Diversification of *ortho*-Fused Cycloocta-2,5-dien-1-one Cores and 8 to 6-Ring Conversion by Sigma Bond C-C Cleavage

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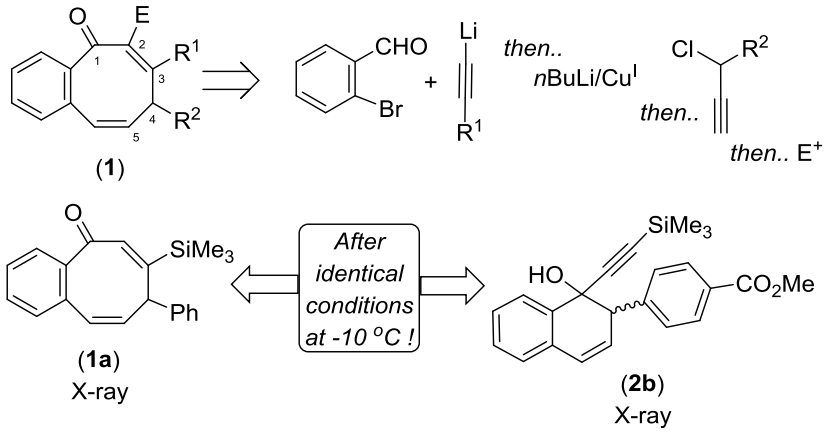
Abstract: Sequential treatment of 2-$C_6H_4Br(CHO)$ with $LiC{\equiv}CR^1$ (R^1 = $SiMe_3$, *t*Bu), *n*BuLi, $CuBr{\cdot}SMe_2$ and $HC{\equiv}CCHClR^2$ [R^2 = Ph, 4-CF_3Ph, 3-CNPh, 4-(MeO_2C)Ph] at -50 °C leads to formation of an intermediate carbanion (*Z*)-1,2-$C_6H_4\{C_A(=O)C{\equiv}C_BR^1\}\{CH{=}CH(CH^-)R^2\}$ (**4**). Low temperatures (-50 °C) favour attack at C_B leading to kinetic formation of 6,8-bicycles containing non-classical *C*-carbanion enolates (**5**). Higher temperatures (-10 °C to ambient) and electron deficient R^2 favour retro σ-bond C-C cleavage regenerating **4** which subsequently closes on C_A providing 6,6-bicyclic alkoxides (**6**). Computational modelling (CBS-QB3) indicates both pathways are viable and of similar energies. Reaction of **6** with H^+ affords 1,2-dihydronaphthalen-1-ols, or under dehydrating conditions, 2-aryl-1-alkynylnaphthlenes. Enolates **5** react *in situ* with: H_2O, D_2O, I_2, allylbromide, S_2Me_2, CO_2 and lead to the expected ***C***-E derivatives (E = H, D, I, allyl, SMe, CO_2H) in 49-64% yield directly from intermediate **5**. The parents (E = H; R^1 = $SiMe_3$, *t*Bu; R^2 = Ph) are versatile starting materials for $NaBH_4$ and Grignard C=O additions, desilylation (when R^1 = SiMe) and oxime formation. The latter allows formation of 6,9-bicyclics via Beckmann rearrangement. The 6,8-ring iodides are suitable Suzuki precursors for Pd-catalysed C-C coupling (81-87%); while the carboxylic acids readily form amides under T3P® conditions (71-95%).

Introduction

We recently described a new method for the synthesis of 8-membered rings[1] that allows the preparation of gram quantities of cycloocta-2,5-dien-1-one cores (Scheme 1). When 2-bromobenzaldehydes were treated sequentially with acetylides, *n*BuLi, $CuBr{\cdot}SMe_2$, propargylic chlorides and finally an electrophile (typically simple H^+) the phenylene derivatives **1** were attained in moderate yields (25 examples at 26-72%, 14 above 50% yield). This ready access prompted us to consider the applicability of the chemistry to providing libraries of diversified cores of potential future use in medicinal chemistry.[2] Specifically we proposed the questions: (i) What further diversity can be introduced into **1** *via* simple derivatisation? (ii) How far can the diversity of units R^1, R^2 and E^+ units be extended? In fact, the group R^2 became of immediate initial importance as one of our preliminary studies showed this group could profoundly affect the reaction's chemoselectivity (Scheme 1, **1a** *vs*. formation of **2b** instead).

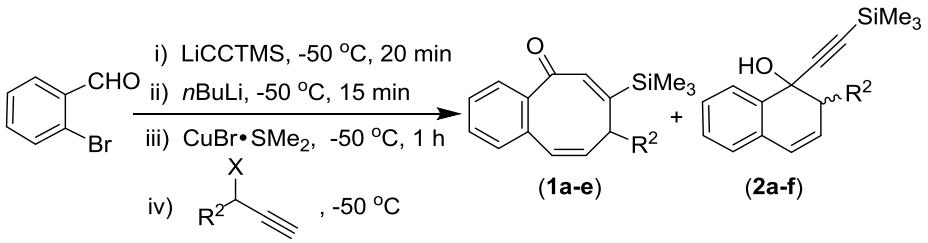


Scheme 1. Methodology for the preparation of 8-rings (**1a**) and initially unexplained competing 6-ring (**2b**) when R^2 is 4-(MeO_2C)Ph.

Results and Discussion

Factors in 8 vs. 6-ring formation. Model reactions using 2-bromobenzaldehyde, TMS-acetylene and various propargylic electrophiles were used to gain understanding of the effect of group R^2 on the reaction (Table 1). Under our standard conditions[1] highly chemoselective 8-ring formation is observed for **1a** and this is isolated in good yield (70%). This chemoselectivity is not affected by the leaving group (Cl, O_2CCF_3, OAc), although the last of these provides lower yields of **1a** due to incomplete conversion. Decreasing the electron density within the aryl group was confirmed to promote specific formation of 6-ring **2b**. X-ray studies (Supporting Information) confirmed a *syn* arrangement of the alcohol and aryl (R^2) group in the major diastereomer of **2b**. In this *syn* isomer, the higher chemical shift and coupling constants of the C*H*R^2 proton (δ_H 4.08, *J* = 2.9, 2.6 Hz) are distinct from the same proton in the *anti* diastereomer (δ_H 4.01, *J* = 4.6, 1.6 Hz); the other derivatives had their relative stereochemistries assigned on this basis. For propargylic chlorides based on 3-CNPh substituents, the 6 vs. 8-ring chemoselectivity is controlled by reaction temperature; reactions at -50 °C and -10 °C, prior to quenching, maximise the yields of **1c** and **2c** respectively. The *bis*-trifluoromethyls **1d**/**2d** behave analogously. When the parent (R^1 = $SiMe_3$, R^2 = Ph) reaction mixture is warmed to room temperature (over 30 minutes), **3a** (48%) is isolated upon protonation and dehydration. Conversely, the chemoselectivity in reactions using the 4-(CO_2Me)Ph substituted propargylic chloride could not be affected by changing the reaction temperature. Even at -50 °C (prior to quenching), no 8-ring formation was observed. The use of lower temperatures (to favour 8-ring formation) was considered, but deemed impractical as the reactions become very slow below -50 °C. Use of both electron rich and deficient substituted (MeO vs. F) 2-bromobenzaldehydes also resulted in product distributions showing increased 6-ring formation at 0 °C (Table 1, **2e** and **3e-f**), when using electron withdrawing R^2 groups in the propargylic chloride. However, use of 3-bromothiophene-2-carbaldehyde even with an electron withdrawing R^2 group led to exclusive formation of only 8-ring **1e**, even under the highest temperature usable that did not induce competing extensive decomposition (0 °C).

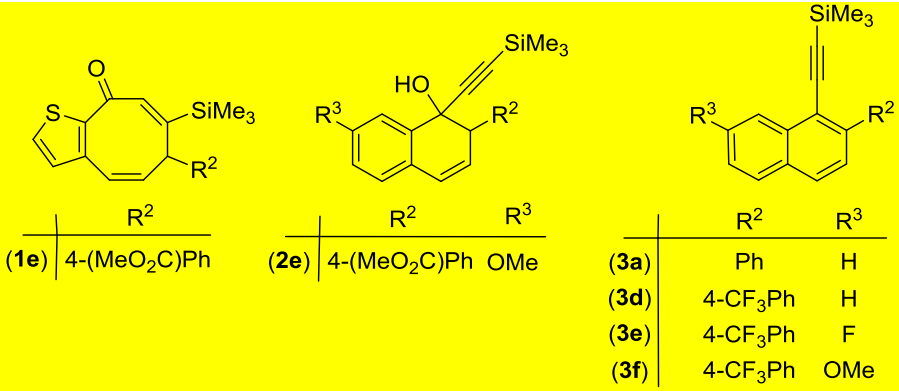
Table 1. Substituent and condition effects on the chemoselectivity of 8- *vs*. 6-ring formation.[a]



..then conditions of Table 1

R^2	X	Conditions prior to quench	(**1**):(**2**)[b]	*dr* (**2**)[d]	Isolated Product (%)[c]
Ph	Cl	Warmed to -10 °C over 0.5 h and hold for 1 h (Standard)	100:0	-	**1a** (70)
Ph	O_2CCF_3	Standard	100:0	-	**1a** (58)
Ph	OAc	Standard	100:0	-	**1a** (19)
Ph	Cl	Standard, then warm to rt over 0.5 h and hold for 1 h	1:4	2:1	**3a**[e,f] (48)
Ph	Cl	Standard, then warm to rt over 0.5 h and hold for 1 h, then re-cool to -10 °C for 1 h	1:4	2:1	-
4-(MeO_2C)Ph	Cl	Standard	0:100	5:1	**2b** (65)
4-(MeO_2C)Ph	Cl	Kept at -50 °C for 16 h	0:100	5:1	-
3-CNPh	Cl	Standard	1:9	2:1	**2c** (48)
3-CNPh	Cl	Kept at -50 °C for 16 h	2:1	-	**1c** (42)
4-(CF_3)Ph	Cl	Standard	1:11	2:1	**3d**[e,f] (47)
4-(CF_3)Ph	Cl	Kept at -50 °C for 16 h	1:1	2:1	**1d** (35)
4-(MeO_2C)Ph	Cl	Using 2-bromo-5-methoxybenzaldehyde and warm to 0 °C (for 1 h)	0:100	3:1	**2e**[e] (52)
4-(CF_3)Ph	Cl	Using 2-bromo-5-flourobenzaldehyde warm to 0 °C and hold (for 1 h)	1:5	1:1	**3e**[e,f] (49)
4-(MeO_2C)Ph	Cl	Using 3-bromothiophene-2-carbaldehyde and warm to 0 °C (for 1 h)	100:0	-	**1e**[e] (27)
4-(CF_3)Ph	Cl	Using 2-bromo-5-methoxybenzaldehyde and warm to 0 °C (for 1 h)	1:3	1:2	**3f**[e,f] (42)

[a] Reagents: LiCCTMS (3.4 mL of 0.50 M THF-hexane solution) treated with 2-bromobenzaldehyde (1.62 mmol), followed by *n*BuLi (1.06 mL of 1.6 M hexane solution), $CuBr{\cdot}SMe_2$ (0.81 mmol), propargylic electrophile (0.79 mmol) added at -50 °C. [b] From crude reaction mixture determined by ^1H NMR spectroscopy. [c] Isolated. [d] *Syn* (OH to R^2):*anti* ratio; stereochemical assignment based on NMR correlation to **2b** (X-ray). [e] The structures of products **1e-3f** are shown below [f] Isolated as naphthalene **3**; dehydration from **2** to **3** achieved with Amberlyst® 15 and 3 Å molecular sieves.



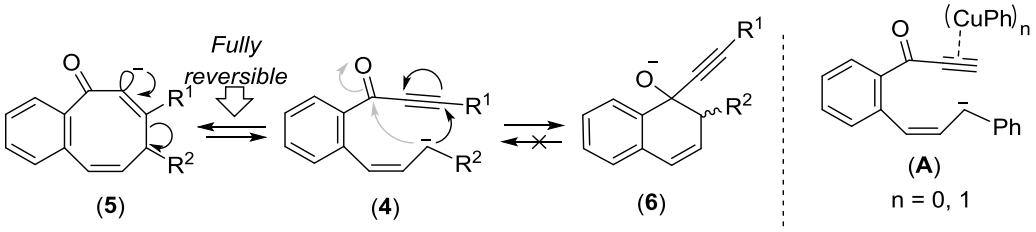
	R^2
(**1e**)	4-(MeO_2C)Ph

	R^2	R^3
(**2e**)	4-(MeO_2C)Ph	OMe

	R^2	R^3
(**3a**)	Ph	H
(**3d**)	4-CF_3Ph	H
(**3e**)	4-CF_3Ph	F
(**3f**)	4-CF_3Ph	OMe

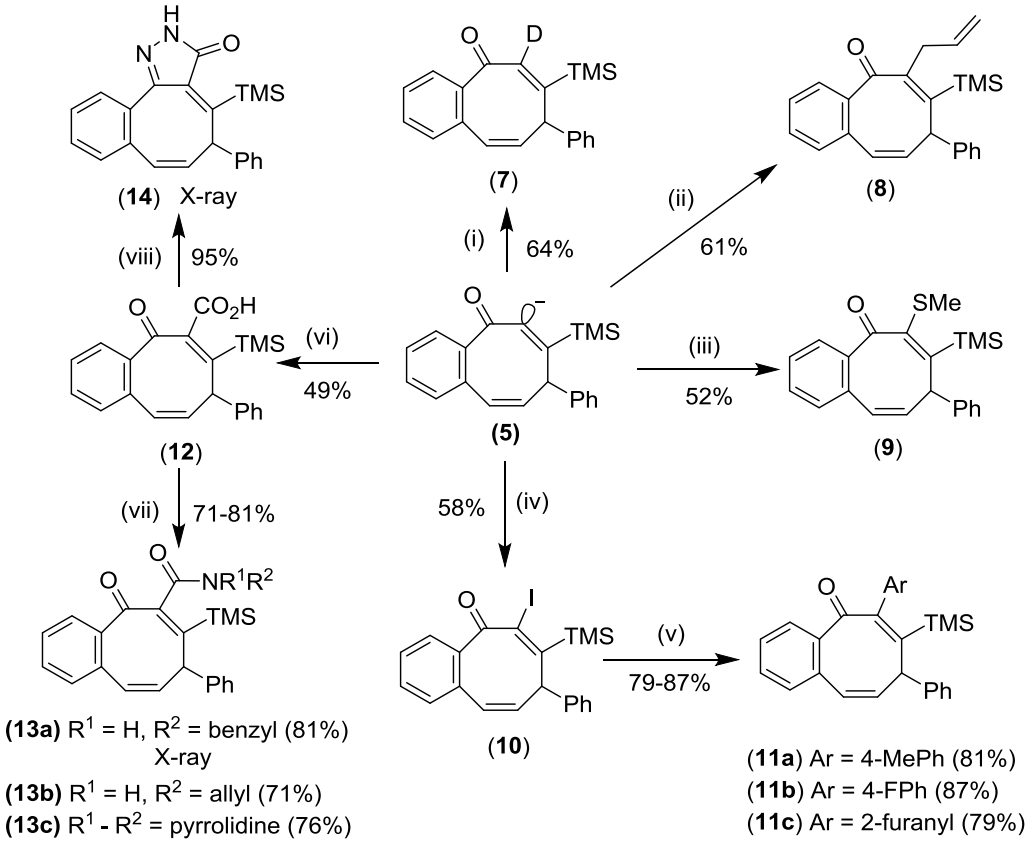
The R^2 substituent and condition dependant formation of mixtures of **1** and **2** is most in accord with interconversion of a common intermediate (**4**) with both a non-classical *C*-enolate (**5**) and alkoxide (**6**) prior to final protonation (Scheme 2). A carbanion formulation for **5** is supported by our previous computational studies[1] (formation of an 8-ring allenoate engenders too much ring strain). The antiperiplanar arrangement in **5** favours C-C σ-bond cleavage regenerating **4** (Scheme 2). Higher temperatures (-10 °C to ambient) result in thermodynamic capture of **4** forming alkoxide **6**. Formation of **6** is not reversible as re-cooling solutions enriched with this anion does not result in the isolation of 8-ring products (see behaviour of **1a**/**2a** in Table 1). Formation of **6** is favoured by groups that stabilise the resultant benzyl anion. The behaviour of **4** has been computationally modelled using simplified structure **A** (n = 0) at the CBS-QB3 level of theory. To decrease computational cost in the model system (**A**), the atom count has been reduced by using R^1 = H, R^2 = phenyl and CuC_6H_5(2-CHOLiC≡CH) has been simplified to CuPh. Viable transition states for both 8- and 6-rings (**B** and **C** respectively – Supporting Information) could be identified with very similar energies. These simple (metal free) models suggest 6-ring formation should be kinetically favoured, and that 8-ring products would be attained as the thermodynamic product – the opposite of what is actually observed. This failure of the computational model is apparently caused by the absence of metal ligation, in particular: (i) the absence of a strong Li-O bond (112 kcal mol^{-1})[3] in the reaction coordinate approaching (**6**) and (ii) the lack of Cu…alkyne coordination in events leading to (**5**) (see Supporting Information). It is clear from Table 1 that the 6 vs. 8-ring reaction pathways are rather close in energy, such that they may be biased by experimental conditions in a useful manner. Support for Cu…alkyne coordination in events leading to **5** were provided by reaction of Li[Cu{C_6H_5(2-CHOLiC≡CPh)}$_2$] (formed from enantioenriched (*R*)-1,2-C_6H_4Br(CHOHC≡CPh), 88% *ee*) with (±)-PhCHClC≡CH (Supporting Information). This resulted in the formation of (-)-**1j** with 20% *ee*. Thus, both chiral cuprate coordination to prochiral **4** and partial chirality transfer appear possible. The alternative possibility of kinetic resolution of (±)-PhCHClC≡CH cannot be completely discounted, however, even if this were the case the reaction manifold would still have to pass through **4** and a 'memory of chirality' effect[4] would be required to explain the observed *ee*. This seems less likely than alkyne coordination which was also favoured in preliminary computational studies using **A** (n = 1, Supporting Information). Conversion of **4** to **6** can be affected by polar co-solvents. Crude ^{1}H NMR of **2a** (prior to conversion to **3a**) shows that addition of DMF (10 equiv. compared to substrate) before warming to room temperature can increase the diastereoselectivity from 2:1 to 4:1. The facility of 6-ring formation is more affected by geometrical factors than the electronic effects of the aldehyde. Both electron rich and poor substitution of the 1,2-C_6H_4 unit provides 6-ring major products (**2e** and **3e-f**). However, replacement of the phenylene unit by a five ring 1,2-thiophenylene negates 6-ring formation completely (**1e**). Calculations (B3LYP/6-31G+(d), vacuum) on the ground states of the model anions (*Z*)-1,2-*Aryl*{C_A(=O)C≡C_BH}{CH=CH(C_CH$^-$)$C_6H_4CO_2$Me} indicate that for *Aryl* = C_6H_4, C_C is significantly closer to C_A (C_A..C_C 3.34 Å, C_B..C_C 3.67 Å). For *Aryl* = C_4S (thienyl) the opposite is true (C_A..C_C 3.63 Å, C_B..C_C 3.29 Å), in line

with experimentally observed formation of **1e**. Finally, we note that cross-over from 8 to 6-ring formation has been noted once before, but with alkoxide nucleophiles not carbanions.[5]



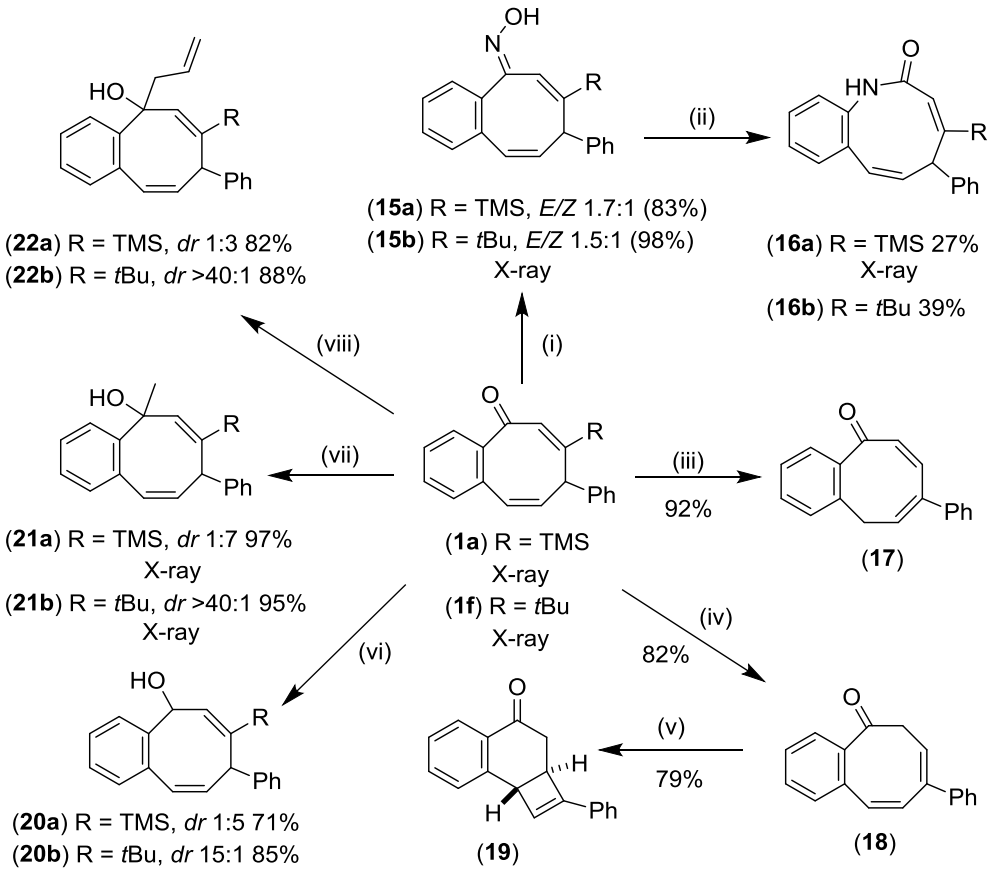
Scheme 2. Mechanistic proposal for σ(C-C) cleavage processes in 8 *vs*. 6-ring formation.

Diversification via non-classical enolate. In many cases the *C*-enolates (**5**) are stable at -10 °C and thus offer an excellent point for rapid core diversification. We sought to extend the preliminary observations we had made in this area.[1] It was found that a range of electrophiles can be added directly into the one-pot cascade sequence to furnish a wider variety of 8-ring derivatives or to install reactive handles (Scheme 3). Trapping enolate **5** with reactive deuterium oxide, allyl bromide and dimethyl disulfide allowed preparation of functionalised ring systems **7-9** (52-64%). These procedures are not appropriate for lower reactivity electrophiles, e.g. DEAD and tributyltin chloride resulted in the formation of the parent **1a** after aqueous work up. Addition of elemental iodine leads to the formation of **10**, in good yield, which lends itself well to further diversification via Suzuki-Miyaura cross coupling reactions providing **11a-c** (79-87%) as representative examples. Amides **13a-c** and pyrazolone **14** can conveniently be synthesised from our previously described[1] carboxylic acid **12** in 71-95% yield. The rapid synthesis of pyrazolone **14** (47% overall yield, 2 steps from 2-bromobenzaldehyde), amides **13a-c** (35-40% overall yield, 2 steps from 2-bromobenzaldehyde) and furyl **11c** (46% overall yield, 2 steps from 2-bromobenzaldehyde) show how this methodology can swiftly incorporate heteroatoms and drug-like motifs into the core scaffold.



Scheme 3. Diversification via non-classical *C*-enolate (**5**, R^1 = $SiMe_3$, R^2 = Ph). Reagents and conditions: (i) D_2O (10 equiv.), -10 °C; (ii) allyl bromide (5 equiv.), -10 °C to ambient; (iii) dimethyl disulfide (5 equiv.), -10 °C to ambient; (iv) I_2 (5.0 equiv.), -10 °C to ambient; (v) arylboronic acid (1.05-1.50 equiv.), $PdCl_2$(dppf) (3-5 mol-%), sodium bicarbonate (5 equiv.) in THF; (vi) Solid CO_2 (ca. 20 fold excess), -10 °C to ambient; (vii) amine (2 equiv.), NEt(*i*-Pr)$_2$ (3 equiv.), T3P® (2 equiv.) in EtOAc; (viii) HOBt (1.2 equiv.), EDC·HCl (1.2 equiv.), hydrazine (2 equiv.) in MeCN/THF.

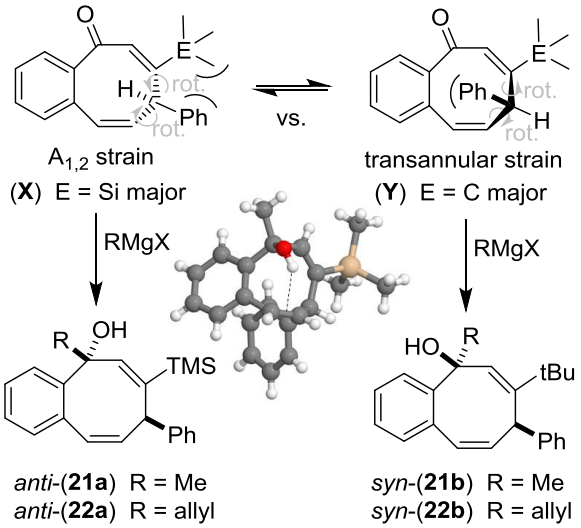
Diversification of 8-ring core structures. We have also explored the potential for representative 8-rings **1a** and **1f** to provide additional derivatives through simple modification (Scheme 4). Ring expansions to 9-membered cyclic amides were achieved via the formation of oximes **15a-b**. These are attained in high yield in the presence of hydroxylamine hydrochloride and sodium acetate providing **15a** (83%, 1.7:1 *E*:*Z*) and **15b** (98%, 1.5:1 *E*:*Z*). Proton, ^{13}C and 2D NMR analysis of **15b** are in accord with the major isomer to be the *E*-oxime. Based on the X-ray structure of the parent carbonyl **1a** and **1f**, we believe that proximity of the OH to the α-vinylic CH in the *E*-oxime causes characteristic shifts for this signal in ^{1}H and ^{13}C NMR spectrums, as has been observed before.[6] In practice, the ^{1}H NMR *E*-oxime α-CH signal of **15b** resonates at 7.35 ppm vs. *Z*-oxime ~6.75 ppm, while in the ^{13}C NMR spectra the *E*-oxime α-CH shows δ_C ~118 vs. δ_C ~124 for the *Z*-oxime. The Beckmann rearrangement of oximes **15a-b** in the presence of toluenesulfonyl chloride furnished 9-membered cyclic amides **16a-b** in moderate yields. Such rearrangements generating medium-sized rings are known to be challenging.[7] However, it should be noted that the consolidated yields of 9-rings **16a-b** over the three-step sequence are competitive with current literature approaches to such systems.[8] The regiochemistry of the rearrangements were confirmed via X-ray analysis of **16a**. Subjecting **1a** to neat trifluoroacetic anhydride cleaved the TMS group from the 8-membered ring and triggered alkene isomerisation to synthesise enone **17** in excellent yield. Conversely, removal of the TMS group with tetrabutylammonium fluoride triggers a different isomerisation that gives conjugated diene **18** in 82% yield. The reasons for differing isomerisation mechanisms are not completely understood, but **18** and **17** are not interconvertible in the presence of trifluoroacetic acid. Fused cyclobutene **19** was synthesised in 79% yield from the intramolecular [2+2] cycloaddition of diene **18**. Microwave heating (150 °C) of the diene in the presence of boron trifluoride etherate gives the Woodward-Hoffmann thermally allowed *trans*-**19**, confirmed by nOe NMR experiments (Supporting Information).



Scheme 4. Diversification of 8-ring cores. Reagents and conditions: (i) hydroxylamine hydrochloride (20 equiv.) and sodium acetate (20 equiv.) in refluxing ethanol; (ii) sodium hydride (3 equiv.) and toluenesulfonyl chloride (1.1 equiv.) in THF; (iii) neat trifluoroacetic acid (5.5 equiv.) from **1a** only; (iv) tetrabutylammonium fluoride (2 equiv.) in THF from **1a** only; (v) boron trifluoride diethyl etherate (0.3 equiv.) in toluene (µw, 150 °C); (vi) lithium aluminium hydride (1 equiv.) in THF; (vii) methylmagnesium bromide (1.7 equiv.) in THF; (viii) allylmagnesium bromide (1.4-1.7 equiv.) in THF.

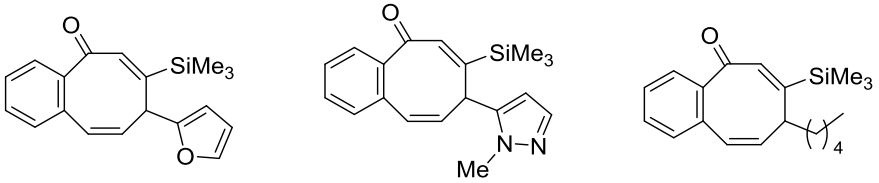
Reduction of the ketones **1a** and **1f** with lithium aluminium hydride affords alcohols **20a-b** in 71 and 85% yields respectively. Reduction of the carbonyl removes the Michael accepting enone moiety potentially increasing its appeal for medicinal chemistry screening. Michael acceptor units are frequently excluded from initial screening protocols to avoid toxicological/suicide substrate issues.[9] Interestingly, our own attempts at 1,4-conjugate additions into **1a** showed a complete resilience to nucleophilic attack at this position. Simple 1,2-addition of methylmagnesium bromide and allylmagnesium bromide into ketones **1a** and **1f** proceeds with high yields of 82-97%. When analysing the stereo outcome of reactions which involve direct 1,2-addition of Grignard reagents to the carbonyl, it became clear that opposite diastereoselectivity was attained from the two parent substrates **1a** (R^1 = $SiMe_3$) and **1f** (R^1 = *t*-Bu); R^2 = Ph in both cases. Conformational bias in the *tert*-butyl (**1f**) vs. TMS-derivative (**1a**) starting materials is the source of this behaviour, based on analysis of their X-ray crystal structures (Supporting Information). For **1a** conformation (**X**) is seen in the solid state (Scheme 5). The phenyl group is pseudo equatorial placing the C*H*Ph proton endocyclic, presumably to minimise transannular strain. In the X-ray structure of **1f**, the shorter =C-CMe_3 vs. =C-$SiMe_3$ bond (1.53 compared to 1.90 Å) leads to significant increase in allylic $A_{1,2}$ strain[10] destabilising conformer (**X**) and leading to the observation of (**Y**) in the solid state for **1f** (Supporting Information). The subsequent conformational change results in endocyclic placement of the phenyl group directly obscuring one of the diastereotopic faces of the carbonyl. The hypothesis that these solid state observations also operate in solution is corroborated by the X-ray structures of the major diastereoisomers resulting from

MeMgBr addition to **1a** and **1f**. For *tert*-butyl (**1f**) (conformer **Y**), addition to the bottom face is seen (Supporting Information) leading to *syn*-**21b** (diastereomeric assignment relates to the orientation of the OH in respect to the phenyl group in all cases, as seen in Scheme 5). Addition to the TMS derivative **1a** led to *anti*-**21a** as the major product. The ^{1}H NMR chemical shift of C*H*Ph proton is indicative of the diastereoisomer formed, a higher frequency signal (δ_H ~4.6 ppm) is indicative of *anti* diastereoisomer formation (vs. δ_H ~4.4 ppm for the equivalent *syn* signal). On this basis, the diastereoselectivity of allyl Grignard additions were also assigned. Relative signal integrations were used to determine the *syn*:*anti* ratio in **21-22**. Blocking of the Bürgi-Dunitz[11] (π*) approach leads to excellent *syn* diastereoselectivity (>40:1) in the formation of **21b-22b**. The *anti* selectivity of **21a-22a** is not as good (7:1 and 3:1 respectively) as both diastereofaces of the carbonyl in **1a** are more open. There are hints that the distal *cis*-C-C π-bond might also act as a directing group (Mg…π-bond in the Grignard addition) as product *anti*-(**21a**) shows an unusual, but potentially related, H…π-bond hydrogen bond (2.2Å, structure in the centre of Scheme 5). However, this suggestion should be regarded as tentative. It seems that similar *syn*/*anti* control issues account for the stereochemical reversal seen in hydride addition to form **20a-b**. Due to the protection offered to the top diastereotopic face in conformation (**Y**), it is tentatively assumed that hydride addition into carbonyl **1f** will also result in the formation of predominantly *syn*-(**20b**).



Scheme 5. Conformational bias of 8-membered rings controls Grignard 1,2-addition diastereoselectivity and X-ray structural observation of H…C=C contact in *anti*-(**21a**) R = Me.

Finally, as the majority of our studies had involved the use of simple aryl groups in the R^2 position of structure **1**, we were very keen to extend the range of propargylic chlorides to include electron rich (hetero)aromatics, electron poor (hetero)aromatics and alkyl functionality. While electron-rich aromatic propargylic chlorides proved too reactive to be used in the reaction (e.g. 2-furanylCHClC≡CH spontaneously decomposes at room temperature in our hands), the less reactive acetate allowed the one-pot synthesis of electron rich **1g**. Conversely, electron poor **1h** containing the pyrazolyl function could be prepared from the corresponding propargylic chloride (Scheme 6). Using 3-chlorooct-1-yne and a slightly modified procedure (Supporting information), we were also able to synthesise alkyl chain containing **1i**.



Scheme 6. Representative variation of substituent R^2 in compounds (**1**).

Conclusion

Due to the simplicity of their synthesis,[1] bicyclic 6,8-ring systems containing the cycloocta-2,5-dien-1-one core are attractive starting materials for diversity chemistry potentially aimed at the development of biological activity libraries. Addition of $LiC{\equiv}CR^1$ to 2-bromobenzaldehyde, followed by subsequent cuprate formation and reaction with $R^2CHClC{\equiv}CH$ provide a non-classical *C*-enolate as the kinetic product at lower temperatures that can be trapped with a wide range of electrophiles to rapidly provide diverse libraries with little synthetic effort (1-3 steps total, consolidated yields >25%). These products themselves are attractive starting points for ring expansion and diastereoselective addition reactions. If allowed to warm, the *C*-enolate rearranges via an unusual retro σ C-C bond cleavage to provide some 6,6-ring systems. In support of the assertion that the strategies presented here are useful in biological activity discovery libraries, several of the compounds herein have already revealed significant activity in open innovation drug discovery programmes.[12]

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Keywords: Annulation • Medium-ring compounds • Synthetic methods • Ring expansion • C-C activation

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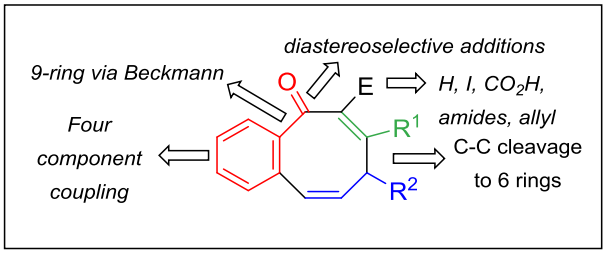
Table of Contents Entry



Graphical abstract text: Simple 1-3 step processes provide access to 6,n-bycyclic ring systems (n = 6,8,9) and other rapidly prepared derivatives.