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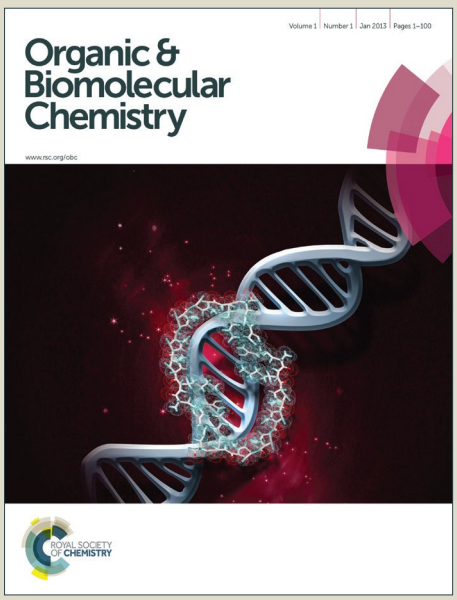

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ARTICLE

Acid-catalysed intramolecular addition of β-ketoesters to 1,3-dienes

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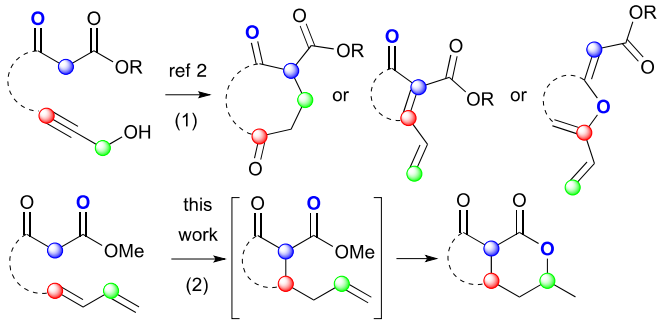
1,3-Dienyl β-keto esters are cyclised into bicyclolactones using the $Bi(OTf)_3$/TfOH catalytic system. This reaction represents a rare case of simultaneous C-C and C-O bond formation at positions 1 and 3 of a 1,3-diene. Application to the synthesis of ramulosin is presented.

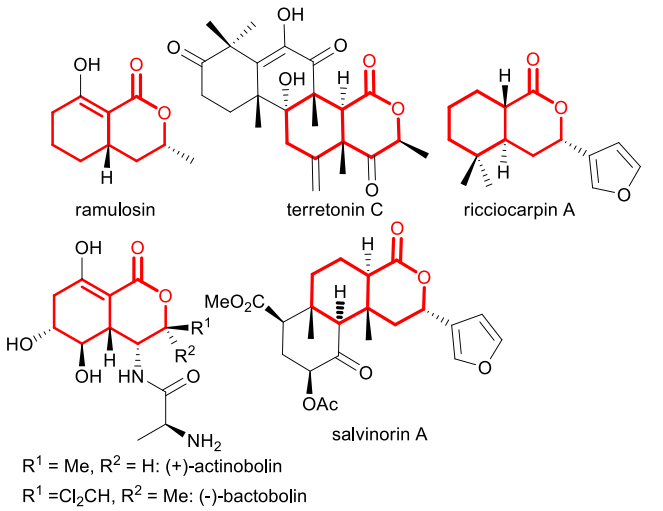
Introduction

Controlling the reactivity of ambident nucleophiles with ambident electrophiles remains a great challenge in organic synthesis.[1] We have recently shown that the sequential calcium-catalysed/organocatalysed condensation of propargyl alcohols tethered to β-keto esters could lead to valuable cyclic compounds by selecting the nucleophilic site, i.e. a carbon or an oxygen of the β-keto ester, and the electrophilic site, i.e. an alkyne or the hydroxylated carbon of the propargyl alcohol moiety (Scheme 1, eq (1)).[2] Here, we describe a rare type of 1,3-addition to 1,3-dienes resulting from the hydroalkylation/hydroalkoxylation tandem reaction of 1,3-dienyl β-keto esters (Scheme 1, eq (2)).[3]



Scheme 1. Condensation of β-keto esters to propargyl alcohols (eq (1)) and to 1,3-dienes (eq (2)).

The two-step addition of carboxylic acids to conjugated dienes to give lactones has been previously described under harsh and not catalytic reaction conditions, using sodium and then excess H_2SO_4 in refluxing benzene.[4] In our case, the β-keto ester moiety acts as a dinucleophile through the methylene carbon and one oxygen, and the 1,3-diene as a dielectrophile, giving rise to synthetically useful bicyclolactones of type hexahydro-1*H*-isochromene-1,8(8a*H*)-dione. This diketo framework or the corresponding keto-enol form, as well as closely related ones such as the octahydro-1*H*-isochromen-1-one motif can be found in a variety of natural products including ramulosin,[5a] terretonin C,[5b] ricciocarpin A,[5c] actinobolin,[5d] bactobolin[5e] and salvinorin,[5f] which exhibit a broad spectrum of antibiotic and neurobiological activities (Scheme 2).



Scheme 2. Natural compounds containing the octahydro-1*H*-isochromen-1-one framework.

Results and discussion

Our model compound to develop the proposed condensation was the oxo-dienoate **3** (Scheme 3). It was readily obtained from commercially available (2*E*,4*E*)-hexa-2,4-dien-1-ol, converted into the corresponding bromide **1** with PBr_3, and methyl 4-methyl-3-oxopentanoate **2**.

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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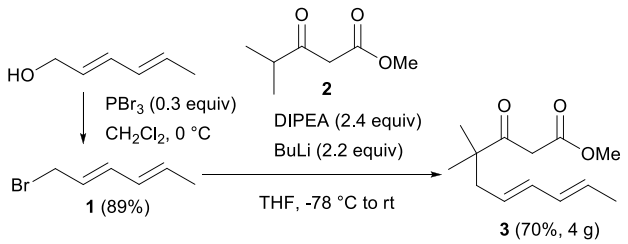
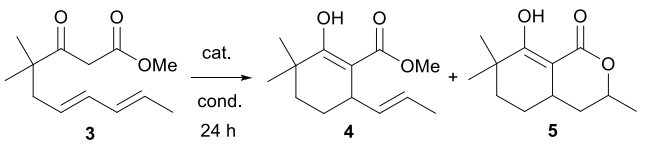


Scheme 3. Typical synthesis of a 1,3-dienyl β-keto ester.

Various catalytic conditions were screened (Table 1). Following our study on the hydroalkylation of unactivated alkenes with β-keto amides,[6] the (JohnPhos)AuCl/Cu(OTf)$_2$ catalytic system[7] was first tested in toluene at 110 °C (entry 1). Product **4**, arising from the hydroalkylation of the internal diene double bond by the β-keto ester, was accompanied by the desired lactonisation product **5**, yet as minor component of the mixture (80/20).

Table 1. Optimisation studies for the intramolecular tandem hydroalkylation/hydroalkoxylation of the 1,3 dienyl β-keto ester **3**.[a]



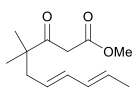
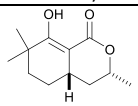
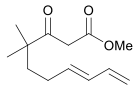
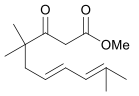
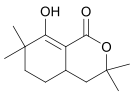
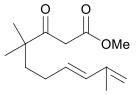
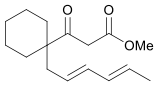
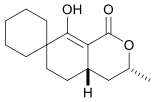
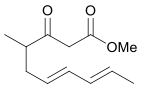
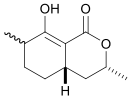
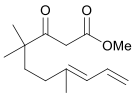
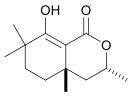
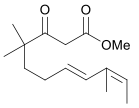
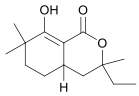
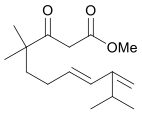
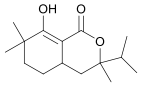
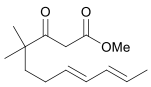
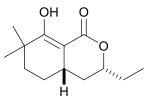
Entry	Cat.	Solvent	T °C	**4**/**5**[b]	% Yield
1	Au/Cu[c]	tol[f]	110	80/20	
2	Au/Cu[c]	wet tol[g]	110	47/53	
3	Au/Cu[c]	wet DCE[h]	80	83/17	
4	Ca(NTf$_2$)$_2$/*n*Bu$_4$PF$_6$[d]	wet tol[g]	110	100/0	
5	Cu(OTf)$_2$	wet tol[g]	110	41/59	
6	AgOTf	wet tol[g]	110	66/34	
7	Al(OTf)$_3$	wet tol[g]	110	88/12	
8	Ga(OTf)$_3$	wet tol[g]	110	78/22	
9	In(OTf)$_3$	wet tol[g]	110	86/14	
10	Bi(OTf)$_3$	wet tol[g]	110	29/71	
11	Bi(OTf)$_3$	wet tol[g]	80	100/0	80
12	TfOH	wet tol[g]	110	0/100	65
13	Tf$_2$NH	wet tol[g]	110	100/0	99
14	**Bi(OTf)$_3$/TfOH**[e]	**wet tol**[g]	**110**	**0/100**	**76**
15	Bi(OTf)$_3$/Tf$_2$NH[e]	wet tol[g]	110	86/14	
16	Bi(OTf)$_3$/PTSA[e]	wet tol[g]	110	82/18	
17	Bi(OTf)$_3$/MsOH[e]	wet tol[g]	110	40/60	

[a] Reactions were run in the presence of 5 mol% catalyst at c = 0.15 M, unless stated otherwise. [b] Ratio determined by ^{1}H NMR. [c] (JohnPhos)AuCl (5 mol%), Cu(OTf)$_2$ (10 mol%). [d] Ca(NTf$_2$)$_2$ (5 mol%), *n*Bu$_4$PF$_6$ (7 mol%). [e] 5 mol% each. Karl Fischer titrations (highest of 3 measurements), water content: [f] < 5 ppm, [g] < 290 ppm, [h] < 1780 ppm.

Since the formation of **5** likely involves the loss of methanol, we reasoned that the presence of exogenous water would favour it.[8] Adding controlled amounts of water directly in toluene (1, 10 and 100 equiv) increased indeed the proportion of **5** but it went along with extensive decomposition. To avoid the presence of droplets of water, toluene was humidified in a separatory funnel by vigorous shaking with water, decanted, collected, and used as such. This technique gave a water content up to 290 ppm against 5 ppm for distilled toluene (Karl Fischer titration). With this wet toluene, the ratio was still in favour of **5** (47/53) and no decomposition occurred (entry 2). In wet 1,2-dichloroethane (DCE, up to 1780 ppm of water), the proportion of **5** dropped to 17% (entry 3). The Niggemann catalytic system Ca(NTf$_2$)$_2$/*n*Bu$_4$PF$_6$,[9] which we had used previously as in Scheme 1, eq (1)[2] or in other transformations,[10] did not lead to **5** (entry 4). A series of metal triflates was next tested in wet toluene (entries 5-10). Among them, Bi(OTf)$_3$ gave the best ratio for **5** (entry 10, 29/71). The superiority of Bi(OTf)$_3$ over other metal triflates for the activation of polyenes[11] especially 1,3-dienes has also been observed in dihydroarylation reactions.[12] Lowering the temperature to 80 °C resulted in the exclusive formation of **5** in 80% yield (entry 11). Dealkylating lactonisations with an excess of TfOH have been reported.[13] In the present case, the use of only 5 mol% TfOH in wet toluene at 110 °C furnished **5** as a sole product in 65% yield (entry 12). On the other hand, **4** was obtained selectively with Tf$_2$NH in 99% yield (entry 13). The yield of **5** could be appreciably increased to 76% by using a catalytic mixture of Bi(OTf)$_3$ and TfOH (entry 14). With other Brønsted acids, the level of selectivity was lower (entries 15-18). Lastly, it should be mentioned that the reaction does not work with the 1,3-dienyl β-keto acid corresponding to **3**, nor the corresponding benzyl amide.

On the basis of this optimisation study, the Bi(OTf)$_3$/TfOH catalytic system was selected and the reaction of **3** was monitored by GC. It revealed that full conversion of **3** into **4** was achieved within 15 min. After 3 h, the **4**/**5** ratio became 30/70, and after 8 h, only **5** was detected as an 86/14 mixture of stereoisomers (Table 2, entry 1). The structure of the major diastereomer of **5** could be unambiguously established by 2D NOE NMR experiments and also by an X-ray diffraction study (Figure 1).‡ Substrate **6** was then tested (entry 2). It differs from **3** regarding the position of the diene fragment, which is internal in **3** and terminal in **6**. However, the same product **5** was obtained, albeit in lower yield.§ Similarly, the intramolecular tandem hydroalkylation/hydroalkoxylation of the constitutional isomers **7** and **9** gave the same product **8** in 58% and 79% yield respectively at 80 °C (entries 3 and 4). Changing the *gem*-dimethyl carbon tether by a cyclohexyl as in **10** resulted in the formation of **11**, isolated in 53% yield as a single diastereomer (entry 5). When only one methyl is present in the carbon tether, as in **12**, the conversion into **13** is moderate (entry 6). This is likely to be due to the absence of *gem*-dialkyl (or Thorpe-Ingold) effect. The major diastereomers remain *trans* as noted. Complete diastereoselectivity was observed from substrate **14** (entry 7). On the other hand, but not surprisingly, no diastereoselection occurred between alkyl groups in **17** and **19**, which were obtained in 71% and 42% yield respectively in a 1/1 ratio (entries 8-9). Nevertheless, these examples show that the title reaction is able to generate quaternary centers from 1,3-dienes. The structure of one of the diastereomer of **17** was ascertained by X-ray analysis (Figure 1).‡ Lastly, with compound **20**, which is a homolog of **5** and **8**, the expected product **21** was obtained in 52% yield with a good diastereoselectivity (entry 10).

Table 2. Scope studies of $Bi(OTf)_3$/TfOH-catalysed intramolecular addition of β-keto esters to 1,3-dienes.[a]

Entry	Substrate	Product (major isomer)	T °C	Time (h)	% Yield (d.r.)[b]
1	 **3**	 **5**	110	8	76 (86/14)
2	 **6**	**5**	110	8	54 (82/18)
3	 **7**	 **8**	80	9	58 (-)
4	 **9**	**8**	80	5	84 (-)
5	 **10**	 **11**	110	12	53 (100/0)
6	 **12**	 **13**	110	24	31 (80/20)
7	 **14**	 **15**	80	24	67 (100/0)
8	 **16**	 **17**	80	4	71 (50/50)
9	 **18**	 **19**	50	5	42 (50/50)
10	 **20**	 **21**	110	24	52 (90/10)

[a] See Supporting Information for details on substrate synthesis. Reactions were run in the presence of 5 mol% $Bi(OTf)_3$ and 5 mol% TfOH in wet toluene (0.15 M) at 110 °C, see note §§. [b] Diastereomeric ratio determined by ^1H NMR; structure of the major isomer obtained by X-ray crystallography for **5**, **17**, and by NOESY experiments for the others.

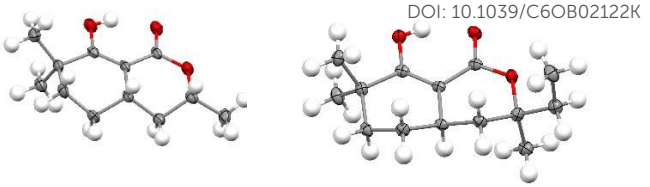
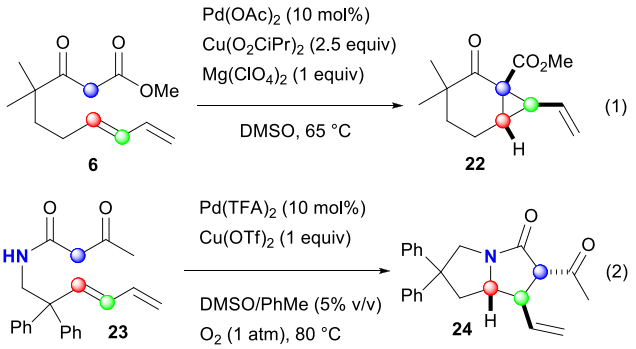


Figure 1. Crystal structures of the major diastereomer of **5** (left) and of one diastereomer of **17** (right) (thermal ellipsoids at 50% probability level).

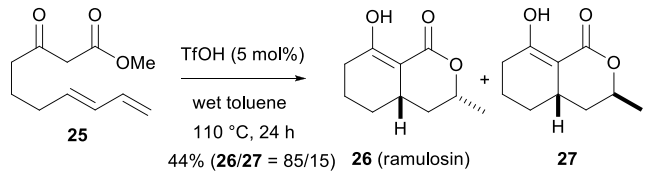
Of note, the analog of **20** with a phenyl group instead of a methyl group at the terminal diene position decomposed under reaction conditions. Degradation of the substrate was also observed with a methyl group at the activated methylene fragment of the β-keto ester framework.

Interestingly, compounds **6**, **9**, **14** and 4 others have been used as substrates for oxidative $Pd(OAc)_2$-catalysed intramolecular cyclopropanation (Scheme 4, eq (1)).[14] Under similar conditions, 1,2-aminoalkylation of 1,3-dienes such as **23** have been described (eq (2)).[15] In the two cases, the coordination of Pd to the internal diene double bond triggers first a nucleophilic attack (of the activated methylene in eq (1) and of the amino group in eq (2)) which results in the formation of a π-allyl palladium species. Then, it undergoes a second nucleophilic attack, by the same nucleophile in the first example and by the activated methylene group in the second one.



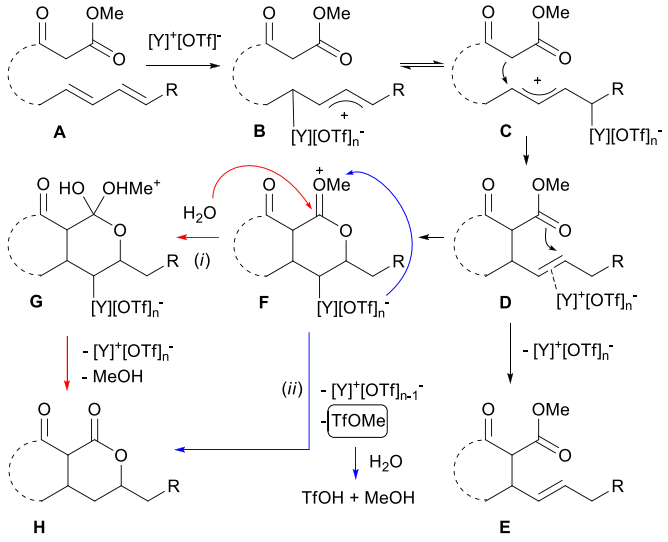
Scheme 4. Pd-catalysed cyclopropanation of 1,3-dienyl β-keto esters (eq (1), ref 12) and 1,2-aminoalkylation of 1,3-dienes (eq (2), ref 13).

Our method, which transforms the two double bonds of the dienes, is thus complementary to these two reactions and further expands the scope of 1,3-dienyl β-keto esters. To show its utility, the title reaction was applied to the synthesis of a natural product: ramulosin, which is a metabolite from an endophytic fungus (Scheme 5).[16] Because substrate **25** does not benefit from a *gem*-dialkyl effect to assist its cyclisation, side reactions took place leading to extensive decomposition with the $Bi(OTf)_3$/TfOH catalytic system. Nevertheless, using TfOH as catalyst, the **26**/**27** diastereomeric mixture was isolated in a reasonable 44% yield. The major isomer proved to be ramulosin as desired.



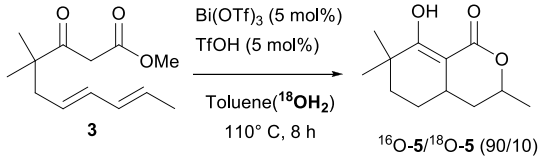
Scheme 5. Synthesis of ramulosin.

A mechanistic scenario for the title reaction shown in Scheme 6. From **A**, we postulate the formation of the regioisomeric allyl cations **B** or **C** by addition of Bi^{3+} or H^+ to the diene fragment.[17] If R = H, **C**, which is the most highly substituted regioisomer, is expected to prevail. This would explain why compounds **3**/**6** and **7**/**9** transform into the same products. Attack of the activated methylene fragment would then lead to **D** and possibly **E** after regeneration of the catalyst. Alternatively, the ester functionality may attack the complexed alkene to furnish the oxonium **F**. Two pathways may account for its dealkylation into **H** and rationalize the role of water at the same time: (*i*) the attack of water giving **G** and then **H** after loss of MeOH and regeneration of the catalyst (red pathway) or (*ii*) dealkylation by a triflate ion to give **G** and TfOMe (blue pathway). The reaction of TfOMe with water would give MeOH and regenerate TfOH, as proposed by Muñoz and Lloyd-Jones.[13]



Scheme 6. Mechanistic proposal ($[Y]^+ = Bi^{3+}$ or H^+).

To distinguish between the two pathways, the reaction of **3** was carried out in toluene humidified with $^{18}OH_2$ (Scheme 7). It allowed us to detect the presence of ^{18}O-**5** by mass spectrometry, yet the incorporation was very as low as 10%. Thus, pathway (*ii*) seems more likely.



Scheme 7. Cyclization of **3** carried out in toluene humidified with $^{18}OH_2$.

Conclusions

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We have developed a new transformation of 1,3-dienyl β-keto esters which exploits two nucleophilic sites of the β-keto ester fragment (C and O) and two not contiguous nucleophilic sites of the diene moiety. The result is a rare type of simultaneous C-C and C-O bond formation at positions 1 and 3 of 1,3-dienes leading to an interesting scaffold that can be found in natural products such as ramulosin and its derivatives. Efforts directed towards the enantioselective version of this reaction are underway.

Experimental

Procedures for intramolecular tandem hydroalkylation /hydroalkoxylation of the 1,3-dienyl β-keto esters: In air, a 10 mL tube equipped with a Teflon-coated magnetic stir bar was charged with $Bi(OTf)_3$ (0.05 equiv), TfOH (0.05 equiv) and wet toluene (c = 0.15 M, see note §§). The substrate (0.2 mmol, 1 equiv) was added and the tube was sealed with a plastic stopper. The tube was immersed and stirred in a preheated oil bath at 110 °C for 24 h. Then, the reaction mixture was cooled to room temperature and quenched with satd aq $NaHCO_3$ (5 mL). The organic layer was extracted with Et_2O, washed with brine, dried over $MgSO_4$, filtered through a short pad of Celite, rinsed with Et_2O and evaporated to afford the crude product. Purification by flash chromatography (cyclohexane/AcOEt, 90/10) afforded the desired product.

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Notes and references

‡ CDC 1001233 and 1497250 contains the supplementary crystallographic data for this paper.
§ With $Bi(OTf)_3$ alone, a 44/65 mixture of **4** and **5** was obtained. With TfOH alone, a 14/86 mixture of **4** and **5** was obtained.
§§ Preparation of wet solvents: Wet DCE or toluene were prepared by vigorous shaking of bulk DCE or toluene with distilled water in a separatory funnel. The wet solvents were collected and used as such.

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