Organic LETTERS

Letter

Cite This: Org. Lett. 2018, 20, 4000−4004

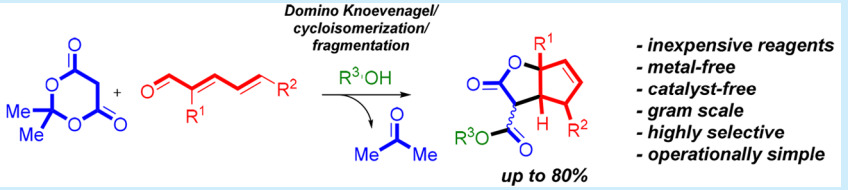
pubs.acs.org/OrgLett

Multicomponent Domino Synthesis of Cyclopenta[*b*]furan-2-ones

Martín J. Riveira,* Maribel O. Marcarino, and Agustina La-Venia

Instituto de Química Rosario, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario-CONICET, Suipacha 531, S2002LRK Rosario, Argentina

Supporting Information



ABSTRACT: A stereoselective multicomponent reaction involving Meldrum's acid, a conjugated dienal, and an alcohol is reported. Valuable cyclopenta[*b*]furan-2-ones are obtained as products of this straightforward transformation, which is accompanied by the formation of four stereocenters, two new cycles, and four new bonds (two C−C and two C−heteroatom). A reaction mechanism was elaborated involving an initial Knoevenagel condensation followed by cycloisomerization and eventual fragmentation.

We have recently noticed that several natural products which have drawn considerable attention due to their neuritogenic or neuroprotective activities (e.g., gelsemiol, **1**,[1] littoralisone, **2**,[2] merrilactone A, **3**,[3] illisimonin A, **4**,[4] and others[5−7]) feature a cyclopenta[*b*]furan-2-one heterobicyclic system in their structures (Figure 1).[8] Whereas a link between

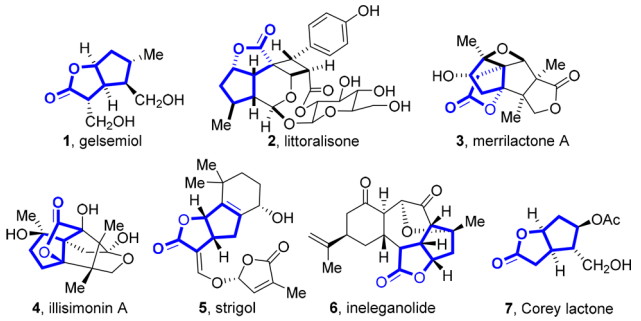


Figure 1. Some distinct cyclopenta[*b*]furan-2-ones.

this structural feature and such biological activities remains to be demonstrated, it is clear that these bicyclic lactones are widely distributed in nature.[9] Strigol (**5**), for example, along with other cyclopenta[*b*]furanone hormones, have important regulatory functions in many stages of plant development.[10] Additionally, ineleganolide, **6**, a recently isolated norcembranoid diterpene, has received considerable attention due to its selective antileukemic activity.[11] Remarkably, apart from abounding in nature, these bicyclic lactones are also versatile intermediates that have been extensively used for the preparation of natural products and derivatives.[5,12] Just to cite one example, notable Corey lactone **7** has been employed by Pfizer and Kabi-Pharmacia pharmaceutical companies as an intermediate in the synthesis of latanoprost, an antiglaucoma drug that achieved 1.7 billion dollars in sales in 2010.[13]

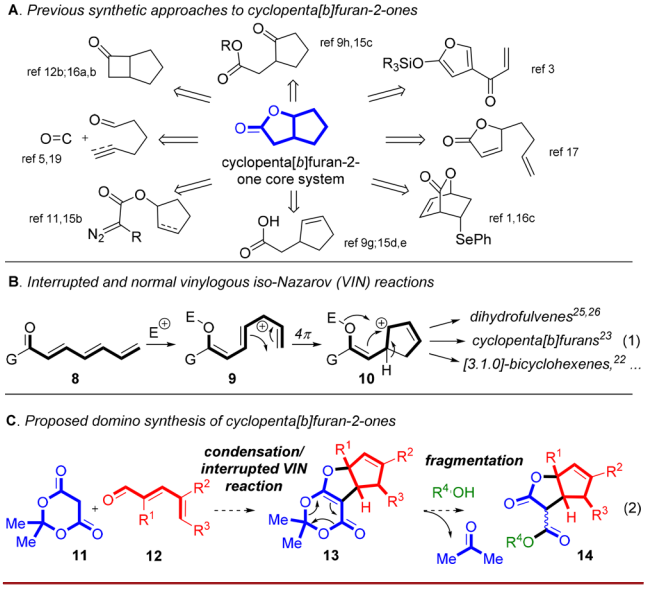
The potential use of these bicyclic lactones in pharmacology has naturally turned them into objects of intense synthetic interest. In particular, the versatility of **7** in the synthesis of prostaglandins and derivatives, extremely bioactive molecules, triggered the development of many established protocols for the synthesis of cyclopenta[*b*]furan-2-ones.[14] In general, most methodologies employ functionalized five-membered carbocycles[15] and also bicyclic systems as starting materials (Scheme 1A).[16] The group of Frontier, on the other hand, relied on a Nazarov cyclization of a conveniently decorated silyloxyfuran derivative to construct the cyclopenta[*b*]furan-2-one core system present in natural product merrilactone A, **3**.[3] A photochemical [2 + 2]-cycloaddition of an elaborated butanolide was also used for the construction of the intricate bielschowskyane skeleton.[17] One-pot synthetic protocols involving acyclic precursors are particularly attractive.[18] In this context, the transition-metal catalyzed hetero-Pauson−Khand reaction using an acyclic enal or ynal derivative and a carbon monoxide source is an attractive transformation for the synthesis of these bicyclic lactones and has been investigated by many groups.[5,19] Additionally, the group of Aggarwal developed a tandem enantioselective organocatalytic cascade/oxidation sequence for the synthesis of a key cyclopenta[*b*]furan-2-one intermediate versatile enough to allow the efficient synthesis of prostaglandin analogues latanoprost and bimatoprost.[20]

Although every protocol has its own merits, as well as shortcomings, it is clear that an efficient and operationally simple procedure is lacking, particularly one that employs readily available materials. The vinylogous iso-Nazarov (VIN)

Received: May 17, 2018
Published: June 6, 2018

DOI: 10.1021/acs.orglett.8b01567
Org. Lett. 2018, 20, 4000−4004

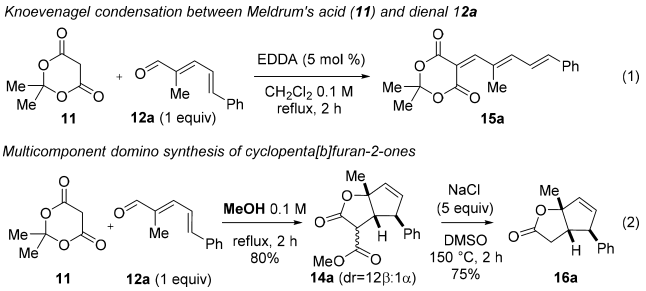
Scheme 1. Previous Synthetic Approaches, the Vinylogous Iso-Nazarov Cycloisomerization, and a Proposed Strategy for Cyclopenta[*b*]furan-2-one Synthesis



reaction has been independently investigated by many groups including Valla's,[21] Trauner's,[22] and ours.[23] This reaction, in an analogous fashion to the classic Nazarov transformation, involves the initial electrophilic activation of a linearly conjugated triene-carbonyl compound **8** followed by a $4\pi e^-$ electrocyclization at the end of the polyene chain (Scheme 1, eq 1).[24] Depending on substrate structure, the brand new cyclopentenyl cation **10** can then lead to a cyclopentadiene product via elimination[25,26] or afford bicyclic systems such as cyclopenta[*b*]furans and [3.1.0]bicyclohexenes through intramolecular nucleophilic trapping processes.[21−23] Based on this synthetic strategy, we envisaged a simple and conceptually different domino protocol for the synthesis of substituted cyclopenta[*b*]furan-2-ones (Scheme 1, eq 2). The Knoevenagel condensation between dicarbonyl component Meldrum's acid **11**[27] and a substituted dienal **12** could afford a suitable polyunsaturated substrate for an interrupted VIN reaction providing cyclopenta[*b*]furan intermediate **13** as product. Fragmentation on **13** would afford a ketene intermediate prone to nucleophilic addition by a suitable alcohol partner, thus providing cyclopenta[*b*]furan-2-one products **14** along with an acetone molecule as byproduct.

To validate such a proposal, model dienal **12a** was subjected to condensation with Meldrum's acid **11** in dichloromethane (Scheme 2, eq 1). When Tietze base EDDA[28] was evaluated as a catalyst in dichloromethane at reflux, condensation proceeded, but to afford classic Knoevenagel product **15a**, no cyclopenta[*b*]furan species of type **13** was found in the reaction mixture. Identification of **15a** was performed with this crude sample as any attempt to purify this red solid resulted in its decomposition. In order to facilitate the purification of **15a**, different reaction conditions avoiding the use of any catalyst were screened for the condensation. Unfortunately, no condensation between **11** and **12a** was observed after the reaction mixture was heated for 2 h in dichloromethane or THF at reflux. The same situation was observed when the solvent was replaced by water, a medium previously reported as convenient for the condensation of Meldrum's acid with aldehydes.[29] To our delight, it was found that, in the absence of

Scheme 2. Multicomponent Domino Synthesis of Cyclopenta[*b*]furan-2-ones Based on a Knoevenagel Condensation

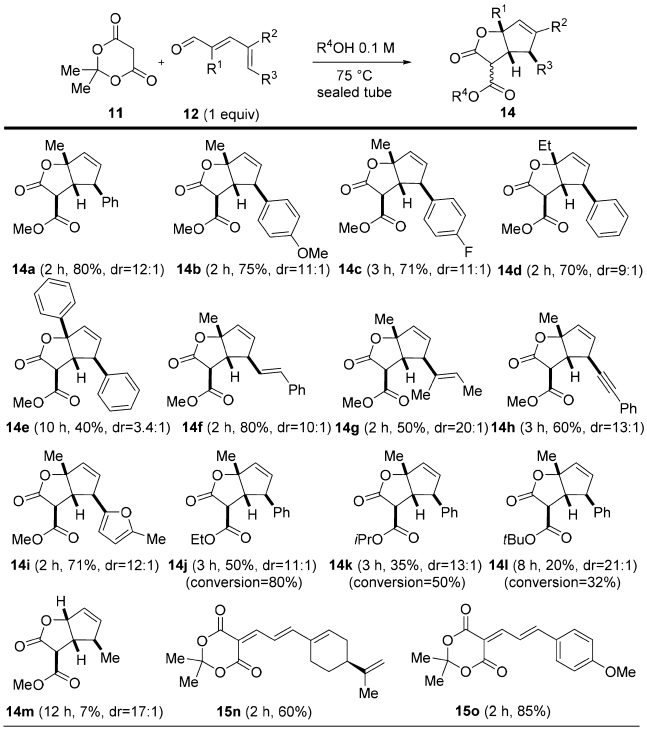


any catalyst, the use of methanol as solvent allowed for the whole originally desired sequence to proceed. As shown in Scheme 2, eq 2, products **14a** are efficiently obtained as an inseparable 12:1 mixture of diastereoisomers in 80% yield.[30] As anticipated, Krapcho decarboxylation[15a] of this mixture afforded the known cyclopenta[*b*]furan-2-one **16a** in 75% yield.[21c] Extraordinarily, the riveting stereoselective transformation toward **14a** builds up two new cycles and is accompanied by the formation of four contiguous stereocenters and four new bonds (two C−C and two C-heteroatom). In addition, the gram-sscale version of the process was perfectly feasible and the same yield of products **14a** was obtained using 1.2 g of **11** (1.81 g of **14a**, 80% yield). Probably as a consequence of the acidity of Meldrum's acid, the use of other C3 nucleophilic synthons such as malonic acid or diethyl malonate in this reaction failed to afford a cyclopenta[*b*]furan-2-one product; in these cases, the substrates rather failed to undergo initial Knoevenagel condensation under the reaction conditions.

With these results in hand, we set out to rapidly test an initial scope for the discovered transformation. As shown in Scheme 3, different dienals **12** and alcohols participated in the developed domino reaction. Dienals bearing terminal phenyl substituents could bear both electron-donating as well as -withdrawing groups in such systems (**14b,c**). The end of the polyene chain was also compatible with heteroaromatics such as furan as well as with alkynes and alkenes (**14f−i**). Although the use of other alcohols instead of methanol as solvent was possible, such a change had a clear negative impact on conversion and yields. Probably as a consequence of steric hindrance, the bulkier the alcohol employed the higher the diastereoselectivity found in these reactions and the lower the conversion (**14j−l**). The nature of the substituent at the α-position of the dienal **12** also had an impact on the diastereomeric ratio and, going from Me, to Et, to Ph, the prevalence of the diastereoisomer pointing to the pendant ester group toward the convex face of the molecule was less marked (**14a,d,e**). Aldehydes **12** without α-branching clearly failed to provide cyclopenta[*b*]furanones as products after condensation with **11**. Sorbaldehyde (*trans,trans*-2,4-hexadienal), for example, initially forms the corresponding Knoevenagel product, which could be isolated in only 30% yield [**15m**, see the Supporting Information (SI)]. When heating is continued for several hours cyclopenta[*b*]furan-2-ones **14m** can be isolated; however, the yield of product formation drops to 7%. The condensation of **11** with a dienal vinylogous to (−)-perillaldehyde, also α-unbranched, afforded Knoevenagel product **15n** which was also resilient enough to undergo further cycloisomerization. Additionally, cinnamaldehydes also failed to participate in the

DOI: 10.1021/acs.orglett.8b01567
Org. Lett. 2018, 20, 4000−4004

Scheme 3. Initial Scope for the Multicomponent Domino Synthesis of Cyclopenta[*b*]furan-2-ones[a]

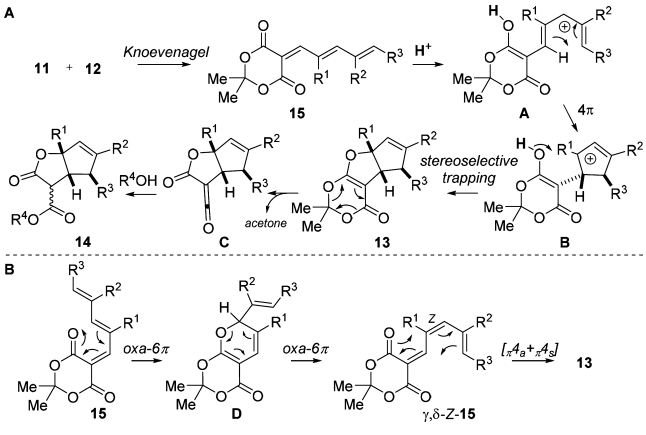


[a]Yields in parentheses refer to isolated yields after chromatographic purification. Conversion was always complete unless otherwise noted. dr refers to β/α ratio; only major **14***β* isomers are shown.

devised transformation, and for instance, aldehyde 4-methoxycinnamaldehyde underwent standard Knoevenagel condensation toward known orange solid **15o**[31] when subjected to the reaction conditions.

A complete mechanistic scenario for the domino transformation is depicted in Scheme 4A. As shown, initial

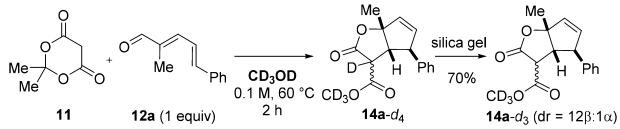
Scheme 4. Proposed Mechanisms for the Multicomponent Domino Synthesis of Cyclopenta[*b*]furan-2-ones



Knoevenagel condensation furnishes planar intermediate **15**. Activation by acid or transient formation of a zwitterion allows for a 4π-electrocyclization to occur at the end of the polyene chain (**A** to **B**), consistent with computational studies on the fate of 1-hydroxyheptatrienyl cations by the group of de Lera.[32] This step would be particularly inefficient for stable polyunsaturated intermediates of type **15**, i.e., when unbranched dienals are used in the initial condensation (R^1 = H). A second ring closure on cyclopentenyl cation **B** would proceed stereoselectively to afford in this way intermediate cyclopenta[*b*]furan **13**. Subsequent fragmentation would deliver ketene intermediate **C** with the concomitant release of acetone. Addition of an alcohol equivalent on **C** eventually yields products **14** obtained as a mixture. Since the relative configuration of the first three stereocenters formed is governed by the conrotatory 4π-electrocyclization and the stereoselective cation-trapping step (*cis*-ring fusion), the last protonation of the enolate generated by attack of the acyl ketene intermediate **C** by the alcohol determines the diastereoselectivity of the process.[33] Alternatively, a pericyclic version of the process can also be conceived featuring an oxa-6πe^- electrocyclization of initially formed **15** toward pyran intermediate **D** (Scheme 4B). This intermediate could deliver, via ring opening, a reactive diastereoisomer of polyunsaturated Knoevenagel product **15**. This species could be prone to an intramolecular $[{}_{\pi}4_s + {}_{\pi}4_a]$-cycloaddition providing cyclopenta[*b*]furan **13**. The same cascade of fragmentation and addition as described above would yield products **14** from **13**.

To gain insight into the reaction mechanism and gather information about possible intermediates involved, we conducted the NMR monitoring (60 °C) of the reaction between **11** and **12a** carried out in deuterated methanol (Scheme 5).

Scheme 5. NMR Monitoring of the Domino Synthesis of Cyclopenta[*b*]furan-2-ones in Deuterated Methanol



Two possible intermediates could be observed in the ^{1}H NMR spectrum prior to the culmination of the reaction. One of these could easily be attributed to Knoevenagel product **15a** by comparison with the spectrum recorded in MeOD from a sample of **15a** obtained when the reaction was conducted in dichloromethane at reflux using EDDA as catalyst (Scheme 2, eq 1). In the ^{1}H NMR spectrum, the other species featured two doublets at 6.62 and 6.34 ppm with *J* couplings of 15.6 and 11.5 Hz, respectively. According to these findings, this putative intermediate could well correspond to a *γ*,*δ*-*Z* isomer of **15a**, garnering support for the involvement of a pericyclic pathway (Scheme 4B). The reaction was complete within 2 h, with the observed product, according to the ^{1}H NMR spectrum, being deuterated bicyclic lactone **14a**-d_4. The acidity of the proton adjacent to both carbonyl groups became apparent as the product isolated after silica gel column chromatography purification corresponded to **14a**-d_3.

In summary, a new, one-pot multicomponent reaction for the synthesis of substituted cyclopenta[*b*]furan-2-ones was developed. Meldrum's acid, a conjugated dienal, and an alcohol were found to participate in an operationally simple and efficient cascade that creates two new cycles and four new bonds stereoselectively. Computational studies are underway to support the elaborated mechanism as well as to understand selectivity issues in this sequence.

DOI: 10.1021/acs.orglett.8b01567
Org. Lett. 2018, 20, 4000−4004

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01567.

General experimental procedures and ^{1}H, ^{13}C, and 2D NMR spectra of all products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: riveira@iquir-conicet.gov.ar.

ORCID

Martín J. Riveira: 0000-0002-1682-9855

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Universidad Nacional de Rosario (BIO426), Fundación Josefina Prats, Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET, PIP 2012-2014 0448), and Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT, BID-PICT-0408, BID-PICT-1069) for financial support.

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DOI: 10.1021/acs.orglett.8b01567
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(30) Upon weeks of storage, the oily mixture **14a** became a solid. According to the ^{1}H NMR spectrum of the sample, the minor isomer underwent isomerization towards major product *β*-**14a**, (see the SI).
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DOI: 10.1021/acs.orglett.8b01567
Org. Lett. 2018, 20, 4000−4004