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Deracemization of thiol esters of α-arylpropionic acids

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Abstract—Racemic thiol esters of α-arylpropionic acids were deracemized by a procedure which featured deprotonation with LDA or KHMDS, transformation into the TMS or TBDMS enol ethers, and enantioselective protonation of the silyl enol ethers using (*R*)-1,1′-bi-2-naphthol/$SnCl_4$. Oxidative hydrolysis of the enantiomerically enriched mixtures of thiol esters thus obtained yielded the (*S*)-enantiomers of ibuprofen and naproxen with ees up to 82%.

1. Introduction

Thiol esters are useful intermediates in organic synthesis, and some of their applications have been the subject of recent reviews.[1,2] In particular, the enolates derived from thiol esters are starting to gain significance in synthesis (for instance C. Fehr et al.[3–5] have shown how they can be employed as excellent substrates in asymmetric protonations). However, the enolization of this class of carbonyl compounds has been studied in much less detail than that of other ester derivatives.[6–8] An additional useful property of thiol esters is their ready hydrolysis to the corresponding carboxylic acids by an oxidative procedure employing H_2O_2 in alkaline conditions.[3]

Recently,[9] we reported on the synthesis of racemic thiol esters of α-arylpropionic acids. The aim of the present paper is to show that, starting from the corresponding racemic thiol esters, it is possible to obtain α-arylpropionic acids enriched in the (*S*)-enantiomer (the pharmacologically active isomer) by a straightforward deracemization procedure. Even if a number of syntheses have been reported to this purpose,[10] many of these antiinflammatory drugs (the profens) are still marketed as racemic mixtures. The (*R*)-isomer seems devoid of any biological activity;[11] however, an unusual biological inversion mechanism has been reported, which allows the (*R*)-enantiomer of some α-arylpropionic acids to be converted, in vivo, into the more active (*S*)-enantiomer, with kinetics markedly dependant on the animal species and the particular substrate.[11]

A mechanism proposed for this reaction involves the enzyme methylmalonyl Coenzyme A racemase:[12] the reaction sequence starts with thioesterification of the α-arylpropionic acid to give the corresponding acyl-coenzyme A (Fig. 1).

In this way the acidity of the methinic proton increases such that it can be removed by the enzyme, to yield the corresponding enolate. In turn, the enolate is protonated in an achiral fashion, leading to racemization. As the (*R*)-enantiomer of α-arylpropionic acids preferentially binds to Coenzyme A, it is also more susceptible to racemization than its antipode: in this way the concentration of the (*S*)-enantiomer will increase with time, and the result is more or less complete inversion (*R*)→(*S*).

Given the above mechanistic hypothesis, we turned our attention to thiol ester enolates as substrates in the deracemization procedure, via enantioselective protonation of the corresponding silyl enol ethers.[13] This method has been chosen for its easy practicability and uncommon reproducibility.

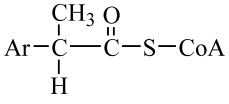

Figure 1.

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2. Results and discussion

Optically active α-arylpropionic acids (*S*)-**5** were prepared from racemic thiol esters **1** following a procedure shown in Scheme 1.

The thiol esters (±)-**1** were first deprotonated with either LDA (lithium diisopropylamide) or KHMDS (potassium hexamethyldisilazide), and the lithium or potassium enolates (*E*)-**2** and (*Z*)-**2** thus obtained were converted to the corresponding silyl enol ethers (*E*)-**3** and (*Z*)-**3** or (*E*)-**4** and (*Z*)-**4**. These, in turn, were stereoselectively protonated to yield a mixture of the starting thiol esters **1**, enriched in the (*S*)-enantiomer. The last step involves oxidative hydrolysis of the thiol esters (*S*)-**1** and (*R*)-**1** to the corresponding carboxylic acids (*S*)-**5** and (*R*)-**5**. This method was applied to the methyl (**1a**), ethyl (**1b**) and butyl (**1c**) thiol esters of ibuprofen, and to the methyl thiol ester of naproxen (**1d**). In the following sections the various steps are examined.

2.1. Enolization of thiol esters 1

The deprotonation of racemic thiol ester **1a** (the methyl thiol ester of ibuprofen), has been studied in some detail. As a pair of diastereomeric enolates can be formed, we investigated the stereochemical outcome of the reaction by varying the base (LDA or KHMDS) and the stoichiometric ratio base:**1a**. To this end the lithium or potassium enolates **2a** were quenched with TMSCl (trimethylsilyl chloride): the formation of the trimethylsilyl enol ethers **3a** is instantaneous, so that the diastereomeric composition of the silyl enol ethers mixture can be safely considered correspond to that of the starting enolates. GC analysis of the mixture of the diastereomeric trimethylsilyl enol ethers **3a** obtained with LDA showed an 85/15 isomer ratio. A proton NOESY experiment on the major isomer revealed the spatial proximity between a Me–Si group (0.3 ppm) and a Me–C=C group (2.1 ppm), thus indicating the *Z* stereochemistry of the double bond.

Markedly different behavior was observed in the deprotonations carried out with LDA and KHMDS (Table 1). The diastereomeric enolate composition obtained with LDA was always close to 85/15 in favor of the (*Z*)-isomer, both when the base was used in excess (1.7:1; entry 1), and when it was used in an equimolar ratio (entry 2). Moreover, in the former case silyl enol ethers were obtained with higher conversions. Thus, LDA was preferentially used in excess.

The *E*/*Z* stereoisomeric ratio obtained with KHMDS in excess (1.7:1) was around 70/30, again in favor of the (*Z*)-isomer (entry 3), but when it was used in an equimolar ratio the (*E*)-isomer was obtained almost exclusively (*E*/*Z* ratio = 98/2, entry 4). Such a stereochemical inversion when the base:substrate ratio approaches equimolarity has been already observed by Ireland et al.[7] in the formation of ester enolates, but employing LDA as base; in our case it only happened with KHMDS.

The effect of adding HMPA to the reaction medium (12%, w/w) was also tested (entries 5, 6): it only resulted in slower conversions, leaving the stereochemistry unchanged. As concerns the temperature dependence, we did not observe any lability of our thiol ester enolates at temperatures higher than –100°C, as reported by Fehr et al.[3] for the enolates of aromatic thiol esters. In all of our experiments the temperature was held at –90°C.

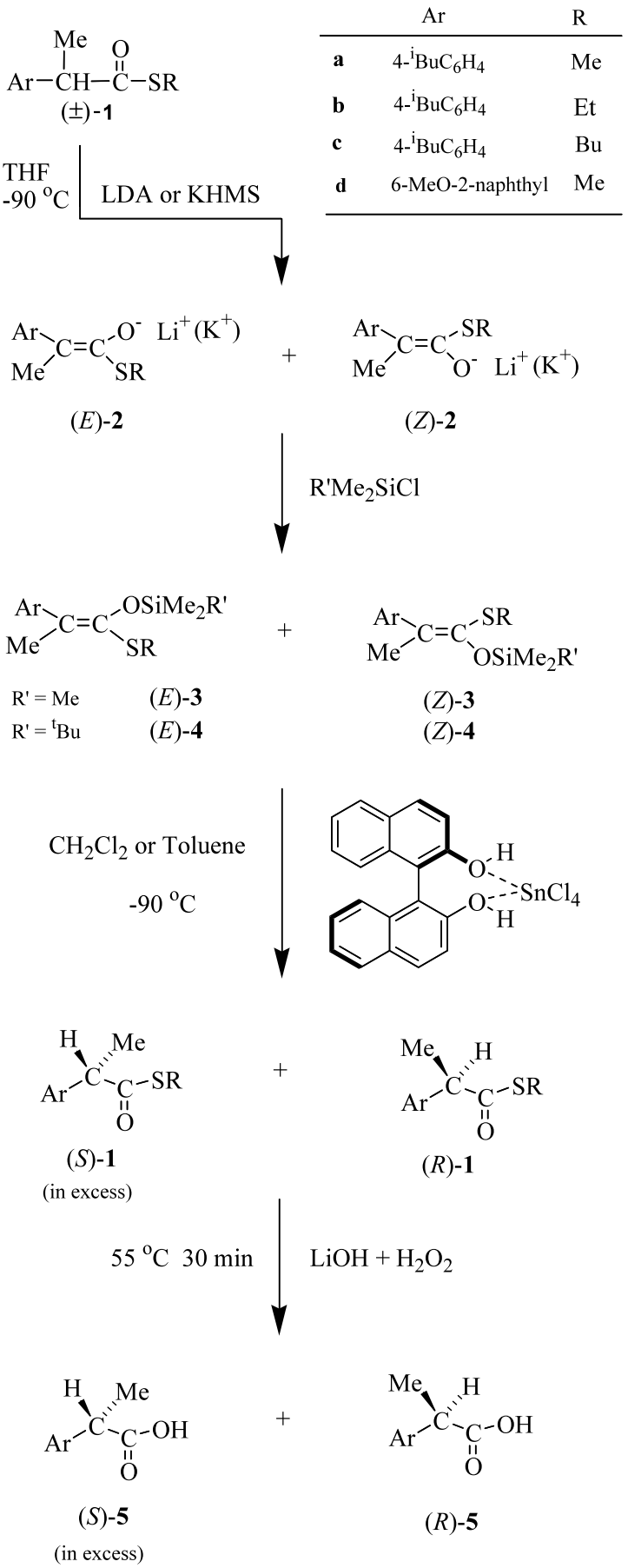
Another important difference between LDA and KHMDS lay in the observed deprotonation rates: LDA reacted very rapidly, and enolate formation was complete in less than 2 min, whereas with the bulky KHMDS deprotonation was complete in more than 30 min.

The course of the deprotonation reaction was found to be essentially the same with the other substrates, i.e thiol esters **1b** and **1d** (Table 1, entries 7, 9–10). The

Table 1. Yields and stereochemical outcome of thiol ester **1a**–**d** deprotonation, and enolate quenching with TMSCl

Entry	Substrate	Base	Substrate:Base	Reaction time (min)	Conv. %	Stereoisomeric ratio of silyl-enol ether (*E*)-**3**:(*Z*)-**3**	Yield (%)
1	**1a**	LDA	1:1.7	3	99	15:85	98
2	**1a**	LDA	1:1.0	5	59	17:83	n.d.[a]
3	**1a**	KHMDS	1:1.7	50	93	31:69	75
4	**1a**	KHMDS	1:1.0	60	90	98:2	78
5	**1a**	LDA + HMPA (12%)	1:1.7	3	24	13:87	n.d.[a]
6	**1a**	KHMDS + HMPA (12%)	1:1.7	30	12	98:2	n.d.[a]
7	**1b**	LDA	1:1.7	3	98	17:83	73
8	**1c**	LDA	1:1.7	10	30	57:43	n.d.[a,b]
9	**1d**	LDA	1:1.7	3	99	16:84	72
10	**1d**	KHMDS	1:1.7	50	88	34:66	69
11	**1d**	KHMDS	1:1.0	60	84	99:1	78

[a] Not determined. In the case of poor conversions, the yields were not determined.
[b] Given the low conversions observed with **1c**, butyl thiol esters were no longer employed in the deracemization procedure.



Scheme 1. The synthetic route to enantiomerically enriched α-arylpropionic acids starting from racemic thiol esters.

reaction was also applied to the butyl thiol ester of ibuprofen **1c** (entry 8), but in this case poor conversions were observed, probably due to a hindered access of the base caused by the bulky alkyl group.

In further experiments the enolates were quenched with TBDMSCl (*t*-butyldimethylsilyl chloride), to obtain TBDMS enol ethers (*E*)-**4** and (*Z*)-**4** (Table 2). The TBDMS enol ethers **4** are less labile than the analogous TMS enol ethers **3**, and better stereoselectivities have been reported for enantioselective protonation.[13] As has already been reported,[7] addition of excess HMPA at the end of the reaction is indispensable in order to achieve high yields of the silyl enol ethers, and we can now verify this.

As can be seen from Table 2, the stereochemical outcome of the reaction is much the same as that observed before, using LDA (entries 1, 2), while with KHMDS (entries 3, 4) the results seem less predictable, and in one case (entry 4) a 1:1 isomer mixture was obtained. It should be recalled that when TBDMSCl is used, enolate quenching is much slower than when TMSCl is used, so that equilibration is possible and the composition of the silyl enol ethers does not necessarily reflect that of the starting enolates.

2.2. Enantioselective protonation

Yamamoto et al.[13] have recently proposed a method of enantioselective protonation, utilizing a molecular complex formed by a chiral Brønsted acid, i.e. (*R*)-1,1′-bi-2-naphthol (BINOL), and a Lewis acid, i.e. $SnCl_4$. The advantage of this method is that relatively stable and isolable silyl enol ethers, rather than enolates, are employed as substrates. We applied this method to the stereoselective protonation of isolable silyl enol ethers **3a**,**b**,**d** and **4a**,**b**,**d**. The e.e.s of the resulting thiol esters were determined by GC analysis using a chiral stationary phase for ibuprofen thiol esters **1a**,**b**; the less volatile naproxen thiol ester **1d** was converted to the corresponding carboxylic acid **5d** and then analyzed by HPLC using a chiral column. In all cases the absolute configuration was assigned by polarimetric measurements on the carboxylic acids **5** obtained after thiol ester hydrolysis.

Interestingly enough, we could follow the stereochemical outcome of the protonation reaction on isomeric mixtures of silyl enol ethers **3** and **4** varying in composition from 70% d.e. (*Z*), passing through a 1:1 isomeric mixture to 98% d.e. (*E*) (Table 3). To our surprise, in all of our experiments the (*S*)-isomers **5** were preferentially obtained with identical ees, in the range 64–82% for silyl enol ethers derived from ibuprofen thiol esters **1a**,**b** (entries 1–9); lower excesses were obtained for naproxen thiol ester **1d** (entries 10–11). Changing solvent from dichloromethane to toluene leads to slightly improved stereoselectivities (entry 4 versus 1), and the same happens in the formation of TBDMS enol ethers (entries 5–7 versus 4).

To interpret these stereochemical outcomes, it appears that the (*E*) silyl enol ether is preferentially protonated on the *Re* face, and the (*Z*) isomer on the *Si* face, leading in both cases to the (*S*)-isomer, and with identi-

Table 2. Yields and stereochemical outcome of thiol ester **1a**, **1b**, **1d** deprotonation, and enolate quenching with TBDMSCl

Entry	Substrate	Base	Substrate:Base	Reaction time (min)	Conv. %	Stereoisomeric ratio of silyl-enol ether (*E*)-**4**:(*Z*)-**4**	Yield (%)
1	**1a**	LDA	1:1.7	3	82	16:84	80
2	**1a**	LDA	1:1.7	3	99	15:85	98
3	**1a**	KHMDS	1:1.1	50	77	96:4	76
4	**1a**	KHMDS	1:1.1	50	91	48:52	90
5	**1b**	LDA	1:1.7	3	99	17:83	99
6	**1d**	LDA	1:1.7	3	99	19:81	99

Table 3. Yields and stereochemical outcomes of the enantioselective protonation of ketene thioacetals **3a**, **3b**, **3d**, **4a**, **4b**, **4d**

Entry	Substrate	Si-R′	Isom. ratio (*E*:*Z*)[a]	Solvent	E.r. (*S*:*R*)	E.e. (%)	Yield (%)
1	**3a**	TMS	15:85	CH_2Cl_2	82:18	64	78
2	**3a**	TMS	32:68	CH_2Cl_2	83:17	66	45
3	**3a**	TMS	92:8	CH_2Cl_2	84:16	68	78
4	**3a**	TMS	15:85	Toluene	86:14	72	99
5	**4a**	TBDMS	15:85	Toluene	88:12	76	99
6	**4a**	TBDMS	48:52	Toluene	90:10	80	98
7	**4a**	TBDMS	16:84	Toluene	91:9	82	98
8	**3b**	TMS	17:83	Toluene	84: 16	68	56
9	**4b**	TBDMS	17:83	Toluene	89:11	78	80
10	**3d**	TMS	99:1	Toluene	72:28[b]	44	55
11	**4d**	TBDMS	19:81	Toluene	82:18[b]	64	90

[a] *E*:*Z* diastereomeric ratio of the starting silyl enol ether mixture.
[b] Enantiomeric excesses were measured on the corresponding carboxylic acids after hydrolysis.

cal selectivities; such equal facial selectivities of (*E*)- and (Z) substrates in an enantioselective protonation has not been reported often.

More recently,[14] a detailed mechanistic hypothesis is discussed by Yamamoto et al., where the authors also report DFT/B3LYP calculations on the geometry of the biphenol–$SnCl_4$ molecular complex. The mechanism proposed by the authors is based, among the others, on two experimental evidences: one is the independence of the enantioselectivity on the bulkiness of the silicon substituent (TMS versus TBDMS); and the second is a marked drop in enantioselectivity in the protonation of the silyl enol ether derived from naproxen methyl ester, existing as an *E*–*Z* mixture, compared to the protonation of substrates existing as pure diastereomers.

In the present work, at least for ibuprofen methyl thiol ester **1a**, we observed better enantioselectivities in the protonation of TBDMS versus TMS enol ethers, and the protonation of silyl enol ethers showing *E*–*Z* isomerism led to enantioselectivities independent of the diastereomeric compositions.

We believe that these findings can bring useful hints to mechanistic elucidation of this important enantioselective protonation reaction, which will need more experimental and theoretical work.

2.3. Hydrolysis of thiol esters

The thiol esters mixtures enantiomerically enriched in the (*S*)-isomers, obtained from the above procedure, were converted to the corresponding carboxylic acids **5** (i.e. ibuprofen and naproxen) by oxidative hydrolysis employing hydrogen peroxide. It was tested both under acidic (neat MeCOOH) and alkaline (LiOH) conditions:[5] we found that the former procedure is slower and leads to lower yields, whereas with LiOH the reaction is complete in 30 min at 55°C and the yields are quantitative. It could be seen by chiral GC that no racemization occurred during alkaline hydrolysis (selected results are reported in Table 4).

Table 4. Yields and enantiomeric excesses from the hydrolysis of selected optically active thiol esters to carboxylic acids

Thiol ester	E.e. (%)	Carboxylic acid	E.e. (%)	Yield (%)
1a	82	**5a**	83	99
1a	72	**5a**	72	99
1b	78	**5b**	78	99

3. Conclusion

We have shown that thiol esters can be advantageously used as intermediates in the synthesis of optically active α-arylpropionic acids, owing to the stability, the ease of preparation of their metal enolates and the smooth hydrolysis of thiol esters to carboxylic acids, which occurs without racemization. For the enantioselective protonation, we could verify that protonation of silyl enol ethers by the chiral complex BINOL/tin tetrachloride is indeed a useful method that gives good enantioselectivities. However, the mechanism by which this reaction occurs still needs to be clarified, in order to explain the stereochemical outcome.

4. Experimental

NMR spectra were recorded in $CDCl_3$ or C_6D_6 on a JEOL EX 400 spectrometer, operating at 399.782 MHz for ^1H and at 100.533 MHz for ^{13}C, using TMS as internal standard. Mass spectra were recorded on an HP 5970 B mass selective detector connected to an HP 5890 GC, cross-linked methyl silicone capillary column. Chiral GC analyses were carried out using a 25 m×0.25 mm capillary column with stationary phase composed of 2,3-diethyl-6-(*t*-butyldimethylsilyl)-β-cyclodextrine 30% in PSO86, deactivated Carbowax; 2°C/min T ramps were used. Chiral HPLC analyses were carried out on a Jasco PU 980 liquid chromatograph, using a Chiralcel AD column eluted with hexane–ethanol–TFA mixtures. Low pressure liquid chromatography was performed with Fluka Silica gel 60 (220–440 mesh); mixtures of petroleum ether (40–60°C boiling range) and diethyl ether were used as eluents. The reactions requiring an anhydrous environment were made with oven dried glassware and freshly dried/distilled solvents, under a continuos argon flow. TMSCl was kept under anhydrous Na_2CO_3, to remove any trace of HCl.

4.1. Thiol esters 1a–c

S-Methyl, *S*-ethyl and *S*-butyl 2-(4-isobutylphenyl)thiopropionates (**1a**, **1b**, **1c**) and *S*-methyl 2-(6-methoxy-2-naphthyl)thiopropionate (**1d**) were prepared as previously reported by us.[9]

4.2. General procedure for the deprotonation of thiol esters 1a–d and enolate 2a–d quenching with TMSCl

LDA was prepared by standard procedures and KHMDS was purchased from Aldrich. A typical procedure employing **1a** as substrate and LDA as base (1.7:1 ratio) is outlined as follows.

2 mL of the LDA solution in dry THF (prepared from 92 μL of diisopropylamine and 270 μL of Bu–Li) were cooled down to −90°C by an acetone/liquid nitrogen bath. A solution of the thiol ester **1a** (90 mg, 0.38 mmol), in 1 mL dry THF, was added dropwise under stirring, and the deprotonation reaction was allowed to take place for 2 min. After this time, an excess of trimethylsilyl chloride (200 μL) was added in one portion. The solution was then brought to rt and evaporated under vacuum. The crude product was dissolved in dry Et_2O and filtered to remove salts. The organic phase was immediately analyzed by GC and GC–MS. Diastereomeric compositions of the silyl enol ether mixtures are reported in Table 1. When KHDMS was

employed as base, it was dissolved in dry THF (2.5 mL), owing to its scarce solubility in the organic solvent.

4.2.1. (*E*)-2-(4-Isobutylphenyl)-2-methyl-trimethylsilylketene *S*-methyl thioacetal, (*E*)-3a. ^{1}H NMR (C_6D_6): δ 0.01 ppm (s, 9H, $SiCH_3$); 0.85 (d, 6H, J= 6.6); 1.70 (m, 1H); 2.10 (s, 3H, CH_3-C=C); 2.26 (s, 3H, SCH_3); 2.34 (d, 2H, CH_2-Ar, J=7.2); 7.00 (d, 2H, Ar, J=8.1); 7.38 (d, 2H, Ar, J=8.1). ^{13}C NMR (C_6D_6): δ 0.1 ppm (q, $SiCH_3$); 14.4 (q, SCH_3); 20.1 (q); 22.2 (q, 2C, $(CH_3)_2CH$); 30.3 (d); 45.1(t); 119.9 (s; ArC=C); 128.5 (d, 2C, Ar); 128.8 (d, 2C, Ar); 138.8 (s; Ar); 139.4 (s, Ar); 141.6 (s, C=C-O). MS m/z (rel. int.): 308 (M^+, 30), 293 (3), 188 (71), 145 (100), 117 (30), 73 (100).

4.2.2. (*Z*)-2-(4-Isobutylphenyl)-2-methyl-trimethylsilylketene *S*-methyl thioacetal, (Z)-3a. ^{1}H NMR (C_6D_6): δ 0.28 ppm (s, 9H, $SiCH_3$); 0.84 (d, 6H, J= 6.6); 1.76 (m, 1H); 1.91 (s, 3H, SCH_3); 2.06 (s, 3H, CH_3-C=C); 2.35 (d, 2H, J=7.1); 7.04 (d, 2H, Ar, J= 8.2); 7.27 (d, 2H, Ar, J=8.2). MS m/z (rel. int.): 308 (M^+, 40), 293 (5); 188 (91), 145 (97), 117 (26); 73 (100).

4.2.3. 2-(4-Isobutylphenyl)-2-methyl-trimethylsilylketene *S*-ethyl thioacetals, (*E*)- and (*Z*)-3b. Mixture of isomers. MS m/z (rel. int.): 322 (M^+, 35); 307 (3); 293 (8); 189 (12);188 (77); 161 (25); 145 (65); 117 (22); 91 (10); 73 (100), 59 (7).

4.2.4. 2-(4-Isobutylphenyl)-2-methyl-trimethylsilylketene *S*-butyl thioacetal (*E*) and (*Z*)-3c. Mixture of isomers. MS m/z (rel. int.): 350 (M^+).

4.2.5. (*Z*)-2-(6-Methoxy-2-naphthyl)-2-methyl-trimethylsilylketene *S*-methyl thioacetal (*Z*)-3d. ^{1}H NMR (C_6D_6): δ 0.32 ppm (s, 9H, $SiCH_3$); 1.91 (s, 3H, SCH_3); 2.16 (s, 3H, CH_3); 3.36 (s, 3H, OCH_3); 6.87 (d, 1H, Ar, J=2.4); 7.15 (m, 2H, Ar); 7.64–7.45 (m, 3H, Ar). ^{13}C NMR (C_6D_6): δ 0.2 ppm (q, $SiCH_3$); 15.0 (q, SCH_3); 19.6 (q, CH_3C=C); 54.5 (q, OCH_3); 105.6 (d, Ar); 119.3 (d, Ar); 123.4 (s, Ar-C=C); 126.4 (d, Ar); 127.0 (d, Ar); 128.3 (d, Ar); 129.1 (s, Ar); 129.5 (d, Ar); 133.8 (s, Ar); 137.6 (s, Ar); 142.3 (s, C=CO); 157.9 (s, Ar-O). MS m/z (rel. int.): 332 (M^+, 3); 212 (13); 141 (6), 74 (13), 73 (100), 59 (14), 45 (36).

4.3. General procedure for the deprotonation of thiol esters 1a,b,d and enolate 2a,b,d quenching with TBDMSCl

Both when LDA and KHMDS were used, the procedure for enolate formation was the same as above. After the times indicated in Table 2, TBDMSCl (330 μL), and HMPA (600 μL) were added in quick succession. The resulting solution was kept under stirring for about one hour, during which time it was allowed to gradually warm to rt. At the end, the solution was evaporated under vacuum; the crude product thus obtained was dissolved in Et_2O and washed twice with water, in order to remove HMPA. The organic phase was dried with Na_2SO_4, filtered, and evaporated under vacuum.

4.3.1. 2-(4-Isobutylphenyl)-2-methyl-*t*-butyldimethylsilylketene *S*-methyl thioacetal (*E*)-4a and (*Z*)-4a. Mixture of isomers. MS m/z (rel. int.): 350 (M^+, 44); 335 (2); 293 (50); 278 (20); 188 (39); 145 (39); 105 (100).

4.3.2. 2-(4-Isobutylphenyl)-2-methyl-*t*-butyldimethylsilylketene *S*-ethyl thioacetal (*E*)-4b and (*Z*)-4b. Mixture of isomers. MS m/z (rel. int.): 364 (M^+, 38); 335 (2); 307 (40); 279 (20); 235 (2); 217 (10); 188 (49); 161 (31); 145 (46); 119 (100); 91 (23); 73 (92).

4.3.3. 2-(6-Methoxy-2-naphthyl)-2-methyl-*t*-butyldimethylsilylketene *S*-methyl thioacetal (*E*)-4d and (*Z*)-4d. Mixture of isomers. MS m/z (rel. int.): 374 (M^+).

4.4. General procedure for the enantioselective protonation of silyl enol ethers 3a,b,d and 4a,b,d

(*R*)-1,1′-Bi-2-naphthol (120 mg, 0.42 mmol) was solved in dry toluene or dichloromethane (2.5 mL), and the solution was cooled to −90°C. A solution of tin tetrachloride (44 μL, 0.38 mmol, as purchased from Aldrich Chem. Co.) in the same solvents (0.5 mL) was added dropwise under stirring. After 5 min, a solution of the silyl enol ether in dry toluene or dichloromethane (2 mL) was added very slowly with no stirring; a brief and gentle stirring was performed every 5–10 drops of substrate added. When addition was complete, the solution was kept at −90°C under stirring for about 30 min (1 h if TBDMS ethers are employed); afterwards it was brought to rt and added with aqueous NaCl. Extraction with Et_2O and usual workup follows. The crude product was purified by chromatography on a short silica gel column eluted with PE–Et_2O (9.8:0.2 for ibuprofen thiol esters and 9:1 for naproxen thiol ester). The thiol esters thus obtained were compared (MS, ^{1}H and ^{13}C NMR) to the racemic samples described in Ref. 9 and were found to be identical.

4.5. General procedure for the hydrolysis of enantiomerically enriched thiol esters (*S*)-1a, (*S*)-1b and (*S*)-1d

To a solution of thiol ester (about 0.40 mmol) in EtOH (5 mL), was added a previously prepared solution of LiOH in H_2O_2 (LiOH 40 mg, 1.68 mmol; 30% hydrogen peroxide 270 μL; H_2O 0.5 mL). The mixture was stirred at 50–55°C for about 30 min and cooled to rt, then quenched with dil. HCl. Afterwards evaporation under vacuum, extraction with CH_2Cl_2 and usual workup are performed. The yields in crude carboxylic acids are always higher than 95%; the products are then purified by recrystallization. For ibuprofen a second check on the enantiomeric excess was made by chiral GC, which confirms the absence of racemization during the hydrolysis.

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