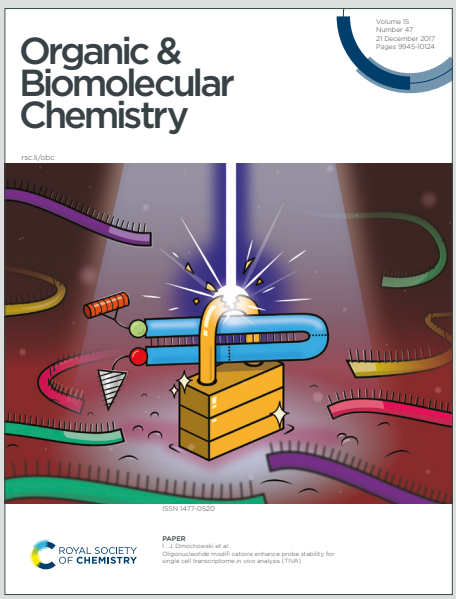
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: C. McErlean, R. T. Rodger and M. S. Graham, *Org. Biomol. Chem.*, 2019, DOI: 10.1039/C9OB01364D.



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DOI: 10.1039/C9OB01364D

ARTICLE

Hyperconjomer stereocontrol of cationic polyene cyclisations

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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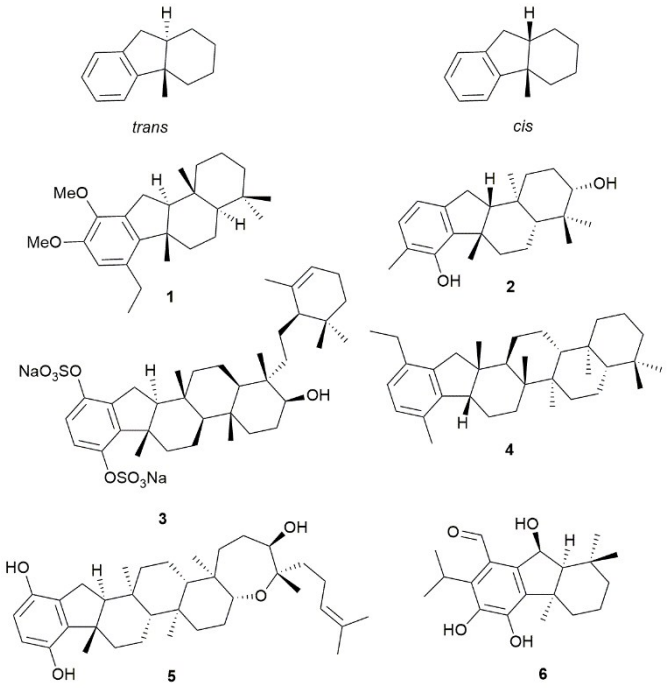
Polyene cyclisations are a powerful method for the direct generation of molecular complexity. This paper describes the use of computational methods to investigate the stereoselectivity of cationic polyene cyclisations of geranylbenzene derivatives. The outcomes highlight the different reactivity of hyperconjomers during the key Friedel-Crafts alkylation step, and informed a successful strategy for the synthesis of (±)-taiwaniaquinone G with improved levels of stereoselectivity.

Introduction

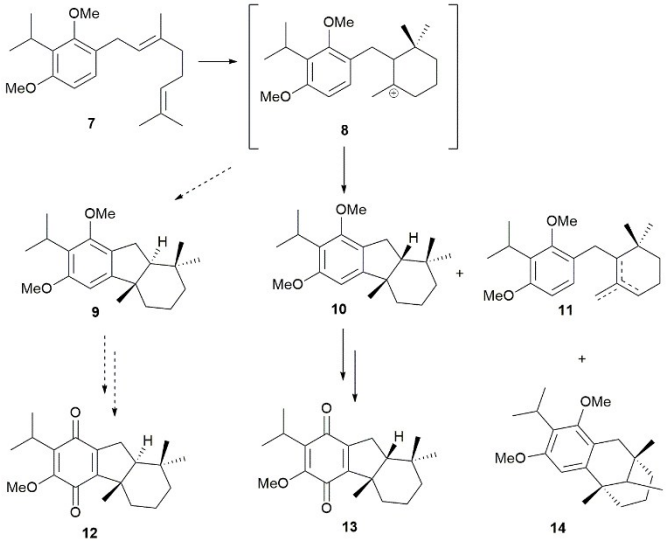
Interrogation of the Super Natural II online database[1,2] of over 325,000 natural products reveals more than 60 compounds containing a hexahydro-1*H*-fluorene fragment, with the majority possessing a 4a-methyl substituent. Of these, only 14 possess a *cis*-configured 6,5-ring fusion, while the majority possess a *trans*-configured ring fusion. Illustrative examples are depicted in Figure 1. Many synthetic approaches to this structural motif been reported,[3, 4] and include ring contraction,[5-7] electrocyclisation,[8] palladium-catalysed cyclisation,[9-11] and Nazarov cyclisation/hydrogenation.[12-15] Arguably the most straight-forward approach employs a cascade cationic polyene cyclisation[16-20] that terminates with a Friedel-Crafts alkylation.[21-24].

We have previously reported a concise total synthesis of the *cis*-fused compound (±)-5-*epi*-taiwaniaquinone G (**13**) using a cationic polyene cyclisation (Scheme 1).[25] In opposition to our expectations, cyclisation of the geranylbenzene derivative **7** favoured production of the *cis*-fused hexahydro-1*H*-fluorene

Figure 1. Prominent hexahydro-1*H*-fluorene containing natural products



Scheme 1. Previous synthesis of *epi*-taiwaniaquinone G (**13**).[25]



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Electronic Supplementary Information (ESI) available: ^{1}H and ^{13}C NMR spectra, and cartesian coordinates of all stationary points. See DOI: 10.1039/x0xx00000x

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product **10** in a ratio of ~7:1. Isolation of alkene by-product **11** and rearranged product **14** unambiguously demonstrated that the cascade cyclisation, Friedel-Crafts sequence proceeded in a step-wise fashion rather than being a concerted process. The stereochemistry of the ring fusion was set during the Friedel-Crafts-type arylation of the carbocation intermediate **8**. Targeting a total synthesis of the *trans*-fused natural product taiwaniaquinone G (**12**),[12, 26, 27] we planned to alter the stereoselectivity of this cyclisation by redesigning the cyclisation substrate. In order to understand the structural elements that would result in the desired *trans*-configured product **9** being generated, we used computational methods to examine cationic cyclisations that produced the hexahydro-1*H*-fluorene architecture. In contrast to the large number of computational studies on cationic polyene cyclisations leading to 6,6,6-fused ring systems,[28-40] studies on the corresponding cyclisations giving 6,5,6-fused ring systems are absent from the literature. The outcomes of our investigations are reported below, and they informed our subsequent synthetic studies and enabled a polyene cyclisation with enhanced stereoselectivity for the rapid synthesis of (±)-taiwaniaquinone G (**12**).

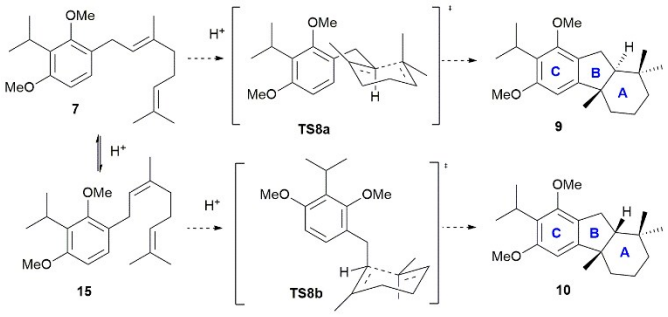
Results and discussion

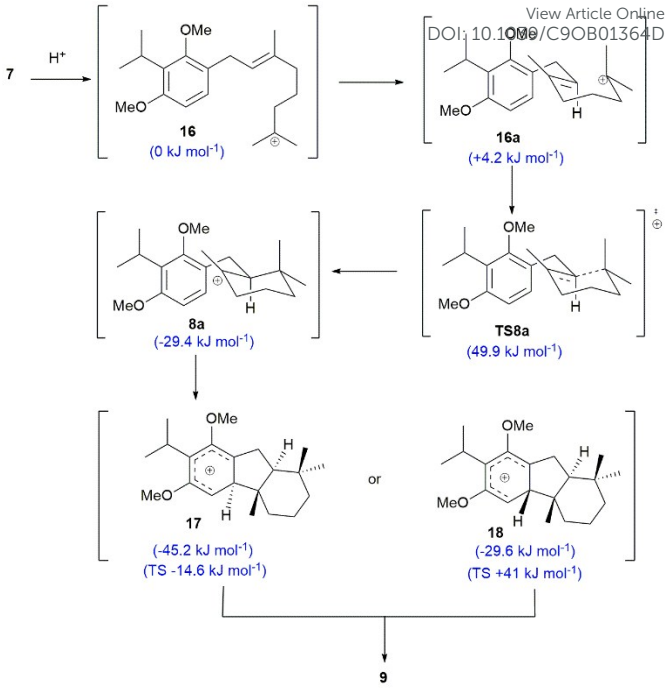
Cis-selective cyclisation: (±)-*epi*-Taiwaniaquinone G

At the outset of our previous synthesis of *epi*-taiwaniaquinone G (**13**)[25] we had anticipated that the initial cyclisation would proceed via a chair-like transition state **TS8a** to give an intermediate that was appropriately arranged for Friedel-Crafts reaction to deliver the desired *trans*-configured ring fusion **9** (Scheme 2). The fact that we obtained predominantly the *cis*-configured product **10** led us to consider the alternative cyclisation of the *Z*-configured alkene **15**. Given the acidic reaction conditions under which the cyclisations were performed, it was conceivable that the *E*-configured alkene **7** isomerised into the Z-alkene **15** prior to cyclohexane formation. Our work began by performing DFT gas phase calculations (ω-B97X-D/6-31G*) to examine the intermediates and transition states leading to the possible products **9** and **10**.

In the first instance, protonation of the distal olefin of the *E*-configured compound **7** gave the cationic species **16** (Scheme3).

Scheme 2. Proposed cyclisations of alkene diastereomers **7** and **15**.



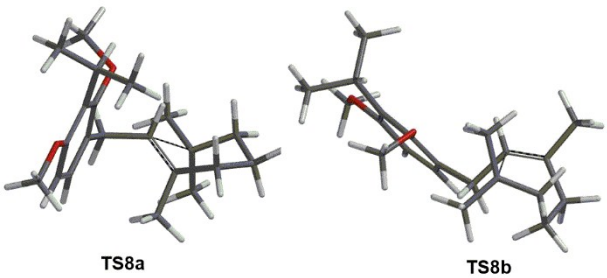


Scheme 3. Cyclisation of *E*-configured alkene **7**.

All calculated ΔG values reported in Schemes 3 and 4 are relative to this cation. In analogy to the work of Antoniotti, Dunach and co-workers who studied cycloisomerisation reactions of polyenes,[41] our calculations showed that A-ring cyclisation of **16** occurred from conformer **16a** through a chair-like transition state (**TS8a**) (Scheme 3 and Figure 2) to give the cationic intermediate **8a**. The benzylic unit in intermediate **8a** occupied the equatorial position and was indeed oriented to undergo reaction with the proximal cation to give either **17** or **18**. The transition state leading to **17** was substantially lower in energy and would, as desired, deliver the *trans*-configured product **9**.

The protonated cyclisation precursor **19** from the *Z*-configured alkene **15** was 17 kJ/mol higher in energy than the corresponding *E*-configured compound **16** (Scheme 4). Cyclisation of the reactive conformer **19a** occurred through a boat-like transition state **8b**. Consequently it possessed a higher activation barrier than cyclisation of the *E*-configured substrate. The lowest energy product cation **8b** from this reaction was appropriately oriented to be trapped by the aromatic ring to give **20** or **21**, with both intermediates leading to the *cis*-configured product **10**.

Figure 2. Comparison of **TS8a** and **TS8b**.



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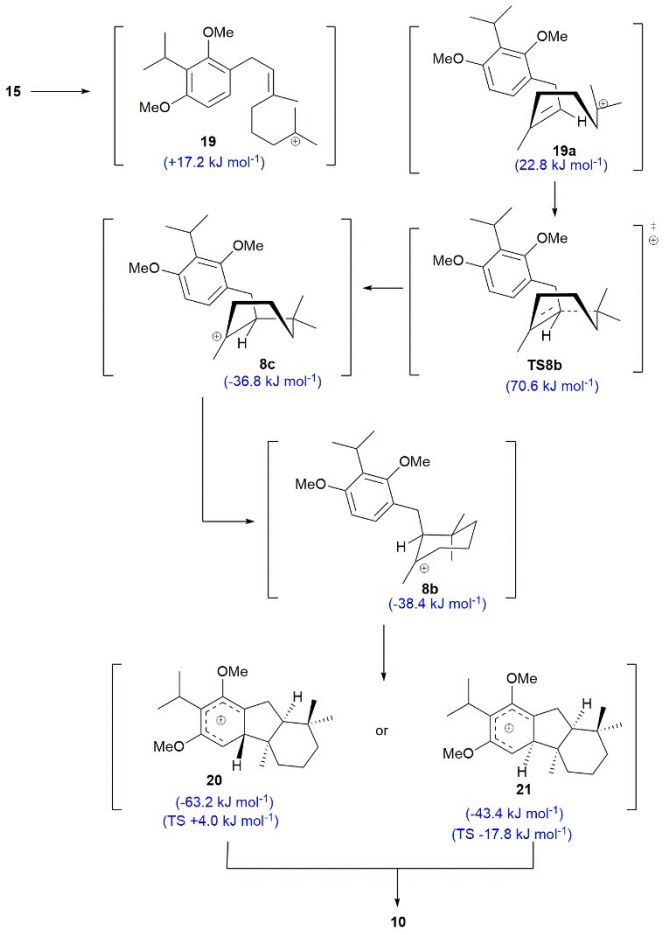


Scheme 4. Cyclisation of *Z*-configured alkene **15**.

Clearly the product ratio that was observed experimentally (~7:1 *cis*:*trans*) from cyclisation of the geranylbenzene

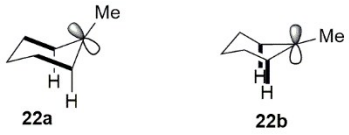


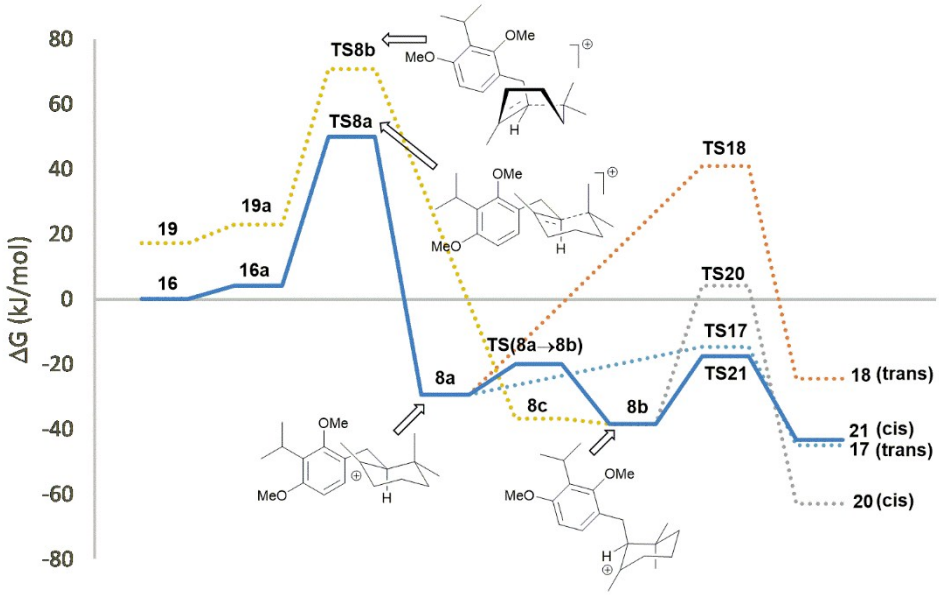
Figure 3. Hyperconjomers of 1-methylcyclohexyl cation.

derivative **7** did not arise by selective cyclisation of the *E*- and *Z*-configured alkenes **7** and **15** respectively.[25] Indeed, *in situ* NMR monitoring of a mixture of the *E*-configured alkene **7** and various acids did not provide evidence for the generation of the *Z*-configured compound **15**. It was therefore likely that the intermediate cations **8a** and **8b** were able to interconvert faster than the subsequent Friedel-Crafts alkylation.

In 1996, Sorensen and co-workers predicted that 1-methylcyclohexyl cations could exist in two isomeric forms, **22a** and **22b** (Figure 3), that they termed hyperconjomers.[42] These isomers differ by the mode of hyperconjugative stabilization. In **22a** electron density is provided by C-C bonds within the cyclohexyl framework, whereas in **22b** the stabilization results from orbital overlap of the axial C-H bonds and the cation. The calculated barrier for the interconversion of 1-methylcyclohexyl cation hyperconjomers was less than 4 kJ/mol.[42] Nonetheless, in 2001 Sorensen, Schleyer and co-workers obtained definitive spectroscopic evidence for the existence of hyperconjomers,[43] and they suggested that the different hyperconjugation modes may govern pathways for nucleophilic attack.† In 2011, Lepore and co-workers reported the first example of hyperconjomers affecting stereocontrol over an intermolecular reaction.[44, 45]

The cationic intermediates **8a** and **8b** (Schemes 3 and 4) are isomeric cyclohexyl cations, i.e. hyperconjomers, with intermediate **8b** being 9.4 kJ/mol more stable. The consequence of hyperconjomer interconversion being a low energy process,‡

Figure 4. Reaction profile for the cyclisation of compound **7**.

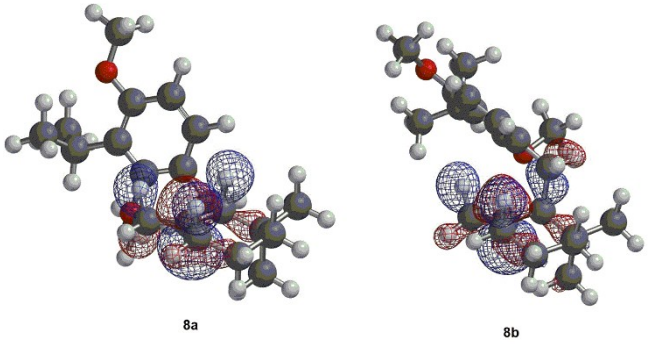


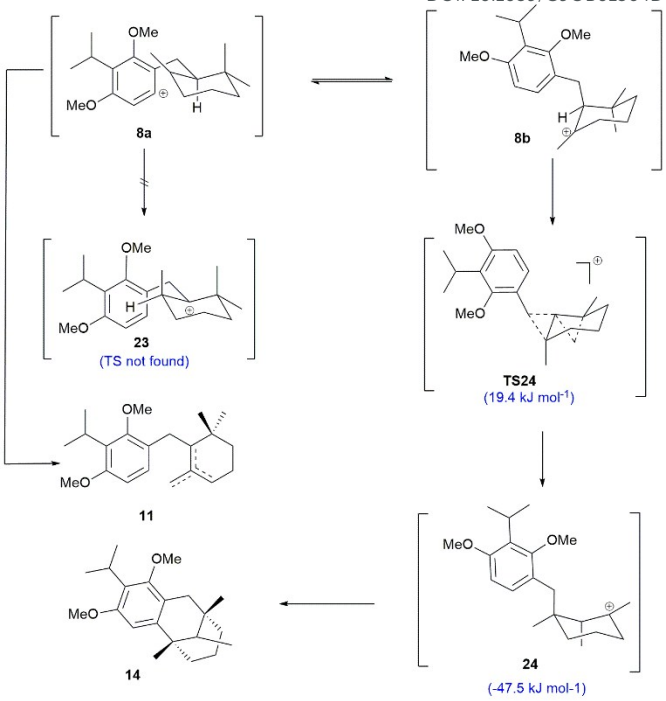
is a Curtin-Hammett scenario in which the product ratio for the cyclisation of compound **7** was determined by the relative differences in activation energies ($\Delta\Delta G^{\ddagger}$) of the Friedel-Crafts alkylation step. The transition state leading to the *cis*-configured intermediate **21** was lower in energy than the corresponding transition state leading to the *trans*-configured intermediate **17** ($\Delta\Delta G^{\ddagger}$ = 3.2 kJ/mol). It is pertinent to remember that solvent effects were not included in our calculations. A reaction profile that accounts for the observed product distribution is depicted in Figure 4. Protonation of the *E*-configured alkene **7** gave **16** which cyclised via a chair-like transition state (**TS8a**) to give intermediate **8a**. Slow Friedel-Crafts reaction allowed for a conformational ring-flip to give **8b** which positioned the benzyl unit in an axial orientation. Subsequent cyclisation preferentially gave the *cis*-configured intermediate **21**, which underwent elimination to give the *cis*-configured product **10**. The minor amount of *trans*-configured product **9** resulted from cyclisation of initially formed intermediate **8a** via the *trans*-configured intermediate **17**.

The relative stability of the axially oriented isomer **8b** can be rationalised by noting the enhanced hyperconjugative stabilisation of the carbocation. Figure 5 shows the LUMO plots for intermediates **8a** and **8b** and clearly illustrates that the relatively electron-rich bond connecting the benzylic carbon to the cyclohexyl ring provides enhanced stabilisation of the carbocation when it is axially oriented, lengthening the benzylic bond from 1.547 Å to 1.604 Å. Although Sorensen, Schleyer and co-workers have shown that the magnitude of this hyperconjugative stabilisation can be affected by solvent,[43] neither explicit nor continuum solvent models were included in our calculations.

Interconversion of intermediates **8a** and **8b** also accounted for the observed by-products of the reaction, compounds **11** and **14** (scheme 5). The initial product of cyclisation **8a** possessed an axially oriented hydrogen atom. The barrier for [1,2-H] migration to give **23** was too great for the process to be feasible.‡‡ Elimination to form alkenes **11** was therefore preferred. In contrast, intermediate **8b** possessed a benzyl unit in the axial position. The corresponding type II dyotropic rearrangement to give **24** had an activation barrier of only 19 kJ/mol.[46, 47] Due to stabilisation of developing positive charge on the benzylic carbon, this was a concerted asynchronous process in which the [1,2]-benzyl shift was significantly

Figure 5. LUMO plots of intermediates 8a and 8b.





Scheme 5. Reaction pathway to rearranged compounds **11** and **14**.

advanced before the [1,2]-methyl shift occurred.[48, 49] Cation **24** that underwent Friedel-Crafts alkylation, leading to product **14**.

The preferential formation of the *cis*-configured product **10** and the rearranged product **14** is the direct result of the existence of hyperconjomers **8a** and **8b** and their different reactivity in an intramolecular Friedel-Crafts reaction. As such, this work represents a clear vindication of Sorensen and Schleyer's prediction that hyperconjugation modes may dictate pathways for nucleophilic attack.

In terms of designing a synthetic strategy toward (±)-taiwaniaquinone G (**12**) (Scheme 1), the outcomes of these computational studies suggested that one way to maximise production of the desired *trans*-fused product **10**, would be to slow the rate of interconversion of the two intermediate cations **8a** and **8b**. In related work, Antoniotti, Dunach and co-workers concluded that interconversion of cationic intermediates was the stereo-determining step in the cyclisation of polyenes to give 6,6-fused systems.[41] To investigate if this was synthetically practicable we examined some related *trans*-selective cyclisations. For these investigations, barriers to cyclisation were calculated directly from the reactive conformations of the intermediate cyclohexyl cations. We recognize that for slow Friedel-Crafts reactions, elimination to the alkene and subsequent re-protonation is a viable route to alternative products.[22] However, given the high energy associated with protonation of an alkene in the gas phase, we have elected to study only the direct conversion of cation intermediates into products.

***Trans*-selective polyene cyclisations**

During their synthesis of the marine sponge metabolite pelorol (**25**), Andersen and co-workers utilised a cationic cyclisation of

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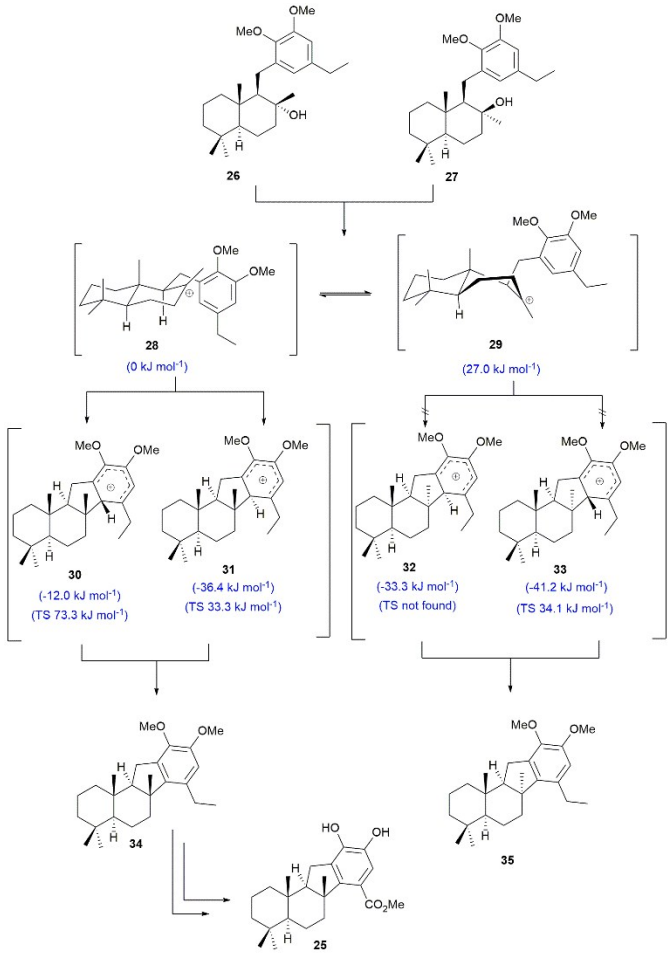
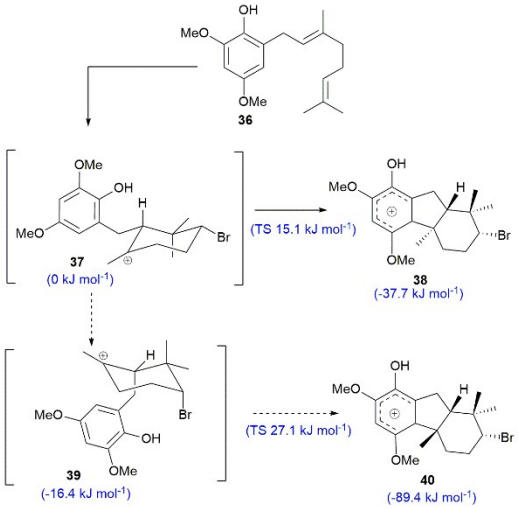


Scheme 6. Andersen's synthesis of pelorol (**25**)

the scarleolide derivatives **26** and **27** to give exclusively the *trans*-fused hexahydro-1*H*-fluorene product **34** (Scheme 6).[24] Gas phase DFT calculations (ω-B97X-D/6-31G*) show that the reaction of both starting alcohols **26** and **27** with acid produces the cationic species **28**, which possesses an equatorially oriented benzylic group and can engage in a Friedel- Crafts alkylation to give the *trans*-configured compounds **30** and **31**, with the transition state leading to **31** being lower in energy and ultimately leading to the observed product **34**. Intermediate **28** is significantly lower in energy than the corresponding hyperconjomer **29**, which possesses an axially oriented benzyl unit. Intermediate **29** could undergo reaction to give compounds **32** and **33**, which both lead to the non-observed but thermodynamically more stable product **35** (see ESI). In that instance, the preference for the *trans*-configured products arises by virtue of intermediate **28** being substantially more populated during the reaction course. While the intermediates in the previous discussion possessed a very flexible cyclohexyl ring, in this instance hyperconjugative stabilization of the cation **29** is over-ridden by ring-strain and developing 1,3-diaxial steric interactions.

Clearly, in the pelorol case, the conformational constraints imposed by the presence of a *trans*-decalin ring system controls the stereochemical course of the Friedel-Crafts alkylation. However, translating this to the design of a synthetic strategy to



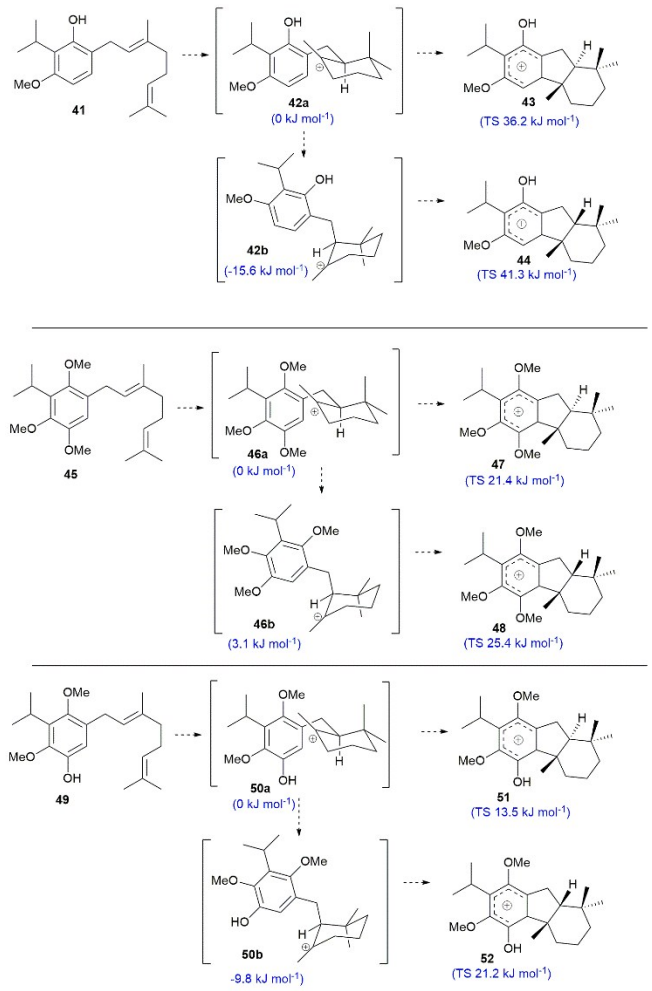
Scheme 7. Yamamoto's brominative cyclisation of geranylbenzene derivative **36**.

(±)-taiwaniaquinone G (**12**) would necessitate the introduction of a cleavable fused-ring system mimicking the decalin framework. Such an approach would add significant complexity to any proposed synthesis.

Recently, Yamamoto and co-workers reported an enantioselective brominative polyene cyclisation of geranylbenzene derivative **36** that gave exclusively the *trans*-configured product (Scheme 7).[50] We wondered if the large bromine atom was acting as a (readily cleavable) conformational constraint that slowed hyperconjomer interconversion. Our calculations show that initial cyclization of **36** gives intermediate **37**, which possesses an equatorially oriented benzyl group.§ This intermediate could undergo Friedel-Crafts cyclisation to give the observed *trans*-fused compound **38**. Compound **38** bears striking similarity to intermediate **8a** in our previous (±)-*epi*-taiwaniaquinone G (**13**) synthesis (see Scheme 3). The ring-flipped hyperconjomer **39**, in which the benzyl unit is axially oriented, is significantly lower in energy than **37**. Therefore, the stereoselectivity of this process was not be the result of the bromine atom acting as a conformational constraint that biased the system towards conformer **37**, but was due to the difference in activation energies leading to the *cis* and *trans*-configured compounds **38** and **40**. Friedel-Crafts cyclisation of intermediate **39**, which would lead to the *cis*-fused intermediate **40**, had a relatively high activation barrier, and was not experimentally observed.[51]§§

From a synthetic design viewpoint, it was instructive that Yamamoto and co-workers reported that the cyclisation of **36** to give **38** was extremely facile and occurred at low temperature (-78 ˚C). We wondered if it was possible for *trans*-selective cyclisations from non-favoured hyperconjomers to be affected by the nucleophilicity of the aromatic ring, which could lead to Friedel-Crafts transition states being engaged (at low temperature) before hyperconjomer interconversion occurred. Overman has previously shown the requirement for a nucleophilic arene to avoid alkene by-products,[22] but the effect

on stereochemistry was not discussed. Relating this to our



proposed synthetic strategy toward (±)-taiwaniaquinone G (**12**),

Scheme 8. Possible cyclisation precursors.

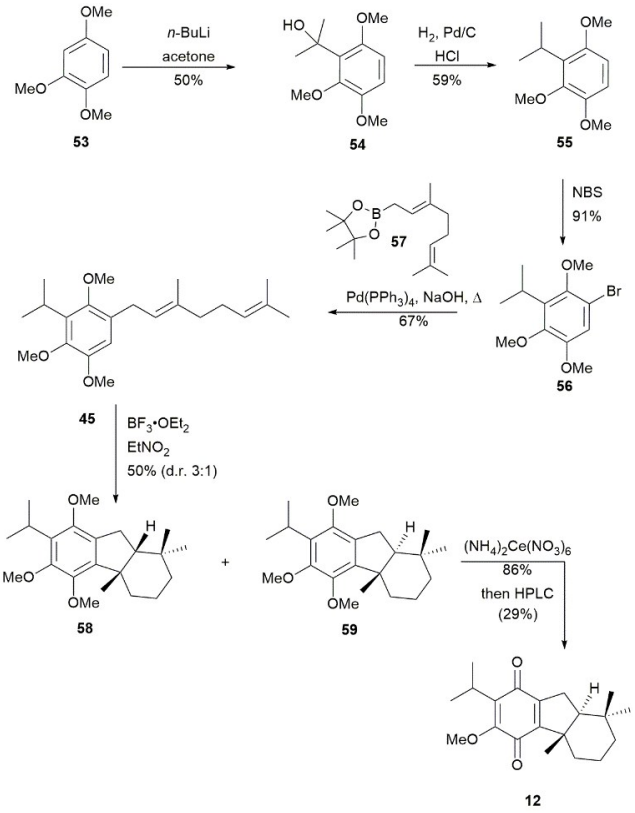
the incorporation of a more electron-rich aromatic ring into the cyclising polyene may bias the reaction towards generation of the desired *trans*-fused hexahydro-1*H*-fluorene. But how nucleophilic did the aromatic ring have to be? Our next step was to survey the energetic requirements leading to *trans*-fused ring systems.

Surveying the energetic requirements for *trans*-selective cyclisation

We computationally examined the cyclisation of three possible precursors for the stereoselective generation of the *trans*-fused hexahydro-1*H*-fluorene system corresponding to (±)-taiwaniaquinone G (**12**). As shown in Scheme 8, phenol **41**, which differs from our previous substrate only by the absence of a methyl group, is not predicted to be nucleophilic enough to undergo fast Friedel-Crafts alkylation as the activation barrier from **42** to **43** is large compared to the corresponding barrier from **8a** to **17** ($\Delta G^{\ddagger}$ 14.8 kJ/mol, see Scheme 3). Indeed, Friedel-Crafts cyclisation is not on the lowest energy pathway, and cyclisation involving the phenolic oxygen is favoured in that instance. The trimethoxy compound **45** is predicted to display improved *trans:cis* selectivity in the Friedel-Crafts alkylation step. Despite the hyperconjomers **46a** and **46b** being energetically similar and the barrier to Friedel-Crafts cyclisation being higher that for **8a** to **17** (Scheme 3), the difference in activation energies ($\Delta\Delta G^{\ddagger}$ = 4 kJ/mol) for the *trans*- and *cis*-fused intermediates **47** and **48** (lowest energy transition states) favours the desired stereochemistry. And finally, the most electron-rich cyclisation precursor **49** is predicted to have the highest selectivity and lowest activation barrier for the desired *trans*-selective cyclisation, and one that is broadly comparable with Yamamoto's *trans*-selective cyclisation. Substrates **45** and **49** were therefore considered to be appropriate compounds to use for the total synthesis of taiwaniaquinone G (**12**).

Total synthesis of (±)-taiwaniaquinone G

As shown in Scheme 9, compound **45** was generated by modifiying the procedure described by Bisai and co-workers.[15] 1,2,4-Trimethoxybenzene (**53**) was subjected to *ortho*-lithiation and reacted with acetone to give **54**. Dehydration and *in situ* transfer hydrogenation gave **55**, which was regioselectively brominated to give **56**. Suzuki cross-coupling with the previously described geranylboronate **57**[25] afforded the desired cyclisation precursor **45** and set the stage for the cationic polyene cyclisation.



Scheme 9. Synthesis of substrate **45**, and (±)-taiwaniaquinone G (**12**).

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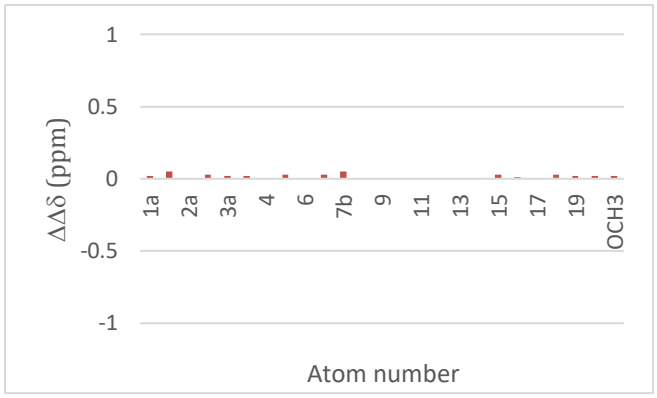
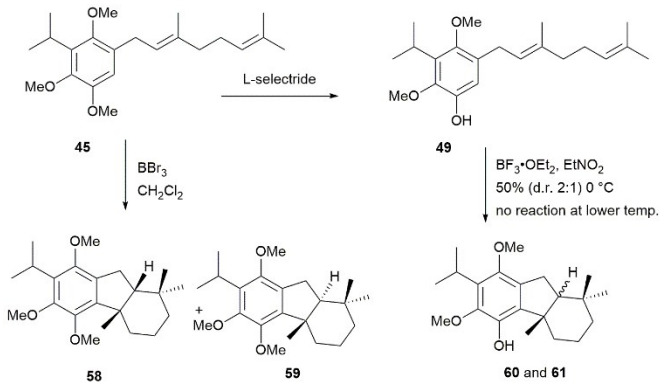


Figure 6. Comparison of ^{1}H NMR chemical shifts of natural[27] and synthetic taiwaniaquinone G (**12**).

Cyclisation of **45** with either $BF_3{\cdot}OEt_2$ or $ClSO_3H$ at room temperature produced a mixture of the desired *trans*-configured hexahydro-1*H*-fluorene **59** in a 1:3 ratio with the non-desired *cis*-isomer **58**. The product ratio from the cyclisation reaction was a significant improvement on the 1:7 ratio observed in our previous work, but was not as high as anticipated. The discrepancy between the levels of selectivity observed in the cyclisation versus the level expected from the calculations shown in Scheme 8 (predicted ratio = 5:1) may be due to the gas phase nature of those calculations. Nonetheless, subsequent oxidation of the 1:3 mixture and HPLC separation provided (±)-taiwaniaquinone G (**12**) (21% after oxidation and separation), which was spectroscopically identical to the reported data for the isolated compound (Figure 6 and ESI).[27]

We sought to further increase the selectivity of the Friedel-Crafts alkylation by employing the phenol **49** (Scheme 10). As such, compound **45** was treated with BBr_3 in an attempt to effect the *in situ* generation of phenol **49**. Disappointingly, the rate of BBr_3-mediated polyene cyclisation proved to be greater than the rate of demethylation, and the same 1:3 product ratio of desired compound **59** to non-desired **58** was returned. Selective demethylation of **45** was accomplished by the action of L-Selectride™ in the manner described by Majetich and co-workers.[52] Cyclisation of phenol **49** at 0 °C delivered the desired *trans*-fused product **61** as the minor product in a slightly improved 1:2 mixture of with the *cis*-fused diastereomer **60**. Frustratingly, conducting the reaction at lower temperatures, which were expected to return higher levels of *trans*-stereoselectivity, resulted in no cyclisation. In the cationic polyene cyclisation of geranylbenzene derivatives such as those discussed above, the highest energy barrier corresponds to the initial cyclisation to form the A-ring (see Figure 3), and this failed to occur at low temperatures.

Scheme 10. Synthesis and cyclisation of phenol substrate **48**.



Experimental

General methods and materials

DFT calculations were carried out with Spartan'16 or Spartan'18 programs. Geometries and energies of transition states and intermediates were obtained using the range separated hybrid generalized gradient approximation functional ωB97X-D with the 6-31G* basis set.[53] The ωB97X-D functional has been shown to have comparable performance to the M06-2X functional and superior performance to the more commonly used B3LYP functional.[53-55] The vibrational frequencies of stationary points were inspected to ensure that they corresponded to minima on the potential energy surface and the Intrinsic Reaction Coordinate (IRC) method was used to confirm that they corresponded to motion along the reaction coordinate. All relative energies (ΔG) are reported uncorrected at 298 K in kJ/mol (see ESI).

2-(2,3,6-Trimethoxyphenyl)propan-2-ol (54). 1,2,4-Trimethoxybenzene (980 mg, 5.80 mmol) and *N*,*N*,*N*,*N*-tetramethylethylenediamine (1.0 mL, 6.8 mmol) were dissolved in tetrahydrofuran (58 mL) and cooled to −78 °C. *n*-Butyllithium (2.0 M in hexanes; 3.0 mL, 6.0 mmol) was added dropwise and the mixture was stirred for 1 h, warming to room temperature. The reaction mixture was again cooled to −78 °C, then acetone (1.3 mL, 1.8 mmol) was added dropwise and the mixture was stirred for 2 h, warming to room temperature. Saturated aqueous ammonium chloride solution (20 mL) was added, then the mixture was extracted with ethyl acetate (3 × 30 mL) and the combined extracts were dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with 10% ethyl acetate in hexanes to give **55** as a yellow oil (650 mg, 2.9 mmol, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.76 (1 H, *d*, *J* = 9.0 Hz), 6.63 (1 H, *d*, *J* = 9.0 Hz), 5.89 (1 H, *s*), 3.85 (3 H, *s*), 3.81 (6 H, *s*), 1.66 (6 H, *s*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6, 148.2, 147.5, 130.2, 110.7, 107.5, 74.4, 61.5, 56.4, 31.4 ppm. MS (ESI) *m/z* (%): 249 ([M + Na]$^{+}$, 100).

2-Isopropyl-1,3,4-trimethoxybenzene (55). Compound **54** (2.0 g, 8.9 mmol) and palladium-on-carbon (10 wt%, 380 mg, mmol) were taken up in ethanol (60 mL) and hydrochloric acid (10 M; 2.0 mL) was added. The reaction mixture was stirred for 5 h under an atmosphere of hydrogen, then the reaction mixture was sparged before opening to the air and filtering over Celite, eluting with ethanol (50 mL). The solvent was removed *in vacuo*, then the residue was dissolved in ether (50 mL), washed with saturated aqueous sodium bicarbonate solution

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DOI: 10.1039/C9OB01364D

(50 mL) and dried over magnesium sulfate. The solvent was removed *in vacuo* to give **55** as a yellow oil (1.1 g, 5.3 mmol, 59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.69 (1 H, *d*, *J*= 8.9 Hz), 6.56 (1 H, *d*, *J* = 8.9 Hz), 3.81 (3 H, *s*), 3.80 (3 H, *s*), 3.76 (3 H, *s*), 3.54 (1 H, *septet*, *J* = 7.1 Hz), 1.31 (6 H, *d*, *J* = 7.1 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1, 148.0, 147.5, 131.1, 109.7, 106.5, 61.1, 56.3, 56.0, 25.3, 21.3 ppm. MS (ACPI): *m/z* (%): 210 ([M]$^+$, 100).

1-Bromo-3-isopropyl-2,4,5-trimethoxybenzene (56). To a solution of **55** (240 mg, 1.20 mmol) in dichloromethane (10 mL) was added *N*-bromosuccinimide (210 mg, 1.20 mmol). The reaction mixture was stirred at room temperature for 2 h, then the solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel, eluting with 5% ether in hexanes to give **56** as a yellow oil (300 mg, 1.0 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.93 (1 H, *s*), 3.83 (3 H, *s*), 3.81 (3 H, *s*), 3.77 (3 H, *s*), 3.46 (1 H, *septet*, *J* = 7.2 Hz), 1.33 (6 H, *d*, *J* = 7.2 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.2, 149.1, 148.2, 136.9, 114.3, 110.9, 61.7, 60.9, 56.2, 26.9, 21.9 ppm. MS (ESI): *m/z* (%): 311/313 ([M+Na]$^+$, 30).

(*E*)-1-(3,7-Dimethylocta-2,6-dien-1-yl)-3-isopropyl-2,4,5-trimethoxybenzene (45). Compound **56** (610 mg, 2.1 mmol), geranyl pinacol boronate[25] (560 mg, 2.1 mmol), powdered sodium hydroxide (1.0 g, 25 mmol) and tetrakis-(triphenylphosphine) palladium(0) (230 mg, 0.20 mmol) were dissolved in toluene (30 mL) and water (7.5 mL), placed under an argon atmosphere and sparged with argon for 10 min. The reaction mixture was heated to 90 °C for 20 h, then cooled to room temperature, diluted with hexane (30 mL) and water (20 mL), separated and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with 30% dichloromethane in hexanes to give **45** as a yellow oil (485 mg, 1.4 mmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.59 (1 H, *s*), 5.31 (1 H, *tq*, *J* = 7.1 Hz, 1.4 Hz), 5.12 (1 H, *tt*, *J* = 6.6 Hz, 1.3 Hz), 3.83 (3 H, *s*), 3.80 (3 H, *s*), 3.67 (3 H, *s*), 3.44 (1 H, *septet*, *J* = 7.2 Hz), 3.35 (2 H, *d*, *J* = 7.1 Hz), 2.19-2.03 (4 H, *m*), 1.73 (3 H, *s*), 1.67 (3 H, *s*), 1.59 (3 H, *s*), 1.35 (6 H, *d*, *J* = 7.2 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.8, 149.6, 146.9, 136.3, 134.9, 131.6, 129.5, 124.3, 123.3, 111.2, 61.9, 60.8, 55.9, 39.9, 28.3, 26.9, 26.2, 25.8, 22.2, 17.8, 16.3 ppm. HRMS (ESI): calcd. for $C_{22}H_{34}O_3Na^+$ 369.240002; found 369.24044. IR (film): ν_{max}= 2955, 2931, 2872, 2833, 1591, 1482, 1454, 1426, 1343, 1253, 1226, 1111, 1042, 1015, 981, 846, 789, 720 cm^{-1}.

7-Isopropyl-5,6,8-trimethoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-fluorene (58 and 59). Compound **45** (300 mg, 0.87 mmol) was dissolved in nitroethane (9 mL) and cooled to 0 °C. Boron trifluoride etherate (0.020 mL, 0.15 mmol) was added and the reaction mixture was stirred for 18 h at room temperature. Saturated aqueous sodium bicarbonate solution (5 mL) was added, then the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, the solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel, eluting with 35% dichloromethane in hexanes to give desired *trans*-fluorene **59** as an inseparable mixture of diastereomers with the *cis* isomer **58** (1:3 *trans:cis*) (150 mg, 0.43 mmol, 50%). Compound **59** *(some peaks obscured):* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.81 (3 H, *s*), 3.75 (3 H, *s*), 3.39 (1 H, *septet*, *J* = 7.2 Hz), 2.74 (1 H, *dd*, *J* = 14.3, 6.3 Hz), 2.55 (1 H, *dd*, *J* = 14.3, 12.9 Hz), 2.39 (1 H, *m*), 1.73 (1 H, *dd*, *J* = 12.9, 6.3 Hz), 1.58–1.53 (2 H, *m*), 1.24–1.17 (1 H, *m*), 1.12 (3 H, *s*), 1.03 (3 H, *s*), 0.96 (3 H, *s*) ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.1, 150.5, 145.5, 144.9, 131.8, 129.4, 59.7, 47.0, 41.4, 36.8, 33.3, 33.1, 27.2, 21.1, 20.3, 20.1 ppm. Compound **58***:* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (3 H, *s*), 3.79 (3 H, *s*), 3.72 (3 H, *s*), 3.39 (1 H, *septet*, *J* = 7.2 Hz), 2.83 (1 H, *dd*, *J* = 15.4, 7.9 Hz), 2.62 (1 H, *dd*, *J* = 15.4, 11.3 Hz), 1.81 (1 H, *dd*, *J* = 11.3, 7.9 Hz), 1.80–1.74 (1 H, *m*), 1.61 (3 H, *s*), 1.46–1.42 (1 H, *m*), 1.42–1.36 (2 H, *m*), 1.32(6 H, *d*, *J* = 7.2 Hz), 1.29–1.24 (2 H, *m*), 1.13 (3 H, *s*), 0.93 (3 H, *s*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.0, 150.3, 146.4, 144.3, 132.3, 128.9, 60.5, 60.4, 56.6, 47.2, 35.2, 35.0, 32.2, 31.3, 31.1, 25.6, 25.5, 22.24, 22.20, 18.7 ppm. HRMS (ESI): calcd. for $C_{22}H_{34}O_3Na^+$ 369.24002; found 369.24035.

Taiwaniaquinone G (12). The diastereomeric mixture of **58** and **59** (120 mg, 0.35 mmol) was dissolved in acetonitrile (3 mL) and cooled to 0 °C. A solution of ceric ammonium nitrate (950 mg, 1.7 mmol) in water (1 mL) was added dropwise and stirred 1 h, warming to room temperature. Saturated aqueous sodium sulfite solution (10 mL) was added and the mixture was extracted with ether (2 × 20 mL), dried over anhydrous sodium sulfate, and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with 25% dichloromethane in hexanes to give taiwaniaquinone G and 5-epi-taiwaniaquinone G as a mixture (94 mg, 0.30 mmol, 86%). A diasteromerically pure sample of taiwaniaquinone G was obtained by preparative HPLC (water/acetonitrile 25:75 isocratic, Sunfire C_{18}) (20 mg, 21%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.93 (3 H, *s*), 3.22 (1 H, *septet*, *J* = 7.1 Hz), 2.59 (1 H, *dd*, *J* = 6.4, 16.8 Hz), 2.31 (1 H, *dd*, *J* = 12.7, 16.8 Hz), 2.30–2.26 (1 H, *m*), 1.82–1.71 (1 H, *m*), 1.64 (1 H, *dd*, *J* = 6.4, 12.7 Hz), 1.65–1.59 (1 H, *m*), 1.51–1.48 (1 H, *m*), 1.45 (1 H, *dd*, *J* = 4.2, 12.8 Hz), 1.21 (3 H, *d*, *J* = 7.1 Hz), 1.20 (3 H, *d*, *J* = 7.1 Hz), 1.14 (1 H, *dd*, *J* = 4.8, 13.9), 1.08 (3 H, *s*), 0.99 (3 H, *s*), 0.93 (3 H, *s*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.4, 182.4, 156.3, 153.9, 148.5, 137.3, 61.2, 58.4, 48.2, 41.2, 35.0, 33.2, 32.9, 27.2, 24.7, 21.2, 20.8, 20.7, 19.8, 18.2 ppm. HRMS (ESI): calcd. for $C_{20}H_{28}O_3Na^+$ 339.19307; found 339.19331.

(*E*)-5-(3,7-Dimethylocta-2,6-dien-1-yl)-3-isopropyl-2,4-dimethoxyphenol (49). Compound **45** (350 mg, 1.0 mmol) was dissolved in tetrahydrofuran (10 mL) and L-selectride (1.0 M in THF; 3.0 mL, 3.0 mmol) was added. The reaction mixture was heated to reflux and stirred for 24 h, then cooled to room temperature and saturated aqueous ammonium chloride solution (20 mL) was added. The reaction mixture was extracted with ether (3 × 30 mL) and the combined organic layers were dried over magnesium sulfate and solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 30% dichloromethane in hexanes to give **49** as a yellow oil (160 mg, 0.48 mmol, 48%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.53 (1 H, *s*), 5.62 (1 H, *s*), 5.32–5.26 (1 H, *m*), 5.18–5.08 (1 H, *m*), 3.83 (3 H, *s*), 3.67 (3 H, *s*), 3.42 (1 H, *septet*),

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3.32 (2 H, *d*, *J* = 7.2 Hz), 2.20–2.02 (4 H, *m*), 1.73 (3 H, *s*), 1.67 (3 H, *s*), 1.60 (3 H, *s*), 1.38 (6 H, *d*, *J* = 7.2 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.9, 143.3, 136.1, 131.6, 127.2, 124.8, 124.4, 123.7, 109.1, 62.0, 56.3, 39.9, 28.1, 26.9, 26.0, 25.8, 20.9, 17.8, 16.3 ppm. HRMS (ESI): calcd. for $C_{21}H_{32}O_3Na^+$ 355.22437; found 355.22483. IR (film): ν_{max} = 3539, 2956, 2925, 2853, 1486, 1455, 1421, 1339, 1288, 1242, 1213, 1103, 1039, 987, 847, 780, 457 cm^{-1}.

7-Isopropyl-6,8-dimethoxy-1,4,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-fluoren-5-ol (60) and (61). Compound **49** (50 mg, 0.15 mmol) was dissolved in nitroethane (1.5 mL) and boron trifluoride etherate (0.020 mL, 0.15 mmol) was added. The reaction was stirred at -5 °C for 3 days, then saturated aqueous sodium bicarbonate solution (5 mL) was added and the reaction mixture was warmed to room temperature, then extracted with ether (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, eluting with 25% dichloromethane in hexanes to give an inseparable 2:1 mixture of diastereomers **60** and **61** as a yellow oil (11 mg, 0.033 mmol, 22%).Compound **60** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.51 (1 H, *s*), 3.75 (3 H, *s*), 3.71 (3 H, *s*), 3.40 (1 H, *septet*, *J* = 7.1 Hz), 2.81 (1 H, *dd*, *J* = 15.1, 7.7 Hz), 2.62 (1 H, *dd*, *J* = 15.1, 10.9 Hz), 1.80 (1 H, *dd*, *J* = 10.9, 7.3 Hz), 1.66–1.61 (2 H, *m*), 1.60 (3 H, *s*), 1.47–1.41 (2 H, *m*), 1.34 (6 H, *dd*, *J* = 7.1, 6.0 Hz), 1.30–1.24 (2 H, *m*), 1.11 (3 H, *s*), 0.91 (3 H, *s*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.9, 147.2, 143.1, 140.4, 125.4, 125.1, 62.2, 60.8, 57.5, 47.3, 35.4, 35.3, 32.4, 30.9, 29.9, 25.6, 25.4, 21.3, 21.2, 18.9 ppm. HRMS (ESI): calcd. for $C_{21}H_{32}O_3Na^+$ 355.22437; found 355.22483. IR (film): ν_{max} = 3523, 2930, 2868, 1456, 1422, 1336, 1260, 1100, 1037, 887 cm^{-1}. Compound **61** (partial data; some peaks obscured): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.46 (1 H, *s*), 3.77 (3 H, *s*), 3.73 (3 H, *s*), 3.40 (1 H, *septet*, *J* = 7.1 Hz), 2.72 (1 H, *dd*, *J* = 14.1, 6.2 Hz), 2.54 (1 H, *dd*, *J* = 14.1, 12.5 Hz), 2.35–2.30 (1 H, *m*), 1.70 (1 H, *dd*, *J* = 12.5, 6.2 Hz), 1.54–1.48 (2 H, *m*), 1.32 (6 H, *d*, *J* = 7.2 Hz), 1.23–1.14 (2 H, *m*), 1.12 (3 H, *s*), 1.03 (3 H, *s*), 0.96 (3 H, *s*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6, 146.9, 144.6, 139.1, 125.5, 124.9, 62.3, 60.8, 60.1, 47.1, 41.2, 36.9, 33.5, 33.2, 31.0, 27.0, 21.4, 21.3, 20.5, 20.2 ppm.

Conclusions

These studies have shown that the cationic polyene cyclisation of geranylbezene derivatives proceed through an initial chair-like transition state to give an intermediate possessing an equatorially disposed aromatic unit. Although this intermediate is appropriately oriented to undergo a *trans*-selective Friedel-Crafts alkylation, the existence of hyperconjomers (cyclohexyl cation isomers) and their different reactivity in the ensuing intramolecular Friedel-Crafts reaction, results in the preferential production of the *cis*-fused 5,6-ring system. This outcome is in line with Sorensen and Schleyer's prediction that hyperconjugation modes may dictate reaction pathways.[42, 43] In the absence of conformational constraints (such as in the pelorol case),[24] the stereochemical outcome of the Friedel-Crafts reaction is intimately linked to the nucleophilicity of the aromatic ring. Compounds with poorly nucleophilic arenes will not engage in the desired cyclisation and will result in the preferential generation of alkene products.† Compounds with only moderately nucleophilic arenes will cyclise at a rate that is slow enough to allow the conformational interconversion of the intermediate hyperconjomers, and will proceed through the lowest energy transition state. This was the case for our previous synthesis of (±)-*epi*-tawaniaquinone G (**13**) (Scheme 1).[25] Compounds possessing a highly nucleophilic arene will undergo fast Friedel-Crafts reaction and result in the *trans*-fused product, as seen in the work of Yamamoto (Scheme 7).[50]

We used this information to design and execute a concise total synthesis of the (±)-taiwaniaquinone G (**12**) that employed a cationic polyene cyclisation of a geranyl derivative containing a trimethoxyphenyl unit. As anticipated, the cyclisation of this more electron rich substrate exhibited improved *trans*-stereoselectivity at the 5,6-ring fusion. Although we were able to access the desired natural product, the level of stereoselectivity could not be further enhanced for this particular polyene cyclisation due to the energetic requirements for forming the A-ring. Nonetheless, we anticipate that judicious choice of aromatic ring will enable the stereoselective synthesis of other *cis*- and *trans*-fused natural products possessing a hexahydro-1*H*-fluorene fragment.

Acknowledgements

RTR and MG are grateful for Australian Government Research Training Program Scholarships. RTR also acknowledges receipt of a Bruce Veness Chandler Research Support Scholarship.

Conflicts of interest

There are no conflicts to declare.

Notes and references

† Similar isomeric structures are predicted for polyene cyclisations that yield 6,6-fused ring systems. In those instances the issue is complicated by efficient π-cation interactions that push the cyclisations toward concerted bond-forming events. See references 28–40.

‡ Semi-empirical calculations suggest an energy barrier of ~ 13 kJ/mol for interconversion of these hyperconjomers. Semi-empirical estimates for the interconversion of all hyperconjomers in the manuscript appear in the ESI, and are broadly similar.

‡‡ Determined using semi-empirical calculations. as we were unable to locate a valid transitions state using DFT.

§ We were unable to locate a transition state for the corresponding concerted polyene cyclisation.

§§ We are also cognizant of the fact that Yamamoto's work involved a spectacularly bulky counter-ion, which may affect the stereoselectivity of the reaction by forming a tight ion-pair. For an example of this see reference 51.

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