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Synthesis of Spirocyclic γ-Lactones by Cascade Beckwith–Dowd Ring Expansion/Cyclization

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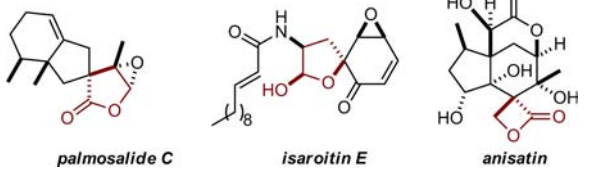
ABSTRACT

A range of spirocyclic γ-lactones have been prepared exploiting a Beckwith–Dowd ring expansion cascade involving 1-, 3-, 4-, and 5-carbon expansion of cyclopentanone and cyclohexanone followed by 5-*exo*-trig or 5-*exo*-dig cyclization. This radical cascade reaction can be achieved with various substrates to provide a broad range of γ-lactones spirofused to 6- to 10-membered cycloalkanones.

Spirocyclic lactones and derived structures are prevalent motifs in medicinal and natural product chemistry (Scheme 1).[1,2] The structural rigidity imparted by spirofusion, in association with the latent functionality of the lactone, is postulated as the source of medicinal activity.[3] Due to the prevalence of this motif, a range of synthetic approaches to spirocyclic lactones have been developed.[4]

Scheme 1. Representative Spirolactones and Derivatives



As part of a program on the assembly of spirocyclic oxygen-containing heterocycles,[5] we envisaged a novel approach to spirocyclic γ-lactones exploiting a cascade ring expansion cyclization sequence (Scheme 2). Such a strategy would potentially be modular and thereby allow flexible assembly of a range of complex γ-lactones.

To realize this approach we intended to exploit Beckwith–Dowd ring expansion[6,7] followed by 5-*exo* radical cyclization. Despite the well-established utility of the Beckwith–Dowd ring expansion,[8,9] its application in radical cascades

(1) For representative natural products bearing spirocyclic γ-lactones and derivatives, see: (a) Brocksom, T. J.; Coelho, F.; Deprés, J.-P.; Greene, A. E.; Freire de Lima, M. E.; Hamelin, O.; Hartmann, B.; Kanazawa, A. M.; Wang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 15313. (b) Bunyapaiboonsri, T.; Yoiprommarat, S.; Intereya, K.; Rachtawee, P.; Hywel-Jones, N. L.; Isaka, M. *J. Nat. Prod.* **2009**, *72*, 756. (c) Lane, J. F.; Koch, W. T.; Leed, N. S.; Gorin, G. *J. Am. Chem. Soc.* **1952**, *74*, 3211. (d) Yamada, K.; Takada, S.; Nakamura, S.; Hirata, Y. *Tetrahedron* **1968**, *24*, 199.

(2) For a recent review on sesquiterpene γ-lactone natural products as anticancer agents, see: (a) Ghantous, A.; Gali-Muhtasib, H.; Vuorela, H.; Saliba, N. A.; Darwiche, N. *Drug Discov. Today* **2010**, *15*, 668. For a review on parthenolide, see: (b) Mathema, V. B.; Koh, Y.-S.; Thakuri, B. C.; Sillanpää, M. *Inflammation* **2011**, *35*, 560. For drug design using spirocyclic γ-lactones, see: (c) Reddy, D. M.; Qazi, N. A.; Sawant, S. D.; Bandey, A. H.; Srinivas, J.; Shankar, M.; Singh, S. K.; Verma, M.; Chashoo, G.; Saxena, A.; Mondhe, D.; Saxena, A. K.; Taneja, S. C.; Qazi, G. N.; Kumar, H. M. S. *Eur. J. Med. Chem.* **2011**, *46*, 3210.

(3) Bouhlel, A.; Curti, C.; Bertrand, M. P.; Vanelle, P. *Tetrahedron Lett.* **2012**, *68*, 3596 and references therein.

(4) For reviews on the synthesis of spirofused compounds, see: (a) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007. (b) Pradham, R.; Patra, M.; Behera, A. K.; Mishra, B. K.; Behera, R. K. *Tetrahedron* **2006**, *62*, 779.

(5) (a) Ngatimin, M.; Frey, R.; Andrews, C.; Lupton, D. W.; Hutt, O. E. *Chem. Commun.* **2011**, *47*, 11778. (b) Ngatimin, M.; Gartshore, C. J.; Kindler, J.; Naidhu, S.; Lupton, D. W. *Tetrahedron Lett.* **2009**, *50*, 6008.

(6) (a) Beckwith, A. L. J.; O'Shea, D. M.; Gerba, S.; Westwood, S. W. *J. Chem. Soc., Chem. Commun.* **1987**, 666. (b) Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565.

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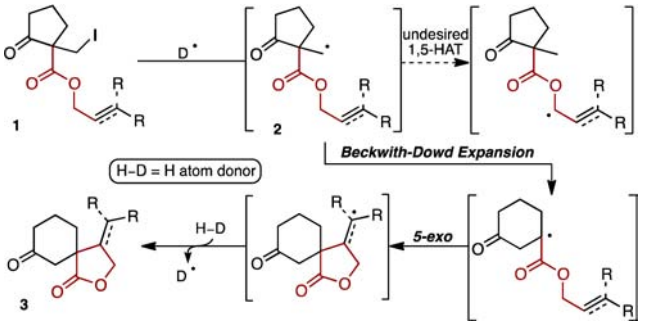
has received little attention. Boger has reported single carbon ring expansion followed by cyclization to provide fused bicyclic cyclopentenes,[10] while Curran has developed a related approach, although this was plagued by premature hydrogen atom transfer (HAT).[11] Finally, Crimmins has exploited β-scission followed by Beckwith–Dowd ring expansion in an elegant synthesis of (±)-lubiminol.[12] Beyond these examples, we are unaware of any studies using Beckwith–Dowd ring expansion in radical cascades.[13]

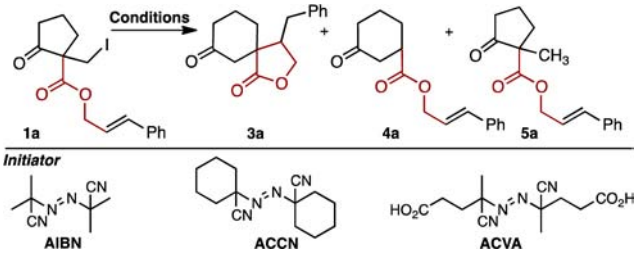
Scheme 2. Reaction Design



We postulated that the synthesis of γ-lactones should be well suited to a Beckwith–Dowd ring-expansion cascade. The rigidity imparted by the ester linkage within β-ketoester **1** should impede the undesired 1,5-HAT of intermediate **2** (Scheme 2), while providing a useful linkage for substrate synthesis.[14,15] Herein, we report initial studies on this topic.

Reaction discovery commenced by subjecting β-ketoester **1a** to the conditions reported by Dowd for ring expansion.[7] Along with the noncyclized material **4a** and the reductively dehalogenated product **5a**, 3% of the desired lactone **3a** could be isolated (Table 1, entry 1). 5-*Exo*-trig cyclizations to form γ-lactones are known to be slow in comparison to the hexenyl variant,[16] with studies by Curran demonstrating that increased temperature favors cyclization.[17] Thus, the initiator was changed to ACCN, and the reaction conducted in toluene heated to reflux. Using these conditions the desired product **3a** now formed in an improved 16% yield, although the Beckwith–Dowd product **4a** still dominated (Table 1, entry 2). Addition of the reducing agent over 12 h improved the yield (Table 1, entry 3), while the higher boiling chlorobenzene provided **3a** in 72% isolated yield (Table 1, entry 4).

Table 1. Optimization of Reaction Conditions



entry	conditions	reducing agent	ratio[a] **3a**:**4a**:**5a**	yield **3a**[b]
1	10 mol % AIBN, 10 mM C_6H_6, 85 °C	Bu_3SnH	1:19:9	3%
2	10 mol % ACCN, 10 mM $C_6H_5CH_3$, 115 °C	Bu_3SnH	1:2:1	16%
3	10 mol % ACCN, 10 mM $C_6H_5CH_3$, 115 °C	Bu_3SnH[c]	5:3:0	53%
4	**10 mol % ACCN, 10 mM ClC_6H_5, 135 °C**	**Bu_3SnH**[c]	**5:1:0**	**72%**
5	10 mol % ACVA, 10 mM ClC_6H_5, 135 °C	Bu_3SnH[c]	3:2:0	58%
6	10 mol % ACCN, 10 mM xylenes, 150 °C	Bu_3SnH[c]	5:1:0	51%
7	**10 mol % ACCN, 10 mM $C_6H_5CH_3$, 115 °C**	**$(TMS)_3SiH$**[c]	**1:0:0**	**85%**

[a] Determined from isolated yields of the components. [b] Isolated yield of a 1:1 diastereomeric and racemic mixture. [c] Addition of reducing agent by syringe pump over 12 h, then 4 additional hours at reflux.

Neither changing the radical initiator to ACVA (Table 1, entry 5) nor conducting the reaction at further elevated temperatures (Table 1, entry 6) improved the transformation. In contrast exploiting $(TMS)_3SiH$ as the reducing agent[18,19] allowed the reaction to be achieved at lower temperatures, in excellent yield, and with none of the Beckwith–Dowd product **4a** (Table 1, entry 7).

(7) (a) Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 3493. For related rearrangements of three and four carbons, see: (b) Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 6548.

(8) For a review, see: Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091.

(9) For computational studies, see: (a) Wilsey, S.; Dowd, P.; Houk, K. N. *J. Org. Chem.* **1999**, *64*, 8801. (b) Ardura, D.; Sordo, T. L. *J. Org. Chem.* **2005**, *70*, 9417.

(10) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1990**, *55*, 5542.

(11) Wang, C.; Gu, X.; Yu, M. S.; Curran, D. P. *Tetrahedron* **1998**, *54*, 8355.

(12) Crimmins, M. T.; Wang, Z.; McKerlie, L. A. *J. Am. Chem. Soc.* **1998**, *120*, 1747.

(13) For elegant examples of ring-expansion cascades, see: (a) Oh, H.-S.; Lee, H. I.; Cha, J. K. *Org. Lett.* **2002**, *4*, 3707. (b) Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2001**, *3*, 1181. (c) Sangostino, M.; Kilburn, J. D. *Tetrahedron Lett.* **1995**, *36*, 1365. (d) Hollingworth, G. J.; Pattenden, G.; Schulz, D. J. *Aust. J. Chem.* **1995**, *48*, 381. (e) Ellwood, C. W.; Pattenden, G. *Tetrahedron Lett.* **1991**, *32*, 1591. For selected radical ring expansions, see: (f) Bacque, E.; Pautrat, F.; Zard, S. Z. *Org. Lett.* **2003**, *3*, 325. (g) Lange, G. L.; Gottardo, C.; Merica, A. *J. Org. Chem.* **1999**, *64*, 6738. (h) Toyota, M.; Wada, T.; Fukumoto, K.; Ihara, M. *J. Am. Chem. Soc.* **1998**, *120*, 4916.

(14) For the use of related materials in synthesis, see: (a) Hierold, J.; Hsia, T.; Lupton, D. W. *Org. Biomol. Chem.* **2011**, *9*, 783. (b) Hierold, J.; Gray-Weale, A.; Lupton, D. W. *Chem. Commun.* **2010**, *46*, 6789.

(15) For a review on β-ketoester haloalkylation, see: Roman, B. I.; De Kimpe, N.; Stevens, C. V. *Chem. Rev.* **2010**, *110*, 5914.

(16) For kinetics of radical cyclization to yield γ-lactones, see: Beckwith, A. L. J.; Glover, S. A. *Aust. J. Chem.* **1987**, *40*, 157 and therein.

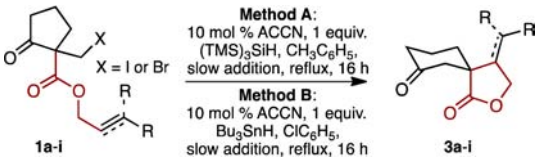
(17) For examples, see: (a) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746. (b) Sibi, M.; Ji, J. *J. Am. Chem. Soc.* **1996**, *118*, 3063. (c) Musa, O. M.; Choi, S.-Y.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1998**, *63*, 786. For the role of temperature in cascades, see: (d) Takasu, K.; Kuroyanagi, J.-I.; Katsumata, A.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 6277. (e) Takasu, K.; Maiti, S.; Katsumata, A.; Ihara, M. *Tetrahedron Lett.* **2001**, *42*, 2157.

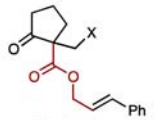
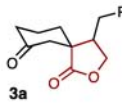
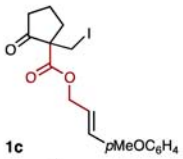
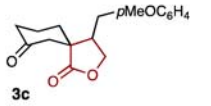
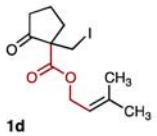
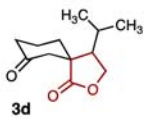
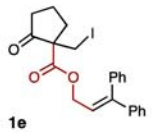
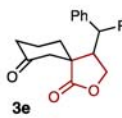
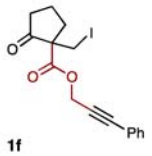
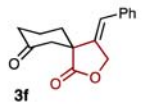
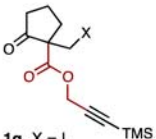
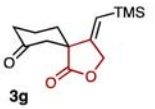
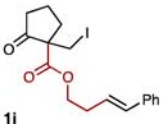
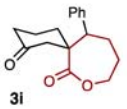
Having identified conditions for the ring-expansion spirocyclization, the flexibility of this cascade was investigated. Initially the nature of the radical precursor was examined by changing the iodide within **1a** to the bromide (i.e., **1b**). While the reaction remained successful, in this case the forcing conditions (Method B: Table 1, entry 4) were required to bring about ring expansion/cyclization (Table 2, entry 1c). The substitution pattern and electronic nature of the olefin were examined, initially with an electron-rich cinnamate side chain, i.e. **1c**, which cyclized using the standard conditions (Method A) to provide γ-lactone **3c** in 90% yield (Table 2, entry 2). Similarly β-dimethyl allyl ester **1d** provided product **3d** in good yield, demonstrating the viability of termination by reduction of a tertiary alkyl radical (Table 2, entry 3). When the related β-diphenyl allyl ester **1e** was subjected to identical conditions none of the expected γ-lactone **3e** was observed, with only the ring-expansion product formed. While cyclization should provide a highly stable radical intermediate, presumably the bulk of the diphenyl group makes cyclization kinetically unfavorable. By exploiting the more forcing conditions (Method B) this cyclization could be achieved providing **3e** with good conversion (Table 2, entry 4).

The degree of unsaturation in the side chain was investigated using alkynes **1f**–**h**. When phenyl acetylene **1f** was subjected to Method B, γ-lactone **3f** formed as a single diastereoisomer[20] in good yield (Table 2, entry 5). Similarly both TMS acetylenes containing an iodide (i.e., **1g**) and those containing a bromide (i.e., **1h**) reacted smoothly to provide γ-lactone **3g** in excellent yields (Table 2, entry 6). The TMS olefin **3g** was targeted as derivatization of related materials is known to provide access to a range of synthetically useful intermediates.[21]

Finally, the allyl group within **1a** was replaced by a homoallyl (i.e., **1i**), thereby providing a substrate capable of Beckwith–Dowd ring expansion followed by 6-*exo*-trig or 7-*endo*-trig cyclization. Under the described conditions (Method B) the Beckwith–Dowd product dominated, although the product of 7-*endo*-trig cyclization, i.e., **3i**, was also isolated in modest yield (Table 2, entry 7).[22]

Table 2. Scope of the Ring Expansion/Cyclization with Variable Esters



entry	starting material	method	product[a]	yield[b]
1a		A		85% X=I
b	1a, X = I b, X = Br	B	3a	72% X=I
c		B		84% X=Br
2		A		90%
	1c		3c	
3		A		89%
	1d		3d	
4		B		(84%)[c] 42%[d]
	1e		3e	
5		B		61%[d]
	1f		3f	
6a		B		83%[d] X=I
b	1g, X = I h, X = Br	B	3g	75%[d] X=Br
7		B		14%[d]
	1i		3i	

[a] Except as noted isolated as a 1:1 diastereoisomeric and racemic mixture. [b] Isolated yield. [c] Conversion as judged by ^{1}H NMR. [d] Isolated yield of single diastereoisomer.

Studies then moved to access γ-lactones spirofused to larger cycloalkanones (Table 3), compounds potentially challenging to prepare in a concise fashion.[23] To access these structures using cascade ring-expansion cyclization either larger cycloalkanones can be exploited as substrates or expansion by more than one-carbon can be conducted; both strategies were examined. Thus, cyclohexanone **1j**

(18) For a review on the use of $(TMS)_3SiH$, see: (a) Chatgilialoglu, C.; Lalevee, J. *Molecules* **2012**, *17*, 527. For application in the Beckwith–Dowd ring expansion, see: (b) Sugi, M.; Togo, H. *Tetrahedron* **2002**, *58*, 3171.

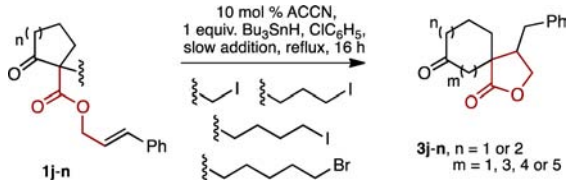
(19) For other reducing agents viable for Beckwith–Dowd rearrangements, see: (a) Studer, A.; Amrein, S.; Schleth, F.; Schulte, T.; Walton, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 5726. (b) Studer, A.; Amrein, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3080. For a review on non-tin reductants in radical chemistry, see: (c) Studer, A.; Amrein, S. *Synthesis* **2002**, 835. For a recent report on the use of chloroform as a hydrogen donor in radical reactions, see: (d) Ko, E. J.; Savage, G. P.; Williams, C. M.; Tsanaktsidis, J. *Org. Lett.* **2011**, *13*, 1944 and references therein for other non-tin reducing agents.

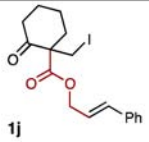
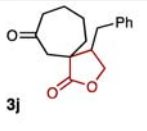
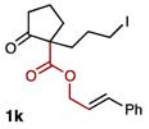
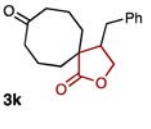
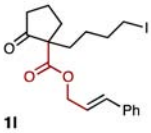
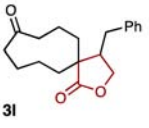
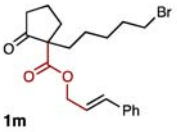
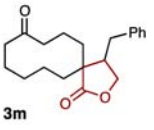
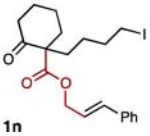
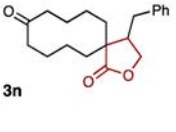
(20) Olefin geometry of olefins **3f** and **3g** assigned by NOE analysis of **3g**.

(21) For the derivatization of related olefins, see: Trost, B. M.; Machacek, M. R.; Faulk, B. D. *J. Am. Chem. Soc.* **2006**, *128*, 6745.

(22) For recent studies exploiting 7-*endo* cyclization in synthesis and discussions on factors affecting this selectivity, see: (a) Yokoe, H.; Mitsuhashi, C.; Matsuoka, Y.; Yoshimura, T.; Yoshida, M.; Shishido, K. *J. Am. Chem. Soc.* **2011**, *133*, 8854. (b) Alcaide, B.; Almendros, P.; Martínez del Campo, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 6684 and references therein.

Table 3. Scope of the Ring Expansion/Cyclization with Variable Expansion



entry	starting material	product[a]	yield[b]
1	 1j	 3j	53%
2	 1k	 3k	73%
3	 1l	 3l	27%
4	 1m	 3m	(30%)[c] 15%[d]
5	 1n	 3n	23%

[a] Where applicable isolated as a 1:1 diastereoisomers and racemic mixture. [b] Isolated yield. [c] Conversion as judged by ^{1}H NMR. [d] Isolated yield of a single diastereoisomer.

when subjected to one-carbon ring expansion using Method B provided cycloheptanone **3j** in 53% yield (Table 3, entry 1). Cyclooctanones could be prepared by three-carbon ring expansion/cyclization of cyclopentanones; this was demonstrated with **1k** providing γ-lactone **3k** in an excellent 73% yield (Table 3, entry 2). The analogous four-carbon expansion provided a 27% yield of cyclononane **3l** (Table 2, entry 3), with the major product arising from reductive dehalogenation. Similar yields were obtained when expanding cyclopentanone **1m** by five carbons to give γ-lactone **3m** (Table 2, entry 4) and expanding cyclohexanone **1n** by four carbons to give the isomeric **3n** (Table 2, entry 5). While these later examples only proceeded in modest yield, the significant structural complexity generated offsets the limited yield. In addition, Dowd observed similar outcomes, when performing expansions to form larger ring systems.[24]

The Beckwith–Dowd ring expansion remains a highly useful reaction to access unusual cycloalkanones from commonly available β-ketoesters. Our studies demonstrate that by the inclusion of allyl or propargyl ester side chains ring-expansion triggered cascades can be achieved. In a number of cases the rate of cyclization can allow premature reduction. However this can be addressed, through the use of higher boiling solvents in association with Bu_3SnH rather than $(TMS)_3SiH$. Using these strategies, a range of complex spirocyclic γ-lactones have been assembled that should serve as useful intermediates in complex target synthesis.[12,25] In addition, application of the Beckwith–Dowd ring expansion, in association with other radical cyclization processes, should provide an avenue for the discovery of other important transformations in chemical synthesis.

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Supporting Information Available. Experimental procedures, characterization of all new compounds, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(23) For reviews on synthetic approaches to medium to large rings, see: (a) Yet, L. *Chem. Rev.* **2000**, *100*, 2963. (b) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881. For anionic ring expansions, and a discussion of methods to access medium sized rings, see: (c) Lavoisier-Gallo, T.; Charonnet, E.; Rodriguez, J. *J. Org. Chem.* **1998**, *63*, 900.

(24) Three-carbon expansion of cyclopentanones proceeds in up to 69% yield. Four-carbon expansion of cyclopentanones proceeds in up to 36% yield; for more details see ref 7b.

(25) For examples of the application of the Beckwith–Dowd ring expansion in total synthesis, see: (a) Mehta, G.; Krishnamurthy, N.; Rao Karra, S. *J. Am. Chem. Soc.* **1991**, *113*, 5765. (b) Banwell, M. G.; Cameron, J. M. *Tetrahedron Lett.* **1996**, *37*, 525. For related ring expansions in total synthesis, see: (c) Heim, R.; Wiedemann, S.; Williams, C. M.; Bernhardt, P. V. *Org. Lett.* **2005**, *7*, 1327. (d) Tilly, D. P.; Williams, C. M.; Bernhardt, P. V. *Org. Lett.* **2005**, *7*, 5155.

The authors declare no competing financial interest.