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Vinylogous Reactivity of Cyclic 2-Enones: Organocatalysed Asymmetric Addition to 2-Enals to Synthesize Fused Carbocycles

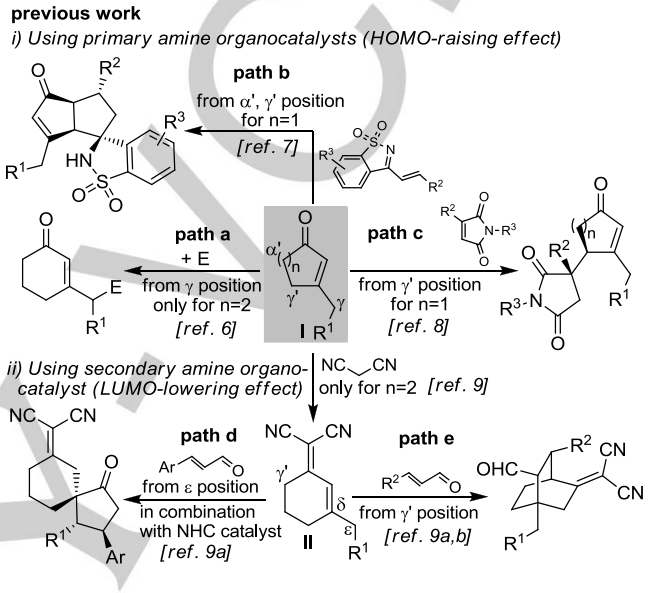
Manolis Sofiadis, Dimitris Kalaitzakis, John Sarris, Tamsyn Montagnon and Georgios Vassilikogiannakis*

Dedication

Abstract: Asymmetric and site selective annulations from the γ and γ' positions of cyclic 2-enones with α,β-unsaturated aldehydes have been developed. The organocatalysed [3+3]-annulations proceeded with high levels of regio- diastereo- and enantioselectivity affording a series of high value fused carbocycles. Further elaboration gave key lactones (both bridged and fused).

Currently, there is a strong drive to find new ways to achieve rapid enhancement in molecular complexity in order to maximize synthetic efficiency and minimize waste. In this context, one-pot cascade reaction sequences have proven to be a potent tool because they form multiple covalent bonds in a single synthetic operation.[1] Furthermore, when these sequences are designed to include asymmetric organocatalysis,[2] stereochemically dense, as well as, skeletally complex molecules can be accessed very rapidly from simple precursors in a highly controlled manner.[3] In this work, we sought to develop novel enantioselective one-pot reaction sequences using a double vinylogous addition reaction.[4] We were drawn to this particular reaction type due to its inherent advantages and the power it has to form key bonds, as exemplified by the major contributions it has already made in the synthesis of complex targets.[4]

Cyclic 2-enones (**I**, Scheme 1) are valuable starting materials for generating complexity due to the multiplicity and differential reactivity of their reaction sites. In order to access potential nucleophilicity, an amine organocatalyst has been harnessed; for example, dienamine organocatalysis may activate the α',[5] γ and γ' positions of **I** (Scheme 1). Only very recently, this HOMO-activation approach has been exploited in vinylogous addition reactions; thus, addressing the principal challenges associated with the regio- and stereo-selective functionalization of 5- and 6-membered cyclic 2-enones.[6-8] In particular, the asymmetric reaction of the γ carbon of 2-cyclohexenones with various electrophiles, in the presence of cinchona alkaloid-based primary amine derivatives, was reported by Melchiorre and Bencivenni (Scheme 1, path a).[6] A dual dienamine activation mode was exploited by Chen and Gao in which cyclic 2-enones produced annulated products by reaction from the α' and γ' positions (Scheme 1, path b).[7] Later, using different primary amine catalysts, Ye demonstrated the regioselective functionalization of 2-cyclopentenones from the



Scheme 1. Organocatalytic functionalizations of cyclic 2-enones.

vinylogous γ' position (Scheme 1, path c).[8] Interestingly, no studies have been conducted which look at selectively functionalising cyclic 2-enones at both the γ and γ' positions in order to synthesize fused carbocycles; a deficit we now address albeit through a new reaction mode (*vide infra*).

Firstly, we devised a new plan that involved a switch in strategy towards relying on a LUMO-lowering effect for the direct γ and γ' functionalization of cyclic enones. In order to apply such an effect, however, it was calculated that two major criteria must be met; namely, the use of a LUMO-lowered electrophile in conjunction with an easily enolizable cyclic enone (we proposed adding an ester handle). Of relevance to the discussion here, is the reactivity of malononitrile derivatives of type **II** with α,β-unsaturated aldehydes (Scheme 1, path d and e) which was described by Zanardi and Chen.[9] In this case, the activation of **I** by derivatization (Scheme 1, **I**→**II**)[10] was essential in order to increase the acidity of the ε and γ' protons, and, thus, facilitate certain annulation reactions (path d, e). This chemistry was restricted to cyclohexyl starting materials.[9]

Herein, we describe how we have implemented the conceptual design described above and in so-doing have developed a novel double vinylogous reactivity for cyclic 2-enones with LUMO-lowered 2-enals under mild conditions. In detail, we envisioned that the presence of an ester group at the α-position of the cyclic 2-enones **1** or **2** (Scheme 2) might facilitate their nucleophilic addition to 2-enals of type **3**. Moreover, in the readily accessible keto esters **1** and **2**, both the γ and γ' positions would be activated meaning that they

[*] M. Sofiadis, Dr. D. Kalaitzakis, J. Sarris, Dr. T. Montagnon, Prof. Dr. G. Vassilikogiannakis
Department of Chemistry, University of Crete
Vasilika Vouton, 71003, Iraklion, Crete, Greece
E-mail: vasil@uoc.gr
ID: Georgios Vassilikogiannakis: 0000-0002-9099-383X

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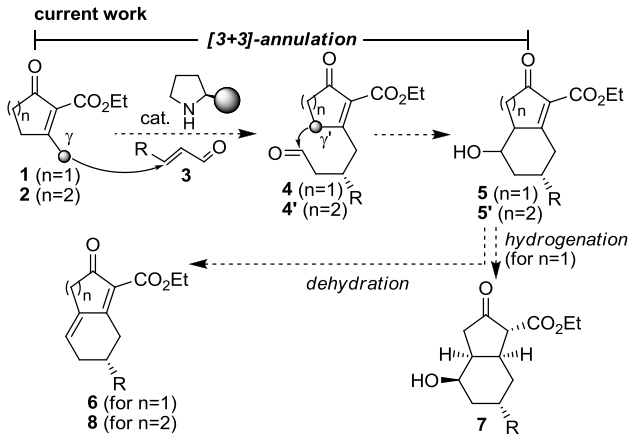
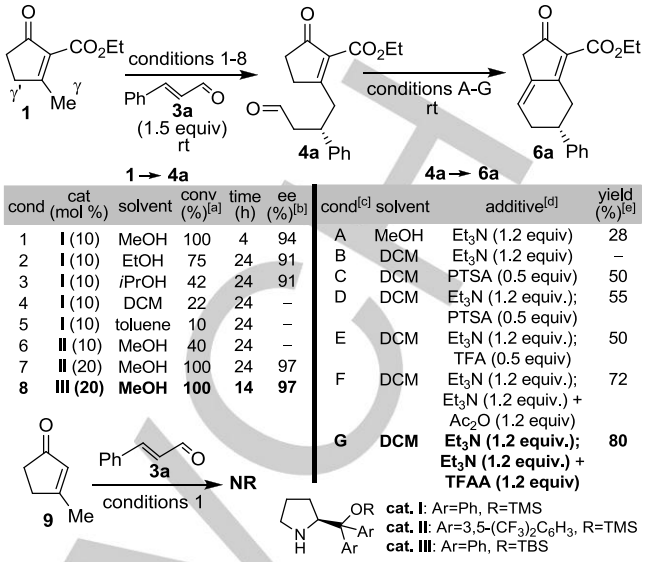


Scheme 2. Envisioned [3+3]-annulation of cyclic 2-enones with α,β-unsaturated aldehydes using a LUMO-lowering strategy.

would constitute excellent substrates for the formation of [3+3]-annulated products with dielectrophilic enals **3**. The successful implementation of this methodology constitutes the first example of an organocatalysed functionalization of cyclic 2-enones at the γ and γ' positions, leading to the high value bicyclo[4,3,0]nonane and bicyclo[4,4,0]decane frameworks (**6**–**8**, Scheme 2) that are present in numerous natural products.[11]

The investigations began with the keto ester **1**[12] which was coupled with cinnamaldehyde **3a** in the presence of a secondary amine organocatalyst (cat. **I**–**III**). Proof of principle for the first step was obtained using cat **I** (10 mol%) and **3a** (1.5 equiv) in MeOH at room temperature. This reaction afforded **4a** with high enantioselectivity (conv. 100%, 94% ee, cond. 1, Scheme 3). Key to this success was the excellent regioselectivity with the enone reacting exclusively at the γ-position. The increased acidity of the γ protons in substrate **1** seems to be essential, since the application of exactly the same conditions to 2-cyclopentenone **9** (Scheme 3) did not promote an analogous reaction. Furthermore, the advantage of using a protic solvent (cond. 1–3, MeOH being the best), was confirmed by the slow reaction in either DCM or toluene (cond. 4, 5). This observation is consistent with a recently published report; in which, evidence was presented that the reaction between acidic carbon nucleophiles and LUMO-lowered 2-enals is accelerated in protic solvents.[13] With regard to the ee levels, cat **II** and **III** proved to be more selective than cat **I** (cond. 7 & 8). Cat **III** was deemed to be the optimal choice due to its enhanced reactivity compared to cat **II** (cond. 8 vs cond. 7), probably a result of its more basic nature.[13]

Now that optimized conditions for the first step (**1**→**4a**) had been established, we could continue with an investigation of the cyclization/dehydration step (**4a** → **6a**). Experiments were performed without isolating **4a** (generated from **1** using cond. 8). We found that the addition of Et_3N (1.2 equiv) to a solution of **4a** in MeOH, promoted the nucleophilic addition of the γ' carbon to the aldehyde group (**4a**→**5a**) followed by dehydration (**5a**→**6a**), ultimately, furnishing **6a**, albeit in a rather low isolated yield (28%, cond. A, Scheme 3). Attempting the same reaction, but this time in DCM (cond. B), led to the formation of the compound **5a**, exclusively. The results improved when either PTSA or TFA



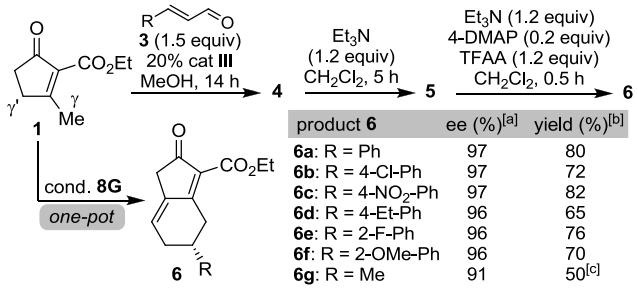
cond	cat (mol %)	solvent	conv (%)[a]	time (h)	ee (%)[b]
1	**I** (10)	MeOH	100	4	94
2	**I** (10)	EtOH	75	24	91
3	**I** (10)	*i*PrOH	42	24	91
4	**I** (10)	DCM	22	24	–
5	**I** (10)	toluene	10	24	–
6	**II** (10)	MeOH	40	24	–
7	**II** (20)	MeOH	100	24	97
8	**III (20)**	**MeOH**	**100**	**14**	**97**

cond[c]	solvent	additive[d]	yield (%)[e]
A	MeOH	Et_3N (1.2 equiv)	28
B	DCM	Et_3N (1.2 equiv)	–
C	DCM	PTSA (0.5 equiv)	50
D	DCM	Et_3N (1.2 equiv.); PTSA (0.5 equiv)	55
E	DCM	Et_3N (1.2 equiv.); TFA (0.5 equiv)	50
F	DCM	Et_3N (1.2 equiv.); Et_3N (1.2 equiv.) + Ac_2O (1.2 equiv)	72
G	**DCM**	**Et_3N (1.2 equiv.); Et_3N (1.2 equiv.) + TFAA (1.2 equiv)**	**80**

Scheme 3. Optimization of the conditions for the synthesis of **6a** from **1.** [a] Determined by ^{1}H-NMR. [b] Determined by chiral HPLC analysis of the final product **6a**. [c] These conditions were applied after cond. 8. [d] When Et_3N, or the acids (PTSA or TFA) were used, the reaction time was 5 h. In the case of the anhydrides (Ac_2O or TFAA), the reaction time was 0.5 h and 4-DMAP (0.2 equiv) was added (see the SI for experimental details). [e] Isolated yields.

were included in the reaction conditions (50–55% yield, cond. C–E). Following these observations, we reasoned that a Et_3N-anhydride combination might prove to be ideal. Thus, a breakthrough was achieved when Et_3N and either acetic anhydride (Ac_2O) or trifluoroacetic anhydride (TFAA) were employed. Full details of this protocol, which furnished **6a** in a very good isolated yield considering the number of steps involved (72% cond. F, 80% cond. G) and with high optical purity (97% ee), are presented in the accompanying SI. The combined optimum conditions for the single-pot synthesis of **6a** from **1**, were, therefore, found to be 8G.

To explore the scope of the reaction, various α,β-unsaturated aldehydes of type **3** were tested with 2-cyclopentenone **1**, under the optimal conditions 8G (Scheme 4). Harnessing aryl-substituted enals (**3a**–**f**), the reaction successfully delivered the desired products **6a**–**f**, regardless of the nature of the aryl-substituent. All the reactions exhibited excellent regioselectivity proceeding exclusively via the intermediate of type **4**. Moreover, all the reactions were performed as single synthetic operations furnishing compounds of type **6** with high ee values (96–97%) and in good isolated yields (65–82%). In contrast, however, conditions 8G were not effective for the alkyl-substituted enal **3g**. Under conditions 8 (Scheme 3), the vinylogous Michael-addition of substrate **1** to **3g** was slow (conv. 15%, 14 h) and not very regioselective (γ/γ' regioisomeric ratio = 5/1). Using conditions 1 (cat **I** instead of **III**) the regioisomeric ratio was the same; however, full conversion was achieved after 14 h. Gratifyingly, the regioselectivity could be enhanced (reaching 16/1) by performing this reaction (**1**→**4g**) at 0 °C for 48 h. In this case, the tandem reaction sequence (**1** → **4g** → **5g**→**6g**) afforded the desired compound **6g** in an isolated yield of 50% and with ee = 91% (Scheme 4).

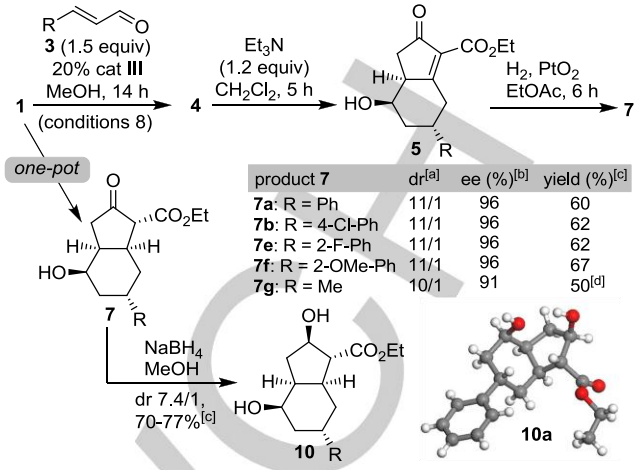


product **6**	ee (%)[a]	yield (%)[b]
6a: R = Ph	97	80
6b: R = 4-Cl-Ph	97	72
6c: R = 4-NO_2-Ph	97	82
6d: R = 4-Et-Ph	96	65
6e: R = 2-F-Ph	96	76
6f: R = 2-OMe-Ph	96	70
6g: R = Me	91	50[c]

Scheme 4. Asymmetric synthesis of carbocycles of type **6**. [a] Determined by chiral HPLC analysis. [b] Isolated yields. [c] The reaction towards **4g** was performed using 15 mol% of cat **I** at 0 °C and 2 equiv of **3g**, for 48 h.

An interesting observation emerged during the optimization of the transformation of **4a** to **5a** (Scheme 3). Specifically, 5 h after the addition of Et_3N (0.5 equiv) to a solution of **4a** in DCM, the reaction yielded four diastereoisomers of compound **5a** (dr=1/1.3/1.4/3.5). This ratio changed significantly (to a dr for **5a** of 11/1) if **4a** was subjected to Et_3N (1.2 equiv) for 5 h (cond. B). This latter result must arise from two different factors which lead to the domination of the most favourable isomer; namely, it is a consequence of a reversible intramolecular aldol, as well as, of the epimerizability of γ'-position in **5** (Scheme 5). We were not able to purify **5** due to its susceptibility to dehydration during chromatography. However, it was envisaged that hydrogenation of the olefin might deliver a more stable product, and, indeed, direct hydrogenation of **5a** (H_2, PtO_2) in EtOAc, afforded the stable compound **7a** (Scheme 5), bearing five stereocenters with a high degree of diastereoselectivity (dr = 11/1, separable diastereoisomers, ee = 96% for the major isomer). The overall yield of this one-pot reaction sequence (**1**→**7a**), was 60%. A number of different enals were tested in this multi-step transformation and the results are shown in Scheme 5. All the products of type **7** were afforded with high dr (10/1–11/1). Since conditions could not be found to separate the enantiomers of **7** by chiral HPLC, the ee values were determined (91–96%) after reduction of pure compounds **7** with $NaBH_4$ (Scheme 5, dr = 7.4/1 in all cases, the major diastereoisomer of **10** was isolated in yields of 70–77%). The absolute configuration was unambiguously, confirmed via single-crystal X-ray analysis of product **10a**.[14] The overall yields for **1** → **7** (50–67%) are remarkably good when the dramatic enhancement in both the 3D-skeletal and the stereochemical complexity achieved through this tandem reaction sequence is taken into account.

With the aim of illustrating the versatility of the ester handle, the next part of the investigation looked at the reactions of compounds of type **7** with bases. Initially, the keto-esters **7** were treated with K_2CO_3 (1 equiv) in refluxing acetone. Under these conditions, the presence of the hydroxyl group on the concave face of **7** facilitated a retro-Claisen condensation,[15] affording lactones **11** in very good isolated yields and with excellent optical purity (**11a**, **11b**, **11f**, **11g**, 89–93% yield, >99% de, 91–97% ee, Scheme 6). Moreover, when **7a** was subjected to K_2CO_3, followed by EtONa in refluxing EtOH, the bridged bicyclic compound **12a** (80% yield, >99% de, Scheme 6) was obtained. This product had been derived via lactone **11a** which then underwent ethanolysis and lactone formation with the other ester

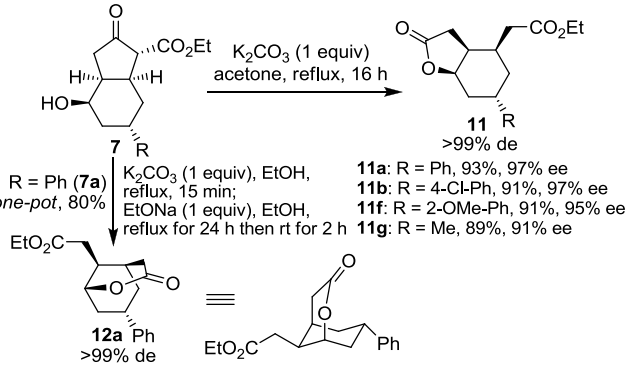


product **7**	dr[a]	ee (%)[b]	yield (%)[c]
7a: R = Ph	11/1	96	60
7b: R = 4-Cl-Ph	11/1	96	62
7e: R = 2-F-Ph	11/1	96	62
7f: R = 2-OMe-Ph	11/1	96	67
7g: R = Me	10/1	91	50[d]

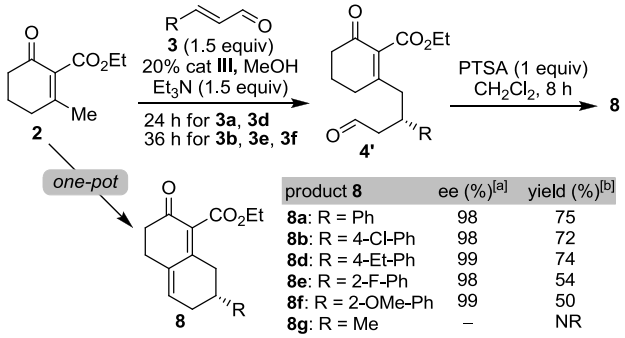
Scheme 5. Asymmetric synthesis of carbocycles of type **7**. [a] Determined by the ^{1}H NMR of crude **7**. [b] Determined by chiral HPLC analysis of compounds **10**. [c] Isolated yields for the major diastereoisomer. [d] The first reaction of the sequence was performed using 15 mol% of cat **I** at 0 °C and 2 equiv of **3g**, for 48 h.

functionality. These bicyclic lactone motifs (**11** and **12**) are found in a plethora of natural products.[16]

To further underscore the strong synthetic credentials of the current methodology, we next sought to examine the application of the protocol to 2-cyclohexenone **2**[12] (Scheme 7). Attempts to react substrate **2** with enal **3a** under conditions 8 did not succeed. Intriguingly, when Et_3N (1 equiv) was added to a solution of **2** in MeOH which contained enal **3a** (1.5 equiv) and cat **III** (20 mol%, Scheme 7), the vinylogous Michael addition occurred with excellent regioselectivity furnishing **4a'** (albeit with moderate conversion of 70% after 24 h). Upon increasing the amount of Et_3N to 1.5 equiv, the reaction proceeded to completion after 24 h. Moving forward to the cyclization-dehydration step (**4a'**→**8a**), a combination of TFAA with Et_3N in DCM proved effective for the formation of the desired carbocycle **8a** (72% yield). The isolated yield was further improved to 75% using PTSA (1 equiv). These transformations were performed without the purification of compound **4a'** and furnished the desired product **8a** with an excellent ee (98%). By employing similar conditions to the reactions of **2** with various aryl-



Scheme 6. Base-assisted controlled derivatization of compounds of type **7**.



product **8**	ee (%)[a]	yield (%)[b]
8a: R = Ph	98	75
8b: R = 4-Cl-Ph	98	72
8d: R = 4-Et-Ph	99	74
8e: R = 2-F-Ph	98	54
8f: R = 2-OMe-Ph	99	50
8g: R = Me	–	NR

Scheme 7. Asymmetric synthesis of carbocycles of type **8**. [a] Determined by chiral HPLC analysis. [b] Isolated yields.

substituted enals (**3b**, **3d–f**), the corresponding carbocyclic compounds of type **8** were all synthesized with remarkably high enantioselectivity (98–99% ee) and in good isolated yields (50-75%). For the alkyl-substituted enal **3g**, the developed conditions were ineffective.

In summary, we have introduced a straightforward synthetic methodology for the asymmetric construction of important fused carbocycles containing the privileged bicyclo[4,3,0]nonane or bicyclo[4,4,0]decane framework, as well as, for certain key fused and bridged lactones. This method oversees a dramatic increase in structural complexity both in terms of the stereocentre density and the 3D skeletal framework. The concept of an organocatalysed coupling of a LUMO-lowered dielectrophile with an easily enolizable cyclic 2-enone through two sequential vinylogous additions (first a regioselective vinylogous Michael addition from the γ position, then a vinylogous aldol from the γ' position) to afford the [3+3]-annulation product, has also been introduced for the first time. All the actions were performed with a high degree of regioselectivity and with remarkable diastereo- and enantioselectivity, in one-pot operations.

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Keywords: Vinylogous reactivity•[3+3]-annulations •organocatalysis•bicyclo[4,3,0]nonanes•bicyclo[4,4,0]decanes

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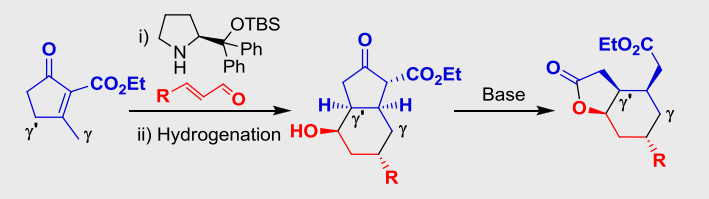

Asymmetric and site selective annulations from the γ and γ´ positions of cyclic 2-enones with α,β-unsaturated aldehydes have been developed. The organocatalysed [3+3]-annulations proceeded with high levels of regio- diastereo- and enantioselectivity affording a series of high value fused carbocycles. Further elaboration gave key lactones (both bridged and fused).

*Manolis Sofiadis, Dimitris Kalaitzakis, John Sarris, Tamsyn Montagnon and Georgios Vassilikogiannakis**

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