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A convenient approach to chiral sulfoxides by enantioselective oxidation with a steroidal furylhydroperoxide

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Abstract

The introduction of a steroidal residue into a position distant from the reaction center shows a beneficial effect on the reactivity of secondary furylhydroperoxides: chiral sulfoxides are obtained by asymmetric oxidation of sulfides and/or kinetic resolution of racemic sulfoxides with reduced reaction times and high enantiomeric excesses.

1. Introduction

Chiral sulfoxides are useful synthons in preparative organic chemistry and one of the typical synthetic procedures is based on transition metal catalyzed asymmetric oxidation of sulfides. Recently, several modifications of the methodologies proposed by Kagan[1] and Modena[2] have been reported: in particular, different hydroperoxides and chiral auxiliaries[3–6] have been employed in the asymmetric sulfoxidation. Recently, we have achieved a convenient one-pot procedure for the synthesis of chiral sulfoxides (70–>95% e.e.), involving two enantioconvergent processes of asymmetric oxidation and kinetic resolution by the employment of furylhydroperoxides as oxidants (Fig. 1).[7]

2. Results and discussion

Our present interest concerning the preparation of chiral hydroperoxides, potentially stereoselective oxidants,[8] suggested an approach based on the synthesis of furylhydroperoxide **1a** and the subsequent

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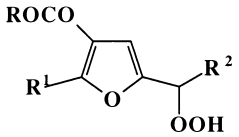
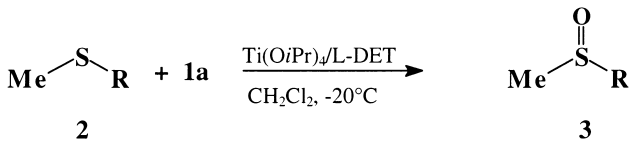


1a
R= 5α-cholestan-3β-yl
R^1= Me
R^2=Me

1b
R=[(1S)-endo]-(-)-bornyl
R^1 = Me
R^2 = Me

Fig. 1.

resolution of the resulting epimeric mixture. Unfortunately, this approach proved to be unsuccessful: in fact, although **1a** was easily accessible in 2–3 g scale by a known, efficient sequence starting from 3-cholestanyl acetoacetate, the separation of the 1:1 diastereoisomeric mixture into enantiomerically pure furylhydroperoxides by conventional crystallization or chromatographic techniques afforded unsatisfactory results. Anyway, **1a** proved to be of noteworthy synthetic value: chiral sulfoxides **3** were obtained with good yields and high enantiomeric excesses through a modified procedure for the asymmetric oxidation of sulfides **2** by the direct employment of **1a** as a diastereoisomeric mixture in the presence of L-diethyl tartrate (L-DET), as the chiral auxiliary (Scheme 1; Table 1).



2 **3**

Scheme 1.

This methodology proved to be characterized by high chemoselectivity: in fact, starting materials **2** were usually recovered in 20–35% yield, while only in entry **a** were negligible amounts of the corresponding sulfone isolated (<3%). All the products **3** were obtained as the (R)-enantiomer preferentially, confirming previous results indicating that the stereochemical outcome of the sulfoxidation does not depend on the configuration of the stereogenic center bearing the hydroperoxy function.[9] It has to be noted that the presence of a steroidal residue significantly enhanced the reactivity of the oxidant under the conditions reported in Table 1, so that oxidation required reaction times much shorter than the ones reported for similar procedures.[7]

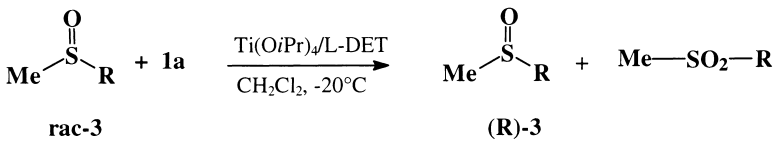
The problem related to the low enantioselectivity observed in the case of dialkyl sulfoxides (entry **f**)

Table 1
Asymmetric oxidation of sulfides **2** with **1a**

Entry	R	Reac. time (h)	Yield 3 (%)[a)]	e.e. (%)[b)]
a	4-NO_2-C_6H_4	3	58	>95 (R)
b	4-Br-C_6H_4	2	61	92 (R)
c	2-Br-C_6H_4	7	58	94 (R)
d	4-Cl-C_6H_4	2	63	90 (R)
e	4-Me-C_6H_4	2	74	84 (R)
f	n-octyl	2	78	39 (R)

[a)] Isolated yields. Molar ratios employed 1a/2/$Ti(OiPr)_4$/L-DET 1/1/1/4. [b)] E.e.s have been determined on representative samples obtained after mixing all the sulfoxide fractions coming from chromatography by ^{1}H-NMR analysis in the presence of R-(-)-(3,5-dinitrobenzoyl)-α-methylbenzyl amine as shift reagent. Absolute configuration established by comparison of the specific rotation with reported value.

was partially circumvented by using **1a** in a process of kinetic resolution based on the enantioselective oxidation of racemic sulfoxides to sulfones (Scheme 2).



rac-3 **(R)-3**

Scheme 2.

In fact, after racemic methyl n-octyl sulfoxide was submitted to the experimental conditions reported in Table 2 (entry **a**), the highly preferential oxidation of the S-enantiomer took place so that the R-sulfoxide could be recovered in satisfactory yield and very high e.e.

Kinetic resolution of racemic aryl methyl sulfoxides was shown to proceed with similar efficiency and selectivity (entries **b**–**f**). It has to be noted that when diisopropyl tartrate was used as the chiral auxiliary, a significant lowering of e.e.s was generally observed (25–50%).

This methodology seems to be particularly attractive since the operationally simple introduction of different chiral alcohol residues in structure **1** allows access to a set of hydroperoxides employable in similar asymmetric oxidations. For example, easily available furylhydroperoxide **1b** (R=bornyl) afforded very satisfactory results both in asymmetric oxidation and in kinetic resolution, as reported in Scheme 3.

3. Experimental

3.1. General information

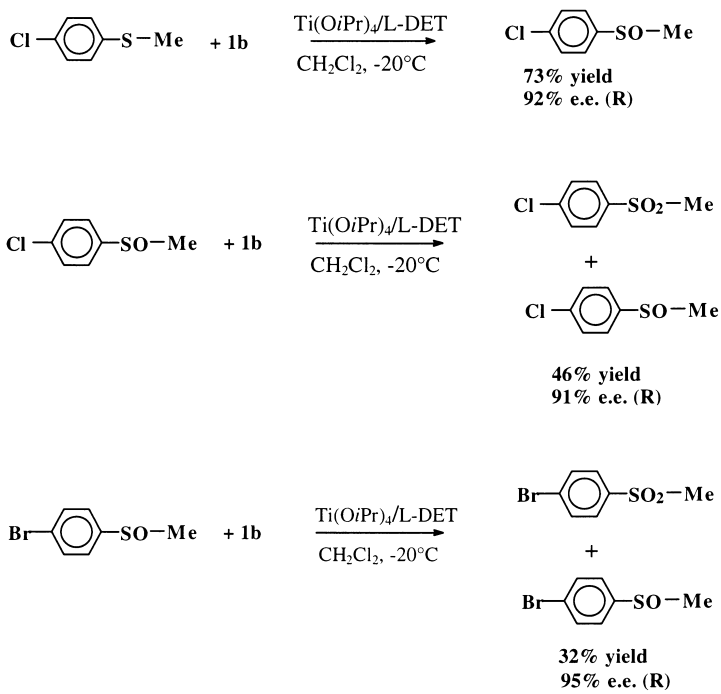
^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Gemini-200 spectrometer. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Chemical shifts are reported in δ (ppm) relative to internal $CHCl_3$ for ^{1}H-NMR and $CDCl_3$ (77.0) for ^{13}C-NMR.

Silica gel (230–400 mesh, Merck) was used for flash chromatography. Analytical thin layer chromatography was carried out on Merck Kieselgel F254 plates. Dichloromethane was stored over activated 4A molecular sieves (2 days at 160°C). Other chemicals (Aldrich or Fluka) were used as commercial products.

Table 2
Kinetic resolution of racemic sulfoxides **3** with **1a**

Entry	R	Reac.Time (h)	Yield (%)[a]	e.e. (%)[b]	E[c]
a	n-octyl	13	31	94	7.8
b	4-ClC_6H_4	14	29	>95	>7.4
c	4-BrC_6H_4	13	34	>95	>9.9
d	C_6H_5	23	32	82	5.3
e	4-MeC_6H_4	20	42	83	10
f	4-$NO_2C_6H_4$	14	40	>95	>15.7

[a] Isolated yields. Molar ratios employed 1a/3/Ti(OiPr)4/L-DET 1.6/2/1/4. [b] See note b of Table 1
[c] E = stereoselection factor calculated according to Kagan's equation[10]



Scheme 3.

3.2. General procedure for the synthesis of **1a** and **1b**

5α-Cholestan-3β-yl and (1S-endo)-(−)-bornyl 3-oxo-butanoate[11] (18 mmol) were submitted to alkylation with trans-2-butenyl bromide (20 mmol) in the presence of lithium hydroxide monohydrate (20 mmol) in anhydrous THF solution[12] (40 ml) at 45°C for 4 days. Then Et_2O (250 ml) was added and the organic phase was washed with brine till neutrality. Silica gel column chromatography afforded pure alkylated 1,3-dicarbonyl compounds in >70% yields.

3.3. 2-(2-Butenyl)-5α-cholestan-3β-yl 3-oxo-butanoate (inseparable mixture of diastereoisomers)

White powder; ^{1}H-NMR ($CDCl_3$): 5.6–5.1 (m, 2H); 4.8–4.6 (m, 1H); 3.37 (t, 1H, J=7.2 Hz); 2.47 (t, 2H, J=7 Hz); 2.18 (s, 3H); 1.63 (d, 3H, J=6.8 Hz); 0.93 (s, 3H); 0.89 (s, 3H); 0.83 (s, 3H). ^{13}C-NMR ($CDCl_3$): 202.6; 168.8; 128.0; 126.7; 74.7; 60.0; 56.4; 54.1; 44.6; 42.5; 40.0; 39.5; 36.6; 36.1; 35.8; 35.4; 33.9; 33.7; 31.9; 31.1; 28.8; 28.5; 28.2; 27.9; 27.3; 27.2; 24.1; 23.8; 22.8; 22.5; 21.1; 18.6; 17.9; 12.2; 12.0. Anal. calcd for $C_{35}H_{58}O_3$: C, 79.79; H, 11.10%. Found: C, 79.82; H, 11.15%.

3.4. 2-(2-Butenyl)-[(1S-endo)]-(−)-bornyl 3-oxo-butanoate (inseparable mixture of diastereoisomers)

White powder; ^{1}H-NMR ($CDCl_3$): 5.6–5.2 (m, 2H); 4.9–4.6 (m, 1H); 3.5–3.4 (m, 1H); 2.5 (t, 2H, J=6.6 Hz); 2.2 (s, 3H); 0.88 (s, 3H); 0.85 (s, 3H); 0.82 (s, 3H). ^{13}C-NMR (selected data for keto-form) ($CDCl_3$, 76.95 ppm): 202.4; 169.5; 128.0; 126.5; 80.9; 50.8; 48.7; 47.7; 44.7; 36.5; 31.1; 28.9; 27.8; 26.9; 19.5; 18.6; 17.7; 13.3. Anal. calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65%. Found: C, 73.90; H, 9.65%.

2-(2-Alkenyl)-1,3-dicarbonyl compounds (10 mmol) were converted into furylhydroperoxides **1a** and **1b** according to the three-step sequence reported in the literature.[13,14] Because of the high yields of

every step, purification of the intermediate products was omitted while pure **1a** and **1b** were obtained in 50 and 55% overall yields, respectively, after silica gel column chromatography by elution with light petroleum/diethyl ether mixture.

*3.5. 5-(1-Hydroperoxyethyl)-2-methyl-3-furoic acid 5α-cholestan-3β-yl ester **1a** (inseparable mixture of diastereoisomers)*

White powder; ^{1}H-NMR ($CDCl_3$): 7.91 (s, 1H); 6.63 (s, 1H); 5.01 (q, 1H, *J*=6.6 Hz); 5.0–4.8 (m, 1H); 2.57 (s, 1H); 1.57 (d, 3H, *J*=6.6 Hz); 0.88 (s, 3H); 0.85 (s, 3H). ^{13}C-NMR ($CDCl_3$): 163.5; 159.2; 151.0; 114.5; 109.8; 76.1; 73.1; 56.5; 56.4; 56.3; 54.2; 44.7; 42.6; 40.0; 39.5; 36.8; 36.2; 35.9; 35.8; 35.5; 34.3; 32.0; 28.6; 28.3; 28.0; 27.7; 24.3; 24.2; 23.8; 23.8; 22.8; 22.6; 21.2; 18.7; 16.3; 13.9; 12.3; 12.1. Anal. calcd for $C_{35}H_{56}O_5$: C, 75.50; H, 10.14%. Found: C, 75.55; H, 10.20%.

*3.6. 5-(1-Hydroperoxyethyl)-2-methyl-3-furoic acid [(1S)-endo)]-(−)-bornyl ester) **1b** (inseparable mixture of diastereoisomers)*

White powder; ^{1}H-NMR ($CDCl_3$): 8.45 (s, 1H); 6.60 (s, 1H); 5.0–4.9 (m, 1H); 2.55 (s, 3H); 2.55 (s, 3H); 1.50 (d, 3H, *J*=6.7 Hz); 0.90 (s, 3H); 0.88 (s, 3H); 0.85 (s, 3H). ^{13}C-NMR ($CDCl_3$): 165.0; 159.7; 151.8; 114.9; 110.2; 80.6; 76.4; 49.1; 48.1; 45.1; 37.2; 37.2; 28.3; 27.6; 25.3; 19.9; 19.0; 16.5; 14.2; 13.8. Anal. calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13%. Found: C, 67.10; H, 8.20%.

The isolation of **1a** (**1b**) as a 1:1 diastereoisomeric mixture was confirmed by ^{1}H-NMR analysis on the corresponding furylcarbinols, obtained by treatment of **1a** (**1b**) with an excess of Me_2S (5 equiv.) in Et_2O solution, in the presence of Eu(hfc)$_3$ as shift reagent.

*3.7. General procedure for asymmetric oxidation of sulfides **2***

A mixture of Ti(OiPr)$_4$ (1 mmol) and L-DET (4 mmol) sulfide (1 mmol) in anhydrous CH_2Cl_2 (10 ml) was stirred for 5 min at room temperature, then for 20 min at −20°C. Then, **1a** (or **1b**) (1 mmol), dissolved in CH_2Cl_2 (15 ml) was added and the reaction was prolonged for the times reported in Table 1. Water (4 ml) was added and a vigorous stirring was maintained for 1 h at room temperature. The resulting white gel was filtered over Celite and washed with CH_2Cl_2. The crude products **3**, after the removal of the solvent, were purified by flash chromatography.

*3.8. General procedure for kinetic resolution of racemic sulfoxides **3***

A mixture of Ti(OiPr)$_4$ (1 mmol), L-DET (4 mmol) and racemic sulfoxides **3** (2 mmol) in anhydrous CH_2Cl_2 ((15 ml) was stirred at room temperature for 5 min, then at −20°C for 20 min; then **1a** (or **1b**) (1.6 mmol) in CH_2Cl_2 (20 ml) was added. After completion of the reaction, the mixture was submitted to the same treatment reported for asymmetric oxidation. Pure sulfoxides, both in racemic and enantiomerically enriched forms were identified on the grounds of ^{1}H-NMR data.

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