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Enantioselective Synthesis of γ– and δ–Lactones

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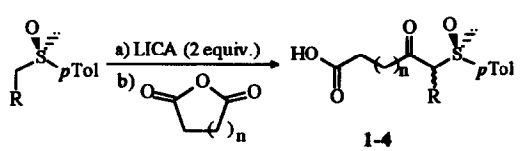
Abstract. The synthesis of enantiomerically pure sulfinyl oxoacids $HO_2CCH_2(CH_2)_nCOCH(R)SOTol$ (n=1 and 2, R=H, CH_3), and their stereoselective reduction with DIBAL catalysed by $ZnBr_2$ are reported. The resulting hydroxysulfoxides were cyclized in situ under acidic conditions yielding high yields of the corresponding γ– and δ–lactones in high enantiomeric purity.

Homochiral γ– and δ–lactone skeletons[1] are present in a wide variety of natural products and used as chiral building blocks.[2] Hence many papers concerning their enantioselective synthesis have appeared in the literature. Out of the different possible precursors[3], optically pure hydroxyesters,[4] prepared both by chemical and enzymatic procedures, have been the most frequently used in recent years. The use of the hydroxyacids, instead of the corresponding esters, as starting products would be advantageous from the lower number of steps usually involved in the synthesis. However, the only two papers[5] where hydroxyacids have been used as lactone precursors have serious limitations that restrict their usefulness, such as the low stereoselectivity of the condensations of the α–sulfinylcarbanions with carbonyl compounds in one case[5a] and the low chemical yield (very common in enzymatic procedures, see ref. 4d and 4e) in the other.[5b]

The high *de* observed in the DIBAL reductions of β–ketosulfoxides,[6] led us to try the synthesis of γ–and δ–lactones in high enantiomeric purity, starting from ketoacids supporting a sulfinyl group as a chiral auxiliary. The key step would be the DIBAL reduction of β–ketosulfoxides also containing a free CO_2H group,[7] and its success would depend upon the influence of such a group on the stereochemical course of these reactions. In this paper we report a convenient synthesis of the sulfinyloxoacids (**1-4**), the conditions to carry out their highly stereoselective reduction into the corresponding hydroxyacids (**5-8**), and the way to obtain the sulfinyl lactones **9-12**.

The synthesis of the sulfinyloxoacids **1-4** (Scheme 1) was carried out by reaction of (*R*)-methyl (or ethyl) *p*-tolylsulfoxide with lithium *iso*-propyl cyclohexyl amide (LICA),[8] and further addition of succinic or glutaric anhydrides, following the procedure previously reported by us.[6b] Compounds **3** and **4** were obtained as a mixture of epimers at the new stereogenic centre (C-α). In this paper we have designated as **a** those diastereoisomers with the same configuration at C-α and sulfur whereas those exhibiting opposite configurations at both stereogenic centers (configuration at sulfur is *R* in all substrates) are named as **b**.

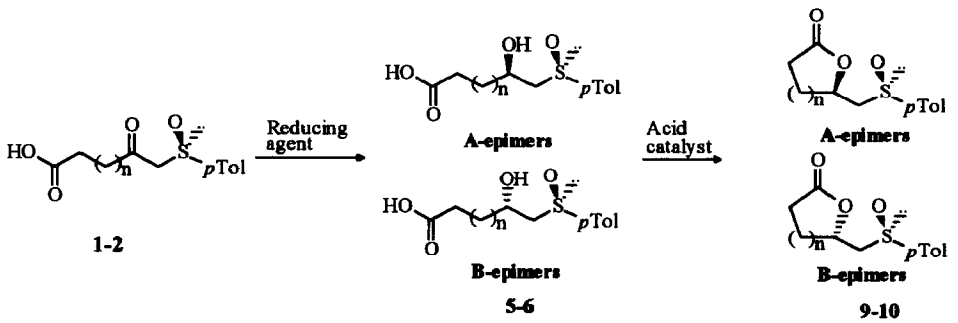


n	R	Compound	Yield(%)
1	H	1	85
2	H	2	96
1	Me	3a:3b(46:54)	88
2	Me	4a:4b(61:39)	95

Scheme 1

The high stereoselectivity observed in the DIBAL reductions of β–ketosulfoxides without substituents at C–α, which have been reported in the literature,[6a] .strongly contrasts with the poor results obtained from sulfinylketoacids **1** and **2**, which were obtained with low stereoselectivity, yielding diastereomeric mixtures **5A+5B** and **6A+6B**[9,10] respectively (**A** and **B** epimers are those exhibiting the same or the opposite

configuration at sulfur and hydroxylic carbon respectively (Scheme 2)).[10] Starting from the epimeric mixtures **3a+3b** and **4a+4b** (without previous separation), complex mixtures[10] containing the four possible hydroxyacids were formed (**7aA+7bA+7aB+7bB** and **8aA+8bA+8aB+8bB**)[9] (Scheme 3). Once purified, these mixtures were treated with *p*-toluenesulfonic acid, yielding the corresponding lactones whose proportions were similar to those of the starting hydroxyacids.[11]



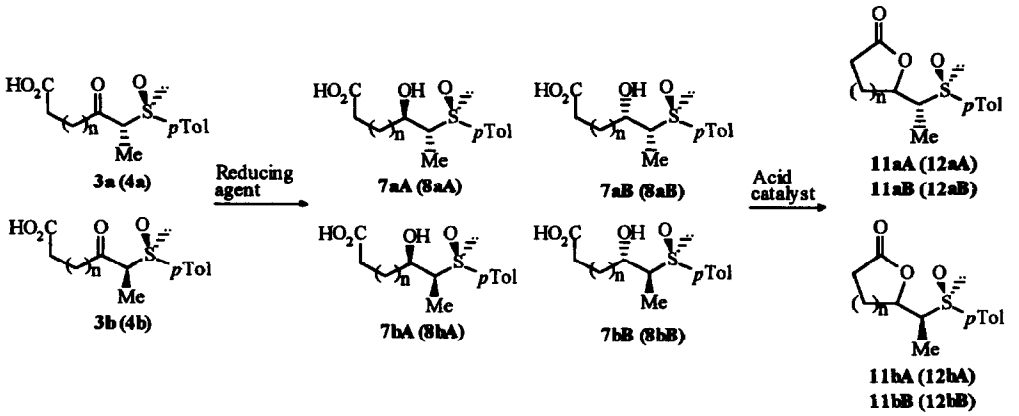
n	Ketoacid[a]	Hydroxyacids[b]	Lactones[b]	Catalyst[c][d]
1	1(DIBAL)	5A(30)+5B(70)	9A(30)+9B(70)	TsOH(74)
2	2(DIBAL)	6A(36)+6B(64)	10A(36)+10B(64)	TsOH(43)
1	1(DIBAL/$ZnBr_2$)	5A	9A	Amberlyst-15(74)
2	2(DIBAL/$ZnBr_2$)	6A	10A	TsOH(73)

[a] Reducing agent; [b] Relative proportion (%); [c] Lactonization catalyst; [d] Lactone overall yield (%) from oxoacid.

Scheme 2

However, when the sulfinyloxoacids **1-4** were chelated with $ZnBr_2$ and then reduced with DIBAL in THF at -78°C, the products were obtained with much greater stereoselectivity. The reactions of **1** or **2** with $ZnBr_2$ (1.6 eq) and DIBAL (3 eq.), followed by treatment of the crude reaction mixture with HCl (5%) to remove aluminum salts, only afforded one hydroxyacid (**5A** or **6A**, Scheme 2) and a small amount of its corresponding lactone (**9A** or **10A**). When these reaction crudes were treated with the resin Amberlyst-15 (the best for γ–lactones) or with *p*-toluenesulfonic acid (the best for δ–lactones), a total lactonization of the hydroxyacids was observed, resulting in the exclusive formation of compounds **9A** and **10A** in high yields (>70% from sulfinyl ketoacids **1** and **2** respectively).

The reduction of the mixtures **3a+3b** and **4a+4b** with DIBAL/$ZnBr_2$ afforded complex mixtures containing lactols in addition to the expected hydroxyacids. When the crude reaction mixtures were treated with NaOH (5%) instead HCl (5%) to remove the aluminum salts, the amount of lactols was strongly decreased, increasing the yields in hydroxysulfoxides (the best results were obtained by using 5 equiv. of both $ZnBr_2$ and DIBAL). After basic extraction of lactols, the nmr spectra of hydroxyacids showed signals corresponding to three diastereoisomers (Scheme 3). Starting from a 46:54 mixture of **3a** and **3b**, a mixture of diastereoisomeric hydroxysulfoxides **7aA** (44%), **7aB** (2%) and **7bA**(54%) (showing the highly diastereoselective reduction of the ketosulfoxides) was obtained. Similar results were observed starting from the mixture **4a+4b**, but with slightly less stereoselectivity (Scheme 3). The cyclization of these diastereomeric mixtures with TsOH or Amberlyst-15 afforded the corresponding lactones (**11** from **7** and **12** from **8**) in the same ratios than those existing in the mixtures of the starting hydroxysulfoxides. Desulfinylation with Raney Nickel (excess) of a 54:44:2 mixture of **11bA+11aA+11aB** afforded (-)-(*S*)–γ-caprolactone, whose optical rotation ($[\alpha]_D$=-49.6 (c=1.1, MeOH), Lit[3b] $[\alpha]_D$=-53.2 (c=1, MeOH)) evidenced a high optical purity (93% e.e.), which is in good agreement with the proportion of the starting lactones established from nmr spectroscopy This result strongly reinforces the configurational assignment of the sulfinyl hydroxyacids.[12]



Ketoacid[a]	Reduction[b]	Hydroxyacids[a]	Lactones[a]	Catalyst[c][d]
3a(46) +3b(54)	DIBAL	7aA(15)+7aB(48) +7bA(23)+7bB(14)	11aA(15)+11aB(48) +11bA(23)+11bB(14)	TsOH(17)
4a(61) +4b(39)	DIBAL	8aA(15)+8aB(63) +8bA(12)+8bB(10)	12aA(15)+12aB(63) +12bA(12)+12bB(10)	TsOH(48)
3a(46) +3b(54)	DIBAL/$ZnBr_2$	7aA(44)+7aB(2) +7bA(54)	11aA(44)+11aB(2) +11bA(54)	Amberlyst-15 (74)
4a(61) +4b(39)	DIBAL/$ZnBr_2$	8aA(55)+8aB(6) +8bA(39)	12aA(55)+12aB(6) +12bA(39)	TsOH(72)

[a] Relative proportion (%); [b] Reducing agent; [c] Lactonization catalyst; [d] Overall yield (%) from ketoacid.

Scheme 3

The results obtained in the presence of $ZnBr_2$ suggest that the stereochemical course of the DIBAL reductions of the sulfinylketoacids must be identical to those postulated for other β–ketosulfoxides without the $-CO_2H$ group,[6a,6c] which seems not to have any influence in these conditions. On the contrary, the low stereoselectivity observed in the absence of the Lewis acids, even in the case of compounds **1** and **2**, contrasts with the results observed for non functionalized β–ketosulfoxides[6a] and suggests that the $-CO_2H$ group may interfere with the stereochemical course postulated for DIBAL reduction of these substrates.[13]

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7. The stereoselective reduction of sulfinyl oxoesters is the key step of the sequence reported in reference 4a. The synthesis of the precursors, which exhibit β-ketosulfoxide structures containing an additional *tert*-butylester group (unencumbered esters react with the lithium carbanion of the methyl *p*-tolyl sulfoxide used in their preparation), required three steps. Moreover the hydrolysis of the *t*-butyl ester must be accomplished previous to the final lactonization. These facts illustrate the disadvantages of the sulfinyl ketoesters as starting products with respect to their corresponding acids.
8. Two equivalents of the α-sulfinyl carbanion (one of them can be easily recovered at the end of the reaction) are necessary to obtain high yields. Substantial decreases in the yields were observed by using bases different to LICA (LDA or $LiN[Me_3Si]_2$ because small amounts of the corresponding amide resulted of the attack on the anhydride).
9. Significant nmr parameters of the hydroxysulfoxides and the lactones:

Compound	δH_3	δH_2 (Δν)	$J_{2,3}$ [a]	δCH_3	Compound	δH_3	δH_2 (Δν)	$J_{2,3}$	δCH_3
5A	4.30-4.18	2.96 (54.6)	8.5/3.4 (6.5/5.8)	-	**9A**	4.70-4.58	3.16 (53.5)	5.7/6.5	-
5B	4.22	2.91-2.87	b	-	**9B**	5.10-5.00	3.10-3.00	b	-
6A	4.30-4.10	2.92 (56.1)	8.8/3.1 (6.5/5.6)	-	**10A**	4.65-4.45	3.13 (59.9)	5.2/6.6	-
6B	4.35-4.15	2.93 (47.1)	9.0/2.8	-	**10B**	5.10-4.90	2.95-2.80	b	-
7aA	4.15-4.00	2.99	7.1	0.95	**11aA**	4.37	3.25	6.9	1.09
7bA	4.40-4.25	2.60	3.2	1.06	**11bA**	4.65	2.80	6.9	1.17
7aB	4.35-4.20	2.73	3.2	1.12	**11aB**	5.21	3.18	3.0	0.98
7bB	3.95-3.80	2.90-2.75	b	0.92	**11bB**	4.90-4.75	2.85-2.70	b	0.99
8aA	4.15-4.00	3.00	7.1	0.93	**12aA**	4.55-4.40	3.26	5.6	1.07
8bA	4.35-4.21	2.61	2.4	1.05	**12bA**	4.55-4.40	2.78	5.5	1.17
8aB	4.40-4.30	2.73	1.6	1.09	**12aB**	5.18	2.78	1.9	0.97
8bB	3.98-3.85	3.05-2.90	b	0.90	**12bB**	4.72	2.85-2.70	b	0.99

[a] Coupling constants (Hz) in DMSO-d_6.
[b] Deceptively simple spectrum.

10. The lactols, resulting from the reduction of the lactones spontaneously formed from hydroxyacids, are usually obtained in these reactions, which decreases the observed yields. Their exclusion from the reaction mixtures has only been possible starting from **1** and using 2.7 equiv. of DIBAL (different ratios substrate:hydride gave 20-30% of lactols).
11. Despite the scarce synthetic value of these reactions, they have been of great interest in the configurational assignment of the substrates. From the nmr spectra of the obtained mixtures, the nmr parameters of the different hydroxysulfoxides and lactones has been unequivocally determined and therefore their relative configuration easily assigned.
12. The configurational assignment of the epimeric ketoacids **a** and **b**, was made by comparison of their nmr parameters with those of other β-ketosulfoxides epimers at C-α,[6c] whereas that of the hydroxyacids (and therefore that of the lactones which derive from them) was based in the coincidence of the three following criteria: i) The known stereochemical evolution of β-ketosulfoxides with DIBAL/$ZnBr_2$ (see reference 6a and 6c); ii) The nmr parameters of the epimers at hydroxylic carbon, using as comparison models for compounds **5** and **6** those obtained for compounds R-CHOH-CH_2SOMe (see Alcudia, F., Brunet, E., García Ruano, J.L., Hoyos, M.A., Prados, P., Rodriguez, J.H., *Org. Mag. Resonance*, **1983**, *21*, 643 and reference cited therein) and for compounds **7** and **8** those of the *erythro* and *threo* CH_3-CHOH-CH(SOMe)-CH_3 (see Alcudia, F., Carretero, J.C., García Ruano, J.L., Martinez, M.C., Rodriguez, J.H., *Tetrahedron*, **1985**, *41*, 2419); iii) the chemical correlation between the mixture of lactones **11** (derived from **7**) and the (-)-(*S*)-γ-caprolactone (see text).
13. The reaction of the -CO_2H group with DIBAL must yield the -$CO_2Al(i\text{-}Bu)_2$ one. The strong Lewis acid character of the aluminum in this species will allow the formation of a chelate with sulfinyl oxygen (precluding its association with DIBAL) and/or the carbonyl oxygen (the possible epimerization at C-α in DIBAL reduction of the **a+b** epimeric mixtures (Scheme 3) would supports this assumption). The stereochemical course for the attack of the hydride on these intermediates must be clearly different and less stereoselective than that postulated for β-ketosulfoxides in reference 6a.

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