

Construction of quaternary stereocentres in the radical-radical cascade cyclisation of barbiturates

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School of Chemistry

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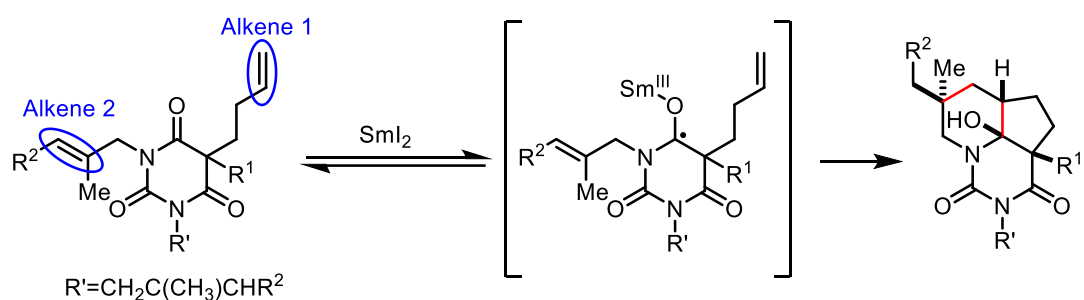
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Abstract

Construction of quaternary stereocentres in the radical-radical cascade cyclisation of barbiturates

The development of radical-radical cyclisation cascade triggered by single-electron transfer to amide-type carbonyl using $\text{SmI}_2\text{-H}_2\text{O-LiBr}$ is described. This transformation allows the construction of tricyclic scaffolds, diastereoselectively, containing three new stereocentres and one synthetically challenging quaternary centre in a single operational step.



Barbiturates are ideal templates as alkene radical traps can be attached to carbon and/or nitrogen and cyclisation avoids undesired reduction or side product formation. The first electron transfer from SmI_2 to form the amide-type radical is reversible, leading to the possibility of trapping that radical with suitably positioned radical acceptors.

Declaration

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Abbreviations

Ac	Acetyl
AIBN	Azobisisobutyronitrile
Ar	Aryl
Bn	Benzyl
Boc	<i>tert</i> -Butyloxycarbonyl
BOM	Benzyloxymethyl acetal
Bu	Butyl
Cat.	Catalytic
CHD	Cyclohexadiene
cod	1,5-cyclooctadiene
DCE	Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DMF	Dimethylformamide
DMPU	N,N'-dimethylpropyleneurea
DMSO	Dimethylsulfoxide
ET	Electron transfer
Et	Ethyl
HMPA	Hexamethylphosphamide
LDA	Lithium diisopropylamide
MCZ	<i>N</i> -methylcarbazole
Me	Methyl
Ms	Methansulfonyl
nOe	Nuclear Overhauser effect
Ph	Phenyl
PMB	4-Methoxybenzyl ether
ppy	2-Phenylpyridine

Pr	Propyl
rt	Room temperature
SET	Single electron transfer
Tf	Trifluoromethanesulfonyl
Ts	<i>p</i> -Toluenesulfonyl
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl ether
TMU	1,1,3,3-tetramethylurea
TMS	Trimethylsilyl ether

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I would like to thank my supervisor Prof. David Procter for giving me the opportunity to work in his research group for the past year, and also for his remarks and engagement through the learning process of this master thesis. I would also like to thank the members of the group, permanent or visiting, for making this year enjoyable. This includes Becky, Alex, José, Sam, Kay, Miles, Xavi, Charlotte, Nico, Harry, Craig, Mateusz, Monserrat, Irem and, especially, Huanming who has had infinite patience and has been extremely supportive during this master. I would in particular also like to thank Xavi, José, Kay, Charlotte, Nico and Huanming for their involvement in proofreading this thesis.

Finally, I have to thank my family for their support and especially to Patri for her love and patience through this year.

1. Introduction

1.1. Samarium(II) iodide and the use of additives

Samarium(II) iodide (SmI_2) was introduced in THF solution by Kagan in 1977.^{1,2} Ever since, it has been widely used by the organic chemistry community due to its high degree of regio-, chemo- and stereoselectivity.³ One of the facts that makes it unique is its mode of action. SmI_2 can undergo either a single electron transfer (SET) mechanism or two electron transfers resulting in a radical or anionic mechanism, respectively.⁴

Since its discovery, SmI_2 has emerged as an excellent functional group reducing agent due to the properties mentioned above. Table 1 shows a selection of the functional groups that can be reduced using samarium(II) in combination with different additives.⁴

Another characteristic that turns SmI_2 into an extremely versatile reductive agent is that the use of additives and co-solvents modifies its reactivity. The three main types of additives are Lewis bases, proton donors and inorganic additives. They can be used to control the rate of reduction, modify the stereoselectivity of a reaction or increase the reductive potential of the reagent (Figure 1).^{5,6}

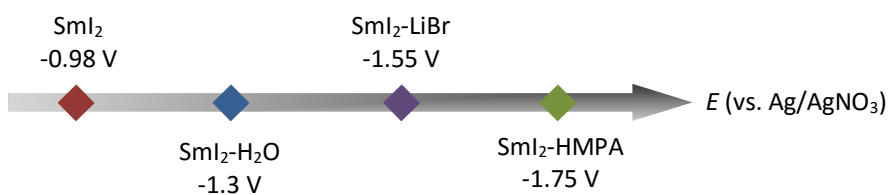
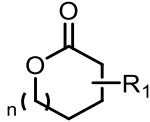
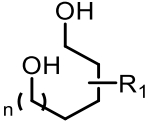
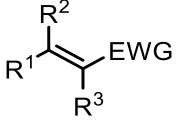
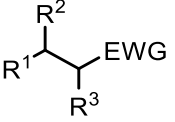
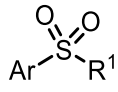
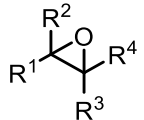
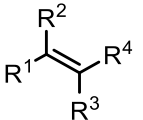


Figure 1. Reduction potential of different SmI_2 reagents

Lewis bases, such as, HMPA,⁷ DMPU or TMU⁸ enhance the reduction potential of samarium by direct coordination, facilitating electron transfer to the substrate.⁹ They also create open coordination sites while displacing iodide ligands to the outer sphere of Sm(II) .¹⁰

Table 1. Reactivity of common functional groups towards SmI_2

Functional group	Product	SmI_2 -additive
R_1-X	R_1-H	HMPA
$\text{R}^1-\text{C}(=\text{O})-\text{R}^2$ $\text{R}^1-\text{C}(=\text{O})-\text{H}$	$\text{R}^1-\text{C}(\text{OH})-\text{R}^2$ $\text{R}^1-\text{C}(\text{OH})-\text{H}$	ROH H ₂ O
		H ₂ O-amine
$\text{R}^1-\text{C}(=\text{O})-\text{XR}^2$ X=O,N; R ² =H,alkyl	$\text{R}-\text{CH}_2-\text{OH}$	H ₂ O-amine
$\text{R}-\text{CN}$	$\text{R}-\text{CH}_2-\text{NH}_2$	H ₂ O-amine
		ROH H ₂ O-HMPA NEt ₃ -H ₂ O
	$\text{Ar}-\text{S}-\text{R}^1$	HMPA/DMPU
R_1-NO_2	R_1-NHOH or R_1-NH_2	ROH
		none

Proton donors such as MeOH, H₂O or *t*-BuOH¹¹ are crucial in reductions since modification of the proton source varies the rate and mechanism of the reduction.¹² For example, water's higher affinity for samarium(II) leads to displacement of bulky solvent (THF).¹³ It is also critical in the stabilisation of the radical anion which makes it suitable to reduce unactivated esters, such as lactones, as reported by Procter.¹⁴

Systems with combinations of various additives are also common in the literature and have been utilized in several processes like the reduction of unactivated amides with SmI_2 -amine-H₂O.¹⁵ LiBr has been also used as a second

additive to $\text{SmI}_2\text{-H}_2\text{O}$ and has showed to be useful in carbon-carbon couplings triggered by ketyl radical anion formation.¹⁶ The role of LiBr is not entirely understood. It has been postulated by Flowers *et. al.* that, in solution, iodide can be displaced to form SmBr_2 , which is a stronger reductant. It is also possible that Li^+ coordinates to the oxygen of the carbonyl, accelerating the rate of reduction and, thus the coupling.⁹ However, the reactivity of this system is still to be fully explored, especially in complex transformations.

1.2. Barbituric acid

In 1864 Adolf von Baeyer synthesised the first barbituric acid from uric acid,¹⁷ and the process was later simplified by Grimeaux through a condensation of malonic acid and urea.¹⁸ Barbituric acid derivatives (barbiturates) were introduced into the market in 1904 as intravenous anaesthetics and to facilitate the treatment of psychiatric and neurological disorders.¹⁹ One of the most well-known barbiturates is phenobarbital, which was used 100 years ago and it is still extensively prescribed nowadays.²⁰ Since then, more than 2500 biologically active barbiturates have been synthesised.²¹ Despite its replacement during the second part of the 20th century by other drugs, due to physical dependence cases and overdose deaths, there is still almost a dozen barbituric acid derivatives that are clinically used.¹⁹

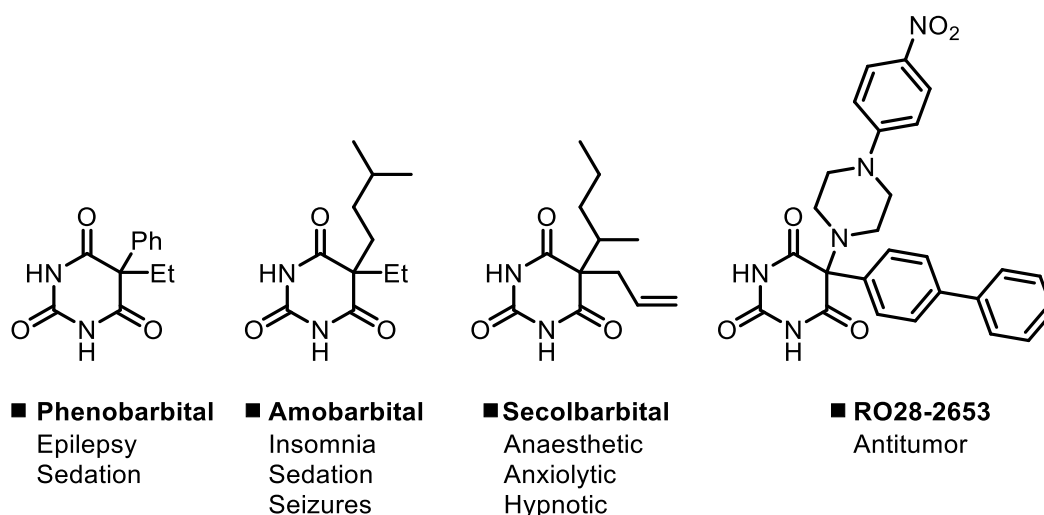
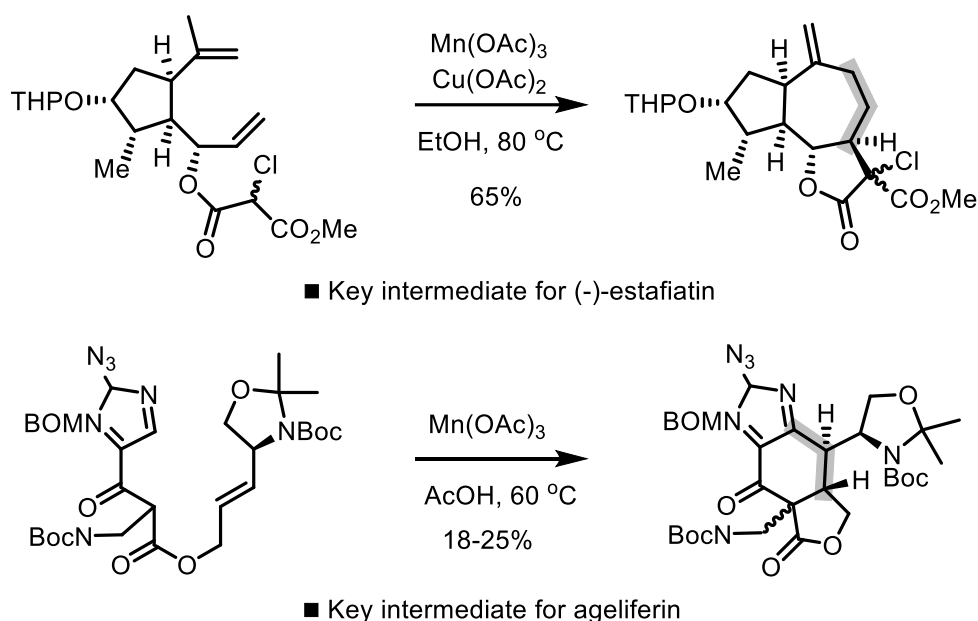


Figure 2. Representative examples of barbiturates used in medicine.

1.3. Radical cascade cyclisations

Radical cascade cyclisations have always attracted the attention of the organic synthetic community due to their high potential to generate complex structures rapidly. However, selectivity, stereospecificity and high functional group tolerance is crucial in such processes.²² These types of reactions are particularly interesting for the formation of complex polycyclic scaffolds that are frequently used in the total synthesis of natural and bioactive compounds. A classic example is the 5-*exo*-tet/7-*endo*-trig cascade used in the synthesis of a key intermediate *en route* to (-)-estafiatin.²³ A more recent one is the 5-*exo*-trig/6-*endo*-trig cascade used for a key intermediate in a synthesis of the antiviral ageliferin²⁴ (Scheme 1).



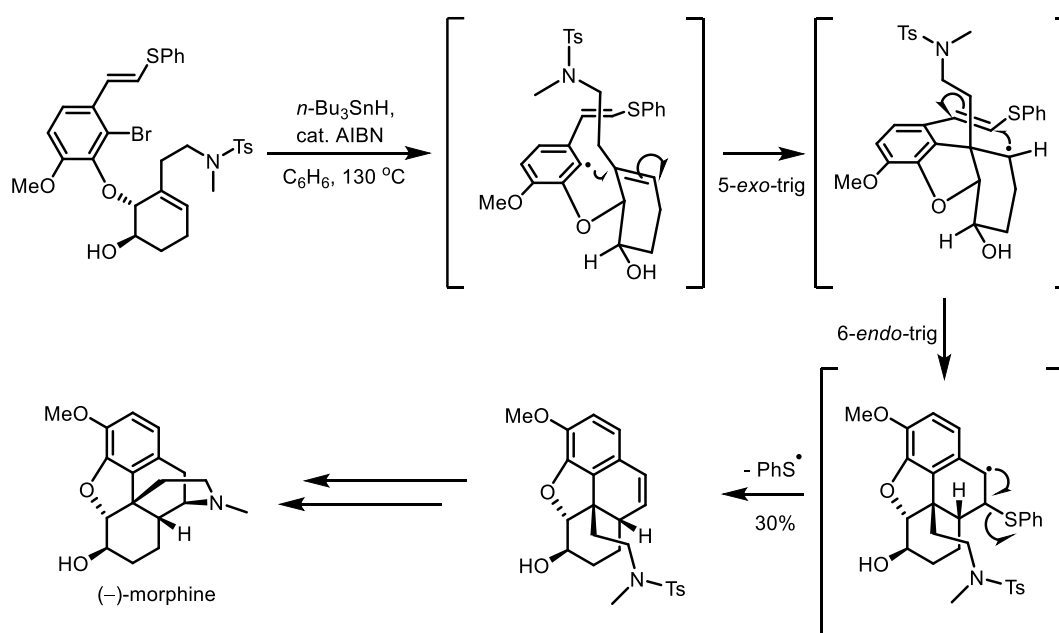
Scheme 1. Examples of oxidative radical cyclisation cascades that lead to natural and bioactive compounds

Of particular interest are those methods that don't require a leaving group to create the radical; the leaving group does not need to be installed during the synthesis of the substrate. Such reactions often use SmI_2 , photoredox chemistry or $\text{Mn}(\text{OAc})_3$ (see above).

Cascade cyclisations have the ability to convert simple starting materials into complex polycyclic molecular architectures in a single synthetic operation.²⁵ There are several examples of total syntheses in which the key step involved a radical

cyclisation cascade.²⁶ One of them is the 5-*exo*-trig/6-*endo*-trig cascade used in the total synthesis of (-)-morphine performed by Parker (Scheme 2).²⁷ A high degree of efficiency and selectivity is accomplished in these reactions, tearing down the abiding idea that radicals are excessively reactive.²⁸ Moreover, some crucial factors like diastereoselectivity can be tuned with subtle changes to the substrates.²⁹

Given the level of complexity that can be achieved in only one step with this kind of transformation, a huge library of reagents have been tested and successfully used in radical cascade cyclisations, such as *n*-Bu₃SnH,³⁰ Mn(OAc)₃,³¹ (TMS)₃SiH,³² and SmI₂.³³

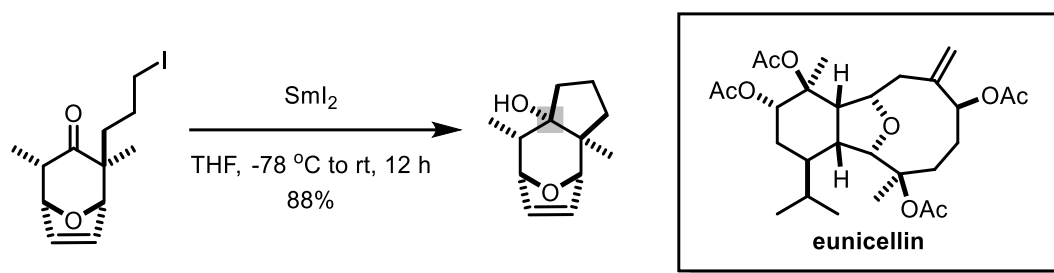


Scheme 2. Parker's use of a radical cyclisation cascade in the total synthesis of morphine

1.4. Samarium (II) mediated reactions

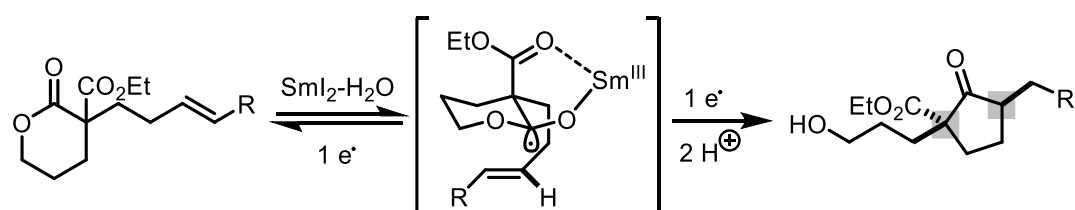
As it is shown in Table 1, SmI₂ can reduce a wide range of functional groups. The reduction product is typically obtained by protonation after two consecutive electron transfers. Alternatively, capture of the radical intermediate, after a single electron transfer, with a radical acceptor allows the formation of carbon-carbon bonds.⁵

Of particular interest are the intramolecular reductive cyclisations that lead to key intermediates in the total synthesis of natural products. For example, in Scheme 3, reduction of alkyl iodide and subsequent reduction of the radical formed gives an organosamarium intermediate, that adds to the ketone to provide the tertiary alcohol product.³⁴



Scheme 3. SmI_2 mediated cyclisation in the synthesis of an intermediate *en route* to eunicellin

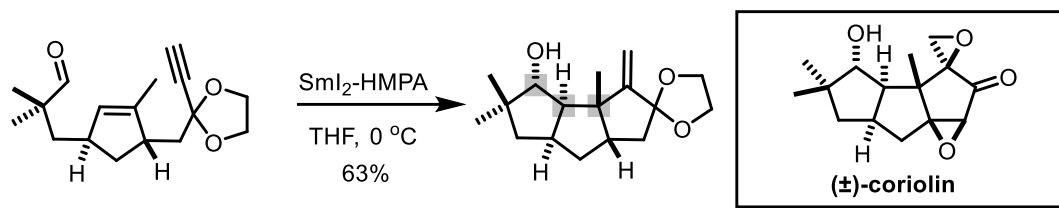
The diastereoselectivity of these reactions can often be rationalised using chelated transition states due to the high oxophilicity of Sm(II) . In the case from our group shown in Scheme 4, first electron transfer to the more reactive lactone carbonyl forms a ketyl radical that upon coordination with the ester leads to a stabilised intermediate with the radical in a pseudo axial orientation. The radical reacts with the alkene to obtain the desired product through a 5-*exo-trig* cyclisation with good diastereoselectivity and yield.³³



Scheme 4. Rationale for the observed diastereoselectivity in the radical cyclisation of lactones

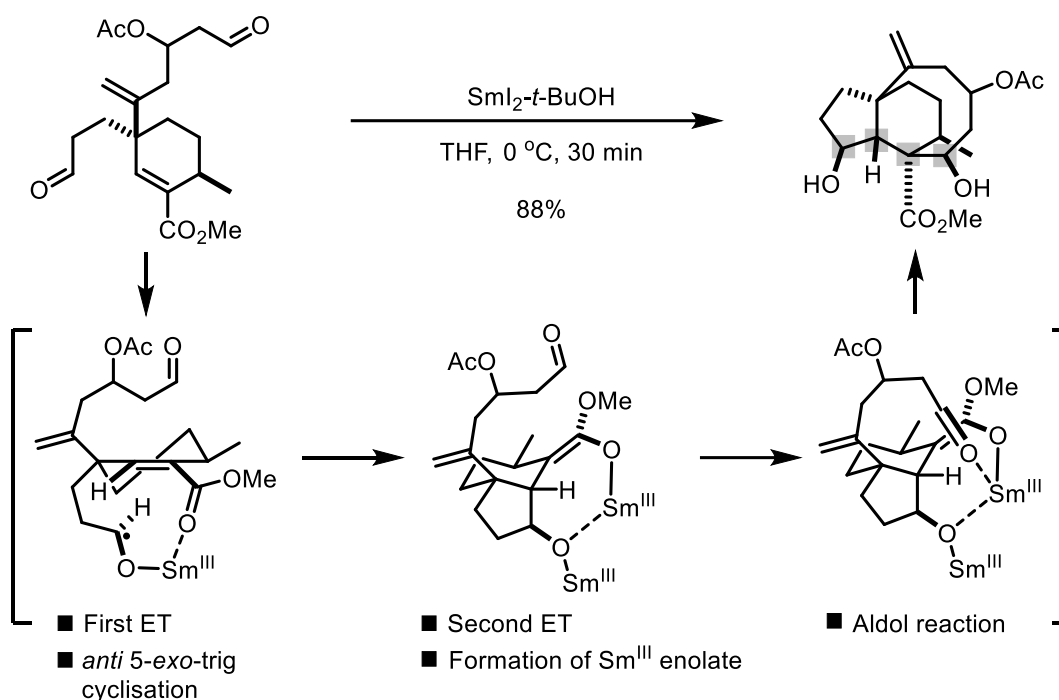
The flexibility in the choice of starting functionality, mild conditions and the high selectivity and functional group tolerance observed are some of the features that make SmI_2 a suitable candidate for the development of radical cascades.³⁵

These factors have made organic chemists take it into consideration when trying to construct highly advanced intermediates and intricate scaffolds. Curran's total synthesis of (\pm)-coriolin (Scheme 5) is a perfect example of this kind of transformation. The key step is a radical cyclisation cascade in which a tricyclic core is assembled with formation of three stereocenters with complete diastereocontrol.³⁶



Scheme 5. Curran's radical cascade in the total synthesis of coriolin

Another good example of SmI_2 radical cascade is the one reported by Procter for the total synthesis of pleuromutilin (Scheme 6). In this case SmI_2 reacts with the most accessible aldehyde, which undergoes an *anti* 5-*exo*-trig cyclisation. Subsequent formation of a Sm(III) enolate and aldol condensation with the remaining aldehyde yields the tricyclic core of pleuromutilin. Samarium coordination to the different oxygen atoms during the course of the reaction is crucial for controlling the chemo- and diastereoselectivity of this extremely complex cascade that gives an 88% yield of the 5,6,8-tricyclic scaffold.³⁷



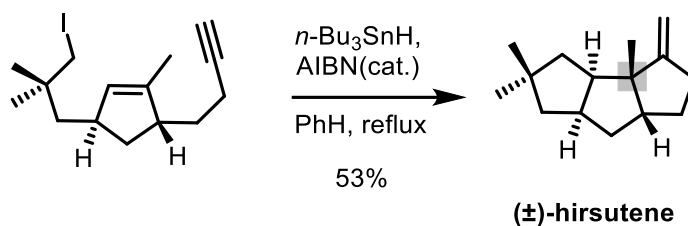
Scheme 6. Sml₂-mediated cascade in the formation of 5,6,8-tricyclic scaffold of pleuromutilin

1.5. Formation of quaternary carbons during radical cascades.

One of the biggest organic synthetic challenges is the formation of quaternary carbon centres. It is important also to note that more than 10% of the top 200 drugs sold in US contain at least one quaternary stereocentre.³⁸ Steric repulsion between the four carbon substituents is one of the main problems that contributes to the challenge of this transformation.³⁹

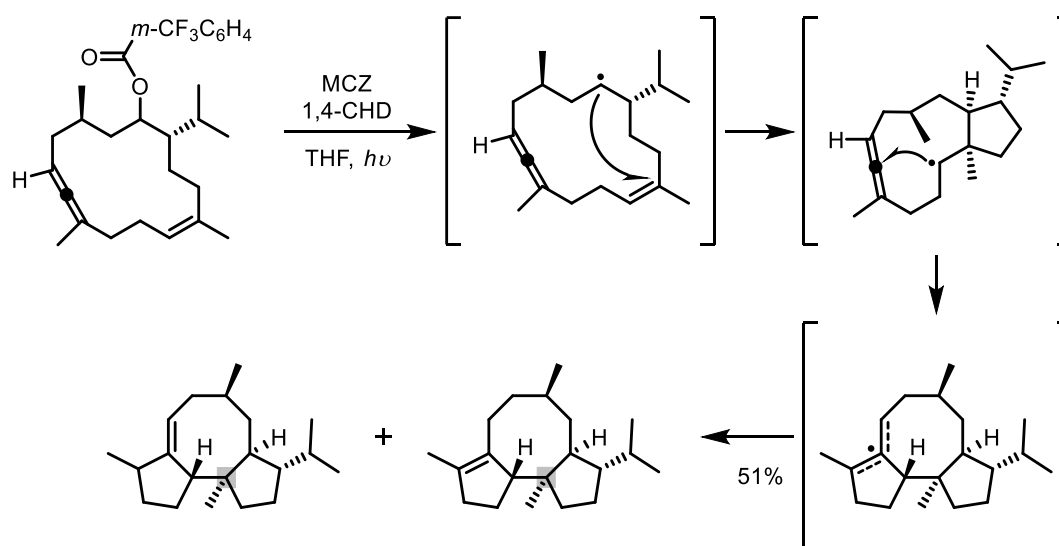
Despite the difficulty, several examples of cascade reactions leading to skeletons with quaternary carbons have been reported in the literature with radical generating reagents playing an important role in them.²⁶

Curran, one of the pioneers of this field, synthesised hirsutene in 13 steps, installing one of the two quaternary carbons in the last step by a radical cascade that proceeded in a 53% yield (Scheme 9).⁴⁰



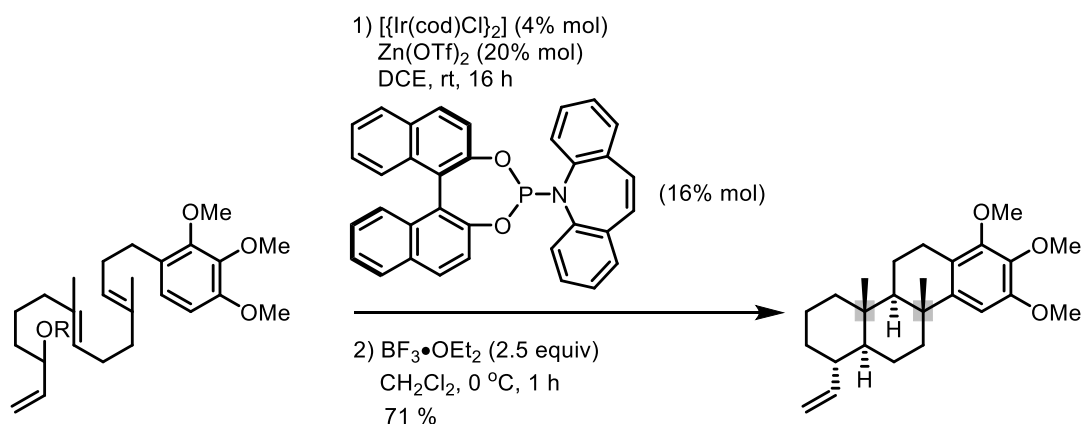
Scheme 9. Radical cascade in the synthesis of hirsutene

Chemoselectivity issues associated with the use of tin radicals have led to the need for other kind of reagents. For example, Myers and Condroski have used an interesting method for radical generation in the key step towards the synthesis of (±)-7,8-epoxy-basmen-6-one by a transannular radical cyclisation.⁴¹ In this example, they generated the radical with *N*-methylcarbazole (MCZ) and light, an obtained 51% yield of the target tricyclic structure bearing a new quaternary centre (Scheme 10).



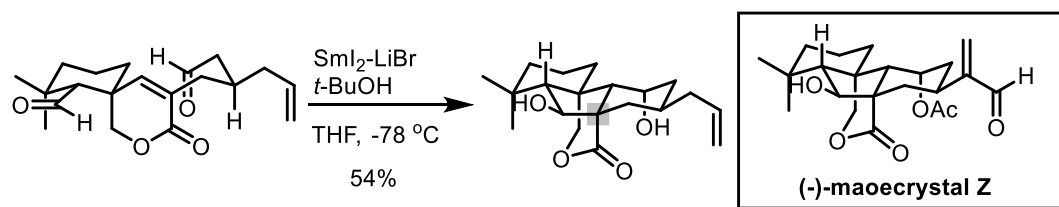
Scheme 10. Transannular radical cascade cyclisation in the synthesis of (±)-7,8-epoxy-basmen-6-one

Not surprisingly, the recent rise of photoredox catalysis⁴² has led to this methodology being used in radical cascades that form quaternary stereocentres. Lie's total synthesis of mycoleptodiscin A (Scheme 11) is made possible thanks to an asymmetric photoredox cascade that forms two quaternary centres.⁴³ In this case a chiral ligand is added to obtain the enantiomerically pure product in 21% yield and requires the addition of $\text{BF}_3 \cdot \text{OEt}$ to improve the isolated yield to 71%.



Scheme 11. Radical cascade towards the synthesis of mycoleptodiscin

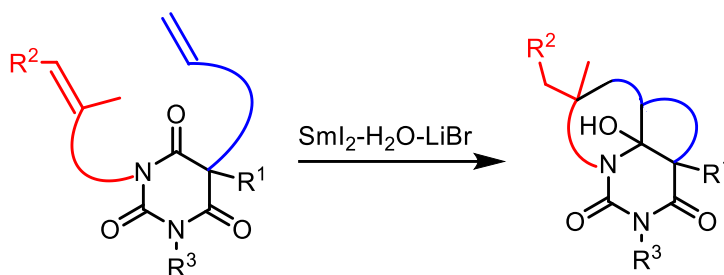
SmI_2 is also a suitable candidate for the formation of quaternary centres through radical cascades. Procter's radical cascade approach to pleuromutilin (Scheme 6) is a good example of such process. Reisman has also used a cascade, similar to Procter's system, to form three stereogenic centres including one quaternary carbon stereocentre, on the elegant total synthesis of (-)-maoecrystal Z (Scheme 12).⁴⁴



Scheme 12. Reisman's radical cascade in the total synthesis of maoecrystal Z

2. Objectives

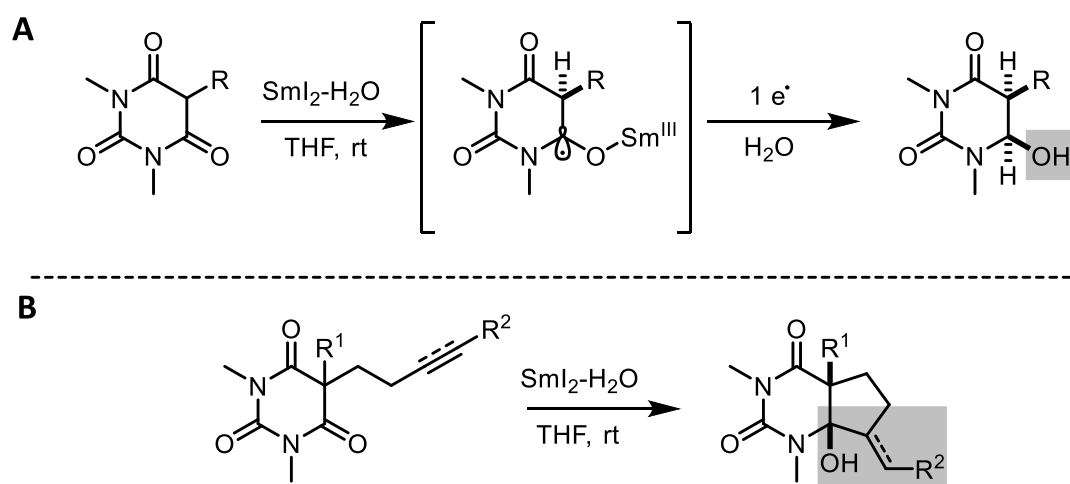
The overall aim of the project is the development of a radical-radical cascade cyclisation in order to construct tricyclic barbiturates with several new stereocentres including a synthetically challenging quaternary centre.



3. Results and discussion

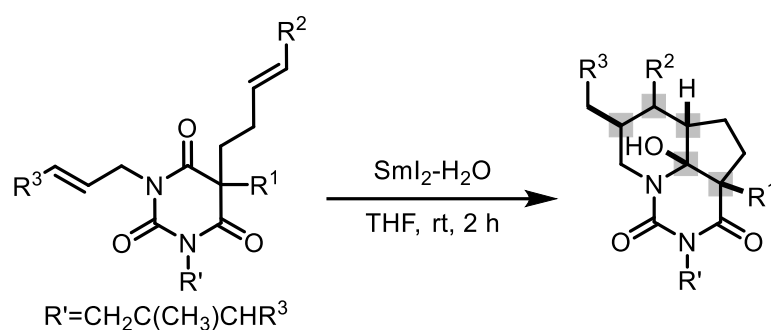
3.1. Previous research carried out in the group

The first example of the selective monoreduction of barbituric acid derivatives developed by Procter paved the way for more complex radical reactions involving this type of scaffold.^{45,46} The feasibility of these transformations is mainly explained by two factors: 1) the amide-like carbonyls are more active than simple amides and certainly more reactive towards electron transfer than the other urea-type carbonyl, which has a higher $\pi^*C=O$ orbital energy, 2) the radical intermediate is anomerically stabilised by the lone pair of the adjacent nitrogen (Scheme 13A).⁴⁵ Such stabilised radical intermediates can be further exploited by reacting them with an intramolecular radical acceptor, for instance a double bond, to form with high diastereoselectivity polycyclic structures with two stereogenic centres (Scheme 13B). Manipulation of the medically relevant barbiturates can be achieved by substitution of the hydroxyl group by a wide range of nucleophiles thanks to the generation of highly electrophilic *N*-acyliminium ions.⁴⁷



Scheme 13. A) Selective monoreduction of barbiturates through an anomerically stabilised radical intermediate. B) Reductive radical cyclisation of barbiturates

Based on these principles and the capability of SmI_2 to perform subsequent cyclisations, it was envisioned that these kinds of substrate could be pushed even further in terms of complexity generation. With this idea in mind the first example of radical cyclization cascade involving ET reduction of an amide-type carbonyl (Scheme 14) was developed in the group.⁴⁸ The cascade converts an achiral barbituric acid derivative into a structurally complex tricyclic scaffold that contains up to five contiguous stereocentres with very high diastereoselectivity (>95:5).

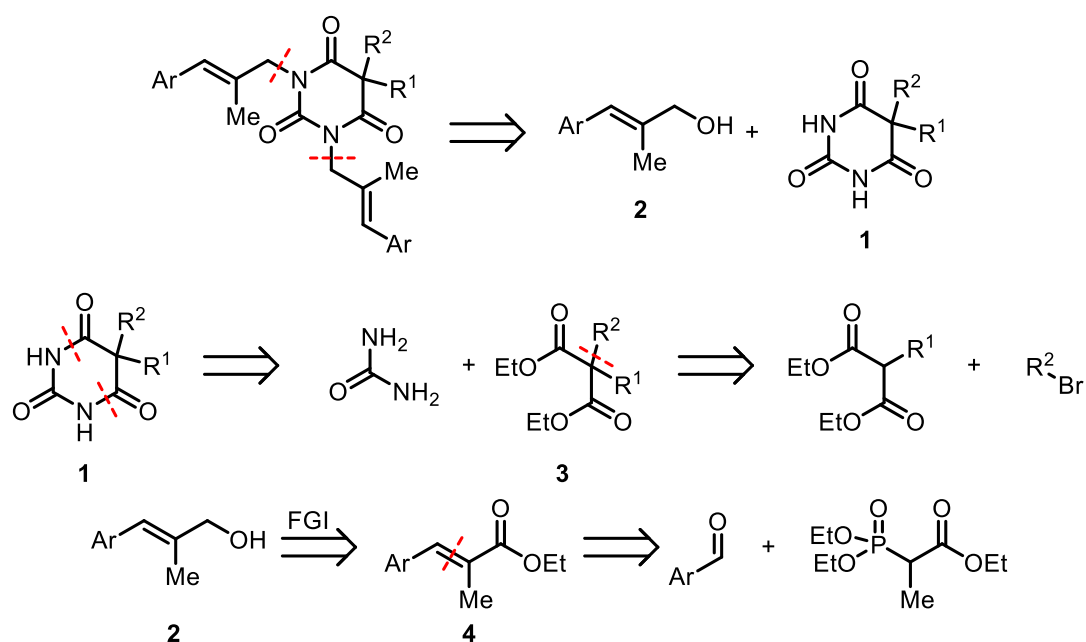


Scheme 14. Radical-radical cyclisation cascade of barbiturates

3.2. Substrate synthesis

The substrates used in the development of our samarium(II)-mediated radical cascade are not commercially available and most of the intermediates were not described in the literature. Thus, it is of crucial importance to highlight the synthesis of these structures starting with a retrosynthetic analysis (Scheme 15).

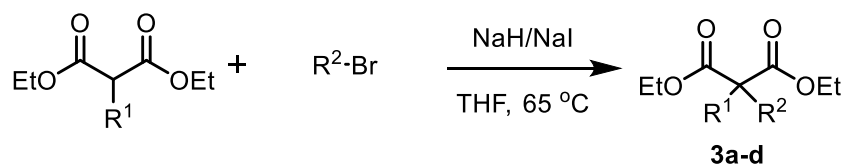
The first obvious disconnection is the C-N bond that divides the target structure into a functionalised barbiturate **1** and an allylic alcohol **2** which contains a double bond that will allow the second cyclisation in our cascade. Barbiturate **1** can be synthesised from urea and a functionalised diethyl malonate **3**, which is one step from the commercial starting material, monoalkyl diethyl malonates.



Scheme 15. Retrosynthetic analysis of the target substrates

3.2.1. Synthesis of barbituric acid core (1)

The first step in the synthesis of the barbituric acid core **1** is the alkylation of diethyl malonate using NaH as a base and a range of alkyl bromides. Modification of the alkyl chain allowed us to probe the feasibility of different radical cascades that will be discussed further on. Methyl and *iso*-propyl α -substituted malonates were used due to their commercial availability and in order to observe their influence in the diastereoselectivity of the cascade process. Subsequent condensation with urea and EtONa gave barbituric acid core **1** (Scheme 16).

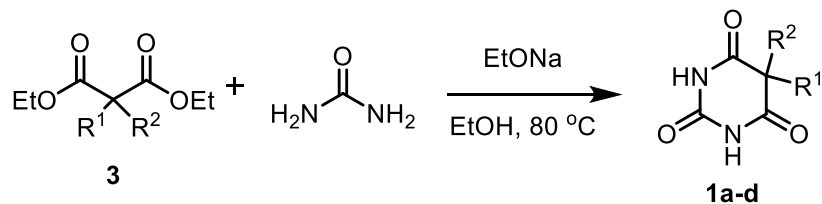


3a: R¹: Me, R²: 3-butenyl 95%

3b: R¹: *i*-Pr, R²: 3-butenyl 30%

3c: R¹: Me, R²: 3-butynyl 55%

3d: R¹: *i*-Pr, R²: 4-pentenyl 71%



1a: R¹: Me, R²: 3-butenyl 90%

1b: R¹: *i*-Pr, R²: 3-butenyl 59%

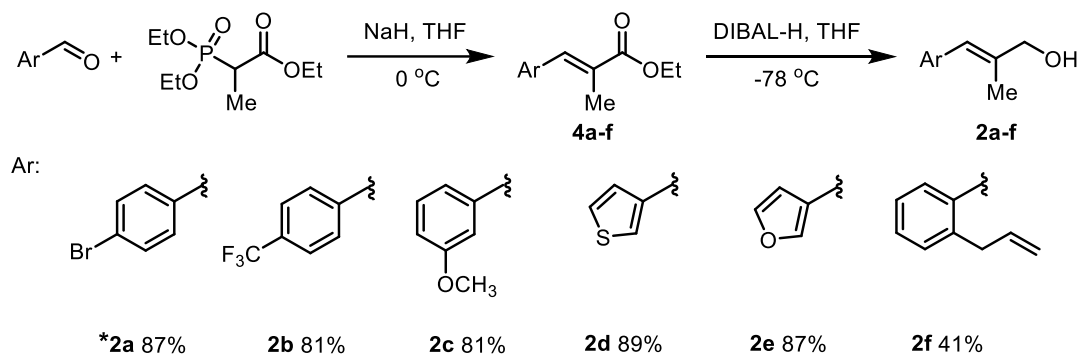
1c: R¹: Me, R²: 3-butynyl 51%

1d: R¹: *i*-Pr, R²: 4-pentenyl 15%

Scheme 16. Synthetic sequence for the construction of the barbituric acid cores

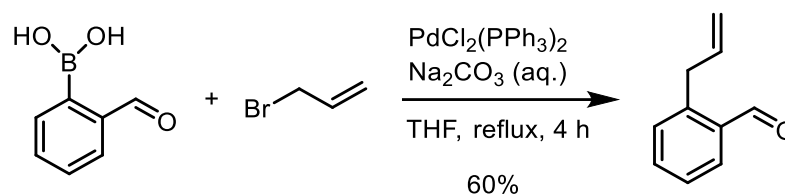
3.2.2. Synthesis of allylic alcohols (2)

The first step of the sequence to prepare homoallylic alcohols **2** is a Horner-Wadsworth-Emmons olefination⁴⁹ of an aryl aldehyde using a phosphonate. Reduction of the ester **4** with DIBAL-H then gave the alcohol **2** in high yields over the two steps. A variety of aromatic aldehydes including those bearing electron-donating, electron-withdrawing groups and heteroaryl aldehydes, were used to investigate the scope of the cascade (Scheme 17).



Scheme 17. Synthetic route to prepare the alcohol side chains. *Yields over two steps

The preparation of alcohol **2f** required an additional Suzuki coupling step to insert the *ortho* allyl substituent (Scheme 18).⁵⁰



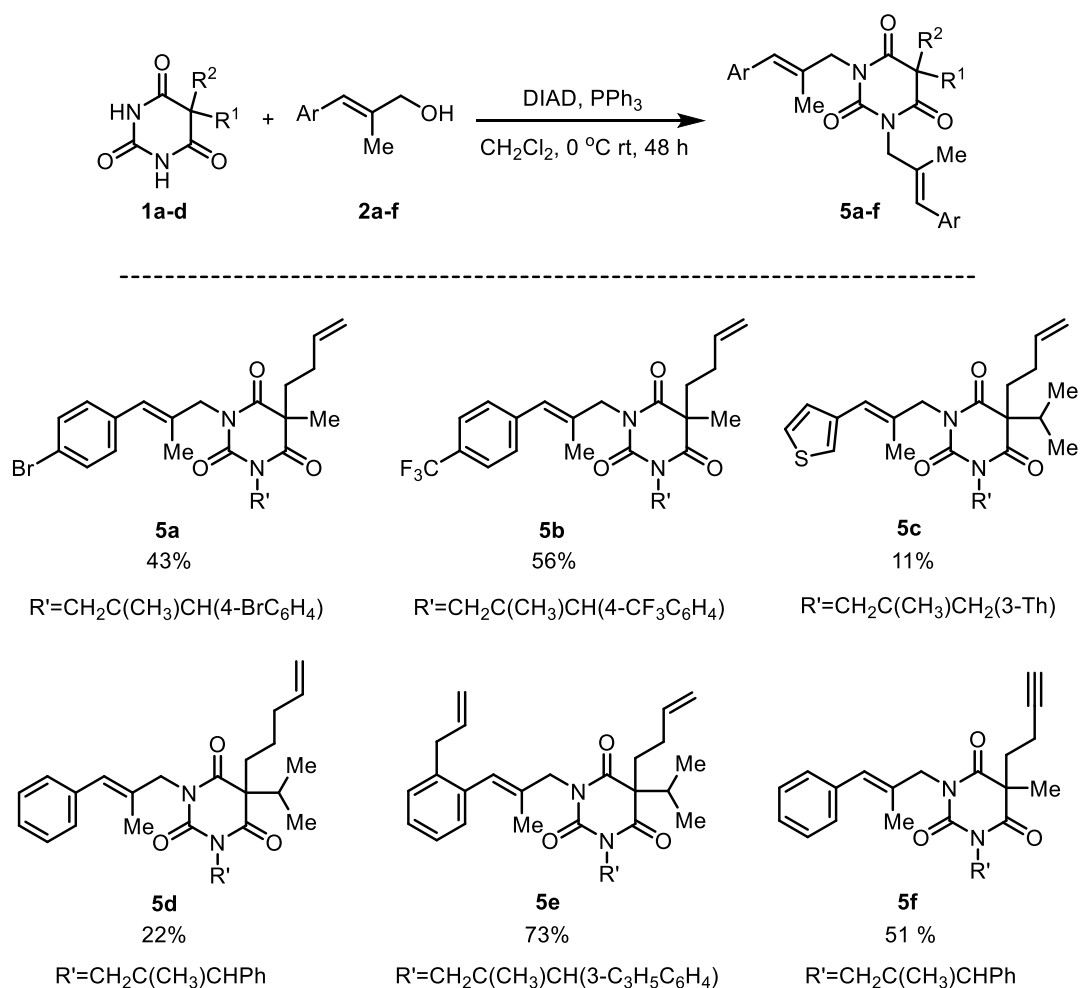
Scheme 18. Suzuki coupling to obtain *ortho* substituted aldehyde

Due to time constraints alcohol **2e** was not used in the next coupling step.

3.2.3. Alcohol and barbituric acid core coupling

Cascade substrates **5** were assembled from **1** and **2** *via* Mitsunobu reaction⁵¹ using diisopropyl azodicarboxylate (DIAD). Commonly used diethyl azodicarboxylate (DEAD) was avoided due to its excessive reactivity and toxicity.

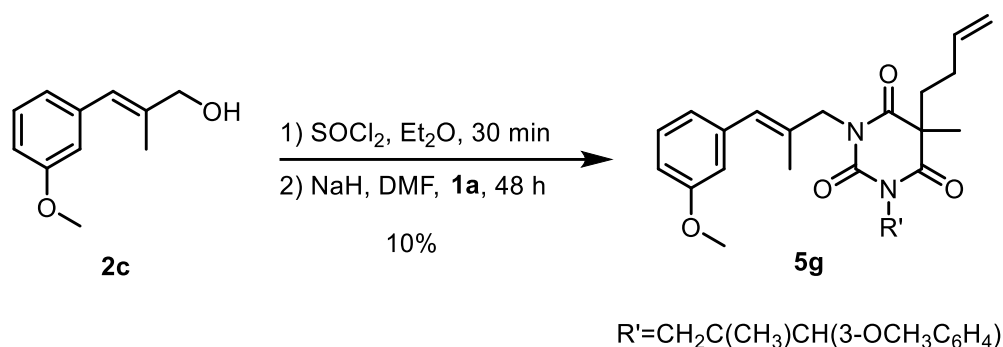
Allylic alcohol **2** bearing electron-rich aromatic rings were found not to be suitable for these reaction conditions, probably due to elimination of the activated hydroxyl group.⁵² In order to solve this problem, several methods aimed at installing a better leaving group for alkylation of nitrogen were attempted.



Scheme 19. Cascade substrates prepared

A methanesulfonyl group was chosen for use in the first trial due to its well-known ability to form a leaving group. However, the desired adduct was not detected and only a complex mixture of products was observed. We then tried a less reactive alternative, and used *p*-toluenesulfonyl chloride in an attempt to form the tosylate. This provided an unexpected outcome. Unfortunately, the desired tosylated alcohol was not observed, isolating instead the corresponding chloride *via* nucleophilic substitution of the desired tosylate. After these two attempts we decided to use a bromide leaving group. Bromination with PBr₃ in ether has been reported in the literature for a very similar alcohol substrate,⁵³ although low conversion and fast decomposition of the product led to the failure of the reaction. An Appel reaction with PPh₃, imidazole and Br₂ was used as an alternative, though regioselectivity issues arose again. The solution to these problems was the treatment of alcohol **2c** with thionyl chloride and the use of the crude reaction

mixture for the alkylation with NaH and barbituric acid derivative **1a**. Under these conditions, a low yield of **5g** was obtained.

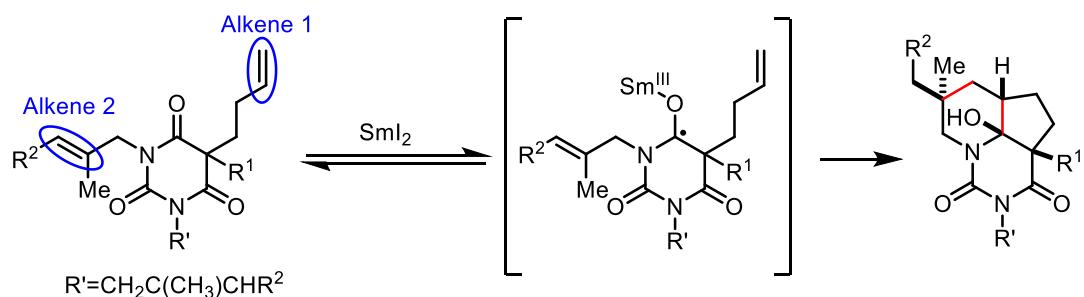


Scheme 20. Alternative coupling of the barbituric acid core and allylic alcohols bearing electron-rich aryl groups

3.3. Construction of quaternary carbons through radical-radical cascades

The development of transformations that create molecules bearing quaternary centres is one of challenges in modern organic synthesis.⁵⁴ It is also of crucial importance if we take into account that such motifs are found in many biologically active natural products.^{38,39}

Based on previous work carried out in the Procter group^{45,48} it was envisaged that a radical-radical cascade cyclisation could be used as a tool to construct scaffolds containing synthetically challenging quaternary carbons, diastereoselectively, in a single operational step.



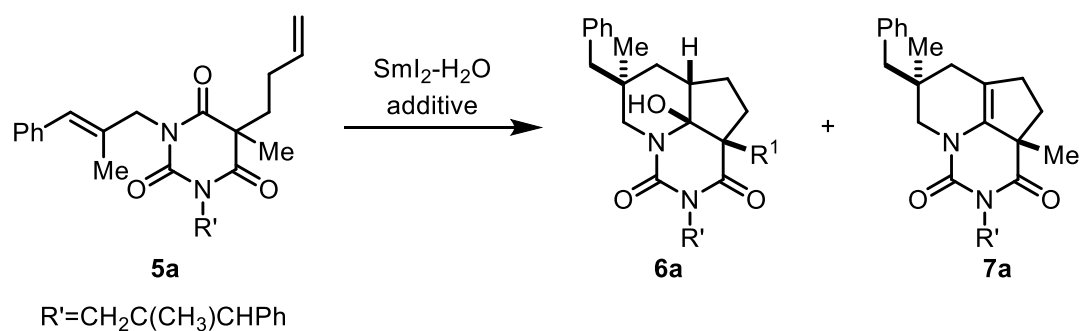
Scheme 21. Radical-radical cascade cyclisation of barbiturates

Barbiturates are ideal templates as alkene radical traps can be attached to carbon and/or nitrogen and cyclisation avoids undesired reduction or side product formation. The first electron transfer from SmI_2 to form the amide-type radical is reversible, leading to the possibility of trapping that radical with a suitably positioned radical acceptor (alkene 1). The radical formed as consequence of that first cyclisation could, ideally, also be trapped by a second radical acceptor (alkene 2) to form the desired polycyclic product bearing an all carbon quaternary stereocentre.⁴⁸

3.4. Cyclisation optimisation

Barbiturate **5a** was selected as a model substrate with which to optimise the cascade cyclisation (Table 2). The use of H_2O as a cosolvent was essential for the reduction of **5a** (Table 2, entry 2). Upon treatment of **5a** with $\text{SmI}_2\text{-H}_2\text{O}$ in THF, hemiaminal **6a** and enamine **7a** cascade products were obtained (entry 3) in 6% and 35% yield, respectively. Increasing the amount H_2O cosolvent didn't produce any significant change. Interestingly, the addition of LiBr resulted in full conversion and higher yields for the formation of both cascade products. Finally, quenching of the reaction with HCl triggered dehydration of hemiaminal **6a** to enamine **7a** (Table 2, entry 7).

As proposed by Flowers, the combination of SmI_2 and LiBr generates SmBr_2 in situ.⁶ Although SmBr_2 has a higher reduction potential than SmI_2 ⁵⁵ the radical intermediate in the cascade appears less susceptible to reduction to the anion under the $\text{SmI}_2\text{-H}_2\text{O-LiBr}$ conditions, and radical cyclization is more efficient. A hindered approach of $\text{SmBr}_2\text{-H}_2\text{O}$ to the radical may lie behind the slower outer-sphere process.⁴⁸

Table 2. Optimisation of the cascade – reactions carried out by Mr. Huan-Ming Huang

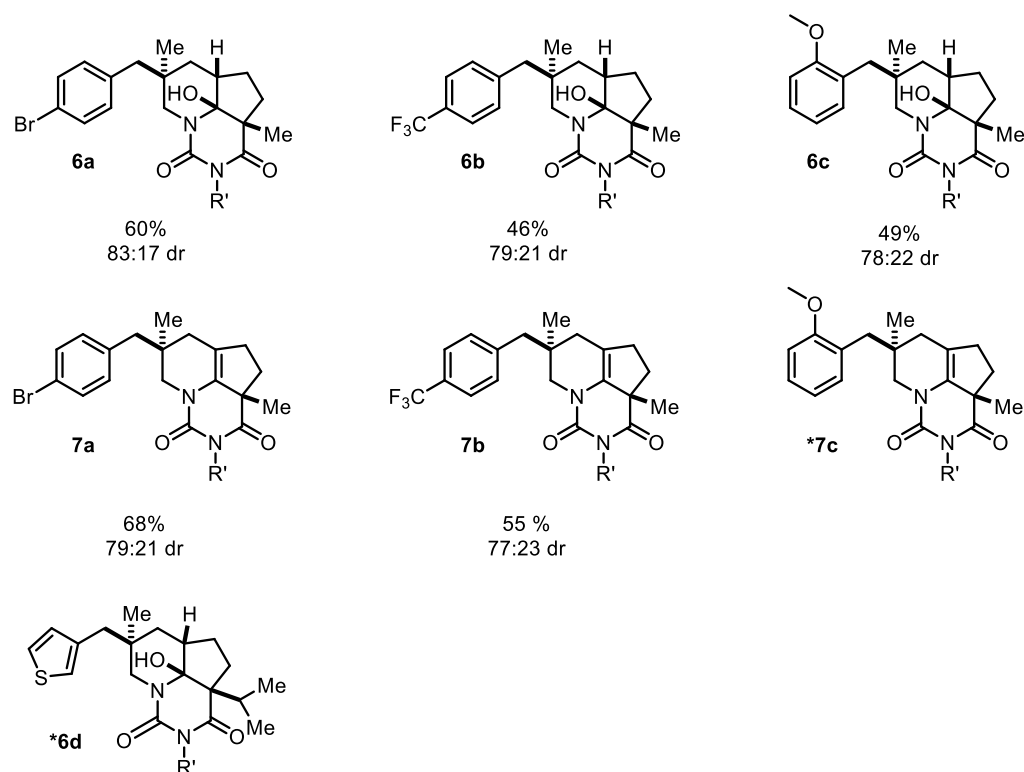
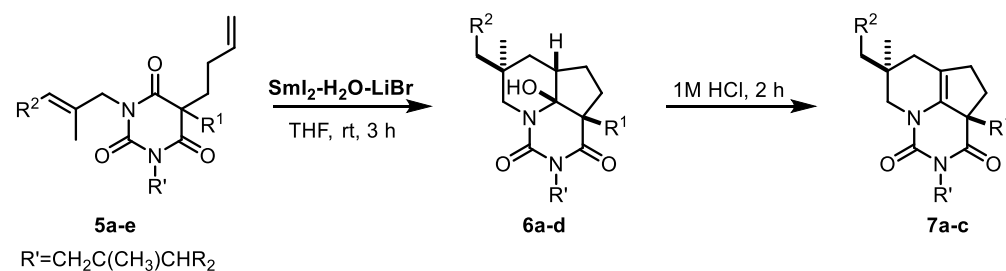
Entry	Sml ₂ (eq.)	H ₂ O (eq.)	LiBr (eq.)	Yield (%)		
				5a	6a	7a
1	3	–	-	100	0	0
2 ^a	3	100	-	38	8	30
3	3	300	-	34	6	35
4 ^b	5	100	-	9	-	50
5 ^c	5	100	60	-	28	42
6 ^d	3	100	60	-	57	28
7 ^e	3	100	60	-	-	76

^a Reaction conditions: **5a** (0.1 mmol, in THF) under N₂, was added H₂O, followed by Sml₂ and the reaction quenched after 6 h. ^b Sml₂ (0.1 M, 5 mL) was added by syringe pump, 1 h, after 5 h, HCl (2 M, 2 mL) was added and stirred for 2 h. ^c LiBr and Sml₂ (0.1 M, 5 mL) was mixed and stirred for 30 min, then the mixture was added by syringe pump, 1 h, then stirred for 5 h. ^d LiBr and Sml₂ (0.1 M, 3 mL) was mixed and stirred for 30 min, then the mixture was added by syringe pump, 1 h, and stirred for 3 h. ^e LiBr and Sml₂ (0.1 M, 3 mL) was mixed and stirred for 30 min, then the mixture was added by syringe pump, 1 h, after 3 h, HCl (2 M, 2 mL) was added and stirred for 2 h.

3.5. Scope of the cascade

After having optimised the reaction conditions, we next studied the scope of the cyclisation cascade. A variety of aromatic sidechains including electron-rich, electron-deficient and heteroaromatics were tolerated in the reaction (Scheme 22). Cyclisation cascade products were obtained in notable yields considering that the process involves the formation of three new stereocentres and one synthetically challenging quaternary centre. Full selectivity of radical cascade with respect to reduction of bromide and trifluoromethyl groups was observed. The relative stereochemistry of the compounds was assigned based on the X-ray structures of

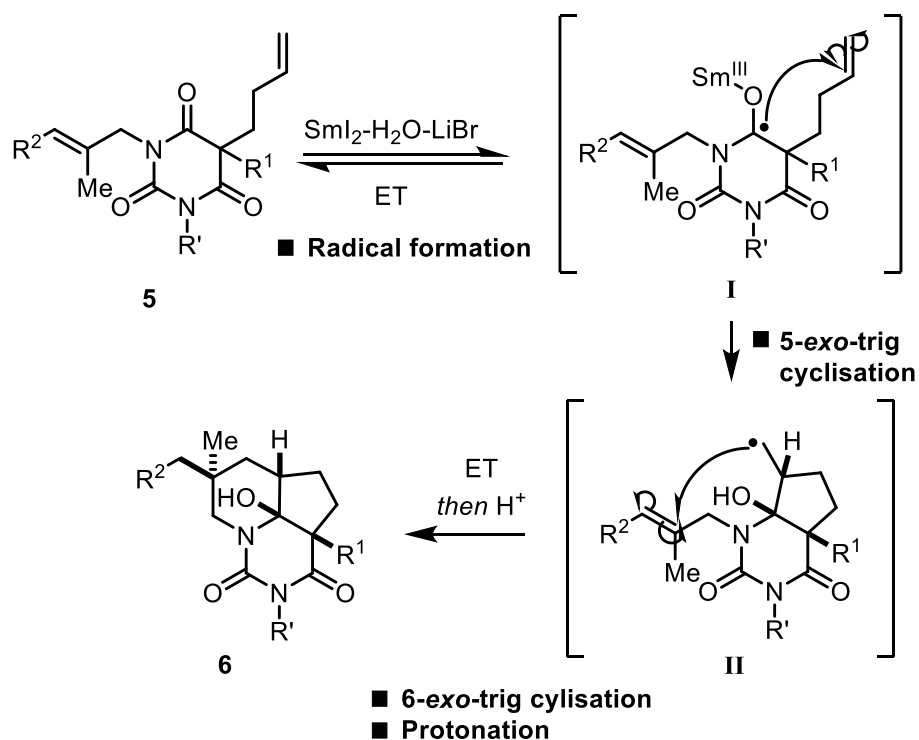
similar adducts previously obtained by the group.⁴⁸ The substitution pattern on the ring had little effect on the diastereoselectivity of the final product.



Scheme 22. Scope of the cascade. *Cyclisation products observed within a complex mixture

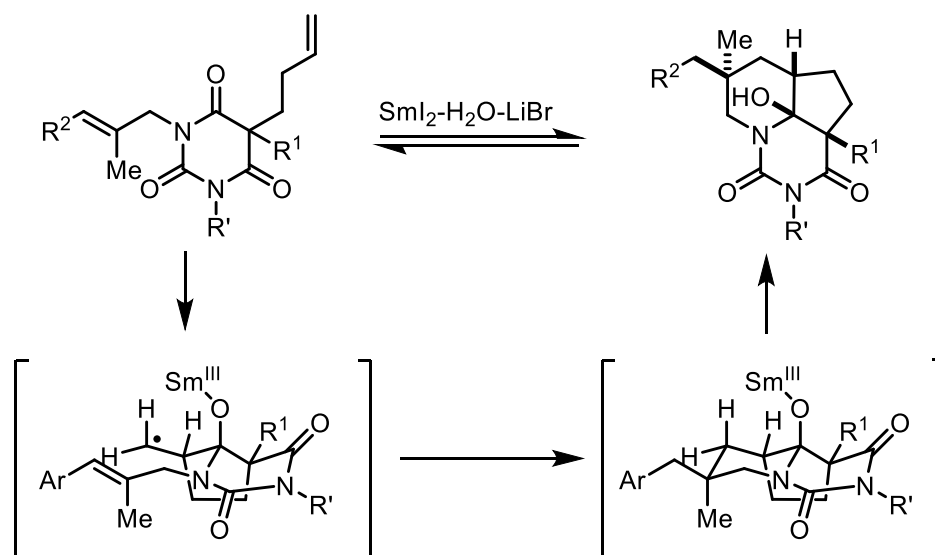
3.6. Cyclisation cascade mechanism and rationale for diastereoselectivity

The proposed mechanism is depicted in Scheme 23. The first radical species **I** formed by single electron transfer by the $\text{SmI}_2\text{-H}_2\text{O-LiBr}$ system is trapped by the alkene tether *via* 5-*exo*-trig cyclisation. Intermediate **II** then reacts with the second radical acceptor through a 6-*exo*-trig cyclisation. A second electron transfer and protonation then delivers the tricyclic cascade product.



Scheme 23. Mechanism of the radical-radical cyclisation cascade

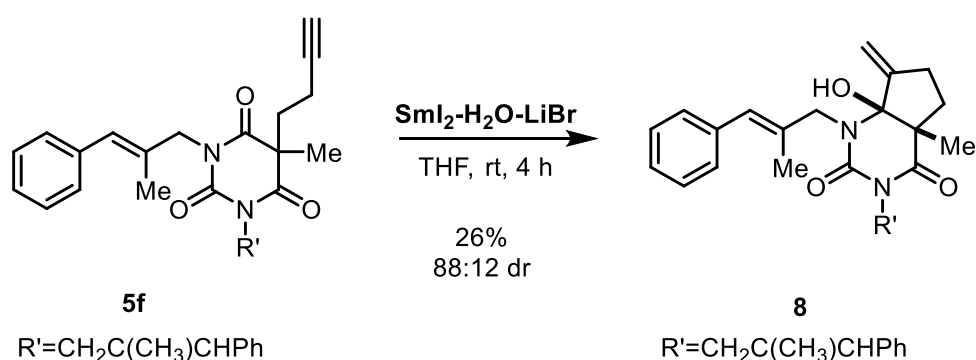
A chair transition state in which substituents adopt pseudoequatorial orientations and transannular interactions are minimized is presented as a reasonable explanation for the origin of the observed relative stereochemistry (Scheme 24).



Scheme 24. Possible origin of diastereocontrol in the cascade cyclisation

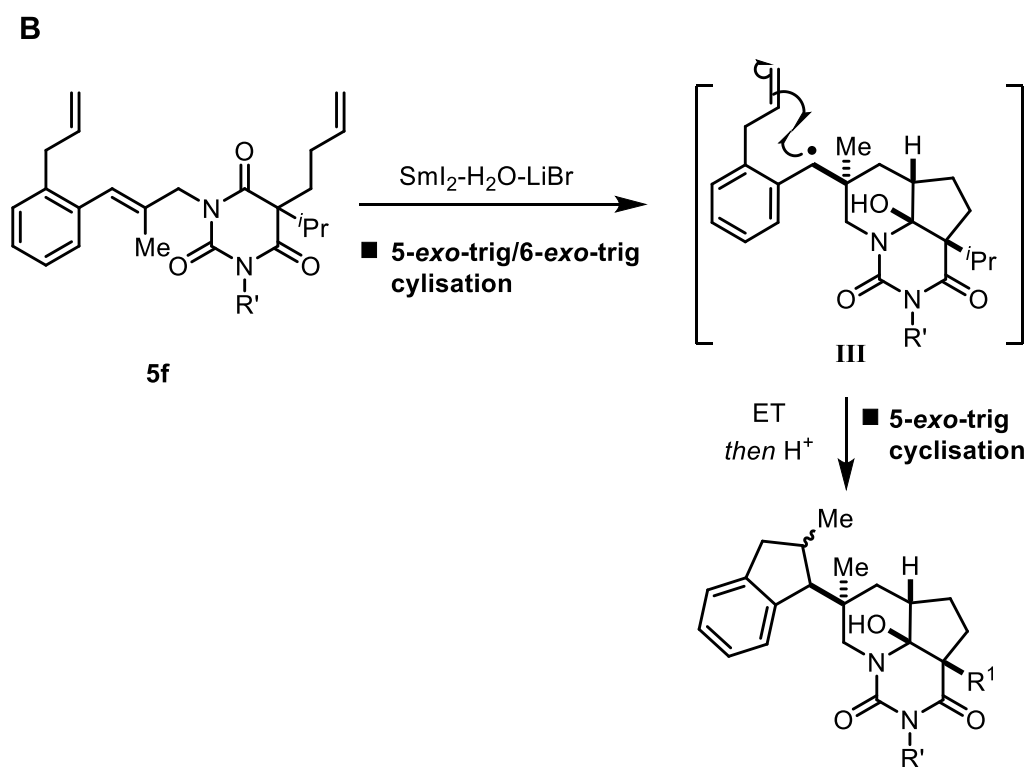
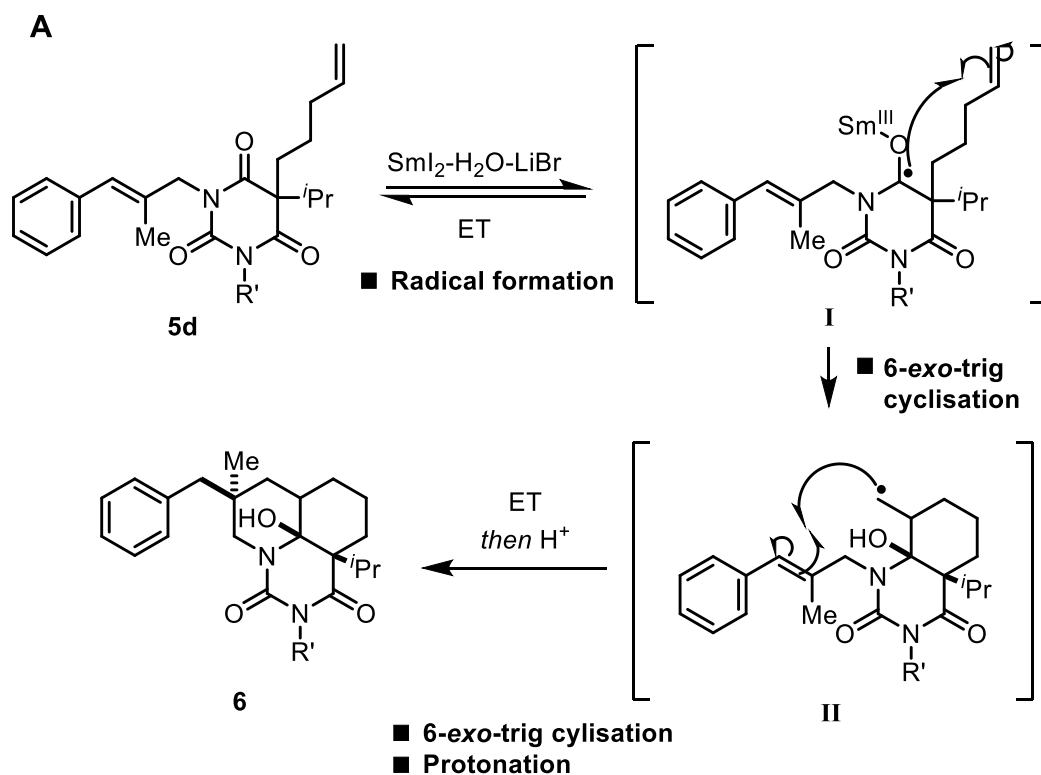
3.7. Alternative radical-radical cyclisation cascades

Three substrates **5d**, **5e** and **5f** were designed in order to study the feasibility of alternative radical cascades. Introduction of an alkyne instead of an alkene in **5f** and treatment with $\text{SmI}_2\text{-H}_2\text{O-LiBr}$ yielded 26% of the monocyclisation product **8** (Scheme 25). The vinyl radical formed in the first cyclisation underwent a second electron transfer, to give a vinyl samarium species, and capture of a proton quicker than the rate of the second cyclisation. Slower addition of $\text{SmI}_2\text{-H}_2\text{O-LiBr}$ did not result in any significant effect on the outcome of the reaction.



Scheme 25. Attempted cascade cyclisation varying the first radical acceptor

Barbiturate substrate **5d** contains a one carbon longer chain on the first radical trap tether. This modification would make the alkene tether trap the first radical species **I** *via* 6-*exo*-trig cyclisation. Intermediate **II** then will react with the second radical acceptor through another 6-*exo*-trig cyclisation leading to a three six membered fused ring product (Scheme 26A). Barbiturate substrate **5e** includes an additional allyl chain in the *ortho* position of the aromatic ring as radical trap. The first two cyclisations of the cascade would be the same as the ones in substrates **5a-d**. Intermediate **III** would then be trapped by the additional allyl chain *via* 5-*exo*-trig cyclisation. Final electron transfer and protonation would then deliver a complex cascade product (Scheme 26B). Due to time constraints these two cascades were not attempted and they will be part of the future work of this project



Scheme 26. Mechanism of two alternative radical-radical cyclisation cascades

3.8. Conclusions

The development of radical–radical cyclisation cascade triggered by single-electron transfer to amide-type carbonyl using $\text{SmI}_2\text{-H}_2\text{O-LiBr}$ has been established. This transformation allows the construction of tricyclic scaffolds containing three new stereocentres and one synthetically challenging quaternary centre in a single operational step from achiral barbiturates. The reaction proceeds diastereoselectively, with notable yields and tolerates a variety of aromatic sidechains including electron-rich, electron-deficient and heteroaromatics.

3.9. Future work

The scope of the reaction will be further expanded to different heteroaromatics as well as more complex substrates. In addition, two new radical-radical cascade cyclisations need to be optimised in order to achieve highly complex tricyclic and tetracyclic structures that contain up to five new stereocentres. The mechanism of these cyclisations also need to be studied to rationalise the stereochemical outcome of the reaction.

4. Experimental

General comments

All experiments were performed under nitrogen atmosphere unless stated otherwise. All solvents were purchased at the highest commercial grade and used as received or after purification by distillation from sodium/benzophenone (THF) and from CaH_2 (DCM), under nitrogen. Diiodoethane was washed according to literature before use.⁵⁶ All other chemicals were purchased at the highest commercial grade and used as received.

^1H NMR spectra were recorded on NMR spectrometers at 400 MHz and 500 MHz and ^{13}C NMR at 101 MHz and 126 MHz. ^1H NMR chemical shifts (δ_{H}) and ^{13}C NMR chemical shifts (δ_{C}) are quoted in parts per million (ppm) downfield from trimethylsilane (TMS) and coupling constants (J) are quoted in Hertz (Hz). Abbreviations for NMR data are s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), b (broad).

Infrared (IR) spectra were recorded on a FTIR spectrometer and mass spectra were obtained using positive or negative electrospray ionisation (ESI), atmospheric pressure chemical ionisation (APCI), electron impact ionisation (EI) or chemical ionisation (CI) techniques. ^1H NMR and ^{13}C NMR spectra were assigned with the aid of COSY, HSQC, HMBC and DEPT135. Column chromatography was carried out using silica gel 60 Å, 240 – 400 mesh.

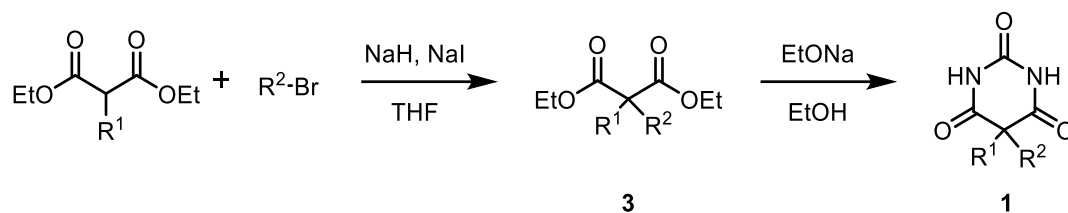
Thin layer chromatography (TLC) was performed on aluminium sheets pre-coated with silica gel, 0.20 mm (Macherey-Nagel, Polygram® Sil G/UV254). TLC plates were visualised by UV absorption, phosphomolybdic acid, vanillin or potassium permanganate solution and heating.

Preparation of samarium diiodide (SmI₂)

An oven-dried flask equipped with a dry stirrer bar was flushed with a strong flow of N₂ for 30 minutes and loaded with samarium metal (-40 mesh, 1.4 equiv.) and washed diiodoethane (1 equiv.). The flask was flushed for another 30 minutes, then freshly distilled and degassed THF (0.1 M) was added under stirring. Stirring was continued under a positive pressure of N₂ overnight at room temperature. The mixture was allowed to settle for one hour and titrated⁵⁶ prior to use.

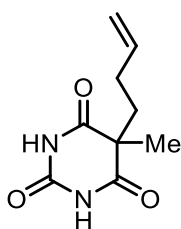
Preparation of Starting Materials

General procedure A: formation of the barbituric acids **1**



Diethyl mono-substituted malonate (1.0 equiv) was added to a suspension of NaH (60% dispersion in mineral oil, 1.1 equiv) in THF (1 M) at 0 °C. When hydrogen gas evolution ceased, NaI (0.5 equiv) and alkyl bromide (1.3-1.5 equiv) were added to the solution and the reaction mixture was stirred at 65 °C overnight. The mixture was quenched by H₂O (50 mL) and the aqueous phase extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure. The crude product was used, typically, directly without further purification. The crude malonate was added to a suspension of urea (2.0 equiv), NaOEt solution (21% in EtOH, 3.0 equiv) and EtOH (0.5 M) and stirred at 80 °C for 16 h. After cooling to room temperature, the solvent was evaporated and the residue was dissolved in water and hydrochloric acid was added dropwise. The precipitate was filtered and purified by column chromatography or crystallised from water to obtain the barbituric acids **1**.⁵⁷

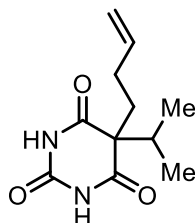
5-(But-3-enyl)-5-methylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**1a**)⁴⁸



General procedure A was followed: diethyl methyl malonate (8.71 g, 1.0 equiv), NaH (2.2 g, 1.1 equiv), NaI (3.74 g, 0.5 equiv), 4-bromobut-1-ene (10.13 g, 1.5 equiv), urea (6.01 g, 2.0 equiv) and NaOEt solution (48.61 g, 3.0 equiv) gave **1a** (8.44 g, 43.1 mmol, 86%) as a beige solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 11.33 (s, 2 H, 2

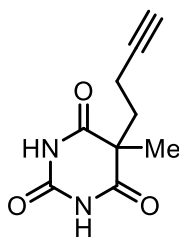
× *NH*), 5.64 - 5.73 (m, 1 H, *CH*=*CH*₂), 4.90 - 4.99 (m, 2 H, *CH*=*CH*₂), 1.83 - 1.91 (m, 4 H, (*CH*₂)₂*CH*=*CH*₂), 1.37 (s, 3 H, *CCH*₃). Data consistent with the literature.⁴⁸

5-(But-3-enyl)-5-isopropylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (1b)⁴⁸



General procedure A was followed: diethyl isopropyl malonate (10.11 g, 1.0 equiv), NaH (2.2 g, 1.1 equiv), NaI (3.74 g, 0.5 equiv), 4-bromobut-1-ene (10.13 g, 1.5 equiv), urea (6.01 g, 2.0 equiv) and NaOEt solution (48.61 g, 3.0 equiv). Purification by column chromatography (70:30 hexanes:ethyl acetate) gave **1b** (1.94 g, 8.66 mmol, 17%) as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm): 11.49 (s, 2 H, 2 × *NH*), 5.61 - 5.78 (m, 1 H, *CH*=*CH*₂), 4.87 - 5.02 (m, 2 H, *CH*=*CH*₂), 2.05 - 2.19 (m, 1 H, *CH*(*CH*₃)₂), 1.93 (apparent d, 2 H, *J* = 8.5 Hz, *CCH*₂*CH*₂*CH*=*CH*₂), 1.83 (apparent d, 2 H, *CCH*₂*CH*₂*CH*=*CH*₂), 0.91 (6 H, d, *J* = 6.7 Hz, *CH*(*CH*₃)₂). Data consistent with the literature.

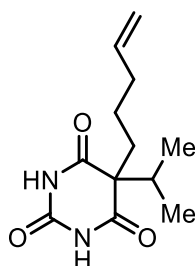
5-(But-3-yn-1-yl)-5-methylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (1c)



General procedure A was followed: Diethyl malonate (5.05 g, 1.0 equiv) was added to a suspension of NaH (1.16 g, 1.1 equiv) in THF (1 M) at 0 °C. When hydrogen gas evolution ceased, NaI (2.17 g, 0.5 equiv) and 4-bromobut-1-yne (5.39 g, 1.4 equiv). Purification by column chromatography (96:4 petrol ether:ethyl acetate) gave **3c** (3.08 g, 16.0 mmol, 55%) as a yellow liquid. **3c** (19.2 mmol, 1.0 equiv), NaH (0.77 g, 1.1 equiv), NaI (1.44 g, 0.5 equiv), methyl iodide (3.82 g, 1.4 equiv), urea (2.31 g, 2.0 equiv) and NaOEt solution (18.66 g, 3.0 equiv) gave **1c** (1.83 g, 9.4 mmol, 49%) as a white solid. m.p. 159.0 - 160.1 °C. ¹H NMR (400 MHz, DMSO-

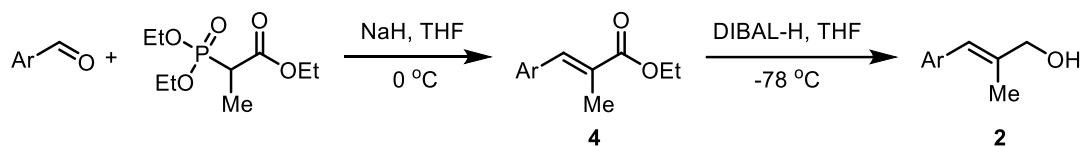
d_6) δ (ppm): 11.36 (2 H, s, 2 \times NH), 2.83 - 2.85 (1 H, m, $\text{CH}_2\text{C}\equiv\text{CH}$), 2.06 - 2.10 (2 H, m, $\text{CCH}_2\text{CH}_2\text{C}\equiv\text{CH}$), 1.97 - 2.01 (2 H, m, $\text{CCH}_2\text{CH}_2\text{C}\equiv\text{CH}$), 1.37 (3 H, s, CCH_3). ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ (ppm): 173.6 (2 \times $\text{HNC}(\text{O})\text{C}$), 150.5 ($\text{HNC}(\text{O})\text{NH}$), 82.8 ($\text{CH}_2\text{C}\equiv\text{CH}$), 72.9 ($\text{CH}_2\text{C}\equiv\text{CH}$), 49.8 ($\text{CCH}_2\text{CH}_2\text{CH}\equiv\text{CH}$), 33.2 ($\text{CCH}_2\text{CH}_2\text{CH}\equiv\text{CH}$), 29.9 ($\text{CCH}_2\text{CH}_2\text{CH}\equiv\text{CH}$), 18.0 (CH_3). IR (ν_{max} , thin film/ cm^{-1}): 3433, 2250, 2125, 1724, 1697, 1052, 1004, 821, 758. MS (ESI⁺) m/z (%): 192.9 (M-H^+ , 100); HRMS (ESI⁺) calcd. for $\text{C}_9\text{H}_{10}\text{N}_2\text{O}_3$ (M-H^+): 193.0691. Found: 193.0608.

5-Isopropyl-5-(pent-4-en-1-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (1d)



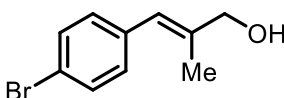
General procedure A was followed: diethyl isopropyl malonate (10.11 g, 1.0 equiv), NaH (2.2 g, 1.1 equiv), NaI (3.74 g, 0.5 equiv), 5-bromopent-1-ene (7.45 g, 1.5 equiv), urea (6.01 g, 2.0 equiv) and NaOEt solution (48.61 g, 3.0 equiv). Purification by column chromatography (70:30 hexanes:ethyl acetate) gave **1d** (1.00 g, 4.41 mmol, 9%) as a white solid. m.p. 137.8 – 138.3 °C. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ (ppm): 11.50 (2 H, s, 2 \times NH), 5.67 - 5.78 (1 H, m, $\text{CH}=\text{CH}_2$), 4.93 - 5.01 (2 H, m, $\text{CH}=\text{CH}_2$), 2.09 - 2.16 (1 H, m, $\text{CH}(\text{CH}_3)_2$), 1.94 - 2.01 (2 H, m, $\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), 1.86 - 1.81 (2 H, m, $\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), 1.07 - 1.13 (2 H, m, $\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), 0.91 (6 H, d, $J = 6.8$ Hz, $\text{CH}(\text{CH}_3)_2$). ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ (ppm): 177.8 (2 \times $\text{HNC}(\text{O})\text{C}$), 155.3 ($\text{HNC}(\text{O})\text{NH}$), 143.1 ($\text{CH}=\text{CH}_2$), 120.4 ($\text{CH}=\text{CH}_2$), 63.4 ($\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), 42.2 ($\text{CH}(\text{CH}_3)_2$), 38.8 ($\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), 38.3 ($\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), 29.4 ($\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), 22.8 ($\text{CH}(\text{CH}_3)_2$). IR (ν_{max} , thin film/ cm^{-1}): 3430, 2252, 1660, 1050, 1023, 1003, 822, 759. MS (ESI⁻) m/z (%): 237 (M-H^+ , 100); HRMS (ESI⁺) calcd. for $\text{C}_{12}\text{H}_{17}\text{N}_2\text{O}_3$ (M-H^+): 237.1245. Found: 237.1230.

General procedure B: formation of the alcohols 2



Triethyl 2-phosphonopropionate (1.5 equiv, 60 mmol) was added slowly to a dispersion of sodium hydride (60% in mineral oil, 1.5 equiv, 60 mmol) in THF (50 mL) at 0 °C. The reaction was stirred for another 1 h at this temperature. The reaction was cooled to -78 °C and aldehyde (1.0 equiv, 40 mmol) was added dropwise. The reaction mixture was warmed slowly to room temperature, stirred for another 3 h, and was poured into saturated NH₄Cl (10 mL). The phases were separated and the aqueous phase was extracted with Et₂O (3 × 40 mL). The combined organic phases were washed with brine, dried over MgSO₄, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (92:8 petroleum ether:ethyl acetate) to give the product as an oil. This oil was dissolved in THF (50 mL), and the solution was cooled to -78 °C. To the solution was added dropwise a 1 M solution of diisobutylaluminum hydride in hexane (80 mL, 80 mmol). After 30 min at -78 °C, the reaction was quenched by addition of methanol (10 mL). The reaction mixture was allowed to warm to room temperature and poured into a saturated solution of Rochelle's salt with stirring until the gel was completely dissolved. The aqueous phase was separated and extracted with diethyl ether. The organic extracts were sequentially washed with water and brine, dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo* to give **2**. Yields are reported over two steps.

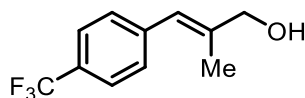
(*E*)-3-(4-Bromophenyl)-2-methylprop-2-en-1-ol (**2a**)



General procedure B was followed: using triethyl 2-phosphonopropionate (11.91 g, 1.5 equiv), NaH (2.2 g, 1.5 equiv), 4-bromobenzaldehyde (7.40 g, 1.0 equiv) in anhydrous THF (30 mL), DIBAL-H (80 mL, 2.0 equiv). Product **2d** was obtained (7.86 g, 34.8 mmol, 87%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.42

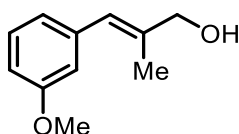
- 7.51 (m, 2 H, *H*Ar), 7.12 - 7.19 (m, 2 H, *H*Ar), 6.47 (s, 1 H, C(Ar)*CH*=C), 4.19 (d, *J* = 1.8 Hz, 2 H, *CH*₂OH), 1.84 - 1.91 (m, 3 H, CH=C*CH*₃), 1.59 (s, 1 H, *OH*). Data consistent with the literature.⁴⁹

(*E*)-2-Methyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol (2b)



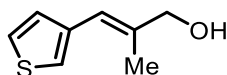
General procedure B was followed: using triethyl 2-phosphonopropionate (11.91 g, 1.5 equiv), NaH (2.2 g, 1.5 equiv), 4-(trifluoromethyl)benzaldehyde (8.71 g, 1.0 equiv) in anhydrous THF (30 mL), DIBAL-H (80 mL, 2.0 equiv). Product **2b** was obtained (6.99 g, 32.4 mmol, 81%) as colourless oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.59 (d, *J* = 8.1 Hz, 2 H, *H*Ar), 7.38 (d, *J* = 8.1 Hz, 2 H, *H*Ar), 6.57 (s, 1 H, C(Ar)*CH*=C), 4.23 (d, *J* = 5.0 Hz, 2 H, *CH*₂OH), 1.90 (d, *J* = 1.3 Hz, 3 H, CH=C*CH*₃), 1.67 (t, *J* = 5.9 Hz, 1 H, *OH*). Data consistent with the literature.⁴⁹

(*E*)-3-(3-Methoxyphenyl)-2-methylprop-2-en-1-ol (2c)⁴⁹



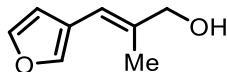
General procedure B was followed: using triethyl 2-phosphonopropionate (11.91 g, 1.5 equiv), NaH (2.2 g, 1.5 equiv), 3-methoxybenzaldehyde (6.81 g, 1.0 equiv) in anhydrous THF (30 mL), DIBAL-H (80 mL, 2.0 equiv). Product **2c** was obtained (5.77 g, 32.4 mmol, 81%) as colourless oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.27 (t, *J* = 7.8 Hz, 1 H, *H*Ar), 6.76 - 6.92 (m, 3 H, *H*Ar), 6.52 (s, 1 H, C(Ar)*CH*=C), 4.20 (d, *J* = 3.7 Hz, 2 H, *CH*₂OH), 3.82 (s, 3 H, *OCH*₃), 1.92 (d, *J* = 1.2 Hz, 3 H, CH=C*CH*₃), 1.57 (bs, 1 H, *OH*). Data consistent with the literature.⁴⁹

(E)-2-Methyl-3-(thiophen-3-yl)prop-2-en-1-ol (2d)



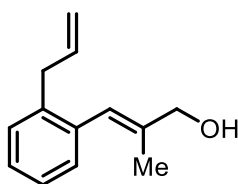
General procedure B was followed: using triethyl 2-phosphonopropionate (11.91 g, 1.5 equiv), NaH (2.2 g, 1.5 equiv), thiophene-3-carboxaldehyde (8.81 g, 1.0 equiv) in anhydrous THF (30 mL), DIBAL-H (80 mL, 2.0 equiv). Product **2d** was obtained (5.46 g, 35.6 mmol, 89%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.30 (dd, $J = 5.0, 3.0$ Hz, 1 H, C(5)**H**), 7.18 (d, $J = 2.8$ Hz, 1 H, C(2)**H**), 7.12 (dd, $J = 5.0, 1.3$ Hz, 1 H, C(4)**H**), 6.50 (s, 1 H, C(Ar)**CH=C**), 4.19 (d, $J = 0.5$ Hz, 2 H, **CH**₂OH), 1.96 (d, $J = 1.3$ Hz, 3 H, **CH**₃), 1.64 (s, 1 H, **OH**). ^{13}C NMR (101 MHz, CDCl_3) δ (ppm): 138.6 (C(Ar)^q), 136.9 (CH=C^q(CH₃)), 128.7 (C(4)**H**), 124.9 (C(5)**H**), 122.6 (C(2)**H**), 119.5 (CH=C), 69.0 (CH₂), 15.7 (CH₃). IR (ν_{max} , thin film/ cm^{-1}): 3328, 2915, 2857, 1662, 1445, 1407, 1374, 1065, 1005, 877, 839, 771. MS (GC/MS) m/z (%): 138 (M, 100); HRMS (APCI) calcd. for C₈H₁₀OS (M+H⁺): 154.0447. Found: 154.0447.

(E)-3-(Furan-3-yl)-2-methylprop-2-en-1-ol (2e)



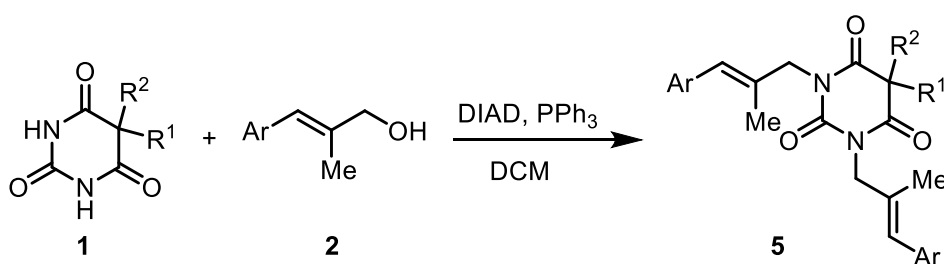
General procedure B was followed: using triethyl 2-phosphonopropionate (11.91 g, 1.5 equiv), NaH (2.2 g, 1.5 equiv), 4-bromobenzaldehyde (9.25 g, 1.0 equiv) in anhydrous THF (30 mL), DIBAL-H (80 mL, 2.0 equiv). Product **2e** was obtained (4.81 g, 34.8 mmol, 87%) as a dark brown oil. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.46 (s, 1 H, C(2)**H**), 7.40 (apparent t, $J = 1.5$ Hz, 1 H, C(5)**H**), 6.48 (dd, $J = 1.8, 0.5$ Hz, 1 H, C(4)**H**), 6.26 (d, $J = 0.5$ Hz, 1 H, C(Ar)**CH=C**), 4.16 (s, 2 H, **CH**₂OH), 1.90 ppm (d, $J = 1.0$ Hz, 3 H, **CH**₃), 1.71 (s, 1 H, **OH**). ^{13}C NMR (101 MHz, CDCl_3) δ (ppm): 142.7 (C(5)**H**), 140.8 (C(2)**H**), 136.7 (C(Ar)^q), 122.4 (CH=C^q(CH₃)), 115.4 (CH=C), 110.9 (C(4)**H**), 68.9 (CH₂), 15.8 (CH₃). IR (ν_{max} , thin film/ cm^{-1}): 3360, 2919, 2861, 1689, 1502, 1375, 1177, 1064, 1006, 871, 780. MS (GC/MS) m/z (%): 154 (M, 100); HRMS (APCI) calcd. for C₈H₁₀O₂ (M+H⁺): 138.0675. Found: 138.0673.

(E)-3-(2-Allylphenyl)-2-methylprop-2-en-1-ol (**2f**)



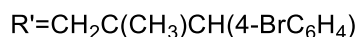
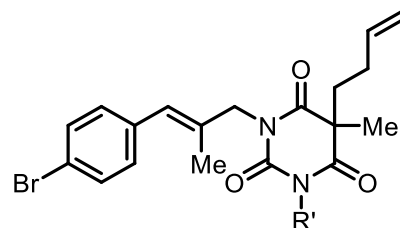
General procedure B was followed: using triethyl 2-phosphonopropionate (2.33 g, 1.5 equiv), NaH (0.39 g, 1.5 equiv), 2-allylbenzaldehyde (0.95 g, 1.0 equiv) in anhydrous THF (10 mL), DIBAL-H (20 mL, 2.0 equiv). Product **2f** was obtained (0.50 g, 2.67 mmol, 41%) as a colourless oil. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.15 - 7.23 (m, 4 H, HAr), 6.57 (d, $J = 1.0$ Hz, 1 H, C(Ar)CH=C), 5.93 (ddt, $J = 16.9, 10.3, 6.3$ Hz, 1 H, $\text{ArCH}_2\text{CH=CH}_2$), 4.94 - 5.04 (m, 2 H, $\text{ArCH}_2\text{CH=CH}_2$), 4.22 (d, $J = 1.0$ Hz, 2 H, CH_2OH), 3.36 (dt, $J = 6.5, 1.5$ Hz, 2 H, $\text{C(Ar)CH}_2\text{CH=CH}_2$), 1.74 (d, $J = 1.3$ Hz, 3 H, CH=CCH_3). ^{13}C NMR (101 MHz, CDCl_3) δ (ppm): 138.2 ($\text{C(Ar)}^q\text{CH}_2\text{CH=CH}_2$), 138.2 ($\text{CH=C}^q(\text{CH}_3)$), 136.9 ($\text{C(Ar)CH}_2\text{CH=CH}_2$), 136.6 ($\text{C(Ar)}^q\text{CH=C}$), 129.6 (C(Ar)H), 129.2 (C(Ar)H), 127.0 (C(Ar)H), 126.0 (C(Ar)H), 123.8 (C(Ar)CH=C), 115.6 (CH=CH_2), 68.6 (CH_2OH), 37.7 ($\text{C(Ar)CH}_2\text{CH=CH}_2$), 15.0 (CH_3). IR (ν_{max} , thin film/ cm^{-1}): 3327, 3060, 2912, 2855, 1637, 1482, 1445, 1041, 913, 751.

General procedure C: formation of the cascade substrates by Mitsunobu reaction



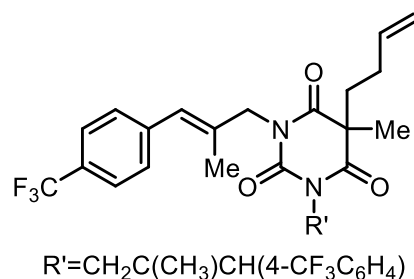
To a solution of the barbituric acid **1** (1.0 mmol, 1.0 equiv), alcohol **2** (2.2 mmol, 2.2 equiv) and PPh_3 (3.0 mmol, 3.0 equiv) in anhydrous CH_2Cl_2 (10 mL) was added DIAD (diisopropyl azodicarboxylate) (3.0 mmol, 3.0 equiv) dropwise at 0 °C. The mixture was warmed to room temperature and stirred under a N_2 atmosphere for 48 h, then concentrated *in vacuo* to give the crude product, which after purification by column chromatography on silica gel gave the desired product **5**.

**1,3-Bis(*E*)-3-(4-bromophenyl)-2-methylallyl)-5-(but-3-en-1-yl)-5-methyl
pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (5a)**



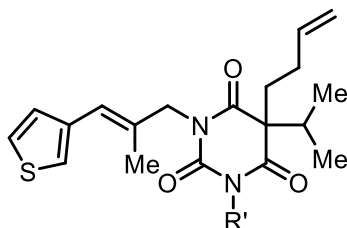
General procedure C was followed: using **1a** (0.58 g, 1.0 equiv), **2a** (1.49 g, 2.2 equiv), PPh₃ (2.36 g, 3.0 equiv) and DIAD (1.82 g, 3.0 equiv) in anhydrous CH₂Cl₂ (20 mL) for 24 h. The mixture was purified by column chromatography (80:20 hexanes:ethyl acetate) and gave **5a** (0.7954 g, 1.30 mmol, 43%) as a colourless sticky oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.41 (d, *J* = 8.5 Hz, 4 H, C(2)**H**), 7.04 (d, *J* = 8.5 Hz, 4 H, C(3)**H**), 6.28 (s, 2 H, 2 x C(Ar)**CH=C**), 5.60 - 5.76 (m, 1 H, **CH=CH**₂), 4.86 - 4.98 (m, 2 H, **CH=CH**₂), 4.53 - 4.64 (m, 4 H, 2 x **NCH**₂), 2.14 - 2.24 (m, 2 H, **CH**₂CH₂CH=CH₂), 1.94 - 2.06 (m, 2 H, CH₂**CH**₂CH=CH₂), 1.86 (s, 6 H, 2 x CH=C**CH**₃), 1.54 - 1.67 (m, 3 H, C(O)C**CH**₃). ¹³C NMR (101 MHz, CDCl₃) δ (ppm): 171.8 (2 x **NC(O)C**), 150.6 (**NC(O)N**), 136.5 (CH₂CH₂**CH=CH**₂), 135.8 (2 x **C**^q), 133.0 (2 x **C**^q), 131.3 (4 x **C(Ar)H**), 130.5 (4 x **C(Ar)H**), 125.6 (2 x C(Ar)**CH=C**), 120.6 (2 x **C**^q), 116.3 (CH₂CH₂CH=CH₂), 51.6 (CH₃**C(CH**₂CH₂CH=CH₂)), 48.6 (2 x **NCH**₂CH=CH₂), 38.0 (CH₂CH₂CH=CH₂), 30.0 (CH₂CH₂CH=CH₂), 26.1 (C(O)C**CH**₃) 16.8 (2 x C=C**CH**₃). IR (ν_{max}, thin film/cm⁻¹): 2935, 1682, 1453, 1428, 1395, 1292, 1072, 1000. MS (ESI⁻) *m/z* (%): 649 (M+K⁺, 100); HRMS (APCI) calcd. for C₂₉H₃₁N₂O₃Br₂ (M+H⁺): 613.0624. Found: 613.0696.

5-(But-3-en-1-yl)-5-methyl-1,3-bis((*E*)-2-methyl-3-(4-(trifluoromethyl)phenyl)allyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (5b)



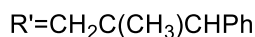
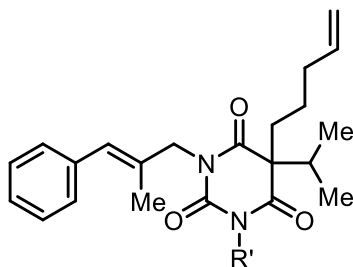
General procedure C was followed: using **1a** (0.20 g, 1.0 equiv), **2b** (0.48 g, 2.2 equiv), PPh₃ (0.79 g, 3.0 equiv) and DIAD (0.61 g, 3.0 equiv) in anhydrous CH₂Cl₂ (10 mL) for 48 h. The mixture was purified by column chromatography (90:10 hexanes:ethyl acetate) and gave **5b** (0.313 g, 0.56 mmol, 56%) as a transparent sticky oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.54 (d, *J* = 8.3 Hz, 4 H, *H*Ar), 7.27 (d, *J* = 8.3 Hz, 4 H, *H*Ar), 6.38 (s, 2 H, 2 x C(Ar)CH=C), 5.61 - 5.77 (m, 1 H, CH=CH₂), 4.89 - 4.99 (m, 2 H, CH=CH₂), 4.64 (s, 4 H, 2 x NCH₂), 2.16 - 2.26 (m, 2 H, CH₂CH₂CH=CH₂), 1.98 - 2.07 (m, 2 H, CH₂CH₂CH=CH₂), 1.89 (s, 6 H, 2 x CH=CCH₃), 1.56 (s, 2 H, C(O)CCH₃). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 171.7 (2 x NC(O)C), 150.6 (NC(O)N), 140.6 (2 x C(Ar)^qCH=C^q), 136.4 (CH₂CH₂CH=CH₂), 134.5 (2 x C=C(CH₃)), 129.0 (4 x C(Ar)H), 128.7 (q, *J* = 32.6 Hz, 2 x CF₃C(Ar)^q), 125.5 (2 x C(Ar)^qCH=C^q), 125.1 (q, *J* = 3.8 Hz, 4 x C(Ar)H), 124.2 (q, *J* = 271.9 Hz, 2 x CF₃), 116.1 (CH₂CH₂CH=CH₂), 51.6 (CH₃C(CH₂CH₂CH=CH₂)), 48.5 (2 x NCH₂CH=CH₂), 38.0 (CH₂CH₂CH=CH₂), 29.9 (CH₂CH₂CH=CH₂), 26.0 (C(O)CCH₃), 16.4 (2 x C=CCH₃). IR (ν_{max}, thin film/cm⁻¹): 2940, 2359, 1687, 1400, 1325, 1122, 1068. MS (ESI⁺) *m/z* (%): 627 (M+Cl⁺, 100); HRMS (ESI) calcd. for C₃₁H₃₀N₂O₃ClF₆ (M+Cl⁺): 627.1860. Found: 627.1855.

5-(But-3-en-1-yl)-5-isopropyl-1,3-bis((E)-2-methyl-3-(thiophen-3-yl)allyl)pyrimidine-2,4,6(1H,3H,5H)-trione (5c)



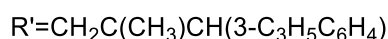
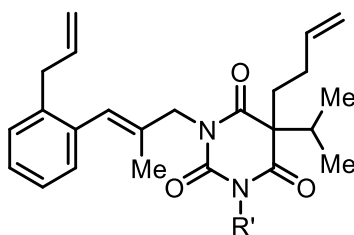
General procedure C was followed: using **1a** (0.18 g, 1.0 equiv), **2d** (0.32 g, 2.2 equiv), PPh_3 (0.74 g, 3.0 equiv) and DIAD (0.57 g, 3.0 equiv) in anhydrous CH_2Cl_2 (10 mL) for 24 h. The mixture was purified by column chromatography (90:10 hexanes:ethyl acetate) and gave **5c** (0.5023 g, 0.1 mmol, 11%) as a yellow sticky oil. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.27 - 7.30 (m, 2 H, *H*Ar), 7.12 (d, $J = 2.5$ Hz, 2 H, *H*Ar), 7.05 (dd, $J = 4.9, 1.1$ Hz, 2 H, *H*Ar), 6.43 (s, 2 H, 2 x C(Ar)CH=C), 5.72 (dd, $J = 16.9, 10.2$ Hz, 1 H, CH=CH₂), 4.89 - 5.01 (m, 2 H, CH=CH₂), 4.65 (s, 4 H, 2 x NCH₂), 2.33 - 2.45 (m, 1 H, CH(CH₃)₂), 2.18 - 2.25 (m, 2 H, CCH₂CH₂CH=CH₂), 1.96 - 2.01 (m, 8 H, 6 H from CH=CCH₃ and 2 H from CCH₂CH₂CH=CH₂), 1.03 (d, $J = 7.0$ Hz, 6 H, CH(CH₃)₂). ^{13}C NMR (101 MHz, CDCl_3) δ (ppm): 171.1 (2 x NC(O)C), 151.1 (NC(O)N), 138.1 (C(Ar)^q), 136.9 (C(Ar)H), 131.4 (2 x CH=C(CH₃)), 128.6 (CH=CH₂), 124.9 (2 x C(Ar)H), 122.9 (C(Ar)H), 122.2 (2 x C(Ar)H), 115.8 (2 x C(Ar)CH=CH₂), 115.9 (CCH₂CH₂CH=CH₂), 59.7 (CH₃C(CH₂CH₂CH=CH₂)), 48.9 (2 x NCH₂), 39.3 (CH(CH₃)), 34.9 (CCH₂CH₂CH=CH₂), 30.1 (CCH₂CH₂CH=CH₂), 18.0 (2 x C=CCH₃), 17.0 (CH(CH₃)).

5-Isopropyl-1,3-bis((E)-2-methyl-3-phenylallyl)-5-(pent-4-en-1-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (5d)



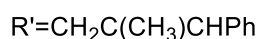
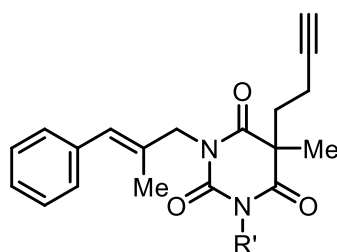
General procedure C was followed: using **1d** (0.48 g, 1.0 equiv), (*E*)-2-methyl-3-phenylprop-2-en-1-ol (0.65 g, 2.2 equiv), PPh_3 (1.57 g, 3.0 equiv) and DIAD (1.21 g, 3.0 equiv) in anhydrous CH_2Cl_2 (20 mL) for 90 h. The mixture was purified by column chromatography (90:10 hexanes:ethyl acetate) and gave **5d** (0.2237 g, 0.45 mmol, 22%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.28 - 7.34 (m, 4 H, *H*Ar), 7.19 - 7.25 (m, 6 H, *H*Ar), 6.47 (s, 2 H, 2 x $\text{C}(\text{Ar})\text{CH}=\text{C}$), 5.72 (dd, $J = 17.1, 10.3$ Hz, 1 H, $\text{CH}=\text{CH}_2$), 4.92 - 5.02 (m, 2 H, $\text{CH}=\text{CH}_2$), 4.70 (s, 4 H, 2 x NCH_2), 2.36 - 2.48 (m, 1 H, $\text{CH}(\text{CH}_3)_2$), 2.12 - 2.19 (m, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), 2.07 (q, $J = 7.3$ Hz, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), 1.95 (d, $J = 1.3$ Hz, 6 H, 2 x $\text{CH}=\text{CCH}_3$), 1.25 - 1.36 (m, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), 1.07 (d, $J = 6.8$ Hz, 6 H, $\text{CH}(\text{CH}_3)_2$). ^{13}C NMR (101 MHz, CDCl_3) δ (ppm): 171.2 (2 x $\text{NC}(\text{O})\text{C}$), 151.0 ($\text{NC}(\text{O})\text{N}$), 137.5 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), 137.1 (2 x $\text{CH}=\text{C}^q(\text{CH}_3)$), 132.1 (2 x $\text{C}(\text{Ar})^q$), 129.0 (4 x $\text{C}(\text{Ar})\text{H}$), 128.1 (2 x $\text{C}(\text{Ar})\text{H}$), 127.2 (2 x $\text{C}(\text{Ar})\text{H}$), 127.1 (2 x $\text{C}(\text{Ar})^q\text{CH}=\text{C}$), 126.6 (2 x $\text{C}(\text{Ar})\text{H}$), 115.3 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), 60.2 ($\text{CCH}_2\text{CH}_2\text{CH}_2$), 48.7 (2 x NCH_2), 39.0 ($\text{CH}(\text{CH}_3)_2$), 35.4 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), 33.7 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), 25.2 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), 18.1 (2 x $\text{C}=\text{CCH}_3$), 16.6 ($\text{C}(\text{CH}_3)_2$). IR (ν_{max} , thin film/ cm^{-1}): 2971, 1679, 1429, 1393, 1278, 740, 697. MS (ESI⁺) m/z (%): 499 ($\text{M}+\text{H}^+$, 100); HRMS (ESI) calcd. for $\text{C}_{32}\text{H}_{38}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 521.2780. Found: 521.2775.

1,3-Bis((*E*)-3-(2-allylphenyl)-2-methylallyl)-5-(but-3-en-1-yl)-5-isopropylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (5e**)**



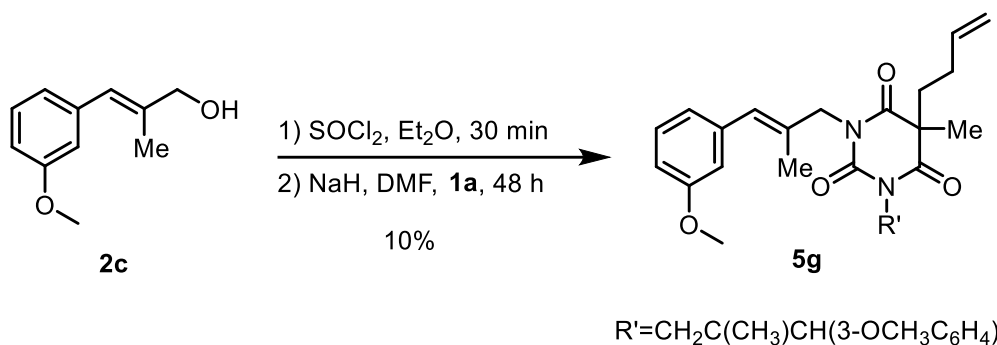
General procedure C was followed: using **1b** (0.22 g, 1.0 equiv), **2f** (0.41 g, 2.2 equiv), PPh₃ (0.79 g, 3.0 equiv) and DIAD (0.61 g, 3.0 equiv) in anhydrous CH₂Cl₂ (10 mL) for 68 h. The mixture was purified by column chromatography (95:5 hexanes:ethyl acetate) and gave **5e** (0.4096 g, 0.73 mmol, 73%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.16 - 7.34 (m, 8 H, *H*Ar), 6.63 (s, 2 H, 2 x C(Ar)CH=C(CH₃)), 5.97 (ddt, *J* = 16.8, 10.3, 6.4, 2 H, 2 x C(Ar)CH₂CH=CH₂), 5.73 - 5.87 (m, 1 H, CH₂CH₂CH=CH₂), 4.99 - 5.11 (m, 6 H, 4 H from C(Ar)CH₂CH=CH₂ and 2 H from C(Ar)CH₂CH=CH₂), 4.75 (s, 4 H, 2 x NCH₂), 3.39 (d, *J* = 6.3 Hz, 4 H, 2 x C(Ar)CH₂CH=CH₂), 2.39 - 2.53 (m, 1 H, CH(CH₃)₂), 2.27 - 2.34 (m, 2 H, CCH₂CH₂CH=CH₂), 1.98 - 2.07 (m, 2 H, CCH₂CH₂CH=CH₂), 1.81 (d, *J*=1.3 Hz, 1 H, CH(CH₃)₂), 1.09 - 1.15 (m, 6 H, CH=C(CH₃)). ¹³C NMR (101 MHz, CDCl₃) δ (ppm): 171.1 (2 x NC(O)C), 151.1 (NC(O)N), 138.3 (2 x C(Ar)CH₂CH=CH₂), 138.3 (2 x CH=C^q(CH₃)), 136.9 (2 x C(Ar)^qCH₂CH=CH₂), 136.8 (CH₂CH₂CH₂CH=CH₂), 132.6 (C(Ar)^q), 129.5 (2 x C(Ar)H), 129.1 (2 x C(Ar)H), 127.2 (2 x C(Ar)H), 127.1 (2 x C(Ar)^qCH=C), 125.9 (2 x C(Ar)H), 115.8 (2 x C(Ar)CH₂CH=CH₂), 115.7 (CCH₂CH₂CH=CH₂), 59.7 (CCH₂CH₂CH₂), 48.4 (2 x NCH₂), 39.3 (CH(CH₃)), 37.6 (2 x C(Ar)CH₂CH=CH₂), 34.8 (CCH₂CH₂CH=CH₂), 30.2 (CCH₂CH₂CH=CH₂), 18.1 (C=CCH₃), 16.3 (C(CH₃)₂). IR (ν_{max}, thin film/cm⁻¹): 2976, 1682, 1429, 1396, 914, 751. MS (ESI⁺) *m/z* (%): 565 (M+H⁺, 100); HRMS (ESI) calcd. for C₃₇H₄₅N₂O₃Na (M+H⁺): 565.3425. Found: 565.3428.

5-(But-3-yn-1-yl)-5-methyl-1,3-bis((E)-2-methyl-3-phenylallyl)pyrimidine-2,4,6(1H,3H,5H)-trione (5f)



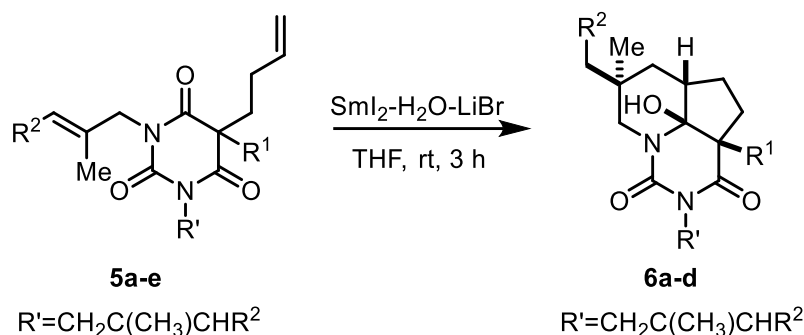
General procedure C was followed: using **1c** (0.19 g, 1.0 equiv), (*E*)-2-methyl-3-phenylprop-2-en-1-ol (0.33 g, 2.2 equiv), PPh₃ (0.79 g, 3.0 equiv) and DIAD (0.61 g, 3.0 equiv) in anhydrous CH₂Cl₂ (10 mL) for 48 h. The mixture was purified by column chromatography (90:10 hexanes/ethyl acetate) and gave **5c** (0.232 g, 0.51 mmol, 51%) as a yellow sticky oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.28 - 7.32 (m, 4 H, *H*Ar), 7.19 - 7.22 (m, 6 H, *H*Ar), 6.40 (s, 2 H, 2 x C(Ar)CH=C), 4.58 - 4.68 (m, 4 H, 2 x NCH₂), 2.36 - 2.39 (m, 2 H, CH₂CH₂C≡CH), 2.25 - 2.29 (m, 2 H, CH₂CH₂C≡CH), 1.92 (m, 1 H, CH₂C≡CH), 1.91 (m, 6 H, 2 x CH=CCH₃), 1.62 (s, 3 H, C(O)CCH₃). ¹³C NMR (101 MHz, CDCl₃) δ (ppm): 171.5 (2 x NC(O)C), 150.6 (NC(O)N), 137.1 (2 x CH=C^q(CH₃)), 132.0 (2 x C(Ar)^q), 129.0 (4 x C(Ar)H), 128.1 (2 x C(Ar)H), 126.7 (2 x C(Ar)H), 126.6 (2 x C(Ar)^qCH=C), 81.8 (CH₂C≡CH), 70.8 (CH₂C≡CH), 48.7 (2 x NCH₂CH=CH₂), 29.9 (CH₂CH₂C≡CH), 27.1 (C(O)CCH₃), 16.4 (C=CCH₃), 14.8 (CH₂C≡CH). IR (ν_{max}, thin film/cm⁻¹): 3431, 2973, 2112, 1680, 1429, 1395, 759. MS (ESI⁺) m/z (%): 455 (M+H⁺, 100); HRMS (ESI) calcd. for C₂₉H₃₀N₂O₃Na (M+Na⁺): 477.2149. Found: 477.2145.

Synthesis of 5-(But-3-en-1-yl)-1,3-bis((E)-3-(3-methoxyphenyl)-2-methylallyl)-5-methylpyrimidine-2,4,6(1H,3H,5H)-trione (5g)



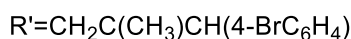
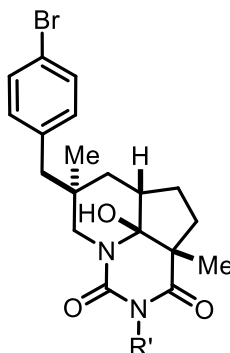
SOCl₂ (1.43 g, 1.2 equiv) was added to a solution of **2c** (1.78 g, 2.2 equiv) in Et₂O (25 mL) at 0 °C. The mixture was warmed to room temperature and stirred under a N₂ atmosphere for 30 min. The reaction mixture was concentrated *in vacuo*. NaH (60%) (0.088 g, 2.2 equiv) was added to an oven-dried flask under N₂, then DMF (4 mL) was added to the NaH and cooled to 0 °C. The barbituric acid **1a** (0.88 g, 1.0 equiv) was added. After the development of H₂, the concentrated reaction crude was added and stirred at 90 °C for 48 h. After cooling to room temperature, H₂O (1 mL) and ethyl acetate (20 mL) were added. The organic phases were combined, washed with brine (5 x 20 mL), dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (90:10 hexanes:ethyl acetate) to give **5g** (0.232 g, 0.45 mmol, 10%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.21 (t, *J* = 7.91 Hz, 2 H, C(Ar)**H**), 6.73 - 6.82 (m, 6 H, C(Ar)**H**), 6.37 (s, 2 H, C(Ar)**CH=C**), 5.65 - 5.75 (m, 1 H, **CH=CH**₂), 4.89 - 5.00 (m, 2 H, **CH=CH**₂), 4.63 (s, 4 H, 2 x **NCH**₂), 3.77 (s, 6 H, 2 x **OCH**₃), 2.16 - 2.24 (m, 2 H, **CH**₂**CH**₂**CH=CH**₂), 1.99 - 2.09 (m, 2 H, **CH**₂**CH**₂**CH=CH**₂), 1.90 (d, *J* = 1.25 Hz, 6 H, 2 x **CH=CCH**₃), 1.61 (s, 3 H, **C(O)CCH**₃). ¹³C NMR (101 MHz, CDCl₃) δ (ppm): 171.8 (2 x **NC(O)C**), 159.4 (**NC(O)N**), 150.6 (**C(Ar)OCH**₃), 138.4 (**C**^q), 136.5 (**CH**₂**CH**₂**CH=CH**₂), 132.4 (**C(Ar)**^q), 129.1 (2 x **C(Ar)H**), 126.8 (2 x **C(Ar)CH=C**), 121.5 (2 x **C(Ar)H**), 116.1 (**CH**₂**CH**₂**CH=CH**₂), 114.4 (2 x **C(Ar)H**), 112.28 (2 x **C(Ar)H**), 55.16 (2 x **OCH**₃), 51.6 (**CH**₃**C(CH**₂**CH**₂**CH=CH**₂), 48.6 (2 x **NCH**₂**CH=CH**₂), 38.1 (**CH**₂**CH**₂**CH=CH**₂), 29.9 (**CH**₂**CH**₂**CH=CH**₂), 26.0 (**C(O)CCH**₃), 16.4 (**C=CCH**₃). IR (ν_{max}, thin film/cm⁻¹): 2936, 1685, 1589, 1429, 1268, 1044. MS (ESI⁺) *m/z* (%): 517 (M+H⁺, 100); HRMS (ESI⁺) calcd. for C₃₁H₃₆N₂O₅Na (M+Na⁺): 539.2502. Found: 539.2516.

General procedure D: $\text{SmI}_2\text{-LiBr-H}_2\text{O}$ mediated cyclisation cascades to give hemiaminal products (2)



To an oven-dried vial charged with anhydrous LiBr (521 mg, 6.0 mmol) was added freshly prepared SmI_2 (0.3 mmol, 3.0 mL, 0.1 M in THF), under a nitrogen atmosphere. The solution was stirred for 30 min at room temperature. A vial containing a stir bar was charged with barbiturate (0.1 mmol, 1 equiv) and placed under a positive pressure of nitrogen (20 min). THF (0.05 M) and degasified water (100 equiv) were added, followed by syringe pump addition over 1 h of the mixture of SmI_2 and LiBr. After the specified time (typically, 3 h), the reaction was quenched by bubbling air through the mixture before dilution with CH_2Cl_2 (30 mL) and aqueous HCl (0.10 M, 20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 \times 20 mL) and the combined organic phases were dried over MgSO_4 , filtered and concentrated. The crude product was purified by column chromatography on silica gel.

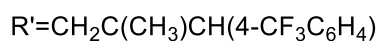
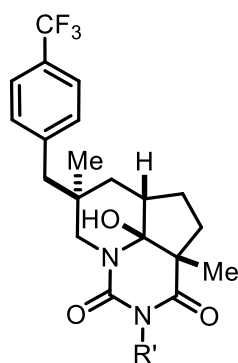
(2a*S*,2a'*S*,7*R*,8a*S*)-7-(4-Bromobenzyl)-4-((*E*)-3-(4-bromophenyl)-2-methylallyl)-2a'*1*-hydroxy-2a,7-dimethyloctahydro-3*H*-4,5a-diazaacenaphthylene-3,5(4*H*)-dione (6a)



According to the general procedure D, using **5a** (61.2 mg, 1.0 equiv), SmI_2 (3 equiv, 3.0 mL, 0.10 M) and H_2O (0.18 mL, 100 equiv) with a slow addition over 1 h, stirring for 3 h and purification by column chromatography (80:20 hexanes:ethyl acetate), gave **6a** (31.8 mg, 0.058 mmol, 58%, 81:19 dr) as a white solid. m.p. 98.1 - 99.2 °C. ^1H NMR (400 MHz, CDCl_3) (major diastereomer only) δ (ppm): 7.38 - 7.44 (m, 4 H, ArH), 7.07 - 7.11 (m, 2 H, ArH), 7.02 - 7.05 (m, 2 H, ArH), 6.22 (s, 1 H, $\text{C}(\text{CH}_3)=\text{CHC}(\text{Ar})$), 4.44 - 4.62 (m, 2 H, $\text{NCH}_2\text{C}(\text{CH}_3)=\text{CHC}(\text{Ar})$), 4.21 (dd, $J = 13.7, 2.1$ Hz, 1 H, 1 H from NCH_2), 2.95 (d, $J = 13.1$ Hz, 1 H, 1 H from CH_2Ar), 2.73 (dd, $J = 13.7, 0.9$ Hz, 1 H, 1 H from NCH_2), 2.51 - 2.61 (m, 1 H, $\text{CH}_2\text{CH}_2\text{CHCH}_2$), 2.37 - 2.43 (d, $J = 12.5$, 1 H, 1 H from $\text{CH}_2\text{C}(\text{Ar})$), 2.16 - 2.31 (m, 2 H, $\text{CH}_2\text{CH}_2\text{CHCH}_2$), 1.79 - 2.01 (m, 4 H, $\text{CH}_2\text{CH}_2\text{CHCH}_2$ and $\text{CH}_2\text{CH}_2\text{CHCH}_2$), 1.86 (d, $J = 1.0$ Hz, 3 H, $\text{CH}=\text{CCH}_3$), 1.41 - 1.48 (m, 3 H, CH_3), 0.78 (s, 3 H, CH_3) (minor, diagnostic peak only) 6.17 (s, 1 H, $\text{C}(\text{CH}_3)=\text{CHC}(\text{Ar})$), 4.07 - 4.10 (dd, 1 H, 1 H from NCH_2). ^{13}C NMR (101 MHz, CDCl_3) δ (ppm): 172.7 ($\text{NC}(\text{O})\text{C}$), 152.4 ($\text{NC}(\text{O})\text{N}$), 136.8 ($\text{C}(\text{Ar})^q$), 136.5 ($\text{C}(\text{Ar})^q$), 134.4 (C^q), 132.4 ($2 \times \text{C}(\text{Ar})\text{H}$), 131.1 ($4 \times \text{C}(\text{Ar})\text{H}$), 130.6 ($2 \times \text{C}(\text{Ar})\text{H}$), 123.5 ($\text{C}=\text{CHC}(\text{Ar})$), 120.4 ($\text{C}(\text{Ar})^q$), 120.1 ($\text{C}(\text{Ar})^q$), 90.8 (COH), 52.1 (C^q), 47.6 ($\text{NCH}_2\text{C}(\text{CH}_3)=\text{CHC}(\text{Ar})$), 45.6 (NCH_2), 42.6 ($\text{CH}_2\text{C}(\text{Ar})$), 41.8 ($\text{CH}_2\text{CH}_2\text{CHCH}_2$), 37.2 ($\text{CH}_2\text{CH}_2\text{CHCH}_2$), 35.8 ($\text{CH}_2\text{CH}_2\text{CHCH}_2$), 33.8 (C^q), 26.3 ($\text{CH}_2\text{CH}_2\text{CHCH}_2$), 26.0 (CH_3), 17.4 (CH_3), 16.3 ($\text{CH}=\text{CCH}_3$). IR (ν_{max} , thin film/ cm^{-1}): 3418, 2952, 2359, 1705, 1651, 1437, 1236, 1072,

1010, 758. MS (ESI⁺) m/z (%): 653 (M+K⁺, 100); HRMS (ESI⁺) calcd. for C₂₉H₃₂N₂O₃Br₂Na (M+Na⁺): 637.0677. Found: 637.0672.

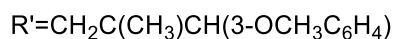
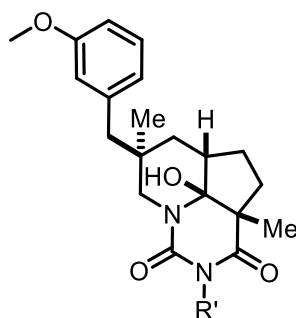
(2a*S*,2a¹*S*,7*R*,8a*S*)-2a¹-Hydroxy-2a,7-dimethyl-4-((*E*)-2-methyl-3-(4-(trifluoromethyl)phenyl)allyl)-7-(4-(trifluoromethyl)benzyl)octahydro-3*H*-4,5a-diazaace naphthylene-3,5(4*H*)-dione (6b)



According to the general procedure D, using **5b** (59.2 mg, 1.0 equiv), Sml₂ (3 equiv, 3.0 mL, 0.10 M) and H₂O (0.18 mL, 100 equiv) with a slow addition over 1 h, stirring for 3 h and purification by column chromatography (80:20 hexanes/ethyl acetate), gave **6c** (27.3 mg, 0.046 mmol, 46%, 79:21 dr) as a white solid. m.p. 168.2 - 168.8 °C. ¹H NMR (400 MHz, CDCl₃) (major diastereomer only) δ (ppm): 7.48 - 7.59 (m, 4 H, ArH), 7.23 - 7.37 (m, 4 H, ArH), 6.31 (s, 1 H, C(CH₃)=CHC(Ar)), 4.49 - 4.67 (m, 2 H, NCH₂C(CH₃)=CHC(Ar)), 4.21 (dd, *J* = 13.7, 1.9 Hz, 1 H from NCH₂), 3.06 (d, *J* = 12.8 Hz, 1 H, 1 H from CH₂Ar), 2.76 (d, *J* = 13.6 Hz, 1 H, 1 H from NCH₂), 2.65 (bs, 1 H, OH), 2.54 - 2.61 (m, 1 H, CH₂CH₂CHCH₂), 2.50 (d, *J* = 12.8 Hz, 1 H from CH₂Ar), 2.17 - 2.33 (m, 2 H, CH₂CH₂CHCH₂), 1.90 (s, 3 H, CH=CCH₃), 1.73 - 2.00 (m, 4 H, CH₂CH₂CHCH₂ and CH₂CH₂CHCH₂), 1.48 (s, 1 H, CH₃), 0.78 (s, 3 H, CH₃) (minor, diagnostic peak only) 6.25 (s, 1 H, C(CH₃)=CHC(Ar)), 4.09 - 4.13 (dd, 1 H, 1 H from NCH₂). ¹³C NMR (101 MHz, CDCl₃) δ (ppm): 172.8 (NC(O)C), 152.5 (NC(O)N), 142.0 (C(Ar)^q), 141.2 (C(Ar)^q), 135.8 (C(Ar)CH₂C(CH₃)), 130.9 (q, *J* = 11.1 Hz, 4 x C(Ar)H), 129.2 (q, *J* = 4.0 Hz, 2 x C(Ar)H), 128.4 (q, *J* = 39.4 Hz, C(Ar)^q), 125.0 (d, *J* = 4.0 Hz, 2 x C(Ar)H), 124.3 (d, *J* = 272.2 Hz, CF₃), 124.2 (d, *J* = 272.7 Hz, CF₃), 123.5 (C=CHC(Ar)), 90.8 (COH), 52.1 (C^q), 47.6 (NCH₂C(CH₃)=CHC(Ar)), 45.6 (NCH₂), 42.9 (CH₂Ar), 41.8 (CH₂CH₂CHCH₂), 37.3 (CH₂CH₂CHCH₂), 35.8 (CH₂CH₂CHCH₂), 33.9 (C^q), 26.3

(CH₂CH₂CHCH₂), 26.0 (CH₃), 17.3 (CH₃), 16.3 (CH=CCH₃). IR (ν_{max}, thin film/cm⁻¹): 2929, 1705, 1677, 1418, 1324, 1122, 1067. MS (ESI⁺) m/z (%): 517 (M+H⁺, 100); HRMS (ESI⁺) calcd. for C₃₁H₃₆N₂O₅Na (M+Na⁺): 539.2502. Found: 539.2516.

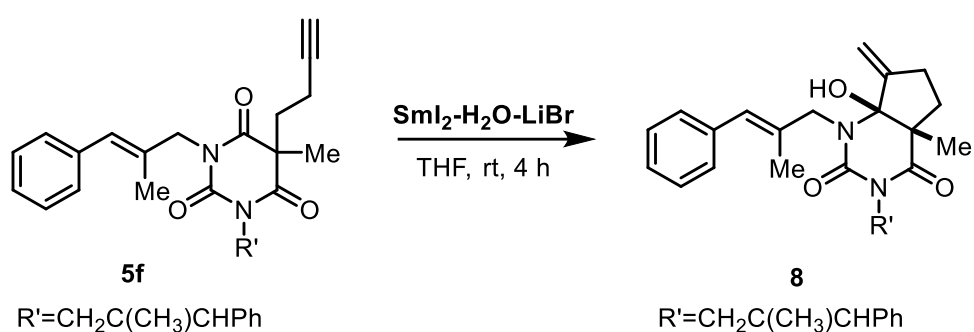
(2a*S*,2a¹*S*,7*R*,8a*S*)-2a¹-Hydroxy-7-(3-methoxybenzyl)-4-((*E*)-3-(3-methoxyphenyl)-2-methylallyl)-2a,7-dimethyloctahydro-3*H*-4,5a-diazaacenaphthylene-3,5(4*H*)-dione (6c)



According to the general procedure D, using **5g** (51.6 mg, 1.0 equiv), Sml₂ (3 equiv, 3.0 mL, 0.10 M) and H₂O (0.18 mL, 100 equiv) with a slow addition over 1 h, stirring for 3 h and purification by column chromatography (80:20 hexanes/ethyl acetate), gave **6c** (25.3 mg, 0.049 mmol, 49%, 78:22 dr) as a colourless sticky oil. ¹H NMR (400 MHz, CDCl₃) (major diastereomer only) δ (ppm): 7.16 - 7.21 (m, 2 H, ArH), 6.80 - 6.83 (m, 1 H, ArH), 6.75 - 6.77 (m, 2 H, ArH), 6.72 - 6.74 (m, 3 H, ArH), 6.28 (s, 1 H, C(CH₃)=CHC(Ar)), 4.50 - 4.63 (m, 2 H, NCH₂C(CH₃)=CHC(Ar)), 4.32 (dd, *J* = 13.6, 2.3 Hz, 1 H, 1 H from NCH₂), 3.76 - 3.78 (m, 6 H, 2 x OCH₃) 2.99 (d, *J* = 12.8 Hz, 1 H, 1 H from CH₂Ar), 2.74 (dd, *J* = 13.6, 1 Hz, 1 H, 1 H from NCH₂), 2.53 - 2.62 (m, 1 H, CH₂CH₂CHCH₂), 2.48 (s, 1 H, OH) 2.42 (d, *J* = 12.6, 1 H, 1 H from CH₂Ar), 2.16 - 2.31 (m, 2 H, 1 H from CH₂CH₂CHCH₂ and 1 H from CH₂CH₂CHCH₂), 1.93 - 1.97 (m, 1 H, 1 H from CH₂CH₂CHCH₂), 1.79 - 1.88 (m, 3 H, 1 H from CH₂CH₂CHCH₂ and 2 H from CH₂CH₂CHCH₂), 1.80 - 1.84 (m, 1 H, 1 H from CH₂CH₂CHCH₂), 1.89 (d, *J* = 1.0 Hz, 3 H, CH=CCH₃), 1.47 (m, 3 H, CH₃), 0.80 (s, 3 H, CH₃) (minor, diagnostic peak only) 6.24 (s, 1 H, C(CH₃)=CHC(Ar)). ¹³C NMR (101 MHz, CDCl₃) δ (ppm): 172.7 (NC(O)C), 159.3 (2 x C(Ar)^q), 152.4 (NC(O)N), 139.4 (C(Ar)^q), 133.9 (C(Ar)^q), 134.4 (C^q), 129.0 (C(Ar)H), 124.7 (C=CHC(Ar)), 121.6 (C(Ar)H), 115.9 (C(Ar)H), 114.5 (C(Ar)H), 112.1 (C(Ar)H),

111.9 (**C**(Ar)H), 90.8 (**COH**), 55.3 (**OCH**₃), 55.2 (**OCH**₃), 52.1 (**C**^q), 47.6 (**NCH**₂**C**(CH₃)=CH**C**(Ar)), 45.9 (**NCH**₂), 42.2 (**CH**₂Ar), 41.8 (**CH**₂**CH**₂**CHCH**₂), 37.3 (**CH**₂**CH**₂**CHCH**₂), 35.8 (**CH**₂**CH**₂**CHCH**₂), 33.8 (**C**^q), 26.3 (**CH**₂**CH**₂**CHCH**₂), 26.2 (**CH**₃), 17.4 (**CH**₃), 16.3 (**CH=CCH**₃). IR (ν_{\max} , thin film/cm⁻¹): 3409, 2930, 1704, 1656, 1598, 1464, 1261, 1039, 747. MS (ESI⁺) *m/z* (%): 519 (**M**+**H**⁺, 20); HRMS (ESI⁺) calcd. for C₃₁H₃₈N₂O₅Na (**M**+**Na**⁺): 541.2660. Found: 541.2673.

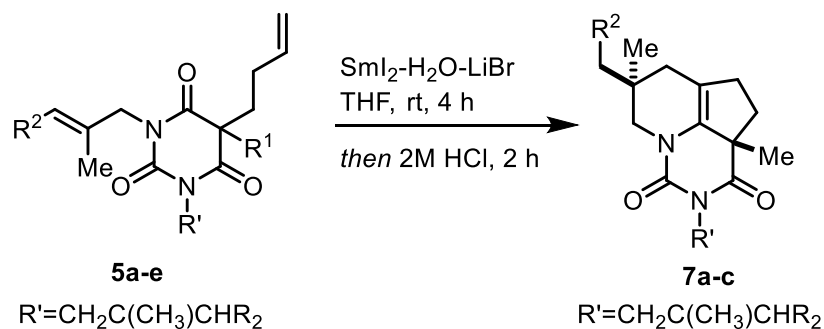
7a-Hydroxy-4a-methyl-1,3-bis((E)-2-methyl-3-phenylallyl)-7-methylenehexahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione (8)



According to the general procedure D, using **5f** (45.4 g, 1.0 equiv), SmI₂ (0.30 mmol, 3 equiv, 3.0 mL, 0.10 M) and H₂O (0.18 mL, 100 equiv) with a slow addition over 1 h, stirring for 3 h and purification by column chromatography (80:20 hexanes/ethyl acetate), gave **8** (12.8 mg, 0.028 mmol, 28%, 88:12 dr) as a colourless sticky oil. ¹H NMR (400 MHz, CDCl₃) (δ ppm): 7.28 - 7.35 (m, 4 H, **ArH**), 7.15 - 7.25 (m, 6 H, **ArH**), 6.33 (d, *J* = 1.5 Hz, 2 H, 2 x **CH=C**(CH₃)), 5.42 (t, *J* = 2.4 Hz, 1 H, 1 H from **C**(OH)**C=CH**₂), 5.32 (t, *J* = 2.1 Hz, 1 H, 1 H from **C**(OH)**C=CH**₂), 4.59 (s, 2 H, **NCH**₂), 4.31 - 4.43 (m, 1 H, 1 H from **C**(OH)**NCH**₂), 4.17 - 4.26 (m, 1 H, 1 H from **C**(OH)**NCH**₂), 2.40 - 2.55 (m, 2 H, **CH**₂**CH**₂**C=CH**₂), 2.48 (s, 1H, **OH**), 2.12 - 2.25 (m, 1 H, 1 H from **CH**₂**CH**₂**C=CH**₂), 1.85 - 1.92 (m, 7 H, 1 H from **CH**₂**CH**₂**C=CH**₂ and 6 H from **CH=CCH**₃), 1.29 - 1.30 (m, 3 H, **CCH**₃). ¹³C NMR (101 MHz, CDCl₃) (δ ppm): 172.5 (**NC**(O)**C**), 152.7 (**C**(OH)**C=CH**₂), 149.3 (**NC**(O)**N**), 137.7 (**C**(Ar)^q), 137.3 (**C**(Ar)^q), 135.5 (**C**^q), 129.0 (4 x **C**(Ar)H), 128.2 (2 x **C**(Ar)H), 128.0 (4 x **C**(Ar)H), 124.8 (**C=CHC**(Ar)), 112.2 (**C**(OH)**C=CH**₂), 92.5 (**COH**), 50.9 (**C**(O)**CCH**₃), 50.4 (**C**(OH)**NCH**₂), 47.6 (**NCH**₂), 32.7 (**CH**₂**CH**₂**C=CH**₂), 26.0 (**CH**₂**CH**₂**C=CH**₂), 17.5 (**CH**₃), 16.1 (2 x **CH=CCH**₃). IR (ν_{\max} , thin

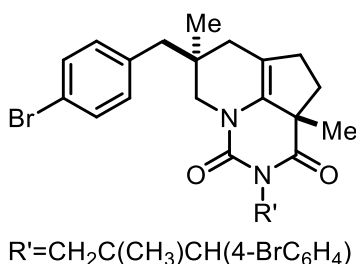
film/cm⁻¹): 3398, 2942, 1710, 1652, 1444, 1358, 1253, 699. MS (ESI⁻) m/z (%): 491 (M+Cl⁺, 100); HRMS (ESI⁺) calcd. for C₂₉H₃₃N₂O₃ (M+H⁺): 457.2486. Found: 457.2490.

General procedure E: Sml₂-LiBr-H₂O mediated cyclisation cascades to enamine products (3)



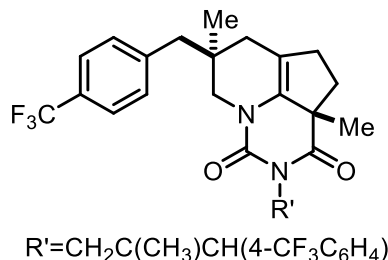
To an oven-dried round bottom flask charged with anhydrous LiBr (521 mg, 6.0 mmol) was added freshly prepared Sml₂ (0.3 mmol, 3.0 mL, 0.10 M) in THF, under nitrogen atmosphere. The solution was stirred for 30 min at room temperature. To an oven-dried vial containing a stir bar was added barbiturate (0.1 mmol, 1 equiv) and the vial placed under a positive pressure of nitrogen. THF (0.05 M, typically, 2.0 mL) and water (typically, 100 equiv) were added, followed by syringe pump of addition the mixture of Sml₂ and LiBr over 3 h with vigorous stirring. After 3 h, HCl (2 M in Et₂O, 2 mL) was added and the resulting solution stirred for 2 h. The reaction was then diluted with CH₂Cl₂ (30 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL), the organic layers were combined, dried over MgSO₄ and concentrated. The crude product was purified by column chromatography on silica gel.

(2*a*S,4*R*)-4-(4-Bromobenzyl)-7-((*E*)-3-(4-bromophenyl)-2-methylallyl)-4-methyl-1,2,2*a*,3,4,5-hexahydro-6*H*-5*a*,7-diazaacenaphthylene-6,8(7*H*)-dione (7*a*)



According to the general procedure E, using **5a** (61.2 g, 1.0 equiv), SmI₂ (3.0 equiv, 3.0 mL, 0.10 M) and H₂O (0.18 mL, 100 equiv) with a slow addition over 1 h, stirring for 3 h, addition of HCl (2 M in Et₂O, 2mL), stirring for 2 h and purification by column chromatography (80:20 hexanes/ethyl acetate), gave **7a** (35.9 mg, 0.068 mmol, 68%, 79:21 dr) as a colourless sticky oil. ¹H NMR (400 MHz, CDCl₃) (major diastereomer only) δ (ppm): 7.34 - 7.45 (m, 4 H, ArH), 6.87 - 7.08 (m, 4 H, ArH), 6.22 (s, 1 H, C(CH₃)=CHC(Ar)), 4.37 - 4.59 (m, 2 H, NCH₂C(CH₃)=CHC(Ar)), 3.85 - 3.94 (m, 1 H, 1 H from NCH₂), 3.07 - 3.16 (m, 1 H, 1 H from NCH₂), 2.42 - 2.52 (m, 3 H, 1H from C(CH₃)CH₂CH₂C=C and 2 H from CH₂Ar), 2.19 - 2.32 (m, 2 H, 1H from C(CH₃)CH₂CH₂C=C and 1 H from C(CH₃)CH₂CH₂C=C), 2.02 - 2.12 (m, 1 H, 1 H from C(CH₃)CH₂CH₂C=C), 1.81 - 1.85 (m, 3 H, CH₃), 1.70 - 1.94 (m, 2 H, CH₂C(CH₃)CH₂Ar), 1.35 - 1.39 (m, 3 H, CH₃), 0.95 (s, 3 H, CH₃) (minor, diagnostic peak only) 6.14 (1 H, s, C(CH₃)=CHC(Ar)), 0.89 (3 H, s, CH₃). ¹³C NMR (101 MHz, CDCl₃) (major diastereomer only) (δ ppm): 174.3 (NC(O)C), 151.0 (NC(O)N), 136.2 (C^q), 132.0 (C^q), 132.1 (2 x C(Ar)H), 131.1 (4 x C(Ar)H), 130.6 (2 x C(Ar)H), 124.1 (CH₂C(CH₃)=CHC(Ar)), 120.5 (C^q), 120.1 (C^q), 116.1 (C^q), 51.3 (NCH₂C(CH₃)=CHC(Ar)), 49.2 (C^q), 47.9 (NCH₂), 43.2 (CH₂C(Ar)), 35.0 (CH₂C(CH₃)CH₂ C(Ar)), 34.1 (C^q), 33.2 (C(CH₃)CH₂CH₂C=C), 30.4 (C(CH₃)CH₂CH₂), 24.6 (CH₃), 23.4 (CH₃), 16.2 (CH₃). IR (ν_{max}, thin film/cm⁻¹): 2926, 2358, 1729, 1676, 1419, 1072, 1010. MS (ESI⁺) m/z (%): 597 (M+H⁺, 410); HRMS (ESI⁺) calcd. for C₂₉H₃₁N₂O₂Br₂ (M+H⁺): 597.0751. Found: 597.0747.

(2a*S*,7*S*)-2a,7-Dimethyl-4-((*E*)-2-methyl-3-(4-(trifluoromethyl)phenyl)allyl)-7-(4-(trifluoromethyl)benzyl)-1,2,2a,6,7,8-hexahydro-3*H*-4,5a-diazaacenaphthylene-3,5(4*H*)-dione (7b)



According to the general procedure E, using **5b** (59.2 g, 1.0 equiv), SmI₂ (0.30 mmol, 3 equiv, 3.0 mL, 0.10 M) and H₂O (0.18 mL, 100 equiv) with a slow addition over 1 h, stirring for 3 h, addition of HCl (2 M in Et₂O, 2mL), stirring for 2 h and purification by column chromatography (80:20 hexanes:ethyl acetate), gave **7b** (32.7 mg, 0.055 mmol, 55%, 77:23 dr) as a colourless sticky oil. ¹H NMR (400 MHz, CDCl₃) (major diastereomer only) δ (ppm): 7.56 (dd, *J* = 13.1, 8.0 Hz, 1 H, ArH), 7.49 (dd, *J* = 8.0, 3.3 Hz, 3 H, ArH), 7.25 - 7.30 (m, 2 H, ArH), 7.15 (d, *J* = 8.0 Hz, 2 H, ArH), 6.33 (m, 1 H, C(CH₃)=CHC(Ar)), 4.40 - 4.67 (m, 2 H, NCH₂C(CH₃)=CHC(Ar)), 3.89 - 3.98 (m, 1 H, 1 H from NCH₂), 3.11 - 3.18 (m, 1 H, 1 H from NCH₂), 2.53 - 2.63 (m, 2 H, CH₂Ar), 2.45 - 2.53 (m, 1 H, 1 H from C(CH₃)CH₂CH₂C=C), 2.23 - 2.36 (m, 2 H, 1H from C(CH₃)CH₂CH₂C=C and 1 H from C(CH₃)CH₂CH₂C=C), 2.06 - 2.16 (m, 1 H, 1 H from C(CH₃)CH₂CH₂C=C), 1.90 - 2.03 (m, 2 H, CH₂C(CH₃)CH₂Ar), 1.84 - 1.89 (m, 3 H, CH₃), 1.38 - 1.40 (m, 3 H, CH₃), 0.98 (s, 3 H, CH₃) (minor, diagnostic peak only) 6.22 (1 H, s, C(CH₃)=CHC(Ar)), 0.92 (3 H, s, CH₃). ¹³C NMR (101 MHz, CDCl₃) (major diastereomer only) (δ ppm): 174.3 (NC(O)C), 150.9 (NC(O)N), 141.4 (C^q), 141.1 (C^q), 136.1 (C^q), 132.0 (C^q), 130.7 (q, *J* = 11.1 Hz, 2 x C(Ar)H), 129.1 (q, *J* = 4.0 Hz, 4 x C(Ar)H), 128.4 (q, *J* = 32.32 Hz, C(Ar)^q), 124.9 (d, *J* = 4.0 Hz, 2 x C(Ar)H), 124.3 (d, *J* = 272.2 Hz, CF₃), 124.2 (d, *J* = 272.7 Hz, CF₃), 124.1 (CH₂C(CH₃)=CHC(Ar)), 51.3 (NCH₂C(CH₃)=CHC(Ar)), 49.3 (C^q), 47.8 (NCH₂), 43.6 (CH₂Ar), 35.2 (CH₂C(CH₃)CH₂Ar), 34.1 (C^q), 33.2 (C(CH₃)CH₂CH₂C=C), 30.4 (C(CH₃)CH₂CH₂), 24.6 (CH₃), 23.4 (CH₃), 16.3 (CH₃). IR (ν_{max}, thin film/cm⁻¹): 2929, 1705, 1676, 1419, 1323, 1120, 1067. MS (ESI⁺) *m/z* (%): 577 (M+H⁺, 100); HRMS (ESI⁺) calcd. for C₃₁H₃₁N₂O₅ (M+H⁺): 577.2273. Found: 577.2284.

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