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Asymmetric Synthesis of 5-Substituted γ -Lactones and Butenolides via Nucleophilic Additions to Oxycarbenium Ions Derived from 5(*R*)-(Menthylloxy)-4(*R*)-(phenylsulfanyl)-2(3*H*)-dihydrofuranone

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Optically active 5-alkyl-substituted butenolides and γ -lactones are attractive building blocks in natural product synthesis¹ and comprise structural moieties frequently present in, e.g., insect pheromones,² cardenolides,³ lignans, and flavor components.⁴ Efficient and stereoselective synthetic routes to these products in enantiomerically pure form are highly desirable.⁵ As part of our explorative studies toward the use of 5(*R*)-(menthylloxy)-2(5*H*)-furanone (**1**) as a chiral synthon,^{6,7} the enantioselective synthesis of a number of naturally occurring lignans has been reported.⁸

5(*R*)-(Menthylloxy)-2(5*H*)-furanone (**1**) reacts with thiophenol and a catalytic amount of triethylamine to give stereospecifically and in excellent yield the trans addition product **2** (Scheme 1), which features an attractive functional group arrangement to generate α -sulfanyl oxycarbenium ion **3**. Here we report the fast and highly stereoselective transformations of **2** to 5-alkyl-substituted 4-(phenylsulfanyl)-2(3*H*)-dihydrofuranones **4** or 4-(menthylloxy)-3-(phenylsulfanyl) carboxylic acids **5**, which are precursors for butenolides and γ -lactones.

Various methods for C–C bond formation via Lewis acid-mediated reactions of acetals with nucleophiles have been developed.⁹ As demonstrated by a number of groups,¹⁰ there is a mechanistic divergence between S_N2 -

Figure 1.

and S_N1 -type processes. It has been shown that Lewis acid-mediated additions of silylated nucleophiles to α - and β -sulfanyl-substituted aldehydes proceed with excellent diastereoselectivities.¹¹ Furthermore, reactions of α -sulfanyl acetals with carbon nucleophiles have been studied by Saigo and co-workers.¹² In furanone **2**, an α -sulfanyl-substituted, mixed acyloxy–alkoxy acetal moiety is present, and upon treatment with a Lewis acid it is observed that the acyloxy acetal bond is always broken¹³ and this reaction path leaves only two likely intermediates (Figure 1). The stereoselectivity of these reactions can be rationalized by the Felkin–Ahn model, and conformers **A** and **B** lead to anti and syn adducts, respectively. Conformer **A** is preferred, and in most cases the anti adduct is the only detectable diastereomer.

When 4(*R*)-(phenylsulfanyl)-substituted furanone **2** is treated at -70°C with 1–2 equiv of TiCl_4 in the presence of a variety of nucleophiles such as allylsilanes, silyl enol ethers, or diorganozinc reagents a very fast reaction occurs. After a reaction time of 5 min and subsequent aqueous workup, β , γ -substituted acids **5** are isolated in 56–72% yield and in most cases with a diastereomeric ratio $>98:2$ according to ^1H and ^{13}C NMR (Scheme 2, path A, Table 1, entries 2, 4, 6, 8, and 12). In addition to the acids **5** small amounts of lactones **4** (5–20%) are also found in the crude product, but these could be easily separated.

When the addition of nucleophiles **9–16** is performed in the presence of 2 equiv of TiCl_4 for 1 min at ambient temperature, followed by aqueous workup, the lactones **4** are obtained. In a few cases small amounts of the acids **5** ($\leq 10\%$) are also formed. Apparently, the intermediate **6** is activated by the excess of Lewis acid present, and upon addition of water hydrolysis to the hydroxy acid **8**

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Scheme 2

Table 1. Additions of Nucleophiles to Oxycarbenium Ions Derived from **2**

Entry	Nucleophile	T ($^\circ\text{C}$)	time (min)	Product (R)	(ratio a)	Yield b %	trans : cis c (anti : syn c)
1		23	1	4a/5a	(>9 : 1)	50	92 : 8
2		-70	5	5a/4a	(8 : 2)	56	9 : 1
3		23	1	4b/5b	(>9 : 1)	65	>98 : 2
4		-70	5	5b/4b	(8 : 2)	59	>98 : 2
5		23	1	4c/5c	(>9 : 1)	66	>98 : 2
6		-70	5	5c/4c	(9 : 1)	72	>98 : 2
7		23	1	4d/5d	(>9 : 1)	74	>98 : 2 ^d
8		-70	5	5d/4d	(8 : 2)	52	>98 : 2 ^d
9		23	1	4e/5e	(>9 : 1)	57	>98 : 2 ^d
10		23	1	4f/5f	(>9 : 1)	74	53 : 47 ^d
11		23	2	4g/5g	(>9 : 1)	56	9 : 1
12		-70	5	5g/4g	(9 : 1)	57	>98 : 2
13		23	5	4h/5h	(>9 : 1)	53	>98 : 2

^aRatio determined by ^1H NMR. ^bIsolated yield of the major isomer.

^cRatio determined by ^1H and ^{13}C NMR of the crude product. ^dDiastereomeric ratio of the exocyclic stereogenic center was in the order of 6 : 4 in all four cases (entry 7-10).

followed by lactonization takes place (Scheme 2, path B). A key feature of the second Lewis acid-mediated step is the stereoselective cleavage of the auxiliary group assisted by the α -sulfanyl functionality. Except for **4f**, trans lactones **4** are formed as the major, or in most cases only detectable, diastereomer. Even in the few cases (entries 1 and 11, Table 1) where small amounts of cis lactones **4** were obtained, these could be separated by simple column chromatography using silica gel.

Single crystal X-ray analysis of **4b** confirmed the trans relationship of the substituents at C_4 and C_5 .²¹ The trans configuration for the products **4a-e,g,h** has been assigned by comparison on the basis of ^1H NMR coupling constants and on the expected mechanistic similarity in this reaction for all nucleophiles used.¹⁴

The enantiomerically pure 5(*S*)-alkyl-4(*R*)-(phenylsulfanyl)-2(3*H*)-dihydrofuranones **4** are excellent precursors for 5-alkyl-substituted butanolides or butanolides,^{15,16} whereas the phenylsulfanyl substituent allows a number

Scheme 3

Scheme 4

of synthetically useful transformations. Reductive desulfurization of **4** could best be performed with Bu_3SnH /AIBN and provided enantiomerically pure 5(*S*)-alkyl-2(3*H*)-dihydrofuranones **17** (Scheme 3). The flavor components and insect pheromones⁴ 5(*S*)-ethyl-2(3*H*)-dihydrofuranone (**17g**) [85% yield, $[\alpha]_D = -50$ (c 1, MeOH) (lit.¹⁷ $[\alpha]_D = -53.2$ (c 1, MeOH))] and 5(*S*)-octyl-2(3*H*)-dihydrofuranone (**17h**) [66% yield, $[\alpha]_D = -35$ (c 0.48, MeOH) (lit.¹⁷ $[\alpha]_D = -36.8$ (c 0.3, MeOH))] were obtained using this procedure.

Alternatively, 5(*S*)-alkyl-2(5*H*)-furanones **19** are accessible via the sulfones **18** (Scheme 4). Oxidation of **4** with Oxone¹⁸ and subsequent elimination with basic alumina in CH_2Cl_2 gave the corresponding 5(*S*)-alkyl-2(5*H*)-furanones **19** in good yields.¹⁹ For example, 5(*S*)-ethyl-2(5*H*)-furanone (**19g**) [95% overall yield, $[\alpha]_D = +105$ (c 4.1, CH_2Cl_2) (lit.²⁰ for 5(*R*)-**19g** $[\alpha]_D = -97.6$ (c 2.08, CH_2Cl_2))] and 5(*S*)-(1-prop-2-enyl)-2(5*H*)-furanone (**19a**) (72% overall yield, $[\alpha]_D = +105$ (c 1.08, MeOH)) were obtained using this procedure.

In conclusion, we have demonstrated that **2** is a valuable synthon for the synthesis of 3,4-disubstituted carboxylic acids, 5-substituted butanolides, and γ -lactones in enantiomerically pure form.

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Supporting Information Available: Experimental procedures for the Lewis acid mediated additions and spectroscopic data for compounds **4a-h** and **5a,b,c,d,g**. (5 pages).

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