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A Substrate-Based Folding Process Incorporating Chemodifferentiating ABB′ Three-Component Reactions of Terminal Alkynoates and 1,2-Dicarbonyl Compounds: A Skeletal-Diversity-Oriented Synthetic Manifold

David Tejedor,[a, b] Alicia Sántos-Expósito,[a, b] and Fernando García-Tellado*[a, b]

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

Abstract: A novel three-component reaction (3CR)-based folding process that is able to generate complexity and skeletal diversity is described. The process utilizes chemodifferentiating organocatalyzed ABB′ 3CRs of a terminal conjugated alkynoate (building block) with 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 (of the 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 combinatorial applications, all of the products share a common reactive functionality that allows them to be collective substrates for a subsequent diversity-generating process.

Keywords: alkynes · dicarbonyl compounds · diversity-oriented synthesis · multicomponent reactions · organocatalysis

Introduction

Multicomponent reactions (MCRs) are well-appreciated manifolds for diversity-oriented molecular construction. In accordance 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 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 for the study of biology.[1] Biginelli,[2] Mannich,[3] and Ugi[4] reactions constitute the basis of many of these combinatorial synthetic manifolds.[5] Typically, these reactions create diversity by generating molecular architectures based on a common molecular core (structural complexity) adorned with different appended functionalities (functional diversity, M_i in Figure 1). While this process 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 when the goal is to create collections of compounds with extensive skeletal and stereochemical diversity.[7] The overcoming of this limiting principle is not a simple task and it requires a careful reactivity design and a synthetic-plan-

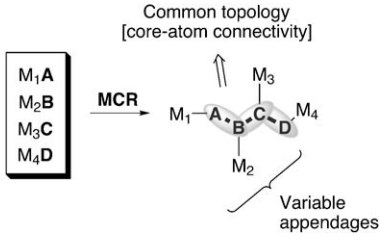


Figure 1. Skeletal-diversity-limiting principle: a unique topology (core-atom connectivity) associates with each MCR; structural variations on each module translate into structural variations of the appended functionalities M_i. M_i = modules, **A**–**D** = reactive functional groups.

[a] Dr. D. Tejedor, A. Sántos-Expósito, Dr. F. García-Tellado
Instituto de Productos Naturales y Agrobiología, CSIC
Astrofísico Francisco Sánchez 3
38206 La Laguna, Tenerife, Canary Islands (Spain)
Fax: (+34) 922-260-135
E-mail: fgarcia@ipna.csic.es

[b] Dr. D. Tejedor, A. Sántos-Expósito, Dr. F. García-Tellado
Instituto Canario de Investigación del Cáncer
(www.icic.es)

ning algorithm completely different from those 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 with different appendages that pre-encode skeletal information (σ elements) into a collection of products with distinct molecular skeletons by using common reaction conditions.[9] In contrast to the challenges faced in generating skeletal diversity with MCRs, these reactions are very well suited to create structural complexity, the other great challenge of DOS. The planning of single DOS manifolds to address both goals is a challenging goal. A logical approach would consist of 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 chemodifferentiating organocatalyzed ABB′ three-component reaction (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 finely tuned balance between the pK_a value and the reactivity of the α-dicarbonyl module controls the chemical outcome of these 3CRs. In addition, all of the products share a common reactive functionality (β-alkoxyacrylate) that allows them to be collective substrates for a subsequent diversity-generating process (maximizing structural diversity while maintaining common reactivity).

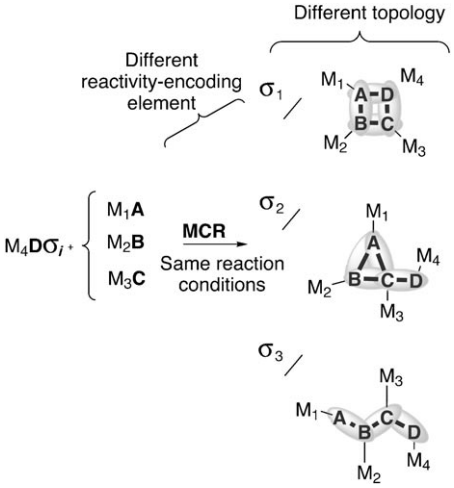
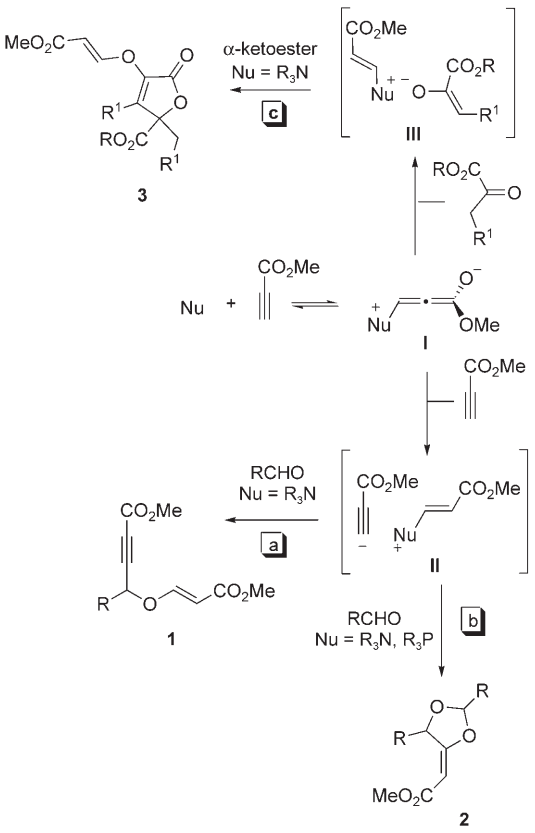


Figure 2. Approach developing a novel substrate-based folding process comprising a common and defined MCR-based manifold to generate an array of structurally different products. σ_i = reactivity-encoding elements.

Abstract in Spanish: *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 quimio-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, nucleofília (catalizador) y electrofília del grupo carbonilo. En conjunto, este proceso de plegamiento molecular basado en el substrato genera tres diferentes arquitecturas moleculares a partir de las mismas funcionalidades (cetonas) y bajo las mismas condiciones de reacción (proioplato 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.*

Results and Discussion

The synthetic manifold: We have recently described a set of chemodifferentiating 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] The key to these systems is the catalytic generation of allenoate **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 (pK_a = 18.8)[13] inhibit these processes and trigger 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) through a catalytic cycle involving a sequential homoaldol condensation/lactonization/Michael addition set of reactions. While the homoaldol condensation allows the chemodifferentiation of two units of the carbonyl-containing module, the Michael addition reaction closes the catalytic cycle by formation of product **3** and catalyst regeneration.



Scheme 1. Chemodifferentiating organocatalyzed ABB′ 3CRs involving terminal alkynoates and carbonyl compounds. Nu = nucleophile.

A common property of these three domino processes is their ability to perform a chemodifferentiating processing of otherwise identical units of starting material. They transform a degenerate set of substrates (two chemical inputs) into a final product whose structure incorporates one of these modules twice in the form of differentiated chemical functions or structural motifs (nondegenerate chemical output). *This remarkable property confers all of the synthetic advantages associated with 3CRs on these bimolecular processes.* 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.

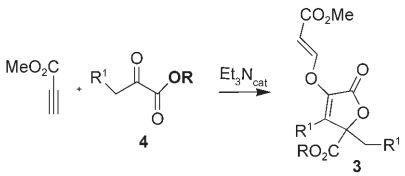
Reactivity-encoding elements: α-Dicarbonyl compounds constitute a wide family of reactive functionalities with enhanced chemical reactivity towards nucleophiles. This reactivity enhancement is mainly associated with the powerful activation of one electron-withdrawing carbonyl group on the other. This electronic effect also accounts for the relative higher acidities of these functionalities with regard to those of the homologous monocarbonyl compounds. The strength of the electron-withdrawing effect can be conveniently tuned by the right choice of 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* and it makes these functionalities excellent reagents for substrate-based folding processes based on our chemodifferentiating ABB′ 3CRs.

From all of 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 wide ranges of both reactivity and acidity while maintaining an overall similarity. In addition, most of them are commercially 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 irresoluble 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 1–7)[11,15] or 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 1–7). Ethyl 2,4-dioxopentanoate (**4h**), incorporating an extra 1,3-diketone functionality, proved to be too stable to productively participate in this reaction system (Table 1, entry 8). Lipophilic α-ketoesters **4c–e** gave high levels of the undesired enolate **III** *O*-alkylation product in dichloromethane. This accompanying side reaction is a serious problem and it becomes a very important route for the loss of resources. Fortunately, it could be completely suppressed by the use of tet-

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



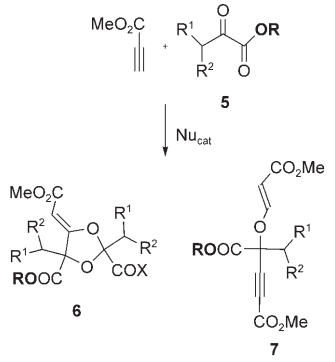
Entry	R^1	OR	**4**	Yield of **3** [%][a]
1	H	OEt	**a**	81
2	Me	OMe	**b**	90
3	Et	OMe	**c**	89[b]
4	Hept	OEt	**d**	87[b]
5	*i*Bu	OEt	**e**	81[b]
6	$PhCH_2$	OEt	**f**	89
7	MeO_2CCH_2	OMe	**g**	85
8	MeCO	OEt	**h**	–

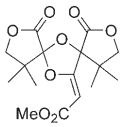
[a] Methyl propiolate (1 mmol), α-ketoester (2 mmol), Et_3N (10 mol%), CH_2Cl_2, 0 °C, 2 h. [b] Reaction performed in tetrahydrofuran (THF).

rahydrofuran, a better coordinating solvent (Table 1, entries 3–5).

The nonacidic β,β-disubstituted α-ketoesters **5a–c** were processed as activated ketones through the acetylide-driven pathway (Scheme 1, path a) 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 (Table 2, entries 1 and 2). Even the sterically encumbered α-ketolactone **5c** was efficiently processed into the crowded 2,5-dispiro-1,3-dioxolane derivative **6c** (84% yield; Table 2, entry 3).

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	Et_3N	**a**	84	–
2	2-thiophene		OMe	Et_3N	**b**	85	–
3				Et_3N	**c**	84 	–
4	Me	Me	OEt	Et_3N	**d**	89	–
				DABCO		–	97
5	*i*Pr	H	OEt	Et_3N	**e**	56[b]	–
				DABCO		–	78

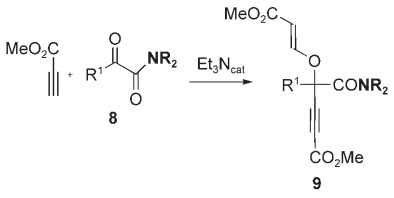
[a] Methyl propiolate (1 mmol), α-ketoester (2 mmol), Et_3N (10 mol%), CH_2Cl_2, 0°C, 2 h. [b] Methyl propiolate (2 mmol), α-ketoester (2 mmol), Et_3N (0.05 mmol). 30% of the *O*-alkylated enolate was obtained (Scheme 3).

The β- and γ-substituted (branched) α-ketoesters displayed an acidity that was too diminished[17] to allow productive incorporation in the enolate-driven processes. Accordingly, these compounds were efficiently processed through 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 an excess of alkynoate and a lower catalyst charge to form the 1,3-dioxolane **6e** with moderate yield (56%, 30% *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 β- or γ-substituted α-ketoesters behave as highly reactive aliphatic aldehydes rather than activated ketones. *The β- or γ-branching of the alkyl chain performs, therefore, the function of a masked skeletal-information-encoding element.*[8]

α-Ketoamides: These compounds are less acidic and reactive than the 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 both proved to be good substrates for these 3CRs (Table 3, entries 1–5). Cyclic or acyclic tertiary amines encoded the reactivity of the adjacent keto group in a similar manner (Table 3, entries 1–3). Only the most lipophilic compound, *N,N*-diethyl 2-oxobutyroamide (**8d**), required an excess of alkynoate to yield the propargylic enol ether **9d** in a useful yield (Table 3, entry 4).

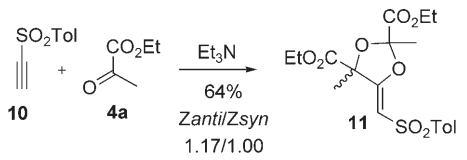
Table 3. ABB′ 3CR based on α-ketoamides.



Entry	R^1	NR_2	**8**	Yield of **9** [%][a]
1	Me	NEt_2	**a**	64
2	Me	$C_5H_{10}N$	**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), Et_3N (10 mol%), CH_2Cl_2, 0°C, 2 h. [b] Methyl propiolate (3 mmol).

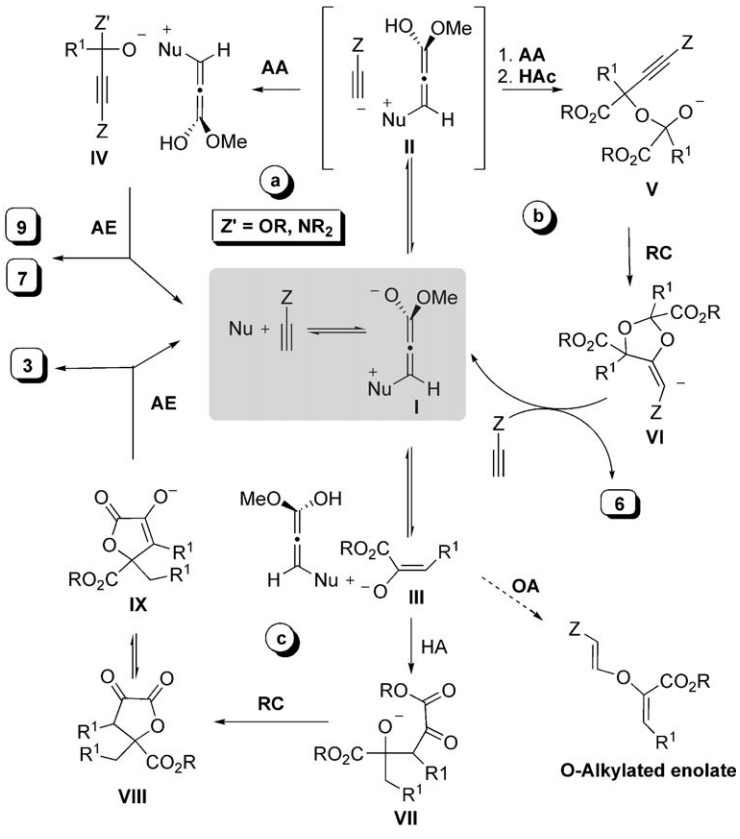
Terminal conjugated alkynes: The influence of the terminal conjugated alkyne was studied with sulfone **10** (Scheme 2) and ethyl pyruvate **4a**. In spite of the extremely high reactivity and acidity of **4a**, sulfone **10** was only processed through the acetylide-driven 3CR to afford the correspond-



Scheme 2. Chemodifferentiating organocatalyzed ABB′ 3CR involving alkyne sulfone **10** and ethyl pyruvate **4a**. Tol = tolyl.

ing 1,3-dioxolane derivative **11**. Remarkably, *sulfone **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 kinetically controlled reaction network involving three different and competitive catalytic cycles, a–c (Scheme 3), each affording a specific skeletal framework. Product selectivity directly arises from the kinetic model utilized by this manifold, which allows the performance of only one cycle at a time. Consequently, when one cycle is working, the other two remain kinetically arrested and the entire chemical transformation is selectively funneled toward one



Scheme 3. Kinetically controlled proposed mechanism for the folding process incorporating an ABB′ 3CR-based synthetic manifold. Three different catalytic cycles lead to three different topologies. AA = acetylide addition, AE = addition–elimination, HA = homoaldolic, HAc = hemiacetalization, OA = *O*-alkylation, RC = ring-closing, Z = CO_2Me, Z′ = OR or NR_2.

of three skeletally 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 by allowing an acetylide-driven process (cycle a or b), or an enolate-driven one (cycle c). In the case of the ethynyl sulfone **10**, this property does not become an issue because the acidity of the ethynyl sulfone must be higher than the acidity of ethyl pyruvate.

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

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**. The nature of the catalyst does not play a special role therein. The catalytic cycle is launched by the formation of enolate **III**. On the other hand, the acetylide-driven processes are characteristic either of the less acidic α-dicarbonyl compounds (β- or γ-substituted α-ketoesters and α-ketoamides) or the nonacidic ones (β,β-disubstituted α-ketoesters) and these processes selectively afford β,β-disubstituted propargylic enol ethers **7** (or **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** (or **9**) or **6**. Ethynyl sulfone **10** reacts through 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 cycle c by generation of enolate **III**. The cycle progresses by homoaldolic 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 γ-lactone **3** with release of the catalyst 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] a fact 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 (β- or γ-substituted α-ketoesters and α-ketoamides) or when 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 acetylide addition on the α-dicarbonyl substrate to generate the corresponding γ,γ-disubstituted prop-

argylic alkoxide intermediate **IV**, which irreversibly adds to the β-ammonium acrylate counterion to afford γ,γ-disubstituted propargylic enol ether **7** (α-ketoeters) or **9** (α-ketoamides) while closing the cycle and regenerating the catalyst. Cycle b requires acetylide addition on the α-dicarbonyl substrate to generate the corresponding propargylic alkoxide **IV** (Z′ = OR). Addition of 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 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 an α-dicarbonyl component with reduced electrophilicity. While DABCO fulfils the first 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 β- or γ-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 two substrate-dependent 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 the pK_a value between the 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 an 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 that is able to generate complexity and skeletal diversity. The process utilizes chemodifferentiating 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 combinatorial applications, all of the products share a common reactive functionality that allows them to be collective substrates for a subsequent diversity-generating process.

Experimental Section

General remarks: ^{1}H 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 AC200 and AMX2-500 spectrometers), respectively. FT-IR spectra were measured in chloroform solutions by 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 analyzer. The analytical thin-layer chromatography plates used were Merck Brinkman UV-active silica gel (Kieselgel 60 F254) on aluminum. Flash column chromatography was carried out with Merck silica gel 60 (particle size less than 0.020 mm) by using appropriate mixtures of ethyl acetate and hexanes as the 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. Initial α-ketoesters and α-ketoamides were either commercially available or were prepared by using standard procedures. All other materials were obtained from commercial suppliers and used as received. Experimental data for **3a** are 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 CH_2Cl_2 (or THF; 2 mL). After the mixture was cooled to 0 °C, triethylamine (0.2 mmol) was added and the reaction mixture was stirred for 1–4 h. 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 (80:20–60:40)).

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 CH_2Cl_2 (2 mL). After the mixture was cooled to −78 °C, triethylamine (0.2 mmol) was added and the reaction mixture was stirred for 1–4 h. The solvent and excess reagents were then removed under reduced pressure. This was followed by isolation of the corresponding product **6** by flash column chromatography (silica gel, *n*-hexane/EtOAc (90:10–70:30)).

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 CH_2Cl_2 (7 mL). After the mixture was cooled to 0 °C, DABCO (for α-ketoesters, 0.2 mmol) or triethylamine (for α-ketoamides, 1.0 mmol) was added and the reaction mixture was stirred for 2–6 h (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 (90:10–70:30)).

Methyl 4-((*E*)-2-(methoxycarbonyl)vinyloxy)-2-ethyl-2,5-dihydro-3-methyl-5-oxofuran-2-carboxylate (3b): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.87 (t, ^3J(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(H,H) = 12.2 Hz, 1H), 7.86 ppm (d, ^3J(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 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 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 $C_{13}H_{16}O_7$: C 54.93, H 5.67; found: C 54.89, H 5.74.

Methyl 4-((*E*)-2-(methoxycarbonyl)vinyloxy)-3-ethyl-2,5-dihydro-5-oxo-2-propylfuran-2-carboxylate (3c): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ =

0.93 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.12 (t, ^3J(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(H,H) = 12.2 Hz, 1H), 7.86 ppm (d, ^3J(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 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 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 $C_{15}H_{20}O_7$: C 57.69, H 6.45; found: C 57.54, H 6.44.

Ethyl 4-((*E*)-2-(methoxycarbonyl)vinyloxy)-3-heptyl-2,5-dihydro-2-octyl-5-oxofuran-2-carboxylate (3d): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.86 (t, ^3J(H,H) = 7.2 Hz, 3H), 0.86 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.28 (t, ^3J(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(H,H) = 7.2 Hz, 2H), 5.50 (d, ^3J(H,H) = 12.5 Hz, 1H), 7.87 ppm (d, ^3J(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 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 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 $C_{26}H_{42}O_7$: C 66.93, H 9.07; found: C 66.85, H 9.16.

Ethyl 4-((*E*)-2-(methoxycarbonyl)vinyloxy)-2,5-dihydro-3-isobutyl-2-isopentyl-5-oxofuran-2-carboxylate (3e): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.87 (d, ^3J(H,H) = 6.6 Hz, 3H), 0.88 (d, ^3J(H,H) = 6.6 Hz, 6H), 0.91 (d, ^3J(H,H) = 6.6 Hz, 3H), 1.10–1.16 (m, 2H), 1.27 (t, ^3J(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(H,H) = 7.4, 14.8 Hz, 1H), 2.20–2.28 (m, 2H), 3.70 (s, 3H), 4.20 (q, ^3J(H,H) = 7.2 Hz, 2H), 5.51 (d, ^3J(H,H) = 2.2 Hz, 1H), 7.88 ppm (d, ^3J(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 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 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 $C_{20}H_{30}O_7$: C 62.81, H 7.91; found: C 62.74, H 7.96.

Ethyl 4-((*E*)-2-(methoxycarbonyl)vinyloxy)-3-benzyl-2,5-dihydro-5-oxo-2-phenethylfuran-2-carboxylate (3f): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.16 (t, ^3J(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(H,H) = 2.2 Hz, 1H), 6.97–6.99 (m, 2H), 7.15–7.32 (m, 8H), 7.97 ppm (d, ^3J(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 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 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 $C_{26}H_{26}O_7$: C 69.32, H 5.82; found: C 69.40, H 6.08.

Methyl 4-((*E*)-2-(methoxycarbonyl)vinyloxy)-2-(2-(methoxycarbonyl)-ethyl)-3-((methoxycarbonyl)methyl)-2,5-dihydro-5-oxofuran-2-carboxylate (3g): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.20–2.44 (m, 2H), 2.55–2.62 (m, 1H), 3.36 (d, ^3J(H,H) = 17.0 Hz, 1H), 3.49 (d, ^3J(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 ppm (d, 1H, *J* = 12.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 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 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 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 $C_{17}H_{20}O_{11}$: 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 (*E-anti*:*E-syn*:*Z-anti*:*Z-syn* ratio = 0.16:0.31:0.31:1.0). The order of increasing polarity by TLC is: *E-anti* ≈ *E-syn* > *Z-anti* > *Z-syn*. *Z-syn* major isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.70 (s, 3H), 3.76 (s, 3H), 3.87 (s, 3H), 5.25 (s, 1H), 7.30–7.69 ppm (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 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 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 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) [$M^+ - CO_2Me$], 189 (5), 179 (8), 161 (2), 105 (100), 84 (29), 77 (16); elemental analysis: calcd (%) for $C_{22}H_{20}O_8$: C 64.07, H 4.89; found: C 64.12, H 4.88. Characteristic data for the *E-anti* isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.19 (s, 3H), 3.59 (s, 3H), 3.74 (s, 3H), 5.95 ppm (s, 1H). Characteristic data for the *E-syn* isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.60 (s, 3H), 3.77 (s, 3H), 3.81 (s, 3H), 5.90 ppm (s, 1H). Characteristic data for the *Z-anti* isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.49 (s, 3H), 3.51 (s, 3H), 3.74 (s, 3H), 5.40 ppm (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 (*E-anti*:*E-syn*:*Z-anti*:*Z-syn* ratio = 0.13:0.33:0.20:1.0). The order of increasing polarity by TLC is: *E-anti* > *E-syn* > *Z-anti* > *Z-syn*. *Z-syn* major isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.70 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 5.39 (s, 1H), 6.95 (dd, ^3J(H,H) = 3.7, 5.0 Hz, 1H), 7.01 (dd, ^3J(H,H) = 3.7, 5.0 Hz, 1H), 7.18 (d, ^3J(H,H) = 1.3, 4.0 Hz, 1H), 7.32 (d, ^3J(H,H) = 1.3, 5.3 Hz, 1H), 7.39–7.42 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 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 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 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) [$M^+ - CO_2Me$], 254 (54), 226 (17), 167 (29), 110 (100), 96 (18); elemental analysis: calcd (%) for $C_{18}H_{16}O_8S_2$: 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: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.48 (s, 3H), 3.57 (s, 3H), 3.81 (s, 3H), 5.85 ppm (s, 1H). Characteristic data for the *E-syn* isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.53 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 5.82 ppm (s, 1H). Characteristic data for the *Z-anti* isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.65 (s, 3H), 3.73 (s, 3H), 3.74 (s, 3H), 5.51 ppm (s, 1H).

Dioxolane from dihydro-4,4-dimethylfuran-2,3-dione and methyl propiolate (6c): 84% combined yield of a mixture of 2 isomers (*Z-anti*:*Z-syn* ratio = 1.62:1.0). The order of increasing polarity by TLC is: *Z-anti* > *Z-syn*. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): *Z-anti*: δ = 1.21 (s, 3H), 1.22 (s, 3H), 1.27 (s, 3H), 1.29 (s, 3H), 3.70 (s, 3H), 4.08 (d, ^3J(H,H) = 9.6 Hz, 1H), 4.09 (d, ^3J(H,H) = 8.8 Hz, 1H), 4.12 (d, ^3J(H,H) = 9.6 Hz, 1H), 4.21 (d, ^3J(H,H) = 8.8 Hz, 1H), 4.89 ppm (s, 1H); *Z-syn*: δ = 1.14 (s, 3H), 1.20 (s, 3H), 1.23 (s, 3H), 1.25 (s, 3H), 3.69 (s, 3H), 4.09 (d, ^3J(H,H) = 8.8 Hz, 1H), 4.10 (s, 2H), 4.12 (d, ^3J(H,H) = 8.8 Hz, 1H), 5.06 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): *Z-anti*: δ = 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 ppm; *Z-syn*: δ = 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 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 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 $C_{16}H_{20}O_8$: 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 (*E-anti*:*E-syn*:*Z-anti*:*Z-syn* ratio = 0.27:0.69:0.43:1.0). The order of increasing polarity by TLC is: *E-anti* > *E-syn* > *Z-anti* > *Z-syn*. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): *E-anti*: δ = 0.78 (d, ^3J(H,H) = 7.2 Hz, 3H), 0.99 (d, ^3J(H,H) = 6.9 Hz, 3H), 1.01 (d, ^3J(H,H) = 7.2 Hz, 3H), 1.16 (d, ^3J(H,H) = 6.6 Hz, 3H), 1.23 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.31 (t, ^3J(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(H,H) = 7.2 Hz, 2H), 4.22–4.31 (m, 2H), 5.60 ppm (s, 1H); *E-syn*: δ = 0.91 (d, ^3J(H,H) = 6.6 Hz, 3H), 1.01 (d, ^3J(H,H) = 6.9 Hz, 3H), 1.03 (d, ^3J(H,H) = 7.2 Hz, 3H), 1.10 (d, ^3J(H,H) = 6.6 Hz, 3H), 1.19 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.28 (t, ^3J(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 ppm (s, 1H); *Z-anti*: δ = 0.82 (d, ^3J(H,H) = 6.9 Hz, 3H), 0.95 (d, ^3J(H,H) = 6.9 Hz, 3H), 1.01 (d, ^3J(H,H) = 6.9 Hz, 3H), 1.05 (d, ^3J(H,H) = 6.9 Hz, 3H), 1.28 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.28 (t, ^3J(H,H) = 7.2 Hz, 3H), 2.20–2.32 (m, 2H), 3.69 (s, 3H), 4.18–4.35 (m, 4H), 5.22 ppm (s, 1H); *Z-syn*: δ = 0.93 (d, ^3J(H,H) = 6.6 Hz, 3H), 0.95 (d, ^3J(H,H) = 6.9 Hz, 3H), 1.03 (d, ^3J(H,H) = 6.9 Hz, 3H), 1.08 (d, ^3J(H,H) = 7.2 Hz, 3H), 1.25 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.26 (t, ^3J(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 ppm (s, 1H); ^{13}C NMR of

the 2 major isomers (100 MHz, $CDCl_3$, 25 °C): *E-syn*: 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 ppm; *Z-syn*: 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 ppm; IR ($CHCl_3$) of the major isomer: *Z-syn*: $\tilde{\nu}$ = 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 $C_{18}H_{28}O_8$: 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 (*E-anti*:*E-syn*:*Z-anti*:*Z-syn* ratio = 0.33:0.80:0.39:1.0). The order of increasing polarity by TLC is: *E-anti* > *E-syn* = *Z-anti* > *Z-syn*. *Z-syn* major isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.88 (d, ^3J(H,H) = 6.6 Hz, 3H), 0.93 (d, ^3J(H,H) = 6.6 Hz, 3H), 0.95 (d, ^3J(H,H) = 6.4 Hz, 3H), 1.02 (d, ^3J(H,H) = 6.6 Hz, 3H), 1.24 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.26 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.68–1.91 (m, 4H), 2.02 (dd, ^3J(H,H) = 5.6, 13.8 Hz, 1H), 2.17 (dd, ^3J(H,H) = 5.3, 14.1 Hz, 1H), 3.68 (s, 3H), 4.11–4.22 (m, 4H), 5.17 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 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 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 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) [$M^+ - CO_2Et$], 295 (9.0), 244 (13), 243 (100), 85 (40), 57 (51); elemental analysis: calcd (%) for $C_{20}H_{32}O_8$: C 59.98, H 8.05; found: C 59.83, H 8.20. Characteristic data for the *E-anti* isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.63 (s, 3H), 5.56 ppm (s, 1H). Characteristic data for the *E-syn* isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.62 (s, 3H), 5.62 ppm (s, 1H). Characteristic data for the *Z-anti* isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.68 (s, 3H), 5.13 ppm (s, 1H).

5-Ethyl 1-methyl 4-((*E*)-2-(methoxycarbonyl)vinyloxy)-4-isopropylpent-2-ynedioate (7d): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.02 (d, ^3J(H,H) = 6.9 Hz, 3H), 1.05 (d, ^3J(H,H) = 6.9 Hz, 3H,), 1.29 (t, ^3J(H,H) = 7.2 Hz, 3H), 2.34–2.44 (m, 1H), 3.67 (s, 3H), 3.78 (s, 3H), 4.26 (dq, ^3J(H,H) = 7.2, 10.9 Hz, 1H), 4.30 (dq, ^3J(H,H) = 7.2, 10.9 Hz, 1H), 5.47 (d, ^3J(H,H) = 12.2 Hz, 1H), 7.55 ppm (d, ^3J(H,H) = 12.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 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 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 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 $C_{15}H_{20}O_7$: C 57.69, H 6.45; found: C 57.79, H 6.42.

5-Ethyl 1-methyl 4-((*E*)-2-(methoxycarbonyl)vinyloxy)-4-isobutylpent-2-ynedioate (7e): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.94 (d, ^3J(H,H) = 6.4 Hz, 3H), 0.97 (d, ^3J(H,H) = 6.6 Hz, 3H), 1.30 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.88–1.97 (m, 1H), 1.99 (dd, ^3J(H,H) = 6.1, 14.0 Hz, 1H), 2.04 (dd, ^3J(H,H) = 6.6, 14.0 Hz, 1H), 3.68 (s, 3H), 3.79 (s, 3H), 4.28 (q, ^3J(H,H) = 7.2 Hz, 2H), 5.47 (d, ^3J(H,H) = 12.2 Hz, 1H), 7.57 ppm (d, ^3J(H,H) = 12.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 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 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 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 $C_{16}H_{22}O_7$: C 58.89, H 6.79; found: C 58.98, H 6.84.

Methyl 4-((*E*)-2-(methoxycarbonyl)vinyloxy)-4-(diethylcarbamoyl)pent-2-ynoate (9a): ^{1}H NMR (400 MHz, $CDCl_3$, 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 ppm (d, ^3J(H,H) = 12.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 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 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 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 $C_{15}H_{21}NO_6$: C 57.87, H 6.80, N 4.50; found: C 57.79, H 6.87, N 4.52.

Methyl 4-((*E*)-2-(methoxycarbonyl)vinyloxy)-4-methyl-5-oxo-5-(piperidin-1-yl)pent-2-ynoate (9b): ^{1}H NMR (400 MHz, $CDCl_3$, 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 ppm (d, ^3J(H,H) = 11.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 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 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 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 $C_{16}H_{21}NO_6$: C 59.43, H, 6.55, N 4.33; found: C 59.41, H 6.75, N 4.70.

Methyl 4-((*E*)-2-(methoxycarbonyl)vinyloxy)-4-(dibenzylcarbamoyl)pent-2-ynoate (9c): ^{1}H NMR (400 MHz, $CDCl_3$, 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), 5.58 (d, ^3J(H,H) = 11.9 Hz, 1H), 7.11–7.19 (m, 4H), 7.26–7.36 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 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 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 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 $C_{25}H_{25}NO_6$: C 68.95, H 5.79, N 3.22; found: C 68.75, H 6.01, N 3.25.

Methyl 4-((*E*)-2-(methoxycarbonyl)vinyloxy)-4-(diethylcarbamoyl)hex-2-ynoate (9d): ^{1}H NMR (400 MHz, $CDCl_3$, 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 ppm (d, ^3J(H,H) = 12.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 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 ppm; IR ($CHCl_3$): 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 $C_{16}H_{23}NO_6$: C 59.06, H 7.13, N 4.31; found: C 59.08, H 7.34, N 4.35.

Methyl 4-((*E*)-2-(methoxycarbonyl)vinyloxy)-4-(diethylcarbamoyl)-4-phenylbut-2-ynoate (9e): ^{1}H NMR (400 MHz, $CHCl_3$, 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 ppm (d, ^3J(H,H) = 12.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 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 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 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 $C_{20}H_{23}NO_6$: 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 (*Z-anti*:*Z-syn* ratio = 1.17:1.0). The order of increasing polarity by TLC is: *Z-anti* > *Z-syn*. *Z-anti* major isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 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(H,H) = 7.2, 10.9 Hz, 1H), 4.17 (q, ^3J(H,H) = 7.2 Hz, 2H), 5.69 (s, 1H), 7.27 (d, ^3J(H,H) = 8.2 Hz, 2H), 7.81 ppm (d, ^3J(H,H) = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 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 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 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) [$M^+ - CO_2Et$], 297 (100), 157 (27), 155 (35), 139 (80), 91 (43); elemental analysis: calcd (%) for $C_{19}H_{24}O_8S$: C 55.33, H 5.87; found: C 55.04, H 5.76. Characteristic data for the *Z-syn* isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.80 ppm (s, 1H).

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