CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

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

Authors: Michael De Paolis, David Reyes Loya, Alexandre Jean, Morgan Cormier, Catherine Fressigné, Stefano Nejrotti, Jérôme Blanchet, and Jacques Maddaluno

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Chem. Eur. J.* 10.1002/chem.201705645

Link to VoR: http://dx.doi.org/10.1002/chem.201705645

Supported by
ACES

WILEY-VCH

10.1002/chem.201705645

Synthetic methodology

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

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

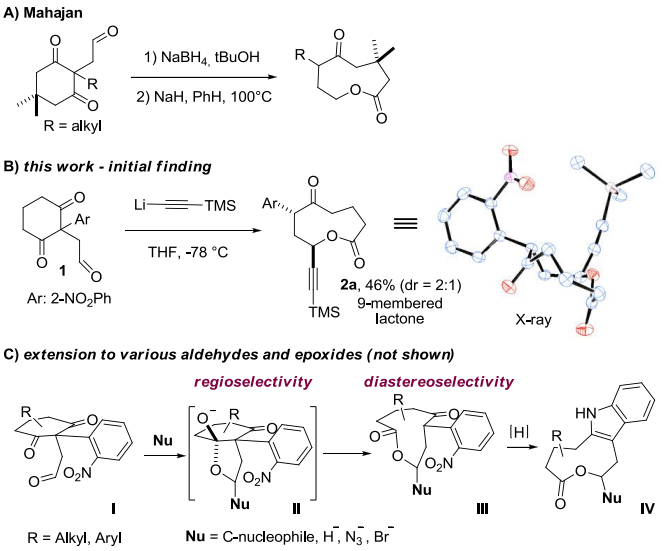
David Reyes Loya,[a] Alexandre Jean,[a] Morgan Cormier,[a] Catherine Fressigné,[a] Stefano Nejrotti,[a] Jérôme Blanchet,[b] Jacques Maddaluno,[a] and Michaël De Paolis[*,a]*

In memory of István E. Markó

Abstract: *The domino anionic fragmentation of 2-nitrophenyl-1,3-cyclohexanediones containing an electrophilic appendage such as aldehyde and epoxide is disclosed. This reaction, initiated by a series of nucleophiles, involves the generation of an intermediate hydroxylate followed by the regioselective formation and fragmentation of an intermediate lactolate into enolate. This strategy, devoid of any protecting group, enlarges the initial ring and provides an original access to decorated 9-membered lactones with a fused indole unit.*

With the ability to bind to proteins with a large and rigid structure, macrocycles offering multisite interactions, such as medium-sized lactones, are pertinent in medicinal chemistry.[1] While the usual disconnection of lactones involves the intramolecular reaction of carboxylic acid with alcohol, this strategy is delicate when directed toward medium-sized lactones due to the risk of intermolecular reaction. Alternatives, such as the ring closing metathesis of alkenes and alkynes or C–H oxidation of linear alkenoic acids, emerged for the elegant synthesis of large-sized lactones.[2] Another way to prepare a lactone without a lactonisation step is based on the ring expansion of activated ketones by internal hydroxylate triggering a fragmentation (Scheme 1A).[3] Still today, the strategy inspires creative access to 10-membered (and more) lactones or lactams by employing aza-nucleophiles.[4] We noted though that despite an early report from Mahajan with dimedone derivatives[5] and the contribution of Rodriguez in the field, anionic fragmentations producing strained 9-membered lactones remained scarce.[6]

The indole and indoline cores are found in numerous natural products and biomolecules. Owing to the inherent and competitive C– and N–nucleophilicity of indole, regio- and chemoselective functionalization at C2/C3 can be tedious without resorting to protecting groups, as well as their incorporation into lactones.[7,8] If natural products combining medium-sized lactone and indole motifs are rather uncommon, the combination of two classic pharmacophores is expected to afford new platforms of interest in molecular biosciences.



Scheme 1. A) Known anionic fragmentation of diketones and B,C) applications to the regio- and diastereoselective ring expansion of 2-nitrophenyl-1,3-diketone scaffold.

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 (Scheme 1B). This result could be explained by an unprecedented domino ring expansion fostered by an anionic fragmentation that was initiated by internal hydroxylate.[9] So far, aldehyde **1** had been brilliantly employed by Bonjoch and Bosch to access highly substituted pyrrolidines en route to complex natural products, a reductive amination step with chiral amines warranting the desymmetrization of **1**.[10] Distinct from this strategy, the domino fragmentation of **1** opened different routes to be harnessed, as illustrated with lactone **2a** in which C-C and C-O bonds were created. Incorporating the carbon nucleophile that induced the fragmentation, lactone **2a** also contained a versatile nitroaryl substituent which facilitates the whole process and provides an entry to elaborated scaffold once converted into indole. Hence, a route toward substituted and strained lactones embedding the indole motif **IV** was developed (Scheme 1C) and applied to several derivatives of 2-nitrophenyl-1,3-cyclohexanedione **I** demonstrating interesting levels of regio- and diastereoselectivity. Proceeding through transient lactolate intermediates **II**, the methodology encompassed the grafting of nucleophiles into the resulting 9-membered ring **III** by reaction with the corresponding aldehydes and epoxides.

Screening of conditions revealed that the preformation of the organocerium reagent of lithium trimethylsilylacetylenide enhanced the yield of **2a** to 55% (dr = 2:1) from **1** while lactone **2b** was produced in 30% yield (dr = 4:1) with lithium phenylacetylenide as

[*] D. Reyes Loya, Dr. A. Jean, Dr. M. Cormier, S. Nejrotti, 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] LCMT, ENSICAEN et Université de Caen, CNRS; 6 bd du Maréchal Juin, 14050 - Caen, France

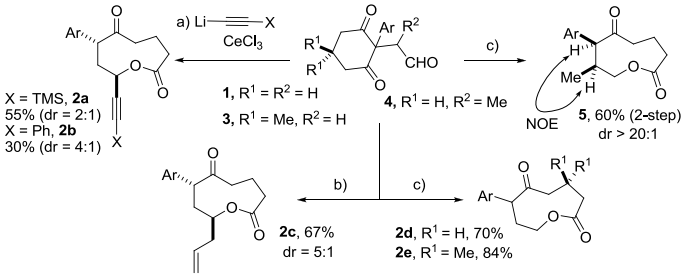
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/chem.201705645

nucleophile (Scheme 2). Explaining the low yield in **2b**, deprotonation of the hindered aldehyde **1** and side reactions of the nucleophile with ketone and nitroaryl moieties are likely to occur. For the same reasons, C(sp^2) and C(sp^3) nucleophiles (vinyl-, allylmagnesium bromide or *n*BuLi) were found poorly compatible with **1**.[11] This drawback was overcome by resorting to a combination of an allyl pronucleophile (*n*Bu_3SnAll) and a mild Lewis acid ($SnCl_4$) that converted aldehyde **1** into lactone **2c** (67% yield, dr = 5:1), a scaffold ready for various synthetic manipulations. On the other hand, reduction of **1** with $NaBH_4$ furnished directly lactone **2d** in 70% yield or lactone **2e** in 84% yield by reaction with aldehyde **3**, derived from dimedone. Applied to α-substituted aldehyde **4**, the reduction warranted a stereoselective access to *cis*-lactone **5** in 60% yield (2 steps, dr > 20:1) owing to an *anti* stereoselective protonation step of the enolate intermediate.

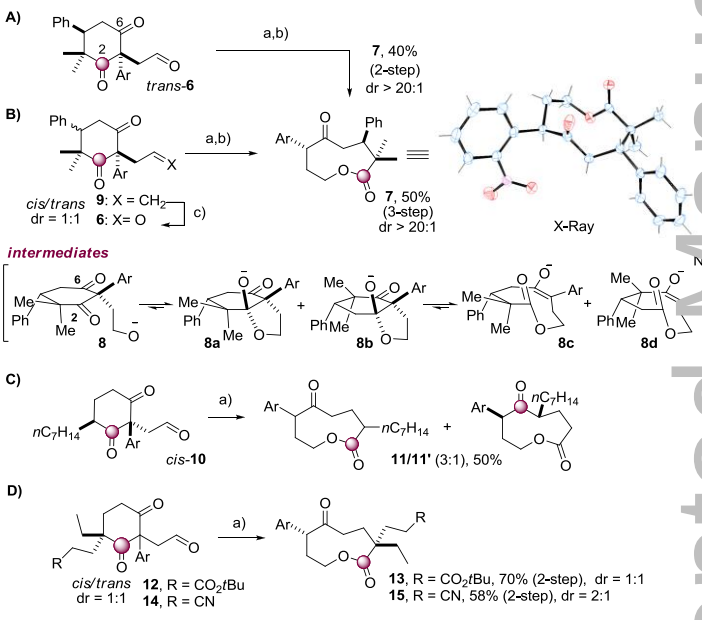


Scheme 2. Ring expansion of **1, 3** and **4** by reaction with nucleophiles (Ar = 2-NO_2Ph). Conditions: a) TMSC≡CLi or PhC≡CLi, $CeCl_3$, THF, –78 °C; b) *n*Bu_3SnAll, $SnCl_4$, CH_2Cl_2, –78 °C; c) $NaBH_4$, *i*PrOH/CH_2Cl_2 or MeOH, 0 °C

To examine the regioselectivity of the fragmentation, non-symmetrical 1,3-cyclohexanediones were prepared by a known sequence of domino double Michael-cyclization that allows the installation of various substituents to the scaffold which, once assembled, could be arylated and allylated in position 2 (see SI for details).[12] As the reaction of the aldehydes with $NaBH_4$ could deliver two regioisomers, we were curious to analyse the outcome of the fragmentation (Scheme 3). A case in point, the isomerically pure *trans*-**6**[13] led to lactone **7** (X-ray) in 40% yield (Scheme 3A), as a single regio- and diastereoisomer. In this case, the process required a basic treatment (K_2CO_3, THF, 80 °C) to complete the fragmentation and convert the various intermediates of the reaction into **7**. Whether this treatment could also promote the epimerization of *dia*-**7** into **7** in the event of its formation could not be determined. At any rate, a mixture of *cis*/*trans*-**6** (dr = 1:1) solely led to isomerically pure **7** in 50% yield (3-step) upon reductive and basic treatment (Eq. 2).[14]

To investigate the regioselectivity of the process, we looked at the electrophilic character of C(2) and C(6) in sodium alcoholate **8**, the starting point of the process. DFT calculations (M06-2X continuum MeOH) and NBO analysis revealed that the most hindered carbonyl – flanked by two quaternary carbons – is more electropositive (C(2) = +0.703 e) than the less hindered one (C(6) = +0.658 e). In an attempt to discern the role of the nitro substituent, DFT calculations were also performed on a similar substrate deprived of the nitro moiety (Ar = Ph). They still indicate a disparity of electropositivity between C(2) (+0.684 e) and C(6) (+0.657 e) but the difference was ebbed.[15] These calculations suggest therefore a significant electronic effect of NO_2-substituent that could emphasise the regioselectivity of the attack by increasing the electropositivity of C(2). Yet, it is very likely that electronic guise only partially explain the observed regioselectivity. Hence steric hindrance of the quaternary carbon combined to considerations regarding the Bürgi-Dunitz angle of the alkoxide trajectory could indeed induce the formation of an amount of the isomeric lactol intermediate **8b** along with **8a**, the privileged isomer due to the high electrophilic character at C(2). But these two isomers could well be in thermodynamic equilibrium, as well as the enolates lactones **8c** and **8d** resulting from their respective fragmentations. And a shift of these equilibria leading to the regioselective production of isomer **8c** is conceivable under the assumption that the steric hindrance of the quaternary carbon acts as an impediment to the transannular Dieckmann reaction of the enolate with the lactone moiety in **8c**. In any case, the exquisite selectivity of the whole process is worth underlining: a single regio- and diastereoisomer was observed where four were expected.

With a less congested substrate however, such as *cis*-**10**, the regioselectivity of the intramolecular nucleophilic attack was minored (Scheme 3C). Hence, lactones **11/11'** were produced in a ratio of 3:1 (50 % yield). Incidentally, the fragmentation of the intermediates occurred spontaneously without the need of subsequent basic treatment. Respectively functionalized with ester and nitrile appendage, the *cis*/*trans* aldehydes **12** and **14** were converted into the lactones **13** and **15** (Scheme 3D) in 70 % and 58% yields (2-step including the ozonolysis of the olefin not shown) with regioselectivity but modest diastereoselectivity in both cases.[16,17]



Scheme 3. Fragmentation of aldehydes **8, 10, 12** and **14** (Ar = 2-NO_2Ph), dr determined by ^{1}H NMR spectroscopy (300 MHz). Conditions: a) $NaBH_4$, *i*PrOH/CH_2Cl_2, 0 °C; b) K_2CO_3, THF, 80 °C; c) O_3, CH_2Cl_2, –78 °C.

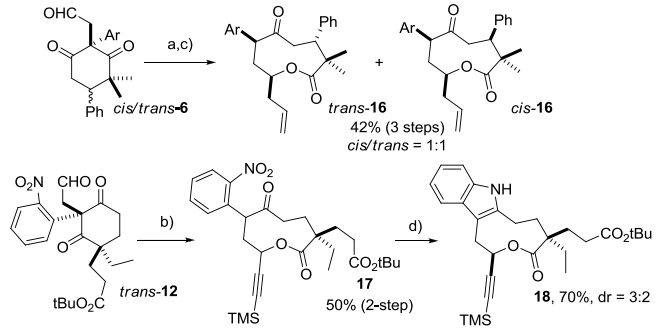
Encouraged by the stereoselective formation of **7** by reduction of aldehyde **6** (see above), we examined the diastereoselectivity of the process with carbon nucleophiles. The domino reaction would produce lactones with three stereocenters but we inferred that a level of stereocontrol could be observed. Pleasingly, allylation of *cis*/*trans*-**6** (dr = 1:1) afforded after basic treatment, lactones *trans*-**16** and *cis*-**16** (42% yield, 3 steps from **9**), two diastereoisomers out of four possible (Scheme 4). Considering the regioselectivity issue, the result is even more interesting since only two isomeric lactones were formed out of eight possible. It is especially noteworthy the secondary hydroxylate still reacted, in spite of its own hindrance, at the most hindered ketone. In the next case, straightforward hydroalkynylation of aldehyde *trans*-**12** gave lactone **17** in good

Accepted Manuscript

This article is protected by copyright. All rights reserved.

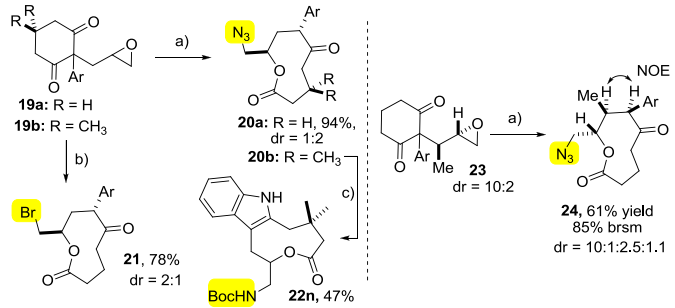
10.1002/chem.201705645

yield (50% yield, 2-step) with ester and alkyne appendages. A complex isomeric mixture was however observed which was not surprising given the results obtained with hydride (Scheme 3D). Yet, subsequent reduction of the nitro group gave indole **18** in 70% yield with modest stereoselectivity (dr = 3:2) but with complete regioselectivity.[16]



Scheme 4. Conditions (Ar = 2-NO_2Ph): a) *n*Bu_3SnAll, $SnCl_4$, CH_2Cl_2, –78 °C; b) TMSC≡CLi, $CeCl_3$, THF, –78 °C; c) K_2CO_3, THF, 80 °C; d) Zn, AcOH, 40 °C.

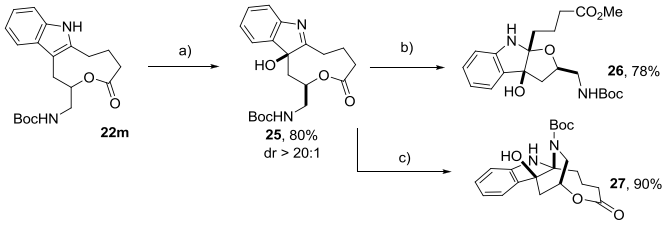
Moreover, we wondered if the epoxide **19a** could be included in the panoply of electrophiles undergoing the domino process (Scheme 5). Gratifyingly, mild nucleophiles such as NaN_3 reacted efficiently with **19a** in the presence of $CeCl_3$ providing azido lactone **20a** in excellent yield (94%, dr = 1:2, *cis*/*trans*).[18] Alternatively, ring opening of the epoxide **19a** was effected with $MgBr_2$●OEt_2 leading to bromo lactone **21** in 77% yield (dr = 2:1).[19] When exposed to NaN_3/$CeCl_3$, the more sensitive epoxide **19b** gave azido lactone **20b** and hydrogenation in the presence of Boc_2O was conducted yielding amino indole **22n** (47%). Concisely, the route leads to a scaffold containing strained and substituted lactone with a fused indole and amine appendage.



Scheme 5. Ring expansion of epoxides **19a,b** and **23** (Ar = 2-NO_2Ph), conditions: a) NaN_3, $CeCl_3.7H_2O$, CH_3CN/H_2O, 80 °C; b) $MgBr_2$●OEt_2, THF, 70 °C; c) H_2, Pd/C, Boc_2O, MeOH. brsm = based on recovered starting material.

With the hindered epoxide **23** (dr = 10:2), the domino sequence produced azido lactone **24** in 61% yield (72% conversion) with a level of stereoselectivity (dr = 10:1:2.5:1), the major isomer being identified by 2D NMR spectroscopy.

In addition to the highly substituted lactone **18**, various lactones **22a-q** were generated upon reductive treatment of the corresponding nitroaryl lactones with alkyl, alkyne, alkene, ester, nitrile and amino appendages that are described in Figure 1. Circumventing the need for protecting groups, an access to functionalized lactones with a fused indole was thus established. To complement the study and illustrate the versatility of the scaffold, synthetic manipulations were carried out. To that end, the diastereoselective oxidation of indole **22m** was achieved with *m*CPBA in THF, this solvent being crucial for the stereoselectivity of the transformation (Scheme 6). Embedded into the 9-membered lactone, hydroxyindolenine **25** was obtained in 80% yield.[20] Furthermore, *trans* esterification of **25** provided furoindoline **26** (78% yield) while exposure of **25** to LiHMDS afforded pyridoindolinic lactone **27** in excellent yield (90%).[21]



Scheme 6. Conditions: a) *m*CPBA, THF, 0 °C; b) MeONa, MeOH, 80 °C; c) LiHMDS, THF, –78 °C. *m*CPBA = 3-chloroperbenzoic acid, LiHMDS = lithium hexamethyldisilazide.

In summary, an unprecedented domino process in the field of anionic fragmentation was illustrated from substituted 2-nitroaryl-1,3-cyclohexanediones bearing aldehyde and epoxide electrophilic appendages. Mild nucleophiles were best suited to initiate the fragmentation process, forging various bonds and leading to 9-membered lactones with the nucleophile incorporated into the scaffold. The counter-intuitive regioselectivity of the attack opened a route to functionalized lactones. Investigated by DFT calculations, the origin of the regioselectivity could initially rely on the higher electrophilic character of the most hindered ketone subtlety emphasised by the electronic effect of the nitro moiety. The stereoselectivity issues were also explored with promising results for a future asymmetric access to this class of rigid lactones. Once converted into lactones with a fused indole unit, appendages are available for functionalization or interactions with biological hosts. Alternatively, they were easily converted into elaborated hydroxyindolenine, furoindoline and pyridoindoline.

Acknowledgements

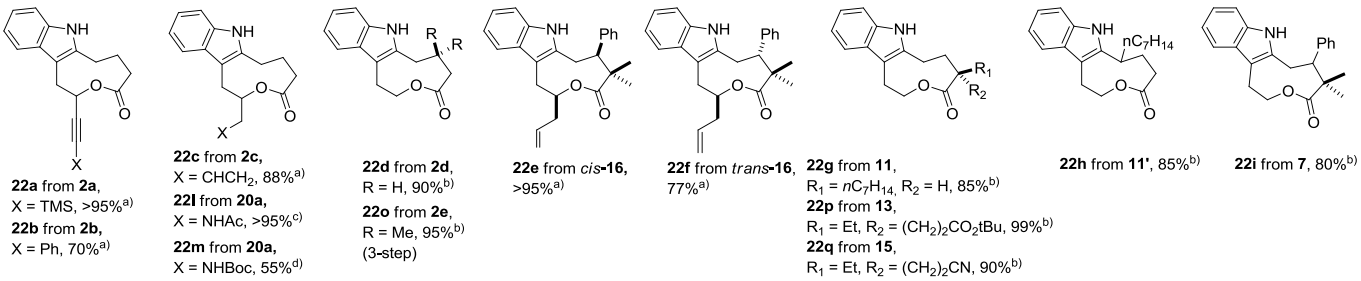


Figure 1. Preparation of lactones **22a-q** from the corresponding nitroaryl precursors, conditions: a) Zn, AcOH, 40 °C; b) H_2, Pd/C, MeOH, rt; c) H_2, Pd/C, Ac_2O, THF/*t*BuOH, rt; d) H_2, Pd/C, Boc_2O, MeOH, rt.

This article is protected by copyright. All rights reserved.

Accepted Manuscript

We gratefully acknowledge the CRUNCh network for a grant (D.R.L.), ISCE-CHEM (Interreg IV, European Program), Labex SynOrg (ANR-11-LABX-0029) and ANR (GPYRONE, 14-CE06-0016-01) for financial support. We thank Erasmus for a fellowship (S.N.), Brice Kauffmann (IECB, Pessac, France) and Prof. Paul Williard (Brown University, USA) for X-ray analysis, Masahiro Abe (Normandie Université) for further experiments. Calculations were run at CRIANN supercomputing facilities, supported by Région Normandie, France and the European Union.

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

Keywords: domino · regioselectivity · medium-sized lactones · ring expansion

[1] For reviews, see: a) C. J. Roxburgh *Tetrahedron*, **1993**, *49*, 10749-10784; b) G. Rousseau, *Tetrahedron*, **1995**, 51, 2777-2849; b) A. Parenty, X. Moreau, J.-M. Campagne, *Chem. Rev*. **2006**, *106*, 911–939; c) I. Shiina, *Chem. Rev*. **2007**, *107*, 239–273; Examples of strategy; see: d) M. Ebine, Y. Suga, H. Fuwa, M. Sasaki, *Org. Biomol. Chem.* **2010**, *8*, 39–42; e) W. Zhao, Z. Wang, J. Sun, W. Zhao, Z. Wang, J. Sun, *Angew. Chem.* **2012**, *124*, 6313–6317; *Angew. Chem. Int. Ed.* **2012**, *51*, 6209–6213; f) J. J. Ciardiello, W. R. J. D. Galloway, C. J. O'Connor, H. F. Sore, J. E. Stokes, Y. Wu, D. R. Spring, *Tetrahedron*, **2016**, *72*, 3567-3578; g) L. A. Wessjohann, O. Kreye, D. G. Rivera, *Angew. Chem.* **2017**, *129*, 3555–3559; *Angew. Chem. Int. Ed.* **2017**, *56*, 3501–3505.

[2] a) R. H. Grubbs, *Handbook of Metathesis*, *Vol. 2*, Wiley-VCH, Weinheim, **2003**; J. Cossy, S. Arseniyadis, C. Meyer, *Metathesis in Natural Product Synthesis*, Wiley-VCH, Weinheim, **2010**; b) for review on alkene metathesis: C. Samojłowicz, M. Bieniek, K. Grela, *Chem. Rev*. **2009**, *109*, 3708-3742; c) for review on alkyne metathesis, see: A. Fürstner *Angew. Chem. Int. Ed*. **2013**, *52*, 2794–2819; d) for recent case, see: C.-X. Zhuo, A. Fürstner *Angew. Chem.* **2016**, *128*, 6155–6160; *Angew. Chem. Int. Ed*. **2016**, *55*, 6051–6056; e) for seminal ring closing metathesis studies applied to macrolides, see: D. Villemin, *Tetrahedron Lett*. **1980**, *21*, 1715–1718; f) A. F. Houri, Z. Xu, D. A. Cogan, A. H. Hoveyda, *J. Am. Chem. Soc.*, **1995**, *117*, 2943–2944; g) for others recent strategy, see: Y. Bai, D. C. Davis, M. Dai, *Angew. Chem.* **2014**, *126*, 6637–6640; *Angew. Chem. Int. Ed.* **2014**, *53*, 6519–6522; h) M. Kanematsu, M. Yoshida, K. Shishido, *Angew. Chem.* **2011**, *123*, 2666–2668; *Angew. Chem. Int. Ed.* **2011**, *50*, 2618–2620; i) 9-membered ring formation by cycloaddition: L.-C. Yang, Z.-Q. Rong, Y.-N. Wang, Z. Y. Tan, M. Wang, Y. Zhao, *Angew. Chem.* **2017**, *129*, 2973–2977; *Angew. Chem. Int. Ed.* **2017**, *56*, 2927–2931; j) epothilones synthesis by RCM, see: K. C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg, F. Roschangar, F. Sarabia, S. Ninkovic, Z. Yang, J. I. Trujillo, *J. Am. Chem. Soc.* **1997**, 119, 7960–7973; k) D Schinzer, A. Bauer, O. M. Böhm, A. Limberg, M. Cordes, *Chem. Eur. J.* **1999**, *5*, 2483-2491; l) C–H oxidation : K. J. Fraunhoffer, N. Prabagaran, L. E. Sirois, M. C. White, *J. Am. Chem. Soc.* **2006**, *128*, 9032–9033; m) Example of C–H oxidation of cycloethers: R. Mansueto, V. Mallardo, F. Maria Perna, A. Salomone, V. Capriati, *Chem. Commun*. **2013**, *49*, 10160–10162.

[3] a) J. R. Mahajan, *Synthesis*, **1976**, 110–111. For radical approach to the similar targets including 9-membered lactones, see: b) H. Suginome, S. Yamada, *Tetrahedron*, **1987**, *43*, 3371–3386; c) C. De Dobbeleer, A. Ates, J-C. Vanherk, I. E. Markó, *Tetrahedron Lett.* **2006**, *46*, 3889–3893; d) M. Hesse, *Ring Enlargement in Organic Synthesis*, VCH, Weinheim, **1991**; for an excellent review on the ring expansion strategy: e) J. R. Donald, W. P. Unsworth, *Chem. Eur. J.* **2017**, *23*, 8780–8799.

[4] a) U. Kramer, A. Guggisberg, M. Hesse, H. Schmid, *Angew. Chem. Int. Ed.* **1977**, *16*, 861–862; b) V. Bhat, R. C. Cookson, *J. Chem. Soc., Chem. Comm.*, **1981**, 1123–1124; c) R. C. Cookson, P. S. Ray, *Tetrahedron Lett.*, **1982**, *23*, 3521–3524; d) K. Kostova, M. Hesse, *Helv. Chem. Acta.* **1984**, *67*, 1713–1724; e) S. D. Najdi, M. M. Olmstead, N. E. Schore, *J. Organomet. Chem.*, **1992**, 335–358; f) J. R. Mahajan, I. S. Resck, *J. Chem. Soc., Chem. Comm.*, **1993**, 1748–1749; g) N. Ono, H. Miyake, A. Kaji, *J. Org. Chem.*, **1984**, *49*, 4997–4999; h) C. Kitsiou, J. J. Hindes, P. l'Anson, P. Jackson, T. C. Wilson, E. K. Daly, H. R. Felstead, P. Hearnshaw, W. P. Unsworth, *Angew. Chem.* **2015**, *127*, 16020–16024; *Angew. Chem. Int. Ed.* **2015**, *54*, 15794–15798; i) L. G. Baud, M. A. Manning, H. L. Arkless, T. C. Stephens, W. P. Unsworth, *Chem. Eur. J.* **2017**, *23*, 2225–2230; For a strategy employing a leaving group instead of an electron-withdrawing group: j) G. H. Posner, K. S. Webb, E. Asirvatham, S. Jew, A. Degl'Innocenti, *J. Am. Chem. Soc.* **1988**, *110*, 4754–4762; k) T. Wang, J. Chen, D. W. Landrey, K. Zhao *Synlett*, **1995**, 543–544; l) M. A. Hatcher, K. Borstnik, G. H. Posner, *Tetrahedron Lett.* **2003**, *44*, 5407–5409; m) G. H. Posner, M. A. Hatcher, W. A. Maio, *Org. Lett.* **2005**, *7*, 4301–4303; n) W. A. Maio, S. Sinishtaj, G. H. Posner, *Org. Lett.* **2007**, *9*, 2673–2676; For a demonstration of ring expansion with metalated ureas, see: o) J. E. Hall, J. V. Matlock, J. W. Ward, K. V. Gray, J. Clayden, *Angew. Chem.* **2016**, *128*, 11319–11323; *Angew. Chem. Int. Ed.* **2016**, *55*, 11153–11157; For a demonstation of radical ring expansion of tertiary alchohol, see: p) L. Li, Z-L. Li, F-L. Wang, Z. Guo, Y-F. Cheng, N. Wang, X-W. Dong, C. Fang, J. Liu, C. Hou, B. Tan, X-Y. Liu *Nat. Commun.* **2016**, *7*, 13852–13863.

[5] J. R. Mahajan, J. R. Botelho, I. S. Resck, *J. Braz. Chem.* **1990**, *1*, 13–16.

[6] For instance, Rodriguez, Quintard *et al.* demonstrated recently an organocatalytic strategy in which such fragmentation was suitable for the preparation of 10- and 11-membered lactones excepted 9-membered lactones that were inaccessible: a) M. Roudier, T. Constantieux, A. Quintard, J. Rodriguez, *Eur. J. Org. Chem*., **2015**, 5709–5711; b) T. Lavoisier-Gallo, E. Charonnet, J.-M. Pons, M. Rajzman, R. Faure, J. Rodriguez, *Chem. Eur. J.* **2001**, *7*, 1056–1068.

[7] a) M. Amat, M. D. Coll, D. Passarella, J. Bosch, *Tetrahedron: Asymmetry* **1996**, *7*, 2775–2778; b) K. S. Bhandari, J. A. Eenkhoorn, A. Wu, V. Snieckus, *Synth. Commun*. **1975**, *5*, 79–86; c) A. Wu, V. Snieckus, *Tetrahedron Lett.* **1975**, *16*, 2057–2060; d) L. Ilies, M. Isomura, S. Yamauchi, T. Nakamura, E. Nakamura, *J. Am. Chem. Soc.* **2017**, *139*, 23–26; e) R. J. Sundberg, F. X. Smith, *J. Org. Chem.* **1975**, *40*, 2613–2621; f) C. Szántay, H. Bölskei, E. Gács-Baitz, *Tetrahedron* **1990**, *46*, 1711–1732; g) R. J. Sundberg, J. Hong, S. Q. Smith, M. Sabat, I. Tabakovic, *Tetrahedron* **1998**, *54*, 6259–6292; h) H.-H. Zhang, C.-S. Wang, C. Li, G.-J. Mei, Y. Li, F. Shi, *Angew. Chem.* **2017**, *129*, 122–127; *Angew. Chem. Int. Ed.* **2017**, *56*, 116–121; i) A. Patra, S. Mukherjee, T. K. Das, S. Jain, R. G. Gonnade, A. T. Biju, *Angew. Chem.* **2017**, *129*, 2774–2778; *Angew. Chem. Int. Ed.* **2017**, *56*, 2730–2734; j) ring expansion of N-propargyltetrahydrocarboline with gold catalyst: L. Zhang, Y. Wang, Z.-J. Yao, S. Wang, Z.-X. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 13290–13300; k) B. Harish,, M. Subbireddy, S. Suresh, *Chem. Comm*. **2017**, *53*, 3338–3341; l) J. A. Leitch, C. L. McMullin, M. F. Mahon, Y. Bhonoah, C. G. Frost, *ACS Catal*. **2017**, *7*, 2616–2623; m) G. E. Benitez-Medina, M. Amézquita-Valencia, A. Cabrera, P. Sharma, *ChemCatChem* **2017**, *9*, 1450–1460; n) S. Panda, J. M. Ready, *J. Am. Chem. Soc.* **2017**, *139*, 6038–6041; o) K. L. White, M. Movassaghi, *J. Am. Chem. Soc.* **2016**, *138*, 11383–11389.

[8] For such purpose, the Witkop photocyclization emerged as an interesting solution, enabling access to medium-sized lactams embedding indoles, see: a) P. J. Gritsch, C. Leitner, M. Pfaffenbach, T. Gaich, *Angew. Chem. Int. Ed*. **2014**, *53*, 1208–1217; b) B. Bajtos, B. L. Pagenkopf, *Eur. J. Org. Chem.* **2009**, 1072–1077.

[9] a) L. F. Tietze, G. Brasche, K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, 2006; b) L. F. Tietze, *Chem. Rev*., **1996**, *96*, 115–136.

[10] a) J. Bonjoch, D. Solé, J. Bosch, *J. Am. Chem. Soc.* **1993**, *115*, 2064–2065; b) J. Bonjoch, D. Solé, J. Bosch, *J. Am. Chem. Soc.* **1995**, *117*, 11017–11018; c) D. Solé, J. Bosch, J. Bonjoch, *Tetrahedron* **1996**, 52, 4013–4028; d) D. Solé, J. Bonjoch, S. García-Rubio, E. Peidró , J. Bosch, *Angew. Chem.* **1999**, *111*, 408–410; *Angew. Chem. Int. Ed.* **1999**, *38*, 395–397.

[11] Yields in lactones were below 15% with Grignard reagents while degradation of **1** was observed with organolithium reagents even in the presence of $CeCl_3$.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

[12] a) T. Ishikawa, R. Kadoya, M. Arai, H. Takahashi, Y. Kaisi, T. Mizuta, K. Yoshikai, S. Saito, *J. Org. Chem.* **2001**, *66*, 8000–8009; b) T. Ishikawa, K. Kudo, K. Kuroyabu, S. Uchida, T. Kudo, S. Saito, *J. Org. Chem.* **2008**, *73*, 7498–7508; For the allylation of 1,3-diketones, see: c) G. Rousseau, F. Robert, Y. Landais, *Synthesis* **2010**, 1223–1228

[13] Ascertained by X-ray of the corresponding olefin, see SI

[14] 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. From the ^{1}H and ^{13}C NMR analysis of the crude, no other regioisomer could be detected.

[15] In agreement with these calculations, we noted during a previous study the prevalent enolization of the most hindered carbonyl in 4,4-dialkylcyclohexane-1,3-dione: R. B. Devi, M. Henrot, M. De Paolis, J. Maddaluno, *Org. Biomol. Chem*., **2011**, *9*, 6509–6512.

[16] The mixture of isomers could not be separated by flash chromatography.

[17] As a current limitation of the methodology, aldehydes derived from **1** with one of the ketone α-substituted with phenyl or heteroatoms (F, OAc) were decomposed upon treatment with $NaBH_4$. Additionally, aldehyde **4** failed to react with organocerium alkynyl reagent.

[18] When treated with organomagnesium, organocerium or organolithium alkynyl reagents in the presence of Lewis acids, only degradation of the starting materials occurred. The combination of both reagents ($NaN_3/CeCl_3.7H_2O$) was required, see: G. Sabitha, R. S. Babu, M. Rajkumar, J. S. Yadav, *Org. Lett.* **2002**, *4*, 343–345.

[19] 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.

[20] CCDC 1532416, 1532415 contain 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.

[21] The spontaneous ring contraction of hydroxyindolenine by [1,5] sigmatropic shift in spiro-oxindole was not observed; a) T. J. Greshock, R. M. Williams, *Org. Lett.* **2007**, *9*, 4255–4258

[22] The relative configuration of **25** was deduced from the analysis of the product **27** by 2D NMR spectroscopy.

Accepted Manuscript

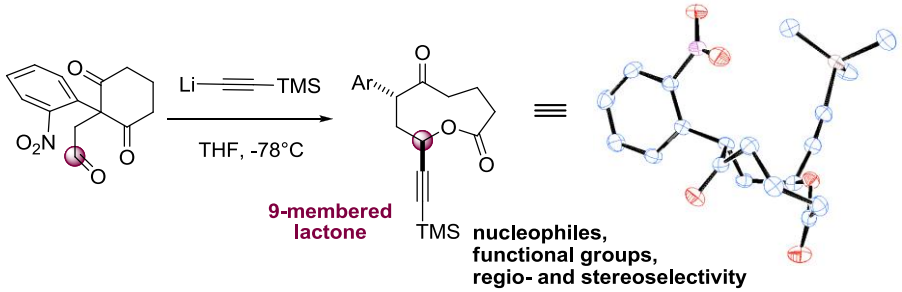
This article is protected by copyright. All rights reserved.

10.1002/chem.201705645

Synthetic methodology

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

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



Continuity with change: The domino ring expansion of 2-nitrophenyl-1,3-cyclohexanediones connected to an electrophilic appendage – aldehyde and epoxide – into 9-membered lactones was developed. Regio- and stereoselectivity were observed upon treatment with carbon, aza, bromide and hydride nucleophiles, opening access to highly substituted lactones.

Accepted Manuscript

This article is protected by copyright. All rights reserved.