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Novel Fragmentation Reaction of 2-Alkyl- and 2,4-Dialkyl-3-iodo-1-oxocyclohexan-2,4-carbolactones

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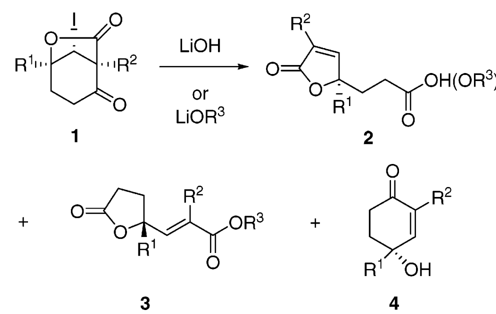
2-Alkyl- and 2,4-dialkyl-3-iodo-1-oxocyclohexan-2,4-carbolactones undergo lithium hydroxide- and lithium alkoxide-induced fragmentation reactions to provide butenolides, γ-hydroxycyclohexenones, and/or γ-butyrolactones. In general, product distribution is governed by two factors: (1) the nature of nucleophiles and (2) the steric bulkiness of the substituents at C-2 and C-4 of the cyclohexanones. Lithium hydroxide-induced fragmentation provides butenolides and γ-hydroxycyclohexenones. In contrast, lithium alkoxide-promoted fragmentation results in predominantly 5-substituted γ-butyrolactones along with a small amount of butenolides in limited cases. Fragmentation products induced by lithium hydroxide are largely influenced by the steric bulkiness of the substituents at C-2 and C-4 of the cyclohexanone ring. The bulky substituents render the exclusive formation of butenolides.

Introduction

Optically active 2-alkyl- and 2,4-dialkyl-3-iodo-1-oxocyclohexan-2,4-carbolactones (**1**) are readily available through an efficient asymmetric Birch reduction−alkylation protocol developed in our laboratories.[1] Previously, we reported that these iodolactones undergo lithium hydroxide- and lithium alkoxide-induced fragmentation, as shown in Scheme 1.[2] This process provides synthetically versatile chiral building blocks, such as butenolides (**2**), γ-butyrolactones (**3**), and/or γ-hydroxycyclohexenones (**4**) in enantiomerically pure form. In particular, the predominant formation of butenolide **2** from **1** induced by lithium hydroxide offers a general method for preparing optically active 3,5-disubstituted butenolides.[3] It appears that the product distribution of the fragmentation is influenced primarily by the steric bulkiness of the C-2 (R^2 group) and C-4 (R^1 group) substituents of the carbolactones **1** and by the nature of the nucleophiles used, such as hydroxide and alkoxide. Intrigued by this unique transformation and its synthetic potential, we elected to explore the scope and limitations of the process.

We examined several fragmentation substrates possessing substituents at C-2 and C-4 of **1**, which differ in steric bulkiness and functionality. Herein, we (1) describe the full details of these studies focusing on the C-2 and C-4 substituent effect and (2) propose a working mechanism for the fragmentation process promoted by both hydroxide and alkoxide nucleophiles.

SCHEME 1



Results and Discussion

Preparation of Fragmentation Substrates 2-Alkyl- and 2,4-Dialkyl-3-iodo-1-oxocyclohexan-2,4-carbolactones (1a−l). The requisite substrates for fragmenta-

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† Deceased January 20, 2000.

(1) (a) Schultz, A. G. *Acc. Chem. Res.* **1990**, *23*, 207. (b) Schultz, A. G. *J. Chin. Chem. Soc.* (*Taipei*) **1994**, *41*, 487. (c) Schultz, A. G. *Chem. Commun.* **1999**, 1263.

(2) For a preliminary account of this work, see: Schultz, A. G.; Dai, M.; Khim, S.-K.; Pettus, L.; Thakkar, K. *Tetrahedron Lett.* **1998**, *39*, 4203.

(3) For recent syntheses of butenolides, see: (a) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625. (b) Larock, R. C.; Riefling, B.; Fellows, C. A. *J. Org. Chem.* **1978**, *43*, 131. (c) Herrmann, J. L.; Berger, M. H.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1979**, *101*, 1544. (d) Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193. (e) Hanessian, S.; Hodges, P. J.; Murray, P. J.; Sahoo, S. P. *J. Chem. Soc., Chem. Commun.* **1986**, 754. (f) Figureredo, M.; Font, J.; Virgili, A. *Tetrahedron* **1987**, *43*, 1881. (g) Tanabe, Y.; Ohno, N. *J. Org. Chem.* **1988**, *53*, 1560. (h) Buchwald, S. L.; Fang, Q.; King, S. M. *Tetrahedron Lett.* **1988**, *29*, 3445. (i) Hoye, T. R.; Humpal, P. E.; Jimenez, J. I.; Mayer, M. J.; Tan, L.; Ye, Z. *Tetrahedron Lett.* **1994**, *35*, 7517. (j) Trost, B. M.; Muller, T. J. J.; Martinez, J. *J. Am. Chem. Soc.* **1995**, *117*, 1888. (k) Marshall, J. A.; Wolf, M. A. *J. Org. Chem.* **1996**, *61*, 3238. (l) Kablaoui, N. M.; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 5818. (m) Renard, M.; Ghosez, L. *Tetrahedron Lett.* **1999**, *40*, 6237. (n) Rousset, S.; Thibonnet, J.; Abarbri, M.; Duchêne, A.; Parrain, J.-L. *Synlett* **2000**, 260. (o) Yao, M.-L.; Deng, M.-Z. *J. Org. Chem.* **2000**, *65*, 5034. (p) He, Y.-T.; Yang, H.-N.; Yao, Z.-J. *Tetrahedron* **2002**, *58*, 8805. (q) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2456. (r) Ma, S.; Yu, Z. *J. Org. Chem.* **2003**, *68*, 6149. (s) Yoneda, E.; Zhang, S.-W.; Zhou, D.-Y.; Onitsuka, K.; Takahashi, S. *J. Org. Chem.* **2003**, *68*, 8571.

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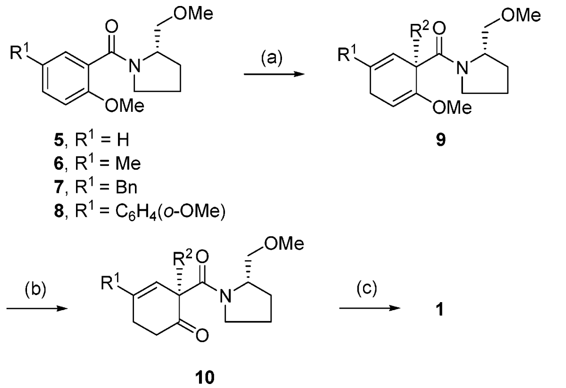
SCHEME 2[a]



[a] Reagents and conditions: (a) K, NH_3, THF, *t*-BuOH (1 equiv), piperylene, R^2X; (b) 6 N HCl, MeOH, rt; (c) I_2, THF/H_2O, rt.

TABLE 1. Preparation of Fragmentation Substrates 1a–l

entry	R^1	R^2	yield (%)[a] 9	10	1
a	H	Me	95	95	90
b	H	$(CH_2)_3Cl$	93	89	75
c	H	$(CH_2)_4Cl$	89	92	85
d	H	$(CH_2)_2C_6H_4$(*o*-Br)	89[b]	97	82
e	H	$(CH_2)_3OBn$	87	86	86
f	H	$CH_2O(CH_2)_2TMS$	82	95	84
g	Me	Me	100	100	79
h	Me	Et	100	98	80
i	Me	$(CH_2)_3CH{=}CH_2$	91	95	62
j	Me	$(CH_2)_2OPMB$	75	71	73
k	Bn	Et	93	96	81
l	C_6H_4(*o*-OMe)	Me	78	93	98

[a] Isolated yields. [b] LiBr was added for metal exchange.

tion reactions, 2-alkyl- and 2,4-dialkyl-3-iodo-1-oxocyclohexan-2,4-carbolactones (**1a**–**l**), were prepared from chiral benzamides **5**–**8**, as shown in Scheme 2 and summarized in Table 1. Birch reduction of chiral benzamides **5**–**8** resulted in the chiral amide enolates, which were alkylated in situ using alkyl halides to provide the corresponding enol ether 1,4-cyclohexadienes **9** as single diastereomers. Acid-catalyzed hydrolysis of **9** gave the corresponding β,γ-enones **10**. Subsequent iodolactonizations[4] of **10** using iodine in THF/H_2O afforded the enantiomerically pure 2-alkyl- and 2,4-dialkyl-3-iodo-1-oxocyclohexan-2,4-carbolactones **1a**–**l**.

Lithium Hydroxide-Induced Fragmentation of 1a–l. With the required substrates in hand, we first investigated the fragmentation of **1a**–**l** promoted by lithium hydroxide. As shown in Scheme 3 and Table 2, the addition of lithium hydroxide (2.0 equiv) to a solution of **1a**–**l** in THF/H_2O (5:1, v/v) at room temperature resulted in a mixture of the butenolides **11** and γ-hydroxycyclohexenones **12**[5] in excellent yield. It is evident

(4) (a) Corey, E. J.; Shibasaki, M.; Knolle, J. *Tetrahedron Lett.* **1977**, *19*, 1625. (b) Harding, K. E.; Tiner, T. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 4, p 363. (c) Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 7904.

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SCHEME 3

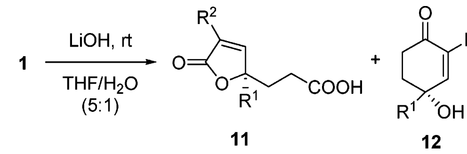
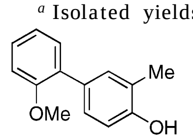


TABLE 2. Fragmentation of 1 with LiOH

entry	1	R^1	R^2	yield (%)[a] 11	12
1	**1a**	H	Me	28	58
2	**1b**	H	$(CH_2)_3Cl$	68	15
3	**1d**	H	$(CH_2)_2C_6H_4$(*o*-Br)	74	7
4	**1e**	H	$(CH_2)_3OBn$	77	13
5	**1f**	H	$CH_2O(CH_2)_2TMS$	78	9
6	**1g**	Me	Me	38	47
7	**1h**	Me	Et	88	8
8	**1i**	Me	$(CH_2)_3CH{=}CH_2$	81	5
9	**1j**	Me	$(CH_2)_2OPMB$	88	10
10	**1k**	Bn	Et	81	2
11	**1l**	C_6H_4(*o*-OMe)	Me	76	*b*

[a] Isolated yields. [b] Compound **13** was isolated in 8% yield.



13

that the steric bulkiness at R^1 and R^2 controls the fragmentation product distribution. For example, when R^1 is H and R^2 is Me (entry 1, Table 2), γ-hydroxycyclohexenone **12a** was the major product (**11a**:**12a**, 1:2). As the steric bulkiness of R^2 increased (entries 2–5, Table 2), butenolides **11b**,**d**–**f** became the major products (**11b**,**d**–**f**:**12b**,**d**–**f**, 5–11:1). A similar trend was observed for the fragmentation of the 2,4-disubstituted substrates **1g**–**j** (entries 6–9, Table 2). Interestingly, when R^1 is bulkier than R^2 (Bn vs Et for entry 10 and *o*-methoxyphenyl vs Me for entry 11), **11k** (81% yield) and **11l** (76% yield) were formed almost exclusively. In the case of **1l**, the biphenyl **13** was observed as a minor side product, possibly resulting from the sequential dehydration–aromatization of the intermediate tertiary benzylic alcohol **12** or spontaneous decomposition of **1l**.[6]

Structural assignments of butenolides **11** and γ-hydroxycyclohexenones **12** were established by the diagnostic chemical shift differences of vinyl protons in the ^1H NMR. We have previously established that the vinyl protons of butenolides **11** resonate downfield at a region between 6.78 and 7.27 ppm compared to the vinyl protons of γ-hydroxycyclohexenones **12**, which resonate between 6.09 and 6.85 ppm ($\Delta\delta = 0.32$–0.94).

Two plausible mechanisms which would account for the observed formation of **11** and **12** are shown in Figure 1. In pathway A, the nucleophilic addition of hydroxide to the ketone carbonyl moiety of **1** results in intermediate **14**, which undergoes a ring-opening reaction through a Grob-type fragmentation[7] to give lactone enolate **15** followed by a loss of iodide to provide butenolide **11**.

In contrast, the formation of **12** could be explained by the competitive addition of hyroxide to the lactone carbonyl moiety of **1**. Thus, in pathway B, the hydroxide

(6) **1l** was found to slowly decompose to **13**.

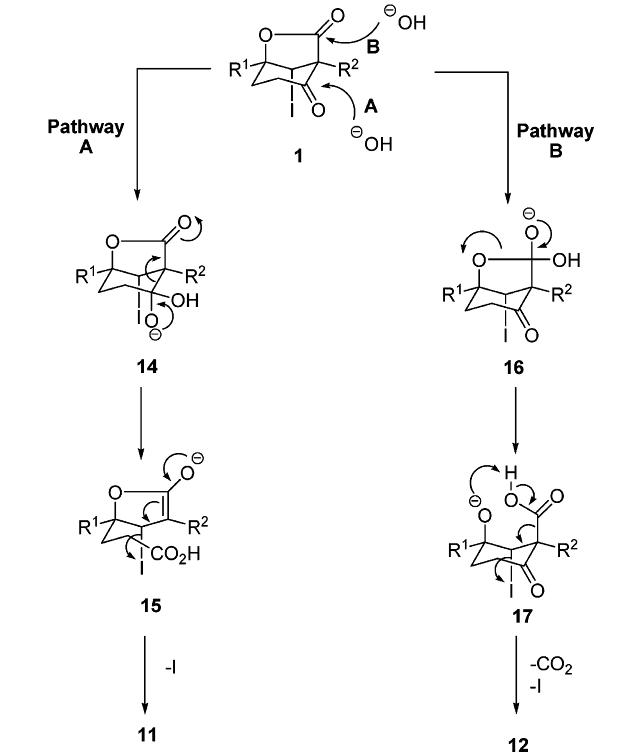


FIGURE 1. Proposed mechanisms for the fragmentation of **1** with LiOH.

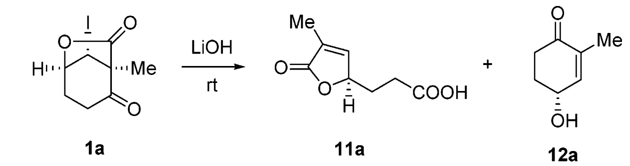
ion attacks the lactone moiety of **1** resulting in intermediate **16**, which subsequently undergoes a ring opening to give the *tert*-alkoxide intermediate **17**. Intramolecular decarboxylative fragmentation of **17** would provide the γ-hydroxycyclohexenone **12**.

It is clear that the chemoselectivity of hydroxide addition is greatly influenced by the steric bulkiness of the R^2 substituents. Substituents larger than the methyl group significantly impede the *Re*-face attack of hydroxide on the lactone moiety of **1**, while the corresponding *Si*-face attack would be sterically disfavored due to the presence of axial C-6 hydrogen. Consequently, addition of hydroxide to the ketone moiety of **1** exclusively furnishes butenolide **11**.

Considering the overall yield, the ease of workup, and the reaction time for this process, we screened several bases such as $NaHCO_3$, Na_2CO_3, K_2CO_3, LiOH, NaOH, KOH, CsOH, $Ba(OH)_2$, and tetrabutylammonium hydroxide. Of the bases screened, LiOH was found to be the choice.

The effect of solvent composition on this fragmentation process was also investigated. The results are summarized in Table 3. When the ratio of THF to H_2O was ≤ 1, fragmentation of **1a** provided the γ-hydroxycyclohexenone **12a** as the major product (entries 1 and 2, Table 3). As the ratio of THF to H_2O was increased to 5−10:1, the ratio of **11a** to **12a** increased to approximately 1:1 (entries 3 and 4, Table 3). The variation in product ratios as a function of solvents suggests that protic polar solvent facilitates and stabilizes the formation of intermediate **17** (pathway B in Figure 1) by promoting the enhanced solvation of lithium ions. We hypothesized, therefore, that intermediate **17** is more solvated in protic solvents such as THF/H_2O (1:2), thereby leading to the formation of **12a** as the major product.

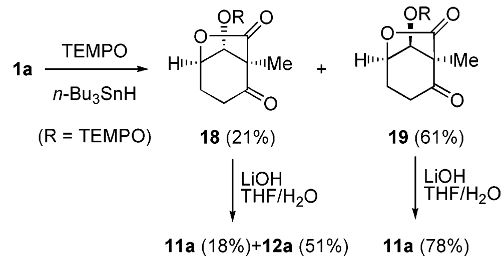
TABLE 3. Product Distributions as a Function of Solvents



entry	THF:H_2O	yield (%)[a] **11a**:**12a**	^{1}H NMR ratio[b] **11a**:**12a**
1	1:2	12:71	21:79
2	1:1	15:72	27:73
3	5:1	28:58	45:55
4	10:1	41:40	59:41

[a] Isolated yields. [b] On the basis of the integration of vinyl protons of the crude mixture (7.03 ppm for **11a** and 6.09 ppm for **12a**).

SCHEME 4

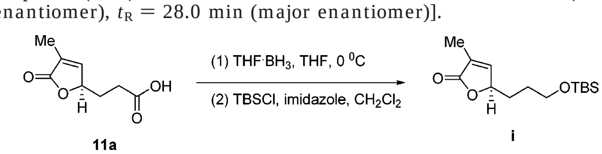


To determine the enantiomeric purities of the fragmentation products, **11a** and **12a** were structurally modified and analyzed by chiral HPLC. Analysis showed that **11a** and **12a** are produced in >99 [8] and >96% ee,[9] respectively, indicating that the fragmentation proceeds with complete retention of stereochemistry.

Stereoelectronic Effect of the Leaving Groups of 1 in Fragmentation. To investigate the stereoelectronic effect of the leaving groups at C-3 of **1** in these fragmentation processes, we needed access to both axial and equatorial leaving groups (Scheme 4).[10] Iodide exchange of **1** catalyzed by substrates containing 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) allowed

(7) (a) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1. (b) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535. (c) Becker, K. B.; Grob, C. A. In *The Chemistry of Double-Bonded Functional Groups*; Patai, S., Ed.; Wiley: New York, 1977; Part 2, p 653. (d) Weyersthal, P.; Marschall, H. Fragmentation Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 6, p 1041.

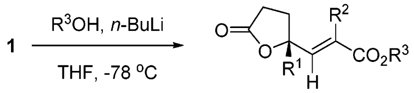
(8) The enantiomeric purity of **11a** was determined with the silyl ether derivative **i**, and its racemic derivative was prepared from the pyrrolidine amide corresponding to **5** [chiral OJ column, hexane/2-propanol (99:1), 0.35 mL/min, $\lambda = 220$ nm, $t_R = 24.0$ min (minor enantiomer), $t_R = 28.0$ min (major enantiomer)].



(9) A racemic sample of **12a** was prepared from the pyrrolidine amide corresponding to **5** and was used as a control for the analysis [chiral OJ column, hexane/2-propanol (25:1), 0.55 mL/min, $\lambda = 220$ nm, $t_R = 40.8$ min (major enantiomer), $t_R = 44.5$ min (minor enantiomer)].

(10) Schultz, A. G.; Zhang, X. *Chem. Commun.* **2000**, 399.

SCHEME 5

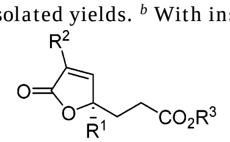


20-29

TABLE 4. Fragmentation of 1 with LiOR[3]

entry	**1**	R[1]	R[2]	R[3]	product	yield (%)[a]
1	**1a**	H	Me	Me	**20**	87
2	**1a**	H	Me	Bn	**21**	80
3	**1a**	H	Me	PMB	**22**	87
4	**1b**	H	$(CH_2)_3Cl$	Me	**23**	68
5	**1b**	H	$(CH_2)_3Cl$	Bn	**24**	65
6	**1c**	H	$(CH_2)_4Cl$	Bn	**25**	63
7	**1d**	H	$(CH_2)_2C_6H_4$(*o*-Br)	Me	**26**	35[b]
8	**1h**	Me	Et	Me	**27**	31[c]
9	**1h**	Me	Et	Bn	**28**	47
10	**1h**	Me	Et	PMB	**29**	32

[a] Isolated yields. [b] With inseparable **30**. [c] With inseparable **31**.



30, R^1 = H, R^2 = $(CH_2)_2C_6H_4$(*o*-Br), R^3 = Me
31, R^1 = Me, R^2 = Et, R^3 = Me

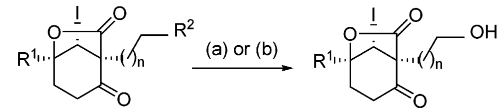
such access. Utilizing the procedure described by Boger,[11] **1a** was heated with TEMPO (5 equiv) and *n*-Bu_3SnH (3 equiv) in benzene to give **18** and **19** in 21 and 61% yield, respectively.[12] Predominant formation of **19** over **18** is a consequence of the preferential equatorial approach of TEMPO to the resulting secondary radical in a way that relieves 1,3-interaction with the axial hydrogen atom at C-5.[13] Under the standard fragmentation conditions (LiOH, THF/H_2O, room temperature), **18** provided a mixture of **11a** (18%) and **12a** (51%). In contrast, **19** provided chemoselective hydrolytic fragmentation resulting only in **11a** (78%).

Lithium Alkoxide-Induced Fragmentation. Fragmentation of **1** promoted by lithium alkoxides was also examined, as shown in Scheme 5. The results summarized in Table 4 indicated that when, in general, R^1 is H, fragmentation yielded *γ*-butyrolactones **20**−**25**[14] (entries 1−6) as single fragmentation products in 63−87% yield. However, when R^2 is a relatively bulky group (entry 7), fragmentation provided not only *γ*-butyrolactone **26** but also butenolide **30** in a ratio of 1.7:1. It was found that the 2,4-disubstituted substrates (entries 8−10) gave much lower chemical yields of the fragmentation products **27**−**29** as well as lower chemoselectivity (a ratio of 2:1 of **27**:**31**, entry 8). The nature of the alkoxide (methyl, benzyl, and *p*-methoxybenzyl) employed seems to have no significant impact on either the yield or the chemoselectivity of the process.

Structural assignments of *γ*-butyrolactones **20**−**29** were characterized via chemical shifts of the vinyl protons in the ^1H NMR spectra.[15] The vinyl protons of **20**−**29** resonate downfield between 6.67 and 6.85 ppm as a doublet of quartets (J = 8.1, 1.4 Hz, **20** and **21**), a doublet (J = 8.1−8.8 Hz, **22**−**26**), and a singlet (**27**−**29**). Large coupling constants (J = 8.1−8.8 Hz) observed for the vinyl protons of **20**−**26** suggest that a vinyl proton and the adjacent methine proton have an orthogonal stereochemical relationship. Indeed, the anticipated orthogonal stereochemical relationship of a vinyl proton and the adjacent methine proton was unambiguously confirmed by the X-ray crystal structure of **22**.[16] The expected reduced acidity of the methine proton might explain why the *γ*-vinylogous butyrolactones **20**−**26** do not epimerize even under the relatively basic reaction conditions.[2] The (*E*)-geometric configuration of the trisubstituted alkene was also confirmed by the X-ray crystal structure of **22**. The structure of butenolide ester **30** was assigned by comparison with the independently prepared esterification product (MeOH, TFA, room temperature) from butenolide carboxylic acid **11d**.

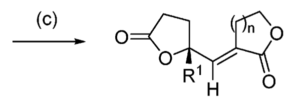
We further examined the feasibility of this fragmentation process in an intramolecular fashion (Scheme 6). Thus, the *O*-protecting groups in R^2 of **1e** and **1j** were removed[17] to afford hydroxy carbolactones **32** and **33**, which existed presumably as a mixture of the hydroxy ketone and the hemiketal tautomers. It was somewhat surprising that even under mild basic conditions (Et_3N), **32** and **33** underwent facile intramolecular fragmentation affording bislactones **34** and **35** as sole products in 96 and 86% yield, respectively. Diagnostic downfield shifts

SCHEME 6[a]



1e, R^1 = H, R^2 = OBn, n = 2
1j, R^1 = Me, R^2 = OPMB, n = 1

32, R^1 = H, n = 2, 76%
33, R^1 = Me, n = 1



34, R^1 = H, n = 2, 96%
35, R^1 = Me, n = 1, 86% for 2 steps

[a] Reagents and conditions: (a) DDQ, CH_2Cl_2, sealed tube for **32**; (b) DDQ, CH_2Cl_2/H_2O, rt for **33**; (c) Et_3N, THF, rt.

(11) (a) Boger, D. L.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 1271 and references therein. (b) Schultz, A. G.; Dai, M.; Tham, F. S.; Zhang, X. *Tetrahedron Lett.* **1998**, *39*, 6663.

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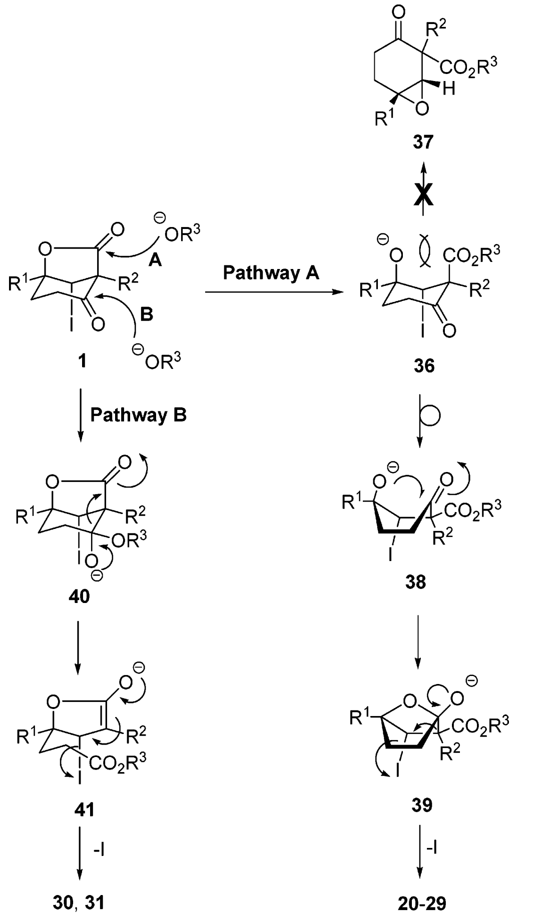

FIGURE 2. Proposed mechanisms for the LiOR^3-promoted fragmentation of **1**.

of the vinyl protons (6.98 ppm for **34** and 6.66 ppm for **35**) and the large coupling constant (J = 7.8 Hz for **34**) in ^{1}H NMR spectra indicated the formation of the γ-butyrolactones. The absolute structure of **35** was determined by X-ray crystallography.[16]

We postulate that there are two fragmentation pathways for **1**. As depicted in Figure 2, lithium alkoxide attacks either the lactone carbonyl moiety to give γ-butyrolactones **20**−**29** (pathway A) or the ketone carbonyl moiety to give butenolides **30** and **31** (pathway B). In pathway A, when an alkoxide anion attacks the lactone carbonyl moiety of **1**, it affords 4-alkoxy cyclohexanone intermediate **36**. The fact that the β,γ-epoxycyclohexanone **37** was not observed strongly implies that **36** undergoes a rather rapid conformational change from a chair conformation to a boat conformational **38** in order to relieve the 1,3-diaxial interaction between alkoxide anion and the ester group of **36**. The boat conformation of **38** facilitates transannular cyclization to give the transannular lactol anion **39**, and subsequent fragmentation leads to the formation of γ-butyrolactones **20**−**29**. In the case of pathway B, **1** undergoes alkoxide anion addition to the ketone carbonyl moiety to afford intermediate **40**, which then undergoes a ring-opening reaction to give the stabilized lactone enolate **41**. Subsequent elimination would yield butenolides **30** and **31**.

Conclusion

In summary, we have demonstrated that optically pure 2-alkyl- and 2,4-dialkyl-3-iodo-1-oxocyclohexan-2,4-carbolactones undergo lithium hydroxide- and lithium alkoxide-induced fragmentation reactions to afford butenolides, γ-hydroxycyclohexenones, and/or γ-butyrolactones. The product distributions of this process are governed by the nature of nucleophiles used and the steric bulkiness of substituents at C-2 and C-4 of the cyclohexanones. Fragmentation induced by lithium hydroxide was found to be a general method for obtaining optically active 3,5-disubstituted butenolide, which otherwise is not readily available.[18] Lithium alkoxide-induced fragmentation exclusively provides γ-butyrolactone.

Experimental Section

For general experimental procedures, see the Supporting Information.

The following compounds were prepared by literature methods: 2-(2′-bromophenyl)-1-iodoethane,[19] 1-iodo-3-benzyloxypropane,[20] 1-(2′-trimethylsilyl)ethyloxy-1-chloromethane,[21] and 2-(p-methoxybenzyloxy)-1-iodoethane.[22]

General Procedure for the Fragmentation of 1 with LiOH·H$_2$O. To a solution of **1a** (255 mg, 0.9 mmol) in THF/H$_2$O (12 mL, 5:1) was added LiOH·H$_2$O (76 mg, 1.8 mmol). The resulting solution was stirred overnight at room temperature. The reaction mixture was neutralized with 10% aqueous HCl solution and extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (hexanes/EtOAc, 3:1) of the crude residue gave **11a** (34 mg, 27%) and **12a** (53 mg, 58%). (5R)-[3-Methyl-5-(2′-hydroxycarbonyl)ethyl]-furan-2(5H)-1-one (**11a**): white solid; mp 82−84 °C; $[\alpha]^{25}_D$ −35.8 (c 0.67); ^{1}H NMR δ 7.03 (d, J = 1.4 Hz, 3H), 5.00−4.97 (m, 1H), 2.58−2.49 (m, 2H), 2.22−2.15 (m, 1H), 1.93−1.91 (m, 3H), 1.87−1.79 (m, 1H); ^{13}C NMR δ 177.9, 173.9, 147.9, 130.7, 79.6, 29.0, 28.2, 10.6; IR ν 3467, 2931, 1736 cm^{-1}; CIMS 171 (M$^+$ + 1, 100); HRMS calcd for $C_8H_{11}O_4$ (M$^+$ + 1) 171.0657, found 171.0657. (4R)-4-Hydroxy-2-methyl-2-cyclohexen-1-one (**12a**): colorless liquid; $[\alpha]^{28}_D$ +48.0 (c 0.98); ^{1}H NMR δ 6.09 (m, 1H), 4.52 (m, 1H), 2.60−2.54 (m, 2H), 2.36−2.26 (m, 2H), 1.97−1.89 (m, 1H), 1.75 (m, 3H); ^{13}C NMR δ 199.3, 147.9, 135.6, 66.4, 35.3, 32.7, 15.6; IR ν 3411, 1669 cm^{-1}; CIMS 127 (M$^+$ + 1, 100); HRMS calcd for $C_7H_{10}O_2$ (M$^+$ + 1) 127.0759, found 127.0759.

Preparation of 18 and 19. A solution of **1a** (1.44 g, 5.14 mmol) and TEMPO (4.01 g, 25.7 mmol) in benzene (100 mL) was deoxygenated by bubbling N_2 into the solution for 10 min. n-Bu$_3$SnH (1.38 mL, 5.14 mmol) was added, and the solution was warmed to 70 °C. Two additional solutions of n-Bu$_3$SnH (1.38 mL each) in benzene were added during the next 30 min. The reaction mixture was heated for an additional 30 min. The reaction mixture was cooled and then washed with 10% HCl solution, brine, and water. The organic layers were separated and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to give **18** (335 mg, 21%) and **19** (972 mg, 61%). (2R,3R,4R)-1-Oxo-2-methyl-3-(2′,2′,6′,6′-tetramethyl-1′-piperidinyloxy)cyclohexan-

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2,4-carbolactone (**18**): mp 102−104 °C; $[\alpha]^{26}_{D}$ −95 (*c* 0.79); ^{1}H NMR δ 5.02 (t, J = 4.6 Hz, 1H), 4.82 (d, J = 5.1 Hz, 1H), 2.62 (dd, J = 8.8, 1.8 Hz, 1H), 2.54 (m, 2H), 2.42 (m, 1H), 1.62 (m, 1H), 1.53 (s, 3H), 1.51 (s, 3H), 1.49 (s, 3H), 1.40 (m, 5H), 1.15 (br s, 6H); ^{13}C NMR δ 199.3, 172.2, 90.7, 75.3, 61.5, 40.5, 39.2, 34.3, 28.7, 26.2, 24.4, 16.8, 16.3, 16.0, 13.9, 13.2; IR ν 1790, 1725 cm^{-1}; CIMS 310 (M$^+$ + 1, 100). (2*R*,3*S*,4*R*)-1-Oxo-2-methyl-3-(2′,2′,6′,6′-tetramethyl-1′-piperidinyloxy)cyclohexan-2,4-carbolactone (**19**): mp 128−130 °C; $[\alpha]^{26}_{D}$ −126 (*c* 0.82); ^{1}H NMR δ 5.40 (d, J = 4.4 Hz, 1H), 4.25 (s, 1H), 2.56 (dd, J = 6.9, 2.2 Hz, 2H), 2.42 (m, 1H), 1.88 (m, 1H), 1.62−1.35 (m, 6H), 1.40 (s, 3H), 1.20 (s, 3H), 1.16 (s, 3H), 1.11 (s, 3H), 1.07 (s, 3H); ^{13}C NMR δ 199.5, 174.7, 86.8, 76.9, 76.6, 62.5, 61.9, 60.0, 50.0, 40.4, 34.7, 34.0, 33.6, 5.0, 20.8, 20.6, 17.0, 8.80; IR ν 1775, 1718 cm^{-1}; CIMS 310 (M$^+$ + 1, 100). Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80. Found: C, 65.17; H, 8.59. The foregoing combustion analysis of this sample indicates that the sample was probably wet. A sample of compound **19**, sufficient for re-analysis, is no longer available.

Fragmentation of 18 with LiOH·H$_2$O. To a solution of **18** (175 mg, 0.57 mmol) in THF/H_2O (4 mL, 5:1) was added LiOH·H_2O (470 mg, 1.14 mmol). The resulting solution was stirred overnight at room temperature. The reaction mixture was neutralized with 10% HCl solution and extracted with diethyl ether. The combined organic solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a colorless oil. Flash column chromatography (hexanes/EtOAc, 3:1 to 2:1) of the crude residue gave **11a** as a single product (75 mg, 78%).

Fragmentation of 19 with LiOH·H$_2$O. To a solution of **19** (101 mg, 0.33 mmol) in THF/H_2O (2.5 mL, 5:1) was added LiOH·H_2O (140 mg, 0.65 mmol). The resulting solution was stirred overnight at room temperature. The reaction mixture was neutralized with 10% HCl solution and extracted with diethyl ether. The combined organic solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a colorless oil. Flash column chromatography (hexanes/EtOAc, 3:1 to 2:1) of the crude residue gave **11a** (10 mg, 18%) and **12a** (21 mg, 51%).

General Procedure for the Fragmentation of 1 with Lithium Methoxide. Methyl (2*E*)-2-Methyl-3-[(2*R*)-3-tetrahydro-5-oxofuranyl]-2-propenoate (20). To a solution of MeOH (30 μL, 0.8 mmol) in THF (5 mL) was added *n*-BuLi (180 μL, 0.5 mmol, 2.5 M solution in hexanes) at −78 °C. The resulting solution was stirred for 0.5 h. To this solution was added dropwise a solution of **1a** (106 mg, 0.4 mmol) in THF (5 mL) at −78 °C. The resulting solution was stirred overnight at room temperature. The reaction mixture was diluted with water and extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (hexanes/EtOAc, 3:1) of the crude residue gave the desired product **20** (61 mg, 87%) as a colorless oil: $[\alpha]^{27}_{D}$ −46.5 (*c* 0.71); ^{1}H NMR δ 6.67 (dq, J = 8.1, 1.4 Hz, 1H), 5.25 (dd, J = 15.1, 8.1 Hz, 1H), 3.75 (s, 3H), 2.60−2.53 (m, 2H), 2.50−2.44 (m, 1H), 2.04−1.96 (m, 1H), 1.91 (d, J = 1.4 Hz, 3H); ^{13}C NMR δ 176.4, 167.4, 137.6, 131.2, 76.3, 52.1, 28.3, 28.2, 13.0; IR ν 1780, 1718 cm^{-1}; CIMS 185 (M$^+$ + 1, 100), 153 (30). Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.59; H, 6.61.

(2*R*,3*R*,4*R*)-2-(3′-Hydroxy)propyl-3-iodo-1-oxocyclohexan-2,4-carbolactone (32). 1e (840 mg, 2.03 mmol) and DDQ (1.38 g, 6.09 mmol) were dissolved in CH_2Cl_2 (15 mL) at a sealed tube. The reaction mixture was heated at 60 °C for 8 h and then cooled to room temperature. The solid was removed through a thin pad of Celite. The filtrate was concentrated under reduced pressure to give a yellow oil. The crude product was purified by flash column chromatography (hexanes/EtOAc, 1:1) to afford **32** (501 mg, 76%) as a colorless oil, which was used without further purification for the next reaction (hydroxyketone/hemiketal, 10:1): $[\alpha]^{26}_{D}$ −125.2 (*c* 0.76); ^{1}H NMR δ 4.94 (s, 1H), 4.77 (d, J = 5.4 Hz, 1H), 3.63 (m, 2H), 2.69−2.60 (m, 2H), 2.58−2.53 (m, 1H), 2.44−2.37 (m, 1H), 1.99 (m, 1H), 1.81 (m, 1H), 1.58 (br s, 1H), 1.41 (m, 2H); ^{13}C NMR δ 198.2, 170.1, 77.6, 62.7, 33.2, 27.6, 26.2, 23.7, 21.5; IR ν 3522, 1780, 1723 cm^{-1}; CIMS 325 (M$^+$ + 1).

(3*E*)-Tetrahydro-3-[[(2*R*)-tetrahydro-5-oxofuranyl]-methylene]-2*H*-pyran-2-one (34). To a solution of crude **32** (45 mg, 0.14 mmol) in CH_2Cl_2 (1 mL) was added 2 drops of Et_3N at room temperature. The reaction mixture was stirred overnight. Water and CH_2Cl_2 were added, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to give **34** (26 mg, 96%) as a white solid: $[\alpha]^{24}_{D}$ −41.4 (*c* 0.58); ^{1}H NMR δ 6.93 (d, J = 7.8 Hz, 1H), 5.16 (q, J = 7.3 Hz, 1H), 4.32 (t, J = 5.6 Hz, 2H), 2.70 (m, 1H), 2.56 (m, 4H), 2.46 (m, 1H), 2.05 (m, 1H), 1.94 (m, 1H); ^{13}C NMR δ 176.3, 165.3, 140.3, 129.9, 128.6, 75.7, 69.0, 28.3, 28.2, 24.3, 22.6; IR ν 1763, 1719 cm^{-1}; CIMS 197 (M$^+$ + 1, 100). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 60.93; H, 6.17.

(2*R*,3*R*,4*R*)-2-(2′-Hydroxy)ethyl-3-iodo-4-methyl-1-oxocyclohexan-2,4-carbolactone (33). To a solution of **1j** (100 mg, 0.23 mmol) in CH_2Cl_2/H_2O (21 mL, 20:1) was added DDQ (61 mg, 0.27 mmol) at room temperature. The reaction mixture was stirred for 3 h and quenched with water and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give **33**. The crude residue was directly used for the next reaction without further purification: ^{1}H NMR δ 4.66 (s, 1H), 3.48 (m, 1H), 3.33 (m, 1H), 2.27−1.53 (m, 6H), 1.00 (s, 3H); ^{13}C NMR δ 198.4, 171.2, 84.5, 65.3, 58.6, 50.5, 33.6, 33.5, 33.3, 33.2, 28.1, 22.5, 22.4.

(5*R*)-5-[(*E*)-(Dihydro-2-oxo-3(2*H*)-furanylidene)methyl]-dihydro-5-methyl-2(3*H*)-furanone (35). Crude **33**, contaminated with 4-methoxybenzaldehyde, was dissolved in THF (10 mL), and Et_3N (0.20 mL, 1.4 mmol) was added. The reaction mixture was stirred for 3 h and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (hexanes/EtOAc, 1:1) of the crude residue gave **35** (38 mg, 86%) as a white solid: mp 132−134 °C; $[\alpha]^{25}_{D}$ +30.0 (*c* 1.0); ^{1}H NMR δ 6.66 (m, 1H), 4.34 (m, 2H), 3.15−3.01 (m, 2H), 2.59 (m, 2H), 2.32−2.19 (m, 2H), 1.56 (s, 3H); ^{13}C NMR δ 176.0, 171.6, 139.7, 126.0, 85.0, 66.1, 34.8, 28.7, 26.1, 25.7; IR ν 1766, 1744 cm^{-1}; CIMS 197 (M$^+$ + 1, 100). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 60.95; H, 6.24.

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Supporting Information Available: Experimental procedures and characterization data for compounds discussed in the text (but not described in the Experimental Section), ^{1}H NMR spectra for **11e**, **13**, and **19**, and ORTEP drawings and crystal data and structure refinement for **23** and **35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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