Table I. Lanthanide-Induced Shifts and Association Constants for Derivatives of 1-4[a]

	b, R = $COCF_3$			c, R = $Si(CH_3)_3$			d, R = $Si(CH_3)_2$-t-C_4H_9		
compd	max[b,c] LIS	bound[c,d] shift	K	max[b] LIS	bound[c,e] shift	K	max[b] LIS	bound[c,e] shift	K
1	2.2	15.0	0.3	5.8	16.0[f]	1.1[f]	0.2	16.0	0.02
2	3.6	15.0	0.6	0.8	16.0	0.1	0.02	16.0	0.002
3				0.1	7.5	0.001	0.003	7.5	0.001
4	0.5	9.5	0.2[g]	0.11	13[d]	0.01			

[a] All shifts in parts per million relative to internal Me_4Si; equilibrium constants have units of M^{-1}. [b] At a LSR/substrate ratio of 3. [c] LIS of the hydrogens on the α-carbon for **1** and **2** and on the β-carbon for **3** and **4**. [d] Estimated from the bound shifts of analogous esters or ethers.[9] [e] Estimated from the LIS of **1c**. [f] Calculated[10] from the observed LIS. [g] Data from ref 9.

predicted[2] with the pseudocontact equation[13] in order to determine whether or not complexation with shift reagent occurs at more than one site. On the assumption that complexation of derivatives of **5** and **6** with $Eu(fod)_3$ occur exclusively at the 3-keto and 17-keto groups, respectively, the predicted[2,13] bound shifts of the respective hydrogens at C-17 of **5** and C-3 of **6** (i.e., α to the OR substituent) fall in the range of 0.5–0.7 ppm. Any complexation at the "blocked" position would result in a larger observed LIS for the corresponding proton. In the case of trifluoroacetates **5b** and **6b** the respective bound shifts of these hydrogens are 3.1 and approximately 1.0 ppm. Similarly, the experimental bound shift for the fluorines in **6b** is 0.8 ppm, but the value predicted for complexation at the 17 keto group is only 0.2 ppm. Clearly some complexation with $Eu(fod)_3$ occurs at the trifluoroacetoxy group as well as at the ketone oxygen, and this reaffirms our conclusion that a trifluoroacetate is not an adequate blocking group for LSR studies. On the other hand, the experimental bound shift of the 17α proton in the *tert*-butyldimethylsilyl ether **5d** is within 0.05 ppm of the predicted value of 0.7 ppm, and both the experimental and predicted LIS for the silyl methyl groups of the trimethylsilyl ether of **6c** are found to be 0.4 ppm. This demonstrates that silylation of the difunctional steroids **5a** and **6a** permits them to be accurately evaluated as monofunctional compounds. Recall, however, that the data in Table I indicate that a trimethylsilyl group does not always completely prevent complexation, particularly in the case of primary alcohols. The *tert*-butyldimethylsilyl group is therefore more reliable as a protective group for lanthanide-induced shift studies.

In summary, the effectiveness at preventing coordination with LSR and the remarkable ease with which this blocking group can be introduced and removed[14] combine to make *tert*-butyldimethylsilyl ethers the derivatives of choice for shift reagent studies. Since the site of complexation must be accurately known, previous attempts at rigorous evaluation of molecular structure with shift reagents have been resticted to monofunctional compounds. Our results demonstrate that *tert*-butyldimethylsilyl ethers allow, for the first time, the use of lanthanide shift reagents for reliable and accurate structure evaluation of polyfunctional organic compounds.

Experimental Section

Trifluoroacetates of 1-propanol and 2-propanol were prepared by H_2SO_4 catalyzed esterification of the alcohols with CF_3CO_2H in $CHCl_3$. Trifluoroacetates **4b**, **5b**, and **6b** were prepared by reaction of the alcohols with trifluoroacetic anhydride.

Trimethylsilyl ethers were prepared from the alcohols by using hexamethyldisilazane and chlorotrimethylsilane according to the procedure of Langer, Connell, and Wender.[15]

***tert*-Butyldimethylsilyl ethers** were prepared by reaction of the alcohols with *tert*-butylchlorodimethylsilane and imidazole in dimethylformamide using the procedure reported by Corey and Venkateswarlu.[14]

Nuclear magnetic resonance spectra were obtained by using Varian EM-360 (1-4, CCl_4) and JEOL FX90Q (5 and 6, $CDCl_3$) spectrometers at ambient temperature. Carbon and proton chemical shifts were measured relative to internal Me_4Si, and fluorine shifts were measured relative to the deuterium of the solvent. For shift reagent runs we employed the incremental dilution method[11] and utilized shift reagent (Aldrich, EuFOD, No. 16 093-8) which had been sublimed [ca. 160 °C (0.05 torr)] prior to use.

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Registry No. 1a, 71-23-8; **1b**, 383-66-4; **1c**, 1825-63-4; **1d**, 17348-67-3; **2a**, 67-63-0; **2b**, 400-38-4; **2c**, 1825-64-5; **2d**, 17348-66-2; **3a**, 75-85-4; **3c**, 6689-16-3; **3d**, 81898-29-5; **4a**, 768-95-6; **4b**, 58652-54-3; **4c**, 36960-53-9; **5a**, 521-18-6; **5b**, 2022-58-4; **5d**, 58701-44-3; **6a**, 481-29-8; **6b**, 3959-78-2; **6c**, 10426-95-6.

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Improved Procedure for Synthesis of Chiral Sulfoxides[1]

Jozef Drabowicz, Bogdan Bujnicki, and Marian Mikołajczyk*

Center of Molecular and Macromolecular Studies, Polish Academy of Sciences, Department of Organic Sulfur Compounds, 90-362 Łodz, Boczna 5, Poland

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Chiral sulfoxides have attracted much attention in the past 2 decades as model compounds in studies of sulfur stereochemistry.[2] Recently, they became key intermediates for highly efficient asymmetric syntheses.[3] For this reason, a variety of chemical methods have been developed for the synthesis of chiral sulfoxides in various states of opitcal purity.[4] Among these, the most important and

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Table I. Synthesis of Optically Active Sulfoxides 2[a]

	sulfinate 1			sulfoxide 2				
run	R^1	$[\alpha]_D$,[b] deg	solvent[i]	R^2	% yield[c]	$[\alpha]_D$,[b] deg	optical purity,[d] %	sulfide yield,[h] %
1[j]	Tol	−195	B	Me	82	+150.1	89.5	0
2[j]	Tol	−195	E	Me	61	+143.0	85.0	4.5
3[9]	Tol	−210	E[g]	Me	55	+143.2	85.1	
4[j]	Tol	−195	B	Et	92	+198.0	97.5	1.7
5[j]	Tol	−195	E	Et	78	+184.5	90.8	5.7
6[5]	Tol	−201	E	Et	62	+186.0	91.5	
7[j]	Tol	−195	B	*i*-Pr	79	+172.5	97.7	trace
8[j]	Tol	−195	E	*i*-Pr	40	+173.2	98.2	3.6
9[8]	Tol	−198	E	*i*-Pr	22	+176.5	100-	
10[j]	Tol	−195	B	*n*-Bu	73	+186.0	99.5	0
11[8]	Tol	−198	E	*n*-Bu		+187.0	100-	
12[j]	Tol	−195	B	Ph	88	+20.0	91.0	0
13[7]	Tol	−205	E[g]	Ph	52	+20.7	94.0	
14[9]	Tol	−210	E	Ph	59	+21.8	99.1	
15[j]	Me	−60.2	B	*n*-Pr	72	−48.1[e]	34.6	trace
16[j]	Me	−60.2	E	*n*-Pr	58	−47.4[e]	34.0	3.7
17[j]	*n*-Bu	−49.3	B	Me	68	+40.0[f]	35.7	
18[j]	*n*-Bu	−49.3	E	Me	56	+41.2[f]	36.8	

[a] All reactions were carried out by using 10–30 mmol of *O*-menthyl sulfinate 1 and 20–60 mmol of the benzene or ether solution of Grignard reagent. [b] In acetone solution. [c] Yields of the products after chromatography; pure by TLC analysis. [d] Optical purity values were calculated on the basis of the highest values reported in the same solvent: $[\alpha]_D$ +168° for TolSOMe from ref 3; $[\alpha]_D$ −203.6° for TolSOEt (Cope, A. L.; Caress, E. A. *J. Am. Chem. Soc.* **1966**, *88*, 1711); $[\alpha]_D$ +176.5° for TolSO-*n*-Pr from ref 9; $[\alpha]_D$ +139° for MeSO-*n*-Pr from the Ph.D. Thesis of J. D., Polish Academy of Sciences, Łódz, 1974; $[\alpha]_D$ +122° for MeSO-*n*-Bu (Lockard, J. P.; Schroeck, L. W.; Johnson, C. R. *Synthesis* **1973**, 484). [e] In ethanol (96%). [f] In isooctane. [g] With organocopper reagent. [h] From GLC analysis of the crude reaction mixture before purification by chromatography. [i] B = benzene, E = ether. [j] This work.

commonly used is the Andersen synthesis[5] which consists of the reaction of the diastereomerically pure (or enriched in one diastereomer) *O*-menthyl arene- or alkanesulfinates with Grignard reagents carried out in ether solution. However, in many cases this method affords chiral sulfoxides in moderate or low yields depending on the structure of both starting materials, i.e., sulfinate ester and Grignard reagent. For example, Andersen[5] obtained ethyl *p*-tolyl sulfoxide in 62% yield. Moreover, he also reported[6] that the reaction between *O*-menthyl methanesulfinate and phenylmagnesium bromide results in the formation of the crude methyl phenyl sulfoxide in 50% yield only. Phenyl *p*-tolyl sulfoxide was prepared from (−)-*O*-menthyl *p*-toluenesulfinate in 52% yield by Scorrano et al.[7] Mislow and co-workers[8] synthesized a number of chiral alkyl *p*-tolyl sulfoxides. However, the only yield given is that for isopropyl *p*-tolyl sulfoxide (22%).

As a result of the extensive studies on the synthesis of chiral sulfoxides by the method discussed above, Harpp et al.[9] came to the conclusion that the reaction conditions must be carefully selected, otherwise considerable quantities of sulfides and other impurities which are difficult to separate are produced. They recommended the use of organolithium cuprates instead of Grignard reagents for the conversion of sulfinates to sulfoxides. However, in this case also the yields of sulfoxides were in the range between 16% and 59%.

In the course of our studies on the synthesis of chiral sulfinyl compounds, we observed recently a striking effect of benzene as solvent on the yield and stereospecificity of the reaction of (−)-*O*-menthyl *p*-toluenesulfinate and (diisopropylamino)magnesium bromide.[10] This observation, as well as the fact that the reactions involving Grignard reagents are strongly influenced by the solvent used,[11] prompted us to reinvestigate the reaction of *O*-menthyl sulfinates 1 with Grignard reagents in benzene solution in

$$\underset{1}{R^1S(O)OMen} + R^2MgX \xrightarrow{\text{benzene}} \underset{2}{R^1S(O)R^2}$$

the hope of obtaining chiral sulfoxides 2 of greater chemical and optical purity in higher yields.

The reactions were carried out in a standard way; i.e., the Grignard reagent in benzene was added dropwise to a benzene solution of menthyl sulfinate 1 at room temperature. The reaction mixture was stirred for ca. 30 min to give a clear solution. After the typical workup (hydrolysis with saturated ammonium chloride solution, extraction) chiral sulfoxides 2 were isolated by column chromatography on silica gel. The results obtained are collected in Table I. For comparative purposes Table I also contains the corresponding data (yield and optical purity of 2 and the percent of sulfide as an impurity) for the reaction carried out in ether solution.

An inspection of the data in Table I reveals that in all cases the yields of sulfoxides 2 are much higher when the reaction is performed in benzene solution. Comparison of runs 1 and 3 or 12 and 13 in Table I indicates also that the conversion of sulfinates 1 into sulfoxides 2 by means of Grignard reagents in benzene solution is more efficient than that utilizing organocopper compounds. It is worthwhile to mention that the yields of sulfides formed as byproducts are much lower when the reactions of Grignard reagents with sulfinates are performed in benzene.

In conclusion, the reaction of Grignard reagents with *O*-menthyl sulfinates in benzene solution may be recommended as a method of choice for the preparation of chiral sulfoxides.

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Experimental Section

Starting Materials. (-)-(*S*)-*O*-Menthyl *p*-toluenesulfinate was prepared by the method of Phillips;[12] mp 106–107 °C; $[\alpha]_{589}$ -195° (*c* 1.97, acetone) (lit.[13] mp 108–109 °C; $[\alpha]_{589}$ -210°[18]). (-)-(*S*)-*O*-Menthyl *n*-butanesulfinate was prepared according to Mislow et al.;[8] $[\alpha]_{589}$ -49.3° (*c* 1.75, acetone) (lit.[8] $[\alpha]_D$ -50°). (-)-(*S*)-*O*-Menthyl methanesulfinate was prepared according to the procedure described by Andersen;[6] $[\alpha]_{589}$ -60.2° (*c* 1.35, acetone) (lit. $[\alpha]_D$ -99 ± 1° (*c* 2.04, acetone)).

The Grignard reagents used in this work were prepared as usual in ether solution. Then, ether was removed in vacuo at room temperature, and benzene was added (100 mL for each 0.03 mol of R^2MgX) to the residue.

Synthesis of Chiral Sulfoxides 2. General Procedure. A solution of *O*-menthyl sulfinate 1 (1 equiv) in benzene (30 mL/10 mmol of 1) was added dropwise to a benzene solution of Grignard reagent (2 equiv) at room temperature. After completion of the addition, the reaction mixture was stirred for 0.5 h at room temperature. Then, the reaction mixture was treated with aqueous ammonium chloride solution, saturated with sodium chloride, and extracted with chloroform. The combined organic layers were washed with 5% sodium carbonate solution and water and dried over magnesium sulfate. Evaporation of the solvents yielded an oil which was purified by chromatography on silica gel with hexane, hexane–ether, and chloroform as eluents. The yields and optical rotations of sulfoxides 2 obtained in this way are collected in Table I.

Registry No. (-)-(*S*)-1 (R^1 = *p*-toluene), 1517-82-4; (-)-(*S*)-1 (R^1 = Bu), 81769-14-4; (-)-(*S*)-1 (R^1 = Me), 81769-15-5; (+)-2 (R^1 = *p*-toluene;R^2 = Me), 1519-39-7; (+)-2 (R^1 = *p*-toluene; R^2 = Et), 1519-40-0; (+)-2 (R^1 = *p*-toulene; R^2 = I-Pr), 1517-74-4; (+)-2 (R^1 = *p*-toluene; R^2 = Bu), 20288-49-7; (+)-2 (R^1 = *p*-toulene; R^2 = Ph), 16491-20-6; (-)-2 (R^1 = Me; R^2 = Pr), 37177-70-1; (+)-2 (R^1 = Bu; R^2 = Me), 763-95-1.

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Synthesis and Stereochemistry of 1,5-Diazatricyclo[4.4.0.0^{3,5}]decane

Guy S. Ricart, Didier J. Barbry,* and Daniel C. Couturier

Laboratoire de Synthèse Organique, Université des Sciences et Techniques de Lille, 59655 Villeneuve d'Ascq Cédex, France

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The bicyclo[3.1.0]hexane moiety has been the subject of many spectroscopic investigations due to the peculiar cyclopropane effect exerted in polycyclic compounds.[1] We report the conformational analysis of the unknown, 1,5-diazatricyclo[4.4.0.0^{3,5}]decane (**8**) obtained by cyclization of a mixture of the 2-(4-hydroxybutyl)-1,3-diazabicyclo-[3.1.0]hexane epimers **5** and **6** which are new compounds in this series.[2]

Synthesis

The aminolysis of 2-(dimethylamino)tetrahydropyran (**1**) with 2-(aminomethyl)aziridine (**2**) affords a good yield of a mixture of the isomeric compounds **5** and **6** (Scheme I) in a 65:35 ratio (by integration of NMR signals). All attempts (TLC, GLC, HPLC) to separate **5** and **6** failed. The diastereoselectivity observed in this reaction arises from the difference in the reactivity of the two intermediates **3** and **4** (in their preferred *E* configuration): compound **5** is expected to result from the less hindered attack of the aziridine on the imino carbon. Similar imino alcohol participation in those aminolyses was previously noted.[3]

Treatment of the mixture of **5** and **6** with triphenylphosphine–carbon tetrachloride in a basic medium (triethylamine) gives only one liquid compound, **8**, in 21% yield, plus polymeric material. The mechanism of the reaction of triphenylphosphine–carbon tetrahalide with alcohols and β-amino alcohols has been described,[4] and a Walden inversion has been observed in the ring closure of ephedrine.[5] In the transition state of an S_N2 pathway, entering and leaving groups are opposite (180° position); distortion of bond angles and distances favors alternative reactions. With an axial N-3 lone pair, ring closure of **5** would require severe steric interactions; with an equatorial N-3 lone pair, orbital overlapping (N-3 lone pair and C–O σ bond) is noneffective (deviation from the ideal transition state) so that competitive intermolecular reaction is favored. The tricyclic compound is expected to result from the cyclization of **6** which can take place without steric hindrance and with the required trajectory if the N-3 lone pair is equatorial (this equatorial position is preferred as indicated below). Similar ring closure of two isomeric 2-(4-hydroxybutyl)-4-methyltetrahydro-1,3-thiazoles has been reported;[6,7] in that case the formation of two compounds had been observed. Then stereocontrol appears in the cyclization of the mixture of **5** and **6**, due to the presence of the aziridinyl ring.

Conformational Analysis

The structures of the two epimers **5** and **6** were established by NMR spectroscopy. The chemical shifts of C-1′ and C-6 of the major isomer appear upfield relative to those of the minor one: this normal γ effect[8] indicates in **5** a cis relationship of the aziridino methylene and the 2-substituent. The H-6 signals have been assigned according to the ethylenimine rule[9] ($J_{erythro} > J_{threo}$); the H-6 trans to the N-1 lone pair is more shielded than the cis H-6, in agreement with literature data.[10] The two epimers display similar vicinal coupling constants ^3J(H-4,H-5), and so the 1,3-diazabicyclo[3.1.0]hexane moiety would adopt the same conformation in both cases. The low value (ca. 0.5 Hz) observed for ^3J(H-4$_{endo}$,H-5) indicates that the relevant dihedral angle is in the range of the minimum of the Karplus curve (ca. 80° is measured on Dreiding stereomodels): these data suggest a "boatlike" form for the

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