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Asymmetric Synthesis and Fragmentation Reactions of 2-Alkyl- and 2,4-Dialkyl-3-iodo-1-oxocyclohexan-2,4-carbolactones. Single Enantiomer Preparation of $\Delta^{\alpha,\beta}$-Butenolides, 2-Alkyl-4-hydroxy-2-cyclohexen-1-ones and Butyrolactones.†

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Abstract: Fragmentation reactions of keto iodolactones **4** provide access to butenolides **5**, 2-alkyl-4-hydroxy-2-cyclohexen-1-ones **6**, and butyrolactones **9**. $\Delta^{\alpha,\beta}$-Butenolides **5e** and **5f** were converted to heterocycles **14-16** by way of intramolecular cycloaddition reactions.

Keywords: Asymmetric synthesis; Cycloadditions; Enolates; Fragmentation reactions

$\Delta^{\alpha,\beta}$-Butenolides have been used as intermediates for the synthesis of a wide range of natural products, including the macrolide antibiotics.[1] Although many methods for the construction of butenolides are available, only a few provide access to 3,5-disubstitution and 3,5,5-trisubstitution.[2] It is noteworthy that 3,5-disubstituted butenolides are structural components of the Annonaceous acetogenins,[3] the sesquiterpene dilactones elephantin and elephantopin,[4] furanocyclic diterpenes such as pseudopterolide,[5] the marine alkaloids aceropterine and pseudopterane,[6] and certain stemona alkaloids.[7] Herein we describe chemistry that provides 3,5-disubstituted and 3,5,5-trisubstituted butenolides as single enantiomers by fragmentation of 2-alkyl- and 2,4-dialkyl-3-iodo-1-oxocyclohexan-2,4-carbolactones.

The preparation of 2-alkyl-3-iodo-1-oxocyclohexan-2,4-carbolactones **4a-h** is shown in Scheme 1. Birch reductions of **1a-d** to give the chiral amide enolates[7] and alkylations with methyl iodide, 1-chloro-3-iodopropane, 1-chloro-4-iodobutane, 2-(2'-bromophenyl)-1-iodo-ethane or ethyl iodide gave the corresponding 1,4-cyclohexadienes **2a-h** as single diastereomers. Enol ether hydrolyses gave the β,γ-enones **3a-h** and iodolactonizations[7d,e] afforded the enantiomerically pure 2-alkyl-3-iodo-1-oxocyclohexan-2,4-carbolactones **4a-h**.[8a]

Treatment of **4a** with LiOH in THF and H_2O (1:1) gave a mixture of butenolide carboxylic acid **5a** and 2-methyl-4-hydroxy-2-cyclohexen-1-one **6a**; separation by flash chromatography on silica gel (hexane, ethyl acetate) gave **5a** in 15% yield and **6a** (72%). Higher proportions of THF in the fragmentation reaction mixture resulted in the formation of more of the butenolide carboxylic acid **5a** at the expense of **6a**: a 5:1 mixture of THF and H_2O gave a 45:55 mixture of **5a** and **6a**; a 10:1 mixture of THF and H_2O gave a 59:41 mixture of **5a** and **6a** (^{1}H NMR analysis). Other bases ($NaHCO_3$, KOH, $Ba(OH)_2$ and CsOH) were examined but they did not appear to offer any advantages over LiOH. Of more importance with regard

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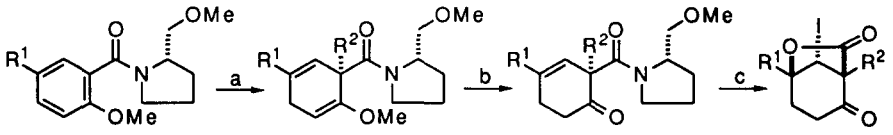
Scheme I



1a, R^1 = H
b, R^1 = Me
c, R^1 = CH_2Ph
d, R^1 = *o*- $MeOC_6H_4$

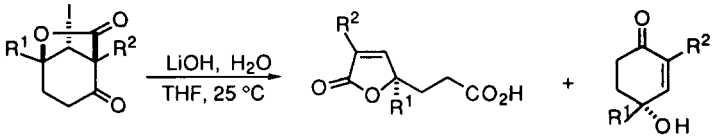
2a, R^1 = H; R^2 = Me, 95%
b, R^1 = H; R^2 = $(CH_2)_3Cl$, 93%
c, R^1 = H; R^2 = $(CH_2)_4Cl$, 89%
d, R^1 = H; R^2 = *o*-$BrC_6H_5C_2H_4$, 89%
e, R^1 = Me; R^2 = Et , 100%
f, R^1 = CH_2Ph; R^2 = Et, 93%
g, R^1 = Me; R^2 = Me, 100%
h, R^1 = *o*-$MeOC_6H_4$; R^2 = Me, 78%

3a, 95%
b, 89%
c, 92%
d, 97%
e, 98%
f, 96%
g, 100%
h, 93%

4a, 90%
b, 75%
c, 85%
d, 82%
e, 80%
f, 81%
g, 79%
h, 98%

Reaction conditions: (a) K, NH_3, THF, t-BuOH (1 equiv); piperylene; R^2X; (b) 6 N HCl, MeOH, 25 °C; (c) I_2, THF, H_2O

to the degree of partitioning between fragmentation pathways is the relative size of the substituent R^2 in **4** as noted for fragmentations of **4b** and **4d**.[8b] Along with the relative size of the substituent at C(2), the presence of substitution at C(4) also has a dramatic effect on product distribution. Fragmentations of **4e**, **4f** and **4h** provide the corresponding butenolide carboxylic acids in excellent yields.



4a, R^1 = H; R^2 = Me
b, R^1 = H; R^2 = $(CH_2)_3Cl$
d, R^1 = H; R^2 = *o*-$BrC_6H_5C_2H_4$
e, R^1 = Me; R^2 = Et
f, R^1 = CH_2Ph; R^2 = Et
g, R^1 = Me; R^2 = Me
h, R^1 = *o*-$MeOC_6H_4$; R^2 = Me

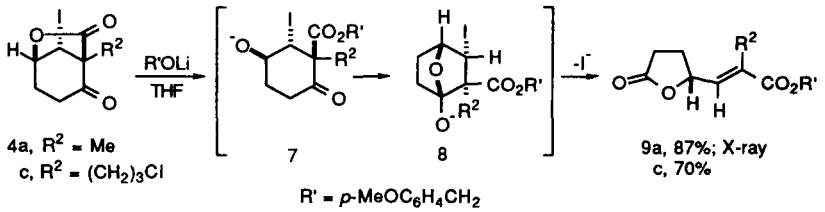
5a, 15%
b, 68%
d, 74%
e, 88%
f, 81%
g, 38%
h, 85%

6a, 72%
b, 15%
d, 7%
e, 8%
f, 2%
g, 47%
h, ---

Conversions of **4** to the butenolide carboxylic acids **5** presumably involve hydroxide-induced cleavage of the cyclohexanone ring to give a lactone enolate; β-elimination of iodide from the enolate would give **5**. The iodide substituent in **4** is axial and, therefore, not antiperiplanar to the C(1)-C(2) bond of the cyclohexanone ring, suggesting that this Grob-type fragmentation probably is not concerted.[9] On the other hand, 4-hydroxycyclohexenones **6** may be formed by a concerted fragmentation-elimination resulting from addition of hydroxide to the axial lactone carbonyl group of **4**. The trend in product distribution for fragmentations of **4a-d** and **4e** vs **4g** suggests that addition to the lactone carbonyl group is retarded as the size of the group R^2 increases.

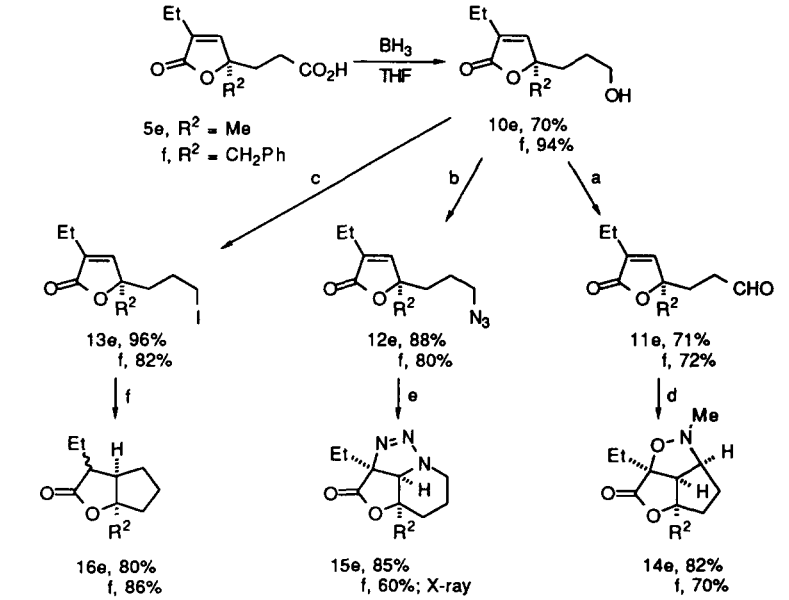
There is a remarkable change in product distribution when lithium alkoxides are used in place of aqueous alkali metal hydroxides (Scheme 2). With *p*-$MeOC_6H_4CH_2OLi$ (generated from the reaction of the

Scheme 2



alcohol with BuLi) in anhydrous THF, lactone ring opening occurs to give alkoxide **7**, which, instead of converting to an epoxide,[7e] undergoes transannular addition to the C(1) carbonyl group to give **8**; fragmentation of **8** gives the chiral butyrolactone **9**. Analytical studies have demonstrated that **5**, **6**, and **9** are formed without racemization.[10] It is noteworthy that the X-ray determined molecular structure for **9a** shows that the C-H bond at the stereogenic center is orthogonal to the p-orbitals of the α,β-unsaturated ester. Thus, epimerization of **9a** does not occur even though alkoxide bases are required to convert **4a** to **9a**.

Scheme 3



Reaction conditions: (a) PCC, SiO_2, CH_2Cl_2; (b) MsCl, Et_3N, CH_2Cl_2; NaN_3, DMF; (c) Ph_3P, imidazole, I_2; (d) MeNHOH, THF, 25 °C; (e) benzene, reflux; (f) AIBN, Bu_3SnH, PhH, reflux.

Butenolides obtained by way of the asymmetric Birch reduction-alkylation protocol have outstanding potential for intramolecular carbocyclic and heterocyclic ring constructions. Reduction of the carboxylic acid group in **5e** and **5f** with BH_3•THF gives the 5-(3'-hydroxypropyl)butenolides **10e** and **10f**. Oxidations of **10e** and **10f** with PCC give the corresponding carboxaldehyde derivatives **11e** and **11f**. The intramolecular radical-olefin cyclizations **13** → **16**, the intramolecular azide-olefin cycloadditions **12** → **15** and the intramolecular nitrone-olefin cycloadditions **11** → **14** provide useful fused ring systems for further

synthetic transformations. The application of chemistry described in this note to asymmetric organic synthesis currently is under investigation.

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8. (a) New compounds were characterized by ^{1}H and ^{13}C NMR, IR, low resolution MS and combustion analyses. (b) Yields for **5b-5h** and **6b-6h** were determined from fragmentations of **4b-4h** in 5:1 mixtures of THF and H_2O.
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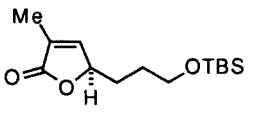
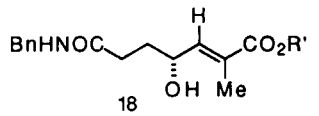
10. The enantiomeric purity of **6a** was determined by chiral HPLC analysis: Chiralcel OJ column, 25:1 hexanes/2-propanol, 0.55 mL/min, λ = 221 nm, t_R = 40.8 min (major enantiomer), t_R = 44.5 (minor) >99% ee. The enantiomeric purity of **5a** was determined by chiral HPLC analysis of the silyl ether derivative **17**: Chiralcel OJ column, 99:1 hexanes/2-propanol, 0.35 mL/min, λ = 220 nm, t_R = 24.0 min (minor enantiomer), t_R = 28.0 min (major) >96% ee. The enantiomeric purity of butyrolactone **9a** was determined by ^{19}F NMR analysis of the Mosher ester of **18** (CF_3CO_2H reference) δ 4.33 (major diastereomer), 4.03 (minor) >98% ee; corrected for the 98% ee of the Mosher reagent (S)-MTAPCl. Racemic samples of **5a**, **6a** and **9a** were prepared from the pyrrolidine amide corresponding to **1** and were used as controls for the analytical studies.



17



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