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A route to the 9,10-secosteroid astrogorgiadiol featuring a key sp^2–sp^3 Suzuki type cross-coupling

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ABSTRACT

The described semi-synthetic route differs from the previously published approaches by an original C-7–C-8 disconnection. The kinetic enol triflate of Grundmann ketone was chosen as the CD-ring platform on which to couple an A-ring synthon via a challenging sp^2–sp^3 cross-coupling. A range of A-ring synthons was synthesized to allow the investigations of various conditions of metal-catalyzed couplings. Suzuki-type chemistry provided a useful (89% yield) answer. Whereas the last step of the designed route—a regioselective opening of the epoxide obtained from the alkene, product of the coupling reaction—proved more challenging than expected, a hydroboration endgame route completed a formal synthesis of (−)-astrogorgiadiol.

1. Introduction

(−)-Astrogorgiadiol **1**, a 9,10-secosteroid, metabolite isolated from a gorgonian collected in Japan by Fusetani's team in 1989[1] has since been the object of great interest due to its biological potential. Tested in vitro against 16 human tumor related protein kinases, (−)-astrogorgiadiol and related calicoferols and astrogorgols showed inhibitions in the micromolar range against important kinases involved in cancer development.[2] It has also shown unique property of osteopontin downregulation.[3] Since osteopontin plays a key-role in metastatic diseases, such as cancers,[4–6] in demyelinating diseases, such as multiple sclerosis,[7–10] in the development of virulent asthma,[11,12] and in osteoporosis,[13,14] this bioactivity makes astrogorgiadiol a synthetic target of choice.

Hitherto two synthetic disconnections have been proposed (Scheme 1). The group of Taber has been successful in its design of a total synthesis with a Robinson annulation between an enantiomerically pure D-ring synthon (**3**) and an A-ring/C-ring precursor synthon (**2**) as a key step.[15] Two new routes to this latter synthon have since been disclosed: one by Taber's group as an improvement for large scale synthesis,[16] and my own efforts taking advantage of the opening of 6-methoxy-1-tetralol.[17]

The second retrosynthetic analysis proposes a C-6–C-7 disconnection. The route, designed by De Riccardis, is semi-synthetic, using Grundmann ketone, which is converted in the hydrindan **5** in three steps for a key radical coupling with the benzylic iodide **4** obtained in seven steps from 2-methyl-5-nitrobenzoic acid (Scheme 1).[18] Two sets of conditions for the radical coupling were successful but only with 21% yield for Giese–Chatgilialolu's procedure and 28% for Hershberger's procedure. Two more steps allowed the completion of the synthesis.

The moderate yield of this radical reaction has triggered the design of a new retrosynthetic analysis: another semi-synthetic route taking full advantage, like De Riccardis route, of the readily available Grundmann ketone. But instead of the C-6–C-7 disconnection, the proposed analysis features a C-7–C-8 disconnection. The endeavor to perform a sp^2–sp^3 cross-coupling between a CD-ring platform **7** derived from Grundmann ketone and an A-ring synthon **6** obtained from 3-methylanisole was audacious but proved successful as reported in this article.

2. Results and discussion

2.1. CD-ring platforms

The first synthon **11** was obtained in 53% yield starting from the commercially available (+)-vitamin D_3 (Scheme 2). Ozonolysis followed by reduction and reoxidation secured Grundmann ketone (**9**) in very good yield (89%). This procedure was introduced by

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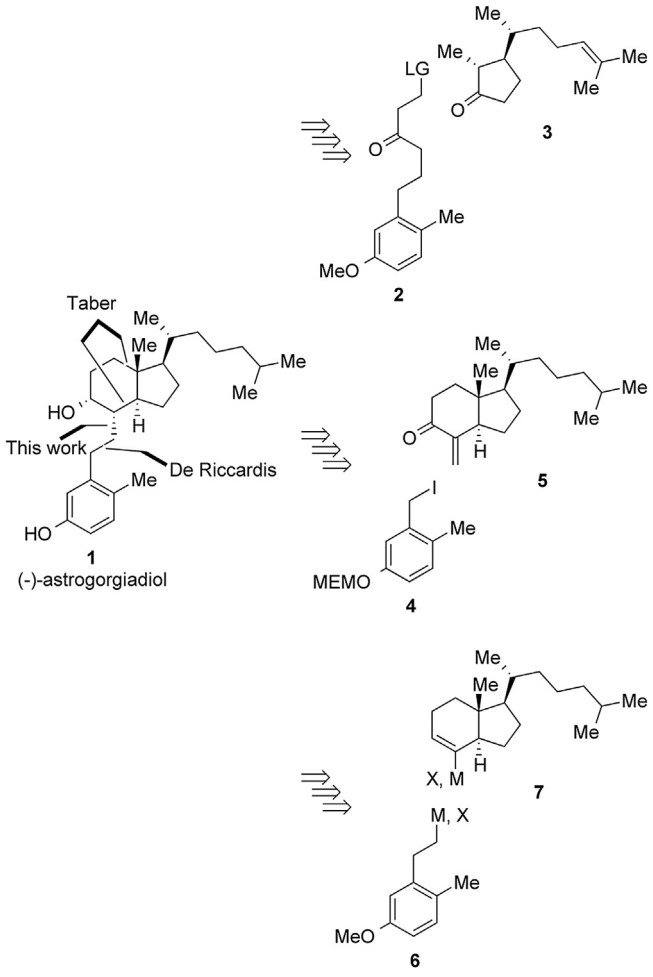
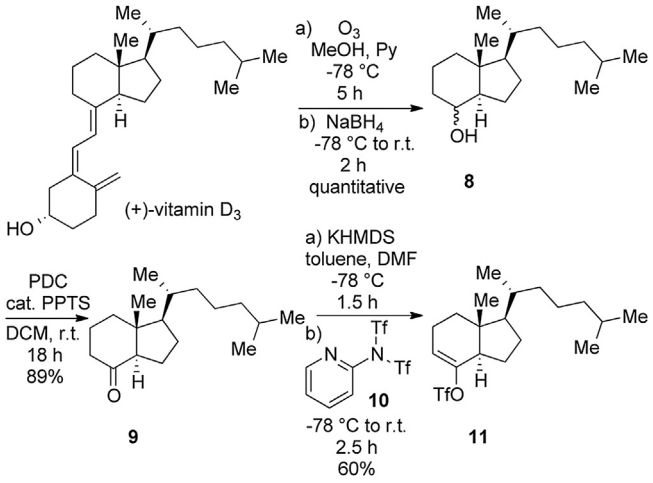


Scheme 1. Retrosynthetic analysis of (−)-astrogorgiadiol.

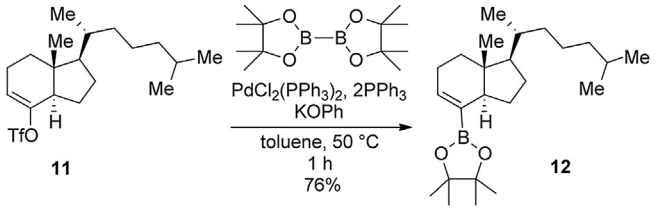
Mouriño et al.,[19] who preferred this sequence over the mere ozonolysis for the easy separation of the product. The kinetic enolate was then prepared using KHMDS at −78 °C and trapped after 2 h with the triflate donor **10** developed in Comins group[20,21] and which is now commercially available. The reaction however proceeds in a maximum of 60% yield whereas other attempted procedures were found to be irreproducible, often leading to the thermodynamic enolate. Notably, the use of phenyl triflimide as



Scheme 2. Synthesis of the CD-ring platform **11**: the kinetic enol triflate of Grundmann ketone.

reported by Mouriño et al.[22,23] and used by other groups[18,24–27] proved capricious in my hands.

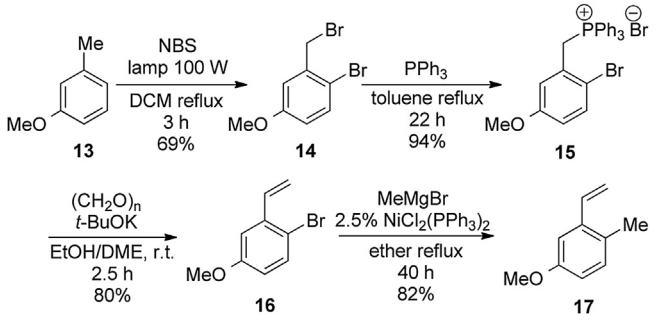
Boronation of the enol triflate **11** following Takagi et al. procedure[28] was successful in securing **12**, an alternative platform for Suzuki-type couplings (Scheme 3). In the ^{13}C NMR spectrum of the unsaturated boronate **12**, the signal corresponding to C-8 is so broad that it is indistinguishable from the baseline. This is due to the quadrupole effect, since the boron resides in an unsymmetrical environment.



Scheme 3. Synthesis of the alternative CD-ring platform **12**: ene boronate derived from the kinetic enol of Grundmann ketone.

2.2. A-Ring coupling partners

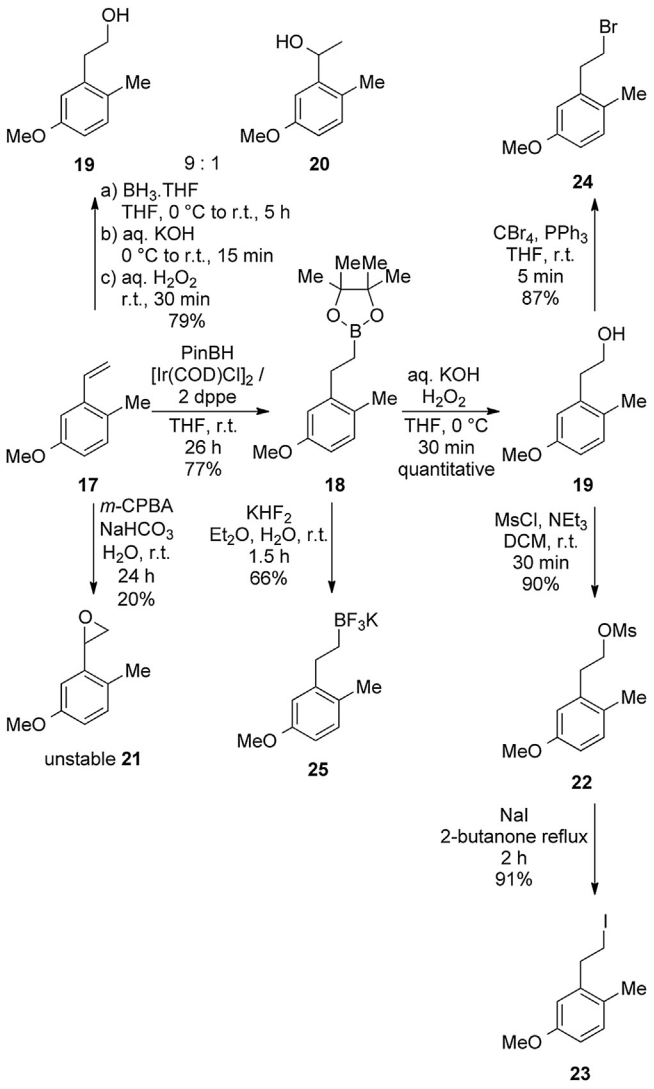
The styrene derivative **17** was obtained via a four-step sequence in 43% yield (Scheme 4). When treated with *N*-bromosuccinimide under the radiation of a 100 W tungsten filament lamp in refluxing dichloromethane, 3-methylanisole **13** led to the dibromo compound **14** as reported by Hoye et al.[29] It has to be noted that two different pathways are involved: radical (Wohl–Ziegler reaction) for the benzylic position and polar (electrophilic aromatic substitution) for the aryl position. The primary bromide **14** could then selectively be converted into the phosphonium salt **15** by treatment with triphenylphosphine in refluxing toluene for 20 h. The latter was then reacted with paraformaldehyde for a Wittig reaction securing the 1-bromo-4-methoxystyrene **16**. Coupling with methylmagnesium bromide in the presence of $NiCl_2(PPh_3)_2$ (Kumada coupling) secured 1-methyl-4-methoxystyrene **17** as a colorless liquid.



Scheme 4. Synthesis of the styrene **17**, precursor of A-ring synthons.

To get hold of phenethyl boronic esters in order to envision Suzuki type couplings, hydroboration of the styrene derivative **17** was to be done. Borane, as expected, led to a mixture of regioisomers. Attempts with pinacol borane or 9-BBN alone failed to provide the desired compound. I then turned to catalyzed hydroboration. The selective hydroboronation of styrene derivatives has recently received a lot of interest. The most commonly used catalyst for catalyzed hydroboration is Wilkinson's catalyst $RhCl(PPh_3)_3$.[30] But this catalyst in the case of styrene favors the boronation on the benzylic position and not on the desired terminal position. The mechanism invokes a η^3-benzylrhodium intermediate[31,32] accounting for the Markovnikov selectivity.

Depending on the catalyst, one intermediate is favored towards the other. Yamamoto et al.[33] compared different catalysts and found that the best procedure to get regiospecificity for the terminal position was the use of $[Ir(COD)Cl]_2$ with 2 equiv of diphenylphosphinoethane as a bidentate ligand. This procedure used with pinacol borane in THF at rt for 26 h secured the boronic ester **18** with total regioselectivity in 77% yield (Scheme 5). The broad signal in ^{13}C NMR at 11.6 ppm is the sign that the carbon C-7 is correctly attached to the boron atom. This peak and the peak at 27.4 ppm replace the peaks at 115.2 ppm and 134.9 ppm, respectively.

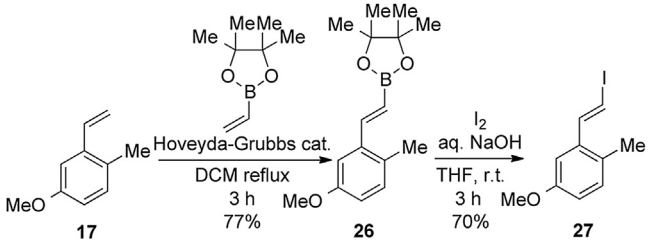


Scheme 5. Synthesis of a range of A-ring synthons from styrene precursor **17**.

Direct conversion of the pinacolic ester **18** into iodide **23** with iodine according to Brown's procedure[34] or with iodine monochloride according to Kabalka's[35] was not successful. The primary alcohol **19** obtained from the styrene derivative was thus identified as an intermediate to secure the desired phenethyl halides. The epoxide **21** obtained from reaction of the styrene **17** with *m*-CPBA was not stable enough to become a suitable precursor for the alcohol **19**. The use of disiamylborane or 9-BBN, which should have secured selectively alcohol **19** from styrene **17**, proved unsuccessful whereas borane was effective but not stereospecific. Flash chromatography was able to separate the 9:1 mixture of the 2 isomers **19** and **20** obtained in 79% yield. Treatment of the pinacolic ester **18** with hydrogen peroxide and potassium hydroxide led to a quantitative formation of the alcohol **19** (both steps could be done in a single reaction vessel) (Scheme 5). Once obtained, the alcohol **19** could be converted into the halide. The iodide **23** was obtained in two steps via a Finkelstein-type procedure.[36] Alcohol **19** was treated with mesyl chloride in the presence of triethylamine in dichloromethane at rt for 30 min, allowing the formation of the mesylate **22** in 90% yield. The mesylate compound **22** was then reacted with sodium iodide in refluxing 2-butanone for 2 h yielding the desired iodide **23** in 91% yield. The bromide **24** was obtained in 87% yield via an Appel reaction[37] by treatment of the primary alcohol **19** with carbon tetrabromide and triphenylphosphine after just 5 min in THF at rt.

I also converted the boronic ester **18** into the potassium fluoroborate **25** according to Molander's procedure[38] in 66% yield (Scheme 5) in order to broaden the number of possible A-ring coupling partners **6** (Scheme 1). The NMR spectra of this ionic compound had to be recorded in D_2O. The ^{13}C NMR signal for C-7 is so broad that it can only be determined using the HMQC experiment and focusing on the area correlated to the ^1H NMR signal of CH_2-7. Compared to the pinacol boronate compound **18**, the signals for pinacol carbons and protons have disappeared. These two elements confirmed that the pinacol boronate **18** had been converted into another ionic boron compound successfully.

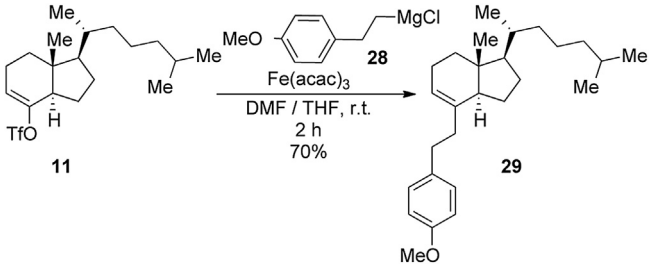
In an effort to diversify the potential coupling partners **6** and in case the sp^2–sp^3 cross-coupling would fail, I envisioned that halostyrene derivatives might be secured using cross-metathesis, motivated by the work of Grubbs.[39] And, to my delight, the styrene derivative **17** reacted smoothly (77% yield) with vinyl pinacolboronate under ruthenium catalysis to provide the unsaturated boronate compound **26** (Scheme 6) and the latter was easily converted (70% yield) to the iodo compound **27**. If I was to consider sp^2–sp^2 cross-coupling instead of sp^2–sp^3 cross-coupling, these two A-ring coupling partners **26** and **27** are easily and efficiently accessible.



Scheme 6. Cross-metathesis of styrene **17** and vinyl pinacolboronate to secure the conjugated boronate **26**, further converted in the β-iodo styrene **27**.

2.3. sp^2–sp^3 cross-coupling

Exploring Fürstner's chemistry,[40,41] the coupling of the CD-ring platform **11** with 4-methoxyphenethylmagnesium chloride **28** was catalyzed by iron(III) acetylacetonate giving **29** in 70% yield (Scheme 7). It is noteworthy that the use of DMF as a cosolvent was necessary and that the use of the suggested THF/NMO mixture as solvent led to no reaction.

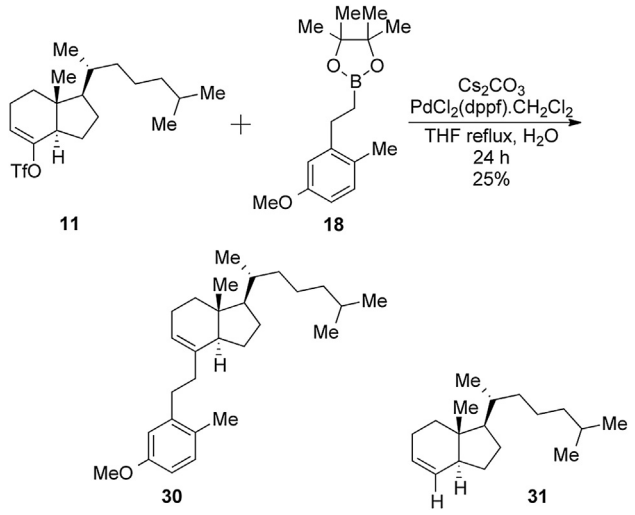


Scheme 7. Iron catalyzed sp^2–sp^3 cross-coupling with model phenethyl Grignard.

Despite this encouraging result and the similarity of **28** to the A-ring synthon **6**, all attempts to perform the two-step one-pot sequence—formation of organozinc, organomagnesium or organolithium starting from **23** or **24** and coupling with iron ($Fe(acac)_3$ for Kumada type reaction[40]), nickel ($NiCl_2(dppe)$ for Kumada type reactions[42]) or palladium ($Pd[P(t\text{-}Bu)_3]_2$ or $Pd(PPh_3)_4$ for Negishi type reactions and organolithium coupling) catalysts remained unsuccessful. Because of the success of the coupling of **28** with **11**, I assume that the conversion of the halide into an organometallic species is the problematic step. Despite my efforts to activate this step (Rieke magnesium activation,[43,44] halogen-magnesium exchange, zinc activation[45]), the strategy did not prove successful. I did not pursue further investigations in this field, hypothesizing that the organometallic I aimed to form could degrade into the benzylic species resulting from an internal rearrangement with the aryl methyl group, species which was not isolated. I, instead, focused my efforts on Stille type and Suzuki–Miyaura type cross-coupling.

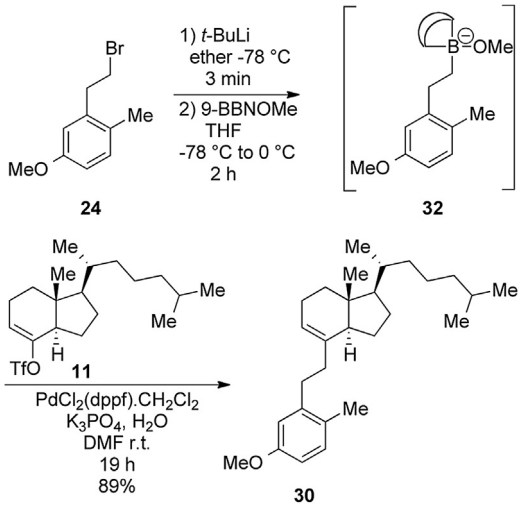
Fouquet et al.[46,47] developed recently a Stille type cross-coupling of activated alkyltin reagents. This coupling requires a hypervalent tin species, which is obtained by reaction of the organic halide with Lappert's stannylene $Sn(N(TMS)_2)_2$. Bromide **24** was thus converted to the hypervalent species using Lappert's stannylene and TBAF in THF but it could not be coupled to triflate **11** under $Pd_2(dba)_3$ catalysis in refluxing dioxane or with additional triphenylarsine ligand in DMF.

With the pinacol boronate **18** in hand, I investigated the possibility of coupling it with the enol triflate **11** via Suzuki–Miyaura type reactions, as the last years have seen lots of progress in this field with the development of new ligands and new methods. The Zhou and Fu procedure[48] with nickel catalyst and bathophenanthroline was unsuccessful. Zou and Falck's method—reported in 2001[49]—consists of the in situ generation of the lithium borate ester derived from an alkyl boronic ester followed by the palladium-catalyzed coupling with an electrophile. One of the successful examples of this reaction is the coupling of *n*-butyl pinacol boronate with 4-*tert*-butylcyclohexenol triflate, which exhibits great similarity to my challenge. Unfortunately, when this procedure was applied to the substrates **11** and **18**, only 15% yield of the desired compound **30** was obtained, the main product **31** arising from a hydride coupling. I therefore tried the same procedure with an addition of lithium bromide, which inhibited the reaction. Molander's conditions[38] allowed the formation of 25% of the desired product **30**, the major product being again the product of reduction **31** (Scheme 8). A coupling attempt with the phenylethyl potassium fluoroborate derivative **25** led again to the reduction product **31** as the major product.



Scheme 8. Low-yielding Suzuki coupling with phenethyl boronate **18**.

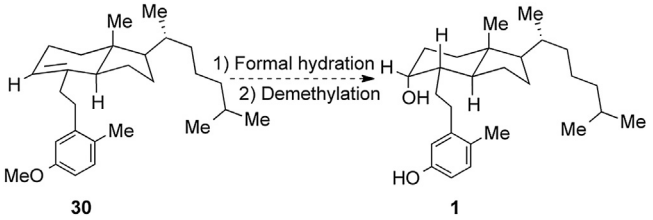
The breakthrough was the use of slightly modified Marshall's conditions[50] starting from the bromide **24** and converting it to the methoxy boronate **32** through an addition of 9-BBN–OMe before reacting it with the triflate **11** (Scheme 9). These conditions yielded **30** in 89% yield along with an inseparable impurity (~10%), which could be removed in the next step. This proved to be a reliable, efficient way to achieve this key step of the synthesis.



Scheme 9. High-yielding sp^2–sp^3 cross-coupling of the CD-ring platform **11** with the phenethyl bromide A-ring synthon **24**.

2.4. Endgame

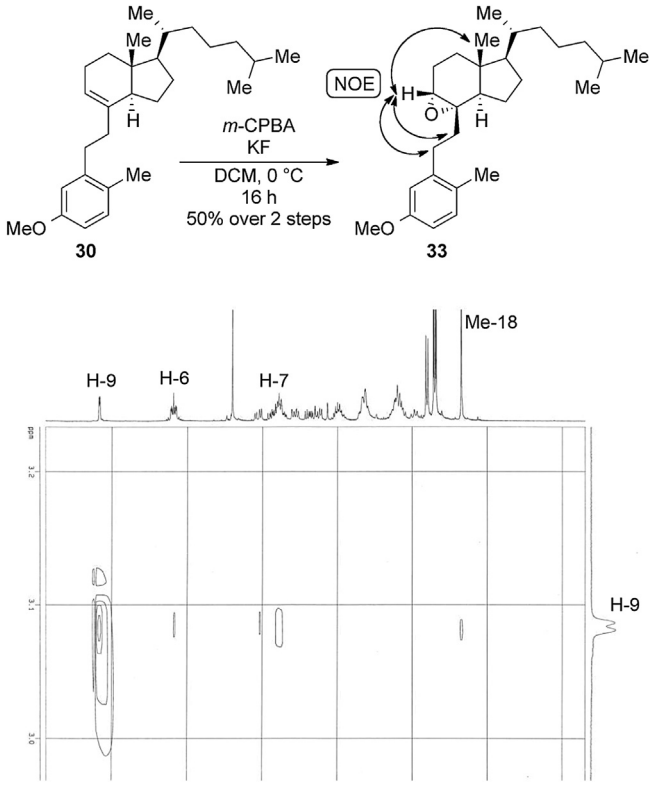
With all of the carbon atoms installed, the need to formally hydrate regioselectively and stereoselectively the C-8–C-9 double bond arose. That would mean that the hydroxy moiety and the phenethyl moiety had to be in a cis relationship with the hydroxy moiety axial and the phenethyl moiety equatorial (Scheme 10).



Scheme 10. Required formal hydration and demethylation to complete the synthesis.

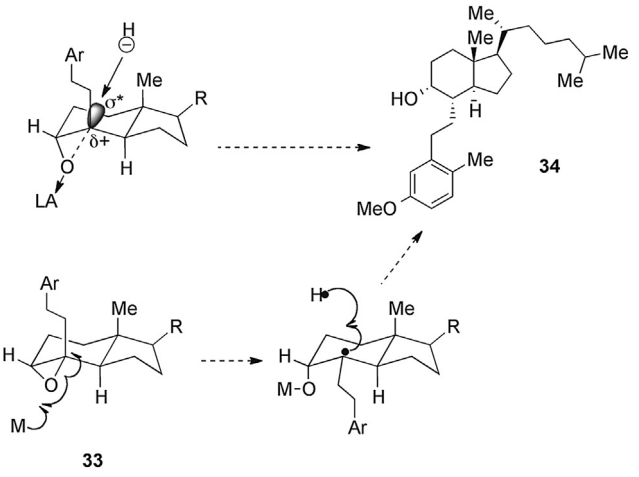
Epoxidation of the double bond using standard conditions took place on the less hindered face of the C-ring and installed the oxygen on the desired face (Scheme 11). NOESY experiment of the obtained epoxide **33** showed that the hydrogen on C-9 is proximate to the hydrogens on C-18 and to the hydrogens on C-7 and C-6 establishing the expected stereochemistry. The signals in ^{13}C NMR have shifted from 142.2 to 61.0 ppm for C-8 and from 119.6 to 57.9 ppm for C-9.

An appropriate Lewis acid should complex the oxygen atom of the epoxide **33**. In order to minimize the steric hindrance, the latter should be as far away as possible from the phenylethyl chain and



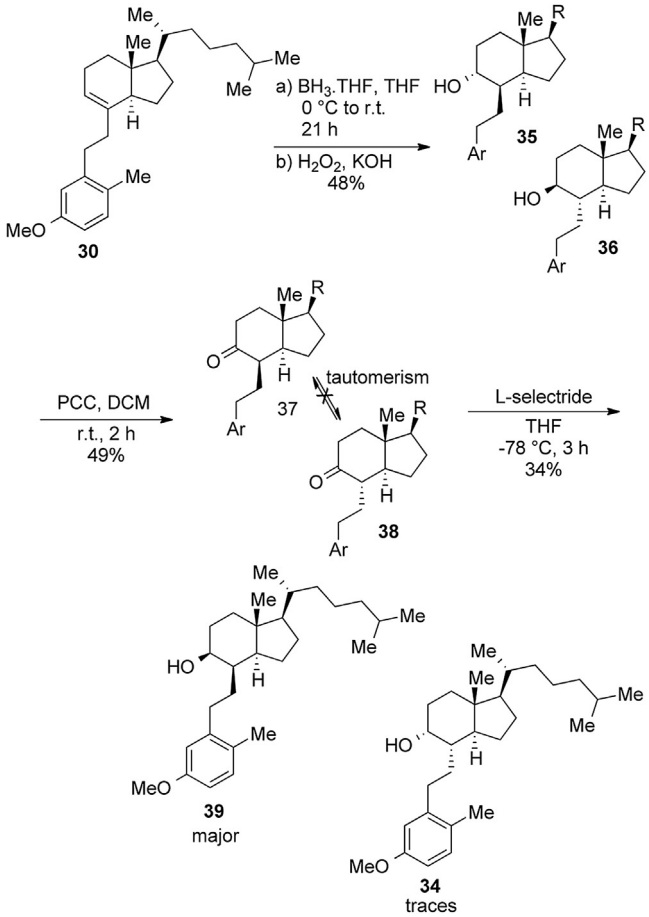
Scheme 11. Epoxidation of the coupled product **30** and excerpt of NOESY spectrum showing spatial proximity of H-9, H-6, H-7, and Me-18 in the product **33**.

would therefore elongate and weaken the O–C-8 bond more than the O–C-9 bond (Scheme 12). The $\delta+$ charge should then be situated on the C-8 atom, allowing the hydride to add in the σ^* in a loose SN2 transition state. Furthermore, in such a transition state, the building of the positive charge on the tertiary carbon is favored compared to the secondary carbon due to the donating effect of the σ_{C-C}. The occurring Walden inversion would invert the configuration of the phenethyl moiety, establishing the stereochemistry of the target **34**. If we consider a radical pathway, the expected opening of the epoxide **33** should lead to the most substituted radical, i.e., C-8 rather than C-9 (Scheme 12). This radical would be long-lived enough for the phenethyl moiety to switch to a pseudo equatorial conformation (conformation observed by De Riccardis for the ketone analogue of this species).[18] An axial attack of the hydrogen atom would then be favored, leading to an equatorial rather than axial positioning of the phenethyl moiety. Although the epoxidation was readily achieved, the opening of epoxide **33** proved to be problematic. I investigated polar pathways using Lewis acids and radical pathways but none of my attempts gave the expected molecule **34**. Were notably attempted Hutchins conditions (cyanoborohydride and boron trifluoride etherate in THF),[51] the replacement of boron trifluoride by triphenylborane in the latter conditions, reduction with triethylsilane together with trimethylsilyl triflate or tris(pentafluorophenyl)boron, reaction with triethylsilyl triflate and L-Selectride, or sodium borohydride and pinacol borane. Among the investigated radical reactions, I attempted the Epling and Wang photochemical approach with sodium borohydride,[52] AIBN or TEMPO promoted reduction with tributyltin hydride or tris(trimethylsilyl)silane, and reduction with titanocene dichloride, manganese dust and cyclohexadiene or γ-terpinene following the work of Rajanbabu[53,54] and Gansäuer.[55–57] In a general trend, radical conditions left the epoxide unreacted as did weak Lewis acids, whereas stronger Lewis acids degraded epoxide **33** into unidentified products.



Scheme 12. Expected stereoselectivity for the polar and radical reduction of epoxide **33**.

Hydroboration of the C-8–C-9 double bond was performed with borane–THF, which gave, as expected by the hindrance of the two faces, **35** as the major product along with traces of **36** after column chromatography (Scheme 13). Oxidation with PCC and aqueous work-up gave an oil, whose spectra account for one main compound along with a trace of another structurally very close compound. Determination of the nature of this compound, i.e., whether conversion of **37** into **38** through keto–enolic



Scheme 13. Hydroboration of the coupled product **30** followed by oxidation and L-Selectride reduction of the C-9 hydroxy group.

tautomerism had occurred during the reaction, was not obvious since the data for these two compounds are scarce where they are reported. Taber[15] only reported the shift for C-9 in ^{13}C NMR for these two isomers: 215.5 ppm for **37** and 213.0 ppm for **38**. For calicoferol E (the phenol-deprotected version of **38**), full data can be found:[18,58] for C-9 the reported shifts are 213.2 and 213.4 ppm, respectively. The shift I observed for C-9 was 211.3 ppm and I was therefore unsure of the outcome of the reaction. I decided to proceed to the reduction with L-Selectride (Scheme 13). Preparative TLC gave 10 mg of the C-3-hydroxy methyl-protected (8*R*,9*S*) diastereomer of (−)-astrogorgiadiol **39** as the major product along with traces of the desired product **34**, whose NMR spectra are in good agreement with Taber's data. The stereochemistry was established through NOE experiments and a study of the coupling constants in ^{1}H NMR. It can therefore be concluded that the expected keto–enolic tautomerism did not occur, as this equilibrium would have favored the equatorial positioning of the phenethyl chain rather than axial and thus converted **37** into **38**.

Comparing the spectra of **35**, **39**, and **34** (Fig. 1), some interesting facts have to be noted. The signals for H-9 in **35** and **34**, in which the hydrogen is equatorial, sit at approximately 4.0 ppm whereas it is more shielded (3.8 ppm) for **39**, where the hydrogen is axial. These signals are broad singlets for **35** and **34** accounting for small equatorial/equatorial and equatorial/axial coupling constants but it is a multiplet for **39** due to the stronger axial/axial (H-9/H-11) constant. Looking at the signals for C-18, it is striking that the presence of the phenylethyl chain in axial position has shifted the signal downfield (12.7 ppm for **35**; 13.5 ppm for **39**) compared to **34** where this chain is equatorial (11.0 ppm).

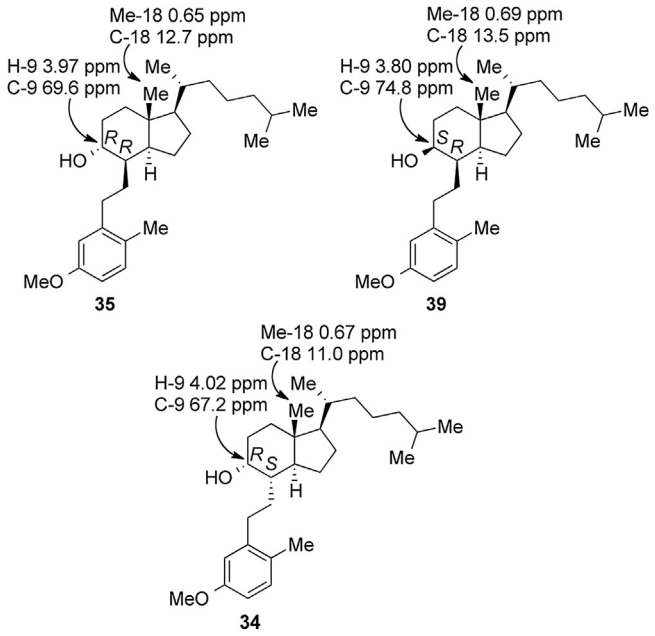
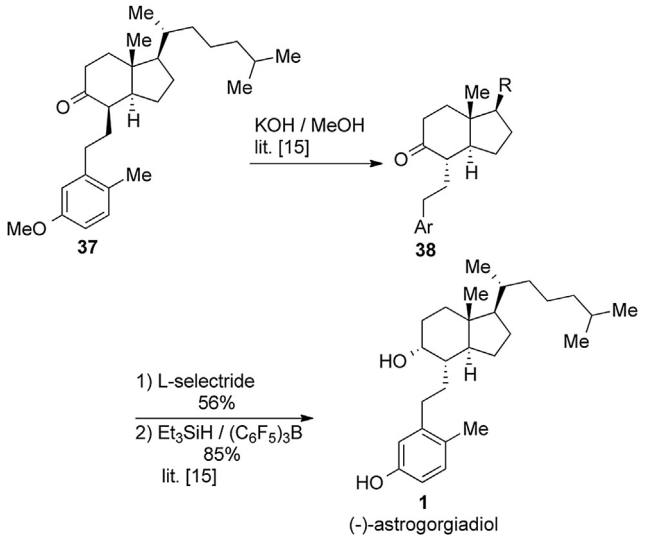


Fig. 1. Comparison of **35**, **39**, and **34** chemical shifts in NMR spectra.

Taber reports the conversion of **37** to **38** using KOH/MeOH.[15] Therefore, the synthesis of **37** along with traces of **38** constitutes a formal synthesis of (−)-astrogorgiadiol (Scheme 14). Compound **37** can be converted to **38**, which can be reduced to **34** before proceeding to the deprotection of the phenol following Taber's procedure[15] to yield (−)-astrogorgiadiol.



Scheme 14. Completion of the formal synthesis of (−)-astrogorgiadiol.

3. Conclusion

In my investigation towards a practical semi-synthesis of (−)-astrogorgiadiol, a strategy was conceived, based on the coupling of the kinetic enol triflate of Grundmann ketone as the CD-ring platform with the phenethyl halide or boronate as the A-ring coupling partner. The CD-ring platform was obtained starting from (+)-vitamin D_3. The requisite phenethyl bromide, iodide, pinacol boronate, and trifluoroborate were obtained starting from 3-methylanisole. The challenging sp^2–sp^3 coupling of the two fragments was accomplished using a Suzuki–Miyaura type reaction, by way of a 9-BBN methoxy boronate. For the endgame of the synthesis, a hydroboration route and an epoxidation route were investigated. The hydroboration strategy allowed the completion of a formal synthesis of (−)-astrogorgiadiol. This synthesis paves the way for the generation of other 9-10-secosteroids analogues of (−)-astrogorgiadiol, which could outperform the parent natural molecule for osteopontin downregulation or cancer related kinase inhibition.

4. Experimental section

4.1. General

All starting materials were obtained commercially from Aldrich, Avocado, Acros, Lancaster, BDH or Strem and used without further purification. All solvents were dried prior to use except when indicated otherwise. Flash chromatography was conducted using Merck silica gel 60 (40–60 μm). TLC was carried out on pre-coated glass-backed plates (Merck Kiesel-gel 60 F_{254}), visualized at 254 nm and stained with anisaldehyde or phosphomolybdic acid. Infra-red (IR) spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer. The wave number is given in cm^{-1} with peak intensity signified as s, m, and w for strong, medium, and weak, respectively. Mass spectra (FAB, CI or EI) were recorded at the Departmental Mass Spectrometry Service of the University College London on a VG Analytical 70S instrument by Dr. Lisa Harris and John Hill. Proton Nuclear Magnetic Resonance spectra were recorded on Bruker AMX-500, 400 or 300 NMR Spectrometers. The NMR spectra were recorded with reference to the residual solvent peak ($CHCl_3$ in $CDCl_3$ at 7.24 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR). ^{13}C DEPT, HMQC, HMBC and COSY were used to determine structures. In the description of the spectra, the numbering of the carbon

atoms refers to the numbering that the carbon atoms would have in (−)-astrogorgiadiol (steroids numbering).

*4.1.1. (1R,3aR,7aR)-7a-Methyl-1-((R)-6-methylheptan-2-yl)-2,3,3a,6,7,7a-hexahydro-1H-inden-4-yl trifluoromethanesulfonate (**11**).* A solution of Grundmann ketone **9**[19] (10.6 g, 40 mmol, 1 equiv) in DMF (80 mL) was added by cannula over 1 h to a solution of KHMDS in toluene (0.5 M, 160 mL, 80 mmol, 2 equiv) diluted in DMF (80 mL) at −78 °C. After 90 min, a solution of **10** (17.9 g, 50 mmol, 1.25 equiv) in DMF (100 mL) was added by cannula over 50 min. The mixture was allowed to warm to rt. After 90 min, water (400 mL) and ether (200 mL) were added and the two phases were separated. The aqueous phase was extracted with ether (2×200 mL), the combined organic phase was dried on $MgSO_4$, concentrated under vacuum, and purified by column chromatography (silica, neat petroleum ether) yielding 60% **11** (9.50 g, 24.0 mmol) as a colorless oil. R_f 0.90 (petroleum ether/ethyl acetate 5:1). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 5.55 (m, 1H, H-9), 2.45 (m, 1H), 2.28 (m, 2H), 1.98 (m, 2H), 1.74 (m, 1H), 1.52–1.00 (m, 12H), 0.92 (d, J=6.5 Hz, 3H, Me-21), 0.85 (d, J=6.6 Hz, 3H, Me-26 or Me-27), 0.84 (d, J=6.6 Hz, 3H, Me-27 or Me-26), 0.74 (s, 3H, Me-18). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 150.0 (C-8), 116.0 (C-9), 54.3, 50.1, 45.2, 39.4, 36.0, 34.8, 29.7, 28.3, 28.0, 23.9, 23.8, 22.8, 22.5, 21.5, 18.6, 11.3. HRMS (EI) calculated for $C_{19}H_{31}F_3O_3S$ (M^+): 396.19405, found 396.19300.

*4.1.2. 4,4,5,5-Tetramethyl-2-((1R,3aS,7aR)-7a-methyl-1-((R)-6-methylheptan-2-yl)-2,3,3a,6,7,7a-hexahydro-1H-inden-4-yl)-1,3,2-dioxaborolane (**12**).* A mixture of **11** (991 mg, 2.5 mmol, 1 equiv), bis(pinacolato)diboron (698 mg, 2.75 mmol, 1.1 equiv), $PdCl_2(PPh_3)_2$ (52.6 mg, 0.075 mmol, 0.03 equiv), PPh_3 (39.3 mg, 0.15 mmol, 0.06 equiv), and KOPh [8] (496 mg, 3.75 mmol, 1.5 equiv) in toluene (15 mL) was heated to 50 °C for 1 h. Water (15 mL) and ether (10 mL) were added and the two phases were separated. The aqueous phase was extracted with ether (10 mL) and the combined organic phase was dried on $MgSO_4$, concentrated under vacuum, and purified by column chromatography (silica, 1% ethyl acetate in petroleum ether) yielding 76% **12** (716 mg, 1.91 mmol) as a clear oil. R_f 0.47 (petroleum ether/ethyl acetate 9:1). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.40 (br t, J=3.1 Hz, 1H, H-9), 2.15 (m, 2H), 2.09 (m, 1H), 1.96 (m, 2H), 1.87 (m, 1H), 1.6–0.9 (m, 12H), 1.23 (s, 6H, 2× Me), 1.21 (s, 6H, 2× Me), 0.91 (d, J=6.6 Hz, 3H, Me-21), 0.85 (d, J=6.6 Hz, 3H, Me-27 or Me-26), 0.84 (d, J=6.6 Hz, 3H, Me-26 or Me-27), 0.62 (s, 3H, Me-18). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 142.5 (C-9), 82.7 (2× C-pin), 54.2, 49.6, 41.5, 39.5, 36.3, 36.2, 36.2, 28.5, 28.0, 25.8, 25.3, 25.1, 24.4, 23.9, 22.8, 22.6, 18.8, 11.0. IR (neat, cm^{-1}): 2954 (s), 2870 (m), 1705 (s), 1467 (m), 1382 (m), 1150 (s), 960 (m), 852 (w), 755 (s), 668 (m).

*4.1.3. (2-Bromo-5-methoxybenzyl)triphenylphosphonium bromide (**15**).* Compound **14** (169 g, 603 mmol, 1 equiv) and triphenylphosphine (159 g, 603 mmol, 1 equiv) were dissolved in toluene (1.2 L) and the mixture was refluxed for 22 h. The precipitate was filtered and dried under high vacuum yielding 94% **15** (308 g, 568 mmol) as a white crystalline solid (mp: 254 °C). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.78 (m, 3H, H-para), 7.70 (m, 6H, H-ortho), 7.62 (m, 6H, H-meta), 7.18 (m, 2H, H-1 & H-2), 6.68 (dt, J=8.9, 2.8 Hz, 1H, H-4), 5.57 (d, J=14.3 Hz, 2H, H-6), 3.53 (s, 3H, OMe). HRMS (positive ion FAB) calculated for $C_{26}H_{23}BrOP$ (M−Br): 461.06698, found 461.06608.

*4.1.4. 1-Bromo-4-methoxy-2-vinylbenzene (**16**).*[59] Compound **15** (308 g, 568 mmol, 1 equiv) and paraformaldehyde (170 g, 5.68 mol, 10 equiv) were suspended in DME (710 mL). A solution of potassium *tert*-butoxide (316 g, 2.84 mol, 5 equiv) in ethanol (910 mL) was then slowly added by cannula over 2 h. Once the addition was over, the mixture was stirred for another 30 min then concentrated under vacuum. Ether (1 L) was added, the mixture was filtered, and concentrated under vacuum. The procedure was repeated with ether (1 L) and with petroleum ether (2×1 L) to remove triphenylphosphine oxide. The resulting oil was purified by elution through a short pad of silica with neat petroleum ether and allowed to dry under high vacuum yielding 80% **16** (97 g, 455 mmol) as a clear oil. R_f 0.51 (2 elutions with neat petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.41 (d, J=8.8 Hz, 1H, H-1), 7.06 (d, J=3.0 Hz, 1H, H-4), 7.00 (dd, J=17.4, 10.9 Hz, 1H, H-6), 6.69 (dd, J=8.8, 3.0 Hz, 1H, H-2), 5.68 (dd, J=17.4, 0.9 Hz, 1H, H-7 trans to H-6), 5.35 (dd, J=10.9, 0.9 Hz, 1H, H-7 cis to H-6), 3.79 (s, 3H, OMe). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 158.9 (C-3), 138.1 (C-5), 135.8 (C-6), 133.4 (C-1), 116.7 (C-7), 115.2 (C-2), 114.3 (C-10), 111.9 (C-4), 55.4 (OMe). HRMS (EI) calculated for C_9H_9BrO (M^+): 211.98313, found 211.98333. Data consistent with literature values.[59]

*4.1.5. 4-Methoxy-1-methyl-2-vinylbenzene (**17**).* A solution of methylmagnesium bromide in ether (3 M, 607 mL, 1.82 mol, 4 equiv) was added to **16** (97 g, 455 mmol, 1 equiv) and $NiCl_2(PPh_3)_2$ (7.4 g, 11.4 mmol, 0.025 equiv) in ether (1 L) at 0 °C and the mixture was stirred for 40 h at reflux. The reaction was then carefully quenched at 0 °C with a saturated solution of NH_4Cl in water (300 mL). Ether (300 mL) and brine (600 mL) were then added. The supernatant was separated and the slurry extracted with ether (3×300 mL). The combined organic phase was washed with brine (300 mL), dried on $MgSO_4$, and concentrated under vacuum. The obtained oil was purified by elution with neat petroleum ether through a short pad of silica on a sinter funnel yielding 82% **17** (55.2 g, 373 mmol) as a clear oil. R_f 0.72 (petroleum ether/ethyl acetate 5:1). ^{1}H NMR (500 MHz MHz, $CDCl_3$, δ): 7.05 (d, J=8.3 Hz, 1H, H-1), 7.03 (d, J=2.4 Hz, 1H, H-4), 6.91 (dd, J=17.4, 10.9 Hz, 1H, H-6), 6.74 (dd, J=8.3, 2.4 Hz, 1H, H-2), 5.63 (d, J=17.4 Hz, 1H, H-7 trans to H-6), 5.29 (d, J=10.9 Hz, 1H, H-7 cis to H-6), 3.80 (s, 3H, OMe), 2.28 (s, 3H, Me-19). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 157.9 (C-3), 137.6 (C-5), 134.9 (C-6), 132.1 (C-1), 127.7 (C-10), 115.2 (C-7), 113.3 (C-2), 110.6 (C-4), 55.3 (OMe), 18.7 (C-19). IR (neat, cm^{-1}): 2948 (m), 2834 (w), 1605 (m), 1570 (m), 1492 (s), 1463 (m), 1420 (m), 1285 (s), 1243 (s), 1200 (m), 1163 (m), 1113 (m), 1030 (s), 989 (m), 908 (s), 873 (m), 855 (m), 802 (s), 720 (m), 696 (m), 665 (m). HRMS (positive CI) calculated for $C_{10}H_{13}O$ (M+H): 149.09663, found 149.09693. No data for this compound were provided in the literature where it is described.[60,61]

*4.1.6. 2-(5-Methoxy-2-methylphenethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**18**).* A solution of pinacol borane in THF (1 M, 90 mL, 90 mmol, 1.2 equiv) was added to a mixture of **17** (11.1 g, 75 mmol, 1 equiv), $[Ir(COD)Cl]_2$ (504 mg, 0.75 mmol, 0.01 equiv), and diphenylphosphinoethane (598 mg, 1.5 mmol, 0.02 equiv) in THF (60 mL) at rt. After 26 h, the reaction was quenched by addition of methanol (70 mL). Water (150 mL) and ether (200 mL) were then added and the two phases were separated. The aqueous phase was further extracted with a mixture of ether (200 mL) and methanol (40 mL). The combined organic phase was then dried on $MgSO_4$, concentrated under vacuum, and purified by column chromatography (silica, petroleum ether/ethyl acetate 9:1) yielding 77% **18** (15.9 g, 57.5 mmol) as a clear oil. R_f 0.59 (petroleum ether/ethyl acetate 5:1). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.01 (d, J=8.3 Hz, 1H, H-1), 6.77 (d, J=2.7 Hz, 1H, H-4), 6.62 (dd, J=8.3, 2.7 Hz, 1H, H-2), 3.77 (s, 3H, OMe), 2.67 (t, J=8.2 Hz, 2H, H-6), 2.22 (s, 3H, Me-19), 1.23 (s, 12H, 4× Me), 1.08 (t, J=8.2 Hz, 2H, H-7). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 157.8 (C-3), 143.7 (C-5), 130.6 (C-1), 127.7 (C-10), 113.9 (C-4), 110.7 (C-2), 83.1 (2× C-pin), 55.1 (OMe), 27.4 (C-6), 24.8 (4× Me), 18.3 (C-19), 11.6 br (C-7). IR (neat, cm^{-1}): 2977 (m), 2935 (m), 1609 (m), 1580 (w), 1500 (m), 1369 (s), 1315 (s), 1249 (s), 1143 (s), 1042 (s), 967 (m), 847 (s), 798 (m). MS (positive CI) (m/z, %): 276 (M, 19), 261

(M−Me, 11), 205 (35), 177 (MH−C(Me$_2$)C(Me$_2$)O, 100), 149 (M−BPin, 38), 135 (M−CH$_2$BPin, 63). HRMS (positive CI) calculated for $C_{16}H_{26}BO_3$ (M+H): 277.19749, found 277.19780.

*4.1.7. 2-(5-Methoxy-2-methylphenyl)ethanol (**19**).* A solution of KOH in water (5%, 4 mL) followed by a solution of H_2O_2 in water (27.5%, 4 mL) were added to a solution of **18** (1.10 g, 4 mmol, 1 equiv) in THF (4 mL) at 0 °C. After 30 min the mixture was extracted with ether (3×5 mL). The combined organic phase was washed with brine (5 mL), dried on $MgSO_4$, and purified by column chromatography (silica, petroleum ether/EtOAc 2:1), yielding quantitatively **19** (663 mg, 4.0 mmol) as a yellow oil. R_f 0.28 (petroleum ether/ethyl acetate 2:1). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.06 (d, J=8.3 Hz, 1H, H-1), 6.73 (d, J=2.7 Hz, 1H, H-4), 6.67 (dd, J=8.3, 2.7 Hz, 1H, H-2), 3.78 (t, J=7.0 Hz, 2H, H-7), 3.76 (s, 3H, OMe), 2.83 (t, J=7.0 Hz, 2H, H-6), 2.25 (s, 3H, Me-19). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 157.7 (C-3), 137.6 (C-5), 131.0 (C-1), 128.3 (C-10), 115.3 (C-4), 111.4 (C-2), 62.3 (C-7), 55.1 (OMe), 36.5 (C-6), 18.3 (C-19). IR (neat, cm^{-1}): 3340 (s br), 2945 (m), 2834 (w), 1609 (m), 1579 (m), 1499 (s), 1465 (m), 1421 (w), 1304 (m), 1286 (m), 1249 (s), 1210 (m), 1159 (m), 1117 (m), 1041 (s), 849 (m), 802 (s), 711 (m). MS (EI) (m/z, %): 166 (M, 8), 148 (M−H_2O, 7), 131 (100), 121 (M−C_2H_4OH, 14), 109 (81), 91 (M−C_2H_4OH−MeO, 60). HRMS (EI) calculated for $C_{10}H_{14}O_2$ (M$^+$): 166.09883, found 166.09839. Data in partial agreement with the literature.[62]

*4.1.8. 1-(5-Methoxy-2-methylphenyl)ethanol (**20**).* A solution of BH_3·THF in THF (1 M, 14.7 mL, 14.7 mmol, 1.2 equiv) was slowly added to **17** (1.81 g, 12.2 mmol, 1 equiv) at 0 °C and the mixture was allowed to warm to rt. After 5 h, the mixture was cooled to 0 °C and a solution of KOH in water (5%, 12 mL) was carefully added. The mixture was warmed to rt and a solution of H_2O_2 in water (27.5%, 12 mL) was added. After 30 min, ether (12 mL) was added and the two phases were separated. The aqueous phase was extracted with ether (3×12 mL) and the combined organic phase was washed with brine (24 mL), dried on $MgSO_4$, and purified by column chromatography (silica, petroleum ether/EtOAc 2:1) yielding 79% **19** and **20** (1.59 g, 9.57 mmol) as a 9:1 mixture. Further purification by column chromatography (silica, petroleum ether/EtOAc 2:1) allowed to isolate **20** as a colorless oil for analysis. R_f 0.43 (petroleum ether/ethyl acetate 2:1). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.08 (s, 1H, H-4), 7.02 (d, J=8.1 Hz, 1H, H-1), 6.70 (d, J=8.2 Hz, 1H, H-2), 5.08 (m, 1H, H-6), 3.78 (s, 3H, OMe), 2.26 (s, 3H, Me-19), 1.43 (d, J=6.4 Hz, 3H, H-7).

*4.1.9. 2-(5-Methoxy-2-methylphenyl)oxirane (**21**).* *m*-CPBA (77%, 247 mg, 1.1 mmol) was added portionwise to a heterogeneous mixture of **17** (148 mg, 1 mmol) in a solution of $NaHCO_3$ in water (0.3 M, 6 mL) at 0 °C. After 15 min, the mixture was warmed to rt. After 24 h, another portion of *m*-CPBA (247 mg, 1.1 mmol) was added. After 15 min, the mixture was extracted with ether (10 mL). The aqueous phase was further extracted with ether (2×5 mL). The combined organic phase was washed with a solution of $NaHCO_3$ in water (0.3 M, 10 mL), dried on $MgSO_4$, and concentrated under vacuum. Purification by elution through a short pad of silica (petroleum ether/ethyl acetate 5:1) yielded 20% **21** (34 mg, 0.21 mmol) as a clear oil. ^{1}H NMR (500 MHz, C_6D_6, δ): 7.04 (d, J=2.8 Hz, 1H, H-4), 6.86 (d, J=8.3 Hz, 1H, H-1), 6.72 (dd, J=8.3, 2.8 Hz, 1H, H-2), 3.62 (dd, J=4.0, 2.5 Hz, 1H, H-6), 3.31 (s, 3H, OMe), 2.58 (dd, J=6.0, 4.0 Hz, 1H, H-7 trans to H-6), 2.22 (dd, J=6.0, 2.5 Hz, 1H, H-7 cis to H-6), 2.03 (s, 3H, Me-19).

*4.1.10. Potassium trifluoro(5-methoxy-2-methylphenethyl)borate (**25**).* KHF_2 (469 mg, 6 mmol, 6 equiv) and water (0.8 mL) were added at rt to a solution of boronate **18** (279 mg, 1 mmol, 1 equiv) in ether (1.67 mL). After 1.5 h, acetone (3×15 mL) was added and the supernatants were collected, combined, and concentrated under vacuum. The resulting solid was recrystallized from acetone/ether yielding 66% **25** (169 mg, 0.658 mmol) as a white crystalline solid (mp: 240 °C). ^{1}H NMR (500 MHz, D_2O, δ): 7.15 (d, J=8.2 Hz, 1H, H-1), 6.91 (d, J=2.8 Hz, 1H, H-4), 6.75 (dd, J=8.2, 2.8 Hz, 1H, H-2), 3.82 (s, 3H, OMe), 2.53 (m, 2H, H-6), 2.25 (s, 3H, Me-19), 0.51 (m, 2H, H-7). ^{13}C NMR (125 MHz, D_2O, δ): 157.7 (C-3), 147.5 (C-5), 131.7 (C-1), 129.5 (C-10), 114.4 (C-4), 111.8 (C-2), 56.0 (OMe), 29.0 (C-6), 19.1 br (C-7), 17.9 (C-19). IR (neat, cm^{-1}): 2924 (w), 2836 (w), 1618 (w), 1579 (w), 1494 (m), 1464 (w), 1441 (w), 1348 (w), 1307 (m), 1284 (m), 1251 (m), 1221 (m), 1209 (m), 1160 (w), 1110 (m), 1078 (s), 1052 (s), 1031 (s), 959 (s), 913 (m), 887 (s), 799 (m), 735 (m), 717 (s). MS (negative ion FAB) (m/z, %): 217 (M−K, 14), 199 (M+H−KF, 100), 168 (32), 153 (100). HRMS (negative ion FAB) calculated for $C_{10}H_{13}BF_3$ (M−K): 217.10115, found 217.10189.

*4.1.11. 2-(2-Bromoethyl)-4-methoxy-1-methylbenzene (**24**).*[16] Triphenylphosphine (1.50 g, 5.7 mmol, 1.9 equiv) and carbon tetrabromide (1.89 g, 5.7 mmol, 1.9 equiv) were added to a solution of **19** (499 mg, 3 mmol, 1 equiv) in THF (7.5 mL) at rt. After just 5 min, ether (10 mL) was added and the mixture was filtered. Brine (20 mL) was added to the filtrate and the two phases were separated. The aqueous phase was further extracted with ether (3×10 mL). The combined organic phase was dried on $MgSO_4$, concentrated under vacuum, and purified by column chromatography (silica, 2% ethyl acetate in petroleum ether) yielding 87% **24** (595 mg, 2.6 mmol) as a half solid. R_f 0.86 (petroleum ether/ethyl acetate 2:1). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.05 (m, 1H, H-1), 6.70 (m, 2H, H-2 & H-4), 3.76 (s, 3H, OMe), 3.49 (t, J=8.1 Hz, 2H), 3.12 (t, J=8.1 Hz, 2H), 2.24 (s, 3H, Me-19). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 157.9 (C-3), 138.2 (C-5), 131.3 (C-1), 128.0 (C-10), 115.1 (C-2), 112.1 (C-4), 55.3 (OMe), 37.2 (C-6), 31.5 (C-7), 18.4 (C-19). MS (EI) (m/z, %): 230 (M+2, 14), 228 (M, 15), 176 (41), 135 (M−CH_2Br, 79), 91 (100). HRMS (EI) calculated for $C_{10}H_{13}BrO$ (M$^+$): 228.01443, found 228.01417. Data consistent with literature values.[16]

*4.1.12. 5-Methoxy-2-methylphenethyl methanesulfonate (**22**).* Methanesulfonyl chloride (557 μL, 7.2 mmol, 1.2 equiv) was slowly added to a solution of **19** (997 mg, 6 mmol, 1 equiv) and triethylamine (4.18 mL, 30 mmol, 5 equiv) in DCM (20 mL) at rt. The exothermic reaction was stirred for 30 min, then quenched with HCl (0.1 M, 60 mL). DCM (60 mL) was added and the two phases were separated. The aqueous phase was further extracted with DCM (2×60 mL). The combined organic phase was washed with brine (60 mL), dried on $MgSO_4$, concentrated under vacuum, and purified by column chromatography (silica, petroleum ether/ethyl acetate 5:1) yielding 90% **22** (1.32 g, 5.40 mmol) as a clear oil. R_f 0.37 (petroleum ether/ethyl acetate 2:1). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.06 (d, J=8.0 Hz, 1H, H-1), 6.71 (s, 1H, H-4), 6.70 (d, J=8.0 Hz, 1H, H-2), 4.36 (t, J=7.3 Hz, 2H, H-7), 3.76 (s, 3H, OMe), 3.02 (t, J=7.3 Hz, 2H, H-6), 2.86 (s, 3H, O_2SMe), 2.25 (s, 3H, Me-19). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 158.0 (C-3), 135.4 (C-5), 131.4 (C-1), 128.4 (C-10), 115.4 (C-4), 112.3 (C-2), 69.2 (C-7), 55.3 (OMe), 37.4 (O_2SMe), 33.2 (C-6), 18.4 (C-19). IR (neat, cm^{-1}): 3026 (w), 2939 (w), 1610 (m), 1580 (m), 1505 (s), 1466 (m), 1351 (s), 1304 (m), 1251 (m), 1170 (s), 1120 (m), 1034 (m), 952 (s), 909 (m), 804 (m), 750 (s), 667 (m).

*4.1.13. 2-(2-Iodoethyl)-4-methoxy-1-methylbenzene (**23**).* NaI (4.05 g, 27.0 mmol, 5 equiv) was added to a solution of mesylate **22** (1.32 g, 5.40 mmol, 1 equiv) in 2-butanone (54 mL) at rt and the mixture was heated to reflux for 2 h. Ether (50 mL) and water (50 mL) were then added and the two phases were separated. The aqueous phase was further extracted with ether (30 mL) and the combined organic phase was dried on $MgSO_4$ then concentrated under vacuum yielding 91% **23** (1.36 g, 4.93 mmol) as a half solid. R_f 0.80 (petroleum ether/ethyl acetate 2:1). ^{1}H NMR (500 MHz, $CDCl_3$,

δ): 7.05 (d, J=8.2 Hz, 1H, H-1), 6.71 (d, J=8.2 Hz, 1H, H-2), 6.69 (s, 1H, H-4), 3.77 (s, 3H, OMe), 3.27 (t, J=8.0 Hz, 2H, H-7), 3.14 (t, J=8.0 Hz, 2H, H-6), 2.23 (s, 3H, Me-19). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 157.9 (C-3), 140.1 (C-5), 131.3 (C-1), 127.7 (C-10), 114.7 (C-2), 112.1 (C-4), 55.3 (OMe), 38.3 (C-6), 18.2 (C-19), 3.7 (C-7).

*4.1.14. (E)-2-(5-Methoxy-2-methylstyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**26**).* A solution of **17** (437 mg, 2.95 mmol, 1 equiv) in DCM (5 mL) followed by vinyl boronate pinacol ester (0.5 mL, 2.95 mmol, 1 equiv) was added to a suspension of Hoveyda–Grubbs second generation catalyst (92 mg, 0.148 mmol, 0.05 equiv) in DCM (10 mL) under nitrogen. The mixture was heated to reflux for 3 h, concentrated under vacuum, and purified by column chromatography (silica, petroleum ether/ethyl acetate 9:1) yielding 77% **26** (619 mg, 2.26 mmol) as a clear oil. R_f 0.51 (petroleum ether/ethyl acetate 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.59 (d, J=18.2 Hz, 1H, H-6), 7.08 (d, J=2.7 Hz, 1H, H-4), 7.03 (d, J=8.3 Hz, 1H, H-1), 6.75 (dd, J=8.3, 2.7 Hz, 1H, H-2), 6.06 (d, J=18.2 Hz, 1H, H-7), 3.76 (s, 3H, OMe), 2.33 (s, 3H, Me-19), 1.30 (s, 12H, 4× Me). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 157.8 (C-3), 147.0 (C-6), 137.4 (C-5), 131.3 (C-1), 128.6 (C-10), 128.2 (C-7), 114.8 (C-4), 110.3 (C-2), 83.3 (2× C-pin), 55.2 (OMe), 24.8 (4× Me), 18.8 (C-19). IR (neat, cm^{-1}): 2977 (m), 1621 (m), 1572 (w), 1495 (m), 1456 (m), 1348 (s), 1324 (m), 1244 (m), 1207 (m), 1141 (s), 1039 (m), 995 (m), 969 (m), 849 (m), 811 (m), 718 (w). MS (EI) (*m*/*z*, %): 274 (M, 88), 268 (100), 174 (M−C(Me$_2$)C(Me$_2$)O, 76). HRMS (EI) calculated for $C_{16}H_{23}BO_3$ (M^+): 274.17348, found 274.17383.

*4.1.15. (E)-2-(2-Iodovinyl)-4-methoxy-1-methylbenzene (**27**).* A solution of NaOH in water (3 M, 0.4 mL, 1.2 mmol, 3 equiv) was added to a solution of **26** (109.7 mg, 0.4 mmol, 1 equiv) in THF (1 mL) at rt under vigorous stirring. After 10 min, a solution of iodine in THF (0.2 M, 2.5 mL, 0.5 mmol, 1.25 equiv) was added dropwise over 3 h, waiting for the disappearance of the orange color between each drop. Persistence of the color showed the end of the reaction at which point a saturated solution of $Na_2S_2O_3$ in water (5 mL) was added. Extraction with ether (3×5 mL) followed and the combined organic phase was dried on $MgSO_4$, concentrated under vacuum, and purified by column chromatography (silica, 2% ethyl acetate in petroleum ether) yielding 70% **27** (77 mg, 0.28 mmol) as a clear oil. R_f 0.65 (petroleum ether/ethyl acetate 5:1). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.59 (d, J=14.7 Hz, 1H, H-6), 7.03 (d, J=8.3 Hz, 1H, H-1), 6.84 (s, 1H, H-4), 6.76 (d, J=8.3 Hz, 1H, H-2), 6.69 (d, J=14.7 Hz, 1H, H-7), 3.80 (s, 3H, OMe), 2.25 (s, 3H, Me-19). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 157.9 (C-3), 143.3 (C-6), 137.7 (C-5), 131.2 (C-1), 127.0 (C-10), 114.0 (C-4), 110.9 (C-2), 77.9 (C-7), 55.3 (OMe), 18.8 (C-19).

*4.1.16. (3R,3aR,7aS)-7-(4-Methoxyphenethyl)-3a-methyl-3-((R)-6-methylheptan-2-yl)-2,3,3a,4,5,7a-hexahydro-1H-indene (**29**).* A solution of 4-methoxyphenethylmagnesium chloride in THF (0.5 M, 0.6 mL, 0.3 mmol, 1.2 equiv) was added dropwise to a mixture of **11** (99 mg, 0.25 mmol, 1 equiv) and precatalyst $Fe(acac)_3$ (8.82 mg, 0.025 mmol, 0.1 equiv) in DMF (1 mL) at rt. After 2 h, water (30 mL) was added and the mixture was extracted with ethyl acetate (2×25 mL). The combined organic phase was dried on $MgSO_4$, concentrated under vacuum, and purified by column chromatography (silica, neat petroleum ether then 5% ethyl acetate in petroleum ether) yielding 70% **29** (67.3 mg, 0.176 mmol) as a colorless oil. R_f 0.73 (petroleum ether/ethyl acetate 9:1). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.08 (m, 2H, H-ortho), 6.80 (m, 2H, H-meta), 5.22 (s, 1H, H-9), 3.77 (s, 3H, OMe), 2.65 (m, 1H), 2.56 (m, 1H), 2.2–0.94 (m, 20H), 0.94 (d, J=6.5 Hz, 3H, Me-21), 0.86 (d, J=6.6 Hz, 3H, Me-27 or Me-26), 0.85 (d, J=6.6 Hz, 3H, Me-26 or Me-27), 0.67 (s, 3H, Me-18). DEPT 45 (75 MHz, $CDCl_3$, δ): 129.2 (2× C-ortho), 119.5 (C-9), 113.6 (2× C-meta), 55.3 (OMe), 54.6, 51.1, 39.5, 37.4, 36.4, 36.3, 36.2, 34.2, 28.4, 28.1, 24.6, 23.9, 23.0, 22.9 (C-27 or C-26), 22.6 (C-26 or C-27), 18.8 (C-21), 11.3 (C-18). IR (neat, cm^{-1}): 2931 (s), 2868 (m), 1724 (s), 1611 (m), 1512 (s), 1465 (m), 1366 (m), 1245 (s), 1175 (m), 1035 (m), 821 (m). MS (positive CI) (*m*/*z*, %): 383 (M+H, 2), 355 (M−CH_2CH_2Ar, 5), 207 (100).

*4.1.17. (3R,3aR,7aS)-7-(5-Methoxy-2-methylphenethyl)-3a-methyl-3-((R)-6-methylheptan-2-yl)-2,3,3a,4,5,7a-hexahydro-1H-indene (**30**). Molander's conditions*:[38] Compound **11** (119 mg, 0.3 mmol, 1 equiv), **18** (82.8 mg, 0.3 mmol, 1 equiv), Cs_2CO_3 (293 mg, 0.9 mmol, 3 equiv), and $PdCl_2$(dppf)·CH_2Cl_2 (22 mg, 0.027 mmol, 0.09 equiv) were heated to reflux in THF (3 mL) and water (0.3 mL) for 24 h. Ether (10 mL) and brine (5 mL) were then added and the two phases were separated. The organic phase was dried on $MgSO_4$, concentrated under vacuum, and purified by column chromatography (silica, neat petroleum ether then 1% ethyl acetate in petroleum ether) yielding 25% **30** (30 mg, 0.076 mmol) as a clear oil. *Marshall's conditions*:[50] A solution of *t*-BuLi in pentane (1.7 M, 4.9 mL, 8.4 mmol, 4.2 equiv) was added to a solution of **24** (516 mg, 2.2 mmol, 1.1 equiv) in ether (40 mL) at −78 °C under nitrogen. After 3 min, a solution of 9-BBN–OMe in THF (1 M, 9.2 mL, 9.2 mmol, 4.6 equiv) was added, followed by THF (40 mL) addition. After a further 20 min, the cold bath was removed and the mixture was allowed to warm to rt over 2 h. A solution of K_3PO_4 in water (3 M, 3 mL) was then added followed by a solution of **11** (793 mg, 2 mmol, 1 equiv) in DMF (40 mL) and $PdCl_2$(dppf)·CH_2Cl_2 (146 mg, 0.2 mmol, 0.1 equiv). The mixture was then stirred for a further 19 h. Ether (250 mL) and water (250 mL) were then added and the two phases were separated. The aqueous phase was extracted with ether (2×100 mL), then the combined organic phase was dried on $MgSO_4$, concentrated under vacuum, and purified two times by column chromatography (neat petroleum ether then 1% ethyl acetate in petroleum ether) yielding 89% **30** (700 mg, 1.77 mmol) together with an inseparable impurity (~10%). R_f 0.32 (1% ethyl acetate in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.02 (d, J=8.3 Hz, 1H, H-1), 6.69 (d, J=2.7 Hz, 1H, H-4), 6.63 (dd, J=8.3, 2.7 Hz, 1H, H-2), 5.27 (s, 1H, H-9), 3.76 (s, 3H, OMe), 2.68 (m, 1H), 2.55 (m, 1H), 2.22 (s, 3H, Me-19), 2.2–0.9 (m, 20H), 0.94 (d, J=6.5 Hz, 3H, Me-21), 0.86 (d, J=6.6 Hz, 3H, Me-27 or Me-26), 0.85 (d, J=6.6 Hz, 3H, Me-26 or Me-27), 0.68 (s, 3H, Me-18). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 157.8 (C-3), 142.2 (C-8), 138.7 (C-5), 130.7 (C-1), 127.9 (C-10), 119.6 (C-9), 114.6 (C-4), 110.7 (C-2), 55.2 (OMe), 54.5 (C-17), 51.1 (C-14), 42.3 (C-13), 39.5 (CH_2), 36.4 (C-7), 36.2 (C-20), 36.2 (C-11), 35.6 (CH_2), 33.0 (C-6), 28.4 (CH_2), 28.0 (C-25), 24.6 (CH_2), 23.9 (CH_2), 23.0 (CH_2), 22.8 (C-26 or C-27), 22.6 (C-27 or C-26), 18.8 (C-21), 18.4 (C-19), 11.2 (C-18).

*4.1.18. (1aR,3aR,4R,6aR,6bS)-6b-(5-Methoxy-2-methylphenethyl)-3a-methyl-4-((R)-6-methylheptan-2-yl)octahydro-1aH-indeno[4,5-b]oxirene (**33**).* A solution of **30** (690 mg, 1.74 mmol, 1 equiv) in DCM (35 mL) was added over 5 min to a mixture of *m*-CPBA (70%, 858 mg, 3.48 mmol, 2 equiv) and KF (303 mg, 5.22 mmol, 3 equiv) in DCM (18 mL) at 0 °C. The mixture was stirred for 30 min and then left static at 4 °C for 16 h before it was poured in a saturated solution of Na_2SO_3 in water (50 mL). The two phases were separated and the aqueous phase was further extracted with DCM (50 mL). The combined organic phase was dried on $MgSO_4$, concentrated under vacuum, and purified by column chromatography (silica, neat petroleum ether then 1% ethyl acetate in petroleum ether) yielding 50% **33** (362 mg, 0.877 mmol) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.01 (d, J=8.2 Hz, 1H, H-1), 6.67 (d, J=2.7 Hz, 1H, H-4), 6.63 (dd, J=8.2, 2.7 Hz, 1H, H-2), 3.75 (s, 3H, OMe), 3.08 (d, J=2.6 Hz, 1H, H-9), 2.59 (m, 2H, H-6), 2.20 (s, 3H, Me-19), 2.1–0.9 (m, 20H), 0.90 (d, J=6.6 Hz, 3H, Me-21), 0.86 (d, J=6.6 Hz, 3H, Me-27 or Me-26), 0.85 (d, J=6.6 Hz, 3H, Me-26 or Me-27), 0.67 (s, 3H, Me-18). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 157.9 (C-3), 141.6 (C-5), 130.9 (C-1), 127.8 (C-10), 114.5 (C-4), 110.8 (C-2), 61.0 (C-8), 57.9 (C-9), 55.2 (OMe), 53.4, 53.3, 41.5 (C-13), 39.4 (C-24), 36.1 (C-20), 36.0, 35.0,

32.9 (C-25), 28.5 (C-6), 28.0 (C-7), 28.0, 23.9, 23.1, 22.8 (C-27 or C-26), 22.5 (C-26 or C-27), 22.5, 19.0 (C-21), 18.4 (C-19), 11.9 (C-18). IR (neat, cm^{-1}): 2954 (s), 1610 (w), 1502 (m), 1466 (m), 1381 (w), 1250 (m), 1208 (w), 1161 (w), 1115 (w), 1048 (w), 912 (w), 798 (w), 716 (w).

*4.1.19. (1R,3aS,4R,5R,7aR)-4-(5-Methoxy-2-methylphenethyl)-7a-methyl-1-((R)-6-methylheptan-2-yl)octahydro-1H-inden-5-ol (**35**).* A solution of borane in THF (1 M, 325 μL, 0.325 mmol, 1.2 equiv) was added to a solution of **30** (107 mg, 0.27 mmol, 1 equiv) in THF (2.7 mL) at 0 °C under nitrogen. After 30 min at 0 °C, the mixture was slowly warmed to rt and stirred for a further 20 h. The mixture was then cooled to 0 °C and a solution of KOH in water (5%, 2 mL) was added, followed by a solution of H_2O_2 in water (27%, 2 mL), and ether (2 mL). The mixture was then warmed to rt and stirred for 30 min. The mixture was extracted with ether (3×6 mL). The combined organic phase was dried on $MgSO_4$, concentrated under vacuum, and purified by column chromatography (silica, 5% ethyl acetate in petroleum ether) yielding 48% **35** (and traces of **36**) (53 mg, 0.129 mmol) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.02 (d, J=7.9 Hz, 1H, H-1), 6.67 (d, J=2.7 Hz, 1H, H-4), 6.64 (dd, J=7.9, 2.7 Hz, 1H, H-2), 3.97 (s, 1H, H-9), 3.76 (s, 3H, OMe), 2.66 (m, 1H), 2.40 (m, 1H), 2.20 (s, 3H, Me-19), 1.90–0.86 (m, 22H), 0.86–0.83 (m, 9H, Me-21 & Me-27 & Me-26), 0.65 (s, 3H, Me-18). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 157.8 (C-3), 141.9 (C-5), 130.8 (C-1), 127.8 (C-10), 114.8 (C-4), 110.5 (C-2), 69.6 (C-9), 56.8, 55.3 (OMe), 45.4, 45.1, 42.0, 39.5, 36.0, 35.8, 35.5, 34.4, 28.7, 28.0, 27.3, 25.9, 23.7, 23.2, 22.8 (C-26 or C-27), 22.5 (C-27 or C-26), 18.5 (C-21), 18.4 (C-19), 12.7 (C-18).

*4.1.20. (1R,3aS,4R,7aR)-4-(5-Methoxy-2-methylphenethyl)-7a-methyl-1-((R)-6-methylheptan-2-yl)hexahydro-1H-inden-5(6H)-one (**37**).* PCC (56 mg, 0.26 mmol, 2 equiv) was added at rt to a solution of **35** (and traces of **36**) (53 mg, 0.129 mmol, 1 equiv) in DCM (650 μL). The mixture turned brown rapidly. After 2 h, water (5 mL) was added and the mixture was extracted with ether (2×5 mL). The combined organic phase was dried on $MgSO_4$ and concentrated under vacuum, yielding 49% crude ketone **37** (and traces of **38**) (26 mg, 0.064 mmol) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.02 (d, J=8.2 Hz, 1H, H-1), 6.67 (d, J=2.7 Hz, 1H, H-4), 6.63 (dd, J=8.2, 2.7 Hz, 1H, H-2), 3.76 (s, 3H, MeO), 2.62 (m, 1H), 2.43 (m, 1H), 2.24 (m, 1H), 2.18 (s, 3H, Me-19), 2.16–0.90 (m, 20H), 0.90 (s, 3H, Me-18), 0.87 (d, J=5.3 Hz, 3H, Me-21), 0.85 (d, J=6.6 Hz, 3H, Me-27 or Me-26), 0.84 (d, J=6.6 Hz, 3H, Me-26 or Me-27). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 211.3 (C-9), 157.8 (C-3), 141.3 (C-5), 130.9 (C-1), 127.9 (C-10), 114.8 (C-4), 110.9 (C-2), 55.8 (OMe), 55.2, 53.4, 53.0, 41.9 (C-13), 39.4, 38.6, 35.7, 35.4 (C-20), 35.2, 33.2, 28.6, 28.1, 28.0 (C-25), 23.8, 22.8 (C-27 or C-26), 22.5 (C-26 or C-27), 22.3, 18.4 (C-19 or C-21), 18.3 (C-21 or C-19), 13.4 (C-18).

*4.1.21. (1R,3aS,4R,5S,7aR)-4-(5-Methoxy-2-methylphenethyl)-7a-methyl-1-((R)-6-methylheptan-2-yl)octahydro-1H-inden-5-ol (**39**).* A solution of L-Selectride in THF (1 M, 192 μL, 0.192 mmol, 3 equiv) was added to a solution of **37** (and traces of **38**) (26 mg, 0.064 mmol, 1 equiv) in THF (1.6 mL) at −78 °C. After 3 h, acetone (400 μL) was added and the reaction mixture warmed to rt. A saturated solution of NH_4Cl in water (5 mL) was added and the mixture was extracted with DCM (2×5 mL). The combined organic phase was dried on $MgSO_4$ and concentrated under vacuum. Preparative TLC (silica, 20% ethyl acetate in petroleum ether) yielded traces of **34** and 34% **39** (10 mg, 0.024 mmol) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.02 (d, J=8.3 Hz, 1H, H-1), 6.71 (d, J=2.7 Hz, 1H, H-4), 6.63 (dd, J=8.2, 2.7 Hz, 1H, H-2), 3.80 (m, 1H, H-9), 3.76 (s, 3H, OMe), 2.72 (m, 1H), 2.41 (m, 1H), 2.23 (s, 3H, Me-19), 2.0–0.9 (m, 22H), 0.84 (d, J=6.7 Hz, 3H, Me-27 or Me-26), 0.83 (d, J=6.7 Hz, 3H, Me-26 or Me-27), 0.83 (d, J=6.3 Hz, 3H, Me-21), 0.69 (s, 3H, Me-18). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 157.7 (C-3), 142.6 (C-5), 130.8 (C-1), 128.0 (C-10), 115.0 (C-4), 110.5 (C-2), 74.8 (C-9), 56.1, 55.2 (OMe), 51.7, 43.4, 41.9 (C-13), 39.5, 38.3, 36.9, 35.8, 35.3 (C-20), 28.3 (C-6), 28.0 (C-25), 27.9 (C-7), 25.2, 23.8, 23.2, 22.8 (C-26 or C-27), 22.5 (C-27 or C-26), 18.5 (C-21), 18.4 (C-19), 13.5 (C-18).

*4.1.22. (1R,3aS,4S,5R,7aR)-4-(5-Methoxy-2-methylphenethyl)-7a-methyl-1-((R)-6-methylheptan-2-yl)octahydro-1H-inden-5-ol (astrogorgiadiol methyl ether) (**34**).* ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.02 (d, J=8.2 Hz, 1H, H-1), 6.70 (d, J=2.7 Hz, 1H, H-4), 6.63 (dd, J=8.2, 2.7 Hz, 1H, H-2), 4.02 (br s, 1H, H-9), 3.75 (s, 3H, OMe), 2.71 (m, 1H), 2.43 (m, 1H), 2.22 (s, 3H, Me-19), 1.9–0.9 (m, 22H), 0.90 (d, J=6.6 Hz, 3H, Me-21), 0.85 (d, J=6.6 Hz, 3H, Me-27 or Me-26), 0.84 (d, J=6.6 Hz, 3H, Me-26 or Me-27), 0.67 (s, 3H, Me-18). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 157.8 (C-3), 142.4 (C-5), 130.8 (C-1), 127.9 (C-10), 114.5 (C-4), 110.7 (C-2), 67.2 (C-9), 56.2, 55.3 (OMe), 47.8, 42.9, 40.9, 39.5, 36.2, 35.8, 34.2, 31.1, 30.4, 30.2, 28.0, 27.8, 24.5, 23.8, 22.8 (C-26 or C-27), 22.6 (C-27 or C-26), 18.7 (C-21), 18.4 (C-19), 11.0 (C-18). Data consistent with literature values.[15,58]

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.11.102. These data include MOL files and InChiKeys of the most important compounds described in this article.

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