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A ring-closing metathesis-oxidation approach for the synthesis of seven-membered ring analogues of purpurogallin

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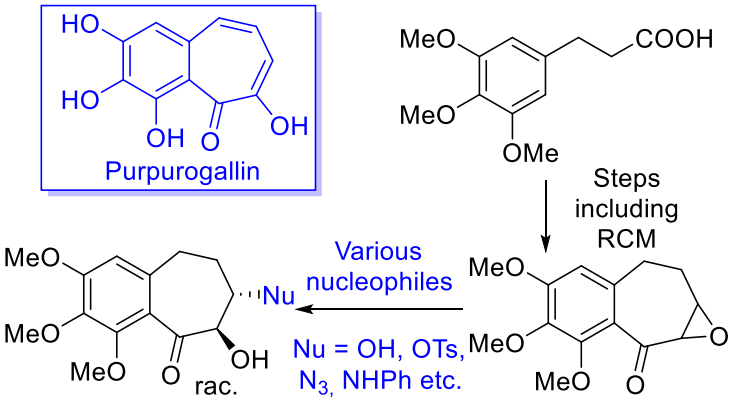
Dedication Manuscript dedicated to Prof. Hans-Günter Schmalz, due to his contributions to organic synthetic chemistry, the mentorship of students and colleagues, and for his friendship that has impacted many.[1]

Received 11-25-2025 **Accepted** 01-31-2026 **Published on line** 02-08-2026

Abstract

Various methoxy- and phenoxy-substituted benzannulated cycloheptenones and cycloheptanones have been synthesized as purpurogallin analogues by using ring-closing metathesis (RCM) and oxidation reactions as key steps. The structure of one of the products, 8-hydroxy-1,2,3-trimethoxy-5,6-dihydro-*7H*-benzo[*a*]cyclohepten-7-one was confirmed by single-crystal X-ray diffractometry. Furthermore, ring-opening of α-keto-epoxide 3,4,5-trimethoxy-1a,7,8,8a-tetrahydro-*2H*-benzo[4,5]cyclohepta[1,2-*b*]oxiren-2-one with a variety of nucleophiles provided a small library of purpurogallin-inspired derivatives.



Keywords: Purpurogallin analogues, benzannulated cycloheptenones, ring-closing metathesis, α-keto-epoxide ring-openings.

Introduction

Methoxy- and hydroxy-substituted benzannulated cycloheptenones and cycloheptanones are important structural motifs in a variety of pharmacologically relevant natural products.[2,3] These include well known compounds such as purpurogallin **(1)**, the colchicinoids **2a-d**, colchocone **(3)** and the allocolchicinoids **4a-c** (Figure 1).[4-6] The benzotropolone, purpurogallin **(1)**, extracted from various *Quercus sp*. (Nategall) species, is a natural pigment thought to be produced by oxidation of pyrogallol.[7] Purpurogallin **(1)** is also a member of the "tea polyphenol" family, which includes theaflavine **(5)**; these compounds have elicited interest due to their biotherapeutic potential.[8-12]

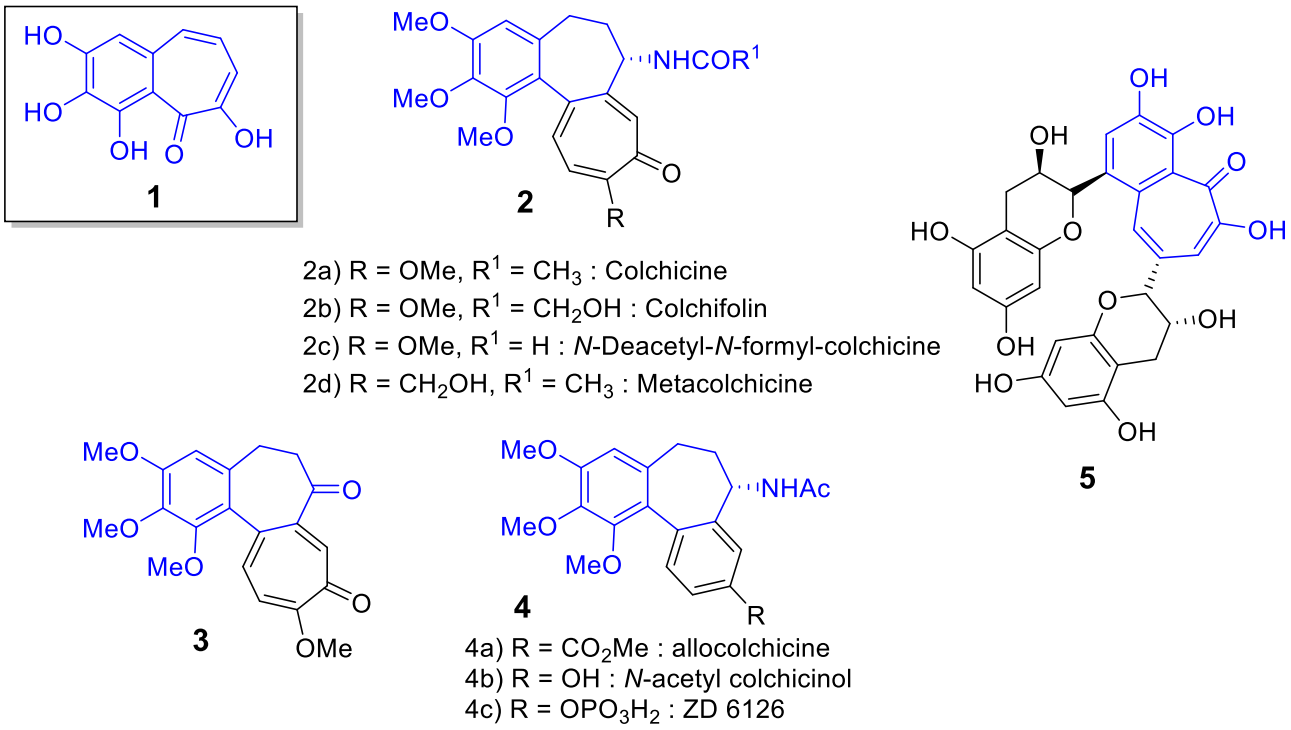


Figure 1. Examples of naturally occurring compounds and synthetic analogues containing the tropolone substructure.

Compounds containing the tropolone and the benzotropolone nuclei,[13,14] have been found to possess interesting antitumor activity.[15] Purpurogallin **(1)** has been shown to be an inhibitor of the polo-box domain (PBD) of human polo-like kinase-1 (Plk-1).[16] Purpurogallin **(1)** and its derivatives have also been shown to inhibit anti-apoptotic Bcl-2 family proteins such as Bcl-x_L and Bcl-2. It was proposed that the mechanism of antitumor action may be linked at least in part to its ability to inactivate Bcl-2 proteins.[17] More recently, it has been shown that purpurogallin **(1)** is active against esophageal squamous cell carcinomas (ESCC) and that the compound suppressed ESCC cell growth by impacting the mitogen-activated protein kinase 1/2 (MEK1/2) signalling system.[18] Of further interest, is that purpurogallin analogues and derivatives have found application in non-cancer-related research, such as application in viral Influenza A enzyme inhibitors.[19]

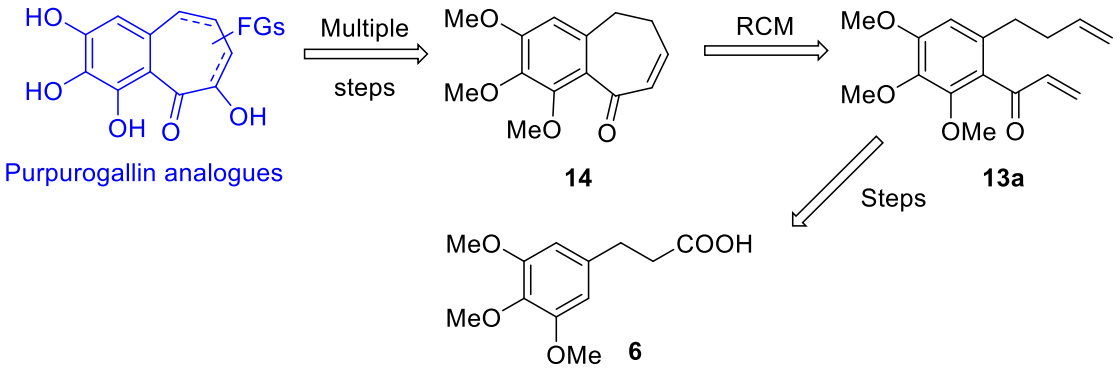
The biological significance of purpurogallin **(1)** and its derivatives, as demonstrated by the examples briefly described in the preceding paragraph, attracted our attention in view of synthesizing further analogues of purpurogallin **(1)**. We were particularly interested in purpurogallin analogues with modifications based on the "tropolone" part of the purpurogallin **(1)** structure. From the research performed on purpurogallin

derivatives, it should come as no surprise that analogues of this compound are of significant interest, especially in order to evaluate the bioactivity of these compounds. It should also be noted that the synthesis of purpurogallin derivatives through changes in the seven-membered tropolone moiety of the structure is not trivial, and that the direct derivatization of purpurogallin derivatives has often resulted in limited libraries of such compounds – for recent examples of purpurogallin derivative/analogue syntheses, see references[20,21].

Over the last decade, a ring closing metathesis (RCM) approach has frequently been utilized in our laboratories for the construction of benzo-fused heteroaromatic systems (for examples, see the following references[22-27]) As a result, we wished to utilize the RCM reaction as the key step in our synthesis.

To achieve our goal, it was decided to utilize RCM to synthesize the seven-membered ring which is arguably the more important part of the purpurogallin **1** backbone, and then to attempt derivatization on the intermediates generated. It should also be noted here that Brückner and colleagues have utilized ene-ene and ene-yne metathesis to elegantly deliver the 6,7-benzotropolone backbone found in compounds such as purpurogallin **(1)**,[28,29] and closely related compounds,[30,31] and that we collaborated with this group on a RCM-focused endeavour.[32]

In our approach to the generation of purpurogallin analogues, the 2,3,4-trimethoxy-8,9-dihydro-benzocyclohepten-5-one **(14)** was retro-synthetically disconnected by the cleavage of the sp^2–sp^2 carbon-carbon bond of the cycloheptenone ring to afford the key 1-(6-but-3-enyl-2,3,4-trimethoxy-phenyl)-propenone **(13a)**, which in turn could be synthesized from the commercially available precursor 3-(3,4,5-trimethoxy)-phenylpropionic acid **(6)** (see Scheme 1).

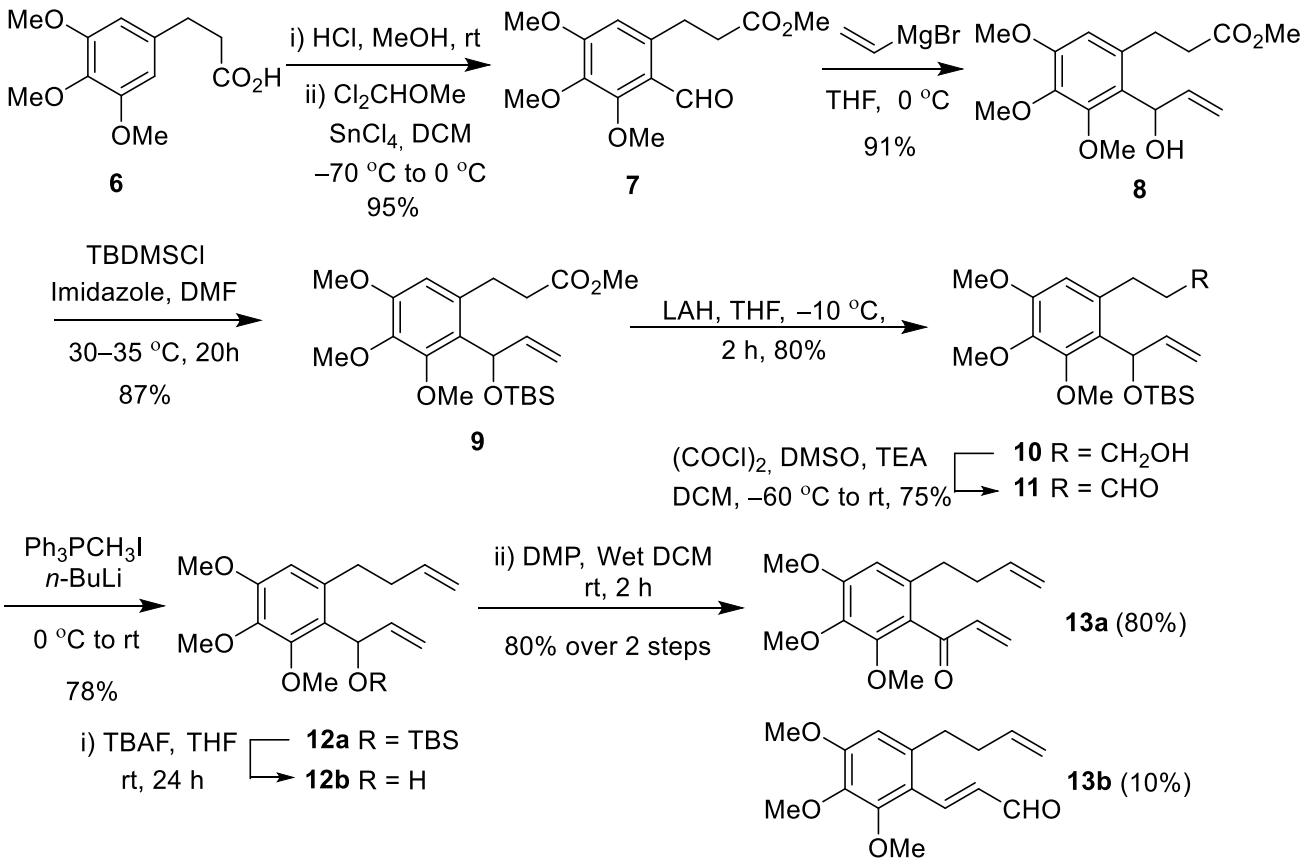


Scheme 1. Envisaged approach to the purpurogallin analogues.

Results and Discussion

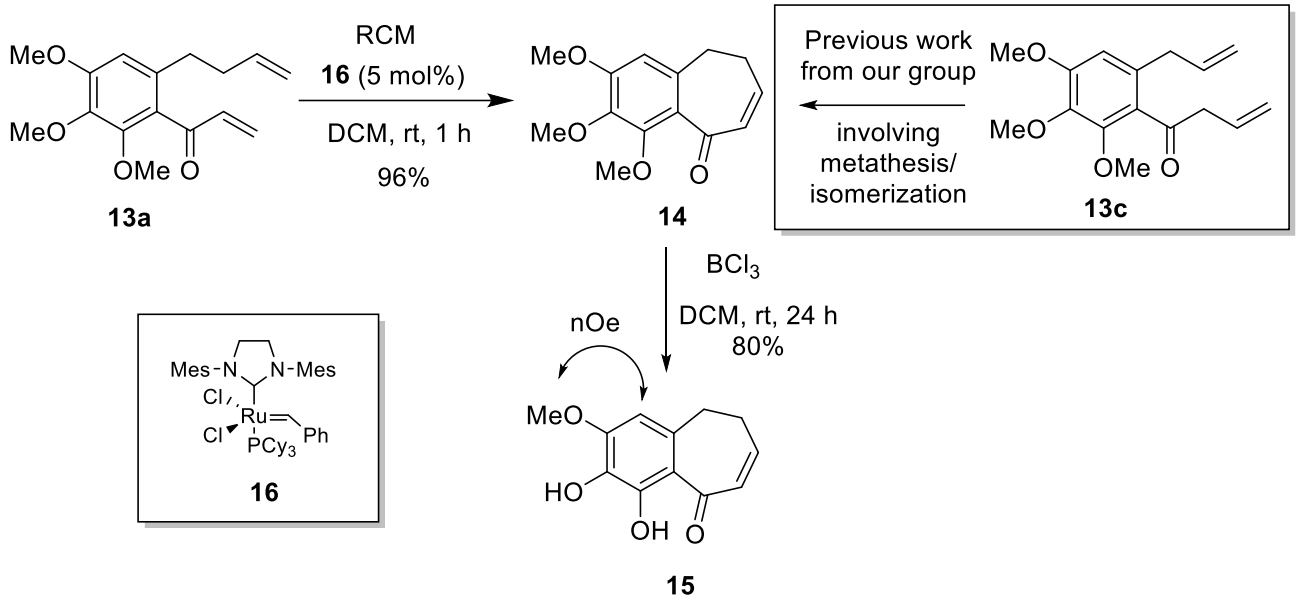
The synthetic strategy was initiated from the commercially available acid **6**. Conversion of the acid functionality of **6** into the corresponding methyl ester and subsequent formylation under Rieche conditions (dichloromethyl methyl ether/$SnCl_4$) to give aldehyde **7**, was done as previously described by Boyer and Hanna.[33] The aldehyde functionality then underwent facile Grignard addition with vinyl magnesium bromide to give alcohol **8** in 90% yield (Scheme 2). Protection of the resulting alcohol with *tert*-butyldimethylsilyl chloride (TBDMSCl) then led to **9** in 87% yield. Reduction of this compound with lithium aluminium hydride then afforded alcohol **10**, which was immediately oxidized under Swern conditions to afford aldehyde **11**. A subsequent Wittig reaction on substrate **11** using a methyltriphenylphosphonium iodide/*n*-BuLi combination provided diene **12a**. Deprotection of the silyl ether with TBAF resulted in the expected alcohol **12b**, which was immediately oxidized to the corresponding

ketone using the Dess-Martin periodinane in moist DCM.[34] This facile two-step procedure afforded keto-diene **13a** in 80% yield, along with the side-product **13b** in 10% yield; the latter compound being formed as a result of an unexpected, but not unheard of, oxidative rearrangement (see latter discussion).[35]

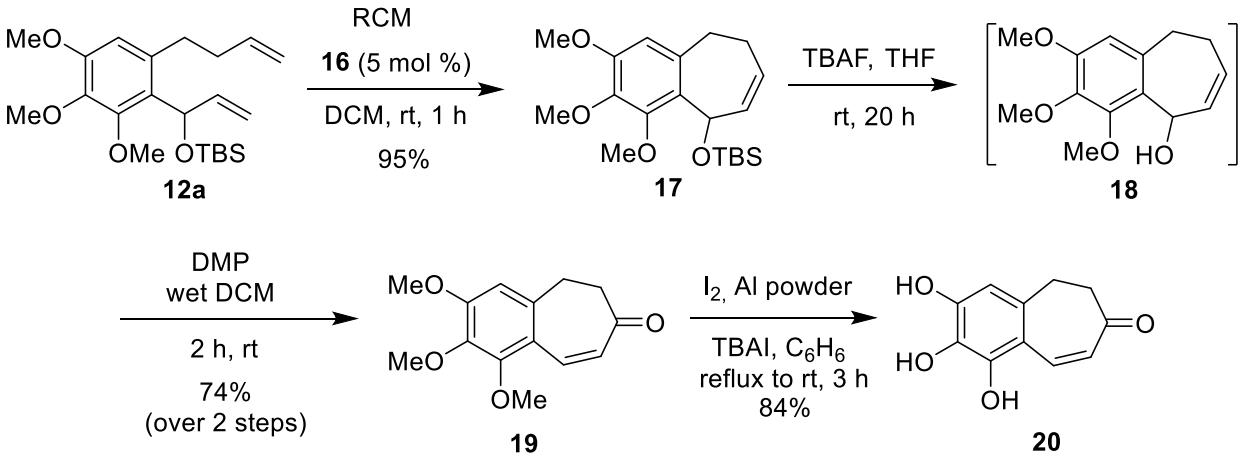


Scheme 2. Synthesis of key substrate 1-[6-(3-butenyl)-2,3,4-trimethoxyphenyl]-2-propen-1-one **(13a)**.

Treatment of keto-diene **13a** with 5 mol % Grubbs' second-generation catalyst **16**[36] in DCM under reflux for 1 h, successfully initiated the RCM reaction to afford the desired benzocycloheptenone **14** in 95% yield, as a white solid (the structure for which was confirmed by single crystal X-ray crystallography in our previous study, albeit that this compound was obtained after a metathesis/unexpected isomerization process from the diene **13c**).[32] At this stage it was intended to perform a global demethylation. After trying several methods, all of which met with failure, the demethylation of two of the methoxy groups was achieved with the help of boron trichloride, giving the first purpurogallin analogue **15** in a satisfactory 80% yield. The position of the remaining recalcitrant methoxy group in **15** was confirmed using NOESY studies, in which the methoxy group at C-2 showed a strong interaction with the lone aromatic proton at C-1 (Scheme 3).



Scheme 3. Synthesis of 2,3,4-trimethoxy-8,9-dihydro-benzocyclohepten-5-one **(14)** and 3,4-dihydroxy-2-methoxy-8,9-dihydro-benzocyclohepten-5-one **(15)**.

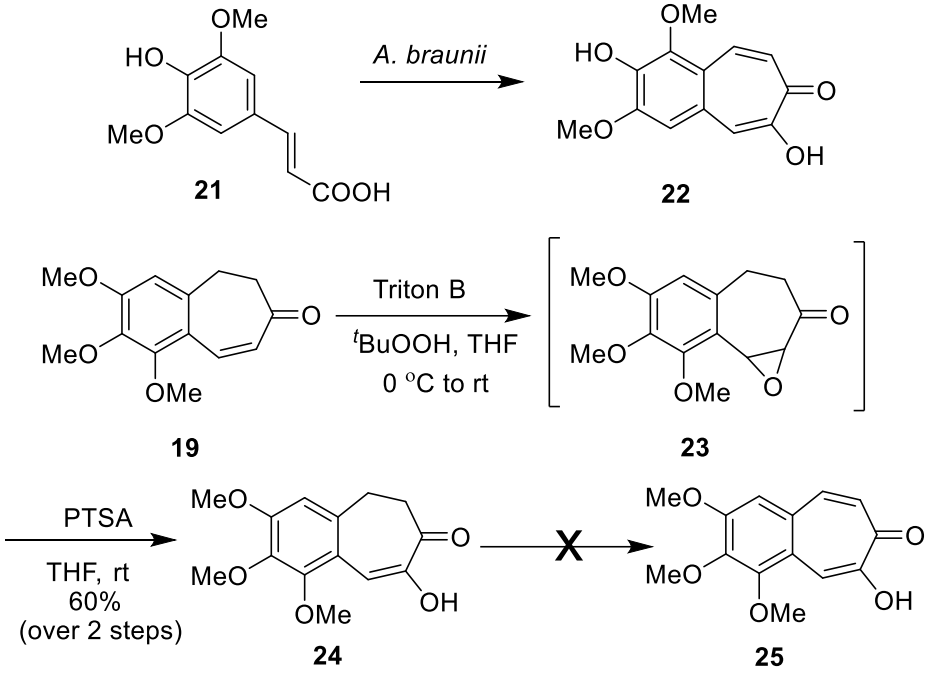


Scheme 4. Synthesis of 1,2,3-trimethoxy-5,6-dihydro-benzocyclohepten-7-one **(19)** and 1,2,3-trihydroxy-5,6-dihydro-benzocyclohepten-7-one **(20)**.

With the aim of obtaining purpurogallin-inspired compounds with atoms at different oxidation states, an RCM reaction was also performed on substrate **12a**, again with 5 mol % Grubbs' second-generation catalyst **16**, which afforded the cyclised product **17** in 95% yield (Scheme 4). Deprotection of the cyclised product with TBAF under standard conditions led to the benzannulated secondary alcohol **18**. Although this product was not fully characterized (see NMR spectrum in SI of sufficiently clean crude material for the subsequent step), it was expected that its oxidation to the corresponding ketone would provide another route to enone **14**. However, use of the Dess-Martin periodinane protocol in moist DCM afforded product **19** (74% yield over 2 steps), the result of an oxidative rearrangement. In terms of structural confirmation of the product, the ^{1}H NMR spectrum clearly showed signals associated with the isolated CH_2-CH_2 and CH=CH fragments. To the best of our knowledge application of the Dess-Martin periodinane oxidation for the oxidative rearrangement of secondary allylic

alcohols is quite uncommon, although other oxidants have regularly been successfully utilized in this type of process.[35] This time, exhaustive demethylation of compound **19** was readily achieved with the help of *in situ* produced aluminium iodide,[37] to afford another novel purpurogallin analogue **20** in a good yield of 84% (Scheme 4).

Perusal of the literature revealed that compound **20** showed interesting structural similarities to the compound 3,6-dihydroxy-2,4-dimethoxy-7*H*-benzocyclohepten-7-one **(22)**. This compound was previously obtained by the biotransformation of sinapinic acid **(21)** by the green algae *Ankistrodesmus braunii* as reported by Temussi and co-workers. (Scheme 5).[38] It was thus decided to investigate the possibility of introducing an enol group to scaffold **19**, to closer mimic the purpurogallin **(1)** structure. To this end, epoxidation of compound **19** with *tert*-butylhydroperoxide, in the presence of triton B (benzyltrimethylammonium hydroxide, solution of 40% w/w in water) at room temperature afforded epoxide **23** (Scheme 4).[39] This compound was found to be relatively unstable as it decomposed during attempted purification by silica gel column chromatography. Hence, it was decided to immediately isomerize the crude epoxide **23,** obtained after work-up, under anhydrous condition with *p*-toluenesulfonic acid or sulfuric acid (two drops) in THF, to generate the desired hydroxyketone **24** in a moderate yield of 60% over the two synthetic steps. The structure of compound **24** was confirmed by single crystal X-ray crystallography, as depicted in Figure 2, in which the ORTEP diagram highlights the structural features resulting from the initial oxidative rearrangement process. Unfortunately, despite numerous attempts, including the use of DDQ at elevated temperatures, we were unable to install the C-5–C-6 double bond to obtain the desired analogue **25**.



Scheme 5. Structure of known 3,6-dihydroxy-2,4-dimethoxy-7*H*-benzocyclohepten-7-one **(22)**[38] and synthesis of 8-hydroxy-1,2,3-trimethoxy-5,6-dihydro-benzocyclohepten-7-one **(24)**.

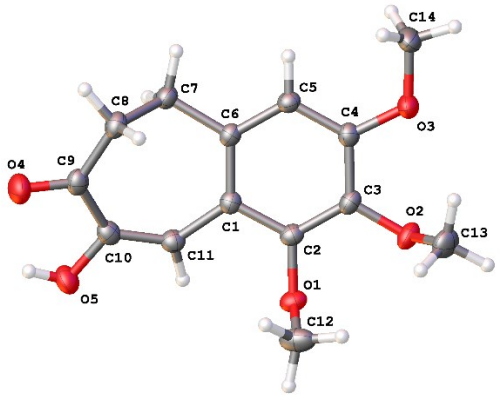
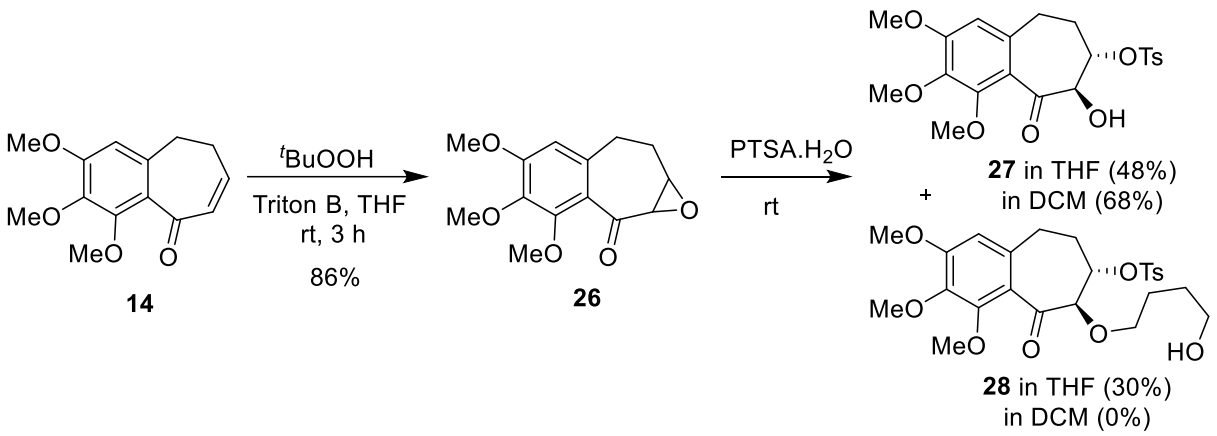


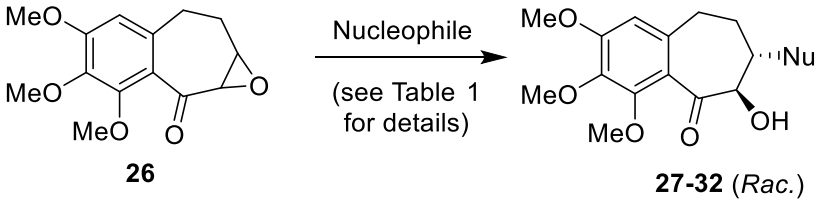
Figure 2. Single crystal X-ray structure of compound **24**. ORTEP diagrams drawn at 50% probability level.

Inspired by the success of the epoxidation strategy depicted in Scheme 5, it was decided to apply a similar protocol to compound **14**. In this respect, the epoxide **26** was readily generated by application of *tert*-butylhydroperoxide and triton B protocol (Scheme 6). In terms of NMR spectroscopy, it was interesting to note that protons H-1a and H-8a appeared as an overlapping 2-proton singlet at δ 3.56. Compound **26** was then exposed to acidic conditions in THF, but unfortunately it was not possible to introduce the α-hydroxyl group as previously accomplished. In our hands, it was furthermore noted that the epoxide **26** was much more stable compared to the isomeric **23** and exposure of **26** to an excess of *p*-toluenesulfonic acid (in comparison with the catalytic amount used in the isomerization of **23**) and prolonged stirring at room temperature, resulted in two ring-opened products. The first product, **27**, obtained in 48% yield was identified as a product in which the oxygen atom of a tosyl group had ring-opened the epoxide, presumably due to its relatively high concentration of *p*-TSA. The second product **28** was obtained in 30% yield, in which acidic decomposition of THF appears to have resulted in an additional four carbon-containing fragment appended to the scaffold. The regiochemistry of **28** was deduced as follows: the two 1-proton multiplets at δ 4.36 and 3.29 are ascribed to H-8 and H-7, respectively. Their connectivity in the 2D COSY spectrum, together with cross peaks between H-7 and H-6 and the HMQC connectivity between H-8 (δ 4.36) and C-9 (δ 200.8) is clear evidence of their juxtaposition. The signals for C-8 and C-7 are also found to be very close in the HSQC spectrum *viz*., δ 81.8 and 83.0 respectively. To avoid formation of **28**, the THF was replaced with dichloromethane, and when the reaction was repeated, only compound **27** was obtained in a reasonable 68% yield (Scheme 6). An interesting aspect of the ^{1}H NMR spectrum of **27** was the fact that protons H-7 and H-8 appeared as a sharp 2-proton multiplet at δ 4.50-4.40 which demonstrated connectivity in the 2D COSY spectrum to the hydroxyl substituent at δ 3.60.



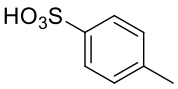
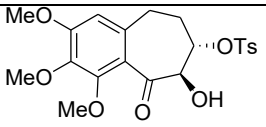
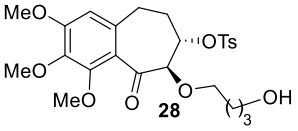
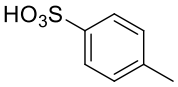
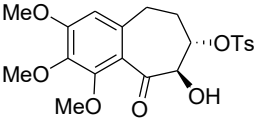
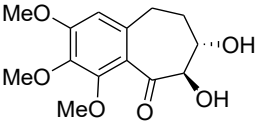
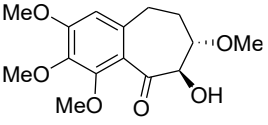
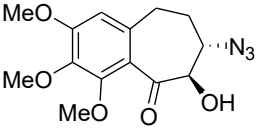
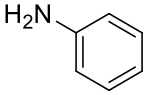
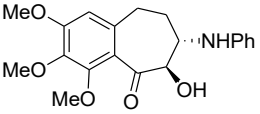
Scheme 6. Epoxidation to afford compound **26** and subsequent epoxide ring-opening experiments to form products **27** and **28** (for reaction conditions see Table 1).

Further studies showed that this approach was suitable for the ring-opening of epoxide **26** with a variety of nucleophiles, and even utilization of hot water as solvent readily afforded the diol **29** (Scheme 7), in which clear coupling between H-8 (δ 4.28) and C-9 (δ 201.3) was observed in the HMQC spectrum. In this respect several racemic analogues were synthesized by the *trans* ring-opening of epoxide **26** with the nucleophiles listed in Table 1. It should be appreciated that the nucleophilic ring-opening of α-keto epoxides has been investigated (for a review on the synthetic utility of epoxy ketones see reference[40]), with research groups reporting the outcomes of ring-opening with harder nucleophiles[41] or under acidic conditions[42] (generally leading to α-functionalization) to conditions including softer nucleophiles[43] and metal catalysis[44] (often resulting in the β-substituted product). Ring-openings have also been performed under enzymatic conditions[45] and solid-supported reagents.[46,47] In addition, the relative stereoselectivity of these reactions has also been found to be dependent on the reaction conditions.[41,43] In our reactions, the products obtained were single racemic products, and future investigations on these types of reactions will need to focus on further confirmation of the regio- and stereochemical outcomes of various nucleophiles, and the conditions under which they are applied, in terms of expanding the biochemical space provided by purpurogallin analogues.



Scheme 7. Nucleophilic ring-opening of epoxide **26** with various nucleophiles (see Table 1 for nucleophiles utilized).

Table 1

Entry	Nucleophile	Solvent	Product (*Rac.*)	Temp. (°C)	Time (h)	Yield (%)
1		THF	 **27** +  **28**	20–25	24	**(27)** 48 + **(28)** 30
2		DCM	 **27**	20–25	12	68
3	H_2O[a]	H_2O	 **29**	90	5	65
4	MeOH[a]	MeOH	 **30**	20–25	8	75
5	NaN_3	H_2O	 **31**	90	3	59
6		H_2O	 **32**	90	5	60

[a] H_2SO_4 catalyst added

Conclusions

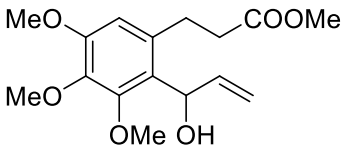
In conclusion, we have demonstrated that the cycloheptenone ring of purpurogallin **(1)** can be constructed from open chain olefins by an ene-ene ring-closing metathesis reaction utilizing the Grubbs' second-generation catalyst **16**. In this respect, a route to compounds with a benzo-annulated cycloheptenone ring, giving rise to various analogues of purpurogallin **(1)**, has been achieved. This synthetic protocol produced examples of compound modifications based on the tropolone moiety of purpurogallin in which compounds **14**, **15**, **19**, **20**, **24** and **27–32** were successfully synthesized.

Experimental Section

General. All solvents used in silica gel column and preparative chromatography were distilled prior to use. Solvents used in reactions were pre-dried in their reagent bottles and then distilled over the appropriate drying mediums under a nitrogen atmosphere. Tetrahydrofuran (THF) was predried over sodium wire and distilled from sodium metal wire and with benzophenone as indicator. Dichloromethane and methanol were distilled from calcium hydride.

Thin layer chromatography (TLC) was performed on aluminium-backed ALUGRAMSil G/UV254 plates pre-coated with 0.25 mm silica gel 60. Silica gel 60 (particle size 0.063–0.200 mm) was used as the adsorbent for conventional preparative column chromatography. All melting points were obtained on a hot-stage microscope. Infrared spectra obtained are reported on the wavenumber (cm^{-1}) scale, in the range 400–4000 cm^{-1}. Hydrogen (^{1}H NMR) nuclear magnetic resonance spectra were recorded at 300 MHz and 500 MHz. Carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded at 74 MHz and 125 MHz. Most of the spectra were recorded in deuterated chloroform ($CDCl_3$) and a few in deuterated methanol (MeOD-d_4). Some high-resolution electrospray ionization mass spectra (ESI-FTMS) were recorded using a Thermo LTQ Orbitrap high resolution mass spectrometer coupled to an HPLC System supplied with a "Hypersil GOLD" column, whilst others were recorded on an API Q-TOF Ultima. Furthermore, other mass spectra were recorded on a MS 9/50, VG 70E MS or a VG 70 SEQ mass spectrometer. For X-ray crystallography, intensity data were collected on a APEX II CCD area detector diffractometer with graphite monochromated Mo Kα radiation (50 kV, 30 mA) using the APEX 2 data collection software. The collection method involved ω-scans of width 0.5° and 512 × 512 bit data frames. Data reduction was carried out using the program SAINT+ and face indexed absorption corrections were made using the program XPREP. The crystal structure was solved by direct methods using SHELXTL. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F2 using SHELXTL. Hydrogen atoms were first located in the difference map, then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using SHELXTL, PLATON and OLEX2. In vacuo refers to the removal of solvent under reduced pressure (~20 mm Hg, 45 °C) on a rotary evaporator and final drying on an oil pump (~1–2 mm Hg) at rt.

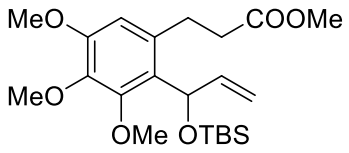
Methyl 3-[2-(1-hydroxy-2-propenyl)-3,4,5-trimethoxyphenyl]propanoate (8)



Vinylmagnesium bromide (35.4 mL, 35.4 mmol, 1M solution in THF) was added drop-wise at –10 °C and under Ar to a solution of methyl 3-(2-formyl-3,4,5-trimethoxyphenyl)propanoate **7**[33] (5.0 g, 17 mmol) in dry THF (100 mL). The reaction mixture was then stirred at –10 °C for 2 h, quenched into a saturated solution of NH_4Cl (100 mL) and then diluted with EtOAc (250 mL). The biphasic mixture was subsequently warmed to rt, the layers separated and the aqueous phase extracted with EtOAc (2 × 100 mL). The combined organic extracts were then washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product **8** (5.0 g, 91%) as a light-yellow thick liquid which was used without further purification in the next synthetic step. IR (neat): ν_{max} (film)/cm^{-1}: 3500, 2941, 1735, 1598, 1495, 1453, 1406; ^{1}H NMR (300 MHz; $CDCl_3$):

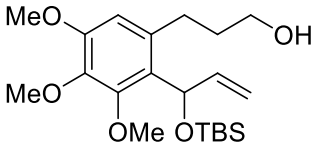
δ 6.50 (s,1H), 6.23–6.13 (m, 1H), 5.34–5.28 (m, 1H), 5.17 (d, *J* = 1.5 Hz, 1H), 5.14–5.08 (m, 1H), 3.89 (s, 3H), 3.87 (br s, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.68 (s, 3H), 2.94 (td, *J* = 7.2, 3.8 Hz, 2H), 2.58 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 173.1, 152.7, 152.3, 141.5, 140.7, 133.6, 126.1, 113.7, 108.5, 70.4, 61.1, 60.5, 55.9, 51.6, 35.7, 28.4; *m/z* (EI): 333 (M^+ + 23, 6%), 293 (24), 267 (100), 219 (52), 204 (20); HRMS: calcd for $C_{16}H_{22}O_6$ (M^+ + Na) 333.1309, found: 333.1308.

Methyl 3-[2-(1-{[*tert*-butyl(dimethyl)silyl]oxy}g-2-propenyl)-3,4,5-trimethoxyphenyl]propanoate (9)



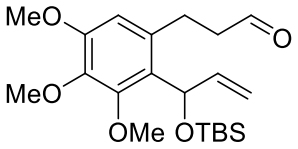
The alcohol **8** (5.0 g, 16 mmol) was dissolved in dry DMF (20 mL), after which imidazole (2.19 g, 32.2 mmol) and *tert*-butyldimethylsilyl chloride (4.86 g, 32.2 mmol) were added at rt under Ar. The mixture was then stirred at 30–35 °C for 20 h. After cooling, the reaction mixture was diluted with Et_2O (200 mL), washed with the following: HCl solution (1.2 M, 50 mL), H_2O (50 mL), brine (50 mL), and then dried over Na_2SO_4. This was followed by filtration and concentration of the organic phases under reduced pressure. The resulting residue was finally purified by silica gel column chromatography (Eluent: 20% EtOAc/hexane) to give the desired compound **9** (6.0 g, 87%) as a colourless thick liquid. IR (neat): ν_{max} (film)/cm^{-1}: 2930, 1738, 1596, 1494, 1462, 1405; ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.56 (s, 1H), 6.10–6.02 (m, 1H), 5.90–5.89 (m, 1H), 5.26–5.20 (m, 1H), 5.09–5.05 (m, 1H), 3.92 (s,3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.74 (s, 3H), 3.17 (t, *J* = 7.8 Hz, 2H), 2.74–2.53 (m, 2H), 0.94 (s, 9H), 0.15 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 173.8, 152.3, 151.0, 141.3, 140.0, 136.4, 126.8, 112.9, 109.2, 68.6, 61.4, 60.7, 55.7, 51.4, 36.1, 27.5, 25.9, 18.2, –4.8, –5.0; *m/z* (EI): 475 (M^+ , 70%), 467 (40), 447 (M^+ + 23, 100), 431 (35), 421 (8); HRMS: calcd for $C_{22}H_{36}O_6Si$ (M^+ + Na) 447.2178, found: 447.2180.

3-[2-(1-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-propenyl)-3,4,5-trimethoxyphenyl]-1-propanol 10



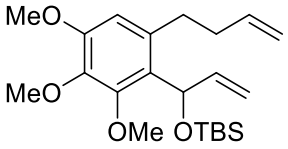
A solution of ester **9** (6.0 g 14 mmol) in dry THF (120 mL) was added dropwise under Ar to a solution of $LiAlH_4$ (1.07 g, 28.3 mmol) in dry THF (30 mL) cooled to –10 °C. The reaction mixture was then stirred at –10 °C for 2 h and then quenched by the sequential slow addition of H_2O (10 mL), NaOH solution (10%, 10 mL) and EtOAc (250 mL). The quenched reaction mass was allowed to warm to rt, filtered through a Celite bed and the filtrate washed with EtOAc (50 mL). The combined organic layers were then washed with brine solution (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the alcohol **10** (4.48 g, 80%) as a colourless thick liquid which was used without further purification in the next step. IR (neat): ν_{max} (film)/cm^{-1}: 3435, 2930, 1596, 1493, 1462, 1405, 1329, 1250; ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.43 (s, 1H), 6.18–6.02 (m, 1H), 5.84–5.81 (m, 1H), 5.26–5.24 (m, 1H), 5.09–5.04 (m, 1H), 3.76 (s, 3H), 3.74 (s, 6H), 3.56 (dd, *J* = 11.5, 6.1 Hz, 2H), 2.73 (t, *J* = 8.1 Hz, 2H), 1.80–1.71 (m, 2H), 1.59 (br s, 1H), 0.78 (s, 9H), 0.00 (s, 3H), –0.15 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 152.2, 151.1, 141.7, 139.7, 137.5, 126.7, 112.6, 109.1, 68.8, 62.6, 61.4, 60.7, 55.7, 34.5, 28.3, 25.9, 18.3, –4.8, –4.9; *m/z* (EI): 439 (M^+, 16%), 423 (26), 419 (M^+ + Na, 100), 413 (52); HRMS: calcd for $C_{21}H_{36}O_5Si$ (M^+ + Na) 419.2224, found: 419.2219.

3-[2-(1-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-propenyl)-3,4,5-trimethoxyphenyl]propanal 11



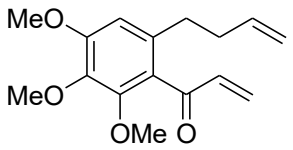
To a solution of $COCl_2$ (1.5 g, 12 mmol) in dry DCM (30 mL) at –65 °C under Ar, was added dropwise a solution of DMSO (1.9 g, 25 mmol) in dry DCM (5 mL). After being stirred at –65 °C for 15 min, a solution of alcohol **10** (4.0 g, 10 mmol) in dry DCM (15 mL) was added dropwise, after which the reaction was stirred for 30 min. Et_3N (5.1 g, 50 mmol) was then added slowly and the reaction stirred for a further 15 min. The reaction mixture was warmed to rt, quenched with H_2O (30 mL) and further diluted with DCM (100 mL). The layers were separated and the aqueous layer was extracted with DCM (30 mL). The combined organic layers were sequentially washed with aqueous solutions of HCl (1N, 25 mL) and $NaHCO_3$ (10%, 25 mL) followed by brine (25 mL). The organic solvent was then dried over Na_2SO_4 and concentrated at reduced pressure to give the crude product which was purified by silica gel column chromatography (Eluent: 10% EtOAc/hexane) to give aldehyde **11** (2.99 g, 75%) as a light-yellow liquid. IR (neat): ν_{max} (film)/cm^{-1}: 2930, 1724, 1596, 1493, 1462, 1405, 1250; ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.84 (t, *J* = 1.5 Hz, 1H), 6.53 (s, 1H), 6.08–5.97 (m, 1H), 5.94–5.92 (m, 1H), 5.26–5.18 (m, 1H), 5.10–5.05 (m, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.18 (t, *J* = 7.9 Hz, 2H), 2.88–2.68 (m, 2H), 0.94 (s, 9H), 0.15 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 202.2, 152.3, 151.0, 141.4, 140.0, 136.2, 126.7, 112.8, 109.3, 68.5, 61.4, 60.7, 55.8, 45.9, 25.9, 24.6, 18.3, –4.8, –5.0; *m/z* (EI): 417 (M^+ + 23, 42%), 414 (M^+, 20), 413 (100), 409 (6); HRMS: calcd for $C_{21}H_{34}O_5Si$ (M^+ + Na) 417.2067, found: 417.2061.

({1-[6-(3-Butenyl)-2,3,4-trimethoxyphenyl]-2-propenyl}aoxy)(*tert*-butyl)dimethylsilane 12a



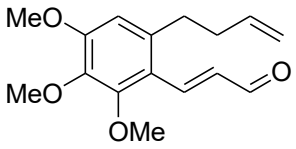
n-Butyllithium (7.1 mL, 11 mmol, 1.6 M solution in hexane) was added dropwise under Ar and at rt to a solution of methyltriphenylphosphonium iodide (4.6 g, 11 mmol) in dry THF (30 mL). The resulting yellow-orange solution was stirred at rt for 30 min. and cooled to 0–5 °C, after which a solution of aldehyde **11** (2.99 g, 7.56 mmol) in dry THF (15 mL) was added dropwise over 10 min. under Ar to the resulting ylide solution at 0–5 °C. The reaction mixture was then warmed to rt and stirred for 1 h, diluted with Et_2O (200 mL) and further stirred at rt for 30 min. The resultant solid suspension was collected by filtration through cotton wool and washed with Et_2O (25 mL). The combined filtrate was then concentrated under reduced pressure to afford a residue which was purified by silica gel column chromatography (Eluent: 10% EtOAc/hexane) to afford alkene **12a** (2.32 g, 78%) as a colourless oil. IR (neat): ν_{max} (film)/cm^{-1}: 2930, 1596, 1492, 1462, 1404, 1323, 1250; ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.40 (s, 1H), 6.10–6.02 (m, 1H), 5.87–5.76 (m, 1H), 5.73–5.71 (m, 1H), 5.26–5.20 (m, 1H), 5.00–4.88 (m, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 2.77 (t, *J* = 7.9 Hz, 2H), 2.32–2.13 (m, 2H), 0.79 (s, 9H), 0.00 (s, 3H), –0.17 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 152.1, 151.1, 141.6, 139.7, 138.7, 137.6, 126.7, 114.3, 112.6, 109.2, 68.7, 61.4, 60.7, 55.7, 35.5, 31.4, 25.9, 18.2, –4.8, –4.9; *m/z* (EI): 435 (92%), 431 (40), 415 (M^+ + 23, 100), 413 (59); HRMS: calcd for $C_{22}H_{36}O_4Si$ (M^+ + Na) 415.2275, found: 415.2274.

1-[6-(3-Butenyl)-2,3,4-trimethoxyphenyl]-2-propen-1-one 13a



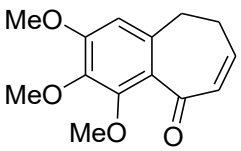
TBAF (8.9 mL, 8.9 mmol, 1M solution in THF) was added under Ar, and at rt, to a solution of **12a** (2.0 g, 5.1 mmol) in dry THF (15 mL). The reaction mixture was then stirred at rt for 24 h. When the reaction was complete (TLC), the mixture was diluted with Et_2O (200 mL), washed with saturated NH_4Cl solution (50 mL) and brine (50 mL), after which it was dried over Na_2SO_4. The solvent was concentrated under reduced pressure to give **12b** (~ 2.0 g) as a crude residue which was utilized in the next reaction without further purification. The crude alcohol was dissolved in moist DCM (50 mL, DCM saturated with H_2O), which was cooled (0–5 °C), and to which the Dess-Martin periodinate reagent (4.3 g, 10 mmol) was added in small portions over 10 min. The reaction mixture was then stirred at rt for 2 h, before being quenched into a 1:1 mixture of 10% $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (50 mL). The phases were then separated, and the aqueous layer extracted with DCM (2 × 50 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product as a residue. The residue was subjected to flash silica gel column chromatography (Eluent: 10% EtOAc/hexane) to give the desired product **13a** (1.13 g, 80% over two steps) as a light yellow oil, along with side product **13b**, 3-[6-(3-butenyl)-2,3,4-trimethoxyphenyl]acrylaldehyde (0.14 g, 10% over two steps), also as a light yellow liquid (see next section for characterization). **13a**: IR (neat): ν_{max} (film)/cm^{-1}: 2938, 1663, 1595, 1452, 1397, 1322, 1253, 1195; ^{1}H NMR (300 MHz; $CDCl_3$): δ (ppm) 6.68–6.58 (m, 1H), 6.54 (s, 1H), 6.04–6.00 (m, 1H), 5.97 (dd, *J* = 7.3, 1.1 Hz, 1H), 5.84–5.71 (m, 1H), 5.04–4.94 (m, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 2.54 (dd, *J* = 9.3, 6.5 Hz, 2H), 2.31–2.24 (m, 2H); ^{13}C NMR (75 MHz; $CDCl_3$): δ (ppm) 197.2, 154.2, 150.9, 139.7, 138.8, 137.7, 135.4, 130.4, 126.0, 115.0, 108.5, 61.5, 60.8, 56.0, 35.4, 32.4; *m/z* (EI): 299 (M^+ + Na, 20%), 277 (M^+ + H, 100), 235 (18); HRMS: calcd for $C_{16}H_{20}O_4$ (M^+ + H) 277.1440, found: 277.1445.

3-[6-(3-Butenyl)-2,3,4-trimethoxyphenyl]acrylaldehyde 13b



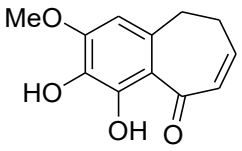
IR (neat): ν_{max} (film)/cm^{-1}: 2937, 1673, 1587, 1490, 1453, 1402, 1322, 1240, 1194; ^{1}H NMR (300 MHz; $CDCl_3$): δ (ppm) 9.65 (d, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 16.0 Hz, 1H), 6.95 (dd, *J* = 16.0, 7.8 Hz, 1H), 6.57 (s, 1H), 5.92–5.79 (m, 1H), 5.12–5.02 (m, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 2.83 (dd, *J* = 9.0, 6.8 Hz, 2H), 2.40–2.28 (m, 2H); ^{13}C NMR (75 MHz; $CDCl_3$): δ (ppm) 195.5, 155.2, 154.2, 147.2, 140.8, 139.0, 137.1, 131.3, 119.1, 115.6, 109.0, 60.8, 60.5, 55.9, 35.3, 33.6; *m/z* (EI): 299 (M^+ + Na, 7%), 278 (20), 277 (M^+ + Na, 100), 233 (25), 207 (10); HRMS: calcd for $C_{16}H_{20}O_4$ (M^+ + H) 277.1440, found: 277.1442.

2,3,4-Trimethoxy-8,9-dihydro-5*H*-benzo[*a*]cyclohepten-5-one 14[32]



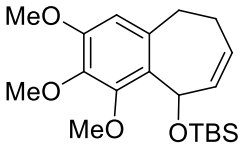
Grubbs' second generation catalyst **16** (0.173 g, 5 mol %) was added under Ar to a degassed solution of keto-alkene **13a** (1.13 g, 4.07 mmol) in dry DCM (25 mL). The mixture was then heated under reflux for 1 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure and the residue was subjected to silica gel column chromatography (Eluent: 20% EtOAc/hexane) to afford the cyclised product **14** (0.971 g, 96%), as a white solid. Characterization as reported previously by our group.[32]

3,4-Dihydroxy-2-methoxy-8,9-dihydro-5*H*-benzo[*a*]cyclohepten-5-one 15



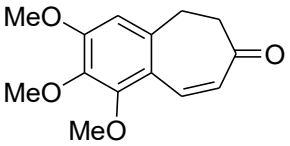
BCl_3 (0.19 g, 1.6 mL, 1.6 mmol, 1M solution in DCM) was added to the solution of **14** (0.10 g, 0.40 mmol) in dry DCM (3 mL). The mixture was then stirred at rt for 24 h. After completion of the reaction (TLC), the reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (2 × 2 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give a residue which was purified by silica gel column chromatography (Eluent: 30% EtOAc/hexane) to afford the desired product **15** (0.070 g, 80%) as a red-coloured solid. R_f = 0.39 (EtOAc/Hexane, 2:3); Mp: 138–142 °C; IR (neat): ν_{max} (film)/cm^{-1}: 3438, 1640, 1607, 1563, 1494, 1444, 1415, 1350, 1306, 1286, 1237, 1193; ^{1}H NMR (500 MHz; MeOD-d_4): δ (ppm) 6.84–6.79 (m, 1H), 6.42 (s, 1H), 6.18 (dt, *J* = 11.9, 1.6 Hz, 1H), 3.89 (s, 3H), 2.98–2.96 (m, 2H), 2.51 (ddd, *J* = 11.9, 5.4, 1.6 Hz, 2H); ^{13}C NMR (125 MHz; MeOD-d_4): δ (ppm) 197.3, 153.7, 153.0, 150.0, 136.5, 134.4, 133.5, 116.5, 106.0, 56.4, 36.6, 30.3; *m/z* (EI): 243 (M^+ + 23, 100%), 221 (M^+ + 1, 80); HRMS: calcd for $C_{12}H_{12}O_4$ (M^+ + H) 221.0814, found: 221.0815.

***tert*-Butyl(dimethyl)[(2,3,4-trimethoxy-8,9-dihydro-5*H*-benzo[*a*]cyclohepten-5-yl)oxy]silane 17**



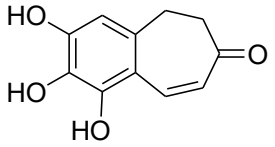
Grubbs' second generation catalyst **16** (0.25 g, 5 mol %) was added at rt under Ar to a degassed solution of alkene **12** (2.32 g, 5.89 mmol) in dry DCM (50 mL). The mixture was then stirred at rt for 2 h. The solvent was removed under reduced pressure and the resulting residue was subjected to silica gel column chromatography (Eluent: 10% EtOAc/hexane) to give the cyclized product **17** (2.04 g, 95%), as an off-white solid. Mp: 40–42 °C; IR (neat): ν_{max} (film)/cm^{-1}: 2929, 1500, 1453, 1343, 1318, 1248; ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.39 (s, 1H), 5.91–5.83 (m, 1H), 5.61–5.55 (m,1H), 5.37 (d, *J* = 7.8 Hz, 1H), 3.94–3.77 (m, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.72 (s, 3H), 2.38–2.29 (m, 2H), 2.12–1.99 (m, 1H), 0.75 (s, 9H), 0.00 (s, 3H), –0.15 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 151.9, 150.1, 139.6, 137.9, 133.4, 129.7, 129.0, 108.8, 62.6, 61.6, 60.8, 55.8, 31.6, 29.7, 25.9, 18.1, –4.4, –4.7; *m/z* (EI): 387 (M^+ + Na, 100%), 341 (25), 338 (15); HRMS: calcd for $C_{20}H_{32}O_4Si$ (M^+ + Na) 387.1962, found: 387.1958.

1,2,3-Trimethoxy-5,6-dihydro-7*H*-benzo[*a*]cyclohepten-7-one 19



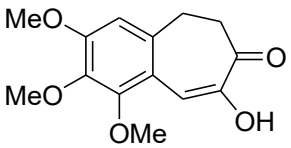
TBAF (8.23 mL, 8.23 mmol, 1M solution in THF) was added under Ar and at rt, to a stirred solution of **17** (2.0 g, 5.5 mmol) in dry THF (15 mL). The reaction mixture was then stirred at rt for 20 h, after which it was diluted with Et_2O (250 mL) and washed with saturated aqueous NH_4Cl solution (50 mL) and brine (50 mL). The organic phase was then dried over Na_2SO_4 and concentrated under reduced pressure to give the crude alcohol **18** (1.5 g), which was used without further purification. The crude alcohol **18** (1.5 g) was dissolved in moist DCM (50 mL, DCM saturated with H_2O) and the Dess-Martin periodinate (4.6 g, 11 mmol) was added in portions at 0–5 °C over 10 min. The reaction mixture was then stirred at rt for a further 2 h, after which it was quenched into a 1:1 solution of 10% $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (50 mL) The layers were separated and the aqueous layer extracted with DCM (2 × 50 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give a crude residue which was subjected to silica gel column chromatography (Eluent: 30% EtOAc/hexane) to afford product **19** (1.01 g, 74% over two steps) as a white solid. Mp: 60–62 °C; IR (neat): ν_{max} (film)/cm^{-1}: 2943, 1656, 1588, 1559, 1496, 1341, 1320, 1274, 1191; ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.48 (d, *J* = 12.9 Hz, 1H), 6.58 (s, 1H), 6.13 (d, *J* = 12.9 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.86 (s, 3H), 2.92 (t, *J* = 5.7 Hz, 2H), 2.72 (t, *J* = 5.7 Hz, 2H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 201.6, 154.5, 153.7, 140.5, 138.9, 136.2, 127.4, 121.3, 107.8, 61.7, 60.9, 56.0, 42.3, 30.0; *m/z* (EI): 250 (M^+, 10%), 249 (M^+ + H, 100), 233 (2), 193 (2); HRMS: calcd for $C_{14}H_{16}O_4$ (M^+ + H) 249.1127, found: 249.1127.

1,2,3-Trihydroxy-5,6-dihydro-7*H*-benzo[*a*]cyclohepten-7-one 20



Iodine (15.3 g, 60.4 mmol) was added to a suspension of Al powder (2.2 g, 80 mmol) in dry C_6H_6 (50 mL). The mixture was stirred and heated under reflux for 30 min. and then cooled to 5 °C, after which a few crystals of TBAI (5–10 crystals) were added, followed by a solution of **19** (1.0 g, 4.0 mmol) in C_6H_6 (10 mL). The reaction mass was warmed to rt and stirred for a further 3 h, after which it was quenched into an aqueous HCl solution (2M, 50 mL). The mixture was extracted with EtOAc (3 × 50 mL), which was washed sequentially with a $NaHCO_3$ solution (10%, 25 mL), followed by brine (25 mL) and then dried over Na_2SO_4 and concentrated under reduced pressure to give a residue which was purified using silica gel column chromatography (Eluent: 30% EtOAc/hexane) to give a sticky solid which was re-crystallized [DCM (4 mL)/hexane (8 mL)] to afford the desired product **20** (0.70 g, 84%) as a light yellow solid. Mp: 142–145 °C; IR (neat): ν_{max} (film)/cm^{-1}: 3425, 3237, 1652, 1563, 1453, 1283, 1172; ^{1}H NMR (300 MHz; MeOD-d_4): δ 7.68 (d, *J* = 12.6 Hz, 1H), 6.30 (s, 1H), 5.95 (d, *J* = 12.6 Hz, 1H), 2.79 (t, *J* = 5.7 Hz, 2H), 2.63 (t, *J* = 5.7 Hz, 2H); ^{13}C NMR (75 MHz; MeOD-d_4): δ 205.0, 149.4, 148.9, 140.1, 136.3, 132.2, 124.8, 115.9, 108.5, 43.2, 30.3; *m/z* (EI): 207 (M^+ + H, 100%), 181 (2); HRMS: calcd for $C_{11}H_{10}O_4$ (M^+ + H) 207.0657, found: 207.0654.

8-Hydroxy-1,2,3-trimethoxy-5,6-dihydro-7*H*-benzo[*a*]cyclohepten-7-one 24

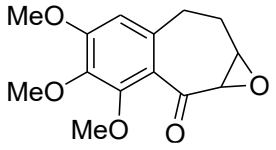


To a solution of **19** (0.25 g, 1.0 mmol) in THF (15 mL) at rt was added triton B (1.0 mL, 40% wt solution in H_2O) and ^{t}BuOOH (1.0 mL, 70% wt solution in H_2O). The reaction mixture was then stirred at 25 °C for 3 h, after which

it was quenched into a saturated aqueous solution of NH_4Cl (20 mL) which was extracted with EtOAc (2 × 25 mL). The combined organic phases were then washed with brine solution (20 mL), dried over Na_2SO_4 and concentrated to give the crude epoxide **23**, which was utilized without further purification. This residue was dissolved in dry THF (20 mL) and anhydrous *p*-toluenesulfonic acid (0.17 g, 1.0 mmol) or H_2SO_4 (2 drops) were added at rt while stirring. After 30 min. the solvent was concentrated and the crude residue obtained subjected to silica gel flash column chromatography (eluent: 20% EtOAc/hexane) to afford the desired compound **24** (0.16 g, 60% over two steps) as a white solid. Mp: 110–112 °C; IR (neat): ν_{max} (film)/cm^{-1}: 3415, 2940, 1643, 1617, 1498, 1436, 1415, 1343, 1285, 1214; ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.23 (s, 1H), 6.56 (s, 1H), 6.51 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 2.90–2.78 (m, 4H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 195.9, 152.9, 152.6, 146.2, 140.9, 135.8, 120.2, 111.7, 108.0, 61.5, 60.9, 56.0, 38.9, 29.7; *m/z* (EI): 265 (M^+ + H, 70%), 263 (M^+ – H, 25), 249 (100), 245 (32); HRMS: calcd for $C_{14}H_{16}O_5$ (M^+ + H) 265.1076, found: 265.1062.

X-ray crystal structure details of compound 24: crystallized from EtOAc-Hexane, formula: $C_{14}H_{16}NO_5$, M=264.09, colour of crystal: colourless, needle, crystal size 0.42 × 0.41 × 0.24 mm^3, *a* = 7.58290(10) Å, *b* = 8.7042(2) Å, *c* = 10.3228(2) Å, *V* = 617.33(2) Å^3, $\rho_{cal\ c}$ = 1.422 Mg/m^3, μ = 0.108 mm^{-1}, F(000) = 280, *Z* = 2, *T*=173(2) K, 13421 reflections collected, 2977 [R(int) = 0.0331] independent reflections, θ_{max} 27.98°, 436 refined parameters, maximum residual electron density 0.320 and –0.199 e.Å^{-3}, R1 = 0.0461, wR2 = 0.1045. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC 2505525.

3,4,5-Trimethoxy-1a,7,8,8a-tetrahydro-2*H*-benzo[4,5]cyclohepta[1,2-*b*]oxiren-2-one 26

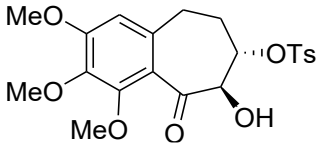


To a solution of **14** (0.25 g, 1.0 mmol) in THF (15 mL) at rt was added triton B (1.0 mL, 40% wt solution in H_2O) and ^{t}BuOOH (1.0 mL, 70% wt solution in H_2O). After being stirred at 25 °C for 3 h, the reaction mass was quenched into a saturated aqueous solution of NH_4Cl (20 mL) and extracted with EtOAc (2 × 25 mL). The combined organic layer was washed with brine solution, dried over Na_2SO_4 and concentrated to give the crude epoxide. This compound was dissolved in Et_2O (8 mL) and stirred at rt for 1 h, after which the solid product crystallized in the flask through slow evaporation of the Et_2O. The solid was recovered by filtration and dried in air to give the pure epoxide **26** (0.23 g, 86%) as a white solid. Mp: 124–126 °C; IR (neat): ν_{max} (film)/cm^{-1}: 2938, 1693, 1593, 1493, 1458, 1411, 1338, 1320, 1294, 1192; ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.39 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.56 (br s, 2 H), 2.98–2.88 (m, 1H), 2.57–2.24 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 201.0, 154.7, 151.8, 141.0, 132.9, 125.2, 107.6, 62.3, 60.9, 59.3, 59.0, 56.0, 31.7, 26.0; *m/z* (EI): 287 (M^+ + 23, 75%), 265 (M^+ + 1, 100), 237 (25); HRMS: calcd for $C_{14}H_{16}O_5$ (M^+ + H) 265.1076, found: 265.1078.

General procedure for epoxide nucleophilic ring-opening:

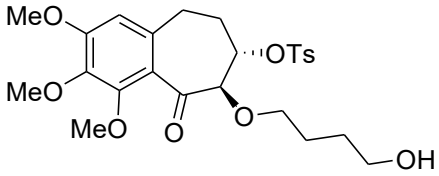
The nucleophile (2 mol equiv.) was added to a stirred suspension of epoxide **26** (~1 mmol) in distilled H_2O, THF, DCM or MeOH (5 mL) in a 10 mL flask fitted with a condenser. The resulting mixture was then stirred at 20–90 °C for 3–24 h and was monitored by TLC. After completion of the reaction, the solvent was removed by distillation under reduced pressure for THF, DCM or MeOH, and extracted with EtOAc in the case of H_2O, washed with brine, dried over Na_2SO_4, and then concentrated to afford the crude product which was subjected to flash column chromatography on silica gel using a suitable solvent mixture of EtOAc and hexane as eluent (see individual experiments for details in this regard) to afford the desired compounds as listed.

8-Hydroxy-1,2,3-trimethoxy-9-oxo-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-7-yl 4-methylbenzenesulfonate 27



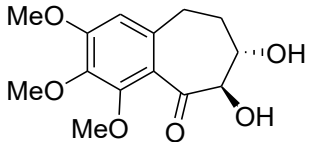
Reaction solvent: DCM; nucleophile: PTSA.H_2O; reaction time: 12 h; reaction temperature: 20–25 °C; chromatography eluent: 20% EtOAc/hexane; amount **27** isolated: 0.30 g; yield: 68%; compound description: light yellow solid. R_f = 0.50 (EtOAc/Hexane, 1:1); Mp: 50–52 °C; IR (neat): ν_{max} (film)/cm^{-1}: 3461, 2939, 1690, 1589, 1492, 1453, 1406, 1331, 1263, 1173; ^{1}H NMR (300 MHz; $CDCl_3$): δ (ppm) 7.86 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 6.48 (s, 1H), 4.50–4.40 (m, 2H), 3.89 (s, 3H), 3.84 (s, 6H, 2 × OMe), 3.60 (d, *J* = 5.5 Hz, 1H, OH), 3.02–2.94 (m, 1H), 2.78–2.69 (m, 1H), 2.45 (s, 3H), 2.36–2.26 (m, 2H); ^{13}C NMR (75 MHz; $CDCl_3$): δ (ppm) 198.5, 155.6, 152.7, 144.7, 141.2, 136.7, 133.8, 129.6 (2C), 128.2 (2C), 123.8, 108.5, 84.6, 79.3, 62.3, 60.9, 56.1, 32.5, 29.7, 21.7; *m/z* (EI): 437 (M^+ + 1, 100%), 265 (88); HRMS: calcd for $C_{21}H_{24}O_8S$ (M^+ + H) 437.1280, found: 437.1278. When the same reaction was performed in THF as solvent and the following conditions: nucleophile: PTSA.H_2O; reaction time: 24 h; reaction temperature: 20–25 °C; chromatography eluent: 20% EtOAc/hexane; amount **27** isolated: 0.21 g; yield: 48% and amount **28** isolated (see next paragraph): 0.15 g; yield: 30%.

8-(4-Hydroxybutoxy)-1,2,3-trimethoxy-9-oxo-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-7-yl 4-methylbenzenesulfonate 28



Reaction solvent: THF; nucleophile: PTSA.H_2O (excess); reaction time: 24 h; reaction temperature: 20–25 °C; chromatography eluent: 20% EtOAc/hexane; amount **28** isolated: 0.15 g; yield: 30%; compound description: Light yellow semi-solid. R_f = 0.39 (EtOAc/Hexane, 1:1); ^{1}H NMR (300 MHz; $CDCl_3$): δ (ppm) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 6.48 (s, 1H), 4.38–4.34 (m, 1H), 4.10–4.04 (m, 2H), 3.88 (s, 6H, 2 × OMe), 3.85 (s, 3H), 3.70–3.54 (m, 2H), 3.31–3.27 (m, 1H), 2.98–2.89 (m, 1H), 2.70–2.62 (m, 1H), 2.44 (s, 3H), 2.05–1.92 (m, 2H), 1.82–1.73 (m, 2H), 1.69–1.58 (m, 2H); ^{13}C NMR (75 MHz; $CDCl_3$): δ (ppm) 200.8, 155.1, 152.5, 144.6, 141.0, 137.4, 133.2, 129.8 (2C), 127.8 (2C), 124.4, 108.3, 83.0, 81.8, 70.5, 69.3, 62.3, 60.9, 56.0, 31.3, 30.1, 25.9, 25.8, 21.6; *m/z* (EI): 509 (M^+ + 1, 100%), 477 (8), 459 (5); HRMS: calcd for $C_{25}H_{32}O_9S$ (M^+ + H) 509.1845 found: 509.1821.

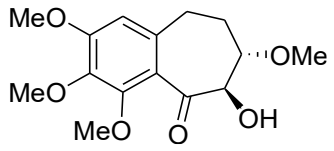
6,7-Dihydroxy-2,3,4-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one 29



Reaction solvent: H_2O; nucleophile: H_2O; reaction time: 5 h; catalyst H_2SO_4 (2-drops); reaction temperature: 90 °C; chromatography eluent: 20% EtOAc/hexane; amount **29** isolated: 0.18 g; yield: 65%; compound description: off-white solid. R_f = 0.33 (EtOAc/Hexane, 1:1); Mp: 88.90 °C; IR (neat): ν_{max} (film)/cm^{-1}: 3376, 2991, 1688, 1592,

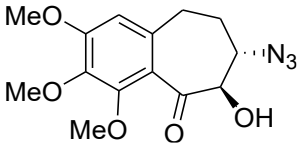
1492, 1452, 1406, 1320, 1239, 1196; ^{1}H NMR (300 MHz; $CDCl_3$): δ (ppm) 6.46 (s, 1H), 4.30–4.26 (m, 1H), 3.97 (bs, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.61–3.57 (m, 1H), 3.10 (bs, 1H), 2.89–2.64 (m, 2H), 2.32–2.18 (m, 1H), 2.08–1.95 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$): δ (ppm) 201.3, 155.2, 152.1, 141.1, 136.0, 124.9, 108.7, 82.4, 76.2, 62.4, 60.9, 56.0, 33.0, 30.9; *m/z* (EI): 305 (M^+ + 23, 45%), 283 (M^+ + 1, 100), 265 (72), 237 (55); HRMS: calcd for $C_{14}H_{18}O_6$ (M^+ + H) 283.1182, found: 283.1180.

6-Hydroxy-2,3,4,7-tetramethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one 30



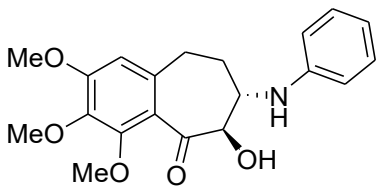
Reaction solvent: MeOH; nucleophile: MeOH; reaction time: 8 h; catalyst H_2SO_4 (2-drops); reaction temperature: 20–25 °C; chromatography eluent: 30-50% EtOAc/hexane; amount **30** isolated: 0.22 g; yield: 75%; compound description: colourless thick liquid. R_f = 0.34 (EtOAc/Hexane, 1:1); IR (neat): ν_{max} (film)/cm^{-1}: 3448, 2937, 1689, 1589, 1491, 1452, 1405, 1330, 1262, 1195; ^{1}H NMR (300 MHz; $CDCl_3$): δ (ppm) 6.48 (s, 1H), 4.46–4.42 (m, 1H), 3.89 (s, 6H, 2 × OMe), 3.86 (bs, 1H), 3.85 (s, 3H), 3.54 (s, 3H), 3.31–3.25 (m, 1H), 3.01–2.93 (m, 1H), 2.73–2.63 (m, 1H), 2.07–2.01 (m, 2H); ^{13}C NMR (75 MHz; $CDCl_3$): δ (ppm) 200.7, 155.1, 152.5, 141.0, 137.4, 124.5, 108.3, 84.4, 81.7, 62.3, 60.8, 57.9, 56.0, 30.5, 30.0; *m/z* (EI): 297 (M^+ + 1, 100%); HRMS: calcd for $C_{15}H_{20}O_6$ (M^+ + H) 297.1338, found: 297.1338.

7-Azido-6-hydroxy-2,3,4-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one 31



Reaction solvent: H_2O; nucleophile: NaN_3; reaction time: 3 h; reaction temperature: 90 °C; chromatography eluent: 30% EtOAc/hexane; amount **31** isolated: 0.18 g; yield: 59%; compound description: white solid. R_f = 0.32 (EtOAc/Hexane, 3:7); Mp: 125–128 °C; IR (neat): ν_{max} (film)/cm^{-1}: 3472, 2941, 2093, 1675, 1590, 1493, 1452, 1406, 1351, 1324, 1287, 1250, 1196; ^{1}H NMR (300 MHz; $CDCl_3$): δ (ppm) 6.46 (s, 1H), 4.42 (dd, *J* = 8.8, 5.8 Hz, 1H), 4.03 (d, *J* = 5.8 Hz, 1H, OH), 3.89 (s, 6H, 2 × OMe), 3.85 (s, 3H), 3.51 (td, *J* = 9.0, 4.4 Hz, 1H), 2.88–2.67 (m, 2H), 2.17–2.09 (m, 1H), 2.03–1.90 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$): δ (ppm) 200.3, 155.4, 152.4, 141.2, 136.1, 124.3, 108.4, 81.5, 67.5, 62.4, 60.9, 56.0, 31.9, 31.3; *m/z* (EI): 330 (M^+ + 23, 15%), 308 (M^+ + 1, 100), 290 (20), 265 (40); HRMS: calcd for $C_{14}H_{17}N_3O_5$ (M^+ + H) 308.1246, found: 308.1245.

7-Anilino-6-hydroxy-2,3,4-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one 32



Reaction solvent: H_2O; nucleophile: $PhNH_2$; reaction time: 5 h; reaction temperature: 90 °C; chromatography eluent: 20% EtOAc/hexane; amount **32** isolated: 0.21 g; yield: 60%; compound description: yellow solid. R_f = 0.29 (EtOAc/Hexane, 3:7); Mp: 170–173 °C; IR (neat): ν_{max} (film)/cm^{-1}: 3474, 2934, 1686, 1591, 1491, 1455, 1404,

1325, 1253, 1190; ^{1}H NMR (300 MHz; $CDCl_3$): δ (ppm) 7.21 (app. t, dd, *J* = 7.8 Hz, 2H), 6.79 (app. t, dd, *J* = 7.3 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 2H), 6.48 (s, 1H), 4.40–4.36 (m, 1H), 3.90 (s, 6H, 2 × OMe), 3.88 (bs, 1H), 3.86 (s, 3H), 3.46–3.42 (m, 1H), 2.92–2.73 (m, 2H), 2.30–2.22 (m, 1H), 2.05–1.95 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$): δ (ppm) 201.7, 155.3, 152.5, 146.6, 141.1, 136.8, 129.3 (2C), 124.8, 118.9, 114.6 (2C), 108.5, 80.3, 62.4, 60.9, 60.0, 56.0, 31.5, 31.4; *m/z* (EI): 380 (M^+ + 23, 5%), 358 (M^+ + 1, 100), 340 (85), 321 (20); HRMS: calcd for $C_{20}H_{23}NO_5$ (M^+ + H) 358.1654, found: 358.1647.

Acknowledgements

We thank past and present staff of the School of Chemistry, University of the Witwatersrand, for NMR spectroscopy and HRMS Spectrometry services, and particularly, Dr. Memory Zimuwandeyi for assistance in finding older NMR spectroscopy FIDs. This work was also supported by the National Research Foundation (NRF), Pretoria, and the University of the Witwatersrand (University and Science Faculty Research Councils) and Stellenbosch University and Faculty of Science. DBY thanks the University of the Witwatersrand Research Office for a postdoctoral fellowship and SO thanks Stellenbosch University for PhD funding through and SO thanks Stellenbosch University for PhD support through a departmental bursary the Faculty of Science.

Supplementary Material

Copies of ^{1}H and ^{13}C-NMR spectra of the synthesized compounds are given in the Supplementary Material file associated with this manuscript. Raw FID data for NMR spectra is available on request from corresponding author.

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