Similar treatment of the more polar Mosher diester with lithium aluminum hydride gave after radial chromatography (−)-**2** as a white solid: mp 107 °C dec; $[\alpha]^{23}_D$ −128.3° (c = 1, CH_2Cl_2).

3,5-Diphenylcyclohex-2-en-1-one Oxime (22). To a stirred solution of 40 g (0.16 mol) of ketone **21**[18] in 1 L of ethanol was added a solution of 22.5 g (0.39 mol) of hydroxylamine hydrochloride in 150 mL of water. The solution was neutralized with 1 N alcoholic KOH to pH 7 and stirred for 4 days at 4 °C, which led to precipitation of a light yellow solid. The heterogeneous mixture was poured into 1 N HCl and thrice extracted with ether. The combined ether extracts were dried (Na_2SO_4) and concentrated in vacuo. The residual yellow solid (42 g) was purified by recrystallization from ethanol. Purification of the mother liquor by flash column chromatography (eluting with 4:1 petroleum ether/ethyl acetate) gave additional **22**; total yield = 38.5 g (91%) of oxime **22** as a white solid: mp 167–170 °C (lit.[19] mp 163–164 °C); IR (film) 3200 (br) 1650, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (10 H, m), 6.65 (1 H, s), 2.75 (5 H, m).

3,5-Diphenylaniline (23).[20] To a stirred mixture of 25.0 g (95 mmol) of oxime **22**, 62 mL (0.66 mol) of acetic anhydride, and 13.5 mL (0.167 mol) of pyridine at 0 °C was added dropwise (over 2 min) 10.5 mL (0.14 mol) of acetyl chloride, during which time a white solid precipitated. The mixture was warmed slowly to 90 °C, at which time the mixture became homogeneous, and then heated at reflux under nitrogen for 2 h. After being cooled to room temperature, the resulting brown solution was poured onto ice and thrice extracted with ether. The combined ether extracts were washed with water, dried (Na_2SO_4), and concentrated in vacuo to give 38 g of a yellow solid, which was not purified (it is a mixture primarily of the amide and imide of **23**) but subjected directly to hydrolysis.

Thus to a mixture of the yellow solid (38 g) and 400 mL of ethanol was added 400 mL of concentrated HCl, and the resulting mixture was heated under reflux for 3.5 h. After being cooled to 0 °C, the crystals were collected by filtration, suspended in 400 mL of water, treated with 350 mL of 5 M NaOH, and stirred at 100 °C for 15 min. The mixture was then cooled to 0 °C, and the crude amine was collected by filtration to give 19.5 g of a light gray solid after washing with cold water and air drying. Recrystallization from ethanol and flash column chromatography (eluting with 6:1 petroleum ether/ethyl acetate) of the mother liquor gave 19 g (81%) of aniline **23** as a gray-white solid: mp 92–95 °C (lit.[6] mp 109–110 °C); IR (film) 3400, 3290, 3180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (11 H, m), 6.90 (2 H, s), 3.50 (2 H, br).

1-Bromo-3,5-diphenylbenzene (24).[21,8] To an ice-cold, vigorously stirred mixture of 15.0 g (61.5 mmol) of **23** in 150 mL of 48% HBF_4 was added dropwise a solution of 75 g of sodium nitrite in 150 mL of water over 2 h. The mixture was then left to stir at 0 °C. The diazonium salt was collected by filtration and washed sequentially with ice-cold water (2×), ice-cold ethanol, and ether (*CAUTION*: although we have experienced no problems with this diazonium salt, diazonium salts have been known to explode, especially in the solid form).

The terphenyldiazonium fluoborate was immediately dissolved in 105 mL of dimethyl sulfoxide, and the resulting solution was added slowly to a vigorously stirred solution of 28.2 g (0.126 mol) of cupric bromide in 60 mL of dimethyl sulfoxide at room temperature over 20 min. After the addition was complete, the reaction mixture was diluted with 750 mL of water and thrice extracted with benzene. The combined benzene extracts were twice washed with water, dried (Na_2SO_4), and concentrated in vacuo to give 22.5 g of yellow solid. Purification by flash column chromatography (eluting with petroleum ether) gave a white solid, which was recrystallized from 95% ethanol to provide 13.7 g (72%) of terphenyl bromide **24**: mp 107–108 °C (after the fact lit.[8] mp 107.5–109 °C); IR (film) 3050, 3020, 2910, 1590, 1580, 1555, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.5. Anal. Calcd for $C_{18}H_{13}Br$: C, 69.90; H, 4.20. Found: C, 69.77; H, 4.31.

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Registry No. (±)-**2**, 118357-17-8; (+)-**2**, 118397-99-2; (−)-**2**, 118357-18-9; **2** (bis (*R*)-Mosher ester isomer 1), 118357-19-0; **2** (bis (*R*)-Mosher ester isomer 2), 118396-92-2; **3**, 27798-73-8; **4**, 118357-03-2; **5**, 118357-04-3; **5** (triacid derivative), 118357-10-1; **6**, 118357-05-4; **7**, 118357-06-5; **8**, 118357-07-6; **9**, 118357-08-7; **10**, 118357-09-8; **11**, 118357-11-2; **12**, 118357-12-3; **16** (cis isomer), 118357-13-4; **16** (trans isomer), 118357-20-3; **17**, 118357-14-5; **18**, 118357-15-6; **19**, 118357-16-7; **21**, 10346-08-4; **22**, 30240-38-1; **23**, 63006-66-6; **24**, 103068-20-8; chloromethyl methyl ether, 107-30-2; dimethyl malonate, 108-59-8.

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Conversion of Antibiotic A82846B to Orienticin A and Structural Relationships of Related Antibiotics

Ramakrishnan Nagarajan,* Donnis M. Berry, Ann H. Hunt, John L. Occolowitz, and Amelia A. Schabel

Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285

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Until recently the clinically important antibiotic, vancomycin, was structurally unique among the class of glycopeptide antibiotics in possessing five aromatic rings with a *N*-methylleucine as the N-terminal amino acid residue. However, several close structural analogues have been reported lately, and these include A51568 factors A and B,[1] the M43 group of antibiotics,[2] A82846 factors A, B, and C,[3] orienticin A, B, and C,[4] and eremomycin.[5] Here we report on the structural relationship of antibiotic A82846B with orienticin A and the structural identity of A82846A to eremomycin.

Amycolatopsis orientalis NRRL 18090 (formerly designated *Nocardia orientalis*) produces glycopeptide antibiotics A82846 factors A, B, and C,[6] and their structures were established as **2**, **3**, and **4**, respectively.[7] Orienticin A, the major component of *Nocardia orientalis* PA42867 has been assigned the structure **5**[4] (Figure 1). Catalytic dechlorination of vancomycin (*1*) occurs initially on the aromatic ring C, and on prolonged reaction the second chlorine on ring A is removed.[8] We undertook a catalytic

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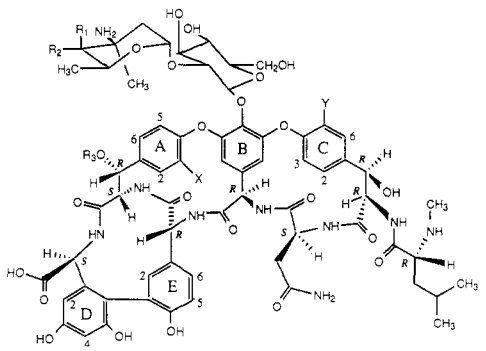
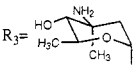
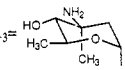


1. Vancomycin X = Y = Cl; R_1 = OH; R_2 = R_3 = H

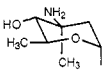
2. A82846A (Eremomycin) X = H; Y = Cl; R_1 = H; R_2 = OH; R_3 =



3. A82846B X = Y = Cl; R_1 = H; R_2 = OH; R_3 =



4. A82846C X = Y = H; R_1 = H; R_2 = OH; R_3 =



5. Orienticin A X = Cl; Y = H; R_1 = H; R_2 = OH; R_3 =

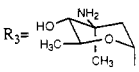


Figure 1.

monodechlorination of A82846B to orienticin A, thereby establishing a direct structural relationship between the A82846 and orienticin antibiotics. Catalytic hydrogenation of A82846B under more vigorous conditions afforded A82846C.

Catalytic hydrogenation of A82846B with 5% palladium on barium sulfate at 15 psi for 2 h gave a product with a MH^+ in the fast atom bombardment mass spectrum (FABMS) of 1557. The high-resolution mass spectrum peak match of MH^+ = 1557.5802, which is consistent for $C_{73}H_{89}N_{10}O_{26}{}^{35}Cl$. This establishes the product to be monodechlorinated A82846B. The fragmentation patterns in the FABMS spectra of A82846A and monodechloro A82846B are similar, and as in the case of A82846A,[3] the FABMS of monodechloro A82846B shows fragments with masses 1414, 1271, 1252, and 1109. These fragments arise due to the sequential cleavages of one 4-epivancosamine, two 4-epivancosamine, one 4-epivancosaminyl-*O*-glucose, and one 4-epivancosamine and one 4-epivancosaminyl-*O*-glucose, respectively. Comparison of the retention times of the above monodechloro 82846B derivative with A82846A and orienticin A in HPLC revealed that, whereas the monodechloro A82846B and orienticin A had retention times of 4.96 and 4.93 min, respectively, which is identical within experimental errors, A82846A had a retention time of 7.70 min. When authentic orientation A was mixed with monodechloro A82846B and examined in the HPLC, a single peak with a retention time of 4.94 min was observed. The monodechloro A82846B derivative was also examined by ^1H NMR spectroscopy, including COSY and NOESY spectra obtained in DMSO solution at 60 °C. Comparison of the nonsugar resonances of monodechloro A82846B with those of orienticin A[9] and monodechloro vancomycin[8] (Table II) indicates that catalytic monodechlorination of A82846B occurred on aromatic ring C of A82846B, as in the case of vancomycin.[8] This shows that the peptide core of monodechloro A82846B, orienticin A,[4] and A82846A are similar; however, in monodechloro A82846B and orienticin A a chlorine is present in aromatic ring A whereas in A82846A the chlorine is present in aromatic ring C. Both A82846B and orienticin A contain one glucose and two 4-epivancosamine[4,10] as their sugar components. Catalytic monodechlorination of A82846B does not alter the structure of sugar residues.[8] On the basis of the above FABMS, HPLC, and ^1H NMR data, *monodechloro A82846B is identical with orienticin A*, and A82846A is a chlorine positional isomer of monodechloro A82846B.

Table I. Comparison of HPLC Retention Times and FABMS Data of A82846 Factors A and B with Orienticin A and Eremomycin

	retention time,[a] min	FABMS (MH^+)
A82846A	7.70	1557
A82846B	7.09	1591
A82846C	5.15	1523
orienticin A	4.93	1557
eremomycin sulfate	7.73	1557
synthetic mixture of A82846A and eremomycin sulfate	7.73	
orienticin A (semisynthetic)	4.96	1557
synthetic mixture of orienticin A and semisynthetic orienticin A	4.94	

[a] The conditions used for HPLC were as follows. Column: Zorbax SCX, 4.6 × 150 mm. Mobile phase: sol A = 10% MeOH, 0.1 m NaH_2PO_4; sol B = 10% MeOH, 0.9 m NaH_2PO_4. Gradient: 20% B to 90% B over a 5-min period, and then hold at 90% B for 2 min. Detection: UV at 225 nm. Injection volume: 20 μL at 1 mg/mL concentration. Psi: 1600.

Table II. Comparison of ^1H NMR Chemical Shifts for Monodechloro Vancomycin, Monodechloro A82846B, and Orienticin A (Nonsugar Resonances)

^1H chemical shifts (TMS = 0.0 ppm)			resonance assignments: monodechloro vancomycin[c]
orienticin[a]	monodechloro A82846B[b]	monodechloro vancomycin[c]	
0.89	0.85	0.87	(N-CH_3)Leu
0.92	0.90	0.90	δ CH_3's
1.42	1.42	1.44	(CH_3)Leu β's
1.52	1.50	1.44	
1.77	1.74	1.73	(N-CH_3)Leu γ
2.18	2.13	2.13	Asn β
2.32	2.31	2.30	Leu N-CH_3
2.56	2.50	2.50	Asn β
3.03	3.00	3.03	(N-CH_3)Leu α
4.23	4.22	4.16	A2′
4.33	4.32	4.34	Asn α
4.48	4.44	4.40	D1′
4.52	4.45	4.43	E1′
4.70	4.73	4.74	C2′
5.15	5.15	5.13	A1′
5.19	5.15	5.15	C1′
5.19	5.15	5.20	B6
5.64	5.66	5.67	B1′
5.76	5.72	5.60	B2
6.38	6.34	6.34	D2
6.39	6.34	6.34	D4
6.71	6.69	6.69	E5
6.79	6.76	6.76	E6
7.09	7.10	7.04	C3
7.12	7.12	7.12	C5
7.15	7.14	7.15	E2
7.22	7.23	7.28	C6
7.29	7.26	7.29	A5
7.33	7.35	7.44	A6
7.59	7.57	7.58	C2
7.86	7.86	7.83	A2

[a] Orienticin A in DMSO-d_6 plus D_2O, 100 °C (400 MHz); ref 9. [b] Monodechloro A82846B in DMSO-d_6, 60 °C (500 MHz). [c] Monodechloro vancomycin in DMSO-d_6, 42 °C (400 MHz); ref 8.

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The glycopeptides A82846A[7] and eremomycin[5] have been assigned the same structure, independently.[11] A82846A and eremomycin showed retention times of 7.70 and 7.73 min, respectively, in the HPLC, and when authentic A82846A and eremomycin were mixed and examined in the HPLC, they eluted as a single peak with a retention time of 7.73 min. This suggests that *A82846A and eremomycin are identical.*

The antibiotic A82846B was hydrogenated with 10% palladium on carbon under 4 atm of pressure for 4 days, and didechlorinated A82846B was obtained. The naturally occurring A82846C has been assigned the structure 4.[7] Comparison of the semisynthetic didechloro A82846B with the natural A82846C by FABMS, HPLC, and ^{1}H NMR data suggested that the above two compounds are identical. This confirms that A82846B and A82846C are identical in all respects, except that A82846B has two additional chlorine atoms in aromatic rings A and C.

Single-crystal X-ray diffraction analyses of the rearranged CDP-I from vancomycin[12] and the analogous rearranged derivative from M43A[2] established the stereochemical identity at all 18 asymmetric centers in these two antibiotics. The monodechloroaglycovancomycin was shown to be identical with the aglycon of orienticin A,[4] thereby establishing that the nine asymmetric centers in these two antibiotics are identical. The ^{1}H NMR comparison of A51568A and vancomycin had shown the structural[1] and, in all probability, the stereochemical identity of A51568A with vancomycin. Finally, on the basis of the comparison of the physical–chemical properties of vancomycin, A51568A, M43A, A82846 factors A, B, and C, orienticin A, and eremomycin, and on the similarities in biological activity and on biogenetic considerations, it is likely that the above antibiotics are similar both structurally and stereochemically. Indeed, the above data suggests that the stereochemical specificity at the nine asymmetric centers in the core heptapeptide aglycons of all the above glycopeptide antibiotics are essential for biological activity.

Comparison of the antibacterial activities reveals that A82846A and A82846B are about 5 times more active than vancomycin,[13] but orienticin A and A82846C are about 2 times less active than vancomycin.[14] These data suggest that *removal of the chlorine in the aromatic ring A in this group of antibiotics has slight, if any, effect on their antibacterial activity.* However, *removal of the chlorine in the aromatic ring C diminishes the activity 10-fold.* Details of the structure–activity relationships of these compounds will be discussed in detail elsewhere.[15]

Experimental Section

The ^{1}H NMR spectra were recorded at 60 °C in DMSO-d_6 solution (concentration was about 2 mg in 0.4 mL) with a Bruker WH-360 spectrometer. Fast atom bombardment mass spectra (FABMS) were determined with a VG ZAB-3F mass spectrometer. Samples were dispersed in thioglycerol and introduced into the spectrometer on a cooled FAB target.

Conversion of A82846B to Orienticin A. To a solution of 100 mg of A82846B in 25 mL of deionized water was added 100 mg of 5% Pd/$BaSO_4$, and the resulting mixture was hydrogenated at ambient temperature at 15 psi for 2 h. An examination by analytical HPLC showed a 1:1 mixture of starting A82846B and a new product. The hydrogenation under pressure was stopped, and the reaction mixture was set aside at ambient temperature. The next morning a small aliquot of the reaction mixture was examined by HPLC before continuing the hydrogenation. However, the HPLC chromatogram of the reaction mixture, after having stood overnight with the catalyst showed only a trace of starting A82846B, and the major product was the new peak observed earlier. The catalyst was filtered, and the filtrate was lyophilized.

The crude product was purified by reversed-phase HPLC with a Zorbax SCX ion-exchange column with a gradient system starting with 10% methanol and 0.1 M NaH_2PO_4 solution to 10% methanol and 0.75 M NaH_2PO_4 solution. The eluates were monitored at 280 nm with a UV detector. The fractions containing the new product were pooled and lyophilized. This pool was then desalted on a HP20 column. Inorganic salts were washed off by eluting the column with five column volumes of deionized water, and the product was eluted with 5% isopropyl alcohol containing 0.5% acetic acid. The eluates were monitored by analytical HPLC using acetonitrile-water gradient system containing 0.2% triethylamine and adjusted to pH 3 by adding the required amount of phosphoric acid. The eluates were monitored at 280 nm by a UV detector. The fractions consisting the new product were pooled, lyophilized and 25.8 mg (27% yield) of monodechloro A82846B was obtained.

This monodechloro A82846B had a MH^+ in high-resolution FABMS of 1557.5802 (calcd 1557.5716), consistent for the composition $C_{73}H_{89}N_{10}O_{26}{}^{35}Cl$. Its HPLC retention time was identical with that of orienticin A but different from that of A82846A. When an authentic sample of orienticin [16] was mixed with the above monodechloro A82846B, there was observed only one peak in the HPLC (Table I). The ^{1}H NMR comparison is shown in Table II.

Conversion of A82846B to A82846C. A slurry consisting of 500 mg of A82846B in 25 mL of water and 1 g of 10% Pd/C was hydrogenated at ambient temperature under 4 atm of pressure for 4 days. The catalyst was filtered, and the filtrate was lyophilized. The crude product was desalted on a HP20 column with five column volumes of deionized water, and the product was eluted with 5% isopropyl alcohol containing 0.1% acetic acid. The appropriate fractions were lyophilized, and 184.1 mg (38% yield) of didechloro A82846B was obtained.

This didechloro A82846B showed a MH^+ = 1523 in the FABMS, and these two antibiotics had the same retention time of 5.15 min. When an authentic sample of A82846C[3] was mixed with didechlorinated A82846B, a single peak with a retention time of 5.15 min was observed.

Comparison of Eremomycin with A82846A. Both A82846A and eremomycin showed the same MH^+ = 1557 in the FABMS spectra. A82846A and eremomycin showed retention times of 7.70 and 7.73 min, respectively, in the HPLC, and when authentic samples of A82846A[3] and eremomycin[16] were mixed and examined in the HPLC, only one peak with a retention time of 7.73 min was observed.

Note Added in Proof. Since we submitted this manuscript for publication, a paper has appeared on the isolation and structure elucidation of chloroorienticins (Tsuji, N.; Kamigauchi, T.; Kobayashi, M.; Terui, Y. *J. Antibiot.* **1988**, *41*, 1506–1510). The structure assigned to chloroorienticin A is the same as A82846B in all respects. These authors have also converted chloroorienticin A to orienticin A by selective hydrogenolysis. Further, the aglycon of chloroorienticin A was identified with that of the aglycon of vancomycin, and the sugar components were characterized as D-glucose and L-4-*epi*-vancosamine. Consequently, it seems that the same antibiotic has been isolated and designated as A82846B by the Lilly Research Laboratories, Eli Lilly and Company, in the USA, as eremo-

(11) Structure studies have shown eremomycin and A82846A to be identical (personal communication, Prof. Y. V. Dudnik, and comparison in Lilly Research Laboratories). See also ref. 5.

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(16) Orienticin A and eremomycin were kindly provided by Dr. Junichi Shoji, Shionogi Research Laboratories, Osaka, Japan, and Professor Y. V. Dudnik, Institute of New Antibiotics, Moscow, USSR, for comparison with monodechlorinated A82846B and A82846A, respectively.

mycin by the Institute of New Antibiotics in the USSR, and as chloroorienticin A by the Shionogi Research Laboratories, Shionogi and Company, in Japan.

Acknowledgment. Orienticin A and eremomycin are gifts from Dr. Jun-ichi Shoji, Shionogi Research Laboratories, Osaka, Japan, and Professor Y. V. Dudnik, Institute of New Antibiotics, Moscow, USSR, respectively, and are gratefully acknowledged. We thank Verna Newton for typing the manuscript.

Preparation of "Free" Sulfoximines by Treatment of *N*-Tosylsulfoximines with Sodium Anthracenide

Carl R. Johnson* and Olivier Lavergne

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

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Since the discovery of the sulfonimidoyl function in 1949, sulfoximines and related derivatives of sulfonimidic acid have received considerable attention.[1] A key feature is the variety of substitutions available to the sulfur-attached imino group. Unfortunately, direct methods for obtaining sulfoximines unsubstituted at nitrogen have serious limitations. The standard procedure involves the reaction of a sulfoxide with hydrazoic acid in a mixture of sulfuric acid and chloroform[2] (Scheme I, method A). In addition to the use of a potentially hazardous reagent,[3] this method is limited to compounds having sulfur substituents that are incapable of forming stable carbonium ions; under the acidic reaction conditions heterolysis of a carbon–sulfur bond usually occurs in cases where the alkyl group is tertiary and to some extent in secondary cases.[2,4] Treatment of a sulfoxide with *O*-(mesitylsulfonyl)hydroxylamine[5] (MSH, method B) provides a general and mild alternate route. The method is limited since MSH is quite difficult to prepare and to handle.[6]

A useful indirect method is the cleavage of the tosyl (*p*-tolylsulfonyl) group of a *N*-tosylsulfoximine (**1**). These compounds are readily available by treatment of a sulfoxide with tosyl azide (or Chloramine-T in the case of dimethyl sulfoxide) in the presence of a copper(II) salt[4] (route 1). They may also be prepared by oxidation of *N*-tosylsulfilimines[7] with alkaline hydrogen peroxide,[8] *m*-chloroperbenzoic acid (*m*CPBA) anion,[9] or sodium periodate–catalytic ruthenium dioxide[10] (route 2). *N*-Tosylsulfoximines have been obtained by reaction of a sulfonimidoyl fluoride[11] or a phenyl sulfonimidate[12] with an alkyllithium (route 3).

Scheme I

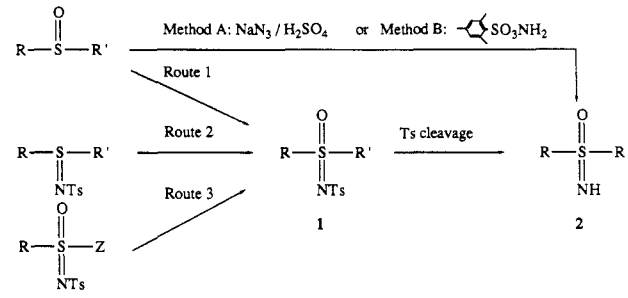

Table I. Isolated Yield of Sulfoximines 2 from Treatment of *N*-Tosylsulfoximes with Sodium Anthracenide in DME at 0 °C

entry	*N*-tosylsulfoximine 1 R	*N*-tosylsulfoximine 1 R′	yields of sulfoximine 2, %
a	CH_3	CH_3	93
b	$C(CH_3)_3$	$(CH_2)_3CH_3$	68
c	$(CH_2)_4$		88
d	CH_3		98
e	CH_3	$N[(CH_2)_3CH_3]_2$	92
f	CH_2CH_3	CCl_2CH_3	21[a]
g	CH_2Ph	CH_3	0[b]
h	Ph	CH_3	0

[a] Isolated product was *S*,*S*-diethylsulfoximine. [b] Starting material recovered.

Three distinct procedures to cleave the tosyl group from *S*,*S*-dimethyl-*N*-tosylsulfoximine (**1a**) to give *S*,*S*-dimethylsulfoximine (**2a**) are found in the literature. Treatment with concentrated sulfuric acid gave **2a** in 40% yield,[13] while irradiation at 253.7 nm in benzene gave 7% of sulfoximine **2a**.[14] A 60% yield was obtained upon treatment of **1a** with sodium in liquid ammonia.[15] Although conceptually sound, some practical difficulties are encountered with the latter procedure since the sodium–liquid ammonia system is somewhat too powerful a reducing agent and requires exactly 2 equiv of sodium per equivalent of sulfoximine. We have found that this problem is circumvented by employing milder reducing reagents such as the sodium arenides.[16]

Tosyl-group cleavage is readily achieved upon treatment of *N*-tosylsulfoximines **1** with a 1,2-dimethoxyethane (DME) solution of sodium anthracenide at 0 °C to give the corresponding free sulfoximines **2** in high yields (Table I). The reaction has the characteristics of a titration.[16] Complete consumption of starting material is indicated by the persistence of the blue color of the anthracenide radical anion. The reagent does not seem to further interact with the product, as the blue color is maintained upon stirring of the reaction mixture with excess reagent at 0 °C for $^1/_2$ h. The yield obtained for entry **a** (Table I) demonstrates the superiority of this method compared to those mentioned above. This procedure allowed preparation of the

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