

Stereocontrolled synthesis of carbocycles *via* four successive pericyclic reactions†

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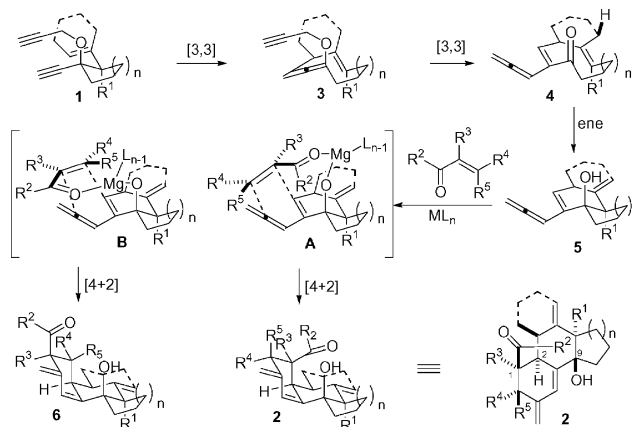
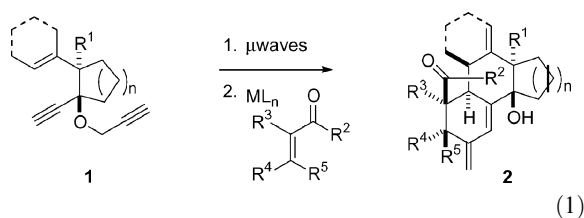
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Herein, we report a highly diastereoselective construction of fused carbocycles using four successive pericyclic reactions.

Creation of new efficient synthetic methods for the rapid assembly of compounds with high levels of molecular complexity constitutes a formidable challenge for synthetic chemists. To this end, reactions occurring in cascade represent an attractive and powerful strategy for the diastereoselective formation of multiple C–C bonds.¹ In the course of our studies towards the development of novel approaches to construct diterpenes and 14- β -hydroxysteroids,² we hypothesized that propargyl ether **1** could be transformed into **2** in a highly diastereoselective manner *via* four successive pericyclic reactions (eqn (1)). The attractive feature of the proposed process resides in the ability to generate, in one pot, four new C–C bonds and as many as four new contiguous stereogenic centers leading to complex carbocyclic frameworks.



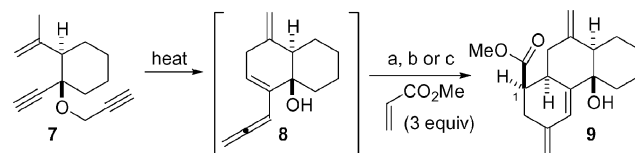
Scheme 1 Proposed mechanism of the oxy-Cope-Claisen-ene-HDDA reaction.

and the dienophile, transition state **A** should be favoured over **B**.

Hence, cycloadduct **2** should be observed as the major regioisomer, having the stereochemical relationship between the hydroxyl group at C9 and the hydrogen at C2 and the carbonyl group at C1 as being *anti* and *syn*, respectively. This particular stereochemistry is embedded in several natural diterpenes, notably, 14- β -hydroxysteroids. To the best of our knowledge, there are no reports in the literature of fused carbocycle syntheses using four successive pericyclic reactions.

We propose that heating **1** would give the macrocyclic allene ether **3** which is poised to undergo a Claisen rearrangement to generate enone **4** (Scheme 1).³ The latter is converted *via* a transannular carbonyl ene reaction to vinylallene **5** which, in the presence of an activated dienophile, undergoes an intermolecular Diels–Alder reaction to form tricycle **2**. There are only a few examples in the literature using vinylallenes as dienes in an intermolecular Diels–Alder reaction.⁴ Moreover, poor regioselectivities were obtained when non-symmetrical dienophiles such as methyl vinyl ketone (MVK) were employed.^{3a,g,i} Inspired by the work of Ward and Abaee,⁵ we recently demonstrated the use of temporary metal tethers to govern the facial selectivity in the Diels–Alder reaction of various 2-vinylcycloalken-1-ols.⁶ We envisioned that vinylallene **5** would undergo a hydroxy-directed Diels–Alder reaction (HDDA) *via* two possible transition states, **A** and **B**. Based on the HOMO–LUMO interactions⁷ between vinylallene **5**

To validate the above hypothesis, a solution of propargyl ether **7**⁸ and triethylamine (10 equiv.) in toluene was heated at 165 °C for 240 min using microwaves (Scheme 2). The solution containing vinylallene **8** was cooled to –78 °C and treated with 0.9 equivalent of vinylmagnesium bromide followed by 3 equivalents of methyl acrylate (method a). To our delight, tricycle **9** was obtained in 35% yield (over four different chemical transformations) as a single diastereomer (dr > 25 : 1). By contrast, a mixture of four diastereomers (including **9** as a minor isomer) was isolated in 63% yield when **7** was exposed to methyl acrylate and triethylamine at 165 °C in the absence of vinylmagnesium bromide. This clearly demonstrates the critical role of magnesium as a temporary



Scheme 2 (a) CH₂=CHMgBr (1.0 M in THF, 0.9 equiv.), toluene, –78 °C, 35%, dr > 25 : 1. (b) Dibal-H (1.1 equiv.), toluene, –78 °C to 0 °C, 43%, dr 8 : 1. (c) MgBr₂·OEt₂ (2.0 equiv.), 2,6-lutidine (4 equiv.), 25 °C, CH₂Cl₂, 42%, dr > 25 : 1.

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† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for compounds **7–25**. See DOI: 10.1039/b803898h

Table 1 Tandem oxy-Cope–Claisen–ene–HDDA reaction^a

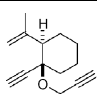

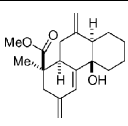

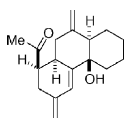

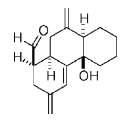
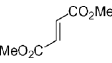
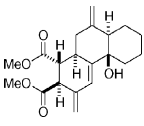
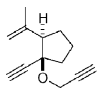

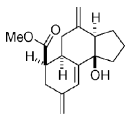

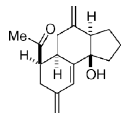
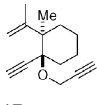

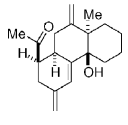

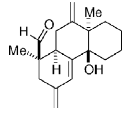
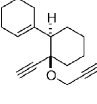

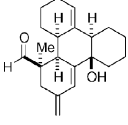

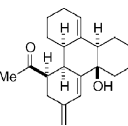
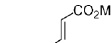
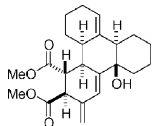
Entry	Substrate	Dienophile	Product ^b	Yield (%) ^c
1				41
			10	
2				49
			11	
3				39 ^d
			12	
4				40
			13	
5				47
			15	
6				40
			16	
7				48
			18	
8				44
			19	
9				44
			21	
10				40
			22	

Table 1 (continued)

Entry	Substrate	Dienophile	Product ^b	Yield (%) ^c
11				36
			23	

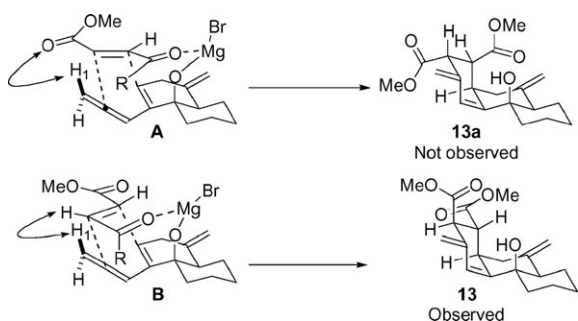
^a 207 °C, 1 h, PhMe and method c. ^b The relative stereochemistry was established without ambiguity by 2-D NMR experiments (COSY, NOESY, HMQC, HMBC). ^c In all cases, dr > 25 : 1 based on ¹H NMR spectroscopy of the crude reaction mixture. ^d dr = 8.4 : 1.

tether. However, some problems arose with the use of organomagnesium reagents to generate the corresponding magnesium vinylallene alkoxide. We found that the reproducibility of this transformation is highly dependent on the quality of the Grignard reagent.⁹

Replacement of the vinylmagnesium bromide by Dibal-H (1.1 equiv.) proved to be a good alternative in terms of yield (43%) and reproducibility. However, we noticed a significant loss in the diastereoselectivity from greater than 25 : 1 to 8 : 1 at C1 (method b). Various temperatures, irradiation times, additives and solvents were scanned. After a thorough optimization of the reaction conditions, we found that heating **7** at 207 °C¹⁰ (microwaves) in degassed toluene in the presence of triethylamine (10 equiv.) for 1 h followed by the addition of MgBr₂·OEt₂ (2 equiv.), 2,6-lutidine (4 equiv.) and methyl acrylate (4 equiv.) in dichloromethane at 25 °C (method c) gave the desired product in reproducible yields (42%) and high diastereoselectivity.¹¹

With this result in hand, the scope of this sequential reaction was next examined (Table 1). Cycloaddition using mono and α,α' -disubstituted dienophiles such as methyl methacrylate and MVK gave the tricycles **10** and **11** in 41 and 49% yield, respectively as the sole isomer (entries 1 and 2). The use of acrolein as the dienophile also led to the desired cycloadduct **12** in 39% yield, although, in moderate diastereoselectivity (dr 8.4 : 1) (entry 3). This is the result of a slow epimerization at C1 under the reaction conditions.¹² Surprisingly, tricycle **13** was obtained upon addition of dimethyl fumarate (entry 4). 2-D NMR studies revealed that the ester group at C1 is oriented *anti* to the hydroxy group at C9.¹³ This can be explained by the proposed mechanism depicted in Scheme 3. An examination of the transition state **A** reveals the presence of steric interactions between the ester group of the dienophile and H1 of the vinylallene moiety. However, in transition state **B**, H1 interacts with a hydrogen thus favouring the formation of **13** over **13a**.

This microwave-assisted process was extended to other propargyl ethers. Five-membered ring propargyl ether **14** was converted to the desired tricycles **15** and **16** in 47 and 40% yield, respectively (entries 5 and 6). Entries 7 and 8 reveal that propargyl ethers having an angular methyl at C5 such as **17** can be stereoselectively transformed into the tricyclic scaffolds **18** and **19** (48–44% yield, dr > 25 : 1). Combination of **20**



Scheme 3 Transition states for the HDDA.

with methacrolein and MVK afforded tetracycles **21** and **22** in 44 and 40% yield (entries 9–10). Finally, tandem oxy-Cope–Claisen–ene–HDDA reaction of **20** with dimethyl fumarate furnished **23** in 36% yield.¹⁴ Notably, this core possesses six stereogenic carbon centers where four are contiguous. Other activated dienophiles such as benzoquinone, DIAD and maleic anhydride were tried without any success. In all cases, only vinylallene **8** was recovered along with some degradation products.¹⁵

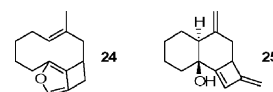
In summary, we have developed a novel stereoselective method for the construction of fused carbocyclic frameworks. The oxy-Cope–Claisen–ene–HDDA reaction sequence has proven to be a powerful synthetic process to elaborate molecular complexity. The reaction can be performed in one pot in toluene using a vinylmagnesium bromide. However, it was found that a two-pot operation employing a $\text{MgBr}_2 \cdot \text{OEt}_2$ –2,6-lutidine combination in CH_2Cl_2 gave better overall yields. Further studies to extend the scope of this reaction and its application to the total synthesis of complex diterpenes are underway and will be reported in due course.

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- The propargyl ethers **7**, **14** and **17** were easily prepared in four steps from commercially available cycloalkene oxide and **20** was obtained in two steps from the corresponding 2-(cyclohexenyl)-cyclohexanone. See the ESI† for procedures.
- Several organomagnesium reagents were tried and we found freshly made solutions of vinylmagnesium bromide in THF gave the best results.
- We found that prolonged exposure to high temperatures (165–220 °C) is detrimental to the reaction.
- For the formation of magnesium alkoxide using $\text{MgBr}_2 \cdot \text{OEt}_2$ and triethylamine, see: E. Vedejs and O. Daugulis, *J. Org. Chem.*, 1996, **61**, 5702.
- Prolonged exposure to the reaction conditions (48 h) led to complete epimerization at C1 (dr 1 : 2.4).
- The relative stereochemistry of **13** was unambiguously established by NOESY correlation on the corresponding triol.
- To our surprise, side products **24** and **25** were obtained in 27 and 4% yields, respectively (entries 1–4). A mechanism to account for these side products is depicted in the ESI.† By contrast, we were unable to characterize or isolate any similar side products from the crude reaction mixtures for entries 5–11.



- It was found that vinylallene **8** is unstable on silica gel even doped with 5% NEt_3 . IR (neat, cm^{-1}) 3441(br), 2932(s), 2855(m), 1954(w), 1713(w), 1687(w), 1447(m); ^1H NMR (CDCl_3) δ 5.80–5.75 (m, 2H), 4.93 (s, 1H), 4.90 (s, 1H), 4.88 (s, 1H), 4.74 (d, J 1.2 Hz, 1H), 2.94 (d, J_{AB} 19.2 Hz), 2.77 (dd, J_{AB} 19.2, J_{AX} 5.0 Hz), 2.23–2.19 (m, 2H), 1.82–1.22 (m, 8H); ^{13}C NMR δ 209.8, 146.2 (C), 137.9 (C), 126.7 (CH), 108.8 (CH₂), 90.3 (CH), 77.0 (CH₂), 72.3 (C), 49.1 (CH), 36.6, 35.0, 26.0, 23.6, 21.5 (CH₂); HRMS (EI) m/z calc. for $\text{C}_{14}\text{H}_{18}\text{O}$ (M^+) 202.1358, found 202.1359