

The Synthesis of Structurally Diverse Macrocycles By Successive Ring Expansion

Christiana Kitsiou, Jordan J. Hindes, Phillip I'Anson, Paula Jackson, Thomas C. Wilson, Eleanor K. Daly, Hannah R. Felstead, Peter Hearnshaw, and William P. Unsworth*

Abstract: Structurally diverse macrocycles and medium-sized rings (9–24 membered scaffolds, 22 examples) can be generated through a telescoped acylation/ring-expansion sequence, leading to the insertion of linear fragments into cyclic β -ketoesters without performing a discrete macrocyclization step. The key β -ketoester motif is regenerated in the ring-expanded product, meaning that the same sequence of steps can then be repeated (in theory indefinitely) with other linear fragments, allowing macrocycles with precise substitution patterns to be “grown” from smaller rings using the successive ring-expansion (SuRE) method.

Important applications in medicinal chemistry,^[1] catalysis,^[2] materials science,^[3] chiral sensing,^[4] supramolecular chemistry,^[5] self-assembly,^[6] nanotechnology,^[7] and natural product synthesis^[8] rely on the synthesis of functionalized macrocycles. At present, macrocycles are typically made by the end-to-end cyclisation of a linear precursor, a difficult and unpredictable transformation; in particular, achieving macrocyclization (**1**→**2**, Figure 1 a) rather than dimerization (**1**→**3**) is a major challenge.^[9] The most common strategy used to combat this is to perform the reactions at high-dilution (typically about 1–5 mM),^[10] but although successful in many cases, such procedures are generally highly substrate-dependent and impractical for large-scale synthesis. Other methods designed to offer “pseudo high-dilution” conditions include the use of solid supports,^[11] biphasic solvent systems,^[12] and DNA-templated synthesis.^[13] Alternatively, dilution can be minimized if the linear precursor is preorganized into a conformation biased towards macrocyclization; for example, using a small molecule/ion template^[14] or by exploiting internal structural elements.^[9b,15] Each of these macrocyclization methods have been applied successfully in the past, but invariably they are optimized for specific substrate classes and/or utilize specialized reaction setups. Thus, there is a need for new macrocyclization strategies that are practical, scalable, and applicable to a broad range of systems.

The methods described above are all designed to improve the efficiency of the difficult end-to-end cyclisation step. Herein, a conceptually different approach is taken, in which

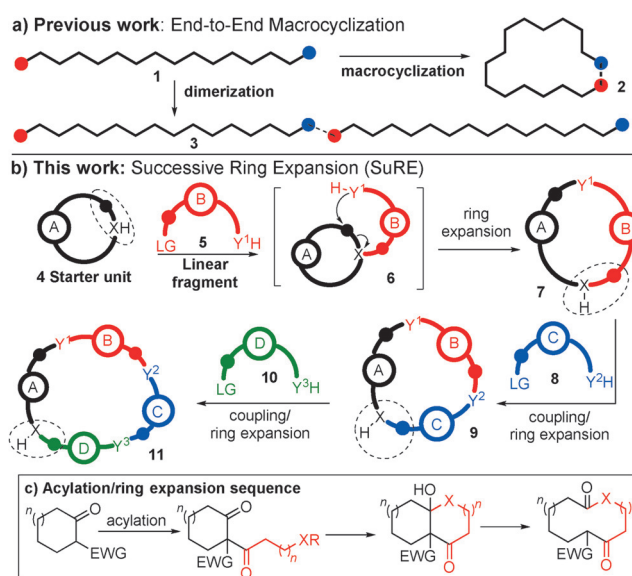
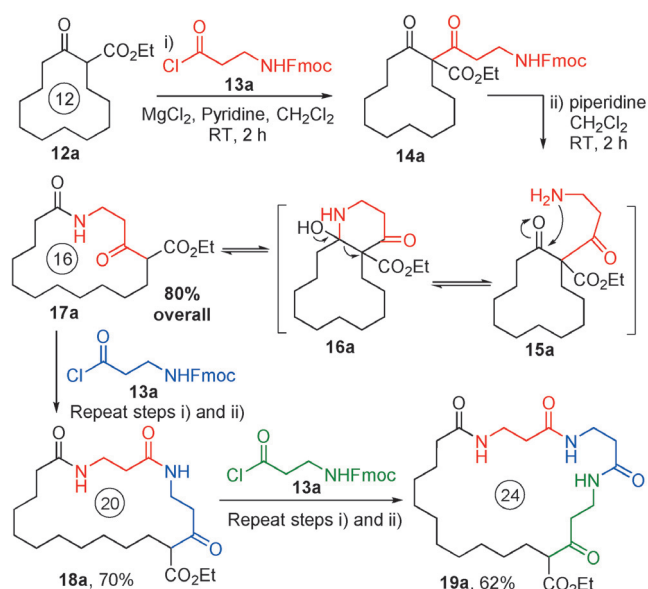


Figure 1. End-to-end macrocyclization and successive ring-expansion (SuRE) methods.

end-to-end macrocyclization is avoided entirely. Successive ring expansion (SuRE; Figure 1 b) is based on the sequential insertion of linear fragments into existing cyclic systems, by coupling a cyclic compound (starter unit **4**) to a linear fragment **5** which can then rearrange (see **6**), initiating ring expansion and forming the product **7**. A key design feature is the replication of the functionality in the cyclic starter unit in the ring-expanded product (dashed circle), as this means that the same coupling/ring-expansion sequence can be repeated, allowing further iterations to be performed in the same way (**7**→**9**; **9**→**11**). The SuRE method can incorporate a range of linear fragments and can theoretically be repeated indefinitely, meaning macrocycles of virtually any ring size and composition are potentially accessible. As no discrete macrocyclization step is involved, the reactions should not require specialized conditions, preorganization, or high dilution to proceed effectively. Of course, ring expansion is not a new concept in itself,^[9,16] but successive ring-expansion processes are far less common. Existing approaches either rely on multiple steps to effect each iteration,^[17] or give rise to less well-defined mixtures of products through ring-expansion polymerization.^[18] In this paper, the SuRE concept is validated using a telescoped two-step sequence to generate macrocyclic lactams and lactones from cyclic β -keto esters (Figure 1 c).

* C. Kitsiou, J. J. Hindes, P. I'Anson, P. Jackson, T. C. Wilson, E. K. Daly, H. R. Felstead, P. Hearnshaw, Dr. W. P. Unsworth
University of York
York, YO24 4PP (UK)
E-mail: william.unsworth@york.ac.uk

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under <http://dx.doi.org/10.1002/anie.201509153>.



Scheme 1. Successive ring-expansion reactions (**12a** to **17a**; **17a** to **18a**; **18a** to **19a**). Fmoc = 9-fluorenylmethoxycarbonyl.

The ring-expansion procedure was established using 12-membered-ring cyclic β -ketoester **12a**^[19] and acid chloride **13a** (Scheme 1). First, a C-acylation reaction was performed (using MgCl_2 and pyridine at room temperature in CH_2Cl_2)^[20] to generate tricarbonyl species **14a**. This intermediate was then treated with piperidine in CH_2Cl_2 to cleave the 9-fluorenylmethoxycarbonyl (Fmoc) protecting group, which also resulted in spontaneous ring expansion, presumably via fused bicyclic **16a**, affording 16-membered ring product **17a** in 80% yield over the telescoped two-step sequence (Scheme 1).^[21] The ease of the ring-expansion step (which is likely to be driven by the formation of a stabilized enolate and an amide group) was encouraging, but in order to validate the SuRE concept, it was necessary to demonstrate that the macrocyclic product could undergo further ring expansion. Thus, the same reaction conditions were then applied to β -keto ester **17a** and pleasingly, this resulted in the formation of 20-membered ring macrocycle **18a** (70% yield). The same sequence was then used for a third time, resulting in the conversion of **18a** into the 24-membered ring product **19a** (62% yield). Importantly, these reactions do not use high-dilution conditions (the reactions are performed at 0.1M) and can be scaled up easily.^[22]

Next, attention turned to exploring the scope of the synthetic method. Cyclic starter units (**12a–g**) and linear fragments (**13a–j**; Figure 2), were synthesized using standard methods (see the Supporting Information).^[23]

The ring expansion can be achieved using carbobenzyloxy (Cbz) derivative **13b** as the linear fragment in place of Fmoc derivative **13a**; in this case, following C-acylation in the usual way, the Cbz group was cleaved by hydrogenolysis, initiating spontaneous ring expansion (Scheme 2).^[24] Methyl and benzyl esters in the starter unit are also tolerated, furnishing macrocycles **17b** and **17c**. The reaction also tolerates other ring sizes; 5–8-membered starter units each reacted with linear fragment **13a** under the standard con-

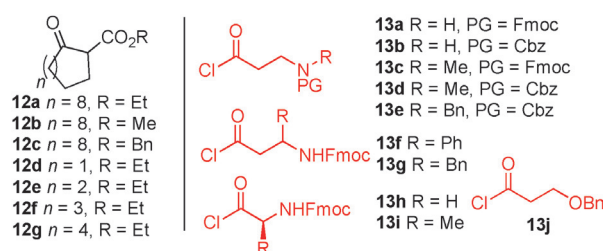
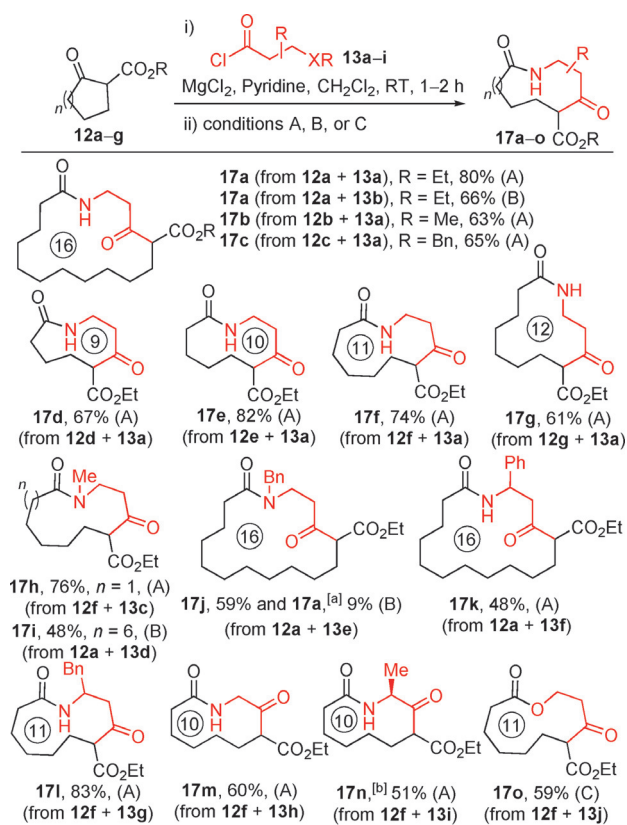


Figure 2. Substrates **12a–g** and **13a–j**. PG = protecting group; Bn = benzyl; Cbz = carbobenzyloxy.

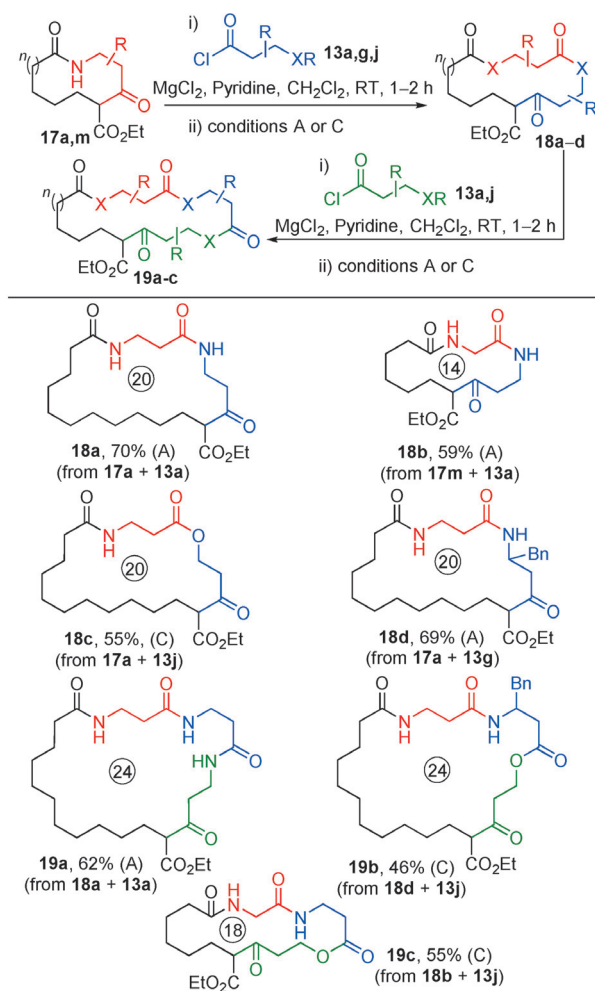


Scheme 2. Scope of the ring-expansion sequence.^[24] i) Dicarboxyl **12** (1 equiv), MgCl_2 (2 equiv), and pyridine (6 equiv) were premixed for 30 min in CH_2Cl_2 (7 mL mmol⁻¹ of **12**) before adding acid chloride **13** (3 equiv) in CH_2Cl_2 (3 mL mmol⁻¹ of **12**) and stirring for 1–2 h at RT. ii) Conditions A: piperidine (10 equiv), CH_2Cl_2 (10 mL mmol⁻¹), RT, 1–2 h; Conditions B: H_2 , Pd/C, EtOAc (10 mL mmol⁻¹), RT, 24 h; Conditions C: H_2 , Pd(OH)₂/C, MeOH (10 mL mmol⁻¹), RT, 24 h. [a] Presumably, **17a** is formed by hydrogenolysis of the NBn group. [b] An optically active product was isolated, **17n**: $[\alpha]_D^{25} = -51.2$ ($c = 1.0$, CHCl_3).

ditions to form 9–12-membered medium ring products **17d–17g** in good yields. *N*-Alkyl and branched linear fragments are also compatible, forming ring-expanded products **17h–17l**, with the structure of 11-membered ring **17h** confirmed by X-ray crystallography (see the Supporting Information).^[25] Linear fragments derived from α -amino acids (forming products **17m** and **17n**) have also been applied successfully, which is likely to be useful in the synthesis of macrocyclic

peptidomimetics.^[1,26,27] Finally, the synthesis of cyclic lactone **17o** from β -ketoester **12f** and benzyl-protected alcohol derivative **13j** indicates that SuRE is not limited to amino acid derived linear fragments.^[28] As with the Cbz-protected variant, hydrogenolysis was used to promote benzyl group cleavage and ring expansion in situ.

The reactions described in Scheme 2 represent a convenient way to generate ring-enlarged products, and notably include 9–11-membered ring products (**17d–f**, **17h**, **17l–o**), compounds that are difficult to synthesize by conventional methods.^[29] Indeed, their formation from 5–7-membered starting materials (ring sizes which are typically far more thermodynamically stable than their respective products) highlights the strength of the driving force for ring expansion. However, the real value of this method is the fact the products themselves are suitable substrates for further ring expansion, as this allows more complex scaffolds to be assembled, as shown in Scheme 3.^[24]



Scheme 3. Examples of successive ring expansion.^[24] i) Dicarbonyl **17/18** (1 equiv), MgCl_2 (2 equiv), and pyridine (6 equiv) were premixed for 30 min in CH_2Cl_2 (7 mL mmol^{−1} of **17/18**) before adding acid chloride **13** (3 equiv) in CH_2Cl_2 (3 mL mmol^{−1} of **17/18**) and stirring for 2 h at RT. ii) Conditions A: piperidine (10 equiv), CH_2Cl_2 (10 mL mmol^{−1}), RT, 1–2 h; Conditions C: H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, MeOH (10 mL mmol^{−1}), RT, 24 h.

Thus, 20- and 14-membered macrocycles **18a** and **18b** were formed in good yield using the standard procedure, by insertion of linear fragment **13a** for a second time. The insertion of different linear fragments is also possible, as demonstrated by the formation of mixed lactam/lactone product **18c** and mixed bis-lactam **18d**. Furthermore, there is no need to stop after two ring-expansion reactions, with 24-membered macrocycles **19a** and **19b**, and 18-membered product **19c**, also being synthesized using the standard procedure. Macroyclic products **19b** and **19c** are especially noteworthy, as they were prepared through the controlled insertion of three different linear fragments (Scheme 3). The practicality and versatility of the SuRE procedure means that it is a genuine alternative to current macrocyclization methods (for example macrocycle “stapling” approaches)^[30] and is expected to be adopted in various research fields that rely on controlled macrocycle synthesis, especially those focused on the generation of diversity.^[26e,31,32]

In summary, a simple but effective strategy for the formation of functionalized medium-sized rings (**17d–f**, **17h**, and **17l–o**) and macrocycles (**17a–c**, **17g**, **17i–k**, **18a–d**, and **19a–c**) is described. The regeneration of the reactive functionality in the starter unit is needed for the ring-expansion procedure to be applied successively, and although in this case the cyclic β -ketoester motif was chosen, a range of other ring-expansion systems can easily be imagined, in which a similar strategy may be applied. Using the SuRE synthetic method, diverse families of macrocycles should be accessible more easily than is possible using existing methods, and because there is no discrete macrocyclization step, their syntheses should be viable on a large scale. The freedom to install precise sequences of functional groups into macrocycles is likely to be of value in the design and development of many such applications in the various research fields highlighted above.^[1–8,26–28] Future work will explore these possibilities, as well as further expanding the substrate scope and challenging the methodology to create even larger, more complex macrocycles.

Acknowledgements

The authors wish to thank the University of York (all authors) for funding, Dr. Adrian C. Whitwood (University of York) for X-ray crystallography, and Profs. Richard J. K. Taylor and Peter O'Brien for helpful advice.

Keywords: macrocycles · medium-sized rings · rearrangement · ring expansion · structural diversity

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 15794–15798
Angew. Chem. **2015**, *127*, 16020–16024

- [1] For information and perspective on macrocycles in medicinal chemistry, see: a) R. H. Kohli, C. T. Walsh, M. D. Burkart, *Nature* **2002**, *418*, 658; b) E. M. Driggers, S. P. Hale, J. Lee, N. K. Terrett, *Nat. Rev. Drug Discovery* **2008**, *7*, 608; c) E. Marsault, M. L. Peterson, *J. Med. Chem.* **2011**, *54*, 1961; d) J. Xie, N. Bogliotti, *Chem. Rev.* **2014**, *114*, 7678; e) A. K. Yudin, *Chem. Sci.* **2015**, *6*, 30.

- [2] For macrocycles in catalysis, see: a) S. Dawn, M. B. Dewal, D. Sobransingh, M. C. Paderes, A. C. Wibowo, M. D. Smith, J. A. Krause, P. J. Pellechia, L. S. Shimizu, *J. Am. Chem. Soc.* **2011**, *133*, 7032; b) Y. Demizu, N. Yamagata, S. Nagoya, Y. Sato, M. Doi, M. Tanaka, K. Nagasawa, H. Okuda, M. Kurihara, *Tetrahedron* **2011**, *67*, 6155.
- [3] For examples of macrocyclic advanced materials, see: a) H. Richtzenhain, A. J. Blake, D. W. Bruce, I. A. Fallis, W.-S. Li, M. Schröder, *Chem. Commun.* **2001**, 2580; b) K. Sato, Y. Itoh, T. Aida, *J. Am. Chem. Soc.* **2011**, *133*, 13767.
- [4] For macrocyclic chiral sensing applications, see: a) T. Ema, D. Tanida, T. Sakai, *J. Am. Chem. Soc.* **2007**, *129*, 10591; b) T. Ema, D. Tanida, K. Sugita, T. Sakai, K.-I. Miyazawa, A. Ohnishi, *Org. Lett.* **2008**, *10*, 2365.
- [5] For recent reviews of catenanes and rotaxanes respectively, see: a) N. H. Evans, P. D. Beer, *Chem. Soc. Rev.* **2014**, *43*, 4658; b) M. Xue, Y. Yang, X. Chi, X. Yan, F. Huang, *Chem. Rev.* **2015**, *115*, 7398.
- [6] For macrocycles which self-assemble into nanotubes for biomedical applications, see: a) D. Pasini, M. Ricci, *Curr. Org. Synth.* **2007**, *4*, 59; b) J. Montenegro, M. R. Ghadiri, J. R. Granja, *Acc. Chem. Res.* **2013**, *46*, 2955; c) I. Alfonso, R. Quesada, *Chem. Sci.* **2013**, *4*, 3009.
- [7] M. Iyoda, J. Yamakawa, M. J. Rahman, *Angew. Chem. Int. Ed.* **2011**, *50*, 10522; *Angew. Chem.* **2011**, *123*, 10708.
- [8] For accounts of macrocyclisation in natural product synthesis, see: a) M. Yu, C. Wang, A. F. Kyle, P. Jakubec, D. J. Dixon, R. R. Schrock, A. H. Hoveyda, *Nature* **2011**, *479*, 88; b) A. Fürstner, *Chem. Commun.* **2011**, *47*, 6505; c) P. Winter, W. Hiller, M. Christmann, *Angew. Chem. Int. Ed.* **2012**, *51*, 3396; *Angew. Chem.* **2012**, *124*, 3452; d) W. P. Unsworth, K. A. Gallagher, M. Jean, J. P. Schmidt, L. J. Diorazio, R. J. K. Taylor, *Org. Lett.* **2013**, *15*, 262; e) T. O. Ronson, R. J. K. Taylor, I. J. S. Fairlamb, *Tetrahedron* **2015**, *71*, 989; f) S. M. Rummelt, J. Preindl, H. Sommer, A. Fürstner, *Angew. Chem. Int. Ed.* **2015**, *54*, 6241; *Angew. Chem.* **2015**, *127*, 6339.
- [9] For useful insight, see: a) M. Hesse in *Ring Enlargement in Organic Chemistry*, Wiley-VCH, Weinheim, **1991**; b) C. J. White, A. K. Yudin, *Nat. Chem.* **2011**, *3*, 509.
- [10] Countless macrocyclisation reactions performed at high-dilution have been reported (for example see Refs. [1–9]). For a theoretical study and more recent perspective, see: a) J. Fastrez, *J. Phys. Chem.* **1989**, *93*, 2635; b) J. C. Collins, K. James, *MedChemCommun* **2012**, *3*, 1489.
- [11] For examples of the use of solid supports in macrocycle synthesis, see: a) S. Mazur, P. Jayalekshmy, *J. Am. Chem. Soc.* **1979**, *101*, 677; b) C. Rosenbaum, H. Waldmann, *Tetrahedron Lett.* **2001**, *42*, 5677.
- [12] A.-C. Bédard, S. K. Collins, *J. Am. Chem. Soc.* **2011**, *133*, 19976.
- [13] a) Z. J. Gartner, B. N. Tse, R. Grubina, J. B. Doyon, T. M. Snyder, D. R. Liu, *Science* **2004**, *305*, 1601; b) B. N. Tse, T. M. Snyder, Y. Shen, D. R. Liu, *J. Am. Chem. Soc.* **2008**, *130*, 15611.
- [14] a) K. Haas, W. Ponikvar, H. Nöth, W. Beck, *Angew. Chem. Int. Ed.* **1998**, *37*, 1086; *Angew. Chem.* **1998**, *110*, 1200; b) N. V. Gerbeleu, V. B. Arion, J. P. Burgess in *Template Synthesis of Macrocyclic Compounds*, Wiley-VCH, Weinheim, **1999**.
- [15] a) R. Hili, V. Rai, A. K. Yudin, *J. Am. Chem. Soc.* **2010**, *132*, 2889; b) H. Fu, H. Chang, J. Shen, L. Yu, B. Qin, K. Zhang, H. Zeng, *Chem. Commun.* **2014**, *50*, 3582; c) C. J. White, J. L. Hickey, C. C. G. Scully, A. K. Yudin, *J. Am. Chem. Soc.* **2014**, *136*, 3728; d) S. Zaretsky, J. L. Hickey, J. Tan, D. Pichugin, M. A. St. Denis, S. Ler, B. K. W. Chung, C. C. G. Scully, A. K. Yudin, *Chem. Sci.* **2015**, *6*, 5446.
- [16] For examples of ring-expansion reactions which operate by a similar mechanism, see: a) A. Guggisberg, B. Dabrowski, U. Kramer, C. Heideberger, M. Hesse, H. Schmid, *Helv. Chim. Acta* **1978**, *61*, 1039; b) V. Bhat, R. C. Cookson, *J. Chem. Soc. Chem. Commun.* **1981**, 1123; c) R. Wälichli, A. Guggisberg, M. Hesse, *Tetrahedron Lett.* **1984**, *25*, 2205; d) K. Oda, T. Ohnuma, Y. Ban, *J. Org. Chem.* **1984**, *49*, 953; e) S. Kim, G. H. Joe, J. Y. Do, *J. Am. Chem. Soc.* **1993**, *115*, 3328; f) K. Kostova, M. Hesse, *Helv. Chim. Acta* **1995**, *78*, 440; g) J. E. Forsee, J. Aubé, *J. Org. Chem.* **1999**, *64*, 4381; h) J. A. Heerklotz, C. Fu, A. Linden, M. Hesse, *Helv. Chim. Acta* **2000**, *83*, 1809; i) B. Moon, S. Han, Y. Yoon, H. Kwon, *Org. Lett.* **2005**, *7*, 1031; j) Y.-M. Jia, X.-M. Liang, L. Chang, D.-Q. Wang, *Synthesis* **2007**, 744.
- [17] Y.-S. Lee, J.-W. Jung, S.-H. Kim, J.-K. Jung, S.-M. Park, N.-J. Kim, D.-J. Chang, J. Lee, Y.-G. Suh, *Org. Lett.* **2010**, *12*, 2040.
- [18] a) N. Hadjichristidis, M. Pitsikalis, S. Pispas, H. Iatrou, *Chem. Rev.* **2001**, *101*, 3747; b) J. A. Castro-Osma, C. Alonso-Moreno, J. C. García-Martínez, J. Fernández-Baeza, L. F. Sánchez-Barba, A. Lara-Sánchez, A. Otero, *Macromolecules* **2013**, *46*, 6388.
- [19] J. A. Marshall, V. H. Audia, *J. Org. Chem.* **1987**, *52*, 1106.
- [20] The C-acylation procedure used was based on a known method, see: M. W. Rathke, P. J. Cowan, *J. Org. Chem.* **1985**, *50*, 2622.
- [21] The identity of macrocycle **17a** is supported by full spectroscopic data (see the Supporting Information). In particular, the ¹³C NMR and DEPT data were important to rule out isomeric species **15a** and **16a**; the presence of a CH signal (δ = 58.2 ppm), two amide/ester C=O signals (169.4, 173.0 ppm), and one ketone C=O signal (206.5 ppm) is consistent only with the ring-expanded product **17a**. Similar signals were clearly detectable in all of the other ring-expanded products (**17–19**) reported herein.
- [22] The ring expansion of compound **12a** to **17a** has been performed on 20 mmol scale (to produce circa 5 g of **17a**) with no appreciable drop in reaction yield.
- [23] See the Supporting Information for preparations. For original literature procedures, see Ref. [19] and the following: a) P. Dowd, S.-C. Choi, *Tetrahedron* **1992**, *48*, 4773; b) M. Yoshida, C. Sugimura, K. Shishido, *Org. Lett.* **2011**, *13*, 3482; c) R. W. A. Luke, P. G. T. Boyce, E. K. Dorling, *Tetrahedron Lett.* **1996**, *37*, 263; d) R.-F. Yang, P.-Q. Huang, *Chem. Eur. J.* **2010**, *16*, 10319; e) G. A. G. Sulyok, C. Gibson, S. L. Goodman, G. Hölzemann, M. Wiesner, H. Kessler, *J. Med. Chem.* **2001**, *44*, 1938; f) A.-H. Li, S. Moro, N. Forsyth, N. Melman, X.-D. Ji, K. A. Jacobson, *J. Med. Chem.* **1999**, *42*, 706.
- [24] In solution in CDCl₃, some of the ring-expanded products exist as equilibrating mixtures of keto/enol tautomers (**17d–g**, **17i–k**, **17m**, **17o**, **18c**, **19c**), rotamers (**17h–j**, **19c**) and diastereoisomers (**17k–l**, **18d**, **19b**). See the Supporting Information for details.
- [25] CCDC 1426909 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
- [26] a) T. Liu, S. H. Joo, J. L. Voorhees, C. L. Brooks, D. Pei, *Bioorg. Med. Chem.* **2009**, *17*, 1026; b) K. Sasaki, D. Crich, *Org. Lett.* **2010**, *12*, 3254; c) M. Gongora-Benítez, J. Tulla-Puche, F. Albericio, *Chem. Rev.* **2013**, *113*, 901; d) T. A. Hill, N. E. Shepherd, F. Diness, D. P. Fairlie, *Angew. Chem. Int. Ed.* **2011**, *50*, 10522; *Angew. Chem.* **2011**, *123*, 10708; e) T. A. Hill, N. E. Shepherd, F. Diness, D. P. Fairlie, *Angew. Chem. Int. Ed.* **2014**, *53*, 13020; *Angew. Chem.* **2014**, *126*, 13234; f) A. Isidro-Llobet, K. H. Georgiou, W. R. J. D. Galloway, E. Giacomini, M. R. Hansen, G. Méndez-Abt, Y. S. Tan, L. Carro, H. F. Sore, D. R. Spring, *Org. Biomol. Chem.* **2015**, *13*, 4570.
- [27] For macrocyclic peptidomimetics as inhibitors of protein–protein interactions, see: a) A. J. Wilson, *Chem. Soc. Rev.* **2009**, *38*, 3289; b) J. Gavenonis, B. A. Sheneman, T. R. Siegert, M. R. Eshelman, J. A. Kritzer, *Nat. Chem. Biol.* **2014**, *10*, 716; c) E. A. Villar, D. Beglov, S. Chennamadhavuni, J. A. Porco, Jr., D. Kozakov, S. Vajda, A. Whitty, *Nat. Chem. Biol.* **2014**, *10*, 723.
- [28] For biologically active medium-sized and macrocyclic lactones, see: V. B. Riatto, R. A. Pilli, M. M. Victor, *Tetrahedron* **2008**, *64*, 2279.

- [29] a) F. Kopp, C. F. Stratton, L. B. Akella, D. S. Tan, *Nat. Chem. Biol.* **2012**, *8*, 358; b) R. A. Bauer, T. A. Wenderski, D. S. Tan, *Nat. Chem. Biol.* **2013**, *9*, 21.
- [30] a) Y. H. Lau, P. de Andrade, S.-T. Quah, M. Rossmann, L. Laraia, N. Sköld, T. J. Sum, P. J. E. Rowling, T. L. Joseph, C. Verma, M. Hyvönen, L. S. Itzhaki, A. R. Venkitaraman, C. J. Brown, D. P. Lane, D. R. Spring, *Chem. Sci.* **2014**, *5*, 1804; b) Y. H. Lau, P. de Andrade, Y. Wu, D. R. Spring, *Chem. Soc. Rev.* **2015**, *44*, 91.
- [31] For general aspects of diversity-oriented synthesis, see: a) S. L. Schreiber, *Science* **2000**, *287*, 5460; b) D. R. Spring, *Org. Biomol. Chem.* **2003**, *1*, 3867; c) D. Morton, S. Leach, C. Cordier, S. Warriner, A. Nelson, *Angew. Chem. Int. Ed.* **2009**, *48*, 104; *Angew. Chem.* **2009**, *121*, 110.
- [32] For examples of diversity-oriented synthesis applied to macrocyclic compounds, see: a) F. Leon, D. G. Rivera, L. A. Wessjohann, *J. Org. Chem.* **2008**, *73*, 1762; b) A. R. Kelly, J. Wei, S. Kesavan, J. C. Marié, N. Windmon, D. W. Young, L. A. Marcaurrelle, *Org. Lett.* **2009**, *11*, 2257; c) A. Isidro-Llobet, T. Murillo, P. Bello, A. Cilibrizzi, J. T. Hodgkinson, W. R. J. D. Galloway, A. Bender, M. Welch, D. R. Spring, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 6793; d) K. M. G. O'Connell, H. S. Beckmann, L. Laraia, H. T. Horsley, A. Bender, A. R. Venkitaraman, D. R. Spring, *Org. Biomol. Chem.* **2012**, *10*, 7545; e) H. S. G. Beckmann, F. Nie, C. E. Hagerman, H. Johansson, Y. S. Tan, D. Wilcke, D. R. Spring, *Nat. Chem.* **2013**, *5*, 861; f) K. V. Lawson, T. E. Rose, P. G. Harran, *Tetrahedron* **2013**, *69*, 7683; g) A. Grossmann, S. Bartlett, M. Janecek, J. T. Hodgkinson, D. R. Spring, *Angew. Chem. Int. Ed.* **2014**, *53*, 13093; *Angew. Chem.* **2014**, *126*, 13309.

Received: September 30, 2015

Revised: October 28, 2015

Published online: November 13, 2015