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Synthesis of chiral 1- and 2-(*p*-tolylsulfinyl)-3-trimethylsilyloxybuta-1,3-dienes and their behaviour in Diels–Alder cycloadditions

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Abstract

The synthesis of (±)-(*E*)-1-(*p*-tolylsulfinyl)-3-trimethylsilyloxybuta-1,3-diene **1** and (S_S)-2-(*p*-tolylsulfinyl)-3-trimethylsilyloxybuta-1,3-diene **2** and their reactions with cyclic dienophiles are described. Cycloaddition of diene **1** with *N*-methylmaleimide **10** was performed under pressure affording a complex reaction mixture from which two epimers at C-3′, (±)-**11a** and (±)-**11b** [2,3,3a,4,5,7a-hexahydro-2-methyl-7a-(1-methylsuccinimide-3-yl)-1*H*-isoindole-1,3,5-triones], were isolated in equal amounts. Diene (±)-**1** cycloadded to the more reactive 4-methyl-1,2,4-triazoline-3,5-dione **14** at atmospheric pressure and room temperature. However, nothing can be said about the stereochemical outcome of this addition since the loss of the chiral auxiliary via the sulfoxide–sulfenate rearrangement gave the bicyclic α,β-unsaturated ketone **17** (2-methyl-2,3,5,6-tetrahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine-1,3,6-trione). Diels–Alder cycloaddition of enantiopure diene **2** with **10** occurred under pressure leading to a diastereomeric mixture of adducts where the trimethylsilyl enol ether moiety spontaneously evolved to the ketone function. The major enantiopure product **18a** [(3a*S*,6*S*,7a*R*,R_S)-2-methyl-6-(*p*-tolylsulfinyl)perhydroisoindole-1,3,5-trione] was isolated and characterized. Cycloadditions of both dienes to dienophile **10** appear highly stereoselective.

1. Introduction

During recent years the sulfinyl group has shown its stereodifferentiating power if linked to a diene moiety involved in Diels–Alder (DA) reactions, so that numerous reports have appeared concerning the synthesis of sulfinyl-substituted 1,3-butadienes[1] and their reactivity as DA partners.[2]

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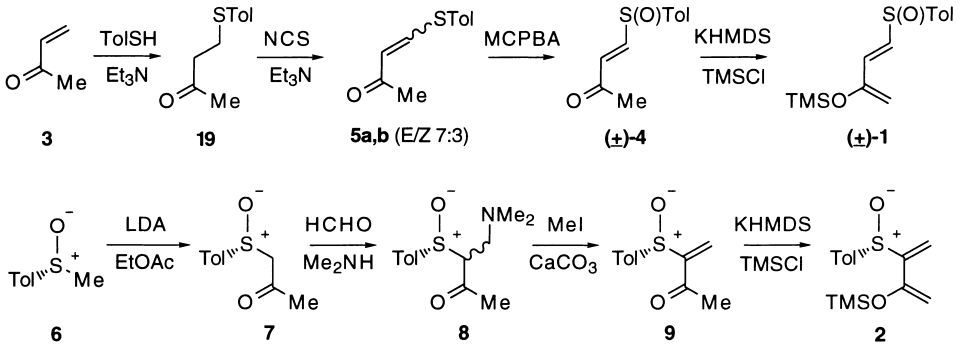
The relevant influence exerted by the sulfinyl group position with respect to the conjugated system has been pointed out for (sulfinylvinyl)cyclohexenes:[3] 2-sulfinyldienes exhibit a higher reactivity in DA cycloadditions than 1-sulfinyldienes. According to this observation, it seemed important to compare the reactivity of open-chain 1- and 2-sulfinyldienes possessing a highly DA activating substituent such as the trimethylsilyloxy group. The simultaneous presence of this substituent and the *p*-tolylsulfinyl group as a chiral auxiliary on a diene system should guarantee a high degree of stereocontrol in DA cycloadditions, an easy removal of the chiral auxiliary from the DA products, and an easy functionalization of the derivatives thus obtained, due to the facile transformation of the trimethylsilyl enol ether into a carbonyl group. On this basis, we reasoned that (*E*)-1-(*p*-tolylsulfinyl)-3-trimethylsilyloxybuta-1,3-diene **1** and (S_S)-2-(*p*-tolylsulfinyl)-3-trimethylsilyloxybuta-1,3-diene **2** (Scheme 1) could be synthetically useful reagents for asymmetric cycloadditions. The previously unknown diene **1** shows the same substituent localization characterized by the Danishefsky diene,[4] and the advantage of being a precursor of cycloadducts in which chiral auxiliary removal should be easily accomplished. The enantiopure diene **2**, prepared by us following a synthetic approach different from that reported previously,[1b] has the sulfinyl group linked to the C-2, thus ensuring, in principle, good reactivity towards common dienophiles.[2f] The synthesis of both dienes **1** and **2** and their DA cycloadditions with cyclic dienophiles are reported in this paper. We were particularly interested in evaluating the role that the 1,3- or 2,3-relationships between the two substituents can play in the reactivity of these butadienes, and their synthetic potentiality for the building of functionalized cyclohexenes.



Scheme 1.

2. Results and discussion

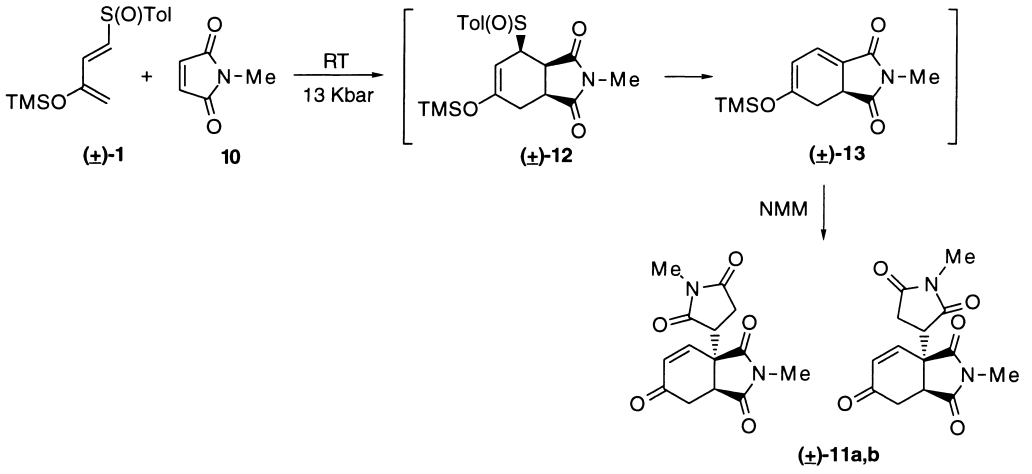
The synthesis of diene **1** was accomplished starting from commercially available methyl vinyl ketone **3** (Scheme 1). The racemic β-sulfinyl α,β-unsaturated ketone **4** was prepared from **3** in three steps, according to literature procedures.[5] When the 7:3 (*E*:*Z*) mixture of sulfides **5**[6] was oxidized by *m*-chloroperbenzoic acid (MCPBA), the sulfoxide **4** obtained had an (*E*)-configuration, in line with previous results.[5b] The enolate anion, generated by treating **4** with potassium bis(trimethylsilyl)amide (KHMDS) in THF/toluene, was trapped by chlorotrimethylsilane[7] affording racemic diene **1** which can be stored at −20°C for several weeks, but rapidly decomposes to ketone **4** on standing at room temperature.

The first asymmetric synthesis of diene **2**, involving three steps from non-commercially available (R_S)-*p*-tolyl vinyl sulfoxide, was published by Maignan et al. in 1992.[1b] The low overall yield

of this approach (~30%) prompted us to exploit the alternative method shown in Scheme 1. Condensation of commercial (R_S)-methyl *p*-tolylsulfoxide **6** with ethyl acetate gave sulfinylketone **7** (88% yield) according to the procedure of Solladié and Ghiatou.[8] Compound **7** was reacted with formaldehyde and dimethylamine to give **8** as a mixture of epimers, which evolved into the enantiopure ketosulfoxide **9**[9] via Hofmann degradation. The combined yield for the transformation of **7**→**9** was 97%. Finally, sulfoxide **9** was subjected to Nakagawa's enolization[7] without any purification, leading to enantiopure diene **2**.

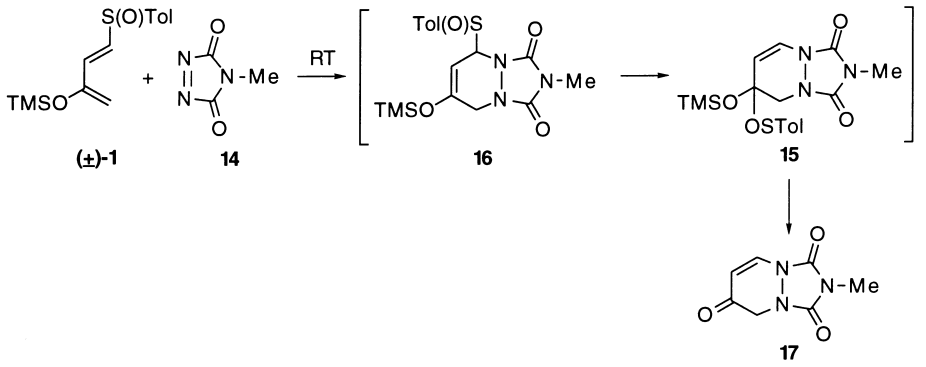
Dienes **1** and **2** were used in DA reactions without chromatographic purification since both easily undergo spontaneous decomposition. NMM **10** was chosen as a typically highly reactive dienophile involving no regiochemistry problems.

Cycloaddition of (±)-**1** with NMM **10** required the use of high pressure (13 Kbar), affording a complex mixture of products from which only two diastereoisomers (±)-**11a**,**b** could be isolated and their structures (Scheme 2) unequivocally assigned on the basis of their spectroscopic parameters. The formation of (±)-**11a**,**b** may be the result of a three-step reaction sequence. The first one involves NMM addition to the less hindered face of diene **1** where the sulfinyl group adopts the spatial arrangement which minimizes the electrostatic repulsive interactions between sulfinyl and carbonyl oxygen atoms.[2a] The second step is the elimination of *p*-toluenesulfenic acid from adduct (±)-**12** giving trimethylsilyloxydiene (±)-**13**, which, in the last step, acts as a nucleophile towards NMM **10**. A 1:1 racemic mixture of epimers at C-3′, (±)-**11a** and (±)-**11b**, was obtained. Taking into account the behaviour of several 1-sulfinyl dienes previously involved in DA reactions with NMM **10**[2a] and the present results [(±)-**11a** and (±)-**11b** differ only in the configuration of the stereogenic centre formed during the last step of the reaction sequence] we suggest that the reaction shown in Scheme 2 was accomplished with a very high stereoselectivity, even if the complexity of the crude reaction mixture does not allow for certainty about complete stereoselectivity.[2a]



Scheme 2.

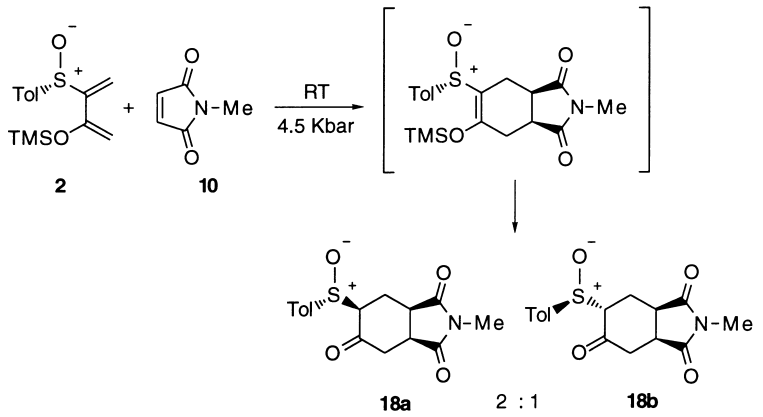
The more reactive 4-methyl-1,2,4-triazoline-3,5-dione **14** was then reacted with diene (±)-**1** (Scheme 3) and the reaction was accomplished at room temperature within 1 h. An inspection of the crude reaction product showed the almost unique presence of sulfenate **15**, by ^{1}H NMR analysis: apart from the typical resonances of the O–S–Tol and O–TMS groups, we could observe H_2-5 resonating as an AB system centred at δ 3.96 ($J_{5A,5B}$ = 15.0) and H-7,8 resonating as two



Scheme 3.

broad doublets at δ 4.90 and 6.42, respectively ($J_{7,8} = 5.0$). The intermediate **15** was obtained by initial [2,3]-sigmatropic rearrangement of cycloadduct **16**, subsequently spontaneously evolved to the α,β-unsaturated ketone **17**. This latter compound was isolated and characterized.

Cycloaddition of **2** with NMM **10** occurred only in dichloromethane under pressure (4.5 Kbar) affording a 2:1 diastereomeric mixture of compounds **18** (Scheme 4), from which the major diastereoisomer **18a** was isolated in enantiomerically pure form by crystallization from hexane/ethyl acetate. All the attempts to isolate **18b** by chromatography were unsuccessful because of the decomposition of the mixture which occurred during chromatography. Chemical shifts and coupling constants from the ^{1}H NMR spectrum of compound **18a** are given in Table 1. The spin–spin coupling constants of the bridgehead nuclei H-3a,7a suggest a preferred extended boat conformation of the fused bicyclic system (Fig. 1), as shown previously for racemic compounds of similar structure.[10] The chemical shifts of H_2-7 appear in line with the conformational preference around the C–S bond shown in Fig. 1, and already observed for 2-sulfinyl cyclohexanones, where the equatorial H_B-7 is clearly shielded by the anisotropic effect of the aromatic ring in 1,3-parallel arrangement.[11] On the basis of these data, for **18a** we suggest the stereochemistry depicted in Fig. 1, with all *cis* substituents, and assign the (3a*S*,6*S*,7a*R*,R_S) absolute configuration to its stereogenic centres. Moreover, an accurate inspection of the ^{1}H NMR absorptions of the 2:1 mixture of **18a**:**18b** allowed us to identify **18b** as the epimer of **18a** at C-6:[11] in particular, we were able



Scheme 4.

Table 1
Selected ^{1}H NMR parameters of compound **18a**

Proton	δ	J		
H-3a(axial)	3.14, ddd	$J_{3a,4A}$ 7.0 ($J_{ax,eq}$)	$J_{3a,4B}$ 11.8 ($J_{ax,ax}$)	$J_{3a,7a}$ 8.8 ($J_{ax,ax}$)
H_A-4 (equatorial)	3.01, dd	$J_{4A,4B}$ 14.0 (J_{gem})		
H_B-4 (axial)	2.59, dd			
H-6(axial)	3.21, dd	$J_{6,7A}$ 12.5 ($J_{ax,ax}$)	$J_{6,7B}$ 5.6 ($J_{ax,eq}$)	
H_A-7(axial)	2.42, dt	$J_{7A,7B}$ 14.2 (J_{gem})	$J_{7a,7A}$ 12.5 ($J_{ax,ax}$)	
H_B-7 (equatorial)	1.95, dt	$J_{7a,7B}$ 5.6 ($J_{ax,eq}$)		
H-7a(axial)	2.89, ddd			

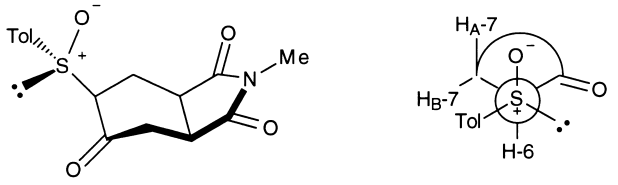


Figure 1. Conformational preferences for compound **18a**

unequivocally to identify H-6 of **18b** resonating as a doublet of doublets at δ 3.52 ($J_{6,7} = 10.2$ and 6.1), together with further significant resonances. All of these results cogently support a cycloaddition between **2** and **10** (Scheme 4) occurring in a completely stereoselective manner, followed by a less diastereoselective Si–O bond cleavage.

In this paper we have reported the synthesis of the previously unknown diene (±)-**1** and first studies of its DA reactivity in comparison with that of diene **2**. The presence of the 3-OTMS substituent on the diene skeleton does not modify the DA reactivity or stereoselectivity of 1-sulfinyldienes, in line with previously reported results,[2a] but strongly decreases the reactivity of 2-sulfinyldienes.[2b,f] We suggest that the lower reactivity of **2** is a result of its difficulty in adopting the *s-cis* conformation required by DA transition states, because of the proximity of the highly sterically demanding *p*-tolylsulfinyl and trimethylsilyloxy substituents on the diene moiety. Generally, dienes **1** and **2** are difficult to handle. The severe reaction conditions required by DA cycloadditions of dienes **1** and **2** with NMM **10** caused further evolution of the initial adducts towards mixtures of diastereoisomers, thereby limiting their use in asymmetric synthesis.

3. Experimental

3.1. General methods and materials

Solvents were purified according to standard procedures. All reactions were monitored by TLC on commercially available precoated plates (Merck silica gel 60 F_{254}), and the products were visualized with a UV light, phosphomolybdic acid and 2,4-dinitrophenylhydrazine. Merck silica gel (230–400 mesh ASTM) was used for column chromatography. Preparative TLC separations were performed on Merck neutral alumina plates. Mps were measured on a microscopic apparatus and are uncorrected. Elemental analyses were performed by the Servicio Interdepartamental de

Investigación (SIdI) de la Universidad Autonóma de Madrid with a Perkin–Elmer 2400 CHNS/O. Specific rotations $[\alpha]_D$ were measured in $CHCl_3$ solutions at room temperature and are given in 10^{-1} deg cm^2 g^{-1}; concentrations (c) are expressed in g/100 ml. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer at 200.1 and 50.3 MHz, respectively, in $CDCl_3$ solutions with $SiMe_4$ as the internal standard; J values are given in hertz; the attributions are supported by double resonance experiments. IR spectra were obtained in $CHCl_3$ solutions with a Philips PU-9716 instrument. Mass spectra were measured by electron impact (EI, 70 eV) with a VG AutoSpec instrument. Cycloadditions under pressure were realized using a UNIPRESSEQUIPMENT 101 LV 30/16.

3.2. 4-(p-*Tolylthio*)-2-butanone **19**[12]

Et_3N (311 μl, 2.2 mmol) was added dropwise at −15°C to a stirred solution of methyl vinyl ketone **3** (15.65 g, 223 mmol) and *p*-thiocresol (40 ml, 334 mmol) in $CHCl_3$ (40 ml). After stirring for 12 h at room temperature, the mixture was diluted with Et_2O and washed with 5% aqueous K_2CO_3 and half-saturated brine. The organic layers were dried (Na_2SO_4) and the solvent was evaporated under vacuum. The crude mixture was purified by column chromatography eluting with hexane:EtOAc (91:9) to give 4-(*p*-tolylthio)-2-butanone **19**: oil; 90% yield; ^1H NMR δ_H 7.3–7.1 (AA′BB′ system, ArH), 3.10 (t, $J_{3,4}=7.5$, H_2-4), 2.74 (t, H_2-3), 2.34 (s, *Me*Ar), 2.14 (s, H_3-1); ^{13}C NMR δ_C 206.4, 136.3, 131.7, 130.2, 129.6, 42.9, 29.8, 27.9, 20.8; IR ν_{max} 2810, 1710, 1490, 1360, 1170 cm^{-1}; EIMS m/z (%) 194 (M, 100), 151 (17), 137 (19), 124 (52), 91 (33).

3.3. (E)-4-(p-*Tolylthio*)-3-buten-2-one **5a**[6]

NCS (14.11 g, 106 mmol) was slowly added to a solution of 4-(*p*-tolylthio)-2-butanone **19** (17.11 g, 88 mmol) in CCl_4 (150 ml) at 0°C. The mixture was allowed to spontaneously reach room temperature, stirred for 2 h and filtered. The solvent was removed under vacuum and the resulting oily residue was dissolved in $CHCl_3$ (150 ml) and treated with Et_3N (1.2 ml). The solution was then heated at reflux and after 45 min cooled to room temperature. The reaction mixture was washed with 10N HCl and a half-saturated brine solution. The organic layers were dried (Na_2SO_4) and concentrated under vacuum. The oily residue was purified by column chromatography beginning the elution with hexane:acetone (96:4) and gradually increasing the acetone percentage up to 100%. 4-(*p*-Tolylthio)-3-buten-2-one **5** was obtained (64% yield) as a 67:33 mixture of (*E*)- and (*Z*)-isomers, respectively, and this mixture was used for preparing racemic sulfoxide **4** (see below). However, crystallization of the mixture **5** from hexane/Et_2O gave (*E*)-4-(*p*-tolylthio)-3-buten-2-one **5a**: mp 59–60°C (found: C, 68.32; H, 6.18; S, 16.76. $C_{11}H_{12}OS$ requires: C, 68.71; H, 6.29; S, 16.67%); ^1H NMR δ_H 7.67 (d, $J_{3,4}=15.2$, H-4), 7.4–7.2 (AA′BB′ system, ArH), 5.92 (d, H-3), 2.38 (s, *Me*Ar), 2.19 (s, H_3-1); δ_C 194.5, 147.2, 139.3, 132.9, 130.3, 129.4, 124.2, 27.0, 20.9; IR ν_{max} 2910, 1650, 1540, 1220, 950, 760 cm^{-1}. (*Z*)-4-(*p*-tolylthio)-3-buten-2-one **5b**: δ_H 7.67 (d, $J_{3,4}=9.6$, H-4), 7.4–7.2 (AA′BB′ system, $J_{ortho}=8.3$, ArH), 6.35 (d, H-3), 2.36 (s, *Me*Ar), 2.27 (s, H_3-1); ^{13}C NMR δ_C 196.1, 149.4, 137.9, 130.5, 130.1, 126.0, 119.7, 26.7, 20.8.

3.4. (±)-(E)-4-(p-*Tolylsulfinyl*)-3-buten-2-one **4**

MCPBA (4.5 g, 26 mmol) was dissolved in CH_2Cl_2 (100 ml) and slowly added to a stirred solution of 4-(*p*-tolylthio)-3-buten-2-one **5** (5 g, 26 mmol) in CH_2Cl_2 (300 ml) at 0°C. The reaction

mixture was stirred for 30 min, diluted with Et_2O and washed with a saturated solution of $NaHCO_3$ and with a half-saturated brine solution. The organic phase was dried (Na_2SO_4), the solvent evaporated under vacuum and the crude mixture was purified by column chromatography eluting with hexane:EtOAc (96:4). Crystallization from hexane/Et_2O gave (±)-(*E*)-4-(*p*-tolylsulfinyl)-3-buten-2-one **4**: mp 78–80°C (found: C, 63.35; H, 5.73; S, 15.43. $C_{11}H_{12}O_2S$ requires: C, 63.44; H, 5.81; S, 15.39%); 63% yield; ^{1}H NMR δ_H 7.5–7.3 (AA′BB′ system, ArH), 7.32 (d, $J_{3,4}=15.1$, H-4), 6.97 (d, H-3), 2.42 (s, *Me*Ar), 2.34 (s, H_3-1); ^{13}C NMR δ_C 195.0, 149.4, 142.6, 138.0, 130.4, 130.0, 124.9, 26.2, 21.4; IR ν_{max} 2910, 1680, 1580, 1210, 1050, 960, 750 cm^{-1}.

3.5. (±)-1-(p-*Tolylsulfinyl*)-3-*trimethylsilyloxybuta-1,3-diene* ***1***

A 0.5 M solution of KHMDS in toluene (10.44 ml, 5.2 mmol) was added dropwise to (±)-(*E*)-4-(*p*-tolylsulfinyl)-3-buten-2-one **4** (0.730 g, 3.5 mmol) in toluene/THF at −78°C under stirring. TMSCl (662 μl, 5.2 mmol) and H_2O (15 ml) were consecutively added at short intervals of 10 min each. The crude product was extracted with hexane (3×20 ml) and the combined organic layers were dried (Na_2SO_4). After evaporation of the solvent, (±)-1-(*p*-tolylsulfinyl)-3-trimethylsilyloxybuta-1,3-diene **1** was obtained and used without further purification: oil; 60% yield; ^{1}H NMR δ_H 7.6–7.3 (AA′BB′ system, ArH) 6.86 and 6.55 (AB system, $J_{1,2}=14.5$, H-1,2), 4.67 and 4.60 (two broad s, H_2-4), 2.44 (s, *Me*Ar), 0.16 (s, Me_3Si).

3.6. (R_S)-4-(N,N-*Dimethylamino*)-3-(p-*tolylsulfinyl*)-2-*butanone* ***8***

A 40% solution of Me_2NH in H_2O (0.192 ml) and a 37% aqueous solution of HCHO (0.114 ml) were added to (R_S)-1-(*p*-tolylsulfinyl)-2-propanone **7**[8,13] (0.01 g, 0.51 mmol) in MeCN (2.5 ml) at 0°C. After stirring (10 min), the solution was diluted with H_2O (10 ml) and extracted with CH_2Cl_2 (3×10 ml). The organic layers were dried (Na_2SO_4) and the solvent evaporated under vacuum to give an epimeric mixture of (R_S)-4-(*N,N*-dimethylamino)-3-(*p*-tolylsulfinyl)-2-butanone **8** which was used for the next steps without further purification: oil; ^{1}H NMR δ_H 7.5–7.3 (two AA′BB′ systems, ArH), 3.99 (m, H-3 of one epimer), 3.62 (m, H-3 of the other epimer), 2.94 (m, H_2-4 of one epimer), 2.78 (m, H_2-4 of the other epimer), 2.41 (s, *Me*Ar), 2.25 and 2.22 (two s, NMe_2), 2.10 (s, H_3-1 of one epimer), 2.09 (s, H_3-1 of the other epimer).

3.7. (S_S)-3-(p-*Tolylsulfinyl*)-3-*buten-2-one* ***9***[9]

(R_S)-4-(*N,N*-Dimethylamino)-3-(*p*-tolylsulfinyl)-2-butanone **8** (0.129 g, 0.51 mmol) in MeCN (2.5 ml) and MeI (0.16 ml, 2.5 mmol) were consecutively added to $CaCO_3$ (0.153 g, 1.53 mmol) at 0°C. The suspension was stirred for 1.5 h and then H_2O (20 ml) was added. The aqueous solution was extracted with CH_2Cl_2 (3×30 ml) and the organic layers were dried (Na_2SO_4). After evaporation of the solvent, (S_S)-3-(*p*-tolylsulfinyl)-3-buten-2-one **9** was obtained, not needing purification: oil; 97% yield from sulfoxide **7**; $[\alpha]_D$ +355 (*c* 1.0) {lit.[9] $[\alpha]_D$ +294 (*c* 0.72 in acetone)}. Spectral data are in accordance with the literature.[9]

3.8. (S_S)-2-(p-*Tolylsulfinyl*)-3-*trimethylsilyloxybuta-1,3-diene* ***2***[1b]

Anhydrous TMSCl (92 μl, 0.73 mmol) was added to a solution of (S_S)-3-(*p*-tolylsulfinyl)-3-buten-2-one **9** (0.10 g, 0.5 mmol) in toluene/THF (1.76/1.60 ml) at −78°C under argon. After 5

min of stirring, a 0.5 M solution of KHMDS in toluene (1.44 ml) was added to the mixture which was maintained under stirring for a further 30 min. The work-up of the reaction was carried out by adding H_2O (10 ml) and extracting the aqueous phase with hexane (3×20 ml). The organic layers were combined and dried (Na_2SO_4) to obtain (S_S)-2-(*p*-tolylsulfinyl)-3-trimethylsilyloxybuta-1,3-diene **2** which was used without further purification: oil; 80% yield (estimated on the basis of spectral data in accordance with the literature).[1b]

*3.9. 2,3,3a,4,5,7a-Hexahydro-2-methyl-7a-(1-methylsuccinimide-3-yl)-1*H-*isoindole-1,3,5-triones* ***11***

A solution of NMM **10** (0.133 g, 1.2 mmol) in anhydrous CH_2Cl_2 (1 ml) was added to racemic 1-(*p*-tolylsulfinyl)-3-trimethylsilyloxybuta-1,3-diene **1** (0.112 g, 0.4 mmol) dissolved in anhydrous CH_2Cl_2 (1 ml) and the reaction was performed in a polyethylene vial under pressure (13 Kbar for 64 h). After evaporation of the solvent, the crude reaction mixture was purified by column chromatography and preparative TLC eluting with hexane:acetone 80:20 to give, in low yields, about equal amounts of the two racemic mixtures **11a** and **11b**, mutually epimers at C-3′ [the symbol (′) identifies atoms pertaining to the succinimide substituent]. (±)-**11a**: oil; ^{1}H NMR δ_H 6.71 (dd, $J_{6,7}=10.5$, $J_{4A,7}=1.1$, H-7), 6.27 (d, H-6), 3.72 (dd, $J_{3',4'A}=9.5$, $J_{3',4'B}=6.0$, H-3'), 3.24 (br AB d, $J_{4A,4B}=18.8$, H_A-4), 3.13 (br d, $J_{3a,4B}=9.3$, H-3a), 3.07 and 3.02 (two s, 2×Me), 2.97 (AB dd, $J_{4'A,4'B}=18.3$, H_A-4′), 2.71 (AB dd, H_B-4), 2.66 (AB dd, H_B-4′); EIMS *m*/*z* (%) 290 (M, 5), 233 (15), 205 (77), 178 (96), 120 (52), 113 (94), 92 (100), 65 (37); HRMS calcd for $C_{14}H_{14}N_2O_5$: 290.0903; found: 290.0909. (±)-**11b**: oil; ^{1}H NMR δ_H 6.70 (dd, $J_{6,7}=10.9$, $J_{4A,7}=1.6$, H-7), 6.27 (d, H-6), 3.93 (br d, $J_{3a,4B}=8.1$, H-3a), 3.33 (dd, $J_{3',4'}=9.1$ and 5.9, H-3′), 3.22 (br AB d, $J_{4A,4B}=18.0$, H_A-4), 3.02 and 3.00 (two s, 2×Me), 3.01 (m, H_2-4′), 2.58 (AB dd, H_B-4); EIMS *m*/*z* (%) 290 (M, 2), 205 (21), 178 (61), 120 (23), 113 (100), 92 (47), 91 (48), 65 (26), 57 (42), 55 (30).

*3.10. 2-Methyl-2,3,5,6-tetrahydro-1*H-*[1,2,4]triazolo[1,2-*a*]pyridazine-1,3,6-trione* ***17***

A solution of 4-methyl-1,2,4-triazoline-3,5-dione **14** (0.051 g, 0.45 mmol) in CH_2Cl_2 (5 ml) was slowly added to racemic 1-(*p*-tolylsulfinyl)-3-trimethylsilyloxybuta-1,3-diene **1** (0.126 g, 0.45 mmol) dissolved in anhydrous CH_2Cl_2 (5 ml), under argon. After stirring (1 h) the solvent was evaporated under vacuum and the reaction mixture purified by preparative TLC eluting with hexane:acetone 75:25 to give the bicyclic compound **17**: 33% yield; ^{1}H NMR δ_H 7.75 (d, $J_{7,8}=8.3$, H-8), 5.59 (d, H-7), 4.37 (s, H_2-5), 3.18 (s, Me); ^{13}C NMR δ_C 184.5, 150.8, 146.5, 132.9, 105.0, 50.6, 25.6; IR ν_{max} 2910, 1790, 1730, 1600, 1470, 1310, 1270, 760 cm^{-1}; EIMS *m*/*z* (%) 181 (M, 37), 126 (10), 96 (100), 68 (7), 56 (21).

*3.11. (3a*S*,6*S*,7a*R*,*R*$_S$)-2-Methyl-6-(*p-*tolylsulfinyl)perhydroisoindole-1,3,5-trione* ***18a***

A solution of NMM **10** (0.143 g, 1.29 mmol) in anhydrous CH_2Cl_2 (1 ml) was added to (S_S)-2-(*p*-tolylsulfinyl)-3-trimethylsilyloxy-1,3-butadiene **2** (0.120 g, 0.43 mmol) dissolved in anhydrous CH_2Cl_2 (1 ml), and the reaction was performed in a polyethylene vial under pressure (4.5 Kbar for 5 days). After evaporation of the solvent, the reaction mixture was purified by column chromatography eluting with CH_2Cl_2:EtOAc 90:10. 2-Methyl-6-(*p*-tolylsulfinyl)perhydroisoindole-1,3,5-trione **18** was obtained as a 1:2 diastereoisomeric mixture which was crystallized from hexane:EtOAc to give (3a*S*,6*S*,7a*R*,*R*$_S$)-2-methyl-6-(*p*-tolylsulfinyl)perhydroisoindole-1,3,5-trione **18a**: mp 150–151°C; $[\alpha]_D$ +538 (*c* 0.9); ^{1}H NMR δ_H 7.4–7.3 (AA′BB′ system, ArH), 3.21 (dd,

$J_{6,7A} = 12.5$, $J_{6,7B} = 5.6$, H-6), 3.14 (ddd, $J_{3a,4A} = 7.0$, $J_{3a,4B} = 11.8$, $J_{3a,7a} = 8.8$, H-3a), 3.03 (s, NMe), 3.01 (dd, $J_{4A,4B} = 14.0$, H_A-4), 2.89 (ddd, $J_{7a,7A} = 12.5$, $J_{7a,7B} = 5.6$, H-7a), 2.59 (dd, H_B-4), 2.44 (s, *Me*Ar), 2.42 (dt, $J_{7A,7B} = 14.2$, H_A-7), 1.95 (dt, H_B-7); ^{13}C NMR δ_C 203.0, 177.1, 176.7, 142.3, 136.9, 130.2, 123.9, 68.8, 38.9, 37.6, 36.7, 25.1, 21.4, 18.5; EIMS *m*/*z* (%) 319 (M, 4), 303 (9), 179 (30), 139 (49), 124 (49), 91 (89), 66 (100).

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