A Substrate-based Folding Process Incorporating Chemo-differentiating ABB' 3CRs of Terminal Alkynoates and 1,2-Dicarbonyl Compounds. A Skeletal Diversity-oriented Synthetic Manifold

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Dedicated to Mrs Pauline Agnew Devlin on the occasion of her retirement

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Abstract. A novel 3CR-based folding process able to achieve complexity generation and skeletal diversity is described. The process utilizes chemo-differentiating organocatalyzed ABB' 3CRs of a terminal conjugated alkynoate (building block) and α -dicarbonyl compounds (diversity-generating blocks) to generate an array of different molecular topologies (γ -lactones, linear propargylic enol ethers or 1,3-dioxolane rings). Amides and esters behave as efficient reactivity-encoding elements (σ) of the attached keto functionality. Three chemical properties govern the chemical outcome of this folding process: acidity, nucleophilicity (catalyst) and carbonyl electrophilicity. Overall, this substrate-based folding process generates three different molecular architectures from the same modular functionalities (ketones) and under the same reaction conditions (methyl propiolate and tertiary amine). In addition, and very importantly for the combinatorial application, all the products share a common reactive functionality to be collective substrates for a subsequent diversity-generating process.

Abstract. Se describe un nuevo proceso de plegamiento molecular basado en reacciones tricomponente ABB' capaz de generar complejidad y diversidad estructural. El proceso utiliza un sistema ABB' 3CR quicio-diferenciante compuesto por un alquino conjugado terminal (bloque para la construcción molecular) y compuestos α -dicarbonílicos (bloques para la generación de diversidad), para generar diversas topologías moleculares ((γ -lactonas, enol éteres propargílicos o anillos 1,3-dioxolánicos). Tanto amidas como ésteres se comportan como eficientes elementos codificadores de la reactividad (σ) del grupo α -cetónico. El resultado de estos procesos de plegamiento molecular está gobernado por tres propiedades químicas: acidez, nucleofilia (catalizador) y electrofilia del grupo carbonilo. En conjunto, este proceso de plegamiento molecular basado en el sustrato genera tres diferentes arquitecturas moleculares a partir de las mismas funcionalidades (cetonas) y bajo las mismas condiciones de reacción (propiolato de metilo, amina terciaria). Además, y tremendamente importante para su posible aplicación en química combinatorial, todos los productos comparten una funcionalidad reactiva común para poder ser utilizados, como un único conjunto, en una siguiente reacción generadora de complejidad.

Introduction

Multicomponent reactions (MCRs) constitute well-appreciated manifolds for diversity-oriented molecular construction. In accord with their own nature, they perform molecular construction in a modular manner, in such a way that the final product incorporates in its structure one or more units of each educt (module), in a precise and determined order. This modular property has been largely exploited in combinatorial chemistry to generate diversity-oriented libraries of small molecules to interrogate biology.^[1] Biginelli,^[2] Mannich,^[3] and Ugi^[4] reactions constitute the base of many of these combinatorial synthetic manifolds.^[5] Typically, these reactions create diversity generating molecular architectures based on a common molecular core (structural complexity) adorned with different appended functionalities (functional diversity) (M_i , Figure 1). While this fact is beneficial for the synthesis of focused libraries because their goal is to create analogues of a predefined core structure (scaffold),^[6] it is detrimental for the diversity-oriented synthesis of libraries, whose goal is to create collections of compounds with extensive skeletal and stereochemical diversity.^[7] Overcoming this limiting principle is not a simple task and it requires a careful reactivity design and a synthetic planning algorithm completely different from that used to create a single compound or a focused-library. Two main synthetic strategies are available for planning skeletal diversity-oriented synthetic (DOS) pathways: reagent-based differentiation and substrate-based folding.^[8] The former utilizes different reagents to transform a common substrate into a collection of products with different molecular frameworks. The second strategy utilizes a collection of substrates having different appendages that pre-encode skeletal information (called σ elements) into a collection of products having distinct molecular skeletons using common reaction conditions.^[9] On the other hand, MCRs are very well suited to create structural complexity, the other great challenge of DOS. Planning of single DOS manifolds to address both goals is a challenging frontier. A logical approach would consist in the adequate integration of the MCR into the folding process.^[10] We present herein a promising approach to this challenge. The approach develops a novel substrate-based folding process incorporating a common and defined MCR-based manifold to generate a structurally different array of products (Figure 2). By the convenient use of reactivity-encoding elements (σ_i), one of the modules is made to react in a differentiated and programmable manner to afford, under the same reaction conditions, different pre-encoded skeletal outcomes. The manifold utilizes a chemo-differentiating organocatalyzed ABB' 3CR^[11] of a terminal conjugated alkynoate (building block) with α -dicarbonyl compounds (diversity-generating blocks) to generate an array of different molecular topologies. A fine-tuning balance between pKa and reactivity of the α -dicarbonyl module controls the chemical outcome of these 3CRs. In addition, all the products share a common reactive functionality (β -alkoxy-acrylate) to be collective substrates for a subsequent diversity-generating process (maximizing structural diversity while maintaining common reactivity).

Results and discussion

The synthetic manifold. We have recently described a set of chemo-differentiating ABB' systems based on a novel reactivity generation concept: the in situ generation of a strong base by the action of a good nucleophile (Scheme 1).^[11,12] Key to these systems is the catalytic generation of allenolate **I** by reaction of a nucleophile (catalyst) on a terminal alkynoate. In the presence of aliphatic aldehydes, allenolate **I** launches two different domino reactions to selectively afford propargylic enol ethers **1** (path **a**, Scheme 1) or 1,3-dioxolane derivatives **3** (path **b**, Scheme 1) as a function of temperature, catalyst and stoichiometry.^[12] Both processes are launched by the catalytic generation of acetylide **II** (acetylide-driven domino processes). We have also recently shown that aldehydes and ketones more acidic than the propiolate itself (pKa = 18.8)^[13] inhibit these processes, triggering a new set of domino reactions based on the formation of enolate **III** (path **c**, Scheme 1).^[11] These new enolate-driven domino processes transform linear (unbranched) α -ketoesters into 3-hydroxy-2(5H)-furanones **3** (isotetronic acid derivatives) via a catalytic cycle involving a sequential homo-aldol condensation-lactonization-Michael addition set of reactions. While the homo-aldol condensation allows the chemo-differentiation of two

units of the carbonyl-containing module, the Michael-addition reaction closes the cycle by formation of product **3** and catalyst regeneration.

A common property of these three domino processes is their ability to perform a chemo-differentiating processing of otherwise identical units of starting material. Note that they transform a degenerated set of educts (2 chemical inputs) into a final product whose structure incorporates one of these educts twice and in the form of differentiated chemical functions or structural motifs (non-degenerated chemical output). *This remarkable property confers these bimolecular processes all of the synthetic advantages associated with the 3CRs.* We categorize them as ABB' 3CRs to highlight their bimolecular nature (A and B), the dual role played by component B along the reaction pathway (B and B')^[14] and their three-component chemical outcomes.

Reactivity-encoding elements. α -Dicarbonyl compounds constitute a wide family of reactive functionalities with enhanced chemical reactivity towards nucleophiles. This reactivity enhancement is mainly associated with the powerful activation of one electron-withdrawing carbonyl group on the other. This electronic effect also accounts for the relative higher acidity of these functionalities with regard to the homologous monocarbonyl compounds. The strength of this electron-withdrawing effect can be conveniently tuned by the right election of the substituents attached to one carbonyl group. Consequently, the α -dicarbonyl system can be considered to be an electronically encoded reactive functionality in which the precise electronic nature of one carbonyl group encodes both the reactivity and acidity of the other. *This property constitutes a novel, convenient and powerful reactivity-encoding element σ* and it converts these functionalities into excellent reagents for substrate-based folding processes based on our chemo-differentiating ABB' 3CRs.

Among all the possible α -dicarbonyl functionalities, we selected α -ketoamides, α -ketonitriles, α -ketoesters and α -diketones. They share a common *keto* group (reactive functionality), decorated with four electronically different carbonyl functions: amides, cyano, esters and ketones (σ elements). They span a wide range of both reactivity and acidity while maintaining an overall similarity. In addition, most of them are commercial available or can be easily prepared.

Preliminary screening showed that 1,2-diketones and α -ketonitriles were not suitable substrates for either enolate-driven or acetylide-driven ABB' 3CR manifolds. While 1,2-ketones afforded irresolvable mixtures of products, α -ketonitriles did not react under these conditions. On the other hand, α -ketoesters and α -ketoamides proved to be excellent substrates for these ABB' 3CRs, and most importantly, they displayed different chemical reactivity profiles (Tables 1-3).

α -Ketoesters. In general, α -ketoesters reacted as reactive enolates to give γ -lactones **3** (Table 1, entries 1-8),^[11,15] as well as activated ketones to give 1,3-dioxolanes **6** (Table 2, entries 1-3) or propargylic enol ethers **7** (Table 2, entries 4 and 5).^[16] α -Ketoesters **4a-g** were consistently and efficiently incorporated into the corresponding isotetronic acid derivatives **3a-g** (85% average yield) (Table 1, entries 1-8). Ethyl 2,4-dioxopentanoate (**4h**), incorporating an extra 1,3-diketone functionality, proved to be too stable to productively participate in this reaction system (entry 9). Lipophilic α -ketoesters **4c-e** gave high levels of the undesired enolate **III** O-alkylation in dichloromethane. This accompanying side reaction is a serious problem, and it becomes a very important missing route of resources. Fortunately, it could be completely suppressed by the use of tetrahydrofuran, a better coordinating solvent (entries 3-5).

The non-acidic β,β -disubstituted α -ketoesters **5a-c** were processed as activated ketones via the acetylide-driven pathway (path **a**, Scheme 1) to generate the fully substituted 1,3-dioxolane derivatives **6a-c** in excellent yields and with high atom-economy (Table 2, entries 1-3). Both aromatic and heterocyclic α -ketoesters were reactive enough to participate in this 3CR (entries 1 and 2). Even the sterically encumbered α -ketolactone **5c** was efficiently processed into the crowded 2,5-di-spiro-1,3-dioxolane derivative **6c** (84% yield) (entry 3).

β -Substituted and γ -substituted α -ketoesters displayed a diminished acidity^[17] to be productively incorporated into the enolate-driven processes. Accordingly, they were efficiently processed via the corresponding organocatalyzed acetylide-driven ABB' 3CRs. Two features are remarkable. Firstly, the chemical outcome of these processes was strongly dependent on the nucleophilicity of the catalyst. While the triethylamine-catalyzed 3CRs generated the 1,3-dioxolane derivatives **6d-e**, the DABCO-catalyzed processes yielded the corresponding γ,γ -disubstituted propargylic enol ethers **7d-e** (Table 2, entries 4 and 5). Secondly, the efficiency of the triethylamine-catalyzed processes diminished when the acidity of the substrate increased. Thus, while ethyl 3-methyl-2-oxobutanoate (**5d**) gave the 1,3-dioxolane derivative **6d** in excellent yield (89%), the more acidic ethyl 4-methyl-2-oxopentanoate (**5e**) required excess of alkynoate and a lower catalyst charge to form the 1,3-dioxolane **6e** with moderate yield (56%) (30% of O-alkylation). (Table 2, entries 4 and 5).

In our previous studies with organocatalyzed ABB' 3CRs involving aldehydes or ketones and methyl propiolate,^[12] no γ,γ -disubstituted propargylic enol ethers were ever detected. On the contrary, activated ketones were uniformly incorporated into the corresponding 2,2,5,5-tetrasubstituted 1,3-dioxolane derivatives. *This implies that these $\beta(\gamma)$ -substituted α -ketoesters behave as highly reactive aliphatic aldehydes rather than activated ketones. β or γ -branching at the alkyl chain performs, therefore, the function of a masked skeletal information encoding element.*^[8]

α -Ketoamides. They are less acidic and reactive than their homologous α -ketoesters^[18] and they cannot actively participate in the enolate-driven 3CR manifolds. They reacted with methyl propiolate in the presence of triethylamine to generate the corresponding γ,γ -disubstituted propargylic enol ethers **9a-e** with good efficiency and complete selectivity (Table 3, entries 1-5). Under these conditions, the catalytic acetylide-driven process affording 1,3-dioxolanic derivatives was completely suppressed. Aliphatic and aromatic α -ketoamides proved to be good substrates for these 3CRs (entries 1-5). Cyclic or acyclic secondary amines encoded in a similar manner the reactivity of the adjacent keto-group (entries 1-3). Only the most lipophilic N,N-diethyl 2-oxobutyroamide **8d** required an excess of alkynoate to yield the propargylic enol ether **9d** in useful yields (entry 4).

Terminal conjugated alkynes. The influence of the terminal conjugated alkyne was studied with sulphone **10** (Scheme 2) and ethyl pyruvate **4a**. In spite of the extremely high reactivity and acidity of **4a**, sulphone **10** only was processed through the acetylide-driven 3CR affording the corresponding 1,3-dioxolane derivative **11**. Remarkably, *sulphone 10 inhibits the otherwise pyruvate-favored enolate-driven process.*

The substrate-based folding process. The folding process utilizes a common ABB' 3CR-based manifold to generate an array of topologically differentiated products. The manifold comprises a kinetic controlled reaction network involving three different and competitive catalytic cycles **a**, **b** and **c** (Scheme 3), each affording a specific skeletal framework. Product selectivity directly arises from the kinetic model utilized by this manifold, which imposes the performance of one cycle at a time. Consequently, when a cycle is working, the other two remain kinetically arrested, and the entire chemical transformation is selectively funneled toward one of three skeletal differentiated products **3**, **6** or **7** (**9**). Three chemical properties govern the manifold performance:

Acidity. The relative acidity of the alkynoate and the α -dicarbonyl substrates biases the chemical outcome of the entire process, allowing an acetylide-driven process (cycle **a** or **b**), or an enolate-driven one (cycle **c**). In the case of the ethynyl sulphone **10**, this property does not become an issue because the acidity of ethynyl sulphone must be higher than the acidity of ethyl pyruvate.

Nucleophilicity. This property is mainly related with the catalyst and it operates only for the acetylide-driven processes incorporating conjugated alkynoates or sulphones.

Electrophilicity. This property is associated with the reactivity of the α -dicarbonyl compound toward nucleophiles and it operates solely for the acetylide-driven processes.

The enolate-driven ABB' 3CR manifold is selective for acidic α -dicarbonyl compounds (α -ketoesters) and it efficiently and uniformly generates isotetronic acid derivatives **3**. Herein, the catalyst nature does not play a special role. The catalytic cycle is launched by the enolate **III** formation. On the other hand, the acetylide-driven processes are characteristic either of the less acidic dicarbonyl α -compounds ($\beta(\gamma)$ -substituted α -ketoesters and α -ketoamides) or the non-acidic ones (β,β -disubstituted α -ketoesters), and they selectively afford $\beta\beta$ -disubstituted propargylic enol ethers **7** (**9**) or 2,2,5,5-tetrasubstituted 1,3-dioxolane derivatives **6**. Both the catalyst nucleophilicity and the dicarbonyl electrophilicity are instrumental in biasing the chemical outcome selectively toward products **7(9)** or **6**. Ethynyl sulphone **10** reacts via acetylide-driven cycle **b** irrespective of the acidity of the α -dicarbonyl compound.

The ABB' 3CR manifold starts with the Michael addition of the catalyst to the terminal alkynoate to generate allenolate **I**. In the presence of acidic α -ketoesters, allenolate **I** launches the cycle **c** by generation of the enolate **III**. The cycle progresses by homo-aldolic addition and lactonization of the corresponding adduct to construct the isotetronate core **IX**, which in turn, irreversibly adds to the β -ammonium acrylate counterion to generate the γ -lactone **3** with catalyst releasing to reinitiate the cycle. In the absence of alkynoate, triethylamine does not catalyze the generation of the isotetronate intermediate **VIII** in an appreciable amount,^[15] confirming the triggering role played by the allenolate intermediate **I** in this catalytic manifold.

A different scenario arises when the α -dicarbonyl compound is less acidic than the terminal alkynoate ($\beta(\gamma)$ -substituted α -ketoesters and α -ketoamides), or it is not enolizable (β,β -disubstituted α -ketoesters). In these cases, allenolate **I** triggers one of the two acetylide-driven cycles **a** or **b** by generation of the ammonium acetylide **II**. Cycle **a** is launched by the acetylide addition on the α -dicarbonyl educt to generate the corresponding γ,γ -disubstituted propargylic alkoxide intermediate **IV**, which irreversibly adds to the β -ammonium acrylate counterion to afford γ,γ -disubstituted propargylic enol ether **7** (α -ketoesters) or **9** (α -ketoamides) to close the cycle and regenerate the catalyst. Cycle **b** requires an acetylide addition on the α -dicarbonyl educt to generate the corresponding propargylic alkoxide **IV** ($Z' = OR$). Addition to another molecule of the α -dicarbonyl substrate generates the corresponding alkoxide adduct **V**. Cyclization to the corresponding vinyl 1,3-dioxolanic anion **VI** and deprotonation of the starting alkynoate generates the final 1,3-dioxolane derivative **6** with liberation of the acetylide **II** to restart the cycle (autocatalysis). Cycle **a** is the more kinetically favored and it requires either a nucleophilic catalyst and a good Michael acceptor β -ammonium acrylate counterion or a α -dicarbonyl component with reduced electrophilicity. While DABCO fulfils the first two conditions, α -ketoamides comply with the latter. Thus, while α -ketoamides are uniformly processed through cycle **a** to generate the corresponding γ -alkyl(aryl), γ -carbamoyl propargylic enol ethers **9**, the more electrophilic $\beta(\gamma)$ -substituted α -ketoesters require DABCO to be transformed into the propargylic derivatives **7**. Cycle **b** is the less kinetically favored pathway and it requires mild nucleophilic catalysts and either highly electrophilic carbonyl substrates or highly nucleophilic alkoxide intermediates **IV** to be competitive. While triethylamine fulfils the catalyst requirements, α -ketolactones and aromatic or heterocyclic α -ketoesters comply with the other two substrate-depending conditions, respectively. O-alkylation of the enol ether can be an important competitive side reaction, mainly when cycle **b** is operating. In general, the smaller the difference in pKa between α -ketoester and alkynoate, the greater the O-alkylation of the enolate and consequently, the less the yield of the three-component adduct. This side reaction can be efficiently diminished by using excess of alkynoate and lower catalyst charges (cycle **b**), or by using coordinating solvents to disrupt the [β -ammonium acrylate - enolate] ionic pair (cycle **c**).

Summary. We have described a novel 3CR-based folding process able to achieve complexity generation and skeletal diversity. The process utilizes chemo-differentiating organocatalyzed ABB' 3CRs of a terminal conjugated alkynoate (building block) and α -dicarbonyl compounds (diversity-generating blocks) to generate an array of different molecular topologies (γ -lactones, linear propargylic enol ethers or 1,3-dioxolane rings). Amides and esters behave as efficient reactivity-encoding elements of the attached keto functionalities. Three chemical properties govern the chemical outcome of this folding process: acidity, nucleophilicity (catalyst) and carbonyl electrophilicity. Overall, this substrate-based folding process generates three different molecular architectures from the same modular functionalities (ketones) and under the same reaction conditions (methyl propiolate and tertiary amine). In addition, and very importantly for the combinatorial application, all the products share a common reactive functionality to be collective substrates for a subsequent diversity-generating process.

Experimental Section

General remarks. ^1H NMR and ^{13}C NMR spectra of CDCl_3 solutions were recorded either at 400 and 100 MHz or at 500 and 125 MHz (Bruker Ac 200 and AMX2-500), respectively. FT-IR spectra were measured in chloroform solutions using a Shimadzu IR-408 spectrophotometer. Mass spectra (low resolution) (EI/CI) were obtained with a Hewlett-Packard 5995 gas chromatograph/mass spectrometer. High-resolution mass spectra were recorded with a Micromass Autospec mass spectrometer. Microanalyses were performed with a Fisons Instruments EA 1108 carbon, hydrogen, and nitrogen analyser. Analytical thin-layer chromatography plates used were E. Merck Brinkman UV-active silica gel (Kieselgel 60 F254) on aluminium. Flash column chromatography was carried out with E. Merck silica gel 60 (particle size less than 0.020 mm) using appropriate mixtures of ethyl acetate and hexanes as eluent. All reactions were performed in oven-dried glassware under nitrogen unless otherwise stated. Dichloromethane was distilled from CaH_2 . THF was distilled from sodium/benzophenone. Triethylamine was distilled from potassium hydroxide pellets. Starting α -ketoesters and α -ketoamides were either commercially available or were prepared using standard procedures. All other materials were obtained from commercial suppliers and used as received. Experimental data for **3a** is given in reference 11.

General Procedure for the synthesis of isotetronic products (3): Methyl propiolate (1.00 mmol) and α -ketoester (2.00 mmol) were dissolved in 2 mL of CH_2Cl_2 (or THF). After the mixture was cooled to 0°C , triethylamine (0.2 mmol) was added and the reaction mixture was allowed to stir for 1-4 hours. The solvent and excess reagents were then removed under reduced pressure. This was followed by isolation of the corresponding isotetronic product **3** by flash column chromatography (silica gel, n-hexane/EtOAc 80/20 to 60/40).

General Procedure for the synthesis of 1,3-dioxolane products (6): Methyl propiolate (1.00 mmol) and α -ketoester (2.00 mmol) were dissolved in 2 mL of CH_2Cl_2 . After the mixture was cooled to -78°C , triethylamine (0.2 mmol) was added and the reaction mixture was allowed to stir for 1-4 hours. The solvent and excess reagents were then removed under reduced pressure. This was followed by isolation of the corresponding products **6** by flash column chromatography (silica gel, n-hexane/EtOAc 90/10 to 70/30).

General Procedure for the synthesis of enol-protected propargylic alcohols (7 or 9): Methyl propiolate (2.00 mmol) and α -ketoester or α -ketoamide (1.00 mmol) were dissolved in 7 mL of CH_2Cl_2 . After the mixture was cooled to 0°C , DABCO (for α -ketoesters, 0.2 mmol) or triethylamine (for α -ketoamide, 1.0 mmol) was added and the reaction mixture was allowed to stir for 2-6 hours (until no more α -ketoester or α -ketoamide was detected by TLC). The solvent and excess reagents were then removed under reduced pressure. This was followed by isolation of the corresponding product **7** or **9** by flash column chromatography (silica gel, n-hexane/EtOAc 90/10 to 70/30).

Methyl 4-((E)-2-(methoxycarbonyl)vinyl)oxy-2-ethyl-2,5-dihydro-3-methyl-5-oxofuran-2-carboxylate (3b): ^1H NMR (400 MHz, CDCl_3 , 25°C): δ = 0.87 (t, $^3J(\text{H,H})=7.4$ Hz, 3H), 1.87–1.93 (m, 1H), 1.93 (s, 3H), 2.22–2.32 (m, 1H), 3.68 (s, 3H), 3.76 (s, 3H), 5.49 (d, $^3J(\text{H,H})=12.2$ Hz, 1H), 7.86 (d, $^3J(\text{H,H})=12.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3 , 25°C): δ = 6.9, 9.5, 27.0, 51.4, 53.3, 87.2, 102.8, 138.2, 143.2, 157.1, 165.0, 166.4, 167.8; IR (CHCl_3): ν = 1131.5, 1191.1, 1438.4, 1641.1, 1718.5, 1739.9, 1781.4, 2954.5, 3022.3 cm^{-1} ; MS (70 eV, EI): m/z (%): 284 (22) [M^+], 253 (19), 252 (18), 227 (44), 225 (100), 155 (57), 57 (52); elemental analysis calcd (%) for $\text{C}_{13}\text{H}_{16}\text{O}_7$: C 54.93; H 5.67; found: C 54.89, H 5.74.

Methyl 4-((E)-2-(methoxycarbonyl)vinyl)oxy-3-ethyl-2,5-dihydro-5-oxo-2-propylfuran-2-carboxylate (3c): ^1H NMR (400 MHz, CDCl_3 , 25°C): δ = 0.93 (t, $^3J(\text{H,H})=7.2$ Hz, 3H), 1.12 (t, $^3J(\text{H,H})=7.4$ Hz, 3H), 1.25–1.34 (m, 2H), 1.81–1.89 (m, 1H), 2.19–2.43 (m, 3H), 3.70 (s, 3H), 3.76 (s, 3H), 5.50 (d, $^3J(\text{H,H})=12.2$ Hz, 1H), 7.86 (d, $^3J(\text{H,H})=12.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3 , 25°C): δ = 12.2, 13.7, 16.3, 18.2, 35.8, 51.4, 53.3, 86.7, 102.7, 138.2, 148.6, 157.2, 165.3, 166.5, 168.1; IR (CHCl_3): ν = 1131.7, 1189.5, 1276.7, 1438.1, 1639.4, 1716.5, 1740.9, 1778.4, 2955.5, 3020.2 cm^{-1} ; MS (70 eV, EI): m/z (%): 312 (16) [M^+], 280 (16), 253 (92), 241 (24), 221 (41), 183 (77), 85 (24), 71 (100); elemental analysis calcd (%) for $\text{C}_{15}\text{H}_{20}\text{O}_7$: C 57.69, H 6.45; found: C 57.54, H 6.44.

Ethyl 4-((E)-2-(methoxycarbonyl)vinyl)oxy-3-heptyl-2,5-dihydro-2-octyl-5-oxofuran-2-carboxylate (3d): ^1H NMR (400 MHz, CDCl_3 , 25°C): δ = 0.86 (t, $^3J(\text{H,H})=7.2$ Hz, 3H), 0.86 (t, $^3J(\text{H,H})=7.2$ Hz, 3H), 1.28 (t, $^3J(\text{H,H})=7.2$ Hz, 3H), 1.24–1.31 (m, 20H), 1.44–1.53 (m, 2H), 1.81–1.88 (m, 1H), 2.21–2.28 (m, 2H), 2.31–2.39 (m, 1H), 3.71 (s, 3H), 4.22 (q, $^3J(\text{H,H})=7.2$ Hz, 2H), 5.50 (d, $^3J(\text{H,H})=12.5$ Hz, 1H), 7.87 (d, $^3J(\text{H,H})=12.5$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3 , 25°C): δ = 14.0, 14.0, 22.5, 22.6, 22.7, 24.9, 26.6, 28.7, 29.1, 29.2, 29.3, 29.6, 31.6, 31.7, 33.7, 51.4, 62.8, 86.9, 102.6, 138.2, 147.8, 157.3, 165.5, 166.5, 167.6; IR (CHCl_3): ν = 1132.7, 1217.4, 1638.3, 1717.6, 1733.2, 1777.2, 2856.8, 2929.4, 3018.3 cm^{-1} ; MS (70 eV, EI): m/z (%): 466 (79) [M^+], 393 (100), 361 (96), 325 (72), 71 (29), 57 (59); elemental analysis calcd (%) for $\text{C}_{26}\text{H}_{42}\text{O}_7$: C 66.93, H 9.07; found: C 66.85, H 9.16.

Ethyl 4-((E)-2-(methoxycarbonyl)vinyl)oxy-2,5-dihydro-3-isobutyl-2-isopentyl-5-oxofuran-2-carboxylate (3e): ^1H NMR (400 MHz, CDCl_3 , 25°C): δ = 0.87 (d, $^3J(\text{H,H})=6.6$ Hz, 3H), 0.88 (d, $^3J(\text{H,H})=6.6$ Hz, 6H), 0.91 (d, $^3J(\text{H,H})=6.6$ Hz, 3H), 1.10–1.16 (m, 2H), 1.27 (t, $^3J(\text{H,H})=7.2$ Hz, 3H), 1.50–1.57 (m, 1H), 1.79–1.87 (m, 1H), 1.91–1.98 (m, 1H), 2.10 (dd, $^3J(\text{H,H})=7.4$, 14.8 Hz, 1H), 2.20–2.28 (m, 2H), 3.70 (s, 3H), 4.20 (q, $^3J(\text{H,H})=7.2$ Hz, 2H), 5.51 (d, $^3J(\text{H,H})=2.2$ Hz, 1H), 7.88 (d, $^3J(\text{H,H})=12.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3 , 25°C): δ = 13.9, 22.3, 22.6, 22.8, 26.1, 27.9, 31.4, 31.6, 34.0, 51.4, 62.8, 87.1, 102.8, 138.6, 146.3, 157.0, 165.5, 166.5, 167.6; IR (CHCl_3): ν = 1124.2, 1258.0, 1639.5, 1726.2, 1781.5, 2959.5 cm^{-1} ; MS (70 eV, EI): m/z (%): 382 (19) [M^+], 309 (100), 283 (29), 277 (71), 239 (39), 99 (46), 81 (38); elemental analysis calcd (%) for $\text{C}_{20}\text{H}_{30}\text{O}_7$: C 62.81, H 7.91; found: C 62.74, H 7.96.

Ethyl 4-((E)-2-(methoxycarbonyl)vinyl)oxy-3-benzyl-2,5-dihydro-5-oxo-2-phenethylfuran-2-carboxylate (3f): ^1H NMR (400 MHz, CDCl_3 , 25°C): δ = 1.16 (t, $^3J(\text{H,H})=7.2$ Hz, 3H), 2.08–2.16 (m, 1H), 2.34–2.41 (m, 1H), 2.47–2.58 (m, 2H), 3.67 (s, 2H), 3.73 (s, 3H), 3.80–4.10 (m, 2H), 5.54 (d, $^3J(\text{H,H})=2.2$ Hz, 1H), 6.97–6.99 (m, 2H), 7.15–7.32 (m, 8H), 7.97 (d, $^3J(\text{H,H})=12.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3 , 25°C): δ = 13.8, 29.0, 30.5, 35.7, 51.5, 62.9, 86.4, 103.3, 126.3, 127.5, 128.3, 128.5, 128.9, 129.0, 134.4, 138.8, 139.8, 144.7, 156.7, 165.0, 166.3, 166.9; IR (CHCl_3): ν = 1128.7, 1438.2, 1624.9, 1639.2, 1719.9, 1780.4, 3019.5 cm^{-1} ; MS (70 eV, EI): m/z (%): 360 (22) [M^+], 328 (39), 287 (42), 255 (78), 217 (35), 143 (38), 115 (42), 91 (100), 85 (40); elemental analysis calcd (%) for $\text{C}_{26}\text{H}_{26}\text{O}_7$: C 69.32, H 5.82; found: C 69.40, H 6.08.

Methyl 4-((E)-2-(methoxycarbonyl)vinyl)oxy-2-(2-(methoxycarbonyl)ethyl)-3-((methoxycarbonyl)methyl)-2,5-dihydro-5-oxofuran-2-carboxylate (3g): ^1H NMR (400 MHz, CDCl_3 , 25°C): δ = 2.20–2.44 (m, 2H), 2.55–2.62 (m, 1H), 3.36 (d, $^3J(\text{H,H})=17.0$ Hz, 1H), 3.49 (d,

$^3J(\text{H,H})=17.0$ Hz), 3.64 (s, 2H), 3.68 (s, 3H), 3.70 (s, 2H), 3.76 (s, 3H), 5.58 (d, 1H, $J = 12.2$ Hz), 7.96 (d, 1H, $J = 12.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3 , 25°C): $\delta=27.6, 29.1, 29.6, 51.5, 52.0, 52.8, 53.7, 85.3, 104.1, 137.1, 140.5, 156.0, 163.9, 166.2, 167.1, 167.4, 172.1$; IR (CHCl_3): $\nu=1129.9, 1205.6, 1224.3, 1438.3, 1641.9, 1741.8, 1783.3, 2955.2, 3023.3$ cm^{-1} ; MS (70 eV, EI): m/z (%): 400 (6.7) [M^+], 368 (19), 340 (16), 310 (17), 309 (100), 281 (17), 115 (40), 85 (18), 59 (33), 55 (31); elemental analysis calcd (%) for $\text{C}_{17}\text{H}_{20}\text{O}_{11}$: C 51.00, H 5.04; found: C 51.07, H 5.10.

Dimethyl 5-((methoxycarbonyl)methylene)-2,4-diphenyl-1,3-dioxolane-2,4-dicarboxylate (6a): 84% combined yield of a mixture of 4 isomers (*Eanti*: *Esyn*: *Zanti*: *Zsyn*. ratio = 0.16: 0.31: 0.31: 1.0). The order of increasing polarity in TLC is: *Eanti* $\approx$ *Esyn* > *Zanti* > *Zsyn*. ***Z-syn*** major isomer: ^1H NMR (400 MHz, CDCl_3 , 25°C): $\delta=3.70$ (s, 3H), 3.76 (s, 3H), 3.87 (s, 3H), 5.25 (s, 1H), 7.30-7.69 (m, 10H). ^{13}C NMR (100 MHz, CDCl_3 , 25°C): $\delta=51.16, 53.25, 53.45, 89.93, 94.20, 109.48, 125.75, 126.03, 128.29, 129.37, 129.86, 134.6, 136.22, 162.05, 164.75, 167.13, 168.01$; IR (CHCl_3): $\nu=3019.6, 2955.0, 1753.6, 1724.5, 1677.6, 1436.8, 1224.5, 1092.3$ cm^{-1} ; MS (70 eV, EI): m/z (%): 353 (18) [$\text{M}^+-\text{CO}_2\text{Me}$], 189 (5), 179 (8), 161 (2), 105 (100), 84 (29), 77 (16); elemental analysis calcd (%) for $\text{C}_{22}\text{H}_{20}\text{O}_8$: C 64.07, H 4.89; found: C 64.12, H 4.88. Characteristic data for the ***E-anti*** isomer: ^1H NMR (400 MHz, CDCl_3 , 25°C): $\delta=3.19$ (s, 3H), 3.59 (s, 3H), 3.74 (s, 3H), 5.95 (s, 1H). Characteristic data for the ***E-syn*** isomer: ^1H NMR (400 MHz, CDCl_3 , 25°C): $\delta=3.60$ (s, 3H), 3.77 (s, 3H), 3.81 (s, 3H), 5.90 (s, 1H). Characteristic data for the ***Z-anti*** isomer: ^1H NMR (400 MHz, CDCl_3 , 25°C): $\delta=3.49$ (s, 3H), 3.51 (s, 3H), 3.74 (s, 3H), 5.40 (s, 1H).

Dimethyl 5-((methoxycarbonyl)methylene)-2,4-di(thiophen-2-yl)-1,3-dioxolane-2,4-dicarboxylate (6b): 85% combined yield of a mixture of 4 isomers (*Eanti*: *Esyn*: *Zanti*: *Zsyn*. ratio = 0.13: 0.33: 0.20: 1.0). The order of increasing polarity in TLC is: *Eanti* > *Esyn* > *Zanti* > *Zsyn*. ***Z-syn*** major isomer: ^1H NMR (400 MHz, CDCl_3 , 25°C): $\delta=3.70$ (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 5.39 (s, 1H), 6.95 (dd, $^3J(\text{H,H})=3.7, 5.0$ Hz, 1H), 7.01 (dd, $^3J(\text{H,H})=3.7, 5.0$ Hz, 1H), 7.18 (d, $^3J(\text{H,H})=1.3, 4.0$ Hz, 1H), 7.32 (d, $^3J(\text{H,H})=1.3, 5.3$ Hz, 1H), 7.39-7.42 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3 , 25°C): $\delta=51.3, 53.5, 53.8, 87.3, 94.0, 107.9, 127.0, 127.2, 127.7, 128.2, 128.5, 136.3, 138.9, 161.4, 164.5, 165.9, 167.1$; IR (CHCl_3): $\nu=1087.4, 1207.4, 1226.0, 1256.2, 1436.9, 1679.4, 1719.9, 1757.8, 2955.1, 3020.1$ cm^{-1} ; MS (70 eV, EI): m/z (%): 365 (6.6) [$\text{M}^+-\text{CO}_2\text{Me}$], 254 (54), 226 (17), 167 (29), 110 (100), 96 (18); elemental analysis calcd (%) for $\text{C}_{18}\text{H}_{16}\text{O}_8\text{S}_2$: C 50.94, H 3.80, S 15.11, found: C 50.93, H 3.78, S 14.97. Characteristic data for the ***E-anti*** isomer: ^1H NMR (400 MHz, CDCl_3 , 25°C): $\delta=3.48$ (s, 3H), 3.57 (s, 3H), 3.81 (s, 3H), 5.85 (s, 1H). Characteristic data for the ***E-syn*** isomer: ^1H NMR (400 MHz, CDCl_3 , 25°C): $\delta=3.53$ (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 5.82 (s, 1H). Characteristic data for the ***Z-anti*** isomer: ^1H NMR (400 MHz, CDCl_3 , 25°C): $\delta=3.65$ (s, 3H), 3.73 (s, 3H), 3.74 (s, 3H), 5.51 (s, 1H).

Dioxolane from dihydro-4,4-dimethylfuran-2,3-dione and methyl propiolate (6c): 84% combined yield of a mixture of 2 isomers (*Zanti*: *Zsyn*. ratio = 1.62: 1.0). The order of increasing polarity in TLC is: *Zanti* > *Zsyn*. ***Z-anti*** major isomer: ^1H NMR (400 MHz, CDCl_3 , 25°C): ***Z-anti*** $\delta=1.21$ (s, 3H), 1.22 (s, 3H), 1.27 (s, 3H), 1.29 (s, 3H), 3.70 (s, 3H), 4.08 (d, $^3J(\text{H,H})=9.6$ Hz, 1H), 4.09 (d, $^3J(\text{H,H})=8.8$ Hz, 1H), 4.12 (d, $^3J(\text{H,H})=9.6$ Hz, 1H), 4.21 (d, $^3J(\text{H,H})=8.8$ Hz, 1H), 4.89 (s, 1H). ***Z-syn*** $\delta=1.14$ (s, 3H), 1.20 (s, 3H), 1.23 (s, 3H), 1.25 (s, 3H), 3.69 (s, 3H), 4.09 (d, $^3J(\text{H,H})=8.8$ Hz, 1H), 4.10 (s, 2H), 4.12 (d, $^3J(\text{H,H})=8.8$ Hz, 1H), 5.06 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3 , 25°C): ***Z-anti*** $\delta=16.9, 18.4, 19.9, 22.6, 41.7, 42.9, 51.5, 76.4, 76.5, 91.3, 91.6, 112.8, 158.8, 163.8, 169.6, 171.0$; ***Z-syn*** 18.4, 18.9, 19.8, 22.1, 40.1, 43.2, 51.5, 75.6, 75.7, 90.1, 94.3, 111.1, 158.3, 163.6, 168.8, 169.3; IR (CHCl_3): $\nu=3020.3, 2972.5, 1817.0, 1727.4, 1679.3, 1470.2, 1438.0, 1120.7, 1096.7, 1047.2, 1011.9$ cm^{-1} ; MS (70 eV, EI): m/z (%): 340 (0.2) [M^+], 282 (24), 214 (21), 213 (25), 182 (51), 167 (43), 83 (100), 70 (44), 69 (98), 55 (67); elemental analysis calcd (%) for $\text{C}_{16}\text{H}_{20}\text{O}_8$: C 56.47, H 5.92; found: C 56.51, H 5.85.

Diethyl 5-((methoxycarbonyl)methylene)-2,4-diisopropyl-1,3-dioxolane-2,4-dicarboxylate (6d): 89% combined yield of a separable mixture of 4 isomers (*Eanti*: *Esyn*: *Zanti*: *Zsyn*. ratio = 0.27: 0.69: 0.43: 1.0). The order of increasing polarity in TLC is: *Eanti* > *Esyn* > *Zanti* > *Zsyn*. ^1H NMR

(400 MHz, CDCl₃, 25°C): **Eanti** δ =0.78 (d, $^3J(\text{H,H})$ =7.2 Hz, 3H), 0.99 (d, $^3J(\text{H,H})$ =6.9 Hz, 3H), 1.01 (d, $^3J(\text{H,H})$ =7.2 Hz, 3H), 1.16 (d, $^3J(\text{H,H})$ =6.6 Hz, 3H), 1.23 (t, $^3J(\text{H,H})$ =7.2 Hz, 3H), 1.31 (t, $^3J(\text{H,H})$ =7.2 Hz, 3H), 2.23–2.34 (m, 1H), 2.86–2.96 (m, 1H), 3.62 (s, 3H), 4.16 (q, $^3J(\text{H,H})$ =7.2 Hz, 2H), 4.22–4.31 (m, 2H), 5.60 (s, 1H). **Esyn** δ =0.91 (d, $^3J(\text{H,H})$ =6.6 Hz, 3H), 1.01 (d, $^3J(\text{H,H})$ =6.9 Hz, 3H), 1.03 (d, $^3J(\text{H,H})$ =7.2 Hz, 3H), 1.10 (d, $^3J(\text{H,H})$ =6.6 Hz, 3H), 1.19 (t, $^3J(\text{H,H})$ =7.2 Hz, 3H), 1.28 (t, $^3J(\text{H,H})$ =7.2 Hz, 3H), 2.26–2.37 (m, 1H), 3.17–3.27 (m, 1H), 3.62 (s, 3H), 4.03–4.25 (m, 4H), 5.65 (s, 1H). **Zanti** δ =0.82 (d, $^3J(\text{H,H})$ =6.9 Hz, 3H), 0.95 (d, $^3J(\text{H,H})$ =6.9 Hz, 3H), 1.01 (d, $^3J(\text{H,H})$ =6.9 Hz, 3H), 1.05 (d, $^3J(\text{H,H})$ =6.9 Hz, 3H), 1.28 (t, $^3J(\text{H,H})$ =7.2 Hz, 3H), 1.28 (t, $^3J(\text{H,H})$ =7.2 Hz, 3H), 2.20–2.32 (m, 2H), 3.69 (s, 3H), 4.18–4.35 (m, 4H), 5.22 (s, 1H). **Zsyn** δ =0.93 (d, $^3J(\text{H,H})$ =6.6 Hz, 3H), 0.95 (d, $^3J(\text{H,H})$ =6.9 Hz, 3H), 1.03 (d, $^3J(\text{H,H})$ =6.9 Hz, 3H), 1.08 (d, $^3J(\text{H,H})$ =7.2 Hz, 3H), 1.25 (t, $^3J(\text{H,H})$ =7.2 Hz, 3H), 1.26 (t, $^3J(\text{H,H})$ =7.2 Hz, 3H), 2.25–2.35 (m, 1H), 2.44–2.54 (m, 1H), 3.68 (s, 3H), 4.10–4.25 (m, 4H), 5.19 (s, 1H); ¹³C NMR of the 2 major isomers (100 MHz, CDCl₃, 25°C): **Esyn** δ =13.8, 14.1, 15.9, 16.7, 17.2, 17.5, 31.0, 34.3, 51.0, 61.6, 61.7, 91.6, 93.2, 111.0, 166.2, 166.3, 167.5, 167.8; **Zsyn** δ =13.9, 13.9, 15.4, 16.4, 16.8, 17.2, 33.2, 36.0, 51.0, 61.9, 62.0, 90.3, 91.3, 112.9, 163.2, 165.2, 167.1, 168.7; IR (CHCl₃) of major isomer **Zsyn**: ν =1038.6, 1224.2, 1673, 1747.9, 2978.8, 3019.4 cm⁻¹; MS (70 eV, EI): m/z (%): 373 (0.2)[M⁺+1], 299 (34), 230 (19), 229 (100), 141 (12), 86 (35), 84 (53), 71 (32); elemental analysis calcd (%) for C₁₈H₂₈O₈: C 58.05, H 7.58; found: C 58.01, H 7.52.

Diethyl 5-((methoxycarbonyl)methylene)-2,4-diisobutyl-1,3-dioxolane-2,4-dicarboxylate (6e): 56% combined yield of a mixture of 4 isomers (**Eanti**: **Esyn**: **Zanti**: **Zsyn**. ratio = 0.33: 0.80: 0.39: 1.0). The order of increasing polarity in TLC is: **Eanti** > **Esyn** = **Zanti** > **Zsyn**. **Z-syn** major isomer: ¹H NMR (400 MHz, CDCl₃, 25°C): δ =0.88 (d, $^3J(\text{H,H})$ =6.6 Hz, 3H), 0.93 (d, $^3J(\text{H,H})$ =6.6 Hz, 3H), 0.95 (d, $^3J(\text{H,H})$ =6.4 Hz, 3H), 1.02 (d, $^3J(\text{H,H})$ =6.6 Hz, 3H), 1.24 (t, $^3J(\text{H,H})$ =7.2 Hz, 3H), 1.26 (t, $^3J(\text{H,H})$ =7.2 Hz, 3H), 1.68–1.91 (m, 4H), 2.02 (dd, $^3J(\text{H,H})$ =5.6, 13.8 Hz, 1H), 2.17 (dd, $^3J(\text{H,H})$ =5.3, 14.1 Hz, 1H), 3.68 (s, 3H), 4.11–4.22 (m, 4H), 5.17 (s, 1H); ¹³C NMR (100 MHz, CDCl₃, 25°C): δ =13.9, 13.9, 23.2, 23.3, 23.5, 23.6, 23.6, 24.7, 43.3, 47.1, 51.1, 62.0, 62.2, 87.5, 90.4, 111.6, 164.5, 165.2, 167.2, 168.8; IR (CHCl₃): ν =1132.8, 1224.1, 1367.7, 1438.3, 1655.5, 1710.6, 1748.8, 2961.5, 3020.2 cm⁻¹; MS (70 eV, EI): m/z (%): 327 (17)[M⁺-CO₂Et], 295 (9.0), 244 (13), 243 (100), 85 (40), 57 (51); elemental analysis calcd (%) for C₂₀H₃₂O₈: C 59.98, H 8.05; found: C 59.83, H 8.20. Characteristic data for the **E-anti** isomer: ¹H NMR (400 MHz, CDCl₃, 25°C): δ =3.63 (s, 3H), 5.56 (s, 1H). Characteristic data for the **E-syn** isomer: ¹H NMR (400 MHz, CDCl₃, 25°C): δ =3.62 (s, 3H), 5.62 (s, 1H). Characteristic data for the **Z-anti** isomer: ¹H NMR (400 MHz, CDCl₃, 25°C): δ =3.68 (s, 3H), 5.13 (s, 1H).

5-Ethyl 1-methyl 4-((E)-2-(methoxycarbonyl)vinyl)-4-isopropylpent-2-ynedioate (7d): ¹H NMR (400 MHz, CDCl₃, 25°C): δ =1.02 (d, $^3J(\text{H,H})$ =6.9 Hz, 3H), 1.05 (d, $^3J(\text{H,H})$ =6.9 Hz, 3H), 1.29 (t, $^3J(\text{H,H})$ =7.2 Hz, 3H), 2.34–2.44 (m, 1H), 3.67 (s, 3H), 3.78 (s, 3H), 4.26 (dq, $^3J(\text{H,H})$ =7.2, 10.9 Hz, 1H), 4.30 (dq, $^3J(\text{H,H})$ =7.2, 10.9 Hz, 1H), 5.47 (d, $^3J(\text{H,H})$ =12.2 Hz, 1H), 7.55 (d, $^3J(\text{H,H})$ =12.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃, 25°C): δ =14.0, 16.5, 16.9, 37.1, 51.1, 53.0, 63.1, 80.1, 80.3, 83.3, 101.1, 152.7, 158.1, 166.6, 167.3; IR (CHCl₃): ν =1126.6, 1245.2, 1436.7, 1647.0, 1717.5, 1750.9, 2239.0, 3022.0 cm⁻¹; MS (70 eV, EI): m/z (%): 312 (0.7)[M⁺], 239(27), 188 (34), 179 (86), 156 (46), 151 (38), 139 (88), 107 (84), 105 (100), 77 (83); elemental analysis calcd (%) for C₁₅H₂₀O₇: C 57.69, H 6.45; found: C 57.79, H 6.42.

5-Ethyl 1-methyl 4-((E)-2-(methoxycarbonyl)vinyl)-4-isobutylpent-2-ynedioate (7e): ¹H NMR (400 MHz, CDCl₃, 25°C): δ =0.94 (d, $^3J(\text{H,H})$ =6.4 Hz, 3H), 0.97 (d, $^3J(\text{H,H})$ =6.6 Hz, 3H), 1.30 (t, $^3J(\text{H,H})$ =7.2 Hz, 3H), 1.88–1.97 (m, 1H), 1.99 (dd, $^3J(\text{H,H})$ =6.1, 14.0 Hz, 1H), 2.04 (dd, $^3J(\text{H,H})$ =6.6, 14.0 Hz, 1H), 3.68 (s, 3H), 3.79 (s, 3H), 4.28 (q, $^3J(\text{H,H})$ =7.2 Hz, 2H), 5.47 (d, $^3J(\text{H,H})$ =12.2 Hz, 1H), 7.57 (d, $^3J(\text{H,H})$ =12.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃, 25°C): δ =13.9, 23.1, 23.5, 24.8, 46.7, 51.2, 53.0, 63.3, 79.4, 79.9, 80.7, 101.3, 152.7, 157.7, 166.9, 167.3; IR (CHCl₃): ν =1128.1, 1259.7, 1436.6, 1646.7, 1717.9, 1752.0, 2243.0, 2956.9, 3020.4 cm⁻¹; MS (70 eV, EI): m/z (%): 326 (0.6)[M⁺],

253 (59), 193 (79), 183 (51), 179 (68), 151 (100), 123 (72); elemental analysis calcd (%) for C₁₆H₂₂O₇: C 58.89, H 6.79; found: C 58.98, H 6.84.

Methyl 4-((E)-2-(methoxycarbonyl)vinyl)oxy-4-(diethylcarbamoyl)pent-2-ynoate (9a): ¹H NMR (400 MHz, CDCl₃, 25°C): δ=1.09 (t, ³J(H,H)=6.9 Hz, 3H), 1.15 (t, ³J(H,H)=6.9 Hz, 3H), 1.78 (s, 3H), 3.27-3.59 (m, 4H), 3.65 (s, 3H), 3.75 (s, 3H), 5.45 (d, ³J(H,H)=12.2 Hz, 1H), 7.49 (d, ³J(H,H)=12.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃, 25°C): δ=12.1, 13.3, 25.5, 41.4, 42.3, 51.2, 53.0, 76.9, 80.2, 81.9, 102.0, 152.7, 155.8, 163.6, 167.0; IR (CHCl₃): ν=3020.1, 2239.3, 1717.0, 1646.5, 1436.2, 1266.5, 1131.3 cm⁻¹; MS (70 eV, EI): m/z (%): 311 (3.3)[M⁺], 182 (40), 101 (14), 100 (100), 72 (75); elemental analysis calcd (%) for C₁₅H₂₁NO₆: C 57.87, H 6.80, N 4.50; found: C 57.79, H 6.87, N 4.52.

Methyl 4-((E)-2-(methoxycarbonyl)vinyl)oxy-4-methyl-5-oxo-5-(piperidin-1-yl)pent-2-ynoate (9b): ¹H NMR (400 MHz, CDCl₃, 25°C): δ=1.57 (m, 6H), 1.81 (s, 3H), 3.59 (m, 4H), 3.68 (s, 3H), 3.78 (s, 3H), 5.47 (d, ³J(H,H)=11.9 Hz, 1H), 7.50 (d, ³J(H,H)=11.9 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃, 25°C): δ=24.3, 25.3, 25.6, 45.0, 47.6, 51.3, 53.1, 76.8, 80.2, 82.0, 102.0, 152.8, 156.1, 162.8, 167.1; IR (CHCl₃): ν=3020.4, 2947.4, 2239.6, 1716.5, 1650.3, 1438.5, 1252.5, 1131.3 cm⁻¹; MS (70 eV, EI): m/z (%): 323 (1.3)[M⁺], 194 (45), 113 (10), 112 (100), 84 (19), 69 (52); elemental analysis calcd (%) for C₁₆H₂₁NO₆: C 59.43, H 6.55, N 4.33; found: C 59.41, H 6.75, N 4.70.

Methyl 4-((E)-2-(methoxycarbonyl)vinyl)oxy-4-(dibenzylcarbamoyl)pent-2-ynoate (9c): ¹H NMR (400 MHz, CDCl₃, 25°C): δ=1.94 (s, 3H), 3.68 (s, 3H), 3.70 (s, 3H), 4.44 (d, ³J(H,H)=14.8 Hz, 1H), 4.62 (d, ³J(H,H)=14.8 Hz, 1H), 4.63 (d, ³J(H,H)=16.4 Hz, 1H), 4.74 (d, ³J(H,H)=16.4 Hz, 1H), 5.31 (d, ³J(H,H)=11.9 Hz, 1H), 7.11-7.19 (m, 4H), 7.26-7.36 (m, 6H), 5.58 (d, ³J(H,H)=11.9 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃, 25°C): δ=25.5, 48.8, 50.5, 51.2, 52.9, 77.1, 81.0, 81.4, 102.5, 127.2, 127.5, 127.6, 128.0, 128.6, 135.2, 136.0, 152.4, 155.3, 165.2, 166.8; IR (CHCl₃): ν=1128.1, 1270.2, 1436.2, 1647.3, 1718.7, 2238.9, 2954.0, 3018.4 cm⁻¹; MS (70 eV, EI): m/z (%): 435 (1.3)[M⁺], 224 (8.3), 211 (19), 92 (15), 91 (100); elemental analysis calcd (%) for C₂₅H₂₅NO₆: C 68.95, H 5.79, N 3.22; found: C 68.75, H 6.01, N 3.25.

Methyl 4-((E)-2-(methoxycarbonyl)vinyl)oxy-4-(diethylcarbamoyl)hex-2-ynoate (9d): ¹H NMR (400 MHz, CDCl₃, 25°C): δ=1.05 (t, ³J(H,H)=7.4 Hz, 3H), 1.12 (t, ³J(H,H)=7.2 Hz, 3H), 1.19 (t, ³J(H,H)=6.9 Hz, 3H), 2.09-2.22 (m, 2H), 3.30-3.42 (m, 2H), 3.45-3.63 (m, 2H), 3.68 (s, 3H), 3.79 (s, 3H), 5.49 (d, ³J(H,H)=12.2 Hz, 1H), 7.48 (d, ³J(H,H)=12.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃, 25°C): δ=8.0, 12.3, 13.4, 31.5, 41.5, 42.1, 51.2, 53.0, 80.7, 80.8, 81.5, 101.5, 152.8, 156.6, 163.6, 167.3; IR (CHCl₃): ν=3020.4, 2236.1, 1716.5, 1646.6, 1436.3, 1258.7, 1132.1 cm⁻¹; MS (70 eV, EI): m/z (%): 325 (0.9)[M⁺], 224 (6.5), 196 (7.1), 100 (100), 72 (29); elemental analysis calcd (%) for C₁₆H₂₃NO₆: C 59.06, H 7.13, N 4.31; found: C 59.08, H 7.34, N 4.35.

Methyl 4-((E)-2-(methoxycarbonyl)vinyl)oxy-4-(diethylcarbamoyl)-4-phenylbut-2-ynoate (9e): ¹H NMR (400 MHz, CHCl₃, 25°C): δ=0.79 (t, ³J(H,H)=7.2 Hz, 3H), 1.12 (t, ³J(H,H)=6.9 Hz, 3H), 3.04-3.13 (m, 1H), 3.17-3.30 (m, 2H), 3.41-3.50 (m, 1H), 3.66 (s, 3H), 3.81 (s, 3H), 5.51 (d, ³J(H,H)=12.2 Hz, 1H), 7.41-7.44 (m, 3H), 7.52-7.54 (m, 2H), 7.63 (d, ³J(H,H)=12.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃, 25°C): δ=12.5, 12.9, 42.0, 42.6, 51.6, 53.6, 81.1, 82.2, 101.6, 126.3, 127.0, 129.7, 130.5, 135.9, 153.3, 158.6, 164.3, 168.0; IR (CHCl₃): ν=3019.3, 2953.9, 2243.6, 1717.4, 1662.1, 1646.8, 1436.2, 1262.3, 1128.3 cm⁻¹; MS (70 eV, EI): m/z (%): 373 (0.3)[M⁺], 299 (100), 229 (59), 155 (24), 105 (25), 100 (34), 71 (77); elemental analysis calcd (%) for C₂₀H₂₃NO₆: C 64.33, H 6.71, N 6.71; found: C 64.62, H 6.55, N 6.55.

Diethyl 2,4-dimethyl-5-(tosylmethylene)-1,3-dioxolane-2,4-dicarboxylate (11): 64% combined yield of a mixture of 2 isomers (*Zanti*: *Zsyn*. ratio = 1.17: 1.0). The order of increasing polarity in TLC is as follows: *Zanti* > *Zsyn*. ***Z-anti*** major isomer ¹H NMR (400 MHz, CDCl₃, 25°C): δ=1.18 (t, ³J(H,H)=7.2 Hz, 3H), 1.20 (t, ³J(H,H)=7.2 Hz, 3H), 1.62 (s, 3H), 1.78 (s, 3H), 2.40 (s, 3H), 4.04 (dq, ³J(H,H)=7.2,

10.9 Hz, 1H), 4.14 (dq, $^3J(\text{H,H})=7.2$, 10.9 Hz, 1H), 4.17 (q, $^3J(\text{H,H})=7.2$ Hz, 2H), 5.69 (s, 1H), 7.27 (d, $^3J(\text{H,H})=8.2$ Hz, 2H), 7.81 (d, $^3J(\text{H,H})=8.2$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3 , 25°C): $\delta=13.7$, 21.5, 21.6, 23.1, 62.4, 62.9, 86.3, 101.8, 111.7, 127.4, 129.3, 139.5, 143.9, 162.0, 168.7, 168.5; IR (CHCl_3): $\nu=1017.6$, 1148.0, 1222.5, 1231.6, 1379.5, 1655.0, 1750.4, 3021.4 cm^{-1} ; MS (70 eV, EI): m/z (%): 339 (99) [$\text{M}^+-\text{CO}_2\text{Et}$], 297 (100), 157 (27), 155 (35), 139 (80), 91 (43); elemental analysis calcd (%) for $\text{C}_{19}\text{H}_{24}\text{O}_8\text{S}$: C 55.33, H 5.87; found: C 55.04, H 5.76. Characteristic data for the **Z-syn** isomer: ^1H NMR (400 MHz, CDCl_3 , 25°C): $\delta=5.80$ (s, 1H).

Acknowledgments. This research was supported by the Spanish Ministerio de Educación y Ciencia and the European Regional Development Fund (CTQ2005-09074-C02-02), and the Instituto Canario de Investigación del Cáncer (ICIC-GI nº 10/2005; ISCiii, RTICCC C03/10). D. T. is the recipient of a postdoctoral I3P Fellowship from the C.S.I.C.

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Scheme 1. Chemo-differentiating organocatalyzed ABB' 3CRs involving terminal alkynoates and carbonyl compounds.

Scheme 2. Chemo-differentiating organocatalyzed ABB' 3CR involving alkyne sulphone **10** and ethyl pyruvate **4a**.

Scheme 3. Kinetic-controlled proposed mechanism for the folding process incorporating an ABB' 3CR-based synthetic manifold. Three different catalytic cycles, three different topologies.

Figure 1. Skeletal diversity-limiting principle: a unique topology (core-atom connectivity) associates with each MCR; structural variations on each module translate into structural variations of the appended functionalities M_i.

Figure 2. Approach developing a novel substrate-based folding process comprising a common and defined MCR-based manifold to generate a structurally different array of products.

Table 1. ABB' 3CR based on α -ketoesters.

Entry	R ¹	OR	4	3 (%) ^[a]
1	H	OEt	a	81
2	Me	OMe	b	90
3	Et	OMe	c	89 ^[b]
4	Hept	OMe	d	87 ^[b]
5	iBu	OEt	e	81 ^[b]
6	PhCH ₂	OEt	f	89
7	MeO ₂ CCH ₂	OEt	g	85
8	MeCO	OEt	h	-

^[a] Methyl Propiolate (1mmol), α -ketoester (2 mmol), Et₃N (10 mol%), CH₂Cl₂, 0°C, 2h. ^[b] THF

Table 2. ABB' 3CR based on aromatic or branched α -ketoesters.

Entry	R ¹	R ²	OR	Nu	5	Yield (%) ^[a]	
						6	7
1	Ph	OMe	OMe	Et ₃ N	a	84	-
2	2-Thiophene	OMe	OMe	Et ₃ N	b	84	-
3				Et ₃ N	c	MeO ₂ C 84	
4	Me	Me	OEt	Et ₃ N	d	89	-
				DABCO		-	97
5	iPr	H	OEt	Et ₃ N	e	56 ^[b]	-
				DABCO		-	78

^[a] Methyl Propiolate (1mmol), α -ketoester (1 mmol) , Et₃N (10 mol%), CH₂Cl₂, 0°C, 2h.. ^[b] Methyl Propiolate (2 mmol), α -ketoester (2 mmol), Et₃N (0.05 mmol). 30% of O-alkylated enolate (Scheme 2)

Table 3. ABB' 3CR based on α -ketoamides.

Entry	R ¹	NR ₂	8	9(%) ^[a]
1	Me	NEt ₂	a	64
2	Me	C ₅ H ₁₀ N	b	68
3	Me	NBn ₂	c	60
4	Et	NEt ₂	d	57 ^[b]
5	Ph	NEt ₂	e	73

^[a] Methyl Propiolate (2 mmol), α -ketoamide (1 mmol), Et₃N (10 mol%), CH₂Cl₂, 0°C, 2h. ^[b] Methyl Propiolate (3 mmol)

Text for TOC

A novel 3CR-based folding process based on a chemo-differentiating organocatalyzed ABB' 3CR of a terminal conjugated alkynoate (building block) and α -dicarbonyl compounds (diversity-generating blocks) to selectively generate an array of different molecular topologies (γ -lactones, linear propargylic enol ethers or 1,3-dioxolane rings). Amides and esters behave as efficient reactivity-encoding elements (σ) of the attached keto functionality. Overall, this substrate-based folding process generates three different molecular architectures from the same modular functionalities (ketones) and under the same reaction conditions (methyl propiolate and tertiary amine). In addition, all the products share a common β -alkoxy-acrylate reactive functionality to be collective substrates for a subsequent diversity-generating process.

Keywords: Diversity-oriented synthesis, alkynes, organocatalysis, multicomponent reactions, 1,2-dicarbonyl compounds.