Tetrahedron Letters 53 (2012) 4173–4178

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Microwave-assisted synthesis of macrocycles via intramolecular and/or bimolecular Ullmann coupling

Li Shen [a], Charles J. Simmons [b], Dianqing Sun [a,*]

[a] Department of Pharmaceutical Sciences, College of Pharmacy, University of Hawai'i at Hilo, Hilo, HI 96720, USA
[b] Department of Chemistry, University of Hawai'i at Hilo, Hilo, HI 96720, USA

ARTICLE INFO

Article history:
Received 15 May 2012
Accepted 29 May 2012
Available online 7 June 2012

Keywords:
Microwave-assisted synthesis
Macrocycle
Diaryl ether
Intramolecular
Bimolecular
Ullmann coupling

ABSTRACT

Microwave-assisted synthesis of macrocyclic diaryl ethers via intramolecular and/or bimolecular Ullmann coupling is described. Using the optimized conditions, a panel of macrocycles, with different substitution patterns, ring sizes, and linkers, has been successfully synthesized using microwave irradiation. To the best of our knowledge, this work represents the first examples of the microwave-assisted synthesis of macrocyclic diaryl ethers via intramolecular and/or bimolecular Ullmann coupling.

Macrocyclic diaryl ether motifs are commonly found in naturally occurring molecules (Fig. 1) and have been reported to mediate a broad range of biological activities.[1] The Ullmann coupling reaction of phenols and aryl halides has been widely used for the synthesis of diaryl ethers since its discovery; however, the scope of Ullmann coupling has been limited by harsh reaction conditions (e.g., high temperature and long reaction time) and low reaction yields.[2] Therefore, much effort has been devoted to the modifications of this classical coupling reaction.[3] For example, the generality has been improved by the introduction of palladium catalysts[4] and with the assistance of novel ligands such as *N*,*N*-dimethylglycine[5] and biarylphosphine.[6] So far, however, most improvements have been achieved with the intermolecular Ullmann coupling of small molecular aryl halides with phenols.

The application of microwave (MW) irradiation in promoting organic reactions has been demonstrated successfully in recent years.[7] It has been shown in many studies that MW irradiation can accelerate reaction rates and improve chemical yields. MW heating has also been explored for intermolecular Ullmann reactions[8] and for the synthesis of diversified macrocycles based on ring-closing metathesis (RCM),[9] Suzuki–Miyaura cross-coupling,[10] and solution and solid-phase synthesis of cyclic peptides and peptidomimetics.[11] However, no reports have been found in the literature concerning MW-assisted intramolecular Ullmann macrocyclization. During the course of our continued effort to synthesize diaryl ether macrocycles, we reported recently the first total synthesis of macrocyclic engelhardione using a sealed pressure tube which led ultimately to the structural revision of its published structure.[12] To further improve the efficiency and to develop a modular synthesis of diaryl ether-based macrocycles, MW methodology has been applied to the intramolecular Ullmann reaction. Herein the synthesis of a panel of macrocycles with different substitution patterns, ring sizes, and linkers via the MW-assisted Ullmann cross-coupling is reported (Scheme 1).

To screen the reaction conditions, the macrocyclization of 1,7-diarylheptan-3-one **1a** to **2a** (Table 1) was selected as a model reaction. The reaction was conducted under an array of different conditions, including conventional heating, sealed pressure tube, and MW irradiation; the results are shown in Table 1. As noted previously,[12] the reaction proceeded slowly under reflux at 150 °C for 20 h to give the macrocyclic product **2a** in 33% yield (entry 1). An improved yield and a significant decrease in reaction time were observed when the reaction was conducted in a sealed pressure tube. The reaction was completed after 4.5 h at 175 °C and 1 h at 200 °C to provide **2a** in 52% and 44% yields, respectively (entries 2 and 3). Using the optimized reaction conditions in a sealed tube as a starting point, further improvement was achieved when the reaction was performed using MW irradiation. When the macrocyclization step was initially performed at 175 °C using MW heating, approximately 5% of **2a** was produced after 10 min based on HPLC monitoring of the reaction mixture with the remaining as the unreacted **1a**. After the temperature was increased to 200 °C, similar to the reaction in a sealed tube, the reaction was completed in 1 h with

* Corresponding author. Tel.: +1 808 933 2960; fax: +1 808 933 2974.
E-mail address: dianqing@hawaii.edu (D. Sun).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.05.142

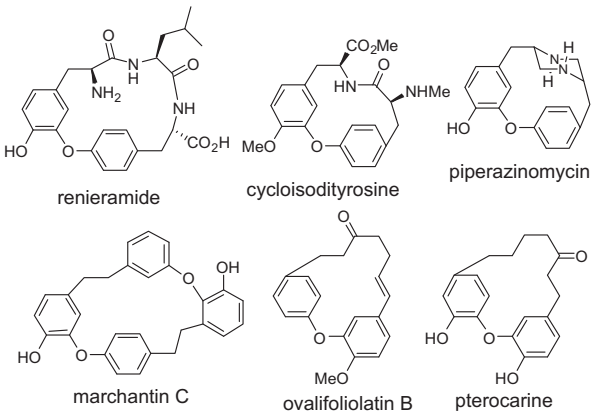
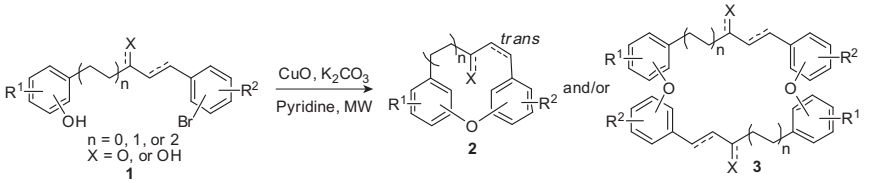
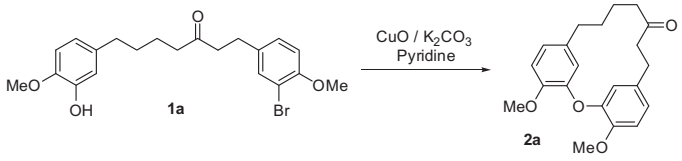


Figure 1. Representative examples of diaryl ether-based natural products.



Scheme 1. MW-assisted synthesis of macrocycles via intramolecular and/or bimolecular Ullmann reaction.

Table 1
Optimization of intramolecular macrocyclic Ullmann coupling[a]



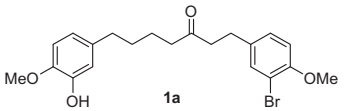
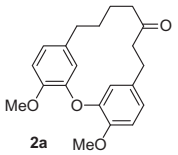
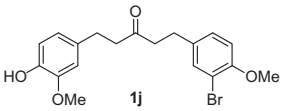
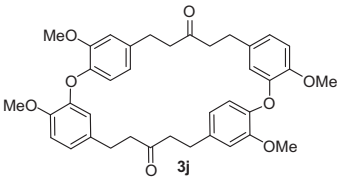
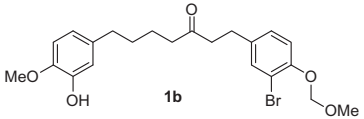
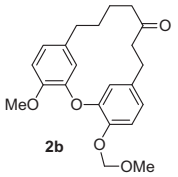
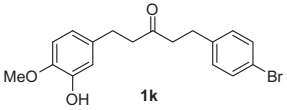
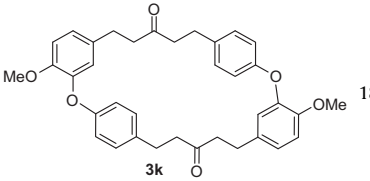
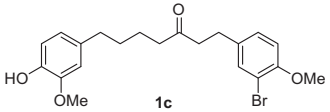
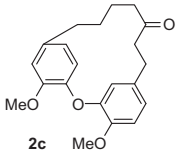
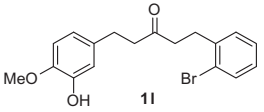
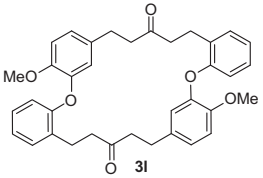
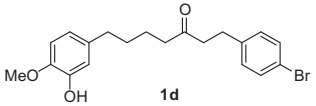
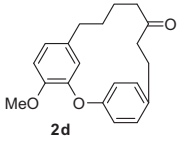
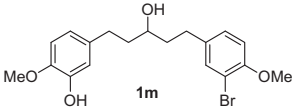
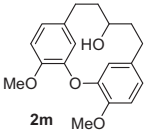
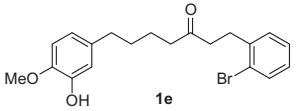
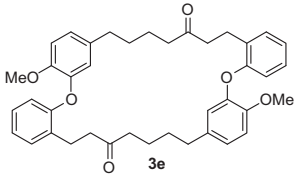
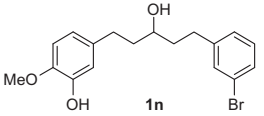
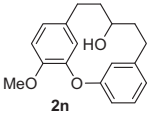
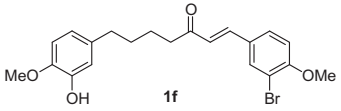
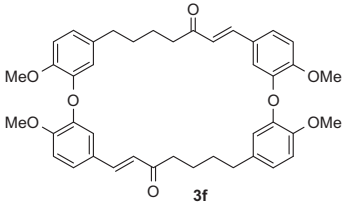
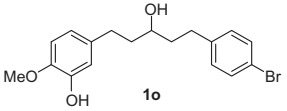
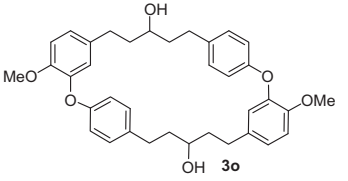
Entry	Condition	Temp (°C)	Time	Yield[b] (%)
1[c]	Reflux	150	20 h	33
2[c]	Sealed tube	175	4.5 h	52
3[c]	Sealed tube	200	1 h	44
4[d]	Sealed tube	>200	30 h	52
5	Microwave	175	10 min	5[e]
6	Microwave	200	1 h	73
7	Microwave	220	35 min	85
8	Microwave	230	15 min	76

[a] All experiments except entry 4 were performed using 0.08 mmol of **1a**, 0.2 mmol of CuO, 0.08 mmol of K_2CO_3, and 4 mL of pyridine.
[b] Isolated yield based on flash column chromatography on silica gel.
[c] Ref. 12.
[d] Ref. 13.
[e] HPLC yield of the reaction mixture.

a much higher yield (73% vs 44%, entries 6 and 3). Further improved results were obtained when the temperature was raised to 220 °C, the reaction finished after 35 min in excellent yield (85%, entry 7). In contrast, the cyclic reaction was completed in 15 min at 230 °C, affording **2a** in a comparable yield (76%, entry 8).

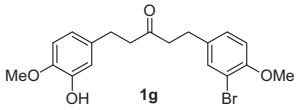
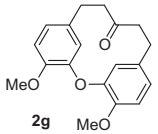
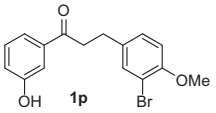
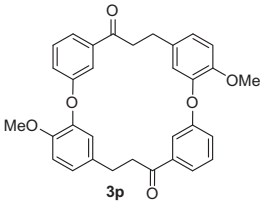
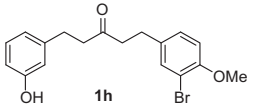
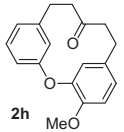
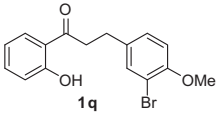
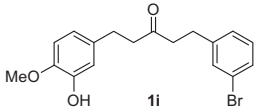
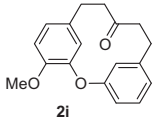
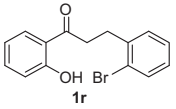
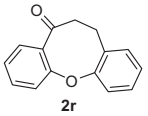
With the optimized MW conditions in hand, a panel of different substrates **1b**–**r**[14] containing diverse phenol and aryl bromide moieties was employed to evaluate the scope and generality of this macrocyclic Ullmann condensation reaction; the results are shown in Table 2. Initially, a set of substrates **1b**–**f** with a seven-carbon linker was investigated (entries 2–6). Consistent with the *meta*–*meta* substituted **2a** with a 14-membered ring (entry 1), the *O*-MOM protected **2b** was obtained in 85% yield using MW irradiation for 40 min (entry 2). In contrast, a lower yield (63%) of **2b** was isolated using a sealed tube at 175 °C for 4 h. As expected, intramolecular 15-membered macrocycles **2c**,**d** were obtained for the *para*–*meta* and *meta*–*para* substituted substrates **1c**,**d** in 44% and 69% yields, respectively (entries 3 and 4). It is worth noting that these

Table 2
MW-assisted synthesis of macrocycles via intramolecular and/or bimolecular Ullmann chemistry[a]

Entry	Substrate	Time	Product	Yield[b] (%)	Entry	Substrate	Time	Product	Yield[b] (%)
1	 **1a**	35 min	 **2a**	85	10	 **1j**	2.5 h	 **3j**	28 (7[g])
2	 **1b**	40 min	 **2b**	85 (63[c])	11	 **1k**	5 h	 **3k**	18
3	 **1c**	35 min	 **2c**	44 (12[d])	12	 **1l**	2.5 h	 **3l**	18
4	 **1d**	40 min	 **2d**	69 (50[d])	13	 **1m**	40 min	 **2m**	48
5	 **1e**	1.5 h	 **3e**	21[e]	14	 **1n**	40 min	 **2n**	56
6	 **1f**	1 h	 **3f**	11[e]	15	 **1o**	1.5 h	 **3o**	44

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Time	Product	Yield[b] (%)	Entry	Substrate	Time	Product	Yield[b] (%)
7	 **1g**	40 min	 **2g**	85 (28[f])	16	 **1p**	6 h	 **3p**	16
8	 **1h**	50 min	 **2h**	83	17	 **1q**	2 h		0[h]
9	 **1i**	40 min	 **2i**	73	18	 **1r**	1 h	 **2r**	25

[a] All experiments were performed using 0.08 mmol of substrate **1**, 0.2 mmol of CuO, 0.08 mmol of K_2CO_3, and 4 mL of pyridine. Reaction mixtures were heated to 230 °C (220 °C for entries 1–3 and 18) using Biotage Initiator 8 Exp Microwave System and monitored by analytical HPLC.

[b] Isolated yield based on flash column chromatography on silica gel.

[c] Isolated yield using a sealed tube at 175 °C for 4 h.

[d] Reported yields using sealed tubes in the same reaction system, see ref 13.

[e] Intramolecular Ullmann coupling products **2e** and **2f** were also obtained in 10% and 9% yields, respectively.

[f] Reaction was performed in a higher concentration (using 0.4 mmol of **1g**, 1 mmol of CuO, 0.4 mmol of K_2CO_3, and 4 mL of pyridine) and completed in 15 min.

[g] Reaction was performed under conventional reflux and was completed after 46 h.

[h] Reaction mixture was heated at 220 °C for 1 h, and then at 230 °C for another 1 h.

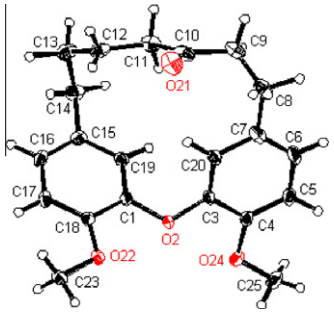


Figure 2. ORTEP view of the molecular structure of **2a** at 100 K; 30% probability ellipsoids are shown.[18]

yields under MW irradiation have been improved than reported yields (12% and 50%, respectively) using sealed tubes.[13] A similar result was anticipated for the *meta–ortho* substituted substrate **1e**; surprisingly, the dimeric macrocycle **3e** was isolated as a major product[15] (21% yield) together with the intramolecular cyclic product **2e** in 10% yield (entry 5). To further investigate the effect of the linker flexibility on the outcome of macrocyclization, the substrate **1f** with a more rigid ketone-conjugated linker was explored, and, as expected, a dramatic decrease of reactivity and reaction yield was noted compared to its close analogue **1a**; again, both the dimeric macrocycle **3f** and the intramolecular coupling product **2f** were afforded in 11% and 9% yields, respectively (entry 6).

Next, the macrocyclization reaction for a second set of substrates with a shorter five-carbon linker was examined and, again, in the case of the *meta–meta* substituted substrate **1g**, the intramolecular Ullmann coupling proceeded smoothly to give the 12-membered macrocycle **2g** in 40 min in 85% yield (entry 7). Comparable and consistent results were obtained for the *meta–meta* substituted **1h**,**i** with only one substituted MeO group affording the identical macrocycles **2h**,**i** in good yields (entries 8 and 9). However, interesting results were obtained for the other five-carbon linked substrates **1j–l** with the *para–meta*, *meta–para*, and *meta–ortho* substitution patterns (entries 10–12). In all cases, the substrates **1j–l** were much less reactive than **1g–i** under the same MW conditions and the bimolecular macrocyclization products **3j–l** were obtained in 18–28% yields after prolonged reaction times (2.5–5 h);[15] no intramolecular Ullmann coupling products were observed (entries 10–12). The formation of the dimeric cyclic products is presumably due to further reduced conformational flexibility of the substrates and unfavorable ring strains needed to perform the intramolecular coupling. Instead, the alternative intermolecular Ullmann coupling occurred first, followed by the bimolecular macrocyclization. In comparison, only 7% of **3j** was isolated for the reaction performed under conventional reflux for 46 h (entry 10). Moreover, to study the potential effect of the carbonyl group in the linker on macrocyclization, reactions of the corresponding reduced variants **1m–o** with the racemic alcohol functionalities were carried out, and both reactions of **1m**,**n** afforded the expected intramolecular cyclic products **2m**,**n** in moderate and lower yields by comparing entries 13 and 14 with corresponding entries 7 and 9. These data are consistent with the previous reports indicating that the ketone functionality may play a role in controlling the substrate's conformation and facilitating subsequent polyketide macrocyclization.[16] In the case of **1o**, it should be noted that the introduction of the secondary alcohol functionality appeared to facilitate the intermolecular coupling and subsequent bimolecular macrocyclization and the reaction was completed in a much shorter time (1.5 h vs 5 h), giving the bimolecular macrocycle **3o** in a higher yield (44% vs 18%) compared to **1k** (entries 15 and 11).

The cyclizations of the substrates **1p–r** with an even shorter three-carbon linker were then studied. Different from its close analogues **1a** and **1h** with a longer seven- and five-carbon linker, the intermolecular cyclization product **3p** was obtained in low yield (16%) for the reaction of the *meta–meta* substituted substrate **1p** (entry 16), whereas the intramolecular macrocycle **2r** was afforded in 25% yield for the reaction of the *ortho–ortho* substituted substrate **1r** (entry 18); however, under the same MW conditions, no product was isolated from the reaction of **1q** with OH and Br groups in *ortho* and *meta* positions, respectively (entry 17). The observed decrease in reactivity is presumably due to further restricted conformational flexibility originating from the conjugated ketone and unfavorable ring strains. Finally, to test the effect of concentration on the outcome of macrocyclization, the reaction of **1g** with a fivefold higher concentration (0.1 M) was tried. It was found that the intramolecular coupling product **2g** was obtained as a sole product despite a much lower yield (28%, entry 7),[17] and no intermolecular cyclization product was observed.

The macrocycles **2** and **3** were characterized by ^{1}H, ^{13}C, and 2D NMR spectroscopy, and high-resolution mass spectrometry (HRMS). The structures of the intramolecular product **2a** and the bimolecular macrocycle **3j** were confirmed by X-ray crystallography, their ORTEP drawings are shown in Figures 2 and 3, respectively.[18,19]

In summary, a modular MW-assisted synthesis has been developed for the intramolecular and/or bimolecular Ullmann condensation of macrocyclic diaryl ethers. Under the optimized MW irradiation conditions, improved yields and shorter reaction times of intramolecular Ullmann coupling were noted compared with conventional heating and sealed tubes. These data show that the outcome of intramolecular and/or bimolecular macrocyclization depends on the linker length and substitution patterns of the substrates. This study further demonstrates that the 14- and 12-membered intramolecular macrocyclization proceeded more favorably for the *meta–meta* substituted substrates. To the best of our knowledge, this work represents the first examples of the MW-assisted synthesis of macrocycles via the Ullmann coupling chemistry. Further biological testing is warranted to screen these macrocyclic novel chemical entities as potential pharmacological tools and/or useful molecular probes.

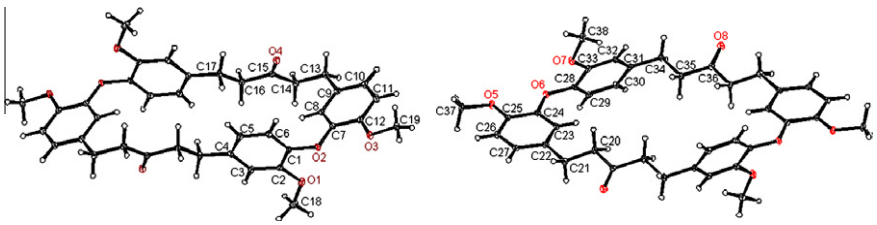


Figure 3. ORTEP views using 30% probability ellipsoids at 90 K of the two crystallographically independent molecules of **3j** in the unit cell; each has inversion centers.[19]

Acknowledgments

We gratefully acknowledge funding from the NIH Academic Research Enhancement Award (AREA) (R15AI092315) and UHH CoP startup funds. We thank Drs. B. Clark and R. Borris at UHH CoP for the assistance with HRMS analysis of macrocyclic compounds. We also thank Dr. A. Wright at UHH CoP for his NMR assistance.

Supplementary data

Supplementary data (experimental procedures and characterization data, copies of NMR spectra and HPLC chromatographs) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.142.

References and notes

1. (a) Pitsinos, E. N.; Vidali, V. P.; Couladouros, E. A. *Eur. J. Org. Chem.* **2011**, *2011*, 1207; (b) Lakshmi Niranjan Reddy, V.; Ravinder, K.; Srinivasulu, M.; Venkateshwar Goud, T.; Malla Reddy, S.; Srujankumar, D.; Prabhakar Rao, T.; Suryanarayana Murty, U.; Venkateswarlu, Y. *Chem. Pharm. Bull.* **2003**, *51*, 1081; (c) Lin, J.; Zhang, W.; Jiang, N.; Niu, Z.; Bao, K.; Zhang, L.; Liu, D.; Pan, C.; Yao, X. *J. Nat. Prod.* **2008**, *71*, 1938.
2. Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.
3. (a) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539; (b) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359; (c) Cai, Q.; Zou, B.; Ma, D. *Angew. Chem.* **2006**, *118*, 1298.
4. Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4321.
5. Ma, D.; Cai, Q. *Org. Lett.* **2003**, *5*, 3799.
6. Salvi, L.; Davis, N. R.; Ali, S. Z.; Buchwald, S. L. *Org. Lett.* **2012**, *14*, 170.
7. (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250; (b) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717; (c) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563; (d) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2001**, *4*, 95.
8. (a) He, H.; Wu, Y.-J. *Tetrahedron Lett.* **2003**, *44*, 3445; (b) Baqi, Y.; Müller, C. E. *Org. Lett.* **2007**, *9*, 1271; (c) D'Angelo, N. D.; Peterson, J. J.; Booker, S. K.; Fellows, I.; Dominguez, C.; Hungate, R.; Reider, P. J.; Kim, T.-S. *Tetrahedron Lett.* **2006**, *47*, 5045; (d) Lipshutz, B. H.; Unger, J. B.; Taft, B. R. *Org. Lett.* **2007**, *9*, 1089.
9. (a) Chapman, R. N.; Arora, P. S. *Org. Lett.* **2006**, *8*, 5825; (b) Pérez-Balado, C.; Nebbioso, A.; Rodríguez-Graña, P.; Minichiello, A.; Miceli, M.; Altucci, L.; de Lera, Á. R. *J. Med. Chem.* **2007**, *50*, 2497.
10. Afonso, A.; Feliu, L.; Planas, M. *Tetrahedron* **2011**, *67*, 2238.
11. (a) Cini, E.; Botta, C. B.; Rodriquez, M.; Taddei, M. *Tetrahedron Lett.* **2009**, *50*, 7159; (b) Nnanabu, E.; Burgess, K. *Org. Lett.* **2006**, *8*, 1259.
12. Shen, L.; Sun, D. *Tetrahedron Lett.* **2011**, *52*, 4570.
13. (a) Bryant, V. C.; Kishore Kumar, G. D.; Nyong, A. M.; Natarajan, A. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 245; (b) Kishore Kumar, G. D.; Natarajan, A. *Tetrahedron Lett.* **2008**, *49*, 2103.
14. Substrates were synthesized according to the previously reported procedures[12] or based on the simple modifications of available synthetic schemes (see Supplementary data for details).
15. For related observations with a bimolecular cyclization lactone product, see: (a) Nakahara, A.; Kanbe, M.; Nakada, M. *Tetrahedron Lett.* **2012**, *53*, 1518; For a bimolecular cyclization lactam product, see: (b) Boger, D. L.; Yohannes, D.; Zhou, J.; Patane, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 3420.
16. (a) Pinto, A.; Wang, M.; Horsman, M.; Boddy, C. N. *Org. Lett.* **2012**, *14*, 2278; (b) Aldrich, C. C.; Venkatraman, L.; Sherman, D. H.; Fecik, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 8910.
17. A lower yield at higher concentration was also noted previously in the synthesis of a similar ring-closing system by the Zhu group, see: Gonzalez, G. I.; Zhu, J. *J. Org. Chem.* **1999**, *64*, 914.
18. *Crystal data for* **2a**: $C_{21}H_{24}O_4$, M_r = 340.42, orthorhombic space group *Pna*2$_1$, a = 9.6740(3) Å, b = 10.5427(3) Å, c = 17.4091(5) Å, V = 1775.56(8) Å^3, Z = 4, ρ = 1.273 Mg/m^3, T = 100 K, in the final least-squares refinement cycles on F, the model converged at R_1 = 0.041, wR_2 = 0.035 and GOF = 1.976 for 1820 reflections with $I > 4\sigma(I)$. Crystallographic data (excluding structure factors) for **2a** (CCDC 878805) and **3j** (CCDC 878806) have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
19. *Crystal data for* **3j**: $C_{38}H_{40}O_8$, M_r = 624.73, triclinic space group $P\bar{1}$, a = 8.1476(2) Å, b = 13.7924(3) Å, c = 14.9725(3) Å, α = 79.7461(15)°, β = 74.6022(12)°, γ = 74.1882(15)°, V = 1550.60(6) Å^3, Z = 2, ρ = 1.338 Mg/m^3, T = 90 K, in the final least-squares refinement cycles on F, the model converged at R_1 = 0.043, wR_2 = 0.064 and GOF = 1.556 for 5157 reflections with $I > 5\sigma(I)$.