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Reductive cyclisation of Morita–Baylis–Hillman adducts. A simple approach towards substituted hydrindanones and decalones

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Abstract—A connective synthesis of substituted hydrindanones and decalones can be accomplished based upon a novel approach involving two key-steps: a Morita–Baylis–Hillman condensation and an intramolecular reductive cyclisation using lithium in ammonia. Decalones, akin to the middle core of the clerodane family of natural products and bearing a quaternary carbon centre, can be readily assembled via this protocol.

A large variety of natural products contain, embedded in their architectural framework, one or more polycyclic subunits. Among them, hydrindanes and decalins are common fragments. The widespread occurrence of these substructures has stimulated the development of numerous and elegant methods for their efficient assembly.[1] However, new procedures that would generate functionalised hydrindanes and decalins from readily available precursors are still in demand.

During our synthetic efforts aimed at the efficient construction of clerocidin **1**[2] and coronatine **2**[3] (Fig. 1),

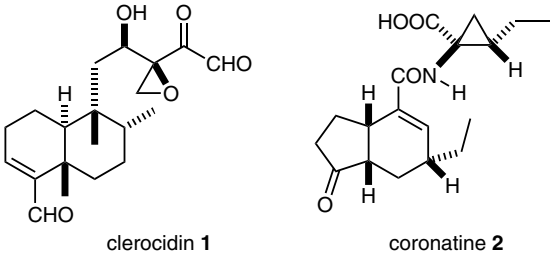

Figure 1. Selected natural products containing a decalin or a hydrindane core.

an easy and flexible access towards diversely substituted decalins and hydrindanes was required.

In this letter, we wish to report some of our preliminary results on the establishment of a simple and connective methodology for the rapid preparation of these important subunits, that hinges upon two key-steps: a Morita–Baylis–Hillman condensation,[4] followed by a reductive cyclisation.[5,6] Our antithetic analysis is depicted in Figure 2.

Oxidative cleavage of the C4–C5 bond of bicyclic compound **3**, accompanied by the concomitant insertion of an oxygenated function at C8, reveals the β-alkoxy-substituted enone **4**. Application of the Baylis–Hilman–Morita retron then generates two simple and readily available fragments: the cyclic enone **5** and the substituted aldehyde **6**.

Our approach thus began with the union of cyclopentenone **7a** and cyclohexenone **7b** with 4-pentenal **8** (Scheme 1). Whilst numerous protocols are reported in the literature for the Morita–Baylis–Hillman condensation of acyclic enones, the coupling of cyclic enones with aliphatic aldehydes has often proved troublesome.[7] After some experimentation, it was found that a slight modification of the procedure reported by Yamada and Ikegami,[8] using *n*-Bu_3P and binol, afforded the desired adducts in essentially quantitative yields. These alcohols were immediately subjected to acetylation, under Yamamoto's conditions[9] (cat. $Sc(OTf)_3/Ac_2O$),

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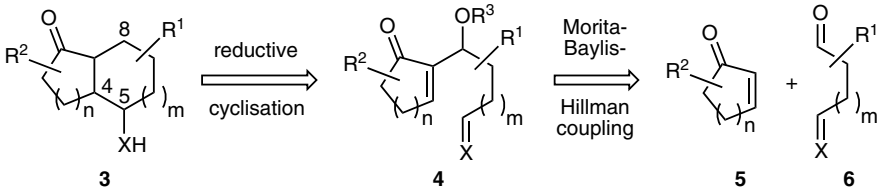
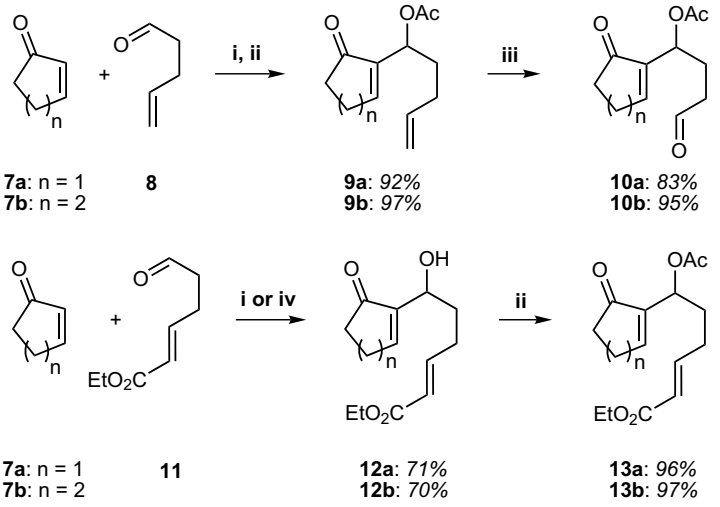


Figure 2. Retrosynthetic analysis.

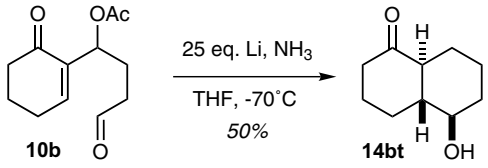


Scheme 1. Assembly of the cyclisation precursors. Reagents and conditions: (i) 3 equiv **7a** or **7b**, 0.6 equiv *n*-Bu_3P, 0.3 equiv binol, THF, rt; (ii) 1.5 equiv Ac_2O, 2 mol % $Sc(OTf)_3$, MeCN, rt; (iii) O_3, Sudan red 7B, CH_2Cl_2 then 1.3 equiv PPh_3, −78 °C to rt; (iv) 1 equiv **7b**, 1.5 equiv Et_2AlI, CH_2Cl_2, 0 °C.

providing the β-acetoxy enones **9a** and **9b** in 92% and 97% overall yields, respectively (Scheme 1).

Finally, chemoselective ozonolysis of the terminal alkene of **9a** and **9b**, in the presence of Sudan red as an indicator,[10] produced the key cyclisation precursors **10a** and **10b** in excellent yields. A similar approach was employed to access the enoate-containing enones **13a** and **13b**. It is interesting to note that, whilst cyclopentenone **7a** reacted smoothly with aldehyde **11** (readily prepared from **8** by a Horner–Emmons reaction, followed by a chemoselective ozonolysis) under modified Ikegami's conditions, cyclohexenone **7b** afforded the desired adduct **12b** in only poor yields. In this case, recourse to the Nozaki Et_2AlI-mediated protocol became mandatory.[11]

With the desired precursors in hand, we then turned our attention to the crucial reductive cyclisation step (Scheme 2).



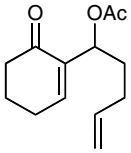
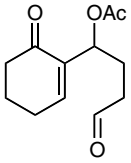
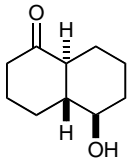
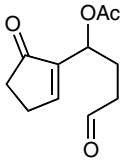
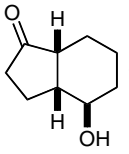
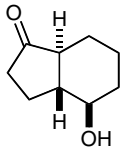
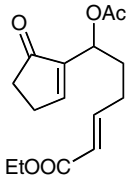
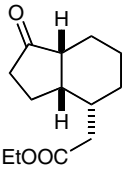
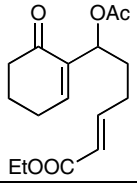
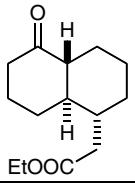
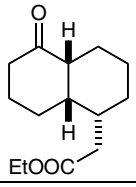
Scheme 2. Reductive cyclisation of **10b**.

When adduct **10b** was treated with SmI_2,[12] under a variety of conditions (various equivalents, addition or not of a proton source such as MeOH or *t*-BuOH, absence or presence of HMPA), only extensive decomposition of the starting material was observed.[13] The Zn–TMSCl procedure reported by Corey and Pyne[14] led mainly to the recovery of **10b**, whilst the use of lithium naphthalenide[15] or Li–DBB[16] afforded only intractable mixtures, from which no single component could be isolated. Finally, when Li in ammonia[17] was employed, the desired decalone **14bt** could be obtained in a reasonable yield and as a single diastereoisomer possessing the trans-ring junction.[18] It is noteworthy that a large amount (25 equiv) of lithium, a rather high dilution and vigorous stirring were required to ensure the success of this reductive cyclisation. Moreover, the addition of isoprene at the end of the reaction was crucial to avoid the formation of over-reduced products.

Having delineated suitable conditions to perform the reductive cyclisation of adduct **10b**, we next applied them to the ring closure of the other β-acetoxy enones. These results are collected in Table 1.

As can be seen from Table 1, substrate **9b**, possessing a terminal alkene instead of an aldehyde function, did not afford the desired decalone (entry 1). Only reduced, monocyclic products could be isolated in this case. When cyclopentenone **10a** was subjected to these conditions, the hydrindanones **14ac** and **14at** could be ob-

Table 1. Reductive cyclisation of Morita–Baylis–Hillman adducts

Entry	Substrate	Product	Yields[a] (%)
1	 **9b**	—[b]	—
2	 **10b**	 **14bt**	50
3	 **10a**	 **14ac** (2:1)  **14at**	40
4	 **13a**	 **15ac**	55
5	 **13b**	 **15bt** (1:1)  **15bc**	65

[a] All yields refer to pure, isolated products.
[b] A complex mixture of monocyclic products was obtained.

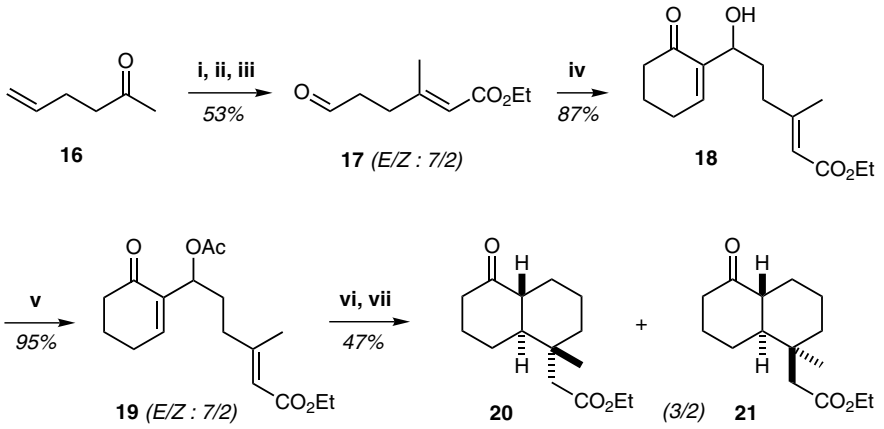
tained in a reasonable yield, though as a 2:1 mixture of epimers (entry 3).[19] It is interesting to note that, as in the case of **14bt** (entry 2), a *syn*-relationship is installed between the hydroxyl group and the adjacent ring junction hydrogen during the reductive cyclisation. In sharp contrast, the lithium in ammonia mediated ring closure of the enoate-containing cyclopentenone **13a** smoothly and exclusively led to the *cis*-hydrindanone **15ac**, bearing an *anti*-relationship between the ester side chain and the adjacent ring junction hydrogen (entry 4). Finally, reductive annulation of cyclohexenone **13b** provided the desired decalones **15bt** and **15bc** in good yields, albeit as a 1:1 mixture of diastereoisomers (entry 5).

Having demonstrated the viability of our approach, we decided to extend it to a more challenging substrate bearing a β,β-disubstituted enoate system. The cyclisation of **19** is particularly important since its ring closure should lead to the formation of a quaternary carbon centre, a prominent feature of the clerodane family of natural products (Scheme 3).

Accordingly, ketone **16** was transformed into aldehyde **17** by an initial Horner–Emmons homologation, followed by an oxidative cleavage of the terminal C–C double bond (cat. OsO_4/NMO then $NaIO_4$). The unsaturated ester **17** was then coupled with cyclohexenone **7b** under Ikegami's conditions, affording in excellent yield the desired Morita–Baylis–Hillman adduct **18**. Finally, acetylation completed the sequence, providing our key-intermediate **19**, in essentially quantitative yield and as a 7:2 mixture of (*E*)/(*Z*)-double bond isomers. The stage was now set for the crucial reductive annulation step. In the event, submitting **19** to excess lithium in ammonia resulted, after equilibration, in the formation of the two diastereomeric decalones **20** and **21**, in a reasonable yield and a 3:2 ratio. Interestingly, compound **21** possesses the correct relative stereochemistry at three of the four chiral centres present in the decalin core of clerocidin **1**.

A plausible mechanism, illustrating the formation of **14bt** from **10b**, is depicted in Figure 3.

Initial addition of an electron to the enone function of **10b** generates probably the extended ketyl radical **22**.[20] This pivotal intermediate can then evolve according to two different reaction pathways. In this strongly reductive medium, a second electron is rapidly transferred from lithium to **22**, affording either the dianion **23** (path A) or the bis-ketyl radical **24** (path B). Intramolecular cyclisation then ensues, either by nucleophilic addition onto the C=X bond or by radical coupling, leading to the dianion **25**.[21] Elimination of the acetate moiety then



Scheme 3. Preparation of decalones with a quaternary carbon centre. Reagents and conditions: (i) 1.1 equiv $(EtO)_2P(O)CH_2CO_2Et$, 1.1 equiv NaH, THF, rt; (ii) 2 mol % OsO_4, 1.1 equiv NMO, acetone/H_2O (10/1), rt; (iii) $NaIO_4$, MeOH/H_2O, 0 °C; (iv) 3 equiv **7b**, 0.5 equiv *n*-Bu_3P, 0.3 equiv binol, THF, rt; (v) 1.5 equiv Ac_2O, 2 mol % $Sc(OTf)_3$, MeCN, rt; (vi) 25 equiv Li, NH_3/THF (15/1), −70 °C, 10 min then isoprene, NH_4Cl; (vii) EtOK, EtOH, rt.

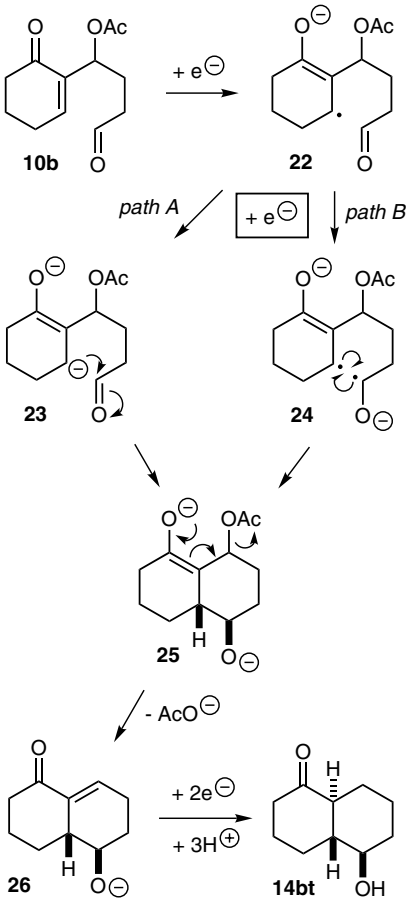


Figure 3. Proposed mechanism for the reductive cyclisation.

produces enone **26**, which is further reduced to the corresponding enolate. Finally, protonation delivers the requisite bicyclic derivative **14bt**. Although at this stage, we cannot distinguish between path A and path B, this mechanism rationalises the necessary use of a strong reducing medium. Indeed, it is imperative to rapidly transform the ketyl radical **22** into either **23** or **24** before it undergoes subsequent, undesired side reactions. It is also important to note that the 'moderate' yields obtained in this unique reductive cyclisation step represent, in fact, the overall yields for at least five elementary processes.

In summary, we have shown that a connective synthesis of substituted hydrindanones and decalones can be achieved by a novel methodology involving two key-steps: a Morita–Baylis–Hillman condensation and an intramolecular reductive cyclisation using lithium in ammonia.[22] Decalones, akin to the middle core of the clerodane family of natural products, and bearing a quaternary carbon centre, can also be readily assembled via this protocol. Current efforts are now directed towards further optimising these conditions, expanding the scope of this method and applying it to the total synthesis of relevant natural products. The results of these investigations will be reported in due course.

Acknowledgements

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18. The structure and stereochemistry of **14bt** was established by comparison of its spectroscopic data with those reported in the literature and by single crystal X-ray diffraction analysis. The stereochemistry of the other bicyclic adducts was determined by extensive RMN studies and comparisons with known derivatives. For example, the coupling constants of the ring junction protons of **14ac**, **14at**, **15ac**, **15bt**, **20** and **21** are 6.7, 12.6, 6.0, 10, 11.6 and 11.9 Hz, respectively. The ^{13}C NMR shift of the axial and equatorial methyl substituents of **20** and **21** resonate at 18.65 and 27.58 ppm, respectively. Complete analytical and spectroscopic data will be provided in the forthcoming full paper.
19. Under basic conditions (K_2CO_3/MeOH), **14at** epimerised to **14ac** (**14at**/**14ac**: 1/4).
20. Cyclic voltamperometric studies, performed in our laboratory on enones and acrylates, indicate that the enone function possesses a lower reduction potential than the corresponding α,β-unsaturated ester. Although we cannot rule out that a specific interaction might exist in substrates **13a**, **13b** and **19**, in which both functions are held in close proximity, the reduction of the enone appears to be the most feasible pathway. The alternative possibility, that is, initial reduction of the aldehyde followed by intramolecular cyclisation, would only occur in the case of the aldehyde-containing substrates.
21. Conceivably, radical **22** might also undergo ring closure, forming directly the bicyclic system. However, the addition of radicals on aldehydes is typically an unfavourable process and the absence of bicyclic adducts in the attempted annulation of **9b** argues against such a mechanism. For the cyclisation of ketyl radicals on terminal alkenes, see: Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132.
22. *Representative experimental procedure*: In a flamed-dried, four-necked, round-bottomed flask maintained under a positive pressure of argon and fitted with a sealed mechanical stirrer and a Dewar condenser, ammonia (300 ml) was passed through a drying tube containing KOH or barium oxide and condensed at −70 °C on Li (194 mg, 27.87 mmol, 25 equiv) suspended in THF (8 ml). Under vigorous stirring, enone **10b** (250 mg, 1.11 mmol, 1 equiv), dissolved in THF (12 ml), was added and the resulting deep blue mixture was stirred for 10 min. Isoprene (55.7 mmol, 50 equiv) was then added, followed immediately by a saturated aqueous ammonium chloride solution. The ammonia was then allowed to evaporate overnight. The product was extracted into Et_2O and CH_2Cl_2. The organic layers were pooled, dried over sodium sulfate and the solvents were removed under reduced pressure. The crude product was further purified by chromatography (silica gel, petroleum ether/ethyl acetate: 2/1) affording pure **14bt** as a white solid (94 mg, 50%). Crystal: mp 106 °C; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.14$–1.43 (m, 5H), 1.54–1.74 (m, 2H), 1.78–1.90 (m, 2H), 1.93–1.98 (m, 1H), 2.02 (ddd, $J = 11.3$, 11.3, 2.7 Hz, 1H), 2.09–2.16 (m, 1H), 2.26–2.42 (m, 3H), 3.39 (ddd, $J = 9.8$, 9.8, 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 22.56$ (CH_2), 24.43 (CH_2), 25.88 (CH_2), 28.07 (CH_2), 35.03 (CH_2), 41.39 (CH_2), 51.49 (CH), 53.11 (CH), 74.91 (CH), 211.61 (C); IR: 3402, 2927, 2857, 1701 cm^{-1}; MS (EI) *m*/*z* (%): 168.0 (31), 150.0 (33), 97.1 (100). HRMS *m*/*z* calcd for $C_{10}H_{16}O_2$: 168.1150. Found: 168.1149.