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Domino Knoevenagel/Diels–Alder sequence coupled to Suzuki reaction: a valuable synthetic platform for chemical biology

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Abstract—A small library of peculiar biphenyl and terphenyl-containing spirocyclic triones has been synthesized in parallel by combining the organocatalytic three-component domino Knoevenagel/Diels–Alder sequence to Suzuki coupling. This methodology is fast, general and serves as a platform to gain access to novel chemical tools to probe protein–protein interactions.

Small organic molecules can exert powerful effects on the macromolecules that comprise living systems. This remarkable activity makes them useful not only as leads for therapeutic research but also as chemical tools to investigate biological phenomena, and small molecules are now being used in this context on an unprecedented scale.[1–3] Collections of compounds are thereby the absolute starting point for any chemical biology study, and this provides a driving force to develop effective strategies for the synthesis of structurally complex and diverse small-molecule libraries.[4–7] Screening in chemical biology often involves the discovery of new cellular processes without the prior knowledge of the protein targets, making the selection of reactions to be incorporated in an effective synthetic plan crucial to the value of the resultant library as a tool to dissect biology. In this context, multi-component coupling reactions (MCRs) are particularly appealing, since they provide expedient access to complex polycyclic products in a single highly atom-economical step by simultaneous reactions of three or more reagents, and allow to easily achieve substituent diversity of the core structure by varying each component.[8,9]

Given our interest in identifying novel biologically active molecules, we recently synthesized a library of terphenyl derivatives[10] which proved this scaffold to be a versatile architecture for the identification of small molecules useful as chemical probes to study cell functions and mechanisms (Fig. 1). As a matter of fact, from the biological evaluation it came up that one of the synthesized compound ([1,1′,4′,1″]-terphenyl-4,3″,5″-triol) was able to arrest the cell cycle in G_0–G_1 phase and also to induce differentiation in leukemia cells.[10]

In addition, many reports by Hamilton and co-workers demonstrated that the terphenyl moiety is a functional and structural mimic of protein α-helix regions, key players in protein–protein associations.[11–13] As a further development of our research project, we have been intrigued by the potential of combining two of combinatorial chemistry's most attractive concepts—natural product-like compounds and multi-component reactions—as powerful strategy for the synthesis of libraries of bioactive compounds.

On this basis, we envisaged that the introduction of terphenyl moiety on natural product-like molecular scaffolds might be a promising tactic to access uniquely

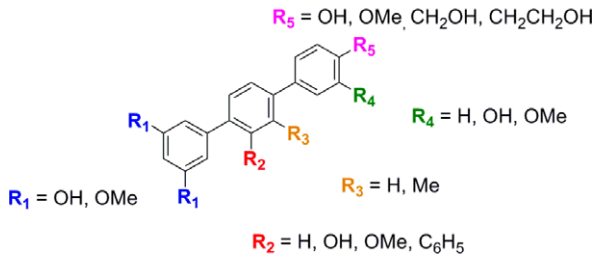

Figure 1. Terphenyl library.

Keywords: Chemical biology; Multi-component reaction; Domino process; Biasing element; Spiro compound.
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shaped small-molecule probes to investigate protein–protein interactions involved in cellular regulatory mechanisms. Toward the same goal, we also turned our attention to the biphenyl moiety that, likewise terphenyl, has been reported as α-helix mimetic scaffold.[14,15] Moreover, the biphenyl moiety is an example of privileged structure[4,16] and this meets our priority in selecting biologically relevant chemical fragments in order to enhance the value of the resulting library as a source of bioactive compounds. On such basis, we initiated this research with the idea of selecting a suitable multi-component reaction that allows the efficient generation of structurally and stereochemically complex skeletons, bearing functionalities, which enable the attachment of the desired biasing elements through C–C bond forming reactions. In the arena of multi-component reactions, we turned our attention to those involving domino processes performed with 1,3-dicarbonyl compounds, given their facile accessibility and great synthetic potential.[17,18] Accordingly, we developed a two-step linear sequence relying on the combination of the three-component domino Knoevenagel/Diels–Alder/Epimerization (K–DA–E) (click reaction)[19–22] for the construction of the natural product-like cores, with Suzuki coupling[23] for the derivatization step.[24]

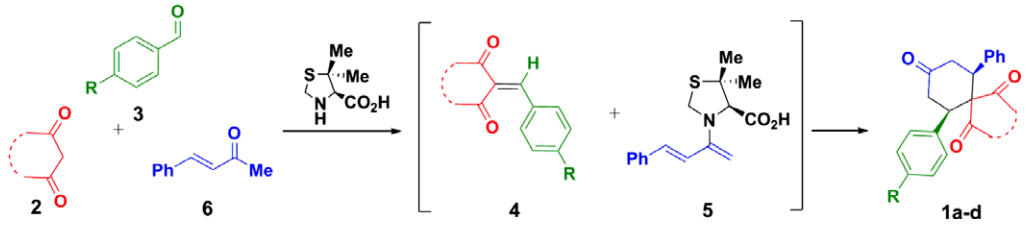
Herein, we report on the application of this synthetic route to the parallel generation of a small library of peculiar biphenyl-substituted 6-phenylspiro[cyclohexane-1,2′-inden]-1′,3′,4′-triones and terphenyl- and biphenyl-substituted 2,4-dioxa-spiro[5,5]undecane-1,5,9-triones.

In the original conception of this synthetic pathway, we have been attracted by several features of the domino K–DA–E sequence. This reaction leads to the construction of a spirocyclic ketone core through the simultaneous formation of three carbon–carbon σ-bonds under amino acid catalysis in one step, starting from aromatic aldehydes, cyclic methylene-activated compounds and 4-substituted-3-buten-2-ones. The reaction is highly diastereospecific affording the thermodynamically more stable *cis*-spirane as a major diastereomer due to the epimerization of the minor trans isomer, occurring under the same conditions with an extended reaction time. In addition, this domino sequence can be carried out in parallel, efficiently leading to the rapid synthesis of a collection of variously substituted derivatives. Notably, the characteristic aliphatic spiro ring system of the achievable molecular scaffolds is a widespread motif in many natural products[25,26] and it has recently been reported on a class of natural terphenyl derivatives bearing this peculiar spiro structure (spiromentins A–J).[27]

Since the primary focus of this study is the synthesis of a series of terphenyl- and biphenyl-containing small molecules, in the present work we employed the aforementioned domino reaction to obtain four core structures **1a–d**, bearing aryl bromide functionality, which enables the introduction of the desired biasing elements (Table 1).

For the construction of the required central cores, we initiated our synthetic plan with the commercial 1,3-indandione **2a**, which was allowed to react with 4-bromobenzaldehyde **3a** in the presence of a catalytic amount of (L)-5,5-dimethyl thiazolidinium-4-carboxylate (DMTC) to give the corresponding Knoevenagel adduct **4aa** in almost quantitative yield. This intermediate can participate as dienophile in Diels–Alder chemistry. Accordingly, **4aa** efficiently underwent concerted

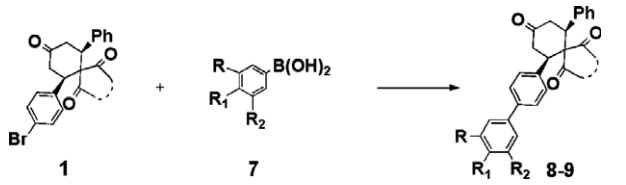
Table 1. Domino Knoevenagel/Diels–Alder/epimerization reaction[a]

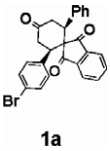
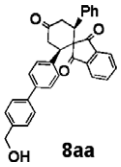
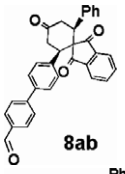
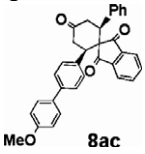
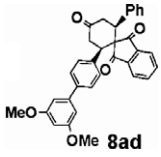
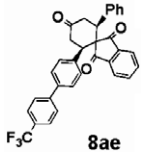
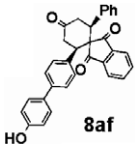
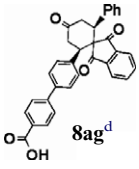
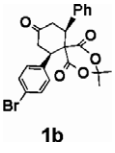
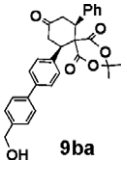
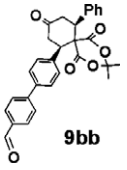
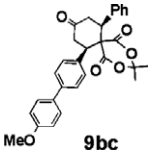
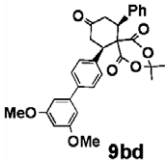
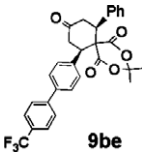
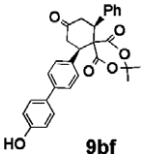


Entry	2	3: R	4	Enone	Product	Yield[b]	dr[c] (cis/trans)
1	 **2a**	**3a**: R = Br	**4aa**	**6**	**1a**	90	>99:1
2	 **2b**	**3a**: R = Br	**4ba**	**6**	**1b**	74	>99:1
3	**2b**	**3a**: R = 4-BrC_6H_4	**4bb**	**6**	**1c**	76	>99:1
4	**2b**	**3a**: R = 3-BrC_6H_4	**4bc**	**6**	**1d**	50	>99:1

[a] Reagents and conditions: aldehyde **3** (1.0 equiv), 1,3-dione **2** (1.0 equiv), (L)-DMTC (0.2 equiv), enone **6** (2.0 equiv), MeOH (1 M), rt, 72 h.
[b] Yield refers to the purified product after flash chromatography.
[c] Ratio determined by ^{1}H NMR of the crude reaction mixture.

Table 2. Suzuki coupling K–DA–E product **1** with various arylboronic acids **7**[a]



Entry	1	7: R, R_1, R_2	Product	Yield[b] (%)
1		**7a**: H, CH_2OH, H		81
2	**1a**	**7b**: H, CHO, H		80
3	**1a**	**7c**: H, OMe, H		93
4	**1a**	**7d**:[c] OMe, H, OMe		40
5	**1a**	**7e**: H, CF_3, H		81
6	**1a**	**7f**: H, OH, H		70
7	**1a**	**7g**: H, COOH, H		54
8		**7a**		66
9	**1b**	**7b**		80
10	**1b**	**7c**		70
11	**1b**	**7b**		57
12	**1b**	**7e**		61
13	**1b**	**7f**		48

[a] Reagents and conditions: K–DA–E product **1** (1.0 equiv), arylboronic acid **7** (2.0 equiv), $Pd(Ph_3P)_4$ (0.5 equiv), aq Na_2CO_3 (2M, 3.0 equiv), PhMe/EtOH 3:1.
[b] Yield refers to the purified product after flash chromatography.
[c] **7d** has been prepared as previously described[10].
[d] The coupling reaction has been run using THF/H_2O 2:1.

[4+2]-cycloaddition reaction with 2-amino-1,3-butadiene **5**, generated in situ from the commercial (*E*)-4-phenyl-3-buten-2-one **6** and (*L*)-DMTC. The domino sequence proceeded in excellent yield to provide the corresponding *cis*-2-(4-bromophenyl)-6-phenylspiro[cyclohexane-1,2′-indene]-1′,3′,4-trione **1a** as single diastereomer, since the expected minor trans isomer could not be detected by NMR analysis of the crude reaction mixture (Table 1, entry 1).[28] Next, we turned our attention to the use of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) **2b** as 1,3-dicarbonyl compound to introduce a potential handle for further synthetic manipulation of the final scaffolds. In fact, Meldrum's acid is a tremendously attractive and useful building block permitting not only electrophilic attack at C-5, but also nucleophilic attack at C-4 and C-6 giving unique ring-opening reactions. Under the same reaction conditions, both 4-bromobenzaldehyde **3a** and the more hindered aromatic aldehydes **3b**,**c**[29] efficiently underwent the whole domino sequence with **2b** delivering the corresponding substituted *cis*-2,4-dioxaspiro[5,5]undecane-1,5,9-triones **1b–d** in good yields and high diastereospecificity (Table 1, entries 2–4).

With these four skeletons in hand, we focused on the elaboration of Csp^2–Br bond via palladium-catalyzed coupling reaction to achieve the desired functionalized products. As Suzuki coupling between aryl halides and

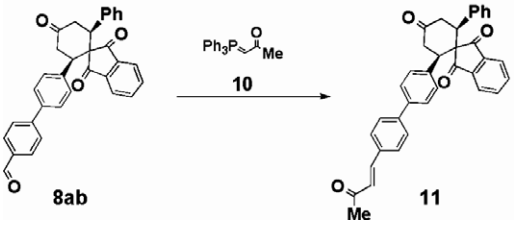
arylboronic acids has become a common and powerful method for biphenyl and terphenyl syntheses[24,30] and since we have previously adapted this methodology to the parallel generation of small-molecule libraries,[10,31] we reasoned that compounds **1a**–**d** could efficiently undergo Suzuki coupling reaction with a variety of arylboronic acids, allowing diverse substitution patterns through the choice of the building blocks.

A Suzuki coupling reaction between derivatives **1a**,**b** and the set of arylboronic acids **7** afforded the corresponding two series of biphenyl-substituted 6-phenyl-spiro[cyclohexane-1,2′-indan]-1′,3′,4′-triones **8** (Table 2, entries 1–7) and biphenyl-substituted 2,4-dioxa-spiro[5,5]undecane-1,5,9-triones **9**, respectively (Table 2, entries 8–13). The coupling reactions have been run in parallel in a Carousel reaction station, using toluene/ethanol as solvent and tetrakis(triphenylphosphine)-palladium(0) as catalyst for the reaction, whereas aqueous Na_2CO_3 provided the basic environment required. The reactions were completed in 3–5 h and flash chromatography of the crude mixtures afforded the final collections of compounds **8** and **9** in moderate to good yields.

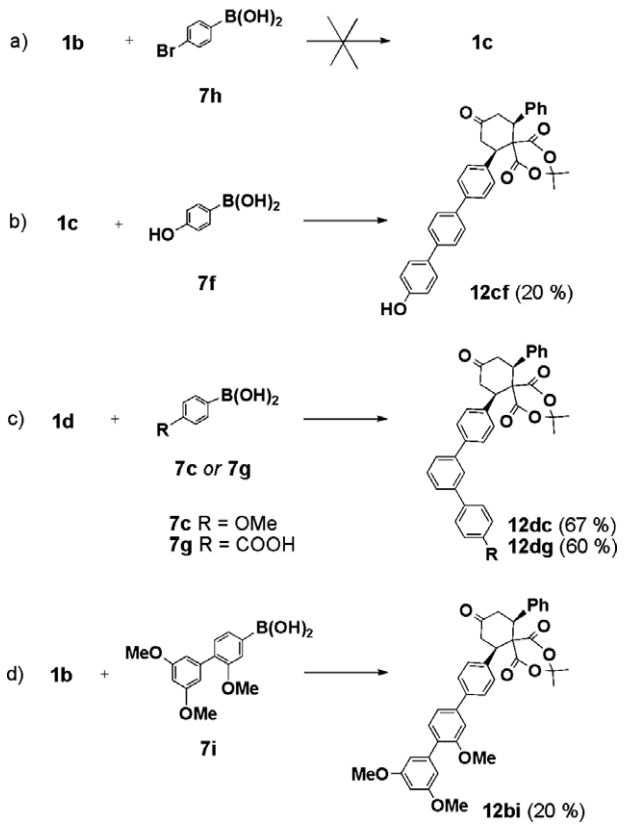
Interestingly, the properly functionalized compounds can undergo further synthetic manipulations to introduce greater substituent diversity, as outlined in Scheme 1. The aldehyde-substituted derivative **8ab** participated Wittig reaction[32] with the commercial ylide **10** delivering the corresponding olefination product **11** as single trans isomer in moderate yield.

We next examined the possibility to synthesize a small set of terphenyl-substituted 2,4-dioxa-spiro[5,5]undecane-1,5,9-triones **12** (Scheme 2).

We first investigated derivative **1b** as a substrate for a double Suzuki cross-coupling protocol. This pathway could lead to the synthesis of terphenyl-based compounds bearing different substituents on aromatic rings of the terphenyl moiety by carrying out each of the two couplings with properly substituted arylboronic acids. Unlikely, the first Suzuki coupling between derivative **1b** and 4-bromophenylboronic acid **7h** failed to efficiently yield the required product **1c** (already obtained by the domino sequence, Table 1), potential substrate for a second coupling, as the reaction was extremely sluggish and the separation of the desired product from the remaining starting material was troublesome due to their similar lipophilicity (Scheme 2, reaction a). We therefore examined different valuable synthetic routes. Facile access to both *p*- and *m*-terphenyl-containing compounds **12cf**, **12dc**, and **12dg** has been obtained using K–DA–E derivatives **1c**,**d** as substrates for a single Suzuki coupling (Scheme 2, reaction b and c). Additionally, to gain greater substituent diversity of the terphenyl moiety, we envisaged the possibility of synthesizing biphenylboronic acids bearing substituents on both aromatic rings and coupled them with derivative **1b** (Scheme 2, reaction d). This path led to the desired product **12bi**, but only in low yield, requiring further optimization of the described approach.



Scheme 1. Reagents and conditions: ylide **10** (1.5 equiv), deionized water 90 °C, 4 h.



Scheme 2. Synthetic routes to terphenyl-containing small molecules.

In summary, we have developed a linear two-step synthetic route based on the combination of the domino three-component Knoevenagel/Diels–Alder sequence to Suzuki coupling to access novel peculiar terphenyl- and biphenyl-based compounds. We demonstrated that this platform is amenable to parallel library generation and valuable to the rapid and facile synthesis of compounds that embody features of natural products in terms of structural and stereochemical complexity. All the synthesized compounds are being tested in several biological screenings within the Broad Institute Chemical Biology Program[33] to identify novel small-molecule probes to elucidate molecular pathways fundamental to cell and disease biology. All results from these studies will be available via the Web-accessible public database ChemBank.[34] These compounds will also be evaluated for their capacity of inhibiting protein–protein interactions involved in cellular regulatory mechanisms. The results of these studies will be reported in due course.

Acknowledgements

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Supplementary data

Experimental procedures and characterization data for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.214.

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28. For the determination of the stereochemistry of *cis*-spiranes **1a**–**d** see Supplementary data.
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