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Synthesis of stereodefined fused δ-hydroxy-γ-lactones from dealkylative cyclization of epoxy-diesters

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ABSTRACT

A dealkylative lactonization of stereodefined aryl-substituted epoxides allows the preparation of densely functionalized fused δ-hydroxy-γ-lactones having three consecutive stereochemically defined stereocenters.

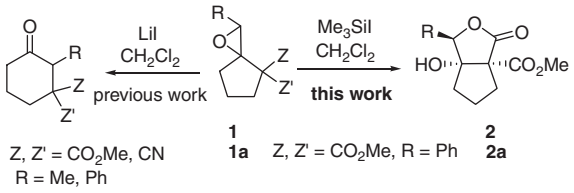
Functionalized-γ-lactones are present in the structures of a great number of natural and unnatural products that often exhibit interesting biological activity such as fungicidal, antitumor, and antimicrobial properties.[1] They also serve as useful intermediates for organic synthesis.[2] Consequently, a variety of methods for their synthesis have been developed.[3]

We have previously reported the preparation of functionalized cyclohexanones, mediated by lithium iodide, from oxaspiroheptanes of general structure **1**.[4] During this study, we unexpectedly found that reaction of the stereodefined epoxy-diester **1a** with excess Me_3SiI (generated in situ from Me_3SiCl and NaI) led exclusively to the formation of the [3.3.0]-bicyclic γ-lactone **2a** having three consecutive stereochemically defined stereocenters (Scheme 1). This reaction may be explained by a stereoselective intramolecular *trans* addition of an ester carbonyl to the Lewis acid-complexed epoxide followed by dealkylation of the oxonium intermediate[5] instead of the ring enlargement reaction observed with LiI.

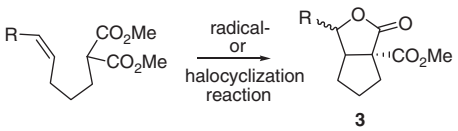
Several procedures have been reported for the Lewis acid- mediated cyclization of epoxyesters to γ-hydroxy lactones, especially zinc chloride to epoxy *t*-butylesters[6] and more recently tin(IV) triflimidate.[7] Protic acid mediated conditions (aqueous H_2SO_4, CSA or PTSA) were also used for this transformation.[8] On the other hand, only few methods are described in the literature for the synthesis of fused bicyclic γ-lactones **3** and they generally involve the radical- or halo-cyclization of linear 4-pentenylmalonates (Scheme 2).[9] However, to our knowledge, no preparation of such compounds having a hydroxy group at the bridgehead position (**2**) has been reported.

Herein, we wish to report the results obtained in the develo pment of this dealkylative cyclization reaction allowing the stereocontrolled preparation of densely functionalized fused δ-hydroxy-γ-lactones **2**.

The aryl-substituted epoxides **1a–j** used in this study as well as the methyl analog **1l** were prepared by epoxidation of the corresponding stereodefined arylidene- and alkylidene-cyclopentanes



Scheme 1. Rearrangement versus lactonization on oxaspiroheptanes **1**.



Scheme 2. Strategy previously used to prepare fused bicyclic γ-lactones.

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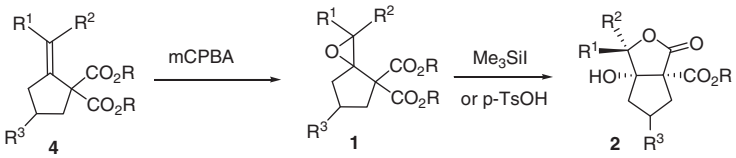
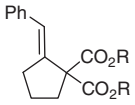
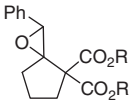
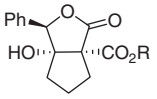
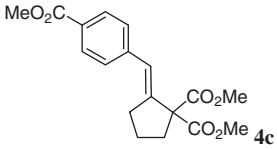
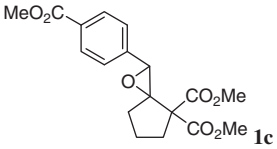
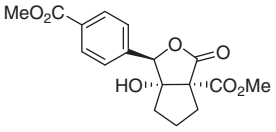
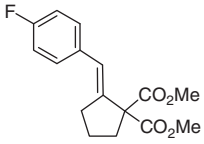
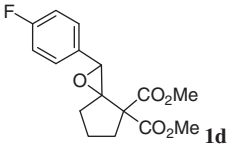
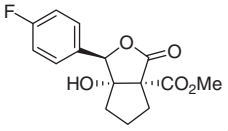
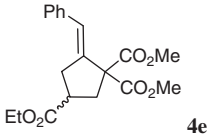
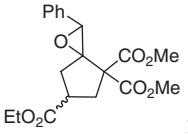
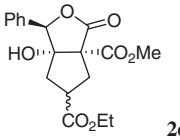
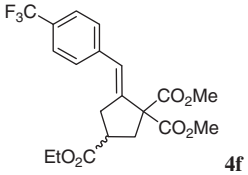
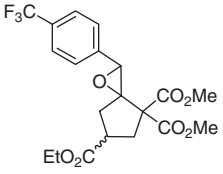
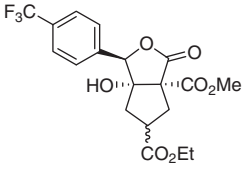
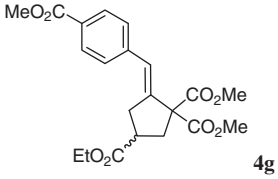
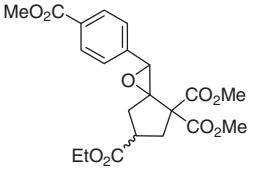
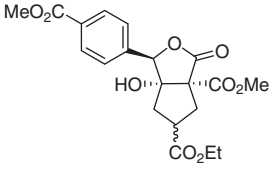
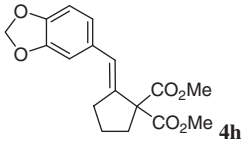
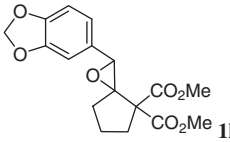
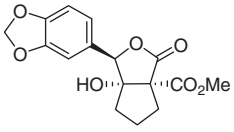
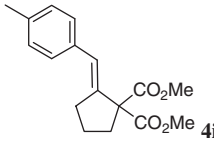
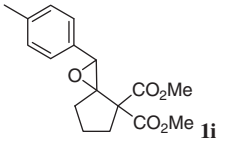
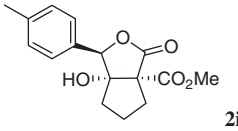
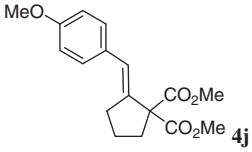
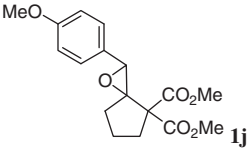
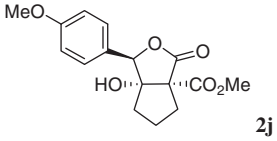
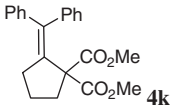
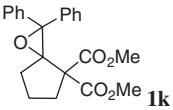
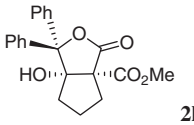
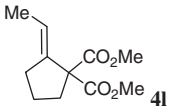
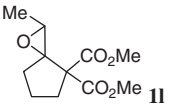
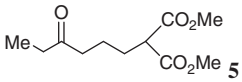
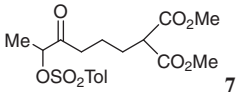
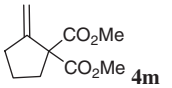
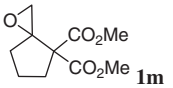
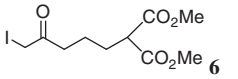
Table 1
Two-step synthesis of fused δ-hydroxy-γ-lactones[a]



Entry	Starting alkene	Epoxidation[b]		Lactonization[e]	
		Conditions **A** or **B** Yield (%)	Epoxides (**1**)[c] (ratio)	TMSI; PTSA Yield (%)	Lactones (**2**) and other products (ratio)[c]
1	 **4a** R = Me	**A**; 81	 **1a**	81; 75	 **2a**
2	**4b** R = Et	**A**; 80	**1b**	87; 87	**2b**
3	 **4c**	**A**; 88	 **1c**	77; 69	 **2c**
4	 **4d**	**A**; 88	 **1d**	90; 89	 **2d**
5	 **4e**	**B**; 51	 **1e** (1.1:1)	61[f]; –	 **2e** (1.2:1)
6	 **4f**	**B**; 73	 **1f** (1.4:1)	59[f]; –	 **2f** (1.2:1)
7	 **4g**	**B**; 69	 **1g** (1:1)	54[f]; –	 **2g** (1.1:1)
8	 **4h**	**B**; 78	 **1h**	(Dec.)	 **2h**
9	 **4i**	**B**; 46	 **1i**	–; 82	 **2i**

(*continued on next page*)

Table 1 (*continued*)

Entry	Starting alkene	Epoxidation[b]		Lactonization[e]	
		Conditions **A** or **B** Yield (%)	Epoxides (**1**)[c] (ratio)	TMSI; PTSA Yield (%)	Lactones (**2**) and other products (ratio)[c]
10	 **4j**	**B**; 34	 **1j**	–; 61	 **2j**
11	 **4k**	**A**; 50[d]	 **1k**	91; –	 **2k**
12	 **4l**	**A**; 83[d]	 **1l**	87 (TMSI)	 **5**
13				50 (PTSA)[g]	 **7**
14	 **4m**	**A**; 97	 **1m**	47 (TMSI)	 **6**
15				Dec. (PTSA)	

[a] Reactions performed on 1 mmol. Yield of the isolated product after flash chromatography.
[b] Reagents and conditions: Condition A: **4**, MCPBA (3 equiv), in CH_2Cl_2 (0.1 M), rt. Condition B: **4**, MCPBA (3 equiv) in a buffered two phase system 0.2 M Na_2CO_3–CH_2Cl_2 (2:1 v/v).
[c] Diastereomeric ratio determined by ^1H NMR.
[d] Reaction performed at reflux temperature.
[e] Lactonization with Me_3SiI: **1**, Me_3SiCl (1.5 equiv), NaI (1.5 equiv) in CH_2Cl_2, 15 h, rt; lactonization with PTSA: **1**, PTSA (0.2 equiv) in CH_2Cl_2, 15 h, rt.
[f] For **1i–k**, Me_3SiCl (3 equiv), NaI (3 equiv).
[g] One equivalent of *p*-TSOH was used.

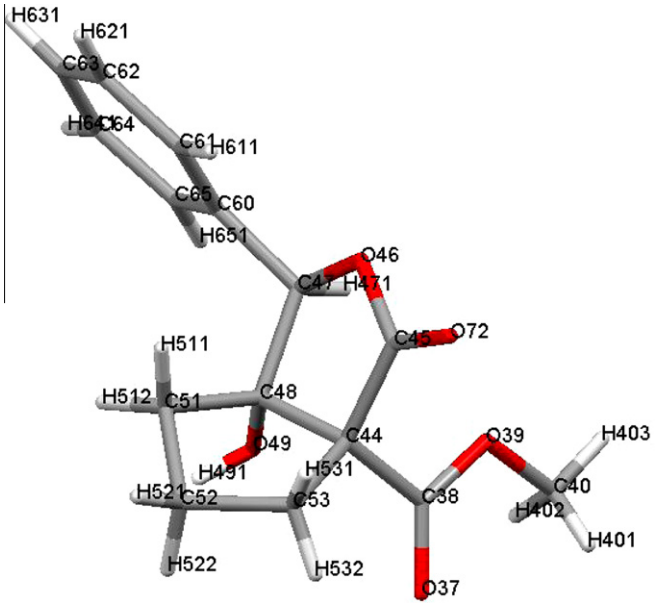


Figure 1. X-ray representation of **2a**.

4a–j and **4l**.[10] To study the generality of this dealkylative cyclization reaction, methylenecyclopentane **4m** and the more substituted unsaturated substrate **4k** were also epoxidized.[11] Thus compounds **4a–d**, **k–m** were treated with *m*-chloroperoxybenzoic acid (MCPBA) in CH_2Cl_2 to afford the corresponding oxiranes in good yields. For the preparation of the acid-sensitive aryl epoxides 4h–j possessing electron-donating groups, the reaction was performed with the same oxidant, but in a buffered two phase system 0.2 M Na_2CO_3–CH_2Cl_2 (2:1 v/v).[12] Finally, treatment of substituted methylenecyclopentanes **4e–g** with MCPBA gave a mixture of the epimeric epoxides at the ethyl ester position in varying diastereomeric ratio (Table 1).

We first studied the reaction of aryl-epoxides with neutral and electron-withdrawing groups on the aryl moiety with Me_3SiI formed in situ from 1.5 equiv of Me_3SiCl and 1.5 equiv of NaI in CH_2Cl_2. As shown in Table 1, reaction of aryl-epoxides **1a–d** was found to be very clean and complete conversion was observed after 15 h at room temperature to give the corresponding fused δ-hydroxy-γ-lactones **2a–d** isolated in a single isomeric form, the *trans* relationship between the aryl group and the created hydroxy being totally controlled (entries 1–4). The structure of these fused lactones was unequivocally assigned by the X-ray crystallographic analysis of **2a** (Fig. 1).[13] In the case of the aryl-epoxide substrates **1e–g**, the reaction conducted on the mixture of epimers needs the use of 3 equiv of Me_3SiI to go to completion and led to the corresponding lactones **2e–g** with no appreciable change in the diastereomeric ratio (entries 5–7). Reaction on the difunctionalized epoxy-ester **1k** led to the expected δ-hydroxy-γ-lactone **2k** in very good yields (entry 11).

When the reaction was conducted on epoxide **1h** bearing a 3, 4-(methylenedioxy)phenyl group, the dealkylative lactonization reaction was unsuccessful. Indeed, only a degradation of the starting material was observed, even when the reaction was conducted

at low temperature, which seems to be due to the instability of this most electron-rich aryl-epoxide under the reaction conditions.[14]

We also decided to test protic acids as catalysts instead of Me_3SiI and we found that simple treatment of the aryl epoxides **1a–d** with 0.2 equiv of *p*-toluenesulfonic acid (PTSA) in CH_2Cl_2 at room temperature has similar effect on this dealkylative lactonization (Table 1, entries 1–4). Under these acidic conditions, the reaction failed to occur with the methylenedioxy derivative **1h**. However, aryl-epoxides **1i–j** with electron-donating group such as the 4-methoxy or 4-methyl moieties proceeded efficiently to give the corresponding lactones **2i–j** in rather good yields.

The reaction of the unfunctionalized epoxy-ester derivative **1m** and the methyl analog **1l** takes a different course when these compounds were treated according to the standard procedures described above. Thus reaction of **1l** and **1m** with Me_3SiI did not give any desired cyclization product but led to the ring opened products **5** and **6**, respectively, in good yields. Under TsOH catalysis, only decomposition of the starting material was observed for unfunctionalized epoxide **1m** while reaction of the methyl substituted epoxide **1l** needed the presence of equimolar amounts of acid to go to completion. Under these conditions the linear α-tosyloxy ketone **7** was obtained. These three linear substrates were believed to result from attack by halide ions or *p*-TsOH on the primary or secondary epoxy carbon followed by a cyclopentane ring opening reaction.[15] A reductive dehalogenation of the resulting α-iodoketone in the presence of iodide ions could be envisaged for the formation of linear adduct **5**.[16]

The difference of reactivity (intra- vs inter-molecular nucleophilic attack of epoxide) between the aryl substituted epoxides **1a**–**k** and epoxides **1l**–**m** may be attributed to stabilizing effects of the aryl substituent on the development of a partial positive charge at the benzylic position.

In conclusion, we have shown that stereochemically defined densely functionalized fused δ-hydroxy-γ-lactones could be prepared via dealkylative cyclization reaction.[17] The synthetic utility of this reaction for the preparation of oxygenated furofuran lignans will be explored in a subsequent work.[18]

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References and notes

1. (a) Yang, X.; Shimizu, Y. *Tetrahedron Lett.* **1993**, *34*, 761–764; Schlewer, G.; Stampf, J.-L.; Benezra, C. *J. Med. Chem.* **1980**, *23*, 1031–1038; (b) Xu, M.-H.; Wang, W.; Xia, L.-J.; Lin, G.-Q. *J. Org. Chem.* **2001**, *66*, 3953–3962; (c) Davidson, B. S.; Ireland, C. M. *J. Nat. Prod.* **1990**, *53*, 1036–1038.
2. (a) Hanessian, S.; Murray, P. J.; Sahoo, S. P. *Tetrahedron Lett.* **1985**, *26*, 5623–5626; (b) Hanessian, S.; Murray, P. J.; Sahoo, S. P. *Tetrahedron Lett.* **1985**, *26*, 5627–5630; (c) Wheatley, J. R.; Bichard, C. J. F.; Mantell, S. J.; Son, J. C.; Hughes, D. J.; Fleet, G. W. J.; Brown, D. J. *Chem. Soc., Chem. Commun.* **1993**, 1065–1067; (d) Gasey, M.; Manoge, A. C.; Murphy, P. J. *Tetrahedron Lett.* **1992**, *33*, 965–968; (e) Delhaye, L.; Merschaert, A.; Diker, K.; Houpis, I. N. *Synthesis* **2006**, 1437–1443.
3. For some recent reviews on the synthesis of γ-lactones see: (a) Gil, S.; Parra, M.; Rodriguez, P.; Segura, J. *Mini-Rev. Org. Chem.* **2009**, *6*, 345–358; (b) Seitz, M.; Reiser, O. *Curr. Opin. Chem. Biol.* **2005**, *9*, 285–292.
4. Bouyssi, D.; Cavicchioli, M.; Large, S.; Monteiro, N.; Balme, G. *Synlett* **2000**, 749–751.
5. (a) Nacro, K.; Baltas, M.; Escudier, J.-M.; Gorrichon, L. *Tetrahedron* **1997**, *53*, 659–672; (b) Enomoto, M.; Kuwahara, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 1144–1148.
6. (a) Nacro, K.; Gorrichon, L.; Escudier, J.-M.; Baltas, M. *Eur. J. Org. Chem.* **2001**, *22*, 4247–4258; (b) Owen, R. M.; Roush, W. R. *Org Lett.* **2005**, *7*, 3941–3944.
7. Antoniotti, S.; Duñach, E. *Tetrahedron Lett.* **2009**, *50*, 2536–2539.
8. (a) Kende, A. S.; Toder, B. H. *J. Org. Chem.* **1982**, *47*, 163–167; (b) Mohr, P.; Rösslein, L.; Tamm, C. *Tetrahedron Lett.* **1989**, *30*, 2513–2516; (c) Concellon, J. M.; Riego, E.; Bernad, P. L. *Org. Lett.* **2002**, *4*, 1303–1305; (d) Wang, J.-X.; Zhang, C.-X.; Li, Y.; You, Q.-D. *J. Chin. Chem. Soc.* **2006**, *53*, 349–358; (e) Urano, H.; Enomoto, M.; Kuwahara, S. *Biosci. Biotechnol. Biochem.* **2010**, *74*, 152–157.
9. Radical cyclization: (a) Baciocchi, E.; Paolobelli, A. B.; Ruzziconi, R. *Tetrahedron* **1992**, *48*, 4617–4622; (b) Powel, L. H.; Docherty, P. H.; Hulcoop, D. G.; Kemmitt, P. D.; Burton, J. W. *Chem. Commun.* **2008**, 2559–2561; (c) Davies, J. J.; Krulle, T. M.; Burton, J. W. *Org. Lett* **2010**, *12*, 2738–2741; Iodocyclization: (a) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140–3157; (b) Kitagawa, O.; Inoue, T.; Hirano, K.; Taguchi, T. *J. Org. Chem.* **1993**, *58*, 3106–3112; (c) Inoue, T.; Kitagawa, O.; Oda, Y.; Taguchi, T. *J. Org. Chem.* **1996**, *61*, 8256–8263.
10. All unsaturated substrates used in this study were obtained according to procedures previously reported by our group: for the preparation of stereodefined arylidene- and alkylidene-cyclopentanes **4a**–**d**, **4h**–**j**, and **4l**, see: Montel, S.; Bouyssi, D.; Balme, G. *Adv. Synth. Catal.* **2010**, *352*, 2315–2320; For the synthesis of substituted methylenecyclopentanes **4e**–**g**, see: Coia, N.; Bouyssi, D.; Balme, G. *Eur. J. Org. Chem.* **2007**, 3158–3165.
11. For the synthesis of methylenecyclopentane **4m**, see: Bouyssi, D.; Monteiro, N.; Balme, G. *Tetrahedron Lett.* **1999**, *40*, 1297–1300; For the synthesis of **4k** see: Fournet, G.; Balme, G.; Gore, J. *Tetrahedron* **1991**, *47*, 6293–6304.
12. Ishikawa, K.; Charles, H. C.; Griffin, G. W. *Tetrahedron Lett.* **1977**, 427–430.
13. Crystallographic data for compound **5a** have been deposited with the Cambridge Crystallographic Data Centre, No CCDC 819990. Copies of the data can be obtained, free of charge, on application to CCDC (e-mail: deposit@ccdc.cam.ac.uk).
14. The instability of such electron-rich aryl epoxides has previously been reported see: Aldous, D. J.; Batsanov, A. S.; Yufit, D. S.; Dalençon, A. J.; Dutton, W. M.; Steel, P. G. *Org. Biomol. Chem.* **2006**, *4*, 2912–2927.
15. Wawrzenczyk, C.; Grabarczyk, M.; Bialonska, A.; Ciunik, Z. *Tetrahedron* **2003**, *59*, 6595–6601.
16. Erian, A. W.; Sherif, S. M.; Gaber, H. M. *Molecules* **2003**, *8*, 793–865; Olah, G. A.; Arvanaghi, M.; Vankar, Y. D. *J. Org. Chem.* **1980**, *45*, 3531–3532.
17. *Typical synthetic procedure for fused δ-hydroxy-γ-lactones*: *cyclization of **1a** to **2a***. A mixture of sodium iodide (1.5 mmol, 223.5 mg) and TMSCl (1.5 mmol, 162 mg) in dry CH_2Cl_2 was stirred for 5 min under Argon atmosphere, after which time epoxy ester **1a** (1 mmol, 294 mg) was added and the resulting mixture was stirred at room temperature for 16 h. The mixture was then diluted with CH_2Cl_2 and washed with water. The crude product was purified by column chromatography (silica gel, cyclohexane/ethylacetate 4:1) affording **2a** as a white solid (mp 116–120 °C, 223.5 mg, 81% yield, one diastereomer). ^1H NMR (300 MHz, $CDCl_3$) δ in ppm: 1.51–1.73 (m, 3H); 1.80–1.88 (m, 1H); 2.33–2.41 (m, 1H); 2.51–2.61 (m, 1H); 2.88 (s, 1H, OH) 3.88 (s, 3H, $COOCH_3$); 5.63 (s, 1H, H6); 7.36–7.40 (m, 5H, Ar). NMR ^{13}C ($CDCl_3$, 75 MHz): δ in ppm: 174.1 ($COOCH_3$), 168.8 (CO), 135.2, 128.9, 128.8, 125.4 (CH Ar), 90.3 (C–OH), 85.4 (C–COOMe), 66.7 (C–HAr), 53.8 (OCH_3), 37.6, 33.4, 24.2 (CH_2). HRMS (CI): [MH]+ found 277.1076, calculated for $C_{15}H_{17}O_5$ = 277.1075.
18. See Jacolot, M.; Pehlivan, L.; Bouyssi, D.; Monteiro, N.; Balme, G. next paper.