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# Formation of spiro ketolactones versus alkoxy radical fragmentation-promoted three-atom ring enlarged lactones from cyclic ketones

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**Abstract**—A dual pathway from readily available 2-allyl-2-carboethoxycycloalkanones **1** provides a new facile stereoselective synthesis either of functionalized spiro ketolactones **4** or of ring enlarged lactones **7** in one-step. Thus, iodination of 5–8-membered 2-allyl-2-carboethoxycycloalkanones **1a**–**d** led, in excellent yields, to spiro ketolactones **4a**–**d**, respectively, as single stereoisomers. On the other hand, iodination of **1a**–**d** under alkoxy radical fragmentation conditions via incipient hemiketals produced the 8-, 9-, 10-, or 11-membered, three-atom ring enlarged, poly-functionalized lactones **7a**–**c** as two stereoisomers and **8** as a single isomer.


Many medium- and large-ring lactones (macrolides) are found among bioactive natural products, yet the synthesis of such multifunctional molecules by ring closure presents a synthetic challenge.[1] Hence, efficient syntheses based on ring enlargement are still desirable. Furthermore, new routes to spirolactones also maintain continued interest.[2]

Recently,[3] we described a ring expansion method by utilizing alkoxy radical fragmentation[4] (ARF) of hemiketals derived from [2.3.1] and [3.3.1] bicyclic γ-hydroxy ketones. The latter were prepared from cyclopentanone or cyclohexanone and led to the synthesis of 7- or 8-membered rings containing several functional groups. This 2-carbon ring expansion was possible because of the favorable equilibrium between the bicyclic γ-hydroxy ketones and their hemiketal isomers. By contrast, analogous 9- and 10-membered rings derived in an analogous manner from cycloheptanone and cyclooctanone via bicyclic γ-hydroxy ketones were not accessible by this route. We demonstrated[3] by MM calculations that while for the 5- and 6-membered ring bicyclic ketones, the energy differences between the hydroxy ketone and hemiketal were small, the bicyclic hemiketals derived from 7- and 8-membered rings were much less stable (by at least 6 kcal/mol) than their corresponding hydroxy ketone isomers. This suggested the requirement for hemiketal formation from these bicyclic hydroxyketones in order for them to undergo alkoxy radical fragmentation.

With a view to general routes toward medium- and large-sized rings, we wanted to ascertain whether ring expansions similar to those in the bicyclic system were feasible in simple γ-hydroxycyclic ketones. Hence, we required a shorter route to hemiketals than the route[3] that had led to the bicyclic system. First, we opted for the presence of an α-carboethoxy group in cyclic ketones, since this would not only facilitate monoalkylation but would also stabilize a free radical during alkoxy radical fragmentation and possibly provide an entry into spirolactones. Second, it was anticipated that halogenation of allylcyclohexanone[5] **1b** would lead, via a three-membered ring iodonium or bromonium ion intermediate, to hemiketal **2b** and hence by ARF to lactones **7b** via 3-atom ring enlargement. In two elegant communications, Posner et al.[6] recently reported the viability of ring enlargements from 4-silylated-2-allylcycloalkanones by epoxidation[6a] or by nucleophilic attack of enolates on small ring ethers.[6b] The epoxidation proceeded with carbonyl participation to produce hemiketals in fair yields, which underwent ring expansion analogous to the conversion of **2** to **7**.

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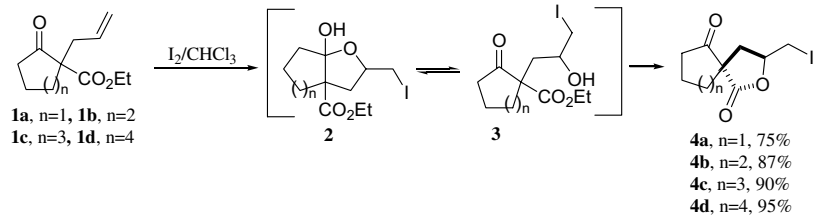
Indeed, we found that iodination of 2-allyl-2-carboethoxycyclohexanone **1b**, readily obtained[5] by allylation of the anion of 2-carboethoxycyclohexanone, led upon work-up to hemiketal **2b**, via ketone attack on an incipient iodonium ion. In turn hemiketal **2b**, formed as two diastereomers, underwent ARF in the presence of diacetoxy iodobenzene (DIB), iodine, and light[4] to a 9-membered ring lactone, **7b**, in good yield.

However, attempts to isolate hemiketals from analogous 5-, 7- or 8-membered cyclic ketones were unsuccessful and led instead to spirolactones in very high yields. In the event, iodination of 2-allyl-2-carboethoxycyclooctanone[7] **1d** produced the spiro keto lactone **4d** as a single isomer in excellent yield (Scheme 1). Indeed, MM calculations again indicated a large difference in energy between the hemiketal and the γ-hydroxy ketone in favor of the latter in the cyclooctanone, but not in the cyclohexanone case. Similarly, iodination of allyl ketones **1a**,**c** led to spirolactones **4a**,**c** in high yields and no hemiketals were observed. A possible pathway for the formation of spirolactones **4** involves carbonyl participation with the formation of hemiketals **2**, formed on work-up. This would be followed by equilibration to hydroxy ketone **3** and ring closure to spirolactone **4**, even before the ARF reaction was attempted. An indication of initial carbonyl participation was provided[8a] by the formation of fused furan **5** on bromination of 2-allyl-2-carboethoxycycloheptanone[8b] **1c**, while the use of excess bromine led to the isolation of spirolactone **6** (Scheme 2).

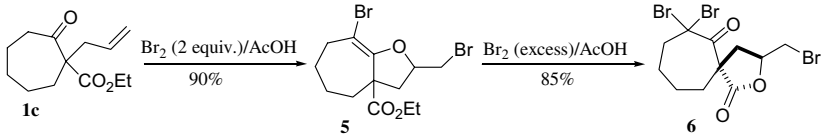
It occurred to us that since halogenation of allylcycloalkanones **1** affords the possibility of initially generating hemiketals rather than γ-hydroxy ketones, it may still be possible to divert any unstable hemiketals **2** to undergo ring expansion via radical fragmentation. Indeed, photochemical reaction of allylcyclopentanone[9] **1a** with iodine in the presence of DIB and 1 equiv of water, to facilitate hemiketal formation from an initially formed α-halo ether, led to isolation of the 8-membered ring lactone **7a**. Thus, **1a** leads directly to spirolactone[10] **4a** in high yield by reaction with a halogen, while in the presence of DIB–$H_2O$–hν the reaction can be diverted to produce 3-atom ring enlargement to lactone[11] **7a**. Similar results were obtained for ring expansion of 6- to 9-membered rings and 7- to 10-membered rings (Scheme 3). Here too hemiketals, formed via carbonyl participation, are likely intermediates. In fact, iodination of 8-membered ring **1d** under ARF conditions gave a complex mixture but the reaction could be optimized by using 2 equiv of iodine to afford a furan derivative **9** (apparently resulting from a hemiketal) and 11-membered unsaturated lactone **8** (Scheme 3).

In the presence of 3.5 equiv of iodine, 3-atom ring enlarged lactones **7a**–**c** were isolated as two separable stereoisomers, apparently due to trapping of the incipient radical either *cis* or *trans* to the $CH_2$–I side chain, while only 2 equiv of iodine (vide supra) furnished the olefinic lactone **8** as a single isomer.

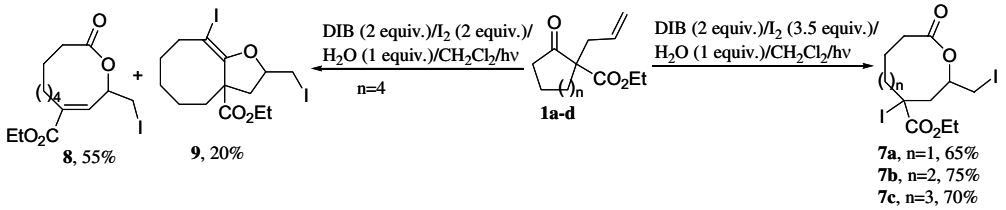
Remarkably, spirolactones **4** were isolated as single isomers in high yields. This indicates that the relative stereochemistry between the ester and the $CH_2$–I side chain is the same in precursor hemiketals **2** as in spirolactones **4** and therefore the two stereoisomers in hemi-




**Scheme 1.**




**Scheme 2.**




**Scheme 3.**

ketal **2b** result from the configuration of the hemiketal OH.

The structures of spirolactones **4** as well as of the ring enlarged lactones **7** and **8** were elucidated by $^1$H NMR, $^{13}$C NMR, DEPT, and Cosy experiments as well as MS. For instance, spirolactone[10] **4a** showed keto as well as ester carbonyls in the IR and $^{13}$C NMR; $^1$H NMR indicated the absence of a carboethoxy ethyl group and DEPT displayed five $CH_2$'s and one CH. The ring enlarged lactone[11] **7a** indicated the presence of two ester groups in the $^{13}$C NMR and IR, while DEPT showed six $CH_2$'s, one CH bonded to O and one Me.

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## References and notes

1. See for instance (a) Gerlach, H.; Kunzler, P.; Oertle, K. *Helv. Chim. Acta* **1978**, *61*, 1226; (b) Malherbe, R.; Rist, G.; Bellus, D. *J. Org. Chem.* **1983**, *48*, 860; (c) Balog, A.; Meng, D.; Kamenecka, T.; Bertinato, P.; Su, D. S.; Sorensen, E. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1996**, *35*, 2801; (d) Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem., Int. Ed.* **1997**, *36*, 166.
2. (a) Paquette, L. A.; Bibart, R. T.; Seekamp, C. K.; Kahane, A. L. *Org. Lett.* **2001**, *3*, 4039; (b) Paquette, L. A.; Seekamp, C. K.; Kahane, A. L.; Hlmey, D. G.; Gallucci, J. *J. Org. Chem.* **2004**, *69*, 7442; (c) Hamelin, O.; Wang, Y.; Depres, J. P.; Greene, A. E. *Angew. Chem.* **2000**, *39*, 4314; (d) Brocksom, T. J.; Coelho, F.; Depres, J. P.; Greene, A. E.; Freire de Lama, M. E.; Hamelin, O.; Hartmann, B.; Kanazawa, A. M.; Wang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 15313.
3. Ramesh, N. G.; Hassner, A. *Eur. J. Org. Chem.* **2005**, 1892.
4. (a) Gonzalez, C. C.; Leon, E. I.; Riesco-Fagundo, C.; Suarez, E. *Tetrahedron Lett.* **2003**, *44*, 6347; (b) Gonzalez, C. C.; Kennedy, A. R.; Leon, E. I.; Riesco-Fagundo, C.; Suarez, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 2326.
5. Fraga, C. A. M.; Teixeira, L. H. P.; Menezes, C. M. S.; Sant'Anna, C. M. R.; Ramos, M. C. K. V.; de Aquino Neto, F. R.; Barreiro, E. J. *Tetrahedron* **2004**, *60*, 2745.
6. (a) Hatcher, M. A.; Brostnik, K.; Posner, G. H. *Tetrahedron Lett.* **2003**, *44*, 5407; (b) Posner, G. H.; Hatcher, M. A.; Maio, W. A. *Org. Lett.* **2005**, *7*, 4301.
7. Cole, B. M.; Han, L.; Snider, B. B. *J. Org. Chem.* **1996**, *61*, 7832.
8. (a) Spirolactone **4b** was obtained in 87% yield from the reaction of a mixture of **2b** and **1b** with iodine in the presence of water for 48 h; (b) Moloney, M. G.; Nettleton, E.; Smithies, K. *Tetrahedron Lett.* **2002**, *43*, 907.
9. Chitkul, B.; Pinyopronpanich, Y.; Thebtaranonth, C.; Thebtaranonth, Y.; Taylor, W. C. *Tetrahedron Lett.* **1994**, *35*, 1099.
10. Typical experimental procedure for spiro ketolactones **4**. 3-Iodomethyl-2-oxaspiro[4.4]nonane-1,6-dione **4a**. A solution of 1-allyl-2-oxocyclopentane carboxylic acid ethyl ester **1a** (0.40 g, 2 mmol) and iodine (1 g, 4 mmol) in chloroform (50 mL) was stirred at room temperature for 15 h. Then the mixture was washed with 5% sodium bisulfite ($3 \times 30$ mL), water ($3 \times 20$ mL) and dried ($Na_2SO_4$). After removal of the solvent, the crude material was purified by column chromatography on silica [eluant: ethyl acetate:*n*-hexane (15:85)] to afford **4a** as a colorless solid, mp 42–43 °C; yield (0.45 g, 75%). IR (KBr) $\nu_{max}$: 1734, 1751 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) $\delta_H$: 4.70–4.67 (1H, m, C*H*–O), 3.40 (1H, dd, *J* 11, 4 Hz, C$H_2$I), 3.30 (1H, dd, *J* 11, 7 Hz, C$H_2$I), 2.66 (1H, dd, *J* 13, 4 Hz), 2.59–2.55 (1H, m), 2.48–2.42 (1H, m), 2.37–2.27 (2H, m), 2.00–1.91 (2H, m), 1.85 (1H, dd, *J* 13, 8 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta_C$: 213.8 (C$^6$=O), 174.0 (O–C$^1$=O), 76.2 (C$^3$H–O), 58.7 (C$^5$), 39.3 ($CH_2$), 37.4 ($CH_2$), 33.9 ($CH_2$), 19.8 ($CH_2$), 7.3 ($CH_2$I). HRMS (CI, $CH_4$): *m*/*z* calcd for $C_9H_{11}IO_3$, 293.975; found ($M^+$) 293.975 (30), ($M^+$+1) 294.984 (46), ($M^+$+1–$CO_2$) 238.965 (60), ($M^+$+1–HI) 167.080 (92), ($M^+$+1–HI–$H_2O$) 149.065 (100).
11. Typical experimental procedure for ring-enlarged lactone **7**: 4-Iodo-2-iodomethyl-8-oxo-oxocane-4-carboxylic acid ethyl ester **7a**. A solution of 1-allyl-2-oxocyclopentane carboxylic acid ethyl ester **1a** (0.59 g, 3 mmol), diacetoxy iodobenzene (DIB) (1.9 g, 6 mmol), iodine (2.6 g, 10.5 mmol) and water (0.06 mL, 3 mmol) in dichloromethane (150 mL) was irradiated using a 100 W tungsten filament lamp for 2 h at room temperature. The mixture was then washed with 5% sodium bisulfite ($3 \times 50$ mL), water ($3 \times 30$ mL) and dried ($Na_2SO_4$). After removal of the solvent, the crude material was purified by silica gel column chromatography [eluant: ethyl acetate:*n*-hexane (1:9)] to afford **7a** as a pair of isomers in a 1:2 ratio. Minor isomer: colorless oil; yield 0.30 g, 23%; IR (Neat) $\nu_{max}$: 1736 cm$^{-1}$ (br); $^1$H NMR (600 MHz, $CDCl_3$) $\delta_H$: 4.68 (1H, tdd, *J* 7, 9, 2 Hz, C*H*–O), 4.22 (2H, q, *J* 7 Hz, $CH_3CH_2$–O), 3.44 (1H, dd, *J* 10, 7 Hz, C$H_2$I), 3.35 (1H, dd, *J* 10, 7 Hz, C$H_2$I), 2.88 (1H, dd, *J* 16, 2 Hz, C$^3H_2$), 2.70 (1H, ddd, *J* 12, 6, 2 Hz), 2.66–2.61 (1H, m), 2.36 (1H, ddd, *J* 10, 5, 4 Hz), 2.27 (1H, dd, *J* 16, 9 Hz, C$^3H_2$), 1.98–1.90 (2H, m), 1.86–1.83 (1H, m), 1.27 (3H, t, *J* 7 Hz, C$H_3$CH$_2$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta_C$: 174.5 (O–C$^8$=O), 172.2 (O–C=O), 79.1 (C$^2$H–O), 62.9 (CH$_2$O), 46.9 (C$^4$), 45.9 (CH$_2$), 37.0 (CH$_2$), 32.7 (CH$_2$), 27.5 (CH$_2$), 13.7 (CH$_3$), 6.8 (CH$_2$I). HRMS (CI, $CH_4$): *m*/*z* calcd for $C_9H_{16}IO_3$, 465.914; found ($M^+$+1) 466.923 (11), ($M^+$+1–HI) 339.001 (21), ($M^+$+1–HI–EtOH) 292.958 (100). Major isomer: colorless oil; yield 0.56 g, 42%; IR (Neat) $\nu_{max}$: 1730 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) $\delta_H$: 4.45 (1H, m, C*H*–O), 4.32 (2H, q, *J* 7 Hz, $CH_3CH_2$–O), 3.47 (1H, dd, *J* 10, 7 Hz, C$H_2$I), 3.38 (1H, dd, *J* 10, 7 Hz, C$H_2$I), 3.22 (1H, d, *J* 15 Hz, C$^3H_2$), 2.74 (1H, ddd, *J* 12, 6, 4 Hz), 2.68 (1H, dd, *J* 15, 10 Hz), 2.62 (1H, ddd, *J* 16, 12, 3 Hz, C$H_2$), 2.44–2.39 (1H, m), 2.37–2.33 (1H, m), 2.15–2.10 (1H, m), 1.85–1.79 (1H, m), 1.35 (3H, t, *J* 7 Hz, C$H_3$CH$_2$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta_C$: 174.5 (O–C$^8$=O), 172.2 (O–C=O), 78.8 (C$^2$H–O), 62.6 (CH$_2$O), 48.9 (CH$_2$), 40.8 (C$^4$), 40.3 (CH$_2$), 32.3 (CH$_2$), 24.5 (CH$_2$), 13.9 (CH$_3$), 6.6 (CH$_2$I). HRMS (CI, $CH_4$): *m*/*z* calcd for $C_9H_{16}IO_3$ 465.914; found ($M^+$+1) 466.922, ($M^+$+1–HI) 338.900 (100), ($M^+$+1–HI–EtOH) 292.870 (96).