Domino Ring Expansion: Regioselective Access to 9-Membered Lactones with a Fused Indole Unit from 2-Nitrophenyl-1,3-cyclohexanediones

Synthetic methodology

DOI: 10.1002/anie.200((will be filled in by the editorial staff))

Ring Expansion by Anionic Fragmentation: Serendipity Opens an Original Access to Indolic Lactones from 2-Nitrophenyl-1,3-cyclohexanediones

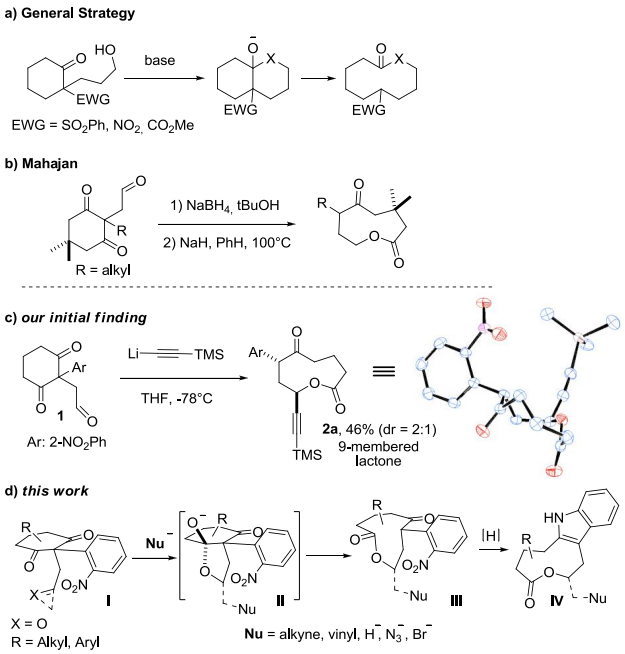
David Reyes Loya,[a] Alexandre Jean,[a] Morgan Cormier,[a] Stefano Nejrati,[a] Jérôme Blanchet,[b] Jacques Maddaluno,[a] and Michaël De Paolis[*,a]*

Dedicated to Professor Jieping Zhu

Abstract: *Initiated by carbon, oxo, aza and hydride nucleophiles, the anionic fragmentation of 2-nitrophenyl-1,3-cyclohexanedione containing an electrophilic appendage is disclosed. Following the generation of the intermediate hydroxylates, the regioselective formation and fragmentation of lactolates into enolates resulted in the ring expansion of the initial ring into medium sized lactone with various substituents and stereoselectivity. This strategy provides original access to polysubstituted indolic medium-size lactones without the use of protecting groups.*

Macrocycles and medium-sized lactones more specifically are structural motifs of interest for applications ranging from medicinal chemistry to molecular recognition as hosts.[1] While the conventional approach toward lactones involves the cyclization of a carboxylic acid and hydroxyl, an elegant alternative emerged with the pioneering study of Mahajan describing the ring expansion of activated ketones.[2] Medium-ring lactones were processed by anionic fragmentation triggered by internal nucleophile (Scheme 1a). The base-induced cleavage of ketones by internal oxy-nucleophile is a strategy that has inspired until very recently creative access to 10-membered lactones and above, as well as lactams.[3] Despite an early report from Mahajan *et al.* with dimedone derivatives,[4] anionic fragmentations producing 9-membered lactones remained scarce (Scheme 1b).[5]

The large structural occurrence of indole and indoline in natural products and biomolecules is well recognized, drawing attention to the synthesis of these motifs. Owing to the inherent and competitive C– and N–nucleophilicity of indole, regio- and chemoselective synthetic elaborations or incorporation of the scaffold into lactones can be tedious, especially with substituted electrophiles.[6,7]



Scheme 1. General strategy involving anionic fragmentation of (di)-ketones and applications to ring expansion of 2-nitrophenyl-1,3-diketone scaffold

To our knowledge, the combination of medium-sized lactone and indole structures seems scarce in natural products, probably due to the sensitivity of lactones toward amines that would lead to amides or lactams.

During a program of total synthesis, we observed that treatment of aldehyde **1** with lithium trimethylsilylacetylide led directly to 9-membered lactone **2a** in 46% yield (dr = 2:1), the major isomer being undoubtedly identified by X-ray analysis (Scheme 1c). Distinctive from the intelligent desymmetrization of aldehyde **1** by reductive amination with chiral amines developed by Bonjoch, Bosch *et al.*, [8] the anionic fragmentation process of **1** and derivatives opened new synthetic routes. Indeed, lactone **2a** not only incorporated the carbon nucleophile that induced the fragmentation process but also contained a versatile nitroaryl substituent which, favouring the process as an electron-withdrawing group, could be subsequently turned into indole, providing thus an entry to elaborated alkaloids.[9] Hence, a route toward substituted and strained lactones embedding the indolic motif **IV** was developed (Scheme 1d) and applied to several derivatives of 2-nitrophenyl-1,3-cyclohexanedione **I**. Proceeding through transient lactol intermediates **II**, the methodology encompassed the grafting of nucleophiles into the resulting 9-membered ring **III** by reaction with the corresponding aldehydes, olefins and epoxides.

[*] D. Reyes Loya, Dr. A. Jean, Dr. M. Cormier, Dr. J. Blanchet, Dr. J. Maddaluno, Dr. M. De Paolis

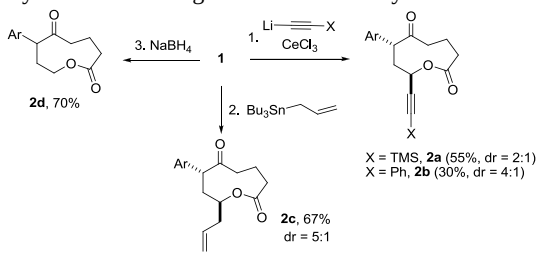
[a] Normandie Université, UNIROUEN, INSA de Rouen, CNRS, Laboratoire COBRA (UMR 6014 & FR 3038), 76000 Rouen, France.
E-mail: michael.depaolis@univ-rouen.fr

[b] Laboratoire de Chimie Moléculaire et Thio-organique, ENSICAEN et Université de Caen Basse-Normandie, CNRS; 6 bd du Maréchal Juin, 14050 - Caen, France

We gratefully acknowledge CRUNCh interregional network for a grant (DRL), ISCE-CHEM (Interreg IV, European Program), Labex SynOrg (ANR-11-LABX-0029) and ANR (GPYRONE) for financial support. We thank Erasmus for a fellowship to S.N. We are appreciative to Prof. P. Williard (Brown Unversity) and B. Kauffmann (IECB) for X-ray analysis.

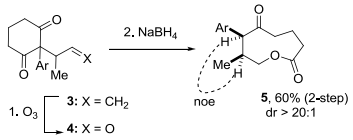
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

The study began by an optimization of the sequence leading to **2a**. While THF appeared the best solvent in comparison with Et_2O (46% vs 16% yield) for achieving the sequence, the preformation of the corresponding organocerium reagent enhanced the yield of **2a** to 55% (dr = 2:1) when operating the reaction at –78°C (Scheme 2). With this protocol, lithium phenylacetylenide was reacted with aldehyde **1** and the procedure delivered lactone **2b** in 30% yield (dr = 4:1). Exploration of the scope of the chemistry revealed that $C(sp^2)$ and $C(sp^3)$ nucleophiles were poorly compatible with the neopentyl carboxaldehyde **1** that contains three carbonyl and nitroaryl moieties. Despite considerable efforts to promote the hydroxyalkylation reaction and the subsequent fragmentation, yields remained below our expectations (< 15% in best cases). Nevertheless, we were able to trigger efficiently the process from **1** with allyltributylstannane in combination with $SnCl_4$ to produce allyl lactone **2c** (67% yield), a versatile scaffold ready for further synthetic manipulations. On the other hand, $NaBH_4$ reacted smoothly with **1** delivering lactone **2d** in 70% yield.



Scheme 2. Ring expansion of **1** by reaction with nucleophiles (Ar = 2-NO_2Ph). Reagents and conditions: 1) TMSC≡CLi or PhC≡CLi, $CeCl_3$, THF, –78°C, 55% or 30%; 2) Bu_3SnAll, $SnCl_4$, CH_2Cl_2, –78°C, 67%; 3) $NaBH_4$, *i*PrOH/CH_2Cl_2, 0°C, 70%

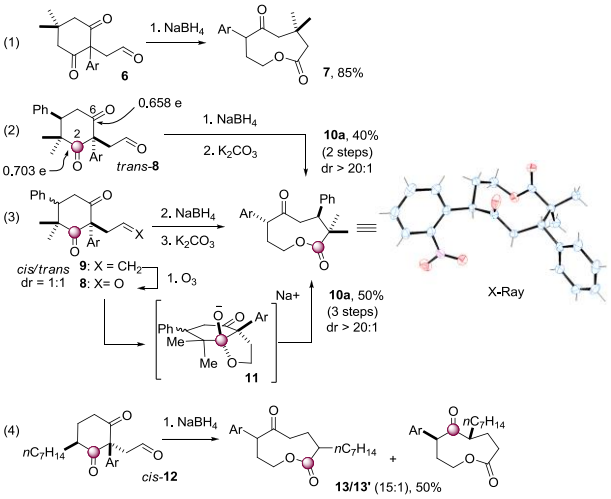
Applied to α-substituted aldehyde **4**, the strategy provided a stereoselective access to *cis*-lactone **5** in 60% yield (2 steps) upon treatment with $NaBH_4$ (Scheme 3). Pleasingly, the protonation step of the enolate intermediate appeared under the complete control of the methyl α–substituent.



Scheme 3. Ring expansion of **1** by reaction with nucleophiles (Ar = 2-NO_2Ph), reagents and conditions: 1) O_3, CH_2Cl_2, -78°C; Me_2S; 2) $NaBH_4$, MeOH, 0°C, 60% (2-step)

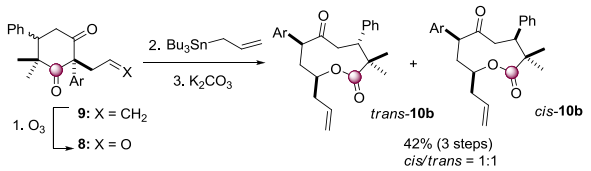
Next, the chemistry was examined with substituted cyclohexanediones. Derived from dimedone, aldehyde **6** was smoothly converted into lactone **7** in 85% yield upon exposure to sodium borohydride (Scheme 4, Eq. 1). With non-symmetrical 1,3-diketones, the regioselectivity of the nucleophilic attack of the hydroxylate was pertinent to study. Initiating the fragmentation, this attack could generate two regioisomers. A case in point, aldehyde **8** featuring the motif 4,4-dimethyl-1,3-cyclohexadione was treated with $NaBH_4$ (Eq. 2). Starting with the isomerically pure aldehyde *trans*-**8**, reductive treatment led initially to lactone **9** in 13% yield among several by-products but interestingly as one diastereoisomer. Accounting probably for this disappointing result, the relative configuration (ascertained by X-ray of the corresponding olefin, see SI) of the carboxaldehyde and the relatively bulky phenyl in 1,4-*cis*-relationship appeared troublesome for an efficient fragmentation. In order to enhance the process, treatment of the crude with K_2CO_3 in THF was carried out to ensure the conversion of lactol intermediates into lactone **10a** (X-ray) with an improved yield of 40% (2 steps). Advantageously, engaging an equal mixture of diastereoisomers (*cis*/*trans*-**8**, dr = 1:1) led directly to isomerically pure lactone **10a** in 50% yield (over 3 steps) upon reductive treatment (Eq. 3).[10] Thus, the stereoselective protonation of the intermediate enolate appeared directed by the 1,4 phenyl substituent. But examination of the regioselectivity of the reaction revealed more surprise. The formation of lactone **10a** indeed implied the fragmentation of lactol **11**, an intermediate that would be produced by reaction at the most hindered ketone by an internal attack of hydroxylate. Inferring that a more subtle analysis was needed, we resorted to DFT calculations (M06XX) to evaluate the electrophilic character of C(2) and C(6) of *trans*-**8**. In agreement with experiments, the most hindered carbonyl – flanked with two quaternary carbons – was found to be more electropositive (C(2) = 0.70301 e) than the less hindered one (C(6) = 0.65843 e), explaining the regioselective formation of **10a**. It is worth underlining the exquisite selectivity of the fragmentation: while four isomers could have been produced as regio- and diastereoisomers, only one was observed.

With less congested ketones such as 4-heptyl-1,3-diketone *cis*-**12**, the regioselectivity of the intramolecular nucleophilic attack was less pronounced. Hence, lactones **13/13'** were produced in a ratio of 3:1 (50 % yield). Still, the major regioisomer **13** arised from a nucleophilic attack to the most hindered ketone.



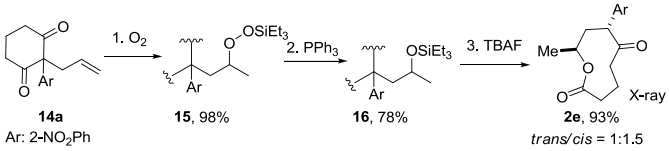
Scheme 4. Ring expansion of aldehydes **6, 8** and **12** by reaction with $NaBH_4$ (Ar = 2-NO_2Ph), ratio determined by ^{1}H NMR spectroscopy (300 MHz). Reagents and conditions: 1) O_3, CH_2Cl_2, -78°C; Me_2S; 2) $NaBH_4$, MeOH or *i*PrOH/CH_2Cl_2, 0°C; 3) K_2CO_3, THF, 80°C

With two stereocenters, the prochiral aldehyde **8** provided an interesting case for the reaction with carbon nucleophile. Indeed, the produced lactone would contain three stereocenters among which, one of them will be controlled by the protonation step. To perform this step, nucleophilic attack of *cis*/*trans*-**8** (dr = 1:1) with allyltributylstannane/$SnCl_4$ was carry out as previously demonstrated and this step was followed by a basic treatment to complete the fragmentation. To our delight, elaborated lactones *trans*-**10b** and *cis*-**10b**, two diastereoisomers over four possible, were isolated in 42% yield (over 3 steps). Owing to steric 1,3-interactions, the protonation step of the enolate appeared therefore efficiently controlled. The regioselectivity was also excellent, one isomer being observed from from reaction at the most hindered ketone which means that only two products were formed over eight possibly expected.



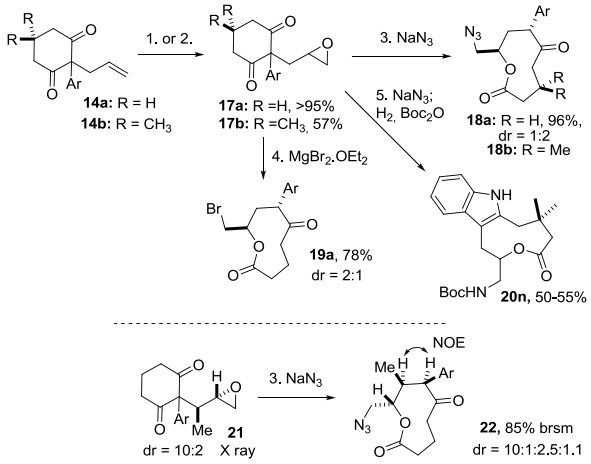
Scheme 5. Allylation of **8** (Ar = 2-NO_2Ph), reagents and conditions: 1) O_3, CH_2Cl_2, -78°C; Me_2S; 2) Bu_3SnAll, $SnCl_4$, CH_2Cl_2, –78°C; 3) K_2CO_3, THF, 80°C, 42% yield (over 3 steps)

To provide extended molecular diversity with acute simplicity and efficiency, the strategy was extended to olefins **14**, a precursor of aldehyde **1** (Scheme 6).[11]



Scheme 6. Ring expansion of peroxide **15** obtained by oxidation of olefin **14** (Ar = 2-NO_2Ph); Reagents and conditions: 1) O_2, $Co(acac)_3$, $tBuO_2H$, Et_3SiH, 1,2-DCE, rt, 98%; 2) PPh_3, THF, rt, 78%; 3) TBAF, THF, rt, 93%, *trans/cis* = 1:1.5

Hence, olefin **14** was oxidized in the presence of oxygen, $Co(acac)_3$, a catalytic amount of tBuOOH and Et_3SiH to provide peroxide **15** (98% yield) according to the procedure established by Inoue.[12] Peroxide **15** was then regioselectively reduced with PPh_3 to provide silylether **16** in 78% yield. Exposed to TBAF to trigger both the alcohol deprotection and the anionic fragmentation, compound **16** was converted into lactone **2e** in 93% yield. Although this sequence was envisaged in one-pot by reduction of **15**, better results were obtained proceeding in two steps.[13] The relative configuration of the minor isomer *trans*-**2e** was determined by X-ray analysis (*trans*/*cis* = 1:1.5). Following the Markovnikov manifold, the oxidation appeared to be completely regioselective and the formation of the isomeric 10-membered lactone was not observed. We were curious to determine if the epoxide of olefin **14a** could be included in the panoply of electrophiles triggering such fragmentation (Scheme 7).



Scheme 6. Preparation and ring expansion of epoxide **17a,b**. Reagents and conditions: 1) mCPBA, CH_2Cl_2, rt, > 95%; 2) mCPBA, $NaHCO_3$, CH_2Cl_2, 10°C, 54% brsm; 3) NaN_3, $CeCl_3.H_2O$, CH_3CN/H_2O, 80°C, 96% for **18a,** 61% (85% brsm) for **22**; 4) $MgBr_2$●OEt_2, THF, 70°C, 77%; 5) NaN_3, $CeCl_3.H_2O$, CH_3CN/H_2O, 80°C; H_2, Pd/C, Boc_2O, MeOH, 61% from **17b**

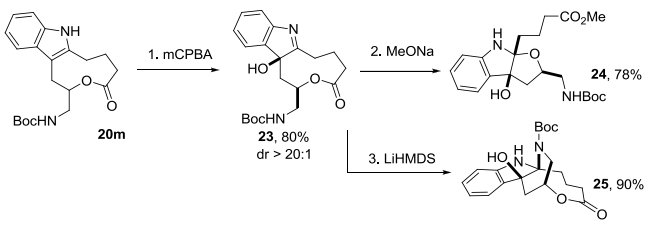
Prepared by oxidation with mCPBA in quantitative yield from **14a**, epoxide **17a** was subsequently treated with organomagnesium, organocerium or organolithium reagents in the presence of Lewis acids. In all cases, decomposition of the starting material was observed. Gratifyingly, milder nucleophiles proved compatible with the molecule. Hence, NaN_3 reacted quantitatively with epoxide **17a** in the presence of $CeCl_3.H_2O$ providing directly azido lactone **18a** in excellent yield (96%, dr = 1:2), both stereoisomers being separable by simple trituration.[14] Noteworthy, the combination of both reagents was required for the successful preparation of this versatile azido lactone ready for [3+2] cycloaddition reaction for instance.

Treatment of **17a** with $MgBr_2$●OEt_2 afforded bromo lactone **19a** in 77% yield (dr = 2:1), a scaffold that could further be functionalized by taking advantage of the C–Br bond. [15]

Derived of dimedone, epoxide **17b** was obtained in 57% yield from the corresponding olefin **14b** upon exposure to milder conditions (*m*CPBA, $NaHCO_3$, 10°C, CH_2Cl_2) than for **14a**. Upon exposure of epoxide **17b** to $NaN_3/CeCl_3.H_2O$, azido lactone **18b** was produced. Before purification and isolation, the sequence was conveniently completed by a reduction step in presence of Boc_2O to achieve the synthesis of the corresponding amino indole **20n** (47%). Of note is the successful conversion of the azide appendage into the corresponding amine without jeopardizing the lactone ring. This sequence was also demonstrated with the more hindered epoxide **21** (dr = 10:2). Longer reaction time was required but azido lactone **22** was obtained in 61% yield (72% conversion) with stereoselectivity (dr = 10:1:2.5:1), the major isomer being identified by 2D NMR spectroscopy.

In all of the presented cases, the unfolding of cyclic diketones enabled an access to highly functionalized lactone templates, ready for further synthetic manipulations. Hence, upon reductive conditions, the indolic motif was embedded into the lactone scaffold, providing thus a concise route to various functionalized alkaloids **20a-o** that circumvents the use of protecting group (Figure 1). Of note is the possibility provided by the methodology to access protected amines such as **20l** or **20m** from the corresponding azide **18a** without cleavage of the lactone ring.

Furthermore, the indolic lactone motif was easily turned into indoline derivatives. In the case in point, oxidation of indole **20m** with mCPBA allowed the diastereoselective preparation of hydroxyl indoline **23** in 80% yield by ring opening of the transient indole 2,3-epoxide.[16] Incidentally, the spontaneous ring contraction of hydroxyl indoline by [1,5] sigmatropic shift in spiro-oxindole was not observed even in basic conditions.[17] Hence, treatment with MeONa/MeOH converted **23** into furoindoline **24** (78% yield) while a simple exposure of **24** to LiHMDS afforded polycyclic pyridoindolinic lactone **25** in excellent yield (90%). The relative configuration of the rigidified structure of **25** was determined by 2D NMR spectroscopy analysis which allowed the deduction of the relative configuration of the precursors.



Scheme 7. Manipulations of lactone **20m**; Reagents and conditions: 1) mCPBA, THF, 0°C, 80%; 2) MeONa, MeOH, 80°C, 78%; 3) LiHMDS, THF, –78°C, 90%

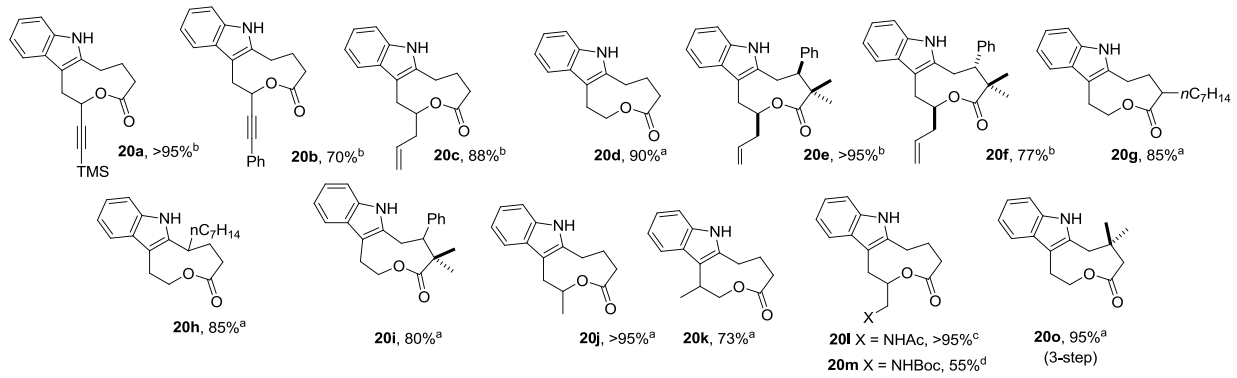


Figure 1. Preparation of indolic lactones **20a-o** from the corresponding nitroaryl precursors; Reagents and conditions: a) H_2, Pd/C, MeOH, rt; b) Zn, AcOH, 40°C; c) H_2, Pd/C, THF/tBuOH, Ac_2O, rt; d) H_2, Pd/C, MeOH, Boc_2O, rt

In summary, a new development in the field of ring expansion by anionic fragmentation has been unveiled. As demonstrated, the ring expansion of substituted 2-nitroaryl-1,3-cyclohexanedione was initiated from carboxaldehyde, olefin and epoxide functional groups as electrophilic appendage. Mild nucleophiles were best suited to initiate the process of fragmentation, leading to 9-membered lactones with the nucleophile incorporated into the scaffold.

In view of the regioselective attack of the internal nucleophile with the most hindered ketone, investigations by calculations were carried out and revealed the higher electrophilic character of this position. The stereoselectivity issue was also explored with promising results for a future asymmetric access to this class of polysubstituted medium-sized lactones that can easily be converted into indolic lactones, indoline, furoindoline and pyridoindoline.

Received: ((will be filled in by the editorial staff))
Published online on ((will be filled in by the editorial staff))

Keywords: anionic fragmentations · indole · lactone · alkaloids ·

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[10] The two diastereoisomers reacted with ozone in different kinetics and it was difficult to prevent the degradation of the ozonide arising from the most reactive olefin. This could explain the fair yield (50%) obtained from this 3-step sequence.

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[13] With the less hindered PBu_3, a mixture of the corresponding alcohol and lactone **2e** was obtained. For regioselective reduction of peroxide obtained this way, see: J. A. Hilf, L. W. Witthoft, K. A. Woerpel, *J. Org. Chem.* **2015**, *80*, 8262–8267.

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[15] This result provided an alternative to the strategy of bromolactonization of carboxylic acid with olefin and a source of electropositive bromide. See for example: Y. A. Cheng, T. Chen, C. K. Tan, J. J. Heng, Y.-Y. Yeung *J. Am. Chem. Soc.* **2012**, 134, 16492−16495.

[16] The relative configuration of **23** was deduced from the analysis of the product resulting from the following experiments.

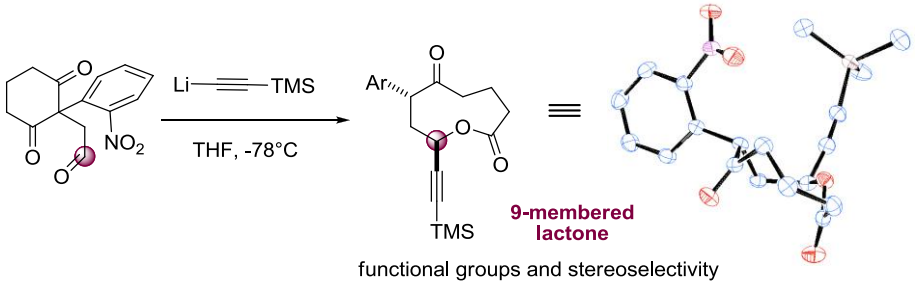
[17] T. J. Greshock, R. M. Williams, *Org. Lett.* **2007**, *9*, 4255–4258.

CCDC1040200 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthetic methodology

David Reyes Loya, Alexandre Jean, Morgan Cormier, Jérôme Blanchet, Jacques Maddaluno, Michaël De Paolis*_____ **Page – Page**

Ring Expansion by Anionic Fragmentation: Serendipity Opens an Original Access to Indolic Lactones from 2-Nitrophenyl-1,3-cyclohexanediones



Continuity with change: An original outcome fitting into the continuity of the ring expansion strategy by anionic fragmentation was serendipitously discovered. 2-Nitrophenyl-1,3-cyclohexanediones connected to an electrophilic appendage were stereoselectively converted in one step into 9-membered lactone upon treatment with carbon, aza, oxo and hydride nucleophiles, opening an access to (indolic) lactones. To demonstrate the potential of the strategy, aldehyde, olefin and epoxide were succesfully tested as electrophilic appendage while the regio- and diastereoselective aspects of the transformation were explored.