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Auto tandem triple cascade organocatalysis: access to bis-lactone and butenolide derivatives†

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The synthesis of bis-lactone and butenolide derivatives was described using alkylidene Meldrum's acid as nucleophiles. The process operates in a triple cascade through an auto tandem catalysis promoted by DBU.

Dimeric butenolides and bis-lactones are found in many natural products and possess interesting biological properties. (−)-Lindenanolide F is a dimeric butenolide, which was isolated by Fujiwara and co-workers in 2002 from the root of *Lindera chunii*, a plant mostly found in Asia.[1] It is frequently used in traditional Chinese medicine to improve the wind-cold-dampness arthralgia syndrome. (−)-Salprzelactone is a seco-norabietane diterpenoid containing a bis-lactone motif, which was isolated by Wu and co-workers in 2013 from the root of *Salvia przewalskii*, a plant native to China.[2] It showed stronger antibacterial activity against *A. aerogenes* than streptomycin, acheomycin and ampicillin. Its total synthesis was first described by Zhai and co-workers in 2017.[3] Bielschowskysin is a diterpene whose structure was reported by Rodriquez and co-workers in 2004.[4] It was isolated from the Caribbean gorgonian octocoral *Pseudopterogorgia kallos* and was reported to exhibit anti-plasmodial activity and selective *in vitro* cytotoxicity against small-cell lung and renal cancer cell lines (Fig. 1).

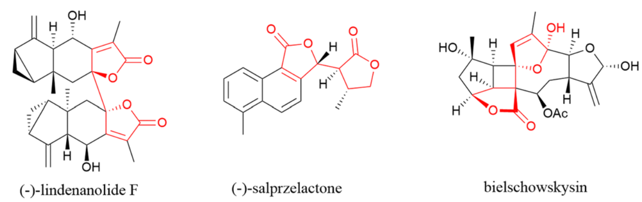
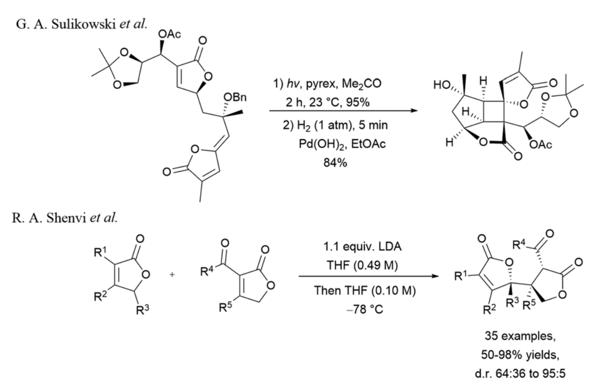


Fig. 1 Natural products possessing a butenolide and saturated and unsaturated bis-lactone motif.

Few approaches towards the synthesis of dimeric butenolides and bis-lactone units have been described in the literature.[5,6] In 2013, Sulikowski and co-workers reported the total synthesis of bielschowskysin in which the formation of the saturated and unsaturated bis-lactone unit was created by means of an intramolecular [2+2]-photocycloaddition upon irradiation of a substrate containing two butenolide moieties.[7] More recently, Shenvi *et al.* described a stereo and heteroselective butenolide coupling leading to the formation of expected product in good to excellent yields.[8] It should be noted that most of these methods required the coupling of two lactones or butanolide moieties that were constructed beforehand (Scheme 1).

Although access to saturated and unsaturated lactones has been developed, the discovery of new strategies is still of great interest. Producing more complex structures while conserving energy, resources and minimizing waste requires new solutions. However, these solutions must remain simple, elegant and efficient in order to remain viable. With this in mind, tandem and multi-catalysis strategies remain one of the best solutions to access rapidly to complex organic structures from simple building blocks while minimizing steps.[9] Among these strategies, auto tandem catalysis (ATC) appears to be a very



Scheme 1 Approaches towards the synthesis of saturated and unsaturated bis-lactone motif.

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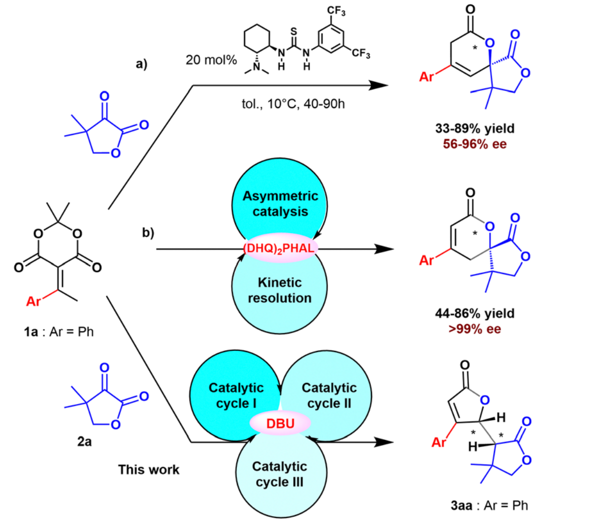
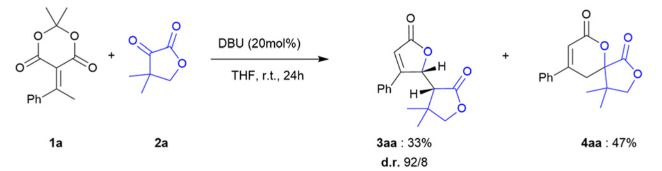


Scheme 2 Previous and present works.



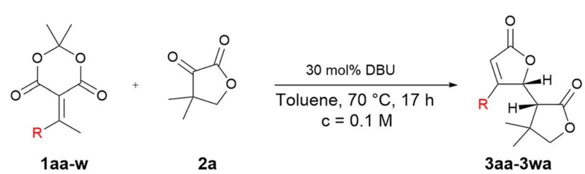
Scheme 3 Base catalysed formation of bis-lactone **3aa**.

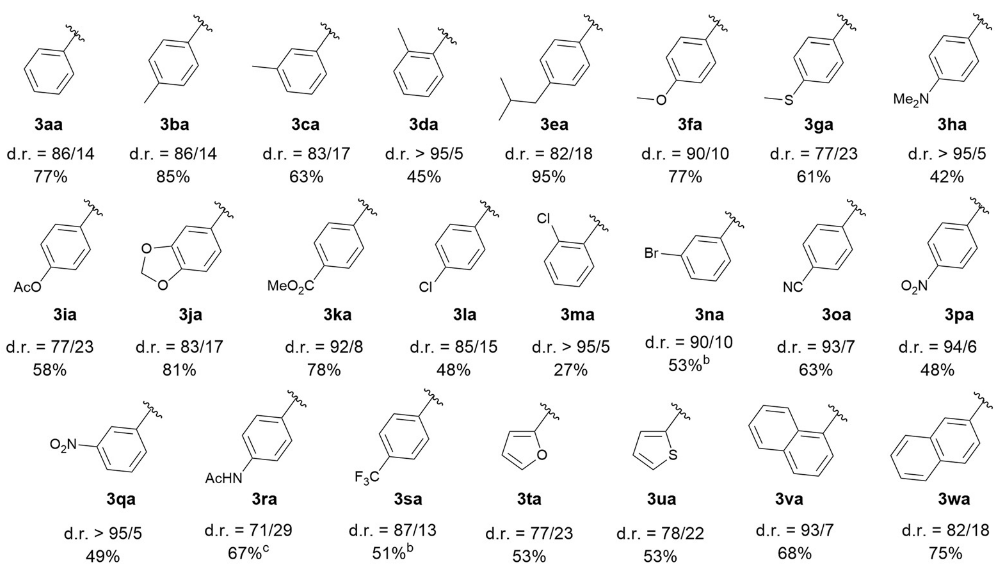
interesting option, since the same catalyst promotes at least several different chemical transformations in one-pot. The main advantages of ATC consist in both the multiple role of a single catalyst, while overcoming the challenging compatibility between reagents in order to achieve an economical step-economy domino process.[10] We have recently discovered a new reactivity of ketone-derived alkylidene Meldrum's acid derivatives for the enantioselective synthesis of 5,6- or 3,6-dihydropyrane-2-one with very high ee (Scheme 2).[10a,11] The selectivity for the conjugated (path a) or non-conjugated dihydropyrane-2-one (path b), is controlled by the nature of the catalyst. The more basic cinchona catalyst induced a second catalytic cycle resulting in an auto tandem process to form preferentially conjugated-dihydropyrane-2-one, starting from the non-conjugated one.

We report herein a triple cascade ATC process leading to the formation of bis-lactone **3aa** from alkylidene derived from Meldrum's acid **1a** and furandione **2a** as electrophiles.

In the course of our study, besides the formation of unprecedented 5,6-dihydropyranone **4aa** from benzylidene Meldrum's acid **1a** and dihydro-4,4-dimethyl-2,3-furandione **2a**, we were surprised to also observe the formation of bis-lactone byproduct **3aa** (33% isolated yield) when the reaction was carried out in the presence of DBU as catalyst in THF (Scheme 3). The structure of the bis-lactone **3aa** was carefully characterized by NMR, MS analysis methods and confirmed by X-ray diffraction analysis. It is noteworthy to mention that this

Table 1 Substrate scope with various alkylidene Meldrum's acid derivatives[a]





Compound	d.r.	Yield
3aa	86/14	77%
3ba	86/14	85%
3ca	83/17	63%
3da	> 95/5	45%
3ea	82/18	95%
3fa	90/10	77%
3ga	77/23	61%
3ha	> 95/5	42%
3ia	77/23	58%
3ja	83/17	81%
3ka	92/8	78%
3la	85/15	48%
3ma	> 95/5	27%
3na	90/10	53%[b]
3oa	93/7	63%
3pa	94/6	48%
3qa	> 95/5	49%
3ra	71/29	67%[c]
3sa	87/13	51%[b]
3ta	77/23	53%
3ua	78/22	53%
3va	93/7	68%
3wa	82/18	75%

[a] Reaction was performed with 0.5mmol of benzylidene **1**, 0.525 mmol of dihydro-4,4-dimethyl-2,3-furandione **2a** and 0.15 mmol of DBU in 5 mL of dry toluene at 70 °C for 17 h. [b] Reaction at 60 °C. [c] Reaction in DMF.

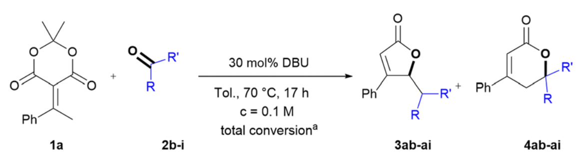
finding is extremely excited not only because structure of **3aa** is found within bioactive molecules, but also its synthesis has not been well developed in literature as previously mentioned.

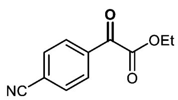
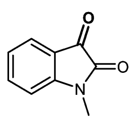
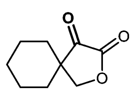
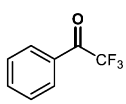
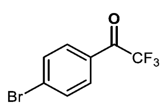
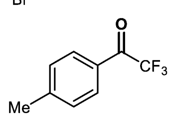
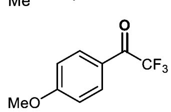
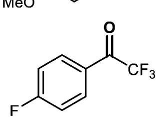
In the first investigation, various parameters were screened, such as solvent, catalyst loading, base, temperature and concentration (see ESI† for details). It was determined that a total conversion and the best yields of bis-lactone **3aa** (77%) as a major product (**3aa**/**4aa** = 98/2) were obtained in toluene at 70 °C and at 0.1 M concentration. This relatively low concentration and moderate temperature is necessary to limit the formation of oligomers promoting selectivity for the bis-lactone **3aa**.[12]

With the optimal conditions in hand, we then investigated the substrate scope by varying the aryl group R on the alkylidene derivatives **1a** (Table 1).

In most cases, a complete formation of the bis-lactone **3aa–3wa** *versus* the conjugated spiro-compound **4aa–4wa** was observed. Only in the case of **3ha**, the spiro-compound was obtained alongside the bis-lactone in a 1 : 1 ratio. Various substituents on the aromatic ring seemed to be tolerated for this transformation. Substrates with alkyl substituents and electron-donating substituents led to the corresponding bis-lactones in good to excellent yields (**3ba**, **3ca**, **3ea**, **3fa**, **3ga** and **3ja**). Acetate, ester, cyano and amino substituents were also well tolerated (**3ia**, **3ka**, **3oa**, **3ha** and **3ra**). However, moderate yields were obtained with substrates containing halogens, nitro and CF_3 substituents (**3la**, **3na**, **3pa**, **3qa** and **3sa**). In these cases, the lower yields might be due to the lower reactivity of the alkylidene Meldrum's acid derivatives or the intermediates formed might be more prone to polymerization (*vide infra*). In other cases, the low yields obtained could be explained by the low solubility of the starting materials in the solvent. Substrates containing ortho-substituted aryl groups (**3da** and **3ma**) proved to be more challenging as the bis-lactones were obtained in 45% and 27% respectively. Finally, naphthyl groups as well as furan and thiophene moieties were also well tolerated (**3ta–3wa**), albeit with moderate yields. Generally speaking, all the products were obtained in moderate to good diastereoselectivity with ratios ranging from 71/29 to 95/5, but in the majority of cases, the diastereoselectivity was greater than 82/18. We assume that the diastereo-determining step is the ring closure of intermediate **6aa** (Scheme 6). It is controlled by both steric (see **3ba**, **3ca**, **3da** and **3va**, **3wa**) and electronic effects (see **3ha**, **3ma**, **3na**, **3oa**, **3pa**, **3qp**) where ortho-substitution or electron-withdrawing group increase the diastereoselectivity up to 95/5 d.r. Moreover, the relative configuration of the major diastereomer **3aa** was (*R*, *S*) determined by X-ray diffraction analysis of its single crystal, which was obtained by recrystallization (see ESI†). Next, the scope of electrophiles was investigated under standard reaction conditions (Table 2).

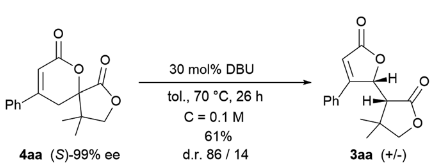
Table 2 Scope of electrophiles[a]



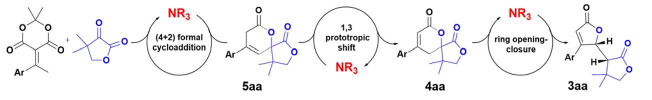
Entry	Substrate		Yield[b] (%) Products	3^c (d.r.)	4
1	**2b**		**3ab**	32 (67/33)	41
2	**2c**		**3ac**	18 (71/29)	31
3	**2d**		**3ad**	59 (nd)	0
4	**2e**		**3ae**	52 (87/13)	24
5	**2f**		**3af**	60 (82/18)	12
6	**2g**		**3ag**	43 (82/18)	22
7	**2h**		**3ah**	25 (80/20)	30
8	**2i**		**3ai**	58 (89/11)	12

[a] Reaction was performed with 0.5 mmol of benzylidene **1a**, 0.525 mmol of electrophile and 0.15 mmol of DBU in 5 mL of dry toluene at 70 °C for 17 h. [b] Isolated yields. [c] Determined by ^1H NMR on crude product.

Finding suitable electrophiles for this transformation proved to be challenging due to the presence of spirolactone **4**.[13] Thus, 4-cyanobenzoylformate led to the formation of the bis-lactone **3ab** in 32% yield (entry 1). Using *N*-methylisatin as an electrophile gave the desired product **3ac** in only 18% yield (entry 2). In a course of our studies, a new furandione was synthesized serving as an electrophile for this reaction, and the expected bis-lactone **3ad** was isolated in 59% yield without any trace of spiro-compound **4ad** (entry 3). Interestingly, fluorinated ketones offer interesting fluorinated butenolides. Thus, trifluoroacetophenone led to the formation of butenolide **3ae** in 52% yield (d.r. 87/13), alongside the spiro-compound **4ae** in 24% yield. Surprisingly, we were unable to increase the **3ae**/**4ae** ratio despite a longer reaction time and/or the addition of more catalyst. This phenomenon was observed for all trifluoromethyl derivatives. It seems that electron-withdrawing substituent favors the formation of butenolide **3**, whereas electron-donating group offers lower yields (compare **3ah–3ag** *vs.* **3af–3ai**). In any case, the diastereoselectivity still remains



Scheme 4 Mechanistical study from enantiopure dihydrolactone **4aa**.

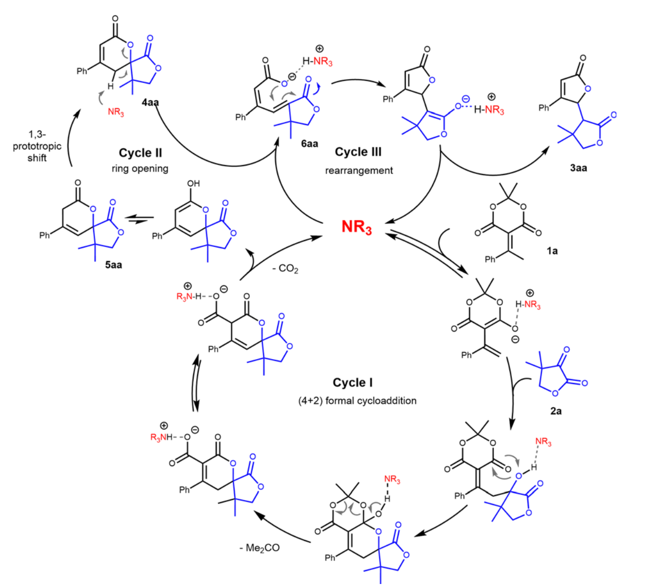


Scheme 5 Triple auto tandem cascade.

stable for **3**. In order to get insight into the mechanism, the reaction was carried out starting from enantioenriched dihydropyranone **4aa** (99%ee) with DBU under the standard reaction conditions. The expected bis-lactone **3aa** was isolated as the sole product (61% yield with 84/16 d.r.) as a racemic form (Scheme 4). This result clearly proves that dihydropyranone **4aa** is an intermediate leading to the formation of the bis-lactone **3aa**. Unfortunately, this transformation is not stereoselective. Therefore, we assume a possible rearrangement involving the achiral transition state intermediate **6aa** (Scheme 6).

Based on our previous works on the synthesis of dihydropyranones,[10a,11] we postulated a base-catalyzed mechanism for the formation of bis-lactones from alkylidene Meldrum's acid derivatives. This sequence proceeds through a triple cascade auto tandem catalysis promoted by the Brønsted base. Dihydropyranone **4aa** was obtained following two catalytic cycles in accordance with our previous work for the asymmetric synthesis of dihydropyranones (Scheme 5).[10a]

The first cycle leads to the non-conjugated dihydropyranone **5aa** from **1a**. The 1,3-prototropic shift process gives the conjugated spirolactone **4aa** in a second catalytic cycle promoted by the same base. The last catalytic cycle consists in the deprotonation of the conjugated dihydropyranone **4aa**, leading to the ring opening and the formation of the achiral diene intermediate **6aa** (Scheme 6). The diene would undergo intramolecular 1,4-addition ring closure to form the desired bis-lactone **3aa**. The presence of significant amount of oligomer in the case of electron-withdrawing substituted alkylidene **1l**, **1n**, **1p**, **1q** or **1s** is probably enhanced by the presence of this highly reactive intermediate **6**.



Scheme 6 Proposed mechanism in a triple cascade auto-tandem process.

In conclusion, we have developed a new method for the synthesis of bis-lactones and fluorinated butenolides from alkylidene Meldrum's acid derivatives with satisfactory overall yields through the one-pot triple steps. We have also demonstrated that this transformation occurs through a DBU-catalyzed auto tandem catalysis in a triple-cascade process, including a rearrangement of a dihydropyranone intermediate *via* a ring-opening step.

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Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Notes and references

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12 An insoluble paste is formed during the reaction. NMR analysis identify it, as an oligomer. The exact structure of this compound was not identified.
13 Benzoylformate derivatives, acenaphthoquinone, phenanthrenequinone as well as various ketoester derivatives also mostly led to the formation of spirolactone 4 as the sole product (See ESI†).