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Regioselection in the synthesis of 4-benzyltetral-1-ones and the new 4-arylbenzosuber-1-ones

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ABSTRACT

The intramolecular Friedel-Crafts acylation of 4,5-diarylpentanoic acids has the possibility to cyclise to either a 6-membered ring to give 4-benzyltetral-1-one or a 7-membered ring to give 4-arylbenzosuber-1-one. Of these, only the former compound class has previously been reported. The impact of the substituents positioning on the outcome of the cyclisation has been investigated. The complete formation of either the tetralone or the benzosuberone regioisomer was possible under the same reaction conditions, dependent upon the ring activation and/or deactivation of the chosen substituents. Selected bromo or methoxy substituents could be used as auxiliaries, included in precursors to afford the desired regioisomer and then subsequently removed.

1. Introduction

The tetralone and benzosuberone classes of benz-fused cycloalkanes have a long history as core scaffolds and intermediates in synthetic organic chemistry. The 1-tetralones have been shown to be a multipurpose core [1–4], appearing as intermediates for the preparation of pharmaceuticals (eg. sertraline [5] (**1**)) and are also found in natural products (eg. vismione B [6] (**2**)) (Fig. 1). Similarly, 1-benzosuberones have been incorporated in a range of biologically active compounds [7] (eg. **3** and **4**) and natural products (eg. theaflavin [8] (**5**)).

One of the most important methods to prepare such compounds is the intramolecular Friedel-Crafts cyclisation, which serves as a useful and facile reaction to access cyclic aryl ketones [1]. The cyclisation reaction of carboxylic acids can be catalysed by hydrogen fluoride [9] or by heating in an excess of polyphosphoric acid [10]. Aluminium chloride is another suitable acid catalyst for the cyclisation of acid chlorides [11].

The Friedel-Crafts cyclisation of 4,5-diarylpentanoic acids present an interesting case as there is the potential for regioisomeric tetralone and benzosuberone products to be formed. Previously this has been shown to favour the formation of the tetralone regioisomer, as is the case for the synthesis of the natural product, sequirin D [10]. 4,5-Bis-*p*-methoxyphenylpentanoic acid (**7**) underwent an intramolecular Friedel-Crafts acylation to form a 4-benzyltetral-1-one (**8**) in the presence of polyphosphoric acid (Scheme 1) [10]. There were no indications of a second benzosuberone regioisomer. The potential formation of the 4-arylbenzosuber-1-one regioisomer (**10**) was noted by Hatam et al., however, none was observed [9]. Recently, Feixas et al. also described the synthesis of 4-benzyltetral-1-ones from a range of 4,5-diarylpentanoic acids with polyphosphoric acid [12]. There was no report of the competing benzosuberone formation.

In fact, the synthesis of 4-arylbenzosuber-1-one has not yet been reported, while each of the other arylbenzosuber-1-one regioisomers (aryl group in the 2-, 3- and 5-positions) have been described [13–15]. We posited that 4-arylbenzosuber-1-one could be a useful intermediate for potential pharmaceutical agents [7,16–18]. For example, rimegepant (**6**), which has recently been approved as a treatment for migraines [19], bears a comparable substitution pattern that could be structurally mimicked by 4-arylbenzosuber-1-one. We hypothesised that the regioselectivity of the cyclisation reaction could be controlled by the inclusion of substituents, A or B, on the aromatic rings allowing access to 4-arylbenzosuber-1-one (**11**) (Scheme 2). The cyclisation is proposed to progress through a Wheland intermediate and so, stabilisation or destabilisation of the competing cations should alter the product balance. As such, we investigated the influence of ring

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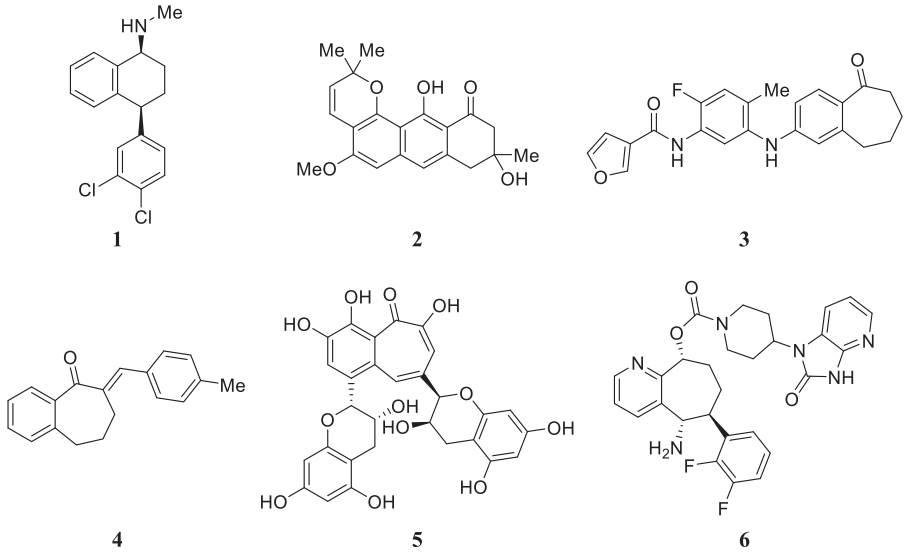
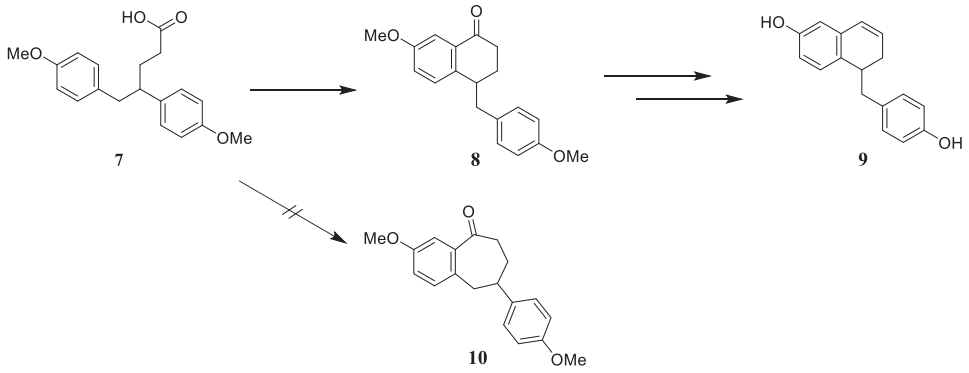
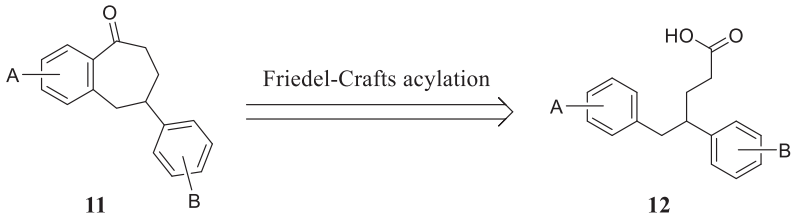


Fig. 1. Example of tetralone and benzosuberone based compounds.



Scheme 1. Synthesis of sequirin D (**9**) [10].



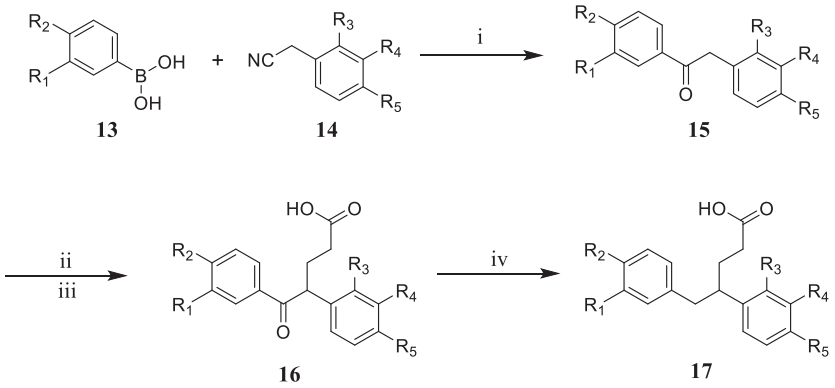
Scheme 2. Retrosynthesis of substituted 4-arylbenzosuber-1-ones (**11**).

activators, such as electron donating groups (methoxy), and ring deactivators, such as electron withdrawing groups (halogens, nitro). Here we report on the outcomes of this study as well as the further manipulation of the substituents to yield the first synthesis of the parent compound of the class.

2. Results and discussion

To access the precursor 4,5-diarylpentanoic acids (**17**), substituted deoxybenzoins (**15**) were elaborated in a sequence of Michael addition with ethyl acrylate, followed by ester hydrolysis and then ketone reduction (Scheme 3).

Firstly, the preparation of the precursor deoxybenzoins **15** was conveniently achieved under palladium-catalysed conditions described by Das et al. using 2-(3,5-dimethyl-1*H*-pyrazol-1-yl) pyridine as the ligand [20]. Alternatively, 1,2-deoxybenzoin **15H** was prepared by Friedel-Crafts acylation of dimethoxybenzene and phenylacetyl chloride. Michael addition between the deoxybenzoins and ethyl acrylate was followed by direct saponification in one pot to yield the carboxylic acids **16**. In some cases, the intermediate ester was isolated (**16E**, **16H**, **16L** and **16M**) and then hydrolysed. The ketone group was reduced using triethylsilane and trifluoroacetic acid according to Kursanov et al. [21] The products (**17**) from this reaction were sufficiently pure to be progressed to



Scheme 3. General synthesis of **17**. i, 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridine, $Pd(OAc)_2$, H_2O:TfOH (3:1), 60 °C, 3.5 h; ii, ethyl acrylate, *t*-BuOK, *t*-BuOH, room temp., 1 h; iii, 1 M aq. NaOH, 60 °C, 1 h; iv, triethylsilane, trifluoroacetic acid, room temp., 16 h.

the next reaction without further purification (see Table 1).

With the key precursors **17** in hand, the Friedel-Crafts cyclisation was performed by treatment with polyphosphoric acid at 80 °C for 4 h (Scheme 4). ^{1}H NMR was used to determine the identity of the regioisomers, tetralone **18** or benzosuberone **19** and the integration of discrete signals was used to assess the regioisomer ratios (**Supplementary data**). The outcome of the cyclisations are summarised in Table 2. Products which contained a mixture of regioisomers were resolved by column chromatography with the exception of **18H** and **19H**.

The resulting product mixtures ranged from exclusive tetralone formation to exclusive benzosuberone formation. Cyclisation of **17A** yielded only the tetralone regioisomer (**18A**) as expected, with no evidence of benzosuberone formation. The inclusion of the bromo substituent at R_1 (**17B**) or a methoxy substituent at either R_2 (**17C**) or R_4 (**17D**) similarly resulted in specific formation of tetralone regioisomers, **18B**, **18C** and **18D** respectively.

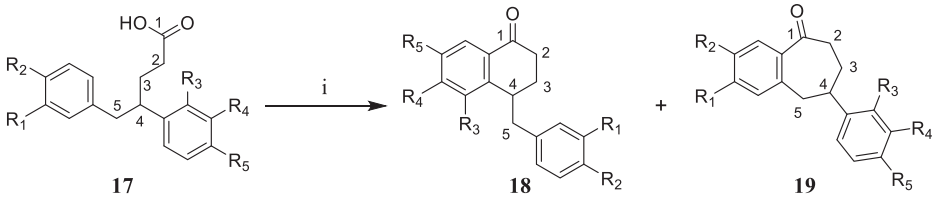
For compounds **17E** and **17F**, the benzosuberone regioisomer (**19E** and **19F**) was observed, albeit as the minor product of the cyclisation. It would appear that the electron withdrawing properties of these halogens caused the 4-phenyl ring to be less reactive during cyclisation, which allowed some of the benzosuberone regioisomer to be produced. The slightly higher ratio observed with **17F** may be due to the *ortho*-fluoro substituent hindering reaction further. Interestingly, a different outcome was observed when a methoxy group was present at R_1 (**17G**) compared to when it was at R_2 (**17C**). In both cases, the methoxy group would be expected to activate the 5-phenyl ring, however, only the methoxy group at R_1 (**17G**) yielded a regioisomeric mixture, favouring benzosuberone (**19G**). This signalled the directing property of the methoxy group. For **17G**, the methoxy group at R_1 is able to stabilise the Wheland intermediate required to form the benzosuberone. Acylation only occurred in the *para*-position with the *ortho*-position likely to be sterically hindered. On the other hand, for **17C** the intermediate to form the benzosuberone could not be stabilised and no benzosuberone formation was observed. The lack of influence by the methoxy group at R_2 was further demonstrated with the cyclisation of **17H** resulting in the same ratio as **17G**.

Table 1
Yields of 15B–O, 16A-O and 17A-O.

	R_1	R_2	R_3	R_4	R_5	15 (Yield %)[a]	16 (Yield %)[a]	17 (Yield %)[b]
A	H	H	H	H	H	–	61	69
B	Br	H	H	H	H	33	71	41
C	H	OMe	H	H	H	40	91	75
D	H	H	H	H	OMe	69	85	87
E[c]	H	H	H	H	Br	40	25	66
F	H	H	F	H	H	85	82	79
G	OMe	H	H	H	H	77	80	99
H[c,d]	OMe	OMe	H	H	H	53	54	96
I	OMe	OMe	F	H	H	80	92	67
J	OMe	OMe	H	H	F	65	35	98
K	OMe	OMe	H	H	Br	79	72	80
L[c]	OMe	OMe	H	H	NO_2	54	38	54
M[c]	OMe	OMe	H	H	OMe	60	25	69
N	OMe	H	H	H	Br	79	52	65
O	H	H	H	NO_2	H	66	80	19

[a] Yields were determined after purification.
[b] Yields of the crude product.
[c] The ester was isolated before hydrolysis (see **General procedure III** and **IV**). The yield of **16** is over the two steps.
[d] A Friedel-Crafts acylation was utilised for the preparation of **15H**.

The results from **17E** to **17H** demonstrated that the regioselectivity could be altered with just one of the phenyl rings being substituted. The next step was to combine these features to see if the regiospecific formation of the benzosuberone regioisomer would be possible under the same conditions. We particularly focused on the 3,4-dimethoxy substitution from **17H**, as the catechol ether group is frequently associated with bioactive molecules [22,23]. In addition, the ^{1}H NMR profile characterised by two aromatic singlets would be a ready indicator for the benzosuberone regioisomer. Remarkably, only the benzosuberone regioisomer was



Scheme 4. Cyclisation of **17**. i, polyphosphoric acid, 80 °C, 4 h.

Table 2
17A-O cyclisation regioselectivity and their yields.

	R_1	R_2	R_3	R_4	R_5	Ratio of 18:19[a]	18 (Yield %)[b]	19 (Yield %)[b]
A	H	H	H	H	H	100:0	40	0
B	Br	H	H	H	H	100:0	59	0
C	H	OMe	H	H	H	100:0	67	0
D	H	H	H	H	OMe	100:0	19	0
E	H	H	H	H	Br	85:15	53	8
F[c]	H	H	F	H	H	80:20	48	11
G	OMe	H	H	H	H	30:70	7	24
H[c]	OMe	OMe	H	H	H	30:70	10	24
I	OMe	OMe	F	H	H	0:100	0	59
J	OMe	OMe	H	H	F	0:100	0	75
K	OMe	OMe	H	H	Br	0:100	0	56
L	OMe	OMe	H	H	NO_2	0:100	0	89
M	OMe	OMe	H	H	OMe	0:100	0	39
N	OMe	H	H	H	Br	0:100	0	53
O	H	H	H	NO_2	H	0:100	0	44

[a] Regioisomer ratios were determined by ^{1}H NMR of the crude mixture.
[b] Yields were determined after purification.
[c] The yields of **18** and **19** were calculated based on the ratio as the regioisomers were not fully separated.

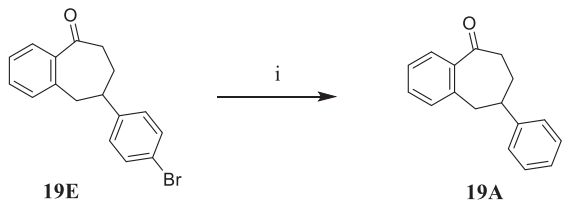
obtained in each case. The combination of appropriate ring activation on the 5-phenyl ring in conjunction with the decreased reactivity of the 4-phenyl ring from electron withdrawing groups excluded tetralone formation (**17I-L**). As observed with **17G** and **17H**, the absence of the methoxy group at R_2 for **17N** had the same result as **17K**.

The 4-methoxy substituent on the 4-phenyl ring (**17M**) also resulted in the complete formation of the benzosuberone regioisomer (**19M**). To form the tetralone, cyclisation occurs in the position *meta* to the methoxy group on the 4-phenyl ring. The inability to resonance stabilise the carbocation intermediate during the electrophilic aromatic substitution may have limited the formation of the tetralone, similar to the result difference between **17C** and **17G**.

The last analogue listed (**17O**) demonstrates that the original regioselectivity can be completely reversed with a single substituent that heavily disfavours reaction with the 4-phenyl ring. As the nitro substituent is an electron withdrawing group, acylation is not favoured in the *ortho* or *para* positions, thus this significantly disfavoured tetralone formation. Collectively, these results show that the regioselectivity can be influenced towards the formation of the benzosuberone by inclusion of the appropriate substituents on either ring.

Finally, we speculated that the directing groups could be removed to access the parent benzosuberone **19A**, which was otherwise inaccessible from this synthetic route. The halogen and ether substituents in products **19E** and **19N** presented as groups that could be removed by a variety of chemical transformations.

Firstly, the successful separation of **19E** from **18E** followed by a debromination of **19E** with hydrogen gas in the presence of palladium on carbon yielded 4-phenylbenzosuber-1-one (**19A**) (Scheme 5). However, with **19E** only being 15% of the cyclisation product crude mixture, this route was relatively inefficient.



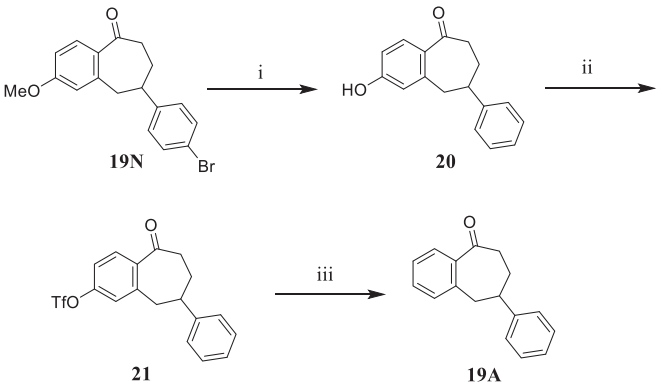
Scheme 5. First-time synthesis of **19A**. i, H_2, Pd/C, methanol, room temp., 2 h, 40%.

In a second route, **19N** was subjected to demethylation in the presence of aluminium chloride (Scheme 6). While the demethylation was successful, it was accompanied by an unexpected but desirable debromination to give **20**. *N*-Phenyl-bis(trifluoromethanesulfonimide) was then used to successfully convert the phenol to a triflate group. Lastly, a palladium-catalysed reduction was used to yield 4-phenylbenzosuber-1-one (**19A**). The overall yield from **17N** to **19A** was 16%, a four-fold improvement upon synthesis from **17E**.

The successful synthesis of **19A** by these methods show that a variety of substituted 4-arylbenzosuber-1-ones might be achieved by employing regioselection auxiliaries to drive the outcome of the Friedel-Crafts cyclisation.

3. Conclusions

We were able to establish the requirements for the formation of either the 4-benzyltetral-1-one or 4-arylbenzosuber-1-one from 4,5-diarylpentanoic acids. The underpinning reactions are well established and the regiochemical outcomes are logical according to conventional mechanistic arguments, but it demonstrated the power of regiochemical directing groups in generating novel molecules. Interestingly, the prior work of Feixas et al. described a series of 4-benzyltetral-1-one compound with varying substitutions



Scheme 6. Alternative synthesis of **19A**. i, $AlCl_3$, toluene, reflux, 2 h, 53%; ii, *N*-phenyl-bis(trifluoromethanesulfonimide), *N*,*N*-diisopropylethylamine, dichloromethane, room temp., 2 h; iii, PPh_3, $Pd(OAc)_2$, formic acid, triethylamine, dimethylformamide, 65 °C, 12 h, 58% over two steps.

[12]. While not addressed in that work, our results would suggest that competing benzosuberone formation would be unlikely in most cases, and at best a minor side product as there are no groups to favour the cyclisation with the 5-phenyl ring. The ring activating and deactivating properties of aromatic substituents can be easily controlled to give the desired ring closure and the ability to remove or alter certain substituents allows them to act as auxiliaries for regioselective syntheses. This then allows further manipulation of the scaffold to allow for more elaborate substitutions such as those represented in Fig. 1. Our demonstration of the synthetic access to 4-arylbenzosuber-1-one opens up an avenue to a range of compounds of pharmaceutical relevance.

4. Experimental section

4.1. General information

All reagents were purchased and used without further purification. Silica gel was used for column chromatography purification. ^{1}H NMR and ^{13}C NMR spectra were collected on a Bruker Advance III Nanobay 400 MHz spectrometer (^{1}H at 400 MHz and ^{13}C at 100 MHz). All spectra were processed using MestReNova 11.0 software. The chemical shifts of ^{1}H and ^{13}C are reported in parts per million (ppm) and were measured relative to the expected chemical shifts of the NMR solvents; $CDCl_3$, 7.26 (77.16 for ^{13}C NMR) and CD_3OD, 3.31 (49.00 for ^{13}C NMR). The format used to report the spectra was as followed: chemical shift (multiplicity, coupling constant (if applicable), integration). Multiplicity was defined as: s = singlet, d = doublet, t = triplet, q = quartet, sd = singlet of doublets, dd = doublet of doublets, dt = doublet of triplets, tt = triplet of triplets and m = multiplet. Apparent splitting was abbreviated as app. and a broad resonance was abbreviated as br. Coupling constants were reported as *J* in Hertz (Hz).

All analytical HPLC analyses were done on an Agilent 1260 Infinity Analytical HPLC coupled with a 1260 Degasser: G1322A, 1260 Binary Pump: G1312B, 1260 HiP ALS autosampler: G1367E, 1260 TCC: G1316A and 1260 DAD detector: G4212B. The column used was a Zorbax Eclipse Plus C18 Rapid Resolution 4.6 × 100 mm 3.5-micron. The sample injection volume was 2 μL which was run in 0.1% TFA in acetonitrile at a gradient of 5–100% over 10 min with a flow rate of 1 mL/min. Detection methods were with 214 nm and 254 nm.

All HRMS analyses were done on an Agilent 6224 TOF LC/MS Mass Spectrometer coupled to an Agilent 1290 Infinity (Agilent, Palo Alto, CA). All data were acquired and reference mass corrected via a dual-spray electrospray ionization (ESI) source. Each scan or data point on the Total Ion Chromatogram (TIC) is an average of 13,700 transients, producing a spectrum every second. Mass spectra were created by averaging the scans across each peak and background subtracted against the first 10 s of the TIC. Acquisition was performed using the Agilent Mass Hunter Fata Acquisition software version B.05.00 Build 5.0.5042.2 and analysis was performed using Mass Hunter Qualitative Analysis version B.05.00 Build 5.0.519.13.

4.2. Synthesis and characterisation

4.2.1. General procedure I for the synthesis of deoxybenzoin analogues (15B-G, I–O)

To a solution of phenylacetonitrile (**14**) (1 mmol, 1.00 equiv.) and boronic acid (**13**) (1.20 equiv.), in water and triflic acid (3:1, 12 mL), was added 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridine (0.05 equiv.) and $Pd(OAc)_2$ (0.05 equiv.). This reaction mixture was stirred at 60 °C for 3.5 h. The mixture was cooled to room temperature, neutralised with sat. aq. $NaHCO_3$ and extracted with diethyl ether (3 × 30 mL). The organic extracts were combined, washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was then purified by column chromatography to yield the product.

4.2.2. General procedure II for the synthesis of carboxylic acid analogues (16A-D, F, G, I–K, N and O)

To a solution of potassium *tert*-butoxide (1.50 equiv.) in *tert*-butanol (15 mL), was added the deoxybenzoin (**15**) (1 mmol, 1.00 equiv.). The reaction mixture was then added ethyl acrylate (2.10 equiv.) in a drop-wise manner. The reaction mixture was stirred at room temperature for 1 h. After consumption of the deoxybenzoin, the solution was added 1 M aq. NaOH (5 mL) and stirred at 60 °C for 1 h. The mixture was cooled and concentrated *in vacuo*. The crude material was diluted in water (30 mL) and washed with ethyl acetate (30 mL). The aqueous layer was made acidic with 1 M HCl to pH ~2. It was then extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined, washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was then purified by column chromatography to yield the product.

4.2.3. General procedure III for the synthesis of ester analogues (16E, H, L and M)

To a solution of the deoxybenzoin (**15**) (1 mmol, 1.00 equiv.) in tetrahydrofuran (15 mL), was added ethyl acrylate (2.10 equiv.). The mixture was cooled to 0 °C, then added a slurry of potassium *tert*-butoxide (0.10 equiv.) in THF. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was concentrated *in vacuo*. The crude material was taken up into ethyl acetate (30 mL) and water (30 mL). The organic phase was separated and the aqueous phase was extracted again with ethyl acetate (2 × 30 mL). The combined organic extract was washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a crude product. The residue was carried forward to **General procedure IV** without further purification.

4.2.4. General procedure IV for the hydrolysis of ester analogues (16E, H, L and M)

The intermediate ester (1 mmol, 1.00 equiv.), from **General procedure III**, was dissolved in a mixture of 1,4-dioxane and 1 M aq. NaOH (1:1, 15 mL) and stirred at 60 °C for 1.5 h. The reaction mixture was cooled and 1,4-dioxane was removed *in vacuo*. The residue was diluted with water (30 mL) and washed with ethyl acetate (30 mL). The aqueous phase was made acidic with 1 M HCl to pH ~2 and was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined, washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was then purified using column chromatography to give the product.

4.2.5. General procedure V for the reduction of the ketone (17A-O)

To a solution of the carboxylic acid (**16**) (1 mmol, 1.00 equiv.) in trifluoroacetic acid (15 mL), was added triethylsilane (2.20 equiv.) in a drop-wise manner under nitrogen. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was made basic with 1 M aq. NaOH to pH ~9 and washed with diethyl ether (30 mL). The aqueous layer was then made acidic with 1 M HCl to pH ~4 and extracted with diethyl ether (3 × 30 mL). The organic extracts were combined, washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. The residue was carried forward to **General procedure VI** without further purification.

4.2.6. General procedure VI for the intramolecular Friedel-Crafts acylation (18A-H & 19E-O)

To **17** (1 mmol, 1.00 equiv.), was added polyphosphoric acid

(15 mL) and stirred at 80 °C for 4 h. The reaction mixture was diluted with water (40 mL) and extracted with diethyl ether (3 × 50 mL). The organic extracts were combined, washed with sat. aq. $NaHCO_3$ (150 mL), brine (150 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was then purified by column chromatography to yield the product.

4.2.7. 1-(3-Bromophenyl)-2-phenylethan-1-one (15B) [24]

General procedure I – Clear liquid (87 mg, 33% yield).; ***Rf*** = 0.31 (10% diethyl ether in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.14 (t, J = 1.8 Hz, 1H), 7.92 (ddd, J = 7.8, 1.7, 1.0 Hz, 1H), 7.68 (ddd, J = 7.9, 2.0, 1.0 Hz, 1H), 7.36–7.32 (m, 3H), 7.29–7.24 (m, 3H), 4.26 (s, 2H).

4.2.8. 1-(4-Methoxyphenyl)-2-phenylethan-1-one (15C) [25]

General procedure I – Yellow gum (155 mg, 40% yield).; ***Rf*** = 0.25 (30% diethyl ether in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.00 (d, J = 8.9 Hz, 2H), 7.34–7.30 (m, 2H), 7.28–7.21 (m,3H), 6.93 (d, J = 8.9 Hz, 2H), 4.23 (s, 1H), 3.86 (s, 2H).

4.2.9. 2-(4-Methoxyphenyl)-1-phenylethan-1-one (15D) [26]

General procedure I – White powder (106 mg, 69% yield).; ***Rf*** = 0.20 (5% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.02–8.00 (m, 2H), 7.57–7.53 (m, 1H), 7.48–7.43 (m, 2H), 7.18 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.23 (s, 2H), 3.79 (s, 3H).

4.2.10. 2-(4-Bromophenyl)-1-phenylethan-1-one (15E) [27]

General procedure I – White powder (84 mg, 40% yield).; ***Rf*** = 0.26 (5% diethyl ether in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.01–7.98 (m, 2H), 7.60–7.56 (m, 1H), 7.50–7.44 (m, 4H), 7.14 (d, J = 8.5 Hz, 2H), 4.25 (s, 2H).

4.2.11. 2-(2-Fluorophenyl)-1-phenylethan-1-one (15F) [28]

General procedure I – White powder (185 mg, 78% yield).; ***Rf*** = 0.25 (5% diethyl ether in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.06–8.03 (m, 2H), 7.61–7.56 (m, 1H), 7.51–7.46 (m, 2H), 7.30–7.22 (m, 2H), 7.13–7.06 (m, 2H), 4.33 (s, 2H).

4.2.12. 1-(3-Methoxyphenyl)-2-phenylethan-1-one (15G) [29]

General procedure I – Clear liquid (149 mg, 77% yield).; ***Rf*** = 0.45 (10% diethyl ether in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.61 (ddd, J = 7.7, 1.6, 1.0 Hz, 1H), 7.53 (dd, J = 2.7, 1.6 Hz, 1H), 7.39–7.31 (m, 3H), 7.28–7.23 (m, 3H), 7.10 (ddd, J = 8.2, 2.7, 1.0 Hz, 1H), 4.27 (s, 2H), 3.84 (s, 3H).

4.2.13. 1-(3,4-Dimethoxyphenyl)-2-phenylethan-1-one (15H) [30]

To a solution of phenylacetic acid (300 mg, 2.20 mmol) in dichloromethane (7 mL), was added oxalyl chloride (186 mg, 126 μL, 1.47 mmol). The reaction mixture was stirred at 60 °C for 1 h. The reaction mixture was cooled to room temperature and was added 1,2-dimethoxybenzene (203 mg, 188 μL, 1.47 mmol) and aluminium chloride (294 mg, 2.20 mmol) gradually. The reaction mixture was then stirred at 60 °C for 4 h. The reaction mixture was cooled, poured into ice water and acidified with 1 M HCl to pH ~4. The organic phase was separated and the aqueous phase was extracted with dichloromethane (2 × 20 mL). The combined organic extract was washed with water (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was then purified by column chromatography (20% diethyl ether in petroleum ether) to give the title product as a fluffy white powder (200 mg, 53% yield). ***Rf*** = 0.13 (20% diethyl ether in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.66 (dd, J = 8.4, 2.0 Hz, 1H), 7.56 (d, J = 2.0 Hz, 1H), 7.34–7.28 (m, 4H), 7.25–7.22 (m, 1H), 6.88 (d, J = 8.4 Hz, 1H), 4.24 (s, 2H), 3.94 (s, 3H), 3.91 (s, 3H).

4.2.14. 1-(3,4-Dimethoxyphenyl)-2-(2-fluorophenyl)ethan-1-one (15I)

General procedure I – White powder (163 mg, 80% yield).; ***Rf*** = 0.32 (20% ethyl acetate in petroleum ether). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.69 (dd, J = 8.4, 2.1 Hz, 1H), 7.57 (d, J = 2.1 Hz, 1H), 7.28–7.22 (m, 2H), 7.12–7.05 (m, 2H), 6.91 (d, J = 8.4 Hz, 1H), 4.28 (s, 2H), 3.95 (s, 3H), 3.93 (s, 3H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 195.2 (C), 162.2 (C), 159.8 (C), 153.6 (C), 149.2 (C), 131.6 (d, J = 4.2 Hz, CH), 129.7 (C), 128.9 (d, J = 8.1 Hz, CH), 124.3 (d, J = 3.7 Hz, CH), 123.3 (CH), 115.5 (d, J = 22.1 Hz, CH), 110.7 (CH), 110.2 (CH), 56.2 (CH_3), 56.1 (CH_3), 38.3 (d, J = 2.3 Hz, CH_2).; **Analytical HPLC:** t_R = 5.75 min, > 95% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{16}H_{15}FO_3 + H]^+$ 275.1078, found 275.1077.

4.2.15. 1-(3,4-Dimethoxyphenyl)-2-(4-fluorophenyl)ethan-1-one (15J) [30]

General procedure I – Orange powder (157 mg, 65% yield).; ***Rf*** = 0.18 (20% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.64 (dd, J = 8.4, 2.0 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 7.23 (dd, J = 8.7, 5.3 Hz, 2H), 7.01 (t, J = 8.7 Hz, 2H), 6.89 (d, J = 8.4 Hz, 1H), 4.21 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H).

4.2.16. 2-(4-Bromophenyl)-1-(3,4-dimethoxyphenyl)ethan-1-one (15K)

General procedure I – White powder (136 mg, 79% yield).; ***Rf*** = 0.18 (20% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.63 (dd, J = 8.4, 2.0 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.4 Hz, 1H), 4.19 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 195.8 (C), 153.7 (C), 149.3 (C), 134.1 (C), 131.9 (CH), 131.3 (CH), 129.7 (C), 123.5 (CH), 121.0 (C), 110.7 (CH), 110.2 (CH), 56.2 (CH_3), 56.1 (CH_3), 44.6 (CH_2). **Analytical HPLC:** t_R = 6.54 min, > 90% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{16}H_{15}^{79}BrO_3 + H]^+$ 335.0277, found 335.0277.

4.2.17. 1-(3,4-Dimethoxyphenyl)-2-(4-nitrophenyl)ethan-1-one (15L) [31]

General procedure I – White powder (121 mg, 54% yield).; ***Rf*** = 0.15 (30% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.20 (d, J = 8.8 Hz, 2H), 7.65 (dd, J = 8.4, 2.1 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 7.44 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.4 Hz, 1H), 4.37 (s, 2H), 3.96 (s, 3H), 3.93 (s, 3H).

4.2.18. 1-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)ethan-1-one (15M) [30]

General procedure I – White powder (117 mg, 60% yield).; ***Rf*** = 0.29 (1% ethyl acetate in dichloromethane).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.65 (dd, J = 8.4, 2.0 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 7.19 (d, J = 8.7 Hz, 2H), 6.89–6.85 (m, 3H), 4.18 (s, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 3.78 (s, 3H).

4.2.19. 2-(4-Bromophenyl)-1-(3-methoxyphenyl)ethan-1-one (15N)

General procedure I – White powder (370 mg, 79% yield).; ***Rf*** = 0.18 (10% diethyl ether in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.58 (ddd, J = 7.6, 1.6, 0.9 Hz, 1H), 7.51 (dd, J = 2.6, 1.6 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.38 (t, J = 7.9 Hz, 1H), 7.15–7.10 (m, 3H), 4.22 (s, 2H), 3.85 (s, 3H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.0 (C), 160.0 (C), 137.9 (C), 133.6 (C), 131.9 (CH), 131.4 (CH), 129.8 (CH), 121.3 (CH), 121.1 (C), 119.9 (CH), 113.0 (CH), 55.6 (CH_3), 45.0 (CH_2).; **Analytical HPLC:** t_R = 6.13 min, > 96% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{15}H_{13}^{79}BrO_2 + H]^+$ 305.0172, found 305.0166.

4.2.20. 2-(3-Nitrophenyl)-1-phenylethan-1-one (15O) [32]

General procedure I – Yellow oil (195 mg, 66% yield).; ***Rf*** = 0.28 (30% diethyl ether in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.17–8.14 (m, 2H), 8.04–8.01 (m, 2H), 7.64–7.59 (m, 2H), 7.54–7.49 (m, 3H), 4.42 (s, 2H).

4.2.21. 5-Oxo-4,5-diphenylpentanoic acid (16A) [33]

General procedure II – After the aqueous layer was made acidic with 1 M HCl to pH ~ 2, a yellow precipitate was collected by vacuum filtration and recrystallised from ethanol to give the title compound as a white powder (833 mg, 61% yield).; ***Rf*** = 0.41 (20% ethyl acetate in petroleum ether + 1% acetic acid). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 10.45 (br. s, 1H), 7.96–7.94 (m, 2H), 7.50–7.45 (m, 1H), 7.40–7.36 (m, 2H), 7.32–7.28 (m, 4H), 7.25–7.19 (m, 1H), 4.67 (t, J = 7.3 Hz, 1H), 2.51–2.43 (m, 1H), 2.38–2.34 (m, 2H), 2.23–2.14 (m, 1H).

4.2.22. 5-(3-Bromophenyl)-5-oxo-4-phenylpentanoic acid (16B)

General procedure II – White powder (72 mg, 71% yield).; ***Rf*** = 0.26 (20% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.07 (t, J = 1.8 Hz, 1H), 7.84 (ddd, J = 7.8, 1.7, 1.0 Hz, 1H), 7.60 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 7.34–7.29 (m, 2H), 7.27–7.21 (m, 4H), 4.61 (t, J = 7.3 Hz, 1H), 2.49–2.41 (m, 1H), 2.37–2.34 (m, 2H), 2.22–2.13 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.9 (C), 178.6 (C), 138.4 (C), 138.2 (C), 136.0 (CH), 131.9 (CH), 130.2 (CH), 129.4 (CH), 128.4 (CH), 127.8 (CH), 127.4 (CH), 123.1 (C), 52.7 (CH), 31.3 (CH_2), 28.5 (CH_2).; **Analytical HPLC:** t_R = 6.07 min, > 95% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{17}H_{15}^{79}BrO_3 + H]^+$ 347.0277, found 347.0268.

4.2.23. 5-(4-Methoxyphenyl)-5-oxo-4-phenylpentanoic acid (16C)

General procedure II – Yellow oil (120 mg, 91% yield).; ***Rf*** = 0.23 (20% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.94 (d, J = 9.0 Hz, 2H), 7.33–7.28 (m, 4H), 7.23–7.18 (m, 1H), 6.85 (d, J = 8.9 Hz, 2H), 4.62 (t, J = 7.3 Hz, 1H), 3.81 (s, 3H), 2.50–2.41 (m, 1H), 2.37–2.33 (m, 1H), 2.21–2.12 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.8 (C), 179.1 (C), 163.5 (C), 139.3 (C), 131.2 (CH), 129.6 (C), 129.2 (CH), 128.3 (CH), 127.4 (CH), 113.9 (CH), 55.6 (CH_3), 52.1 (CH), 31.6 (CH_2), 28.6 (CH_2).; **Analytical HPLC:** t_R = 5.07 min, > 98% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{18}H_{18}O_4 + H]^+$ 299.1278, found 299.1287.

4.2.24. 4-(4-Methoxyphenyl)-5-oxo-5-phenylpentanoic acid (16D)

General procedure II – White powder (67 mg, 85% yield).; ***Rf*** = 0.15 (10% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.95–7.93 (m, 2H), 7.50–7.45 (m, 1H), 7.40–7.35 (m, 2H), 7.20 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 4.61 (dd, J = 7.8, 6.6 Hz, 1H), 3.75 (s, 3H), 2.45–2.33 (m, 3H), 2.20–2.12 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 199.5 (C), 159.0 (C), 136.7 (C), 133.1 (CH), 130.7 (C), 129.5 (CH), 128.9 (CH), 128.7 (CH), 114.7 (CH), 55.4 (CH_3), 51.6 (CH), 31.4 (CH_2), 28.6 (CH_2). Carboxyl carbon not observed.; **Analytical HPLC:** t_R = 5.42 min, > 90% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{18}H_{18}O_4 + H]^+$ 299.1278, found 299.1284.

4.2.25. 4-(4-Bromophenyl)-5-oxo-5-phenylpentanoic acid (16E)

General procedure III and IV – Clear oil (33 mg, 25% yield over two steps).; ***Rf*** = 0.20 (10% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.93–7.91 (m, 2H), 7.52–7.48 (m, 1H), 7.45–7.38 (m, 4H), 7.17 (d, J = 8.5 Hz, 2H), 4.66 (t, J = 7.3 Hz, 1H), 2.49–2.40 (m, 1H), 2.37–2.33 (m, 2H), 2.19–2.12 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 198.9 (C), 178.2 (C) 137.8 (C), 136.4 (C), 133.4 (CH), 132.4 (CH), 130.2 (CH), 128.9 (CH), 128.8 (CH), 121.6 (C), 51.7 (CH), 31.3 (CH_2), 28.5 (CH_2).; **Analytical HPLC:** t_R = 6.34 min, > 95% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{17}H_{15}^{79}BrO_3 + H]^+$ 347.0277, found 347.0271.

4.2.26. 4-(2-Fluorophenyl)-5-oxo-5-phenylpentanoic acid (16F)

General procedure II – White powder (207 mg, 82% yield).; ***Rf*** = 0.21 (10% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.98–7.95 (m, 2H), 7.52–7.48 (m, 1H), 7.42–7.38 (m, 2H), 7.23–7.19 (m, 2H), 7.10–7.04 (m, 2H), 5.05 (dd, J = 7.9, 6.5 Hz, 1H), 2.53–2.43 (m, 1H), 2.42–2.33 (m, 2H), 2.22–2.14 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 198.7 (C), 179.0 (C), 160.2 (d, J = 245.0 Hz, C), 136.2 (C), 133.4 (CH), 129.3 (d, J = 8.2 Hz, CH), 129.1 (d, J = 3.5 Hz, CH), 128.8 (CH), 128.7 (CH), 125.8 (d, J = 15.1 Hz, C), 125.0 (d, J = 3.6 Hz, CH), 115.9 (d, J = 22.7 Hz, CH), 43.9 (CH), 31.5 (CH_2), 27.6 (CH_2).; **Analytical HPLC:** t_R = 5.68 min, > 95% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{17}H_{15}FO_3 + H]^+$ 287.1078, found 287.1076.

4.2.27. 5-(3-Methoxyphenyl)-5-oxo-4-phenylpentanoic acid (16G)

General procedure II – White powder (75 mg, 80% yield).; *Rf* = 0.26 (20% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.53 (ddd, J = 7.7, 1.6, 0.9 Hz, 1H), 7.48 (dd, J = 2.7, 1.6 Hz, 1H), 7.32–7.27 (m, 5H), 7.24–7.19 (m, 1H), 7.02 (ddd, J = 8.2, 2.7, 0.9 Hz, 1H), 4.65 (t, J = 7.3 Hz, 1H), 3.80 (s, 3H), 2.51–2.42 (m, 1H), 2.37–2.34 (m, 2H), 2.22–2.14 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 199.1 (C), 179.1 (C), 159.9 (C), 138.8 (C), 138.0 (C), 129.7 (CH), 129.3 (CH), 128.4 (CH), 127.5 (CH), 121.5 (CH), 119.7 (CH), 113.2 (CH), 55.5 (CH_3), 52.7 (CH), 31.6 (CH_2), 28.6 (CH_2).; **Analytical HPLC:** t_R = 5.55 min, > 95% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{18}H_{18}O_4 + H]^+$ 299.1278, found 299.1286.

4.2.28. 5-(3,4-Dimethoxyphenyl)-5-oxo-4-phenylpentanoic acid (16H)

General procedure III and IV – Fluffy white powder (123 mg, 54% yield over two steps).; ***Rf*** = 0.10 (20% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.60 (dd, J = 8.5, 2.0 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 7.30–7.28 (m, 4H), 7.24–7.19 (m, 1H), 6.80 (d, J = 8.5 Hz, 1H), 4.64 (t, J = 7.3 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 2.51–2.42 (m, 1H), 2.38–2.34 (m, 2H), 2.22–2.13 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.8 (C), 178.8 (C), 153.3 (C), 149.1(C), 139.4 (C), 129.7 (C), 129.2 (CH), 128.3 (CH), 127.4 (CH), 123.6 (CH), 111.1 (CH), 110.1 (CH), 56.2 (CH_3), 56.0 (CH_3), 52.1 (CH), 31.5 (CH_2), 28.7 (CH_2). **Analytical HPLC:** t_R = 5.45 min, > 99% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{19}H_{20}O_5 + H]^+$ 329.1384, found 329.1393.

4.2.29. 5-(3,4-Dimethoxyphenyl)-4-(2-fluorophenyl)-5-oxopentanoic acid (16I)

General procedure II – Clear oil (58 mg, 92% yield).; ***Rf*** = 0.11 (20% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.62 (dd, J = 8.5, 2.1 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.25–7.17 (m, 2H), 7.09–7.04 (m, 2H), 6.83 (d, J = 8.5 Hz, 1H), 5.01 (dd, J = 7.8, 6.6 Hz, 1H), 3.89 (app. br. s, 6H), 2.50–2.42 (m, 1H), 2.41–2.30 (m, 2H), 2.21–2.14 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.2 (d, J = 1.6 Hz, C), 178.7 (C), 160.1 (d, J = 244.6 Hz, C), 153.5 (C), 149.1 (C), 129.2 (C), 129.2 (d, J = 8.2 Hz, CH), 129.0 (d, J = 3.5 Hz, CH), 126.3 (d, J = 15.0 Hz, C), 125.1 (d, J = 3.5 Hz, CH), 123.3 (CH), 115.8 (d, J = 22.7 Hz, CH), 110.9 (CH), 110.3 (CH), 56.2 (CH3), 56.0 (CH3), 43.3 (d, J = 2.0 Hz, CH), 31.5 (CH2), 27.8 (CH2).; **Analytical HPLC:** t_R = 5.31 min, > 95% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{19}H_{19}FO_5 + H]^+$ 347.1289, found 347.1304.

4.2.30. 5-(3,4-Dimethoxyphenyl)-4-(4-fluorophenyl)-5-oxopentanoic acid (16J)

General procedure II – Clear oil (23 mg, 35% yield).; ***Rf*** = 0.16 (20% ethyl acetate in petroleum ether + 1% acetic acid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (dd, J = 8.4, 2.0 Hz, 1H), 7.52 (d, J = 2.0 Hz,

1H), 7.28–7.25 (m, 2H), 6.99 (t, J = 8.7 Hz, 2H), 6.81 (d, J = 8.5 Hz, 1H), 4.65 (t, J = 7.3 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 2.49–2.40 (m, 1H), 2.37–2.33 (m, 2H), 2.18–2.12 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.7 (C), 179.0 (C), 162.1 (d, J = 246.2 Hz, C), 153.4 (C), 149.2 (C), 135.0 (d, J = 3.2 Hz, C), 129.82 (d, J = 8.0 Hz, CH), 129.4 (C), 123.6 (CH), 116.1 (d, J = 21.4 Hz, CH), 110.9 (CH), 110.1 (CH), 56.2 (CH_3), 56.0 (CH_3), 51.0 (CH), 31.5 (CH_2), 28.7 (CH_2).; **Analytical HPLC:** t_R = 5.58 min, > 99% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{19}H_{19}FO_5 + H]^+$ 347.1289, found 347.1300.

4.2.31. 4-(4-Bromophenyl)-5-(3,4-dimethoxyphenyl)-5-oxopentanoic acid (16K)

General procedure II – Yellow oil (184 mg, 72% yield).; ***Rf*** = 0.13 (20% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, CD_3OD)** δ 8.17 (d, J = 8.8 Hz, 2H), 7.71 (dd, J = 8.5, 2.1 Hz, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 2.1 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 4.99 (t, J = 7.3 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.49–2.40 (m, 1H), 2.30–2.25 (m, 2H), 2.16–2.07 (m, 1H).; **^{13}C NMR (100 MHz, CD_3OD)** δ 198.9 (C), 176.6 (C), 155.4 (C), 150.6 (C), 148.5 (C), 148.5 (C), 130.6 (CH), 130.5 (C), 125.0 (CH), 124.9 (CH), 112.2 (CH), 111.7 (CH), 56.5 (CH_3), 56.4 (CH_3), 52.5 (CH), 32.5 (CH_2), 30.1 (CH_2).; **Analytical HPLC:** t_R = 6.06 min, > 99% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{19}H_{19}^{79}BrO_5 + H]^+$ 407.0489, found 407.0491.

4.2.32. 5-(3,4-Dimethoxyphenyl)-4-(4-nitrophenyl)-5-oxopentanoic acid (16L)

General procedure III and IV – Yellow oil (33 mg, 38% yield over two steps).; ***Rf*** = 0.23 (40% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.17 (d, J = 8.8 Hz, 2H), 7.56 (dd, J = 8.5, 2.0 Hz, 1H), 7.52–7.49 (m, 3H), 6.83 (d, J = 8.5 Hz, 1H), 4.83 (t, J = 7.3 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 2.56–2.48 (m, 1H), 2.38 (t, J = 6.9 Hz, 2H), 2.21–2.13 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.6 (C), 177.7 (C), 154.0 (C), 149.5 (C), 147.4 (C), 146.7 (C), 129.3 (CH), 129.2 (C), 124.4 (CH), 123.6 (CH), 110.9 (CH), 110.2 (CH), 56.3 (CH_3), 56.1 (CH_3), 51.4 (CH), 31.3 (CH_2), 28.7 (CH_2).; **Analytical HPLC:** t_R = 5.54 min, > 92% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{19}H_{19}NO_7 + H]^+$ 374.1234, found 374.1237.

4.2.33. 5-(3,4-Dimethoxyphenyl)-4-(4-methoxyphenyl)-5-oxopentanoic acid (16M)

General procedure III and IV – Yellow oil (20 mg, 25% yield over two steps).; ***Rf*** = 0.10 (20% ethyl acetate in petroleum ether + 1% acetic acid). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.59 (dd, J = 8.5, 1.9 Hz, 1H), 7.52 (d, J = 1.9 Hz, 1H), 7.19 (d, J = 8.7 Hz, 2H), 6.83–6.78 (m, 3H), 4.58 (t, J = 7.2 Hz, 1H), 3.88 (s, 3H), 3.88 (s, 3H), 3.74 (s, 3H), 2.46–2.32 (m, 3H), 2.19–2.09 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 198.1 (C), 179.1 (C), 158.9 (C), 153.3 (C), 149.1 (C), 131.3 (C), 129.7 (C), 129.3 (CH), 123.6 (CH), 114.6 (CH), 111.1 (CH), 110.1 (CH), 56.2 (CH_3), 56.0 (CH_3), 55.4 (CH_3), 51.2 (CH), 31.6 (CH_2), 28.7 (CH_2).; **Analytical HPLC:** t_R = 4.85 min, > 99% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{20}H_{22}O_6 + H]^+$ 359.1489, found 359.1499.

4.2.34. 4-(4-Bromophenyl)-5-(3-methoxyphenyl)-5-oxopentanoic acid (16N)

General procedure II – Clear oil (238 mg, 52% yield).; ***Rf*** = 0.20 (40% diethyl ether in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.49 (ddd, J = 7.7, 1.6, 0.9 Hz, 1H), 7.46–7.41 (m, 3H), 7.29 (t, J = 8.0 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 7.04 (ddd, J = 8.2, 2.7, 0.9 Hz, 1H), 4.63 (t, J = 7.3 Hz, 1H), 3.81 (s, 3H), 2.48–2.40 (m, 1H), 2.36–2.33 (m, 2H), 2.18–2.13 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 198.7, 179.1, 159.9, 137.8, 137.7, 132.4, 130.1, 129.7, 121.6, 121.4, 119.8, 113.2, 55.5, 51.9, 31.5, 28.5.; **Analytical HPLC:** t_R = 5.72 min, > 96% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{18}H_{17}^{79}BrO_4 + H]^+$ 377.0383, found 377.0377.

4.2.35. 4-(3-Nitrophenyl)-5-oxo-5-phenylpentanoic acid (16O)

General procedure II – Yellow oil (196 mg, 80% yield).; ***Rf*** = 0.18 (40% diethyl ether in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.21 (t, J = 2.0 Hz, 1H), 8.11 (ddd, J = 8.2, 2.3, 1.0 Hz, 1H), 7.97–7.95 (m, 2H), 7.67 (dt, J = 7.8, 1.3 Hz, 1H), 7.56–7.48 (m, 2H), 7.46–7.41 (m, 2H), 4.88 (t, J = 7.4 Hz, 1H), 2.59–2.50 (m, 1H), 2.39 (t, J = 7.0 Hz, 2H), 2.24–2.16 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 198.3 (C), 177.7 (C), 148.8 (C), 140.8 (C), 136.1 (C), 134.5 (CH), 133.8 (CH), 130.2 (CH), 129.0 (CH), 128.9 (CH), 123.6 (CH), 122.7 (CH), 51.6 (CH), 31.2 (CH_2), 28.7 (CH_2).; **Analytical HPLC:** t_R = 5.17 min, > 98% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{17}H_{15}NO_5 + H]^+$ 314.1023, found 314.1021.

4.2.36. 4,5-Diphenylpentanoic acid (17A) [34]

General procedure V – Clear oil (121 mg, 69% crude yield).; ***Rf*** = 0.49 (20% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.28–7.25 (m, 2H), 7.22–7.18 (m, 3H), 7.16–7.13 (m, 1H), 7.12–7.10 (m, 2H), 7.04–7.02 (m, 2H), 2.95–2.80 (m, 3H), 2.18–2.13 (m, 2H), 2.09–2.03 (m, 1H), 1.95–1.86 (m, 1H).

4.2.37. 5-(3-Bromophenyl)-4-phenylpentanoic acid (17B)

General procedure V – Clear oil (20 mg, 41% crude yield).; ***Rf*** = 0.29 (10% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.30–7.26 (m, 3H), 7.22–7.18 (m, 2H), 7.10–7.07 (m, 2H), 7.05–7.03 (m, 1H), 6.92 (dt, J = 7.7, 1.3 Hz, 1H), 2.88–2.79 (m, 3H), 2.20–2.15 (m, 2H), 2.11–2.01 (m, 1H), 1.96–1.87 (m, 1H).

4.2.38. 5-(4-Methoxyphenyl)-4-phenylpentanoic acid (17C)

General procedure V – Yellow gum (129 mg, 75% crude yield).; ***Rf*** = 0.38 (20% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.29–7.24 (m, 2H), 7.20–7.16 (m, 1H), 7.11–7.09 (m, 2H), 6.93 (d, J = 8.6 Hz, 2H), 6.74 (d, J = 8.7 Hz, 2H), 3.76 (s, 3H), 2.87–2.77 (m, 3H), 2.18–2.13 (m, 2H), 2.09–2.00 (m, 1H), 1.94–1.84 (m, 1H).

4.2.39. 4-(4-Methoxyphenyl)-5-phenylpentanoic acid (17D)

General procedure V – Clear oil (39 mg, 87% crude yield).; ***Rf*** = 0.30 (20% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.22–7.18 (m, 2H), 7.16–7.12 (m, 1H), 7.03–7.00 (m, 4H), 6.80 (d, J = 8.7 Hz, 2H), 3.78 (s, 3H), 2.88–2.86 (m, 2H), 2.83–2.77 (m, 1H), 2.18–2.08 (m, 2H), 2.09–1.99 (m, 1H), 1.91–1.81 (m, 1H).

4.2.40. 4-(4-Bromophenyl)-5-phenylpentanoic acid (17E)

General procedure V – Clear oil (21 mg, 66% crude yield).; ***Rf*** = 0.54 (30% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38 (d, J = 8.4 Hz, 2H), 7.22–7.14 (m, 3H), 7.01–6.94 (m, 4H), 2.93–2.79 (m, 3H), 2.21–2.02 (m, 3H), 1.93–1.84 (m, 1H).

4.2.41. 4-(2-Fluorophenyl)-5-phenylpentanoic acid (17F)

General procedure V – Clear oil (150 mg, 79% crude yield).; ***Rf*** = 0.36 (10% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.23–7.18 (m, 2H), 7.17–7.11 (m, 3H), 7.08–7.03 (m, 3H), 6.99–6.94 (m, 1H), 3.29–3.21 (m, 1H), 2.96–2.93 (m, 1H), 2.21–2.17 (m, 2H), 2.12–1.92 (m, 3H).

4.2.42. 5-(3-Methoxyphenyl)-4-phenylpentanoic acid (17G)

General procedure V – Clear oil (68 mg, 99% crude yield).; ***Rf*** = 0.31 (20% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.29–7.25 (m, 2H), 7.21–7.16 (m, 1H),

7.14–7.10 (m, 3H), 6.69 (ddd, J = 8.3, 2.6, 1.0 Hz, 1H), 6.65 (dt, J = 7.7, 1.2 Hz, 1H), 6.54 (dd, J = 2.6, 1.6 Hz, 1H), 3.71 (s, 3H), 2.91–2.82 (m, 3H), 2.18–2.02 (m, 3H), 1.95–1.88 (m, 1H).

4.2.43. 5-(3,4-Dimethoxyphenyl)-4-phenylpentanoic acid (17H)

General procedure V – Orange oil (46 mg, 96% crude yield).; ***Rf*** = 0.26 (20% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.29–7.25 (m, 2H), 7.21–7.16 (m, 1H), 7.11–7.09 (m, 2H), 6.72 (d, J = 8.2 Hz, 1H), 6.60 (dd, J = 8.1, 2.0 Hz, 1H), 6.41 (d, J = 1.9 Hz, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 2.90–2.76 (m, 3H), 2.27–2.16 (m, 2H), 2.13–2.03 (m, 1H), 1.98–1.89 (m, 1H).

4.2.44. 5-(3,4-Dimethoxyphenyl)-4-(2-fluorophenyl)pentanoic acid (17I)

General procedure V – Yellow oil (32 mg, 67% crude yield).; ***Rf*** = 0.45 (20% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.19–7.03 (m, 3H), 6.97 (ddd, J = 10.6, 8.1, 1.3 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 6.62 (dd, J = 8.1, 2.0 Hz, 1H), 6.48 (d, J = 2.0 Hz, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 3.22 (ddt, J = 12.0, 7.4, 3.7 Hz, 1H), 2.89 (d, J = 7.5 Hz, 2H), 2.24–2.20 (m, 2H), 2.13–2.05 (m, 1H), 2.02–1.92 (m, 1H).

4.2.45. 5-(3,4-Dimethoxyphenyl)-4-(4-fluorophenyl)pentanoic acid (17J)

General procedure V – Clear oil (27 mg, 98% crude yield).; ***Rf*** = 0.34 (20% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.04 (dd, J = 8.7, 5.4 Hz, 2H), 6.95 (t, J = 8.7 Hz, 2H), 6.71 (d, J = 8.2 Hz, 1H), 6.55 (dd, J = 8.1, 2.0 Hz, 1H), 6.41 (d, J = 1.9 Hz, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 2.86–2.78 (m, 3H), 2.20–2.17 (m, 2H), 2.12–2.04 (m, 1H), 1.94–1.88 (m, 1H).

4.2.46. 4-(4-Bromophenyl)-5-(3,4-dimethoxyphenyl)pentanoic acid (17K)

General procedure V – Orange oil (33 mg, 80% crude yield).; ***Rf*** = 0.32 (20% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.39 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 8.2 Hz, 1H), 6.55 (dd, J = 8.1, 2.0 Hz, 1H), 6.40 (d, J = 2.0 Hz, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 2.86–2.78 (m, 3H), 2.22–2.18 (m, 2H), 2.12–2.05 (m, 1H), 1.95–1.87 (m, 1H).

4.2.47. 5-(3,4-Dimethoxyphenyl)-4-(4-nitrophenyl)pentanoic acid (17L)

General procedure V – Yellow gum (26 mg, 54% crude yield).; ***Rf*** = 0.23 (40% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.13 (d, J = 8.8 Hz, 2H), 7.26–7.24 (m, 2H), 6.69 (d, J = 8.2 Hz, 1H), 6.50 (dd, J = 8.1, 2.0 Hz, 1H), 6.46 (d, J = 2.0 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.03–2.91 (m, 2H), 2.82 (dd, J = 13.3, 8.2 Hz, 1H), 2.22–2.13 (m, 3H), 2.01–1.93 (m, 1H).

4.2.48. 5-(3,4-Dimethoxyphenyl)-4-(4-methoxyphenyl)pentanoic acid (17M)

General procedure V – Clear oil (13 mg, 69% crude yield).; ***Rf*** = 0.68 (30% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.00 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 6.71 (d, J = 8.2 Hz, 1H), 6.58 (dd, J = 8.1, 1.9 Hz, 1H), 6.43 (d, J = 1.9 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.73 (s, 3H), 2.82–2.76 (m, 3H), 2.21–2.03 (m, 3H), 1.92–1.83 (m, 1H).

4.2.49. 4-(4-Bromophenyl)-5-(3-methoxyphenyl)pentanoic acid (17N)

General procedure V – Yellow oil (150 mg, 65% crude yield).; ***Rf*** = 0.31 (25% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38 (d, J = 8.4 Hz, 2H), 7.15–7.09 (m, 1H), 6.98 (d, J = 8.4 Hz, 2H), 6.70 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 6.60 (dt, J = 7.5, 1.3 Hz, 1H), 6.53 (t, J = 2.1 Hz, 1H), 3.72 (s, 3H), 2.88–2.82 (m, 3H), 2.19–2.15 (m, 2H), 2.12–2.03 (m, 1H), 1.93–1.85 (m, 1H).

4.2.50. 4-(3-Nitrophenyl)-5-phenylpentanoic acid (17O)

General procedure V – Clear oil (36 mg, 19% crude yield).; ***Rf*** = 0.30 (20% ethyl acetate in petroleum ether + 1% acetic acid).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.05 (ddd, J = 7.6, 2.3, 1.7 Hz, 1H), 7.98 (t, J = 1.9 Hz, 1H), 7.44–7.37 (m, 2H), 7.22–7.12 (m, 3H), 7.00–6.98 (m, 2H), 3.07–2.98 (m, 2H), 2.92–2.86 (m, 1H), 2.22–2.12 (m, 3H), 2.05–1.94 (m, 1H).

4.2.51. 4-Benzyl-3,4-dihydronaphthalen-1(2H)-one (18A) [34]

General procedure VI – Clear oil (11 mg, 40% yield).; ***Rf*** = 0.66 (20% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.06 (dd, J = 7.8, 1.4 Hz, 1H), 7.47 (td, J = 7.5, 1.5 Hz, 1H), 7.34–7.31 (m, 3H), 7.27–7.23 (m, 1H), 7.21–7.17 (m, 3H), 3.27–3.21 (m, 1H), 3.12 (dd, J = 13.6, 6.0 Hz, 1H), 2.90–2.86 (m, 1H), 2.84–2.79 (m, 1H), 2.58 (dt, J = 17.8, 4.9 Hz, 1H), 2.20–2.11 (m, 1H), 1.99–1.92 (m, 1H).

4.2.52. 4-(3-Bromobenzyl)-3,4-dihydronaphthalen-1(2H)-one (18B)

General procedure VI – Yellow oil (11 mg, 59% yield).; ***Rf*** = 0.45 (10% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.06 (dd, J = 7.8, 1.5 Hz, 1H), 7.48 (td, J = 7.5, 1.5 Hz, 1H), 7.40–7.33 (m, 3H), 7.20–7.15 (m, 2H), 7.09–7.07 (m, 1H), 3.25–3.19 (m, 1H), 3.09 (dd, J = 13.7, 6.1 Hz, 1H), 2.86–2.76 (m, 2H), 2.60 (dt, J = 17.8, 5.0 Hz, 1H), 2.22–2.13 (m, 1H), 1.98–1.91 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 198.0 (C), 146.9 (C), 142.2 (C), 133.7 (CH), 132.1 (CH), 132.1 (C), 130.2 (CH), 129.8 (CH), 128.5 (CH), 127.9 (CH), 127.6 (CH), 127.2 (CH), 122.8 (C), 41.0 (CH_2), 40.0 (CH), 34.8 (CH_2), 26.3 (CH_2).; **Analytical HPLC:** t_R = 6.92 min, > 95% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{17}H_{15}^{79}BrO + H]^+$ 315.0379, found 315.0375.

4.2.53. 4-(4-Methoxybenzyl)-3,4-dihydronaphthalen-1(2H)-one (18C)

General procedure VI – White powder (80 mg, 67% yield).; ***Rf*** = 0.36 (15% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.06 (dt, J = 7.8, 1.5 Hz, 1H), 7.46 (td, J = 7.5, 1.5 Hz, 1H), 7.33 (td, J = 7.5, 1.2 Hz, 1H), 7.19–7.17 (m, 1H), 7.08 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 3.81 (s, 3H), 3.18 (dq, J = 9.8, 4.7 Hz, 1H), 3.06 (dd, J = 13.8, 6.1 Hz, 1H), 2.86–2.77 (m, 2H), 2.57 (dt, J = 17.8, 4.9 Hz, 1H), 2.16 (ddt, J = 13.6, 12.1, 4.7 Hz, 1H), 1.95 (dq, J = 13.7, 4.9 Hz, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 198.4 (C), 158.3 (C), 147.6 (C), 133.6 (CH), 132.1 (C), 131.9 (C), 130.1 (CH), 128.6 (CH), 127.5 (CH), 127.0 (CH), 114.1 (CH), 55.4 (CH_3), 40.5 (CH_2), 40.3 (CH), 34.8 (CH_2), 26.2 (CH_2).; **Analytical HPLC:** t_R = 5.89 min, > 98% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{18}H_{18}O_2 + H]^+$ 267.1380, found 267.1376.

4.2.54. 4-Benzyl-7-methoxy-3,4-dihydronaphthalen-1(2H)-one (18D)

General procedure VI – Yellow oil (5 mg, 19% yield).; ***Rf*** = 0.65 (20% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.54 (d, J = 2.8 Hz, 1H), 7.34–7.29 (m, 2H), 7.26–7.22 (m, 1H), 7.18–7.15 (m, 2H), 7.10 (d, J = 8.5 Hz, 1H), 7.04 (dd, J = 8.5, 2.8 Hz, 1H), 3.85 (s, 3H), 3.20–3.15 (m, 1H), 3.10 (dd, J = 13.5, 6.0 Hz, 1H), 2.86–2.76 (m, 2H), 2.56 (dt, J = 17.8, 5.0 Hz, 1H), 2.18–2.09 (m, 1H), 1.97–1.90 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 198.3 (C), 140.2 (C), 140.0 (C), 129.8 (CH), 129.2 (CH), 128.7 (CH), 126.5 (CH), 121.9 (CH), 109.4 (CH), 55.7 (CH_3), 41.5 (CH_2), 39.4 (CH), 34.8 (CH_2), 26.5 (CH_2). Two quaternary carbons not observed.; **Analytical HPLC:** t_R = 6.62 min, > 95% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{18}H_{18}O_2 + H]^+$ 267.1380, found 267.1384.

4.2.55. 4-Benzyl-7-bromo-3,4-dihydronaphthalen-1(2H)-one (18E) & 8-(4-bromophenyl)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (19E) (85:15)

4.2.55.1. General procedure VI. **Isolated 18E:** Clear oil (40 mg, 53% yield).; ***Rf*** = 0.38 (5% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.18 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 8.2, 2.3 Hz, 1H), 7.34–7.30 (m, 2H), 7.27–7.25 (m, 1H), 7.16–7.14 (m, 2H), 7.02 (d, J = 8.3 Hz, 1H), 3.22–3.16 (m, 1H), 3.07 (dd, J = 13.6, 6.4 Hz, 1H), 2.89–2.76 (m, 2H), 2.58 (dt, J = 17.9, 4.9 Hz, 1H), 2.20–2.11 (m, 1H), 1.97 (dq, J = 14.1, 5.0 Hz, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.8 (C), 146.0 (C), 139.3 (C), 136.1 (CH), 133.4 (C), 130.4 (CH), 130.3 (CH), 129.0 (CH), 128.6 (CH), 126.6 (CH), 121.1 (C), 41.1 (CH_2), 39.6 (CH), 34.4 (CH_2), 26.1 (CH_2).; **Analytical HPLC:** t_R = 7.49 min, > 99% purity (214 and 254 nm).; **HRMS:** (APCI+) calc. m/z for $[C_{17}H_{15}^{79}BrO + H]^+$ 315.0379, found 315.0378.

Isolated 19E: Yellow oil (6 mg, 8% yield).; ***Rf*** = 0.22 (5% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.79 (dd, J = 7.6, 1.6 Hz, 1H), 7.45–7.34 (m, 4H), 7.06 (dd, J = 7.5, 0.7 Hz, 1H), 7.01 (d, J = 8.4 Hz, 2H), 3.27–3.16 (m, 2H), 3.09 (dd, J = 13.7, 5.9 Hz, 1H), 2.95 (ddd, J = 17.1, 9.1, 3.0 Hz, 1H), 2.75 (ddd, J = 17.1, 9.1, 2.8 Hz, 1H), 2.21–2.12 (m, 1H), 1.95–1.86 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 205.5 (C), 144.9 (C), 139.0 (C), 138.8 (C), 132.5 (CH), 131.8 (CH), 130.8 (CH), 129.1 (CH), 128.9 (CH), 127.3 (CH), 120.4 (C), 42.4 (CH), 40.3 (CH_2), 39.6 (CH_2), 28.9 (CH_2).; **Analytical HPLC:** t_R = 7.33 min, > 99% purity (214 and 254 nm). **HRMS:** (ESI+) calc. m/z for $[C_{17}H_{15}^{79}BrO + H]^+$ 315.0379, found 315.0365.

4.2.56. 4-Benzyl-5-fluoro-3,4-dihydronaphthalen-1(2H)-one (18F) & 8-(2-fluorophenyl)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (19F) (80:20)

4.2.56.1. General procedure VI. **Isolated 18F:** Clear oil (32 mg, 21% yield).; ***Rf*** = 0.66 (25% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.87 (dd, J = 7.7, 1.4 Hz, 1H), 7.37–7.31 (m, 3H), 7.30–7.19 (m, 4H), 3.56–3.53 (m, 1H), 3.09 (dd, J = 13.7, 4.5 Hz, 1H), 2.90–2.79 (m, 2H), 2.59 (ddd, J = 17.9, 4.0, 2.8 Hz, 1H), 2.12–1.96 (m, 2H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.3 (C), 160.2 (d, J = 246 Hz, C), 139.8 (C), 134.9 (C), 133.7 (C), 129.1 (CH), 128.7 (CH), 127.9 (d, J = 8.2 Hz, CH), 126.7 (CH), 123.1 (d, J = 3.4 Hz, CH), 120.4 (d, J = 22.3 Hz, CH), 39.0 (CH_2), 33.4 (CH_2), 33.2 (CH), 23.9 (CH_2).; **Analytical HPLC:** t_R = 6.75 min, > 95% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{17}H_{15}FO + H]^+$ 255.1180, found 255.1180.

Isolated 19F: Clear oil (6 mg, 4% yield).; ***Rf*** = 0.58 (25% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.80 (dd, J = 7.6, 1.6 Hz, 1H), 7.42 (td, J = 7.4, 1.6 Hz, 1H), 7.35 (td. J = 7.5, 1.4 Hz, 1H), 7.24–7.19 (m, 1H), 7.11–7.03 (m, 4H), 3.60–3.53 (m, 1H), 3.22–3.20 (m, 2H), 2.99 (ddd, J = 16.8, 9.7, 3.3 Hz, 1H), 2.79 (ddd, J = 16.8, 8.4, 2.9 Hz, 1H), 2.20–2.12 (m, 1H), 2.04–1.95 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 205.5 (C), 160.5 (d, J = 245 Hz, C), 139.7 (C), 138.8 (C), 132.6 (d, J = 14.3 Hz, C), 132.4 (CH), 130.7 (CH), 128.9 (CH), 128.1 (d, J = 2.3 Hz, CH), 128.0 (d, J = 1.3 Hz, CH), 127.2 (CH), 124.2 (d, J = 3.6 Hz, CH), 115.7 (d, J = 22.8 Hz, CH), 40.4 (CH_2), 38.7 (d, J = 1.3 Hz, CH_2), 35.5 (d, J = 2.1 Hz, CH), 27.6 (CH_2).; **Analytical HPLC:** t_R = 6.55 min, > 70% purity (214 and 254 nm). **HRMS:** (ESI+) calc. m/z for $[C_{17}H_{15}FO + H]^+$ 255.1180, found 255.1185.

Co-eluted mixture of 18F and 19F: Clear oil (4:1, 52 mg, 34% yield).

4.2.57. 4-(3-Methoxybenzyl)-3,4-dihydronaphthalen-1(2H)-one (18G) & 2-methoxy-8-phenyl-6,7,8,9-tetrahydro-5H-benzo[7] annulen-5-one (19G) (30:70)

4.2.57.1. General procedure VI. **Isolated 18G:** Clear oil (3 mg, 7% yield).; ***Rf*** = 0.34 (10% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.06 (dd, J = 7.9, 1.5 Hz, 1H), 7.47 (td, J = 7.5, 1.5 Hz, 1H), 7.36–7.33 (m, 1H), 7.24–7.20 (m, 2H), 6.81–6.77 (m, 2H), 6.71–6.70 (m, 1H), 3.79 (s, 3H), 3.27–3.18 (m, 1H), 3.10 (dd, J = 13.6, 6.0 Hz, 1H), 2.86–2.77 (m, 2H), 2.58 (dt, J = 17.8, 5.0 Hz, 1H), 2.21–2.12 (m, 1H), 1.98–1.92 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 198.3 (C), 159.9 (C), 147.5 (C), 141.5 (C), 133.6 (CH), 132.1 (C), 129.7 (CH), 128.5 (CH), 127.5 (CH), 127.1 (CH), 121.6 (CH), 115.0 (CH), 111.7 (CH), 55.3 (CH_3), 41.4 (CH_2), 40.0 (CH), 34.9 (CH_2), 26.2 (CH_2).; **Analytical HPLC:** t_R = 6.44 min, > 90% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{18}H_{18}O_2 + H]^+$ 267.1380, found 267.1391.

Isolated 19G: White solid (9 mg, 24% yield).; ***Rf*** = 0.26 (10% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.86 (d, J = 8.6 Hz, 1H), 7.33–7.28 (m, 2H), 7.25–7.21 (m, 1H), 7.18–7.15 (m, 2H), 6.86 (dd, J = 8.7, 2.6 Hz, 1H), 6.60 (d, J = 2.5 Hz, 1H), 3.82 (s, 3H), 3.24–3.15 (m, 3H), 2.97 (ddd, J = 16.7, 9.8, 3.2 Hz, 1H), 2.74 (ddd, J = 16.7, 8.4, 2.7 Hz, 1H), 2.22–2.14 (m, 1H), 2.01–1.92 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 203.8 (C), 162.8 (C), 146.2 (C), 142.6 (C), 131.5 (C), 131.5 (CH), 128.7 (CH), 127.3 (CH), 126.7 (CH), 116.0 (CH), 112.3 (CH), 55.5 (CH_3), 42.9 (CH), 40.4 (CH_2), 40.2 (CH_2), 29.1 (CH_2).; **Analytical HPLC:** t_R = 6.44 min, > 80% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{18}H_{18}O_2 + H]^+$ 267.1380, found 267.1388.

4.2.58. 4-(3,4-Dimethoxybenzyl)-3,4-dihydronaphthalen-1(2H)-one (18H) & 2,3-dimethoxy-8-phenyl-6,7,8,9-tetrahydro-5H-benzo [7]annulen-5-one (19H) (30:70)

4.2.58.1. General procedure VI. **Mixture of 18H and 19H**: Yellow oil (7:3, 16 mg, 34% yield).; ***Rf*** = 0.36 (20% ethyl acetate in petroleum ether).

18H: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, J = 7.8, 1.5 Hz, 1H), 7.47–7.43 (m, 1H), 7.33–7.28 (m, 1H), 7.16–7.14 (m, 1H), 6.82 (d, J = 8.1 Hz, 1H), 6.71 (dd, J = 7.6, 1.5 Hz, 1H), 6.61 (d, J = 1.9 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.25–3.12 (m, 1H), 3.07–2.95 (m, 1H), 2.86–2.73 (m, 2H), 2.59 (dt, J = 9.4, 4.9 Hz, 1H), 2.23–2.17 (m, 1H), 2.01–1.93 (m, 1H).

19H: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.32–7.28 (m, 2H), 7.25–7.20 (m, 1H), 7.16–7.13 (m, 2H), 6.54 (s, 1H), 3.94 (s, 3H), 3.86 (s, 3H), 3.24–3.12 (m, 3H), 2.98 (ddd, J = 16.5, 9.7, 3.2 Hz, 1H), 2.76 (ddd, J = 16.5, 8.5, 2.7 Hz, 1H), 2.23–2.15 (m, 1H), 2.01–1.90 (m, 1H).

4.2.59. 8-(2-Fluorophenyl)-2,3-dimethoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (19I)

General procedure VI – Clear oil (23 mg, 59% yield).; ***Rf*** = 0.24 (20% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.44 (s, 1H), 7.23–7.17 (m, 1H), 7.10–7.02 (m, 3H), 6.54 (s, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.57–3.50 (m, 1H), 3.23–3.12 (m, 2H), 3.00 (ddd, J = 16.3, 10.1, 3.4 Hz, 1H), 2.78 (ddd, J = 16.3, 8.0, 2.8 Hz, 1H), 2.20–2.12 (m, 1H), 2.01–1.92 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 203.2 (C), 160.4 (d, J = 245.2 Hz, C), 152.3 (C), 147.9 (C), 135.0 (C), 132.7 (d, J = 14.5 Hz, C), 130.7 (C), 128.2 (d, J = 4.7 Hz, CH), 128.0 (d, J = 8.4 Hz, CH), 124.2 (d, J = 3.4 Hz, CH), 115.7 (d, J = 22.9 Hz, CH), 113.2 (CH), 111.5 (CH), 56.2 (CH_3), 56.4 (CH_3), 40.5 (CH_2), 38.8 (CH_2), 35.6 (d, J = 2.0 Hz, CH), 27.5 (CH_2).; **Analytical HPLC:** t_R = 6.25 min, > 95% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{19}H_{19}FO_3 + H]^+$ 315.1391, found 315.1403.

4.2.60. 8-(4-Fluorophenyl)-2,3-dimethoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (19J)

General procedure VI – White gum (14 mg, 75% yield).; ***Rf*** = 0.15 (20% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.43 (s, 1H), 7.08 (dd, J = 8.7, 5.4 Hz, 2H), 6.97 (t, J = 8.7 Hz, 2H), 6.51 (s, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.24–3.16 (m, 2H), 3.08–3.02 (m, 1H), 2.96 (ddd, J = 16.6, 9.4, 3.1 Hz, 1H), 2.75 (ddd, J = 16.6, 8.9, 2.6 Hz, 1H), 2.22–2.13 (m, 1H), 1.93–1.84 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 203.5 (C), 161.6 (d, J = 244.6 Hz, C), 152.3 (C), 147.9 (C), 141.9 (d, J = 3.2 Hz, C), 134.4 (C), 130.7 (C),

128.7 (d, J = 7.8 Hz, CH), 115.4 (d, J = 21.1 Hz, CH), 113.4 (CH), 111.5 (CH), 56.2 (CH_3), 56.2 (CH_3), 42.4 (CH), 40.5 (CH_2), 40.0 (CH_2), 29.1 (CH_2).; **Analytical HPLC:** t_R = 6.49 min, > 99% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{19}H_{19}FO_3 + H]^+$ 315.1391, found 315.1394.

4.2.61. 8-(4-Bromophenyl)-2,3-dimethoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (19K)

General procedure VI − White powder (16 mg, 56% yield).; ***Rf*** = 0.23 (20% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.43 (s, 1H), 7.40 (d, J = 8.5 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.51 (s, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.24−3.13 (m, 2H), 3.05 (dd, J = 13.9, 5.9 Hz, 1H), 2.95 (ddd, J = 16.6, 9.4, 3.0 Hz, 1H), 2.75 (ddd, J = 16.6, 8.9, 2.6 Hz, 1H), 2.17 (dddd, J = 16.8, 9.6, 7.1, 2.6 Hz, 1H), 1.92−1.83 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 203.3 (C), 152.3 (C), 148.0 (C), 145.2 (C), 134.2 (C), 131.7 (CH), 130.7 (C), 129.1 (CH), 120.4 (C), 113.4 (CH), 111.5 (CH), 56.3 (CH_3), 56.2 (CH_3), 42.6 (CH), 40.5 (CH_2), 39.7 (CH_2), 28.9 (CH_2).; **Analytical HPLC:** t_R = 6.99 min, > 99% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{19}H_{19}^{79}BrO_3 + H]^+$ 375.0590, found 375.0595.

4.2.62. 2,3-Dimethoxy-8-(4-nitrophenyl)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (19L)

General procedure VI − Beige powder (10 mg, 89% yield).; ***Rf*** = 0.23 (30% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.15 (d, J = 8.8 Hz, 2H), 7.45 (s, 1H), 7.30 (d, J = 8.7 Hz, 2H), 6.50 (s, 1H), 3.94 (s, 3H), 3.86 (s, 3H), 3.37−3.26 (m, 2H), 3.09 (dd, J = 14.5, 6.2 Hz, 1H), 2.99 (ddd, J = 16.6, 9.4, 3.0 Hz, 1H), 2.79 (ddd, J = 16.6, 8.9, 2.6 Hz, 1H), 2.27−2.19 (m, 1H), 1.97−1.88 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 202.8 (C), 153.7 (C), 152.5 (C), 148.2 (C), 146.9 (C), 133.5 (C), 130.7 (C), 128.2 (CH), 124.0 (CH), 113.3 (CH), 111.7 (CH), 56.3 (CH_3), 56.2 (CH_3), 43.1 (CH), 40.4 (CH_2), 39.4 (CH_2), 28.7 (CH_2).; **Analytical HPLC:** t_R = 6.27 min, > 99% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{19}H_{19}NO_5 + H]^+$ 342.1336, found 342.1337.

4.2.63. 2,3-Dimethoxy-8-(4-methoxyphenyl)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (19M)

General procedure VI − White gum (5 mg, 39% yield).; ***Rf*** = 0.58 (30% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.43 (s, 1H), 7.06 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.53 (s, 1H), 3.94 (s, 3H), 3.86 (s, 3H), 3.79 (s, 3H, 3.22−3.05 (m, 3H), 2.96 (ddd, J = 16.6, 9.5, 3.0 Hz, 1H), 2.74 (ddd, J = 16.6, 8.7, 2.6 Hz, 1H), 2.16 (dddd, J = 16.8, 9.6, 7.1, 2.6 Hz, 1H), 1.94−1.85 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 203.8 (C), 158.3 (C), 138.4 (C), 134.9 (C), 130.8 (C), 128.2 (CH), 114.0 (CH), 113.5 (CH), 111.5 (CH), 56.2 (CH_3), 56.2 (CH_3), 55.4 (CH_3), 42.3 (CH), 40.6 (CH_2), 40.2 (CH_2), 29.2 (CH_2). Two quaternary carbons not observed.; **Analytical HPLC:** t_R = 6.33 min, > 99% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{20}H_{22}O_4 + H]^+$ 327.1591, found 327.1575.

4.2.64. 8-(4-Bromophenyl)-2-methoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (19N)

General procedure VI − Clear oil (157 mg, 52% yield).; ***Rf*** = 0.35 (40% diethyl ether in petroleum ether). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.85 (d, J = 8.7 Hz, 1H), 7.42 (d, J = 8.5 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 6.86 (dd, J = 8.7, 2.6 Hz, 1H), 6.56 (d, J = 2.4 Hz, 1H), 3.82 (s, 3H), 3.24−3.15 (m, 2H), 3.11−3.05 (m, 1H), 2.93 (ddd, J = 16.9, 9.4, 3.0 Hz, 1H), 2.73 (ddd, J = 16.9, 8.9, 2.6 Hz, 1H), 2.16 (dddd, J = 14.4, 9.5, 6.8, 2.6 Hz, 1H), 1.94−1.85 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 203.6 (C), 162.9 (C), 145.0 (C), 141.9 (C), 131.8 (CH), 131.6 (CH), 131.5 (C), 129.0 (CH), 120.4 (C), 116.1 (CH), 112.4 (CH), 55.6 (CH_3), 42.4 (CH), 40.3 (CH_2), 40.0 (CH_2), 28.9 (CH_2).; **Analytical HPLC:** t_R = 6.43 min, > 96% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{18}H_{17}^{79}BrO_2 + H]^+$ 345.0485, found 345.0486.

4.2.65. 8-(3-Nitrophenyl)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (19O)

General procedure VI − Yellow oil (14 mg, 44% yield).; ***Rf*** = 0.18 (15% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.12−8.09 (m, 1H), 8.04−8.03 (m, 1H), 7.82 (dd, J = 7.7, 1.5 Hz, 1H), 7.50−7.43 (m, 3H), 7.39 (td, J = 7.5, 1.4 Hz, 1H), 7.07−7.05 (m, 1H), 3.40−3.30 (m, 2H), 3.18−3.13 (m, 1H), 2.99 (ddd, J = 17.1, 9.0, 3.0 Hz, 1H), 2.80 (ddd, J = 17.1, 9.3, 2.8 Hz, 1H), 2.28−2.20 (m, 1H), 1.97 (dtd, J = 14.4, 9.4, 3.0 Hz, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 205.0 (C), 147.9 (C), 138.7 (C), 138.3 (C), 133.6 (CH), 132.7 (CH), 130.7 (CH), 129.7 (CH), 129.1 (CH), 127.6 (CH), 122.3 (CH), 121.9 (CH), 42.6 (CH), 40.2 (CH_2), 39.3 (CH_2), 28.8 (CH_2). One quaternary carbon not observed.; **Analytical HPLC:** t_R = 5.78 min, > 95% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{17}H_{15}NO_3 + H]^+$ 282.1125, found 282.1124.

4.2.66. 2-Hydroxy-8-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (20)

To a solution of 8-(4-bromophenyl)-2-methoxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one (**19N**) (40 mg, 116 μmol) in toluene (6 mL), was added $AlCl_3$ (70 mg, 525 μmol). The reaction mixture was stirred at reflux for 2 h. It was then poured into ice water (15 mL) and was made acidic with 1 M HCl to pH ~ 2. The organic phase was collected and washed with brine. The aqueous phase was further extracted with dichloromethane (2 × 15 mL). The two dichloromethane extracts were combined and washed with brine. The toluene and dichloromethane extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was then purified by column chromatography (25% ethyl acetate in petroleum ether) to give the title compound as a brown oil (16 mg, 53% yield). ***Rf*** = 0.21 (25% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.81 (d, J = 8.5 Hz, 1H), 7.32−7.28 (m, 2H), 7.24−7.20 (m, 1H), 7.17−7.15 (m, 2H), 6.81 (dd, J = 8.5, 2.5 Hz, 1H), 6.68 (br.s, 1H), 6.58 (d, J = 2.5 Hz, 1H), 3.23−3.09 (m, 3H), 2.97 (ddd, J = 16.7, 9.8, 3.1 Hz, 1H), 2.74 (ddd, J = 16.8, 8.5, 2.7 Hz, 1H), 2.17 (dddd, J = 14.4, 9.6, 6.8, 2.7 Hz, 1H), 2.00−1.91 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 204.9 (C), 160.0 (C), 146.0 (C), 143.3 (C), 131.9 (CH), 131.1 (C), 128.7 (CH), 127.2 (CH), 126.7 (CH), 117.5 (CH), 114.3 (CH), 42.8 (CH), 40.4 (CH_2), 40.0 (CH_2), 29.1 (CH_2).; **Analytical HPLC:** t_R = 5.18 min, > 95% purity (214 and 254 nm).; **HRMS:** (ESI+) calc. m/z for $[C_{17}H_{16}O_2 + H]^+$ 253.1223, found 253.1229.

4.2.67. 8-(4-Bromophenyl)-5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-2-yl trifluoromethanesulfonate (21)

To a solution of 8-(4-bromophenyl)-2-hydroxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one (**20**) (15 mg, 59 μmol) in dichloromethane (4 mL), was added diisopropylethylamine (21 mg, 28 μL, 178 μmol) and *N*-phenyl-bis(trifluoromethanesulfonimide) (21 mg, 59 μmol). The reaction mixture stirred at room temperature for 2 h. It was then washed with sat. aq. $NaHCO_3$ (10 mL). The organic phase was collected and the aqueous phase was further extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil (63 mg). The residue was carried forward without further purification. ***Rf*** = 0.59 (25% ethyl acetate in petroleum ether).

4.2.68. 8-Phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (19A)

Method 1: A two-neck round bottom flask was charged with a magnetic stir bar and Pd/C 10% w/w (7 mg, 63 μmol). To the flask was added dichloromethane until all Pd/C was fully immersed. The flask was evacuated and back-filled with nitrogen. To the flask was added a solution of 8-(4-bromophenyl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one (**19E**) (20 mg, 63 μmol) in methanol (5 mL).

The flask was evacuated and back-filled with nitrogen. The evacuation-back-fill sequence was repeated for an additional 2 times. The flask was then filled with hydrogen. The flask was evacuated and back-filled with hydrogen for an additional 2 times and the reaction mixture was stirred vigorously at room temperature for 2 h. The flask was then evacuated and back-filled with nitrogen and the reaction mixture filtered through a pad of Celite, washed with dichloromethane. The filtrate was then concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (5% ethyl acetate in petroleum ether) to give the title compound as a clear oil (6 mg, 40% yield).

Method 2: To a solution of 8-(4-bromophenyl)-5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-2-yl trifluoromethanesulfonate (**21**) (60 mg) in DMF (4 mL), was added triphenylphosphine (0.7 mg, 2.6 μmol), palladium acetate (1.2 mg, 5.2 μmol), formic acid (4.8 mg, 4 μL, 104 μmol) and triethylamine (16 mg, 22 μL, 156 μmol). The reaction mixture was stirred at 65 °C for 12 h. It was then diluted with water (10 mL) and ethyl acetate (10 mL). The organic phase was separated and the aqueous phase was further extracted (2 × 10 mL). The organic extracts were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was then purified by column chromatography (5% ethyl acetate in petroleum ether) to give the title compound as a clear oil (8.2 mg, 58% yield over two steps).

Rf = 0.18 (5% ethyl acetate in petroleum ether).; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.80 (dd, J = 7.6, 1.5 Hz, 1H), 7.42 (td, J = 7.4, 1.6 Hz, 1H), 7.36 (td, J = 7.5, 1.3 Hz, 1H), 7.34–7.29 (m, 2H), 7.25–7.21 (m, 1H), 7.17–7.14 (m, 2H), 7.09 (dd, J = 7.4, 0.7 Hz, 1H), 3.27–3.16 (m, 3H), 2.98 (ddd, J = 16.8, 9.4, 3.2 Hz, 1H), 2.77 (ddd, J = 16.9, 8.8, 2.9 Hz, 1H), 2.23–2.14 (m, 1H), 2.02–1.93 (m, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 205.8 (C), 146.1 (C), 139.7 (C), 138.8 (C), 132.4 (CH), 130.8 (CH), 128.8 (CH), 128.7 (CH), 127.3 (CH), 127.2 (CH), 126.7 (CH), 43.0 (CH), 40.5 (CH_2), 39.8 (CH_2), 29.2 (CH_2).; **Analytical HPLC:** t_R = 6.71 min, > 99% purity (214 and 254 nm).; **HRMS:** (APCI+) calc. m/z for $[C_{17}H_{16}O + H]^+$ 237.1274, found 237.1267.

Notes

The authors declare no competing financial interests.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2021.132034.

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