Intramolecular Stetter cyclisation of Morita–Baylis–Hillman adducts: a versatile approach towards bicycloenediones†

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Bicyclic enediones of various sizes can be efficiently assembled by intramolecular Stetter cyclisation of readily available Morita–Baylis–Hillman adducts.

Bicyclic structures are ubiquitous subunits in a wide variety of natural products such as coronatine[1] and guaiol[2] (Fig. 1). The occurrence of these substructures has stimulated the development of numerous and elegant procedures for their efficient construction.[3] As part of an ongoing research programme directed towards the rapid and flexible synthesis of some of these naturally occurring compounds, we have recently described a method for the assembly of substituted hydrindanones and decalones based upon the reductive cyclisation of Morita–Baylis–Hillman adducts.[4]

In this communication, we wish to report on the discovery and development of a simple methodology for the rapid construction of various bicyclic enediones that hinges upon two key steps: a Morita–Baylis–Hillman coupling,[5] followed by an intramolecular Stetter reaction.[6] As depicted in Fig. 2, cleavage of the C-4/C-5 bond of bicyclic enedione **3**, accompanied by the concomitant insertion of an oxygenated function at C-8, reveals the Morita–Baylis–Hillman adduct **4**, itself readily available from enone **5** and aldehyde **6**.

Our approach thus began with the union of cyclic enones **5a–d** with 4-pentenal **6a** (Scheme 1). After some experimentation, it was found that a slight modification of the procedure reported by Yamada and Ikegami,[7] using *n*-Bu_3P and *rac*-binol, promoted the coupling of 2-cyclopentenone **5a** and 2-cyclohexenone **5b** in excellent yields. In the case of 2-cycloheptenone **5c** and 2-cyclooctenone **5d**, the Nozaki Et_2AlI-mediated protocol was required[8] and the desired adducts **7c–d** were obtained in satisfactory yields. Alcohols **7a–d** were then subjected to acetylation, under Yamamoto's conditions,[9] providing the β-acetoxy enones **8a–d** in good to essentially quantitative yields. Finally, chemoselective ozonolysis of the terminal alkene of **8a–d**, in the presence of Sudan red as an indicator,[10] produced the key cyclisation precursors **9a–d** in 75–95% yield (Scheme 1).

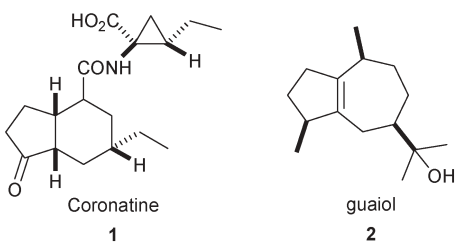

Fig. 1 Selected natural products containing a bicyclic core.

With the desired precursors in hand, we next turned our attention to the crucial cyclisation step: the intramolecular ring closure of an aldehyde onto a cyclic enone. To perform this reaction, the aldehyde had to be transformed initially into an acylanion equivalent. Among several possibilities, the Stetter reaction which exploits this umpolung reactivity[11] and which has recently been the subject of renewed interest attracted our attention.[12] Although the Stetter reaction can be carried out sometimes with good yields and selectivities, its synthetic scope still remains to be explored.[13]

Our studies began with an examination of the intramolecular Stetter cyclisation of the cyclohexenone-aldehyde derivative **9b** (Table 1). Under standard Stetter conditions (0.1 equiv. of thiazolium salt **10a** and 0.6 equiv. of Et_3N in EtOH at reflux), the desired bicyclic enedione **11b** could be obtained in 50% yield (Entry 1). Several reaction parameters were next varied in order to optimise the yields; some selected examples are shown in Table 1. When 1 equiv. of commercially available thiazolium salt **10a** and 1.2 equiv. of Et_3N were employed, in EtOH at reflux, the enedione **11b** could be isolated in a satisfactory 66% yield (Entry 5).

Having delineated suitable conditions for the intramolecular Stetter reaction, we next applied them to the ring closure of β-acetoxyenones **9a–d** (Table 2). When cyclopentenone **9a** was submitted to these conditions, the corresponding bicyclic enedione **11a** was obtained in 50% yield (Entry 1).[14] Increasing the ring size of the substrates led to improved yields. Cycloheptenone and cyclooctenone derivatives **9c–d** afforded the desired enediones **11c–d** in an excellent 80% yield. (Entries 3 and 4).

At this stage, the viability of our approach had been demonstrated and it became evident that Morita–Baylis–Hillman adducts were suitable intermediates to access various bicyclic enediones. In order to extend our methodology, it was decided to synthesise a more challenging adduct: the perhydroazulene core **15**. To achieve this objective, cyclopentenone **5a** was coupled to

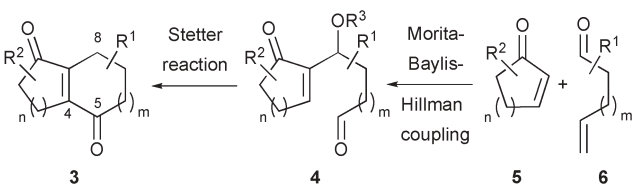

Fig. 2 Proposed retrosynthetic analysis of bicyclic enediones.

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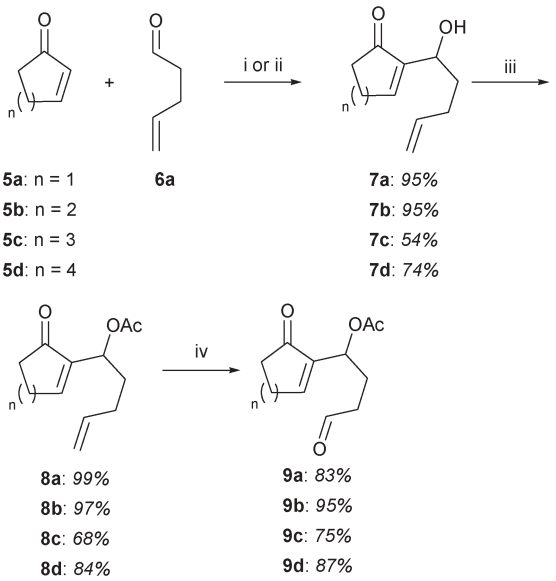
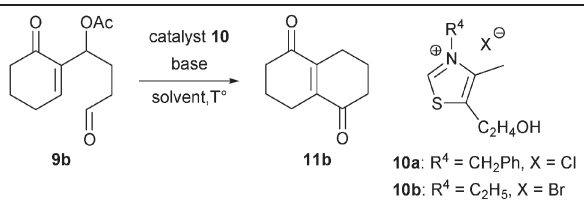


Scheme 1 Assembly of the cyclisation precursors. *Reagents and conditions*: (i) 3 equiv. **5a** or **5b**, 0.6 equiv. *n*-Bu_3P, 0.3 equiv. binol, THF, rt; (ii) **5c** or **5d**, 1.2 equiv. **6a**, 1.4 equiv. Et_2AlI, CH_2Cl_2, 0 °C; (iii) 1.5 equiv. Ac_2O, $Sc(OTf)_3$ cat., CH_3CN, rt; (iv) O_3, Sudan red 7B, CH_2Cl_2 then Ph_3P, −78 °C to rt.

Table 1 Optimisation of the intramolecular Stetter reaction



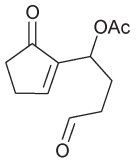
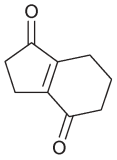
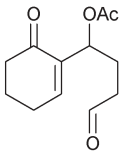
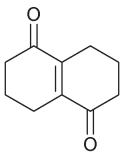
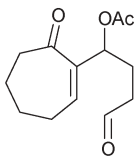
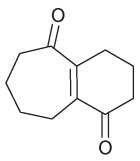
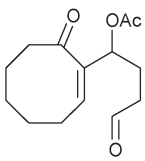
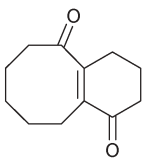
Entry	Catalyst (equiv.)	Base (equiv.)	Solvent	*T* (°C)	Yield[a] (%)
1	**10a** (0.1)	Et_3N (0.6)	EtOH	78	50
2	**10a** (0.1)	Et_3N (0.6)	CH_2Cl_2	40	20
3	**10a** (0.1)	Et_3N (0.6)	dioxane	80	32
4	**10a** (0.2)	Et_3N (0.7)	*t*-BuOH	80	55
5	**10a** (1.0)	Et_3N (1.2)	EtOH	78	66
6	**10b** (1.0)	Et_3N (1.2)	EtOH	78	47
7	**10b** (1.0)	DBU (1.2)	EtOH	78	24

[a] Yields refer to pure, isolated products.

5-hexenal **6b**, under Ikegami's conditions, affording hydroxyenone **12** which was obtained in 81% yield. Acetylation of the hydroxyl group, followed by selective ozonolysis of the terminal alkene, generated the key intermediate **14** in 64% overall yield (Scheme 2). When submitted to our Stetter conditions, substrate **14** produced the corresponding perhydroazulenedione derivative **15** in a satisfactory 46% yield. To the best of our knowledge, this is the first example of the construction of a 7-membered ring using the Stetter reaction.

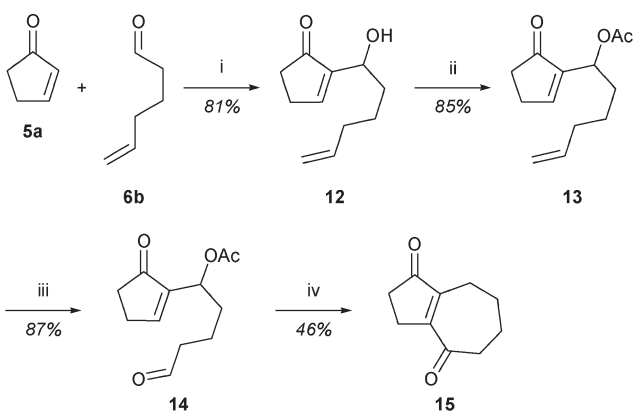
Though enediones are potent functionalities, their reactivity has been little examined.[15] As a relevant preliminary study, we elected to reduce the conjugated C–C double bond using McMurry's procedure,[16] *i.e.* $TiCl_3$ in acidic aqueous solution. In the presence of 4 equiv. of aqueous $TiCl_3$ in acetone, enedione **11a** afforded smoothly the corresponding *cis*-hydrindanone **16a**, as a single

Table 2 Intramolecular Stetter reaction of Morita–Baylis–Hillman adducts

Entry[a]	Substrate	Product	Yield[b] (%)
1	 **9a**	 **11a**	50
2	 **9b**	 **11b**	66
3	 **9c**	 **11c**	80
4	 **9d**	 **11d**	80

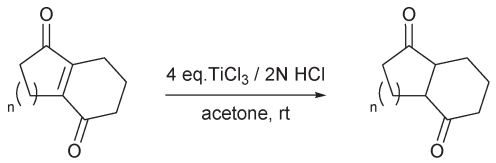
[a] All reactions were performed in the presence of 1 equiv. **10a** and 1.2 equiv. of Et_3N, in ethanol for 2.5 h at reflux. [b] Yields refer to pure, isolated products.

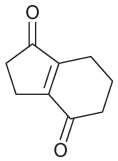
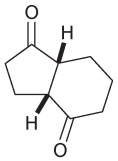
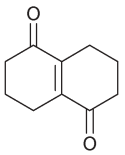
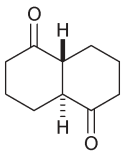
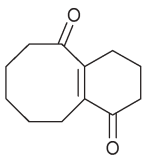
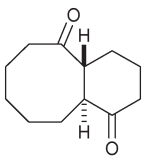
diastereoisomer, in 85% yield (Table 3).[17] Applying the same conditions to the prochiral enedione **11b** led to the *trans*-decalone **16b** in essentially quantitative yield. Similarly bicyclo-[6.4.0]-enedione **11d** was reduced stereoselectively to the *trans*-diketone **16d** in 86% yield.



Scheme 2 Preparation of a perhydroazulene. *Reagents and conditions*: (i) 3 equiv. **5a**, 0.6 equiv. *n*-Bu_3P, 0.3 equiv. binol, THF, rt; (ii) 1.5 equiv. Ac_2O, $Sc(OTf)_3$ cat., CH_3CN, rt; (iii) O_3, Sudan red 7B, CH_2Cl_2 then Ph_3P, −78 °C to rt; (iv) 1 equiv. **10a**, 1.2 equiv. Et_3N, EtOH, reflux, 2.5 h.

Table 3 Reduction of enediones



Entry	Substrate	Product	Yield[a] (%)
1	 11a	 16a	85
2	 11b	 16b	97
3	 11d	 16d	86

[a] Yields refer to pure, isolated products.

In summary, we have developed a short and connective synthesis of bicyclic enediones. This new methodology involves two key steps: a Morita–Baylis–Hillman coupling and an intramolecular Stetter reaction. Various bicyclic structures can be readily assembled *via* this versatile protocol. Moreover, the Stetter reaction has been shown to be a powerful synthetic tool that led, not only to 6-*endo*, but also to 7-*endo-trig* cyclisations. Current efforts are now aimed at delineating the full scope of this methodology, examining the reactivity of enediones and using these substrates in the total synthesis of relevant natural products. The results of these investigations will be reported in due course.

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17 A 24 h reaction time is necessary to complete the conversion of **11a** into the desired diketone **16a** due to the formation of a transient and unexpected 5-hydroxyenone intermediate.