C]	—[C]	—[C]	—[C]	—[C]	—[C]	18.59	>20

[A]DMSO was used as solvent in these assays unless otherwise stated.
[B]Methanol used as solvent in the assaying of this compound because of difficulties dissolving it in DMSO.
[C]Not tested.

Table 2. Anti-angiogenic properties of compounds 23–32 as determined in a rat aorta assay[A]

Compound	% Inhibition of blood vessel growth			
	at 100 μg mL^{-1}	at 10 μg mL^{-1}	at 1 μg mL^{-1}	at 0.1 μg mL^{-1}
23	100	43	68	22
24	100	62	59	36
25	100	42	53	31
26	100	65	43	—[C]
27	100	100	42	17
28	—[B]	100	48	29
29	100	74	58	35
30	100	85	47	18
31	—[C]	100	22	7
32	83	42	—[C]	—[C]
PI-88	74	—[C]	—[C]	—[C]

[A]Assays conducted according to the method of Brown et al.[20] using DMSO as solvent.
[B]Not tested at this concentration due to lack of solubility.
[C]Not tested.

analogous testing of cryptopleurine itself. Nevertheless, the results shown in Table 2 indicate that most of the analogues completely inhibited blood vessel growth at 100 μg mL^{-1}. Even more significantly, compounds **27** and **28** also completely inhibited blood vessel growth at the 10 μg mL^{-1} level, whereas several others were still able to inhibit growth by more than 50% at the 1 μg mL^{-1} level. It is worth noting that every single one of these analogues of alkaloids **1** and **2** is more active, at least at the 100 μg mL^{-1} level, than PI-88, a polysulfated oligosaccharide that exhibits anti-angiogenic properties in vivo and which is now in clinical development as an agent for the treatment of certain cancers.[21] A further important facet of these results is that the phenanthrenes seem to be more active than the corresponding *cis*-stilbenes while chirality has little or no impact on the anti-angiogenic properties of the title analogues. Furthermore, those phenanthrenes that incorporate a free hydroxy group are slightly less active than their methoxy counterparts, perhaps because of a reduction in their lipophilic properties. Interestingly, the phenanthrene and aminomethyl subunits associated with compounds **23**–**30** both seem to be making important contributions to their anti-angiogenic properties as judged by the test results observed for the simpler analogues **31** and **32**.

The origins of the significant anti-angiogenic properties of compounds **23**–**32** have not been established thus far. However, the capacity of certain combretastatin A4 derivatives/analogues to act as vascular targeting agents by binding to tubulin in newly formed endothelial cells that line the tumour vasculature[9b,22] suggests this mode of action may be involved in the present case. This situation, coupled with the considerable interest in the possibility of separating any cytotoxic activity of combretastatin-type compounds from their ability to effect vascular shutdown,[9a,22] serves to highlight the therapeutic potential of C8c–C15 monoseco analogues, such as compounds **23**–**30**, of the title alkaloids.

Conclusions

Four *cis*-stilbene analogues, **23**–**26**, of julandine (**2**) and six phenanthrene analogues, **27**–**32**, of cryptopleurine (**1**) have been synthesized in good overall yields. While these analogues display only modest cytotoxicities, their anti-angiogenic properties, especially those displayed by phenanthrenes **27** and **28**, are particularly striking. As such these compounds should serve as significant leads for further work in this area.

Experimental

General Procedures

Melting points were measured on a Reichert hot-stage microscope apparatus and are uncorrected. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were acquired at 20°C. Proton and carbon NMR spectra were recorded on either a Gemini 300 NMR spectrometer, operating at 300 MHz (for proton) and 75 MHz (for carbon) or a Varian Inova 500 spectrometer operating at 500 MHz (for proton) and 126 MHz (for carbon). NMR spectra are referenced to residual chloroform (δ 7.24, ^{1}H; δ 77.0, ^{13}C), methanol (δ 3.30, ^{1}H; δ 49.0, ^{13}C) or benzene (δ 7.15, ^{1}H; δ 128.0, ^{13}C). Deuterated chloroform ($CDCl_3$) was filtered through basic alumina immediately before use. Chemical shifts were recorded as δ values in parts per million (ppm). Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR spectrometer and samples were analyzed as thin films on NaCl plates unless otherwise specified. A VG Fisions AutoSpec three-sector (E/B/E) double-focusing mass spectrometer (located at the Australian National University) or a Kratos Analytical Concept ISQ instrument (located at the University of Tasmania) operating in a positive-ion electron-impact mode were used to obtain low and high resolution electron impact (EI) spectra. Optical rotations were measured with a Perkin–Elmer 241 polarimeter at the sodium-D line (589 nm) and the concentrations (*c*) (g/100 mL) indicated using spectroscopic grade $CHCl_3$ unless otherwise specified. The measurements were carried out between 15 and 21°C in a cell with a path length (*l*) of 1 dm. Specific rotations $[\alpha]_D$ were calculated using the equation $[\alpha]_D = 100\alpha/(cl)$, where α represents the measured rotation, and are given in 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed by the Australian National University's Microanalytical Services Unit based at the Research School of Chemistry, Canberra, Australia. Dichloromethane was distilled, under nitrogen, from calcium hydride. THF and diethyl ether (ether) was distilled, under nitrogen, from sodium benzophenone ketyl. Methanol was distilled from magnesium methoxide. DMF and triethylamine were both distilled from and stored over potassium hydroxide pellets. A 28% aqueous ammonia solution was used as additive in some of the eluting systems for flash chromatography as well as for the workup of reaction mixtures. Where necessary, reactions were performed under a nitrogen atmosphere. Unless otherwise specified the organic phases arising from the workup of reaction mixtures were dried over anhydrous magnesium sulfate. The reaction mixture was then filtered and concentrated under reduced pressure on a rotary evaporator with the water bath temperature generally not exceeding 40°C. Room temperature is assumed to be ~18°C.

Synthetic Studies

Mandelate Salts of (S)-(+)- and (R)-(−)-2-Methylpiperidine (*35* and *36*, Respectively)

(*R*)-(−)-Mandelic acid (7.58 g, 49.8 mmol, ex. Aldrich Chemical Co.) was added to a solution of (±)-2-methylpiperidine (**34**) (6.16 mL, 52.4 mmol, ex. Aldrich Chemical Co.) in methanol (20 mL) maintained at 0°C and the resulting mixture swirled until the solid had dissolved. The temperature was maintained at 0°C without stirring and diethyl ether (10 × 10 mL) was added in 10 portions, once every 0.5 h, so as to initiate precipitation. A further aliquot of diethyl ether (15 mL) was then added and the mixture was maintained at 0°C for an additional 3 h and then filtered. The crystalline solid thus obtained was washed (cold diethyl ether) and then dried under reduced pressure to give salt **35**[10] (3.44 g, 28%) as a white, crystalline solid, mp 108–110°C (lit.[10] 118–119°C), $[\alpha]_D^{20}$ −60° (*c* 2.5, MeOH) {lit.[10] $[\alpha]_D^{20}$ −60° (*c* 2.5, MeOH)} (Found: C 66.8, H 8.7, N 5.3. $C_{14}H_{21}NO_3$ requires C 66.9, H 8.4, N 5.6%). δ_H (300 MHz, $CDCl_3$) 9.30 (2H, br s), 7.42 (2H, m), 7.29–7.14 (3H, complex m), 4.83 (1H, s), 2.94 (1H, br d, *J* 12.9), 2.71–2.58 (1H, complex m), 2.24–2.13 (1H, complex m), 1.70–1.58 (1H, complex m), 1.58–1.45 (3H, complex m), 1.30–0.98 (2H, complex m), 1.06 (3H, d, *J* 6.4) (one signal not observed). δ_C (75 MHz, $CDCl_3$) 178.2 (COO), 142.5 (C), 128.0 (2 × CH), 127.0 (CH), 126.6 (2 × CH), 74.4 (CH), 52.2 (CH), 43.8 (CH_2), 30.2 (CH_2), 22.5 (CH_2), 21.7 (CH_2), 19.1 (CH_3). ν_{max} (KBr)/cm^{-1} 3165 (br), 2947, 2858, 2704, 2593, 2545, 2507, 1609, 1478, 1446, 1393, 1330, 1280, 1268, 1186, 1089, 1060, 1028, 730, 695, 561, 487. *m/z* (EI, 70 eV) 152 [19%, $(M - C_6H_{13}N^{\bullet})^+$], 107 (100), 84 (82), 79 (77), 77 (66).

The mother liquors arising from recrystallization of the mandelate salt of (*R*)-(−)-2-methylpiperidine were concentrated under reduced pressure to give a syrup that was dissolved in water (15 mL) and the resulting solution was then basified (using 20 mL of a 10% w/v aqueous NaOH). The aqueous phase was extracted with diethyl ether (3 × 15 mL) and the combined organic phases was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give amine **34** (1.48 g, 14.95 mmol) now partially enriched in the (*R*)-(−)-enantiomer. This material was dissolved in methanol (15 mL) and the resulting solution cooled to 0°C. (*S*)-(+)-Mandelic acid (2.20 g, 14.46 mmol, ex. Aldrich Chemical Co.) was added and the resulting mixture swirled until all the solids had dissolved. The temperature was maintained at 0°C and diethyl ether was added in 11 portions, (11 × 10 mL), once every 0.5 h, to allow precipitation to begin. A final aliquot of diethyl ether (25 mL) was then added and the mixture was left to stand, without stirring, for an additional 3 h at 0°C. The mixture was then filtered and the crystalline solid thus obtained was washed (cold diethyl ether) then dried under reduced pressure to give compound **36**[10] (777 mg, 21%) as a white solid, mp 106–108°C (lit.[10] 145–146°C), $[\alpha]_D^{17}$ +60.8° (*c* 2.6, MeOH) {lit.[10] $[\alpha]_D^{20}$ +60° (*c* 2.5, MeOH)} (Found: C 66.9, H 8.7, N 5.5. $C_{14}H_{21}NO_3$ requires C 66.9, H 8.4, N 5.6%). δ_H (300 MHz, $CDCl_3$) 9.30 (2H, br s), 7.42 (2H, m), 7.29–7.14 (3H, complex m), 4.83 (1H, s), 2.94 (1H, br d, *J* 13.0), 2.70–2.57 (1H, complex m), 2.24–2.11 (1H, complex m), 1.71–1.59 (1H, complex m), 1.57–1.41 (3H, complex m), 1.29–0.98 (2H, complex m), 1.06 (3H, d, *J* 6.6) (one signal not observed). δ_C (75 MHz, $CDCl_3$) 178.2 (COO), 142.5 (C), 128.0 (2 × CH), 127.0 (CH), 126.5 (2 × CH), 74.4 (CH), 52.2 (CH), 43.8 (CH_2), 30.2 (CH_2), 22.5 (CH_2), 21.7 (CH_2), 19.1 (CH_3). ν_{max} (KBr)/cm^{-1} 3164 (br), 3027, 2970, 2947, 2857, 2704, 2593, 2545, 2507, 1608, 1478, 1446, 1393, 1330, 1280, 1268, 1186, 1089, 1068, 730, 695, 561, 488. *m/z* (EI, 70 eV) 152 [18%, $(M - C_6H_{13}N^{\bullet})^+$], 107 (100), 84 (68), 79 (77), 77 (65).

*(S)-(+)- and (R)-(−)-2-Methylpiperidine [(S)-(+)-**34** and (R)-(−)-**34**, Respectively]*

NaOH (50% w/v aqueous solution) was added, dropwise, to a magnetically stirred solution of salt **35** or **36** (500 mg, 1.99 mmol) in water (10 mL) maintained at 18°C until a pH of 14 was achieved. The aqueous phase was extracted with diethyl ether (5 × 15 mL) and the combined organic fractions were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a concentrated solution of *(S)-(+)- or (R)-(−)-2-methylpiperidine* in diethyl ether.

*(S)-(+)-2-Methylpiperidine [(S)-(+)-**34**]*[23] was obtained as a clear, colourless ethereal solution in 80–90% yield. δ_H (300 MHz, CD_3OD) 3.01–2.94 (1H, complex m), 2.63–2.51 (2H, complex m), 1.82–1.70 (1H, complex m), 1.68–1.51 (2H, complex m), 1.48–1.30 (2H, complex m), 1.16–1.02 (1H, complex m), 1.04 (3H, d, *J* 6.3) (signal due to N–H not observed). δ_C (75 MHz, CD_3OD) 53.3 (CH), 47.6 (CH_2), 35.1 (CH_2), 26.5 (CH_2), 25.7 (CH_2), 22.7 (CH_3).

*(R)-(−)-2-Methylpiperidine [(R)-(−)-**34**]*[23] was obtained as a clear, colourless ethereal solution in 80–90% yield. δ_H (300 MHz, CD_3OD) 3.02–2.97 (1H, complex m), 2.65–2.54 (2H, complex m), 1.81–1.71 (1H, complex m), 1.68–1.51 (2H, complex m), 1.48–1.31 (2H, complex m), 1.17–1.02 (1H, complex m), 1.05 (3H, d, *J* 6.4) (signal due to N–H not observed). δ_C (75 MHz, CD_3OD) 53.4 (CH), 47.5 (CH_2), 34.9 (CH_2), 26.3 (CH_2), 25.6 (CH_2), 22.5 (CH_3).

*(S)- and (R)-2-Methyl-1-[2′-bromo-3′-(3″,4″-dimethoxyphenyl)prop-2′-enyl]piperidines (**38** and **39**, Respectively)*

Triethylamine (47 μL, 0.337 mmol) was added to a magnetically stirred solution of chloride **37**[8] (90.0 mg, 0.31 mmol) and the relevant enantiomeric form of 2-methylpiperidine (0.325 mmol), i.e., (*S*)-(+)-**34** or (*R*)-(−)-**34**, in DMF (1.0 mL) maintained at 18°C. The ensuing mixture was heated at 60°C for 4 h under an atmosphere of nitrogen and then cooled to 18°C and diluted with ethyl acetate (30 mL). The resulting solution was washed with brine/water (5 × 20 mL of a 1:1 v/v mixture) and brine (1 × 20 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give either compound **38** or **39**.

*(S)-2-Methyl-1-[(Z)-2′-bromo-3′-(3″,4″-dimethoxyphenyl)prop-2′-enyl]piperidine (**38**)* (107.5 mg, 98%) was obtained as a yellow oil, $[\alpha]_D^{15}$ +59.4° (*c* 1.7, MeOH) (Found: $M^{+\bullet}$ 355.0965. $C_{17}H_{24}{}^{81}BrNO_2$ requires $M^{+\bullet}$ 355.0970). δ_H (300 MHz, CD_3OD) 7.36 (1H, d, *J* 1.9), 7.18 (1H, dd, *J* 1.9 and 8.4), 6.99 (1H, s), 6.89 (1H, d, *J* 8.4), 3.80(9) (3H, s), 3.80(5) (3H, s), 3.76 (1H, dd, *J* 0.8 and 14.9), 3.15 (1H, d, *J* 14.9), 2.96–2.88 (1H, complex m), 2.48–2.35 (1H, complex m), 2.12 (1H, dt, *J* 3.8 and 10.8), 1.71–1.44 (3H, complex m), 1.44–1.23 (3H, complex m), 1.11 (3H, d, *J* 6.3). δ_C (75 MHz, CD_3OD) 150.3 (C), 149.7 (C), 131.0 (C), 129.7 (CH), 123.7 (CH), 122.5 (C), 113.5 (CH), 112.2 (CH), 65.5 (CH_2), 57.8 (CH), 56.4 (CH_3), 56.3 (CH_3), 53.2 (CH_2), 35.2 (CH_2), 26.7 (CH_2), 24.9 (CH_2), 19.6 (CH_3). ν_{max} (KBr)/cm^{-1} 2931, 2853, 2790, 1602, 1582, 1515, 1463, 1271, 1143, 1028, 804. *m/z* (EI, 70 eV) 355 (2.9%), 353 (3.1, $M^{+\bullet}$), 340 (3.9), 338 (4.1), 274 (100), 257 (30), 255 (31), 176 (59), 175 (89).

*(R)-2-Methyl-1-[(Z)-2′-bromo-3′-(3″,4″-dimethoxyphenyl)prop-2′-enyl]piperidine (**39**)* (108.6 mg, 99%) was obtained as a yellow oil, $[\alpha]_D^{20}$ −54.9° (*c* 0.5, MeOH). The remaining spectroscopic data obtained on this material matched those presented above for the corresponding *S*-enantiomer.

*(S)- and (R)-2-Methyl-1-[(E)-3′-(3″,4″-dimethoxyphenyl)-2′-(4″-methoxyphenyl)prop-2′-enyl]piperidines (**23** and **24**, Respectively)*

A magnetically stirred mixture of alkenyl bromide **38** or **39** (100.0 mg, 0.28 mmol), 4-methoxyphenyl pinacolboronate **40**[8] (139 mg, 0.59 mmol), ethanol (1.8 mL), and Na_2CO_3 (4.0 mL of a 2 M aqueous solution) in benzene (14.4 mL) was treated with $PdCl_2$(dppf) (17.2 mg, 0.02 mmol) and the resulting mixture was heated at reflux under an atmosphere of nitrogen for 6–7 h while being protected from light. The cooled reaction mixture was then diluted with diethyl ether (20 mL) and the separated organic phase washed with $NaHCO_3$ (2 × 10 mL of a saturated aqueous solution) and brine (1 × 10 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil. This material was subjected to flash chromatography (silica, 95:4.25:0.75 v/v/v dichloromethane/methanol/aqueous ammonia elution) and concentration of the relevant fractions (R_F 0.2) gave the cis-*stilbene **23** or **24***.

*(S)-2-Methyl-1-[(E)-3′-(3″,4″-dimethoxyphenyl)-2′-(4″-methoxyphenyl)prop-2′-enyl]piperidine (**23**)* (77.8 mg, 73%) was obtained as a light-yellow oil, $[\alpha]_D^{20}$ +26.8° (*c* 1.7, MeOH) (Found: $M^{+\bullet}$ 381.2305. $C_{24}H_{31}NO_3$ requires $M^{+\bullet}$ 381.2304). δ_H (300 MHz, CD_3OD) 7.14 (2H, d, *J* 8.8), 6.89 (2H, d, *J* 8.8), 6.71 (1H, d, *J* 8.4), 6.61 (1H, dd, *J* 1.9 and 8.4), 6.53 (1H, s), 6.40 (1H, d, *J* 1.9), 3.84 (1H, d, *J* 13.7), 3.77 (3H, s), 3.73 (3H, s), 3.39 (3H, s), 3.15 (1H, d, *J* 13.7), 3.08–2.99 (1H, complex m), 2.34 (1H, br s), 2.13 (1H, broad t, *J* 11.0), 1.68–1.22 (6H, complex m), 1.05 (3H, d, *J* 6.1). δ_C (75 MHz, CD_3OD) 160.4 (C), 149.4 (C), 149.2 (CH), 138.3 (C), 134.3 (C), 131.5 (C), 131.4 (2 × CH), 130.7 (C), 123.7 (CH), 115.2 (2 × CH), 113.3 (CH), 112.2 (CH), 63.5 (CH_2), 58.1 (CH), 56.3 (CH_3), 55.7 (CH_3), 55.6(6) (CH_3), 53.4 (CH_2), 35.1 (CH_2), 26.6 (CH_2), 25.0 (CH_2), 19.5 (CH_3). ν_{max} (KBr)/cm^{-1} 2932, 1606, 1512, 1464, 1268, 1243, 1142, 1028. *m/z* (EI, 70 eV) 381 (43%, $M^{+\bullet}$), 366 (8), 284 (46), 283 (41), 252 (26), 237 (22), 112 (100).

*(R)-2-Methyl-1-[(E)-3′-(3″,4″-dimethoxyphenyl)-2′-(4″-methoxyphenyl)prop-2′-enyl]piperidine (**24**)* (78.9 mg, 74%) was obtained as a yellow oil, $[\alpha]_D^{19}$ −26.7° (*c* 0.1, MeOH). The remaining spectroscopic data obtained on this material matched those presented above for the corresponding *S*-enantiomer.

*(S)- and (R)-2-Methyl-1-[(2,3,6-trimethoxphenanthren-9-yl)methyl]piperidines (**27** and **28**, Respectively)*

VOF_3 (27.5 mg, 0.22 mmol) was added to a magnetically stirred solution of *cis*-stilbene **23** or **24** (17.5 mg, 0.05 mmol) in dichloromethane (2.0 mL) maintained at 0°C under an atmosphere of nitrogen. The ensuing mixture was stirred at this temperature for 0.25 h and then trifluoroacetic acid (50 μL, 0.61 mmol) was added dropwise. After being stirred for a further 0.25 h at 0°C the reaction mixture was poured into NaOH (10 mL of a 10% w/v aqueous solution). After 5 min of additional stirring the aqueous phase was extracted with dichloromethane (3 × 15 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. This material was subjected to flash chromatography (silica, 90:8:2 → 80:18:2 v/v/v hexane/ethyl acetate/triethylamine gradient elution) and concentration of the appropriate fractions (R_F 0.2 in 4:1 v/v hexane/ethyl acetate) gave the relevant *phenanthrene*.

*(S)-2-Methyl-1-[(2,3,6-trimethoxphenanthren-9-yl)methyl] piperidine (**27**)* (9.1 mg, 48%) was obtained as an oily white solid, mp 46–48°C, $[\alpha]_D^{19}$ +33.1° (*c* 0.2, benzene) (Found: $M^{+\bullet}$ 379.2155. $C_{24}H_{29}NO_3$ requires $M^{+\bullet}$ 379.2147). δ_H (300 MHz, C_6D_6) 8.70 (1H, d, *J* 9.0), 8.08 (1H, d, *J* 2.4), 7.91 (1H, s), 7.64 (1H, s), 7.31 (1H, dd, *J* 2.4 and 9.0), 7.07 (1H, s), 4.61 (1H, d, *J* 12.9), 3.54 (6H, s), 3.51 (3H, s), 3.38 (1H, d, *J* 12.9), 2.85 (1H, dt, *J* 3.8 and 11.5), 2.39–2.27 (1H, complex m), 2.00 (1H, m), 1.64–1.20 (6H, complex m), 1.23 (3H, d, *J* 6.1). δ_C (126 MHz, C_6D_6) 158.6 (C), 150.7 (C), 150.0 (C), 132.5 (C), 132.2 (C), 127.7 (C), 127.5 (CH), 126.3 (C), 125.4 (CH), 124.8 (C), 115.0 (CH), 109.0 (CH), 104.9 (CH), 104.6 (CH), 58.7 (CH_2), 57.9 (CH), 55.6 (CH_3), 55.3 (CH_3), 54.9 (CH_3), 52.2 (CH_2), 35.1 (CH_2), 26.6 (CH_2), 24.2 (CH_2), 18.9 (CH_3). ν_{max} (KBr)/cm^{-1} 2929, 1611, 1511, 1467, 1259, 1232, 1159. *m/z* (EI, 70 eV) 379 (7%, $M^{+\bullet}$), 364 (1), 281 (58), 57 (100).

*(R)-2-Methyl-1-[(2,3,6-trimethoxphenanthren-9-yl)methyl] piperidine (**28**)* (11.9 mg, 63%) was obtained as a light-yellow and oily solid, mp 53–55°C, $[\alpha]_D^{19}$ −36.7° (*c* 0.3, benzene). The remaining spectroscopic data obtained on this material matched those presented above for the corresponding *S*-enantiomer.

*2-[4-(*tert*-Butyldiphenylsilanoxyphenyl)]-4,4,5,5-tetramethyl[1,3,2]dioxaborolan (**42**)*

tert-Butyldiphenylsilyl chloride (0.28 mL, 1.077 mmol) was added, dropwise, to a magnetically stirred solution of boronate **41** (199 mg, 0.904 mmol, ex. Boron Molecular) and imidazole (86 mg, 1.263 mmol) in DMF (1.0 mL) maintained at −30°C under an atmosphere of nitrogen. The ensuing mixture was then allowed to warm to 18°C and stirred at this temperature for 16 h before being diluted with ethyl acetate (20 mL) washed with brine/water (5 × 15 mL of a 1:1 v/v mixture) and then brine (1 × 15 mL). The separated organic phase was dried ($MgSO_4$) then filtered and concentrated under reduced pressure to give a light-brown and oily solid. This material was subjected to flash chromatography (silica, 95:5 v/v hexane/ethyl acetate eluent) and concentration of the relevant fractions (R_F 0.3) gave the *title boronate **42*** (279 mg, 67%) as a white, crystalline solid, mp 119–120°C (Found: $M^{+\bullet}$ 458.2447. C 73.1, H 8.0. $C_{28}H_{35}{}^{11}BO_3Si$ requires $M^{+\bullet}$ 458.2449. C 73.4, H 7.7%). δ_H (300 MHz, $CDCl_3$) 7.79 (4H, m), 7.65 (2H, d, *J* 8.5), 7.49–7.37 (6H, complex m), 6.84 (2H, d, *J* 8.5), 1.34 (12H, s), 1.17 (9H, s). δ_C (75 MHz, $CDCl_3$) 158.3 (C), 136.2 (CH), 135.4 (CH), 132.6 (C), 129.9 (CH), 127.8 (CH), 119.2 (CH), 83.4 (C), 26.4 (CH_3), 24.8 (CH_3), 19.4 (C) (one signal obscured or overlapping). ν_{max} (KBr)/cm^{-1} 2980, 2933, 2895, 2860, 1603, 1516, 1472, 1428, 1397, 1360, 1319, 1143, 1113, 1090, 915, 859, 822, 733, 701, 654, 613. *m/z* (EI, 70 eV) 458 (11%, $M^{+\bullet}$), 402 (52), 401 (100), 400 (44), 301 (24), 197 (41), 83 (31).

*(S)- and (R)-2-Methyl-1-[(E)-3′-(3″,4″-dimethoxyphenyl)-2′-(4″-*tert*-butyldipenylsilanoxyphenyl)prop-2′-enyl] piperidines (**43** and **44**, Respectively)*

A magnetically stirred solution of the alkenyl bromide **38** or **39** (80.0 mg, 0.23 mmol), boronate ester **42** (207 mg, 0.45 mmol), ethanol (1.5 mL), and Na_2CO_3 (3.2 mL of a 2 M aqueous solution) in benzene (11.5 mL) was treated with $PdCl_2$(dppf) (32.8 mg, 0.04 mmol) and the ensuing mixture heated at reflux under an atmosphere of nitrogen for 6 h while being protected from light. The cooled reaction mixture was diluted with diethyl ether (20 mL) and the separated organic phase was washed with $NaHCO_3$ (2 × 10 mL of a saturated aqueous solution) brine (1 × 10 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil. This material was subjected to flash chromatography (silica, 80:18:2 v/v/v hexane/ethyl acetate/triethylamine elution) and concentration of the appropriate fractions (R_F 0.2) gave either *stilbene **43** or **44***.

*(S)-2-Methyl-1-[(E)-3′-(3″,4″-dimethoxyphenyl)-2′-(4″-*tert*-butyldipenylsilanoxyphenyl)prop-2′-enyl]piperidine (**43**)* (96.0 mg, 69%) was obtained as a clear oil, $[\alpha]_D^{18}$ +10.8° (*c* 0.5, MeOH) (Found: $M^{+\bullet}$ 605.3338. $C_{39}H_{47}NO_3Si$ requires $M^{+\bullet}$ 605.3325). δ_H (300 MHz, CD_3OD) 7.70 (4H, m), 7.46–7.33 (6H, complex m), 6.94 (2H, d, *J* 8.7), 6.70 (2H, d, *J* 8.7), 6.65 (1H, d, *J* 8.4), 6.53 (1H, dd, *J* 1.9 and 8.4), 6.45 (1H, s), 6.38 (1H, d, *J* 1.9), 3.72 (3H, s), 3.70 (1H, d, *J* 13.9), 3.35 (3H, s), 3.07 (1H, d, *J* 13.9), 2.95–2.87 (1H, complex m), 2.26–2.15 (1H, complex m), 2.04 (1H, dt, *J* 11.2 and 3.0), 1.66–1.12 (6H, complex m), 1.07 (9H, s), 0.96 (3H, d, *J* 6.2). δ_C (75 MHz, CD_3OD) 156.1 (C), 149.4 (C), 149.2 (C), 138.6 (C), 136.6 (CH), 135.2 (C), 134.0 (C), 131.4 (C), 131.2 (CH), 131.1(6) (CH), 130.4 (CH), 128.9 (CH), 123.6 (CH), 120.9 (CH), 113.4 (CH), 112.2 (CH), 63.4 (CH_2), 57.7 (CH_2), 56.3 (CH_3), 55.8 (CH_3), 53.4 (CH), 47.0 (CH_2), 35.3 (CH_2), 27.0 (CH_3), 26.7 (CH_2), 25.1 (CH_3), 20.2 (C). ν_{max} (KBr)/cm^{-1} 2932, 2858, 1603, 1506, 1464, 1428, 1257, 1114, 1029, 919, 701. *m/z* (EI, 70 eV) 605 (24%, $M^{+\bullet}$), 508 (29), 451 (25), 112 (100).

*(R)-2-Methyl-1-[(E)-3′-(3″,4″-dimethoxyphenyl)-2′-(4″-*tert*-butyldipenylsilanoxyphenyl)prop-2′-enyl]piperidine (**44**)* (104.3 mg, 73%) was obtained a clear, colourless oil, $[\alpha]_D^{18}$ −8.8° (*c* 0.9, MeOH). The remaining spectroscopic data obtained on this material matched those presented above for the corresponding *S*-enantiomer.

*(S)- and (R)-2-Methyl-1-[(E)-3′-(3″,4″-dimethoxyphenyl)-2′-(4″-hydroxyphenyl)prop-2′-enyl] piperidines (**25** and **26**, Respectively)*

TBAF (70 μL of a 1 M solution in THF, 0.07 mmol) was added, dropwise, to a magnetically stirred solution of *cis*-stilbene **43** or **44** (30.0 mg, 0.05 mmol) in THF (2.0 mL) maintained at 18°C. The reaction mixture was then stirred under an atmosphere of nitrogen for 0.5 h before being diluted with ethyl acetate (15 mL). The organic phase was washed with water (2 × 10 mL) and brine (1 × 10 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. This material was then subjected to flash chromatography (silica, 90:9.5:0.5 v/v/v chloroform/methanol/ammonia solution elution) and concentration of the appropriate fractions (R_F 0.3) gave the *title alcohols* in the yields specified below.

*(S)-2-Methyl-1-[(E)-3′-(3″,4″-dimethoxyphenyl)-2′-(4″-hydroxyphenyl)prop-2′-enyl]piperidine (**25**)* (15.9 mg, 87%) was obtained as a yellow oil, $[\alpha]_D^{19}$ +26.1° (*c* 0.38, MeOH) (Found: $M^{+\bullet}$ 367.2151. $C_{23}H_{29}NO_3$ requires $M^{+\bullet}$ 367.2147). δ_H (500 MHz, CD_3OD) 7.07 (2H, d, *J* 8.5), 6.78 (2H, d, *J* 8.5), 6.73 (1H, d, *J* 8.3), 6.65 (1H, dd, *J* 1.9 and 8.3), 6.56 (1H, s), 6.43 (1H, d, *J* 1.9), 3.95 (1H, d, *J* 13.6), 3.74 (3H, s), 3.41 (3H, s), 3.34 (1H, d, *J* 13.6), 3.12 (1H, d, *J* 11.7), 2.51 (1H, br s), 2.30 (1H, t, *J* 10.7), 1.71–1.61 (3H, complex m), 1.57–1.47 (1H, complex m), 1.42–1.29 (2H, complex m), 1.12 (3H, d, *J* 6.3) (signal due to OH proton not observed). δ_C (126 MHz, CD_3OD) 158.3 (C), 149.4 (C), 136.8 (C), 132.2 (C), 131.8 (C), 131.4 (CH), 131.2 (C), 123.9 (CH), 116.8 (CH), 113.6 (CH), 112.2 (CH), 63.0 (CH_2), 58.7 (CH), 56.3 (CH_3), 55.7 (CH_3), 53.3 (CH_2), 34.4 (CH_2), 25.9

(CH_2), 24.5 (CH_2), 19.2 (CH_3). ν_{max} (KBr)/cm^{-1} 3215 (broad), 2933, 2855, 2789, 1609, 1582, 1513, 1464, 1454, 1421, 1327, 1268, 1239, 1160, 1142, 1026, 841, 735. *m/z* (EI, 70 eV) 367 (32%, $M^{+\bullet}$), 270 (21), 269 (26), 112 (100).

*(R)-2-Methyl-1-[(E)-3′-(3″,4″-dimethoxyphenyl)-2′-(4″-hydroxyphenyl)prop-2′-enyl]piperidine (**26**)* (15.5 mg, 85%) was obtained as a yellow oil, $[\alpha]_D^{19}$ −29.2° (*c* 0.39, MeOH). The remaining spectroscopic data obtained on this material matched those presented above for the corresponding *S*-enantiomer.

*(S)- and (R)-2-Methyl-1-[(2,3-dimethoxy-6-*tert*-butyldiphenylsilanoxyphenanthren-9-yl)methyl]piperidines (**45** and **46**, Respectively)*

VOF_3 (32.1 mg, 0.26 mmol) was added to a magnetically stirred solution of *cis*-stilbene **43** or **44** (30.0 mg, 0.05 mmol) in dichloromethane (2.3 mL) maintained at 0°C under an atmosphere of nitrogen. The reaction mixture was stirred for 0.25 h before trifluoroacetic acid (0.05 mL, 0.66 mmol) was added dropwise. The reaction mixture was stirred for an additional 0.25 h at 0°C before the reaction mixture was poured into NaOH (10 mL of a 10% aqueous solution) and the ensuing mixture stirred vigorously for 5 min. The aqueous phase was then extracted with dichloromethane (3 × 15 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. This material was subjected to flash chromatography (silica, 95:4.25:0.75 v/v/v dichloromethane/methanol/ammonia solution elution), and concentration of the relevant fractions (R_F 0.3) under reduced pressure gave the *title phenanthrenes* in the yields specified below.

*(S)-2-Methyl-1-[(2,3-dimethoxy-6-*tert*-butyldiphenylsilanoxyphenanthrene-9-yl)methyl]piperidine (**45**)* (17.5 mg, 58%) was obtained as a yellow oil, $[\alpha]_D^{17}$ +16.1° (*c* 0.3, benzene) (Found: $M^{+\bullet}$ 603.3170. $C_{39}H_{45}NO_3Si$ requires $M^{+\bullet}$ 603.3169). δ_H (500 MHz, C_6D_6) 8.51 (1H, d, *J* 9.3), 8.16 (1H, d, *J* 2.4), 7.90 (4H, m), 7.60 (1H, s), 7.46 (1H, s), 7.40 (1H, dd, *J* 2.4 and 9.3), 7.10 (6H, m), 7.00 (1H, s), 4.46 (1H, d, *J* 13.2), 3.47 (3H, s), 3.43 (3H, s), 3.30 (1H, d, *J* 13.2), 2.78 (1H, m), 2.28 (1H, br s), 1.94 (1H, t, *J* 9.3), 1.59–1.48 (2H, complex m), 1.43–1.12 (4H, complex m), 1.25 (9H, s), 1.14 (3H, d, *J* 6.8). δ_C (126 MHz, C_6D_6) 154.5, 150.5, 149.9, 136.0, 135.9, 135.8, 133.6(2), 133.6(0), 132.4, 132.1, 130.2, 126.5, 125.4, 124.7, 119.7, 111.7, 108.8, 103.9, 58.4, 57.8, 55.4, 55.2, 52.3, 35.1, 26.9, 26.5, 24.2, 19.8, 18.8. ν_{max} (KBr)/cm^{-1} 2932, 1608, 1509, 1465, 1428, 1250, 1235, 1202, 1159, 1114, 935, 855, 822, 701. *m/z* (EI, 70 eV) 603 (14%, $M^{+\bullet}$), 507 (36), 506 (100), 505 (82), 449 (34), 224 (33).

*(R)-2-Methyl-1-[(2,3-dimethoxy-6-*tert*-butyldiphenylsilanoxyphenanthren-9-yl)methyl]piperidine (**46**)* (20.5 mg, 68%) was obtained as a yellow oil, $[\alpha]_D^{19}$ −15.7° (*c* 0.4, benzene). The remaining spectroscopic data obtained on this material matched those presented above for the corresponding *S*-enantiomer.

*(S)- and (R)-2-Methyl-1-[(2,3-dimethoxy-6-hydroxyphenanthren-9-yl)methyl]piperidine (**29** and **30**, Respectively)*

TBAF (40 μL of a 1 M solution in THF, 0.04 mmol) was added dropwise to a magnetically stirred solution of phenanthrene **45** or **46** (17.0 mg, 0.03 mmol) in THF (1.0 mL) maintained at 18°C. The reaction mixture was then stirred under an atmosphere of nitrogen for 0.5 h before being diluted with ethyl acetate (15 mL). The organic phase was washed with water (2 × 10 mL) and brine (1 × 10 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. This material was subjected to flash chromatography (silica, 90:9.5:0.5 v/v/v chloroform/methanol/ammonia solution elution), and concentration of the appropriate fractions (R_F 0.3) gave the *title phenols* in the yields specified below.

*(S)-2-Methyl-1-[(2,3-dimethoxy-6-hydroxyphenanthren-9-yl)methyl]piperidine (**29**)* (8.9 mg, 82%) was obtained as a yellow oil, $[\alpha]_D^{18}$ +44.5° (*c* 0.1, MeOH). (Found: $M^{+\bullet}$ 365.2001. $C_{23}H_{27}NO_3$ requires $M^{+\bullet}$ 365.1991). δ_H (300 MHz, CD_3OD) 8.19 (1H, d, *J* 9.0), 7.86 (1H, d, *J* 2.5), 7.85(8) (1H, s), 7.40 (1H, s), 7.23 (1H, s), 7.09 (1H, dd, *J* 2.5 and 9.0), 4.57 (1H, d, *J* 13.0), 4.00 (3H, s), 3.95 (3H, s), 3.40 (1H, d, *J* 13.0), 2.82–2.70 (1H, complex m), 2.49 (1H, m), 2.07 (1H, m), 1.76–1.61 (2H, complex m), 1.59–1.30 (4H, complex m), 1.35 (3H, d, *J* 6.2) (signal of OH proton not observed). δ_C (500 MHz, CD_3OD) 157.0, 150.8, 150.3, 133.5, 132.1, 128.5, 128.1, 126.2, 126.0, 125.4, 116.8, 109.5, 107.1, 104.8, 59.4, 58.4, 56.4, 56.3, 53.3, 35.5, 29.2, 26.7, 21.8. ν_{max} (KBr)/cm^{-1} 3434 (br), 2933, 1610, 1511, 1467, 1260, 1241, 1202, 1158. *m/z* (EI, 70 eV) 365 (17%, $M^{+\bullet}$), 350 (8), 268 (50), 267 (100).

*(R)-2-Methyl-1-[(2,3-dimethoxy-6-hydroxyphenanthren-9-yl)methyl]piperidine (**30**)* (10.2 mg, 93%) was obtained as a yellow oil, $[\alpha]_D^{19}$ −44.7° (*c* 0.4, MeOH). The remaining spectroscopic data obtained on this material matched those presented above for the corresponding *S*-enantiomer.

*(E)-3,4-Dimethoxy-(4-methoxyphenyl)cinnamic Acid (**49**)*

A solution of 3,4-dimethoxybenzaldehyde (**47**) (11.20 g, 67.4 mmol), 4-methoxyphenylacetic acid (**48**) (11.20 g, 67.4 mmol), acetic anhydride (25 mL), and triethylamine (12 mL) was heated at reflux for 2.5 h under an atmosphere of nitrogen. The reaction mixture was then cooled to 18°C and NaOH (100 mL of a 5% w/w aqueous solution) was added. The water phase was extracted with diethyl ether (1 × 50 mL) and then neutralized with acetic acid, and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic fractions were washed with water (1 × 50 mL) and brine (1 × 50 mL) before being dried over $MgSO_4$. Filtration and concentration under reduced pressure followed by recrystallization of the ensuing solid (methanol) gave the title acid **49**[6a,12] (9.42 g, 45%) as a light-yellow solid, mp 212–213°C (lit.[6a] 213–214°C) (Found: $M^{+\bullet}$ 314.1149. $C_{18}H_{18}O_5$ requires $M^{+\bullet}$ 314.1154). δ_H (300 MHz, $CDCl_3$) 7.84 (1H, s), 7.18 (2H, d, *J* 8.8), 6.94 (2H, d, *J* 8.8), 6.84 (1H, dd, *J* 2.1 and 8.5), 6.72 (1H, d, *J* 8.5), 6.50 (1H, d, *J* 2.1), 3.83 (3H, s), 3.80 (3H, s), 3.44 (3H, s) (signal of carboxylic acid proton not observed). δ_C (75 MHz, $CDCl_3$) 173.3 (COO), 159.2 (C), 150.2 (C), 148.1 (C), 142.2 (CH), 131.2 (CH), 128.7 (C), 127.9 (C), 127.2 (C), 125.8 (CH), 114.3 (CH), 112.4 (CH), 110.4 (CH), 55.8 (CH_3), 55.3 (CH_3), 55.1 (CH_3). ν_{max} (KBr)/cm^{-1} 2953, 2936, 2908, 2837, 2611, 1666, 1597, 1574, 1509, 1465, 1424, 1291, 1267, 1244, 1202, 1174, 1145, 1022, 805. *m/z* (EI, 70 eV) 314 (100%, $M^{+\bullet}$), 252 (19), 237 (20), 210 (23), 209 (39).

*(E)-3′-(3″,4″-Dimethoxyphenyl)-2′-(4″-methoxyphenyl)prop-2′-enyl)dimethyl Amide (**50**)*

Oxalyl chloride (0.083 mL, 0.95 mmol) was added dropwise to a magnetically stirred solution of acid **49** (100 mg, 0.318 mmol) in THF (3 mL) maintained at 18°C. After the initial vigorous reaction had subsided the reaction mixture was heated at reflux for 0.66 h and then cooled and concentrated under reduced pressure. Dimethylamine (3.4 mL of a

2 M solution in THF, 6.8 mmol) was then added to the ensuing concentrate and the resulting mixture was stirred for 16 h at 18°C before water (10 mL) was added. The aqueous phase was extracted with dichloromethane (3 × 10 mL) and the combined organic fractions were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure gave a dark-yellow oil that was subjected to flash chromatography (silica, 95:4.25:0.75 v/v/v dichloromethane/methanol/ammonia solution eluent). Concentration of the relevant fractions (R_F 0.3) gave the *title amide* ***50*** (74.1 mg, 68%) as a viscous yellow oil (Found: $M^{+\bullet}$ 341.1629. $C_{20}H_{23}NO_4$ requires $M^{+\bullet}$ 341.1627). δ_H (300 MHz, $CDCl_3$) 7.23 (2H, d, *J* 8.5), 6.78 (2H, d, *J* 8.5), 6.70 (1H, dd, *J* 1.8 and 8.4), 6.65 (1H, d, *J* 8.4), 6.57 (1H, d, *J* 1.8), 6.52 (1H, s), 3.77 (3H, s), 3.72 (3H, s), 3.47 (3H, s), 2.94 (6H, s). δ_C (75 MHz, $CDCl_3$) 171.8 (CO), 159.0 (C), 148.4 (C), 147.9 (C), 135.5 (C), 130.1 (CH), 128.9 (CH), 128.1 (C), 127.9 (C), 122.5 (CH), 113.9 (CH), 111.7 (CH), 110.4 (CH), 55.6 (CH_3), 55.2 (CH_3), 55.1 (CH_3), 38.5 (CH_3), 34.9 (CH_3). ν_{max} (KBr)/cm^{-1} 3476, 3002, 2935, 2837, 1633, 1512, 1463, 1393, 1289, 1248, 1165, 1137, 1027, 840, 799, 730. *m/z* (EI, 70 eV) 341 (99%, $M^{+\bullet}$), 269 (100), 194 (55).

*(E)-3′-(3″,4″-Dimethoxyphenyl)-2′-(4″-methoxyphenyl)prop-2′-enyl)dimethyl Amine (**51**)*

A solution of the amide **50** (70.0 mg, 0.205 mmol) in THF (6 mL) was added dropwise to a magnetically stirred suspension of $LiAlH_4$ (46.0 mg, 1.21 mmol) maintained at 0°C. The ensuing mixture was stirred at 18°C for 2 h and then quenched with KOH (30%, w/w aqueous solution, 14 mL). The aqueous phase was extracted with diethyl ether (2 × 20 mL) before the organic fractions were combined, and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 95:4.25:0.75 v/v/v dichloromethane/methanol/ammonia solution elution) and concentration of the relevant fractions (R_F 0.2) under reduced pressure gave the *title compound* ***51*** (49.7 mg, 74%) as a clear oil (Found: $M^{+\bullet}$ 327.1834. $C_{20}H_{25}NO_3$ requires $M^{+\bullet}$ 327.1834). δ_H (300 MHz, CD_3OD) 7.14 (2H, d, *J* 8.8), 6.89 (2H, d, *J* 8.8), 6.72 (1H, d, *J* 8.3), 6.63 (1H, dd, *J* 1.9 and 8.3), 6.50 (1H, s), 6.43 (1H, d, *J* 1.9), 3.76 (3H, s), 3.73 (3H, s), 3.40 (3H, s), 3.31 (2H, d, *J* 1.1), 2.22 (6H, s). δ_C (75 MHz, CD_3OD) 160.5 (C), 149.4 (C), 149.3 (C), 138.3 (C), 133.6 (C), 131.2 (CH), 130.7 (CH), 123.8 (CH), 115.3 (CH), 113.4 (CH), 112.2 (CH), 69.5 (CH_2), 56.2 (CH_3), 55.7 (CH_3), 55.6 (CH_3), 45.4 (CH_3) (one signal obscured or overlapping). ν_{max} (KBr)/cm^{-1} 3476, 3294, 2938, 2852, 2836, 2815, 2771, 1696, 1606, 1580, 1512, 1464, 1267, 1243, 1174, 1161, 1142, 1028. *m/z* (EI, 70 eV) 328 (55%), 327 (93, $M^{+\bullet}$), 312 (50), 284 (43), 283 (66), 58 (100).

*[(2,3,6-Trimethoxyphenanthren-9-yl)methyl]dimethylamine (**31**)*

VOF_3 (78.0 mg, 0.63 mmol) was added to a magnetically stirred solution of *cis*-stilbene **51** (46.5 mg, 0.142 mmol) in dichloromethane (6 mL) maintained at 0°C under an atmosphere of nitrogen. The reaction mixture was stirred for 0.25 h before being treated, dropwise, with trifluoroacetic acid (0.14 mL, 1.82 mmol), stirred for an additional 0.25 h at 0°C, and then poured into NaOH (20 mL of a 10% aqueous solution) and stirred vigorously for 5 min. The separated aqueous phase was extracted with dichloromethane (3 × 20 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (silica, 95:4.25:0.75 v/v/v dichloromethane/methanol/ammonia solution elution) and concentration of the relevant fractions (R_F 0.2) under reduced pressure gave the title phenanthrene **31**[13] (25.7 mg, 56%) as a white solid, mp 139–140°C (lit.[13] 139°C) (Found: $M^{+\bullet}$ 325.1678. $C_{20}H_{23}NO_3$ requires $M^{+\bullet}$ 325.1678). δ_H (300 MHz, C_6D_6) 8.59 (1H, d, *J* 9.1), 8.06 (1H, d, *J* 2.5), 7.90 (1H, s), 7.50 (1H, s), 7.31 (1H, dd, *J* 2.5 and 9.1), 7.03 (1H, s), 3.76 (2H, s), 3.54 (3H, s), 3.53 (3H, s), 3.52 (3H, s), 2.21 (6H, s). δ_C (75 MHz, C_6D_6) 158.6 (C), 150.6 (C), 150.1 (C), 132.5 (C), 131.9 (C), 128.2 (CH), 127.8 (C), 126.2 (C), 125.3 (CH), 124.9 (C), 115.1 (CH), 108.9 (CH), 104.7 (CH), 104.5 (CH), 63.9 (CH_2), 55.5 (CH_3), 55.2 (CH_3), 54.9 (CH_3), 45.5 (CH_3). ν_{max} (KBr)/cm^{-1} 3476, 3293, 2938, 2855, 2815, 2768, 1697, 1611, 1513, 1467, 1430, 1253, 1232, 1208, 1159, 1070, 1038. *m/z* (EI, 70 eV) 325 (31%, $M^{+\bullet}$), 282 (38), 281 (100), 149 (36), 58 (57).

*(E)-3,4-Dimethoxy-(4-methoxyphenyl)cinnamic Acid Methyl Ester (**53**)*

Oxalyl chloride (0.43 mL, 4.93 mmol) was added dropwise to a magnetically stirred solution of acid **49** (524 mg, 1.67 mmol) in THF (15 mL) at 18°C. After the initial vigorous reaction subsided the reaction mixture was heated at reflux for 0.66 h and then cooled and concentrated under reduced pressure. The concentrate was diluted with methanol (20 mL) and the resulting mixture stirred at 18°C for 16 h and then diluted with ethyl acetate (50 mL) and washed with water (2 × 30 mL) and brine (1 × 30 mL) before being dried ($MgSO_4$). Filtration and concentration of the filtrate under reduced pressure gave a red oil that was subjected to flash chromatography (silica, 7:3 v/v hexane/ethyl acetate). Concentration of the relevant fractions (R_F 0.4) gave a pink wax that was triturated (methanol) to give the title ester **53**[24] (496 mg, 91%) as a white crystalline solid, mp 91–92°C (Found: $M^{+\bullet}$ 328.1301. C 69.7, H 6.1. $C_{19}H_{20}O_5$ requires $M^{+\bullet}$ 328.1311. C 69.5, H 6.1%). δ_H (300 MHz, $CDCl_3$) 7.71 (1H, s), 7.11 (2H, d, *J* 8.8), 6.88 (2H, d, *J* 8.8), 6.76 (1H, dd, *J* 1.9 and 8.4), 6.64 (1H, d, *J* 8.4), 6.41 (1H, d, *J* 1.9), 3.74 (3H, s), 3.73 (3H, s), 3.70 (3H, s), 3.38 (3H, s). δ_C (75 MHz, $CDCl_3$) 168.2 (CO), 158.8 (C), 149.5 (C), 147.7 (C), 140.0 (C), 130.8 (C), 129.3 (CH), 128.1 (CH), 127.2 (CH), 125.0 (C), 113.9 (CH), 112.0 (CH), 110.1 (CH), 55.4 (CH_3), 54.9 (CH_3), 54.7 (CH_3), 51.9 (CH_3). ν_{max} (KBr)/cm^{-1} 3002, 2951, 2838, 1701, 1599, 1577, 1513, 1464, 1436, 1422, 1333, 1253, 1174, 1144, 1025. *m/z* (EI, 70 eV) 328 (100%, $M^{+\bullet}$), 269 (12), 181 (45).

*Methyl 5′,6′-Dimethoxy-4-oxospiro[cyclohexa(2,5)diene-1,1′-indene]-2′-carboxylate (**54**) and Methyl 2,3,6-Trimethoxy-[7,5′]-(methyl 2′,3′,6′-trimethoxyphenanthrene-9-carboxylate)phenanthrene-9-carboxylate (**55**)*

Method A: A solution of VOF_3 (130 mg, 1.05 mmol) in TFA (3.3 mL) and ethyl acetate (1.7 mL) was added dropwise to a magnetically stirred solution of ester **53** (100 mg, 0.305 mmol) in TFA (4.5 mL) and dichloromethane (3.0 mL) maintained at 0°C under an atmosphere of nitrogen. The reaction mixture was stirred at 0°C for 0.33 h before being poured into citric acid (50 mL of a 5% aqueous solution) and the pH was then adjusted to 8 by adding ammonia (28% v/v aqueous solution). The water phase was extracted with dichloromethane (3 × 40 mL) and the combined organic fractions were washed with water (1 × 50 mL) and brine (1 × 50 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil that was subjected to flash chromatography (silica, 6:4 v/v hexane/ethyl acetate elution). Concentration of the relevant fractions (R_F 0.2)

gave the *title spirodienone* ***54*** (15 mg, 16%) as a light-yellow solid, mp 211–212°C (Found: $M^{+\bullet}$ 312.0996. $C_{18}H_{16}O_5$ requires $M^{+\bullet}$ 312.0998). δ_H (500 MHz, $CDCl_3$) 7.87 (1H, s), 7.04 (1H, s), 6.62 (1H, s), 6.51 (2H, d, *J* 9.8), 6.33 (2H, d, *J* 9.8), 3.91 (3H, s), 3.84 (3H, s), 3.72 (3H, s). δ_C (126 MHz, $CDCl_3$) 186.4 (CO), 163.2 (C), 151.3 (C), 150.1 (C), 147.4 (CH), 144.8 (CH), 137.4 (C), 135.5 (C), 134.4 (C), 130.6 (CH), 106.6 (CH), 106.5 (CH), 56.3 (CH_3), 56.2 (CH_3), 51.7 (CH_3) (one signal obscured or overlapping). ν_{max} (KBr)/cm^{-1} 1703, 1672, 1605, 1552, 1497, 1465, 1324, 1283, 1238, 1219, 1183, 1107, 1039, 1030, 852. *m/z* (EI, 70 eV) 312 (48%, $M^{+\bullet}$), 284 (49), 225 (100), 181 (32), 57 (40).

Method B: A solution of ester **53** (29 mg, 0.09 mmol) in TFA (1.3 mL) and dichloromethane (0.75 mL) was stirred at 0°C for 1 h and then a solution of VOF_3 (38.2 mg, 0.308 mmol) in TFA (0.8 mL) and ethyl acetate (0.4 mL) was added dropwise. The ensuing mixture was then stirred an additional 0.33 h at 0°C before being poured into citric acid (10 mL of a 5% aqueous solution) and the pH was then adjusted to 8 by addition of ammonia (28% v/v aqueous solution). The separated water phase was extracted with dichloromethane (3 × 15 mL) and the combined organic fractions were then dried ($MgSO_4$), filtered, and concentration under reduced pressure to give a yellow oil. This material was subjected to flash chromatography (silica, 6:4 v/v hexane/ethyl acetate elution) and thus affording two fractions, A and B.

Concentration of fraction A (R_F 0.2) afforded compound **54** (7.4 mg, 27%) that was identical, in all respects, with the material obtained by Method A.

Concentration of fraction B (R_F 0.1) gave the *title dimer* ***55*** (19.1 mg, 66%) as a light-yellow solid, mp 230–231°C (Found: $M^{+\bullet}$ 650.2150. $C_{38}H_{34}O_{10}$ requires $M^{+\bullet}$ 650.2152). δ_H (500 MHz, $CDCl_3$) 9.00 (1H, d, *J* 9.5), 8.83 (1H, s), 8.33 (1H, s), 8.23 (1H, s), 8.00 (1H, s), 7.89 (1H, s), 7.42 (1H, d, *J* 9.5), 7.33 (1H, s), 7.31 (1H, s), 7.15 (1H, s), 4.16 (3H, s), 4.06 (3H, s), 4.03 (3H, s), 3.90 (3H, s), 3.85 (3H, s), 3.84 (3H s), 3.80 (s, 3H), 2.74 (3H, s). δ_C (126 MHz, $CDCl_3$) 168.6 (CO), 167.9 (CO), 156.9 (C), 156.3 (C), 151.1 (C), 149.7 (C), 148.9 (C), 148.4 (C), 131.2 (C), 130.9 (C), 130.8 (C), 130.0 (CH), 129.9 (CH), 129.7 (CH), 127.8 (CH), 127.5 (C), 126.9 (C), 126.6 (C), 125.6 (C), 124.6 (C), 124.3 (C), 124.0 (C), 123.9 (C), 122.5 (C), 112.3 (CH), 109.4 (CH), 109.0 (CH), 108.9 (CH), 102.9 (CH), 102.4 (CH), 56.8 (CH_3), 56.1 (CH_3), 56.0 (CH_3), 55.9 (CH_3), 55.7 (CH_3), 54.4 (CH_3), 52.2 (CH_3), 52.0 (CH_3). ν_{max} (KBr)/cm^{-1} 1711, 1616, 1516, 1466, 1432, 1242, 1192, 1144, 1115. *m/z* (EI, 70 eV) 650 (11%, $M^{+\bullet}$), 530 (4), 304 (31), 245 (100), 227 (36), 199 (65), 185 (46), 135 (49).

*(Z)-1-(4-Methoxyhenyl)-2-(3,4-dimethoxyphenyl) ethene (**56**) and (E)-1-(4-Methoxyphenyl)-2-(3,4-dimethoxyphenyl)ethene (**57**)*

Anhydrous $CuSO_4$ (590 mg, 3.70 mmol) was added to a solution of acid **49** (523 mg, 1.67 mmol) in freshly distilled quinoline (16 mL). While being maintained under an atmosphere of nitrogen, the reaction mixture was heated at reflux for 1 h and then cooled to 18°C and poured into HCl (150 mL of a 2 M aqueous solution). The aqueous phase was extracted with benzene (3 × 100 mL) and the combined organic fractions were then washed with NaOH (1 × 100 mL of a 0.2 M aqueous solution), water (1 × 100 mL), brine (1 × 100 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash chromatography (silica, 4:1 hexane/ethyl acetate) afforded fractions A and B.

Concentration of fraction A [R_F 0.3(2)] afforded compound **56**[25] (316 mg, 70%) as a yellow oil (Found: $M^{+\bullet}$ 270.1253. $C_{17}H_{18}O_3$ requires $M^{+\bullet}$ 270.1256). δ_H (300 MHz, $CDCl_3$) 7.20 (2H, d, *J* 8.8), 6.82–6.68 (5H, complex m), 6.42 (2H, d, *J* 1.5), 3.80 (3H, s), 3.71 (3H, s), 3.61 (3H, s). δ_H (300 MHz, C_6D_6) 7.30 (2H, d, *J* 8.9), 6.94 (1H, partially obscured dd, *J* 2.1 and 7.8), 6.92 (1H, s), 6.64 (2H, d, *J* 8.9), 6.51 (2H, d, *J* 1.0), 6.49 (1H, partially obscured dd, *J* 7.8), 3.34 (3H, s), 3.27 (3H, s), 3.23 (3H, s). δ_C (75 MHz, $CDCl_3$) 158.3 (C), 148.0 (C), 147.7 (C), 129.8(5) (CH), 129.8(1) (C), 129.6 (C), 128.3 (CH), 128.2 (CH), 121.4 (CH), 113.2 (CH), 111.3 (CH), 110.5 (CH), 55.4 (CH_3), 55.1 (CH_3), 54.8 (CH_3). ν_{max} (KBr)/cm^{-1} 3003, 2953, 2835, 1606, 1580, 1505, 1463, 1418, 1254, 1172, 1134, 1027, 871, 816, 787, 766. *m/z* (EI, 70 eV) 270 (100%, $M^{+\bullet}$), 255 (27).

Concentration of fraction B [R_F 0.2(8)] afforded compound **57**[25] (23.6 mg, 5%) as a white crystalline solid, mp 136–137°C (lit.[25] 135–137°C) (Found: $M^{+\bullet}$ 270.1252. $C_{17}H_{18}O_3$ requires $M^{+\bullet}$ 270.1256). δ_H (300 MHz, $CDCl_3$) 7.42 (2H, d, *J* 8.8), 7.04–6.99 (2H, complex m), 6.91–6.82 (5H, complex m), 3.93 (3H, s), 3.88 (3H, s), 3.81 (3H, s). δ_H (300 MHz, C_6D_6) 7.37 (2H, d, *J* 8.8), 7.04–7.00 (4H, complex m), 6.82 (2H, d, *J* 8.8), 6.62 (1H, d, *J* 8.8), 3.46 (3H, s), 3.41 (3H, s), 3.32 (3H, s). δ_C (75 MHz, $CDCl_3$) 159.0 (C), 149.0 (C), 148.5 (C), 130.7 (C), 130.2 (C), 127.4 (CH), 126.3(1) (CH), 126.2(8) (CH), 119.4 (CH), 114.0 (CH), 111.1 (CH), 108.4 (CH), 55.9 (CH_3), 55.8 (CH_3), 55.3 (CH_3). ν_{max}(KBr)/cm^{-1} 1607, 1514, 1264, 1226, 1173, 1153, 1140, 1024, 956, 839, 815. *m/z* (EI, 70 eV) 270 (100%, $M^{+\bullet}$), 255 (27).

*2,3,6-Trimethoxyphenanthrene (**32**)*

Air was bubbled through a magnetically stirred solution of *cis*-stilbene **56** (20.6 mg, 0.0763 mmol) in diethyl ether (35 mL) and dichloromethane (1 mL) for 10 min. A catalytic amount of iodine (2 mg) was then added and the reaction mixture was irradiated for 2 h with a medium pressure Hg vapour lamp. The crude product was then concentrated on silica and submitted to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate elution). Concentration of the relevant fractions (R_F 0.2) gave the title phenanthrene **32**[17] (10.5 mg, 51%) as a light-yellow solid, mp 128–129°C (lit.[17] 132–133°C) (Found: $M^{+\bullet}$ 268.1100. $C_{17}H_{16}O_3$ requires $M^{+\bullet}$ 268.1099). δ_H (300 MHz, $CDCl_3$) 7.87 (1H, s), 7.85 (1H, d, *J* 2.5), 7.78 (1H, d, *J* 8.8), 7.58 (1H, d, *J* 8.7), 7.50 (1H, d, *J* 8.7), 7.21 (1H, s), 7.18 (1H, dd, *J* 2.5 and 8.8), 4.10 (3H, s), 4.03 (3H, s), 4.01 (3H, s). δ_C (75 MHz, $CDCl_3$) 158.1 (C), 149.3 (C), 149.0 (C), 130.9 (C), 130.1 (CH), 127.5 (C), 126.1 (C), 124.9 (CH), 124.1 (C), 123.6 (CH), 115.3 (CH), 108.2 (CH), 103.8 (CH), 103.2 (CH), 56.0 (CH_3), 55.9 (CH_3), 55.5 (CH_3). ν_{max} (KBr)/cm^{-1} 1622, 1608, 1513, 1463, 1267, 1218, 1201, 1160, 1102, 1032, 862, 835. *m/z* (EI, 70 eV) 268 (100%, $M^{+\bullet}$), 253 (8), 225 (14), 182 (16), 139 (15).

*X-Ray Crystallographic Study on Compound **54***

Crystal Data

$C_{18}H_{16}O_5$, *M* 312.32, *T* 200(1) K, monoclinic, space group $P2_1/a$, *Z* 4, *a* 7.1178(2), *b* 13.6458(4), *c* 15.9051(5) Å, β 95.471(2)°, *V* 1537.79(8) $Å^3$, D_x 1.349 g cm^{-3}, 3506 unique data ($2\theta_{max}$ 55.0°), 2835 with $I > 3.0\sigma(I)$, *R* 0.051; *Rw* 0.066, *S* 1.68.

Structure Determination

Images were measured on a Nonius Kappa CCD diffractometer ($Mo_{K\alpha}$, graphite monochromator, λ 0.71073 Å) and data extracted using the DENZO package.[26] The structure was solved by direct methods (SIR92).[27] The crystal studied was a 0.688(4) : 0.312 twin. The constrained least-squares refinement program *RAELS2000*[28] was used because it could account for the partial overlap of reflections arising from the twinning perpendicular to c*. Details are given in the deposited material.

Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC number 681077). These data can be obtained free of charge from www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Biological Testing

Cytotoxicity Testing

Stock solutions of the test compounds were prepared at 20×10^{-3} M in neat dimethyl sulfoxide (DMSO) and diluted in tissue culture medium (T-C) containing 100×10^{-6} M Trappsol(R) to assist solubilization. Dose–response studies of the compounds were carried out from 0.16 to 20×10^{-6} M (final concentration) in 96-well T-C plates. The cells were incubated for 72 h at 37°C in a 5% CO_2 incubator. Inhibition of cell proliferation by the test compounds was determined by measuring conversion of Alamar-Blue fluorescent dye at excitation/emission 544/590 nm with a BMG FluoStar plate reader.

Anti-angiogenic Testing

An in vitro angiogenesis assay was used in this study to assess the anti-angiogenic activity of the different compounds. The procedure used rat aorta fragments and is based on a procedure previously described by Brown et al.[20] using human placenta vessel fragments. Thoracic aortas were excised from 3- to 9-month-old female Fischer rats, rinsed in Hanks balanced salt solution containing 2.5 μg mL^{-1} amphotericin B (Sigma, St Louis, MO, USA), cleaned of periadventitial fibroadipose tissue and cross-sectioned at 1 mm intervals. The vessel fragments were also freed of residual clots. Dissecting and sectioning of the vessels was performed with the aid of a dissecting microscope.

Assays were performed in 48-well culture plates (Costar, Cambridge, MA, USA). Five hundred microlitres of 3 mg mL^{-1} fibrinogen (bovine plasma, Calbiochem, La Jolla, CA, USA) in serum-free Medium 199 (InVitrogen, Carlsbad, CA, USA) was added to each well with 5 μg mL^{-1} of aprotinin in phosphate buffered saline (PBS, Sigma) to prevent fibrinolysis by the vessel fragments. One vessel fragment was placed in the centre of each well and 15 μL of thrombin (50 NIH U mL^{-1} in 0.15 M NaCl: EC 3.4.21.5 bovine plasma: Sigma) was added and mixed rapidly with the fibrinogen. Fibrin gel formation usually occurred within 30 s and ideally the vessel fragment remained suspended in the centre of the gel and centre of the well.

Immediately after the embedding of the vessel fragments in fibrin gels, 0.5 mL per well of medium M199, supplemented with 20% fetal calf serum (Sigma), 0.1% ε-aminocaproic acid (Sigma), 1% L-glutamine (100×10^{-3} M), 1%-amphotericin B (fungizone 250 μg mL^{-1}, Sigma), and 0.6% gentamycin (40 μg mL^{-1} in serum-free M199, David Bull Laboratories, Melbourne, Australia), was added. Each test compound (10 mg mL^{-1}, dissolved in DMSO) was added to the medium (maximum final concentration of test compound 100 μg mL^{-1}) and each treatment was performed in six wells. Control cultures received medium that contained 1% DMSO but without any test compound. Vessels were cultured at 37°C in 5% CO_2 in air for 5 days and the medium, with or without test compound, was changed on day 4. Vessel growth was quantified manually under 40× magnification on day 5, with growth being estimated as the percentage of the field (×40) around the vessel fragment that was occupied by vessel outgrowths.

Acknowledgements

We thank the Institute of Advanced Studies for financial support including the provision of a PhD Scholarship to MOS. Dr Paul Savage of CSIRO Molecular Science (Melbourne) is thanked for providing an authentic sample of the alkaloid cryptopleurine (**1**). CRP and AB are supported by an NHMRC Program grant.

References

[1] (a) E. Gellert, N. V. Riggs, *Aust. J. Chem.* **1954**, *7*, 113.
(b) E. Gellert, *Aust. J. Chem.* **1956**, *9*, 489.

[2] X. F. Cai, X. Jin, D. Lee, Y. T. Yang, K. Lee, Y.-S. Hong, J.-H. Lee, J. J. Lee, *J. Nat. Prod.* **2006**, *69*, 1095. doi:10.1021/NP060081Y

[3] For a useful summary of the biological activities as well as the synthesis of these types of alkaloids see: Z. Li, Z. Jin, R. Huang, *Synthesis* **2001**, 2365. doi:10.1055/S-2001-18703

[4] N. K. Hart, S. R. Johns, J. A. Lamberton, *Aust. J. Chem.* **1968**, *21*, 2579.

[5] For a useful commentary on related systems see: D. Staerk, A. K. Lykkeberg, J. Christensen, B. A. Budnik, F. Abe, J. W. Jaroszewski, *J. Nat. Prod.* **2002**, *65*, 1299. doi:10.1021/NP0106384 and references cited therein.

[6] (a) G. G. Trigo, J. Alvarez-Builla, M. M. Söllhuber Kretzer, *An. Quim.* **1978**, *74*, 523. (*Chem. Abstr.* **1978**, *89*, 163824)
(b) G. G. Trigo, M. M. Söllhuber Kretzer, M. T. Grande, *An. Quim.* **1979**, *75*, 985. (*Chem. Abstr.* **1980**, *93*, 8350)
(c) G. G. Trigo, E. Gálves, M. M. Söllhuber, *J. Heterocycl. Chem.* **1979**, *16*, 1625.
(d) G. G. Trigo, E. Gálvez, M. M. Söllhuber, *J. Heterocycl. Chem.* **1980**, *17*, 69.
(e) S. Foldeak, P. Hegyes, *Tetrahedron* **1980**, *36*, 641. doi:10.1016/0040-4020(80)88006-9
(f) T. M. Bargar, J. K. Dulworth, M. C. Graham, *J. Heterocycl. Chem.* **1984**, *21*, 261.
(g) Y. N. Mukerjee, S. P. Gaur, P. C. Jain, N. Anand, *Ind. J. Chem.* **1985**, *24B*, 985.
(h) M. T. Grande, G. G. Trigo, M. M. Söllhuber, *J. Heterocycl. Chem.* **1986**, *23*, 929.
(i) D. Berkes, P. Netchitaïlo, J. Morel, B. Decroix, *Synth. Commun.* **1998**, *28*, 949. doi:10.1080/00397919808003063
(j) C.-W. Yang, T.-H. Chuang, P.-L. Wu, W.-H. Huang, S.-J. Lee, *Biochem. Biophys. Res. Commun.* **2007**, *354*, 942. doi:10.1016/J.BBRC.2007.01.065

[7] S. Foldeak, *Tetrahedron* **1971**, *27*, 3465. doi:10.1016/S0040-4020(01)97758-0

[8] M. G. Banwell, M. O. Sydnes, *Aust. J. Chem.* **2004**, *57*, 537. doi:10.1071/CH03292

[9] (a) J. Griggs, J. C. Metclaf, R. Hesketh, *Lancet Oncol.* **2001**, *2*, 82. doi:10.1016/S1470-2045(00)00224-2
(b) K. Gaukroger, J. A. Hadfield, L. A. Hepworth, N. J. Lawrence, A. T. McGown, *J. Org. Chem.* **2001**, *66*, 8135. doi:10.1021/JO015959Z
(c) A. Cirla, J. Mann, *J. Nat. Prod. Rep.* **2003**, *20*, 558. doi:10.1039/B306797C and references cited therein.
For recent reviews regarding medicinal chemistry studies around combretastatin A4 (CA-4) and its analogues see:
(d) G. C. Tron, T. Pirali, G. Sorba, F. Pagliai, S. Busacca, A. A. Genazzani, *J. Med. Chem.* **2006**, *49*, 3033. doi:10.1021/JM0512903

(e) A. Chaudhary, S. N. Pandeya, P. Kumar, P. P. Sharma, S. Gupta, N. Soni, K. K. Verma, G. Bhardwaj, *Mini Rev. Med. Chem.* **2007**, *7*, 1186. doi:10.2174/138955707782795647

[10] M. F. A. Adamo, V. K. Aggarwal, M. A. Sage, *Synth. Commun.* **1999**, *29*, 1747. doi:10.1080/00397919908086162

[11] (a) A. J. Liepa, R. E. Summons, *J. Chem. Soc., Chem. Commun.* **1977**, 826. doi:10.1039/C39770000826
(b) A. J. Liepa, *Chem. Aust* **1999**, *66*(*9*), 25.
(c) For a general discussion on the use of vanadium reagents in organic synthesis see: T. Hirao, *Chem. Rev.* **1997**, *97*, 2707. doi:10.1021/CR960014G

[12] K. Oishi, K. Kurosawa, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 179. doi:10.1246/BCSJ.53.179

[13] D. O. Shaha, K. N. Trivedi, *Ind. J. Chem.* **1976**, *14B*, 1009.

[14] E. Martínez, J. C. Estévez, R. J. Estévez, L. Castedo, *Tetrahedron* **2001**, *57*, 1981. doi:10.1016/S0040-4020(01)00041-2

[15] B. Halton, A. I. Maidment, D. L. Officer, J. M. Warnes, *Aust. J. Chem.* **1984**, *37*, 2119.

[16] J. E. Nordlander, F. G. Njoroge, *J. Org. Chem.* **1987**, *52*, 1627. doi:10.1021/JO00384A053

[17] H. Pande, D. S. Bhakuni, *J. Chem. Soc., Perkin Trans. 1* **1976**, 2197. doi:10.1039/P19760002197

[18] H. Hamamoto, G. Anilkumar, H. Tohma, Y. Kita, *Chem. Eur. J.* **2002**, *8*, 5377. doi:10.1002/1521-3765(20021202)8:23<5377::AID-CHEM5377>3.0.CO;2-H

[19] (a) S. M. Kupchan, A. J. Liepa, V. Kameswaran, R. F. Bryan, *J. Am. Chem. Soc.* **1973**, *95*, 6861. doi:10.1021/JA00801A071
(b) A. J. Liepa, R. N. Nearn, D. M. J. Wright, *Aust. J. Chem.* **2004**, *57*, 473. doi:10.1071/CH03177

[20] K. J. Brown, S. F. Maynes, A. Bezos, D. J. Maguire, M. D. Ford, C. R. Parish, *Lab. Invest.* **1996**, *75*, 539.

[21] (a) C. R. Parish, C. Freeman, K. J. Brown, D. J. Francis, W. B. Cowden, *Cancer Res.* **1999**, *59*, 3433.
(b) L. M. Khachigian, C. R. Parish, *Cardiovasc. Drug Rev.* **2004**, *22*, 1.

[22] M. B. Hadimani, J. Hua, M. D. Jonklaas, R. J. Kessler, Y. Sheng, A. Olivares, R. P. Tanpure, A. Weiser, J. Zhang, K. Edvardsen, R. R. Kane, K. G. Pinney, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1505. doi:10.1016/S0960-894X(03)00206-3

[23] A. Rauk, D. F. Tavares, M. A. Khan, A. J. Borkent, J. F. Olson, *Can. J. Chem.* **1983**, *61*, 2572. doi:10.1139/V83-443

[24] T. Poettinger, W. Wiegrebe, *Arch. Pharm. (Weinheim)* **1981**, *314*, 240. doi:10.1002/ARDP.19813140310

[25] M. Cushman, D. Nagarathnam, D. Gopal, H.-M. He, C. M. Lin, E. Hamel, *J. Med. Chem.* **1992**, *35*, 2293. doi:10.1021/JM00090A021

[26] DENZO-SMN. Z. Otwinowski, W. Minor, *Processing of X-Ray Diffraction Data Collected in Oscillation Mode*, in *Methods in Enzymology, Volume 276: Macromolecular Crystallography, Part A* **1997**, pp. 307–326 (Eds C. W. Carter Jr, R. M. Sweet) (Academic Press: New York, NY).

[27] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, *27*, 435. doi:10.1107/S002188989400021X

[28] A. D. Rae, *RAELS2000* **2000** (Australian National University: Canberra, Australia).