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Tetrahedron
Tetrahedron 61 (2005) 1517–1521

# Stereoselective hydrolysis of *sec*-mono-alkyl sulfate esters with retention of configuration

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Received 31 August 2004; revised 23 November 2004; accepted 25 November 2004

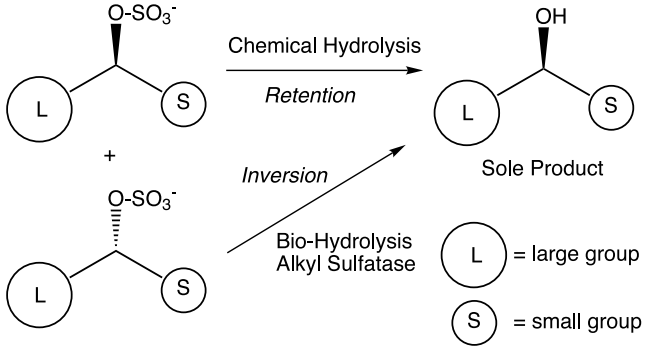
Available online 16 December 2004

**Abstract**—An optimised method for the stereoselective hydrolysis of *sec*-alkylsulfate monoesters with absolute retention of configuration was developed. Under optimised conditions, clean hydrolysis of (*R*)-2-octyl sulfate was achieved in aqueous *t*-butyl methyl ether (3:97) using 0.6 equiv of *p*-toluenesulfonic acid as catalyst and 0.33 equiv of dioxane as mediator to give (*R*)-2-octanol as the sole product in the absence of side reactions, such as racemisation or elimination.


## 1. Introduction

Driven by the increased demand to enhance the economic balance of chemical processes, the development of methods, which allow the transformation of a racemate into a single stereoisomeric product in 100% theoretical yield without the occurrence of an 'unwanted' stereoisomer has become a prime target in asymmetric synthesis.[1] Among the various strategies proposed to date, dynamic resolution,[2] stereoinversions[3] and enantio-convergent processes[4] have proven their applicability.

As depicted in Scheme 1, the latter method constitutes of two reactions, which are generally independent of each other. (i) One enantiomer of the racemic starting material is transformed in a stereo- and enantio-selective fashion with retention (or inversion) of configuration to yield the corresponding homochiral product enantiomer by following a kinetic resolution.[5] (ii) The non-reacting mirror-image enantiomer, however, has to be converted via inversion (or retention) of configuration, thus forming the same enantiomeric product. In an ideal case, combination of both reactions in a simultaneous fashion would create additional benefits of a parallel kinetic resolution.[6] Since the requirements regarding the simultaneous stereo- and enantioselectivity of the respective catalyst(s) are very difficult to fulfil in practice, both reactions are usually combined in a sequential/stepwise fashion, albeit without separation of intermediates in a one-pot procedure. Thus, in the first step,




**Scheme 1.** Deracemisation of *sec*-alcohols via combined bio- and chemical hydrolysis of the corresponding sulfate esters through inversion and retention of configuration, respectively.

the chiral catalyst has to be enantioselective (with respect to the selection of a single enantiomer from the racemate) and stereoselective (with respect to retention/inversion of configuration). The requirements for such 'double' selectivities are hard to meet for chemical catalysts and, as a consequence, biocatalysts are more often used. Once the faster reacting enantiomer has been converted, the requirements for the catalyst to effect the second step becomes easier, that is, only stereoselectivity with respect to inversion/retention is required which could be accomplished by a chemical catalyst.

In order to complete our studies aiming at the development of a deracemisation process for *sec*-alcohols based on the stereo- and enantioselective biohydrolysis of a (*rac*)-*sec*-alkylsulfate ester using microbial alkyl sulfatases acting

*Keywords*: Monoalkyl sulfate ester; Hydrolysis; Retention of configuration; Alkyl sulfatase.
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doi:10.1016/j.tet.2004.11.075

with inversion of configuration,[7] we required a reliable synthetic protocol for the stereoselective hydrolysis of the remaining non-reacted sulfate ester enantiomer with strict retention of configuration.

In contrast to dialkyl sulfate esters,[8] such as dimethyl sulfate, which are highly reactive species and thus intrinsically unstable in aqueous solution, monoalkyl esters are much more stable and thus are more resistant towards hydrolysis. Depending on the reaction conditions, hydrolysis of a monoalkyl sulfate ester may either proceed via C–O versus S–O-bond cleavage.[9] Alkaline hydrolysis acts through nucleophilic attack of [$OH^-$] at carbon by making use of the (formal) leaving group properties of sulfate anion, thus affecting inversion of configuration through breakage of the C–O-bond. On the other hand, acid-catalysed hydrolysis causes protonation of the substrate (assumed to take place at the internal C–O–S oxygen atom rather than at terminal the S–$O^-$ species[10–12]), which causes breakage of the S–O bond. Thus, $HSO_4^-$ is formally expelled, which retains the configuration at carbon. Evaluation of the existing procedures for the chemical hydrolysis of monoalkyl sulfate esters reveals that several methods have been investigated (Scheme 2).

(i) Base-catalysed hydrolysis was shown to proceed with inversion of configuration.[10] However, the reaction rates were found to be exceedingly low and alkaline hydrolysis is not feasible for preparative purposes, although the expected inversion of configuration takes place.[13] This unreactivity may be explained by the properties of sulfate anion ($SO_4^{2-}$), which—being the anion of the weak acid $HSO_4^-$ ($pK_a = 1.9$–$2.7$, depending on the conditions)—is a very bad leaving group. In line with these observations, our own attempts to hydrolyze (*R*)-2-octyl sulfate under alkaline conditions with inversion of configuration using a variety of nucleophiles/bases, such as NaOAc, NaOH, $Ba(OH)_2$, or LiOMe in aqueous-organic solvent systems composed of acetone, dioxane and/or *t*-BuOMe were unsuccessful.

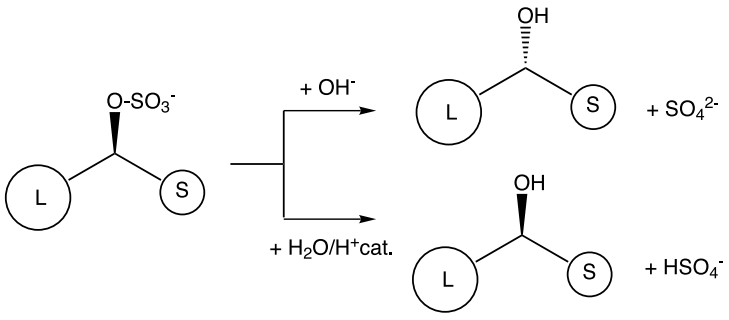
(ii) On the contrary, acidic conditions generate the protonated sulfate monoester species, which is able to (formally) expel $HSO_4^-$ as excellent leaving group—being the anion of a strong acid $H_2SO_4$ ($pK_a = -9$ to $-3$, depending on the conditions).[11] Due to the very acidic $pK_a$ of monoalkyl sulfate esters (the $pK_a$ of methyl monosulfate was calculated/estimated as $pK_a$ $-8.4$[14] or $pK_a$ $-3.4$[15]), only strong acids are effective as catalysts. The formation of sulfur trioxide as short-lived intermediate was initially proposed,[16] but later excluded.[17] Studies on chiral *sec*-monoalkyl esters, however, revealed that the expected retention of configuration is significantly weakened by significant amounts of side reactions, in particular racemisation going hand in hand with elimination, which severely diminishes the overall efficiency of this process.[13]

(iii) A remarkable rate-enhancement in the (pH-independent) hydrolysis of monoalkyl sulfate esters was also shown to be effected by organic solvents possessing Lewis-base electron-donor capabilities through oxygen-lone pairs, such as ethers, DMSO and DMF.[18,23,24] In particular, impressive rate accelerations with respect to the uncatalysed reaction of up to $10^7$ were reported using moist dioxane.[19] This method for the cleavage of sulfate esters is unique with respect to its mechanism and it relies on the unusual stability of the dioxane-sulfur trioxide complex as a Lewis acid–base adduct, first described by Suter et al.[20] A related, but largely unexplained catalytic phenomenon was observed for cyclodextrins.[18]

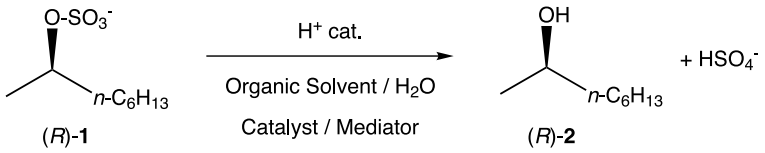
The majority of the studies reported to date on the chemical hydrolysis of monoalkyl sulfate esters emphasised physical-organic and mechanistic/theoretical aspects rather than the development of a reliable synthetic protocol for preparative-scale transformations. Few studies deal with the de-sulfation of sulfated materials from biological origin, such as sulfolipids[21] and steroid sulfates.[22–24]

The most useful study in view of its preparative utility revealed that a combination of methods (ii) and (iii) discussed above by using a strong acid (*p*-TsOH) in moist dioxane gave best results for the chemo-selective hydrolysis of a triterpenoid microbial metabolite.[25] However, solubility problems causing decreased reaction rates persisted for more lipophilic derivatives and rearrangement reactions involving bis-allylic alcohol moieties within the complex natural product structure were observed as side reactions, when MeOH was used as co-solvent.

In order to provide a reliable synthetic protocol for the stereoselective hydrolysis of *sec*-monoalkyl sulfate esters applicable to our deracemisation process, we undertook a more detailed investigation.




**Scheme 2.** Chemical hydrolysis of monoalkyl sulfate ester.




**Scheme 3.** Stereoselective hydrolysis of (*R*)-2-octyl sulfate.

## 2. Results and discussion

Since *Rhodococcus ruber* sulfatase RS2[26] displayed best enantioselectivities on (*rac*)-2-octyl sulfate (*rac*-**1**),[7] the latter compound was chosen as test-substrate. Various reaction conditions for stereoselective hydrolysis were chosen, the expected (*R*)-2-octanol was analyzed by GLC on a chiral stationary phase (Scheme 3, Table 1).

In order to obtain a quick estimate on the efficiency of the method published by Singh,[25] hydrolysis of (*R*)-**1** was performed in aqueous dioxane with a water-content ranging from 25 to 2.5% using 1.5 mol equiv of *p*-TsOH (entries 1–3). In line with previous observations,[18] best yields were obtained at a low water-content (entry 3). Since the use of large amounts of dioxane as a solvent invokes considerable safety-hazards due to its facile formation of peroxides, we next tried to replace it by a safer solvent analog by using dioxane only as a 'mediator' at a fixed concentration of 0.33 mol equiv rather than as a solvent. The influence of the polarity of various solvents from a wide range, such as MeOH, MeCN and $CH_2Cl_2$ was remarkably small; however, we were pleased to see that best results were obtained in the 'peroxide-stable' *t*-butyl methyl ether (entries 4–7). Tuning of the water-content of this solvent system turned out to be optimal at 3% (entries 7–10). In this system, 40 °C was the optimal reaction temperature (cf. entries 8, 11 and 12).

Since pyridine and its derivatives were reported to be able to effect sulfuryl-group transfer reactions between nucleophiles,[17] we anticipated that various heterocyclic donor solvents/mediators might exert catalytic effects in sulfate ester hydrolysis (entries 13–18). This assumption proved to be correct. While pyridine hydrochloride or -toluenesulfonate was ineffective, various *N*-nucleophiles, such as piperidine and piperazine (used as the corresponding hydrochlorides) were found to be moderately effective. Best results, which are comparable to those obtained from the dioxane-*p*-TsOH-system, were obtained by using morpholine *p*-toluenesulfonate (83 and 89% yield, respectively). Since the neutralisation of these *N*-bases required additional equivalents of acid, the benefit of using morpholine over dioxane as 'mediator' was not striking. Further attempts to reduce the amount of dioxane required were undertaken and it was found that 0.33 mol equiv represent the optimum (entries 19–21).

Finally, the nature and amount of the acid catalyst was optimised (entries 22–27). Whereas, no reaction was observed by using phosphate buffer within a range of pH 2–7 (data not shown), the use of amidosulfuric acid (a cheap industrial organic acid) failed, which is probably due to its insufficient acidity ($pK_a$-value ca. 1.0).[27] On the other hand, methanesulfonic acid ($pK_a$ −1.2 to −2) was equally effective as *p*-toluenesulfonic acid ($pK_a$ −1.0).

**Table 1**. Results from stereoselective hydrolysis of (*R*)-2-octyl sulfate

| Entry | Organic solvent/$H_2O$ [%] | Temperature [°C] | Time [h] | Catalyst/mediator [mol equiv] | Yield (*R*)-**2** [%] |
|---|---|---|---|---|---|
| 1 | Dioxane/$H_2O$ [75:25] | 60 | 24 | *p*-TsOH [1.5] | 40 |
| 2 | Dioxane/$H_2O$ [95:5] | 60 | 3 | *p*-TsOH [1.5] | 50 |
| 3 | Dioxane/$H_2O$ [97.5:2.5] | 60 | 4 | *p*-TsOH [1.5] | 85 |
| 4 | $CH_2Cl_2$/$H_2O$ [99:1] | 45 | 2 | *p*-TsOH [0.6], dioxane [0.33] | 38 |
| 5 | MeOH/$H_2O$ [99:1] | 60 | 2 | *p*-TsOH [0.6], dioxane [0.33] | 42 |
| 6 | MeCN/$H_2O$ [99:1] | 45 | 2 | *p*-TsOH [0.6], dioxane [0.33] | 42 |
| 7 | *t*-BuOMe/$H_2O$ [99:1] | 45 | 2 | *p*-TsOH [0.6], dioxane [0.33] | 46 |
| 8 | *t*-BuOMe/$H_2O$ [97:3] | 40 | 2 | *p*-TsOH [0.6], dioxane [0.33] | 62 |
| 9 | *t*-BuOMe/$H_2O$ [95:5] | 40 | 2 | *p*-TsOH [0.6], dioxane [0.33] | 42 |
| 10 | *t*-BuOMe/$H_2O$ [90:10] | 40 | 2 | *p*-TsOH [0.6], dioxane [0.33] | 31 |
| 11 | *t*-BuOMe/$H_2O$ [97:3] | 30 | 2 | *p*-TsOH [0.6], dioxane [0.33] | 20 |
| 12 | *t*-BuOMe/$H_2O$ [97:3] | 50 | 2 | *p*-TsOH [0.6], dioxane [0.33] | 53 |
| 13 | *t*-BuOMe/$H_2O$ [97:3] | 40 | 48 | Py·HCl [2.0] | 0 |
| 14 | *t*-BuOMe/$H_2O$ [97:3] | 40 | 24 | Py·*p*-TsOH [0.55]/DMAP cat. | 0 |
| 15 | *t*-BuOMe/$H_2O$ [97:3] | 40 | 1.5 | Piperidine·HCl [0.5] | 40 |
| 16 | *t*-BuOMe/$H_2O$ [97:3] | 40 | 18 | Piperazine·2 HCl [1.4] | 70 |
| 17 | *t*-BuOMe/$H_2O$ [97:3] | 40 | 0.5 | Morpholine [1.0], *p*-TsOH [2.5] | 89 |
| 18 | *t*-BuOMe/$H_2O$ [97:3] | 40 | 0.5 | *p*-TsOH [1.0], dioxane [1.0] | 83 |
| 19 | *t*-BuOMe/$H_2O$ [97:3] | 40 | 2 | *p*-TsOH [0.6], dioxane [0.11] | 39 |
| 20 | *t*-BuOMe/$H_2O$ [97:3] | 40 | 2 | *p*-TsOH [0.6], dioxane [0.33] | 49 |
| 21 | *t*-BuOMe/$H_2O$ [97:3] | 40 | 2 | *p*-TsOH [0.6], dioxane [0.80] | 43 |
| 22 | *t*-BuOMe/$H_2O$ [97:3] | 40 | 2 | $NH_2$-$SO_3H$ [0.6], dioxane [0.33] | 6 |
| 23 | *t*-BuOMe/$H_2O$ [97:3] | 40 | 2 | Me-$SO_3H$ [0.6], dioxane [0.33] | 76 |
| 24 | *t*-BuOMe/$H_2O$ [97:3] | 40 | 2 | *p*-TsOH [0.5], dioxane [0.33] | 47 |
| 25 | *t*-BuOMe/$H_2O$ [97:3] | 40 | 2 | *p*-TsOH [0.6], dioxane [0.33] | 77 |
| 26 | *t*-BuOMe/$H_2O$ [97:3] | 40 | 2 | *p*-TsOH [0.7], dioxane [0.33] | 74 |
| 27 | *t*-BuOMe/$H_2O$ [97:3] | 40 | 2 | *p*-TsOH [0.8], dioxane [0.33] | 62 |

It is interesting to note that under all conditions mentioned above, neither racemisation nor β-elimination (which would proceed through a carbo-cationic intermediate) were detected as side reactions.

In summary, a preparative-scale method for the stereoselective hydrolysis of *sec*-alkylsulfate monoesters was achieved under strict retention of configuration. Under optimised conditions, acid-catalysed hydrolysis of (*R*)-2-octyl sulfate in presence of 0.33 equiv of dioxane as mediator was achieved in *t*-butyl methyl ether at low water content (3%) on a gram-scale in 90% yield. The reaction proved to be essentially 'clean', as no side reactions, such as racemisation or β-elimination could be detected.

## 3. Experimental

TLC plates were run on silica gel Merck 60 ($F_{254}$) and compounds were visualised by spraying with Mo-reagent [$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (100 g/L), $Ce(SO_4)_2\cdot 4H_2O$ (4 g/L) in $H_2SO_4$ (10%)].

GC analyses were carried out on a Varian 3800 gas chromatograph equipped with FID using a HP 1301 capillary column (30 m×0.25 mn×0.25 μm film, column A) and $N_2$ as carrier gas (14.5 psi). Enantiomeric purities were analysed using a CP-Chiralsil-DEX CB column (25 m×0.32 mm×0.25 μm film, column B) and $H_2$ as carrier gas (14.5 psi).

(*rac*)-2-Octanol was purchased from Aldrich, (*R*)- and (*S*)-2-octanol (ee 97 and 99%, respectively) was obtained from Lancaster. (*Rac*)- and (*R*)-2-octyl sulfate were prepared by sulfatation of the corresponding alcohol using $NEt_3\cdot SO_3$ according to a known procedure.[7b]

Determination of conversion: The degree of conversion was monitored by GC using 2-dodecanol as an internal standard. The conversion was calculated from a calibration curve.

Determination of absolute configuration: (*R*)- and (*S*)-2-Octanol were analysed as the corresponding acetate esters ($Ac_2O$/DMAP/rt/18 h) on GC (column B), their absolute configuration was elucidated by co-injection using authentic reference samples (Table 2).

### 3.1. General procedure for optimisation study

Sulfate ester (*R*)-**1** (50 mg, 0.2 mmol) was dissolved in $H_2O$/*t*-BuOMe (3:97, 20 mL) to give a final concentration of 0.01 mM. Dioxane (0.33 equiv, 0.07 mmol), *p*-TsOH monohydrate (0.6 equiv, 0.12 mmol) and 1 ml of a stock solution of 2-dodecanol (1.05 mg/mL) as internal standard were added and the reaction mixture was stirred at 40 °C for 2 h. After cooling to room temperature, the reaction was quenched with saturated $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3×). The combined organic layers were washed with brine (3×), dried over anhyd $Na_2SO_4$ and the solvent was evaporated under reduced pressure. $R_f$ (2-octanol)=0.53 (petroleum ether/EtOAc=1:3).

### 3.2. Preparative-scale procedure

(*R*)-2-Octylsulfate (1 g, 4.3 mmol, 97% ee) was dissolved in 12 ml $H_2O$ and 388 ml *t*-BuOMe to give a final concentration 0.01 mM. Dioxane (120 mL) and *p*-TsOH monohydrate (470 mg, 2.6 mmol) were added and the reaction mixture was stirred at 40 °C for 5 h. After cooling to room temperature, the reaction was quenched with saturated $NaHCO_3$ (100 mL) and extracted with ethyl acetate (3× 100 mL). The combined organic layers were washed with brine (3×100 mL), dried over anhyd $Na_2SO_4$ and the solvent was evaporated under reduced pressure. (*R*)-**2** was obtained as colourless oil (0.5 g, 90% yield, ≥97% ee). $R_f$=0.53 (petroleum ether/EtOAc=1:3). $[\alpha]_D^{20}-10°$ (*c*=1.0, EtOH).

## Acknowledgements

This study was performed in cooperation with Degussa AG (Frankfurt) within the Competence Center Applied Biocatalysis and financial support by the TIG, the City of Graz, the Province of Styria and Degussa AG is gratefully acknowledged.

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**Table 2**. GC-data

| Compound | Column | Conditions | $t_R$ [min] |
|---|---|---|---|
| (*rac*)-2-Octanol | A | 115 °C/4 min—30°/min—250 °C/0 min | 2.1 |
| (*R*)-2-Octanol | B | 60 °C/7 min—4°/min—80 °C/0 min—160 °C/5 min | 13.2 |
| (*S*)-2-Octanol | B | 60 °C/7 min—4°/min—80 °C/0 min—160 °C/5 min | 11.1 |

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