Pergamon

Tetrahedron Letters 39 (1998) 4203–4206

TETRAHEDRON LETTERS

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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Received 9 March 1998; revised 27 March 1998; accepted 30 March 1998

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.

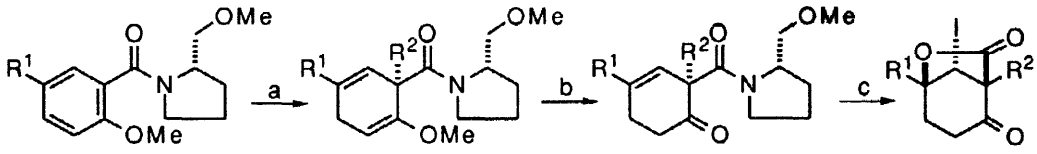
The preparation of 2-alkyl-3-iodo-1-oxocyclohexan-2,4-carbolactones **4a-h** is shown in Scheme 1. Birch reductions of **1a-d** to give the chiral amide enolates[7] and alkylations with methyl iodide, 1-chloro-3-iodopropane, 1-chloro-4-iodobutane, 2-(2'-bromophenyl)-1-iodo-ethane or ethyl iodide gave 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** (^1H 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

†This paper is dedicated to Professor Richard H. Schlessinger, teacher and friend, who died on Dec. 11, 1997.

0040-4039/98/$19.00
PII: S0040-4039(98)00785-0

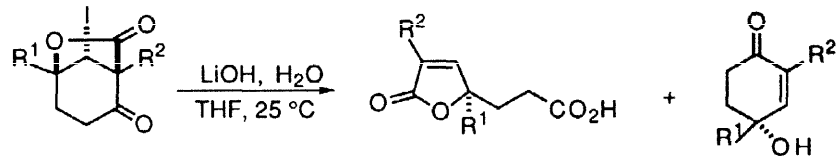
Scheme I



1a, R^1 = H	2a, R^1 = H; R^2 = Me, 95%	3a, 95%	4a, 90%
b, R^1 = Me	b, R^1 = H; R^2 = $(CH_2)_3Cl$, 93%	b, 89%	b, 75%
c, R^1 = CH_2Ph	c, R^1 = H; R^2 = $(CH_2)_4Cl$, 89%	c, 92%	c, 85%
d, R^1 = *o*- $MeOC_6H_4$	d, R^1 = H; R^2 = *o*-$BrC_6H_5C_2H_4$, 89%	d, 97%	d, 82%
	e, R^1 = Me; R^2 = Et , 100%	e, 98%	e, 80%
	f, R^1 = CH_2Ph; R^2 = Et, 93%	f, 96%	f, 81%
	g, R^1 = Me; R^2 = Me, 100%	g, 100%	g, 79%
	h, R^1 = *o*-$MeOC_6H_4$; R^2 = Me, 76%	h, 93%	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.

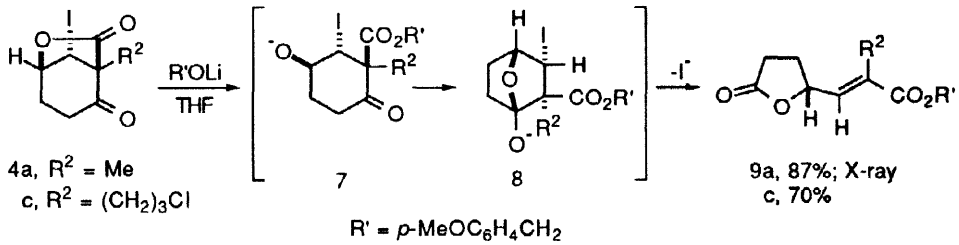


4a, R^1 = H; R^2 = Me	5a, 15%	6a, 72%
b, R^1 = H; R^2 = $(CH_2)_3Cl$	b, 68%	b, 15%
d, R^1 = H; R^2 = *o*-$BrC_6H_5C_2H_4$	d, 74%	d, 7%
e, R^1 = Me; R^2 = Et	e, 88%	e, 8%
f, R^1 = CH_2Ph; R^2 = Et	f, 81%	f, 2%
g, R^1 = Me; R^2 = Me	g, 38%	g, 47%
h, R^1 = *o*-$MeOC_6H_4$; R^2 = Me	h, 85%	h, ---

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.

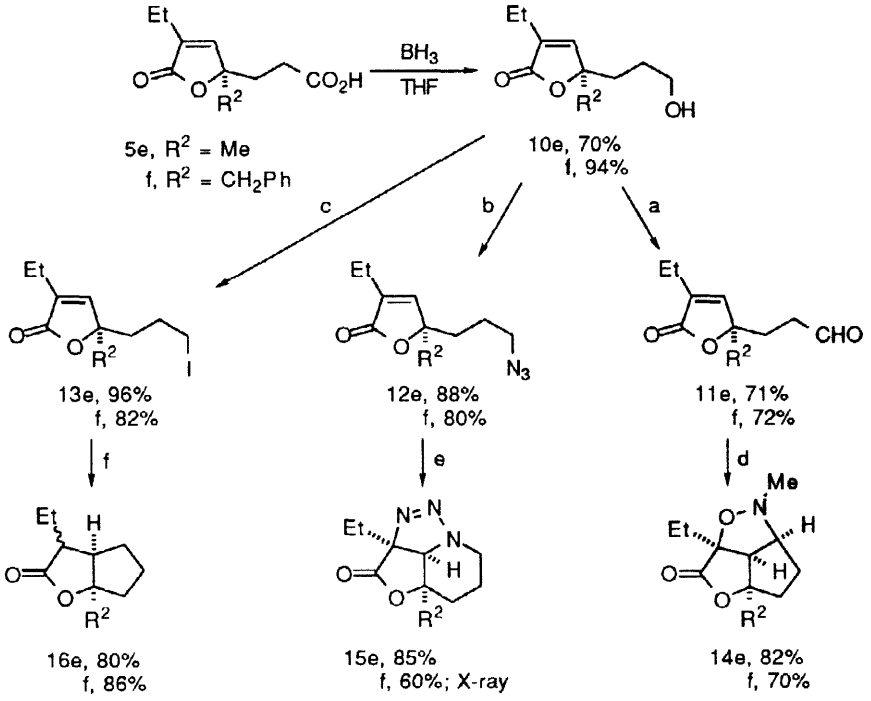
There is a remarkable change in product distribution when lithium alkoxides are used in place of aqueous alkali metal hydroxides (Scheme 2). With *p*-$MeOC_6H_4CH_2OLi$ (generated from the reaction of the

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.

Acknowledgment. This work was supported by the National Institutes of Health (GM 26568). We thank Dr. Fook S. Tham for the X-ray structure determinations.

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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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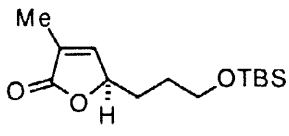
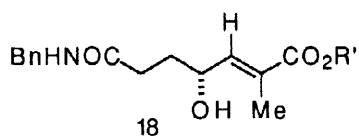
10. The enantiomeric purity of **6a** was determined by chiral HPLC analysis: Chiralcel OJ column, 25:1 hexanes/2-propanol, 0.55 mL/min, λ = 221 nm, t_R = 40.8 min (major enantiomer), t_R = 44.5 (minor) >99% ee. The enantiomeric purity of **5a** was determined by chiral HPLC analysis of the silyl ether 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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