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TETRAHEDRON: *ASYMMETRY*

Ready access to the 6,8-dioxabicyclo[3.2.1]octane ring system using asymmetric heterocycloaddition induced by a chiral sulfoxide: application to the total synthesis of the *Mus musculus* pheromone

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Abstract

A new stereocontrolled total synthesis of the (1*R*,5*S*,7*R*)-*exo*-6,8-dioxabicyclo[3.2.1]oct-3-ene skeleton of the *Mus musculus* pheromone has been achieved via an asymmetric intermolecular Diels–Alder reaction and an intramolecular conjugated addition, controlled by a chiral auxiliary.

1. Introduction

The sulfinyl group has been widely used as a chiral auxiliary in asymmetric syntheses.[1] Within the space of a few years, the synthesis of chiral sulfinyl-1,3-dienes and their use in asymmetric Diels–Alder reactions has become an important development.[1,2] In recent papers,[3–6] we have reported the first examples of intermolecular Diels–Alder reactions using chiral sulfinyloxabuta-1,3-dienes **I** (R=H, CH_3) and an application of this methodology to the synthesis of both enantiomers of 1,7-dioxaspiro[5.5]undecane, the pheromone components of the *Dacus oleae* olive fruit-fly.[6] The results obtained highlighted the great reactivity of these compounds, under extremely mild and non-catalytic conditions, in inverse electronic demand [4+2] heterocycloadditions. These reactions occur without selectivity with enol ethers[3–5] but with a total selectivity with styrenic dienophiles.[5]

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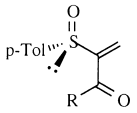
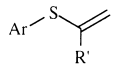


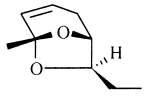
I

R = H
R = CH_3 : (Ss)-**1**



II

R' = H
R' = (R)-*$CH(CH_3)OH$: (R)-**7**

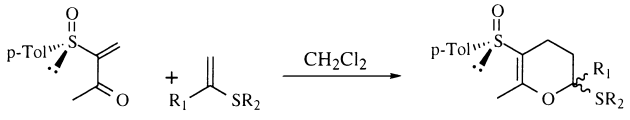


(1R,5S,7R)-**13**
Mus Musculus Pheromone

To complement our work in this field, we investigate here an extension of the cycloadditions of (+)-(*S*)-3-*p*-tolylsulfinylbut-3-en-2-one **1** towards sulfide activated dienophiles **II** as well as an original application to the asymmetric 6,8-dioxabicyclo[3.2.1]octane and oct-3-ene ring system, structures widely found in many naturally occurring compounds,[7] with the total synthesis of the *Mus musculus* (house mouse) pheromone.[8]

2. Results and discussion

The results reported here emphasize the high reactivity of (*S*s)-3-*p*-tolylsulfinylbut-3-en-2-one **1** as a heterodiene. Indeed, cycloadditions of (*S*s)-**1** with simple enol thioethers were performed without a catalyst and at room temperature or by refluxing in dichloromethane (Scheme 1).



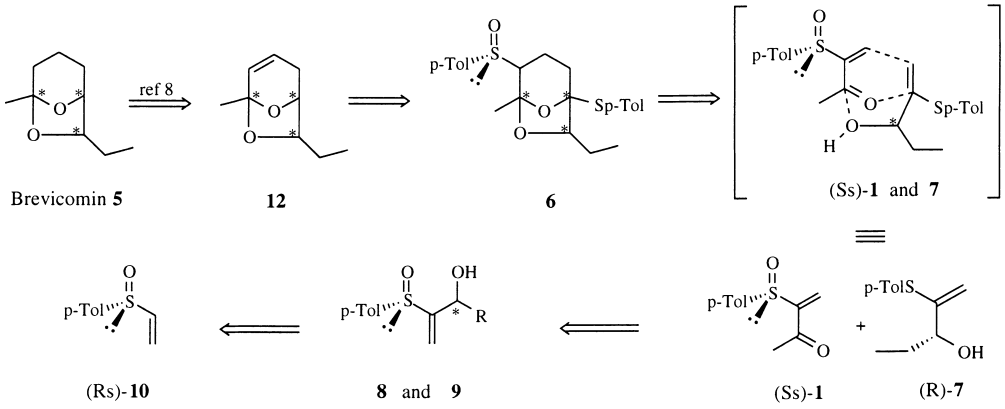
(Ss)-**1** (Ss)-**2** to **4**

Entry	R_1	R_2	Conditions	Products	Yields	d.r.
1	H	CH_2CH_3	RT, 8 hours	(Ss)-**2**	74 %	29/71
2	H	C_6H_5	Δ, 6 days	(Ss)-**3**	70 %	22/78
3	$(CH_3)_2COH$	CH_3-C_6H_4	Δ, 5 days	(Ss)-**4**	55 %	30/70

Scheme 1.

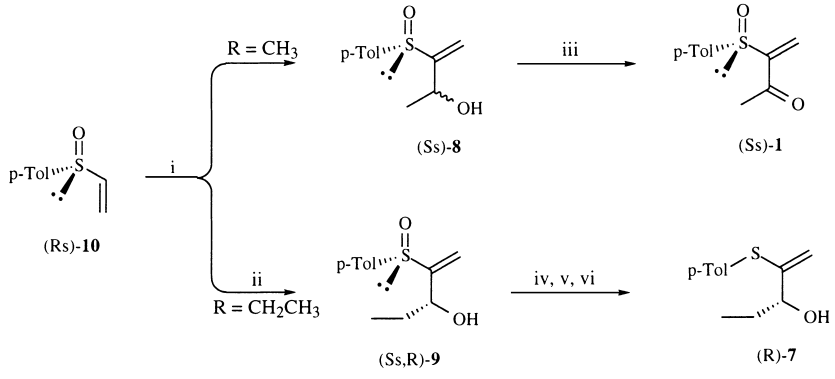
Under these conditions, an interesting selectivity was observed in comparison with the oxygenated series. Indeed, good yields and diastereomeric excesses equal to, or higher than, 40% were observed. These new results, extended to a new chiral-sulfide-activated dienophile **7**, make it possible to plan an application for asymmetric access to the 6,8-dioxabicyclo[3.2.1]octane skeleton of brevicomin **5**. Our synthetic analysis is shown in Scheme 2.

The bicyclic structure of compound **6** can be obtained from the sulfinylbutenone **1** and chiral enol thioether **7**. These two compounds can be easily prepared from (*R*s)-*p*-tolylvinylsulfoxide **10**[9] by addition of the appropriate aldehyde RCHO[10] (R=CH_3 or CH_2CH_3) followed by oxidation of the hydroxy group for R=CH_3, or by reduction of the sulfinyl group for R=CH_2CH_3: this approach offers several advantages: (i) we start exclusively from (*R*s)-*p*-tolylvinylsulfoxide **10** for access to the heterodiene and to the dienophile. Indeed, the sulfinyl group is the chiral auxiliary of (*S*s)-**1** and could be used to build up the stereogenic center of **7**; (ii) during the heterocycloaddition, sulfinyl and sulfide groups act as activating substituents for the diene and the dienophile, respectively; and (iii) we take advantage of the Michael acceptor system formed during the intermolecular Diels–Alder reaction to achieve the intramolecular conjugate addition of the hydroxy group.



Scheme 2.

Alcohols **8** and **9** were prepared[10] by treatment of (*R*s)-**10** with lithium diisopropylamide followed by addition of acetaldehyde [(*S*s)-**8**] or propanal [(*S*s)-**9**] in 61 and 57% yields, respectively. Jones oxidation of the diastereomeric alcohols (*S*s)-**8**[11] affords (*S*s)-**1** in a 95% yield. Compound (*S*s,*R*)-**9** was isolated in a diastereomerically pure form (*de* >98%) by crystallization in diisopropylether.[12] Reduction of the sulfoxide to sulfide was successfully achieved by the P_2I_4/pyridine system[13] in ether after protection of the hydroxyl with TBDMSCl/imidazole in DMF.[14,15] Desilylation with *n*Bu_4NF in THF gives (*R*)-**7** in a 61% overall yield from (*S*s,*R*)-**9** (Scheme 3).

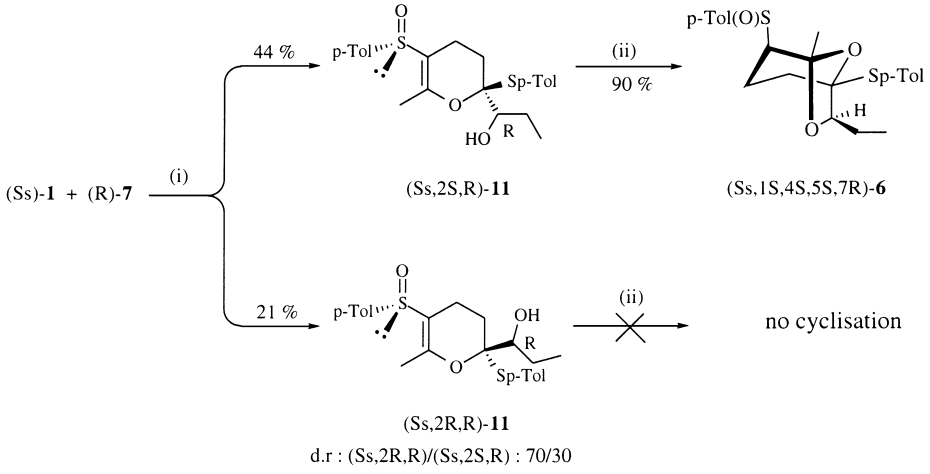


Scheme 3. Reagents and conditions: (i) LDA/THF, RCHO, 61% (R=CH_3) and 57% (R=CH_2CH_3); (ii) separation by crystallization, 22%; (iii) Jones reagent, −20°C, acetone, 95%; (iv) $CF_3SO_3SiMe_2t$Bu, 2,6-lutidine, CH_2Cl_2, 95%; (v) P_2I_4, pyridine, ether, 80%; (vi) *n*Bu_4NF, THF, 81%

The hetero Diels–Alder reaction between (*S*s)-**1** and (*R*)-**7** by refluxing in dichloromethane after 5 days affords cycloadducts (*S*s)-**11** as a 70:30 diastereomeric mixture (Scheme 4).

Due to the presence of the hydroxy group, the two cycloadducts of compound **11** were readily separated by chromatography on silica gel. The low polarity of the major isomer can be explained by the existence of a strong intramolecular hydrogen bond with the suitably orientated proximal hydroxy group. This phenomenon is associated with enhanced chromatographic mobility due to the consequent reduction in the effective polarity of the sulfoxide group.[16]

Thanks to the Michael acceptor system formed during heterocycloaddition, the intramolecular conjugated addition of the alcohol in acidic conditions (*p*-TsOH) allows, in the case of the major isomer (*S*s,2*S*,*R*)-**11** access to dioxabicyclic structure of compound **6** with three resolved stereogenic centers. No cyclization occurs for the minor isomer (*S*s,2*R*,*R*)-**11** under the same conditions. This phenomenon



Scheme 4. Reagents and conditions: (i) CH_2Cl_2/Δ/5 days, 65%; (ii) *p*-TsOH (0.25 equiv.)/CH_2Cl_2/RT/15 h

can be explained by the following consideration: each cycloadduct of compound **11** can adopt two conformations. In the case of the minor isomer, the last result indicates the pseudoequatorial orientation of the hydroxylated chain, a position which excludes hydrogen bonding and intramolecular cyclization (Scheme 5).

(Ss, 2S, R)-**11**
conformation **IA**

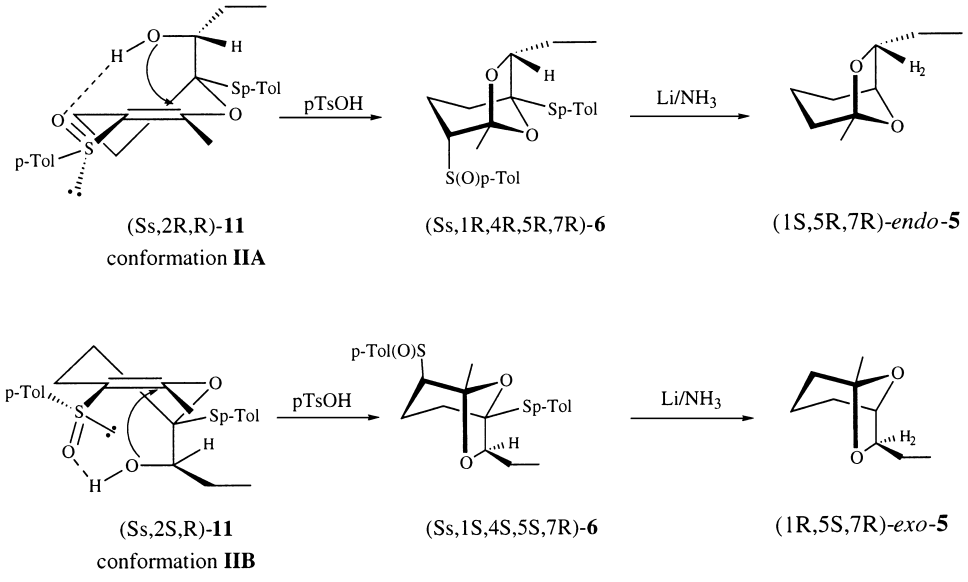
(Ss, 2R, R)-**11**
conformation **IB**

Scheme 5.

On the other hand, for the major isomer of compound **11**, the hydroxylated chain adopts a pseudoaxial orientation which involves intramolecular hydrogen bonding and allows an intramolecular conjugated addition. Moreover, according to the conformation **IIA** or **IIB** preferably adopted by major cycloadduct of compound **11**, we can obtain either (1*S*,5*R*,7*R*)-*endo* or (1*R*,5*S*,7*R*)-*exo*-brevicomin **5**[17,18] after cyclization and cleavage of the two C–S bonds (Scheme 6). The presence of only 10% of *exo*-brevicomin **5** was observed by cleavage of the two C–S bonds using lithium in liquid ammonia[19] (^{1}H NMR spectra of the crude product), this result shows the absolute stereochemistry (*S*s,1*S*,4*S*,5*S*,7*R*) of the bicyclic acetal **6** and (*S*s,2*S*,*R*) for the major cycloadduct of compound **11** (conformation **IIB**).

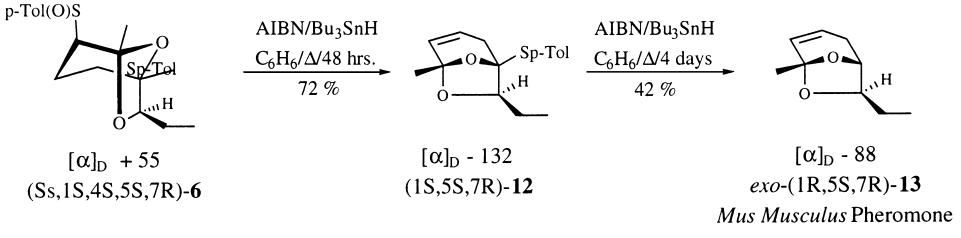
Even though the cleavage in one step of the two C–S bonds enables the absolute configuration of the bicyclic skeleton to be established, the synthesis of the desired bicyclic acetal is not satisfactory. Because of the low yields we considered accessing these structures via a two-step procedure: (i) thermolytic elimination of the sulfoxide; and (ii) reductive cleavage of the sulfide group with tri-*n*-butyltin hydride.

Thermolysis of the sulfinyl group for (*S*s,1*S*,4*S*,5*S*,7*R*)-**6** was performed by refluxing in dry benzene in the presence of a catalytic amount of AIBN and 2 equiv. of Bu_3SnH[20] and afforded (1*S*,5*S*,7*R*)-**12** in 72% yield. After purification by chromatography, (1*S*,5*S*,7*R*)-**12** under the same previous conditions gave, after 4 days, the desired pheromone, (1*R*,5*S*,7*R*)-**13** in 42% yield.[21] For this last step, it is necessary to bubble argon through the reaction mixture to achieve the reductive cleavage of the C–S bond[22]



Scheme 6.

(Scheme 7). The cleavage of the both C–S bonds in one step from compound **6** afforded compound **13** in a lower yield.



Scheme 7.

The enantiomeric purity of (1*R*,5*S*,7*R*)-**13** (*ee* >98%) was determined by gas chromatography using a chiral column (Restek β-DEX, 30 m, helium). The IR, ^{1}H NMR, mass spectra and specific rotation of (1*R*,5*S*,7*R*)-**13** were in accordance with the reported data.[21]

3. Conclusion

In summary, asymmetric heterocycloadditions of (*S*s)-*p*-tolylsulfinylbut-3-en-2-one with simple or chiral-functionalized-sulfide-activated dienophiles were successfully achieved in a high diastereoselective manner (*dr* >70:30). This methodology provides an original and convenient route to the optically active 6,8-dioxabicyclo[3.2.1] skeleton thanks to inter- and intramolecular cyclization reactions.

The absolute stereochemistry of the bicyclic structure and cycloadducts have been established by two different studies: (i) by chemical correlation by transformation into *exo*-brevicomin; and (ii) to illustrate the interest of our work, by the total synthesis of the *Mus musculus* (house mouse) pheromone. The mouse pheromone has been synthesized with a high enantiomeric purity and in only a four steps from (*S*s)-3-*p*-tolylsulfinylbutenone.

4. Experimental

4.1. General procedures

Melting points were determined on a Reichert Thermovar apparatus and are uncorrected. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker AC 400 instrument in $CDCl_3$ using TMS for ^{1}H spectra and the solvent for ^{13}C spectra as internal reference. Multiplicities in the ^{13}C spectra were determined by DEPT experiments.

Unless otherwise noted, all reactions were carried out in anhydrous solvents. IR spectra were recorded on a Mattson spectrometer. Optical rotations were measured at 25°C with a Perkin–Elmer model 343 polarimeter. Mass spectra were recorded on a Finnigan instrument. High resolution mass measurements were performed at the C.R.M.P.O. (Rennes). Enantiomeric excesses were determined on a Hewlett–Packard HP6890 series GC system equipped with a chiral column (Restek β-DEX). Elemental analyses were performed at the C.N.R.S. (Gif-sur-Yvette). Flash chromatography was run on SDS silica gel A.C.C. (230–400 mesh).

4.2. (Ss,)-6-Methyl-5-p-tolylsulfinyl-2-ethylsulfanyl-3,4-dihydro-2H-pyran **2**

A solution of (*S*s)-**1** (208 mg; 1 mmol) and ethyl vinyl sulfide (507 μL; 5 mmol) in dichloromethane (4 mL) was stirred at ambient temperature for 8 h. After concentration in vacuo, the crude product was purified by chromatography on silica gel (cyclohexane:ethyl acetate, 8:2) to afford the major isomer of compound **2** (155 mg) as a white solid and the minor isomer of compound **2** (64 mg) as a colorless oil, in a 74% overall yield. Calcd for $C_{15}H_{20}O_2S_2$: C, 60.77; H, 6.79; S, 21.63; found: C, 60.56; H, 6.85; S, 21.09. The major cycloadduct of compound (+)-**2** (71%): $[\alpha]_D$ +229 (*c* 1; CH_2Cl_2). IR (neat): 3048, 2925, 1645, 1232, 1085, 1037, 848 cm^{-1}. ^{1}H NMR δ 1.28 (t, J=7.4 Hz, 3H); 1.58–1.62 (m, 1H); 1.89–1.96 (m, 1H); 2.06–2.15 (m, 1H); 2.23 (s, 3H); 2.3–2.4 (m, 1H); 2.41 (s, 3H); 2.64–2.80 (m, 2H); 5.38 (t, J=3.6 Hz, 1H); 7.3–7.48 (AA′BB′ system, J=8.2 Hz, 4H). ^{13}C NMR δ 14.11 (t); 15.07 (q); 17.78 (q); 21.26 (q); 24.59 (t); 26.85 (t); 81.11 (d); 113.86 (s); 124.29 (d); 129.58 (d); 139.95 (s); 140.26 (s); 157.39 (s). The minor cycloadduct of compound (−)-**2** (29%): $[\alpha]_D$ −415 (*c* 1.07; CH_2Cl_2). IR (neat): 3048, 2925, 1645, 1232, 1085, 1037, 848 cm^{-1}. ^{1}H NMR δ 1.68 (t, J=7.4 Hz, 3H); 1.49–1.58 (m, 1H); 1.85–1.93 (m, 1H); 1.94–2.02 (m, 1H); 2.25 (s, 3H); 2.36 (s, 3H); 2.41–2.49 (m, 1H); 2.62–2.77 (m, 2H); 5.02 (dd, J=8 and 3 Hz, 1H); 7.23–7.37 (AA′BB′ system, J=8.2 Hz, 4H). ^{13}C NMR δ 12.67 (t); 15.31 (q); 17.78 (q); 21.24 (q); 25.03 (t); 26.98 (t); 80.91 (d); 113.67 (s); 124.48 (d); 129.6 (d); 139.26 (s); 140.09 (s); 156.65 (s).

4.3. (Ss,)-6-Methyl-5-p-tolylsulfinyl-2-phenylsulfanyl-3,4-dihydro-2H-pyran **3**

A solution of (*S*s)-**1** (104 mg; 0.5 mmol) and phenyl vinyl sulfide (55 μL; 1.1 equiv.) in dichloromethane (2 mL) was refluxed for 6 days. After cooling and concentration in vacuo, the crude product was purified by chromatography on silica gel (eluent: cyclohexane:ethyl acetate, 9:1) to give partly separated (*S*s)-**3** (124 mg; 70%) as a white solid. Calcd for $C_{19}H_{20}O_2S_2$: 344.09047; found: 344.0905. IR (KBr): 3052, 2923, 1643 (C=C), 1076, 1031 (S=O) cm^{-1}. The major cycloadduct of compound **3** (78%): ^{1}H NMR δ 1.42–1.63 (m, 1H); 1.94–2.06 (m, 2H); 2.29 (s, 3H); 2.39 (s, 3H); 2.46–2.55 (m, 1H); 5.23 (dd, J=8 and 3 Hz, 1H); 7.28–7.52 (m, 9H, H_{arom}). ^{13}C NMR δ 14.53 (t); 17.84 (q); 21.3 (q); 27.37 (t); 83.59 (d); 114.09 (s); 124.33 (2d); 128.09 (2d); 128.99 (2d); 129.66 (2d); 132.84 (2d); 139.92 (s); 140.37 (s); 157.27 (s). The minor cycloadduct of compound **3** (22%): ^{1}H NMR δ 1.56–1.64 (m, 1H); 1.05–2.17 (m, 2H); 2.23 (s, 3H); 2.35 (s, 3H); 2.37–2.42 (m, 1H); 5.56 (t, J=3.5 Hz, 1H); 7.23–7.42 (m, 9H, H_{arom}). ^{13}C

NMR δ 12.21 (t); 17.69 (q); 21.17 (q); 27.09 (t); 83.60 (d); 114.10 (s); 124.36 (2d); 127.52 (2d); 128.94 (2d); 129.59 (2d); 131.57 (2d); 139.14 (s); 140.14 (s); 156.23 (s).

*4.4. (*S*s)-2-(6-Methyl-2-*p*-tolylsulfanyl-5-*p*-tolylsulfinyl-3,4-dihydro-2*H*-pyran-2-yl)-propan-2-ols **4***

Adducts **4** were prepared in the same way as adducts **3** from (*Ss*)-**1** (52 mg; 0.25 mmol) and 2-methyl-3-*p*-tolylsulfanylbut-3-en-2-ol (78 mg; 0.37 mmol) by refluxing in dichloromethane for 5 days. Chromatography on silica gel (eluent: cyclohexane:ethyl acetate, 9:1; 5:5 then pure ethyl acetate) afforded the major cycloadduct of compound **4** (40 mg) and minor cycloadduct of compound **4** (17 mg) as white solids in 55% overall yield. IR (KBr): 3305 (OH), 3052 (C=CH), 2919, 1644 (C=C), 1492, 1085 (S=O) cm^{-1}. The major cycloadduct of compound **4** (70%): ^{1}H NMR δ 1.29 (s, 3H); 1.35 (s, 3H); 1.73–1.85 (m, 2H); 1.89 (s, 3H); 1.91–1.97 (m, 1H); 2.21 (br s, 1H, OH); 2.33 (s, 3H); 2.37 (s, 3H); 2.70–2.81 (m, 1H); 7.11–7.35 and 7.25–7.46 (AA′BB′ systems, 4d, J=8 Hz, $8H_{arom}$). ^{13}C NMR δ 14.08 (t); 17.22 (q); 21.23 (q); 21.27 (q); 24.49 (q); 25.46 (q); 26.68 (t); 76.68 (s); 94.52 (s); 115.05 (s); 124.25 (2d); 126.79 (s); 129.32 (2d); 129.68 (2d); 137.61 (2d); 139.38 (s); 140.14 (s); 140.32 (s); 155.54 (s). The minor cycloadduct of compound **4** (30%): m.p. 170–171°C (ether). ^{1}H NMR δ 1.26 (s, 3H); 1.29 (s, 3H); 1.72–1.92 (m, 1H); 1.91–2.15 (m, 2H); 2.01 (s, 3H); 2.29 (s, 3H); 2.31–2.42 (s, 1H); 2.38 (s, 3H); 6.98–7.27 and 7.11–7.35 (AA′BB′ systems, 4d, J=8 Hz, $8H_{arom}$). ^{13}C NMR δ 12.32 (t); 17.13 (q); 21.21 (q); 21.36 (q); 24.72 (q); 25.33 (q); 26.78 (t); 76.52 (s); 94.96 (s); 114.79 (s); 124.48 (2d); 127.46 (s); 129.19 (2d); 129.59 (2d); 136.37 (2d); 138.88 (s); 139.07 (s); 140.57 (s); 155.66 (s).

*4.5. (*Ss,S*) and (*Ss,R*)-2-*p*-Tolylsulfinylpent-1-en-3-ols **9***

To a stirred solution of LDA (22 mmol) in dry THF (80 mL) under a nitrogen atmosphere, at −90°C, distilled (*Rs*)-*p*-tolylvinylsulfoxide **10** (3.34 g; 20 mmol) in THF (40 mL) was slowly added. After 10 min at −90°C, freshly distilled ethanal (4.32 mL; 60 mmol) was added dropwise. The reaction mixture was maintained at −90°C for 10 min, then a half-saturated aqueous NH_4Cl solution (40 mL) was added at this temperature. Most of the THF was removed under reduced pressure and the residue was finally extracted with CH_2Cl_2. After drying over $MgSO_4$ and evaporation of the solvent, the crude oil was purified by chromatography (eluent: ether:cyclohexane, 7:3 then pure ether) to give the diastereomeric sulfinylallylic alcohol (*Ss*)-**9** (2.4 g; 57%) as a colorless oil. Crystallization in diisopropylether afforded diastereomerically pure (*Ss,R*)-**9** (0.987 g; 22%) as a white solid. IR (KBr): 3356 (OH), 1590 (C=C), 1079, 1032 (S=O), 932, 813 cm^{-1}. (*Ss,R*)-**9** (41%): $[\alpha]_D$ +195 (*c* 0.54, ethanol). M.p. 91–92°C (ether). ^{1}H NMR δ 0.84 (t, J=7.3 Hz, 3H); 1.58–1.66 (m, 2H); 2.17 (d, J=5.6 Hz, 1H, OH); 2.38 (s, 3H); 4.03 (m, 1H); 5.81 (s, 1H, H_{trans}); 6.04 (s, 1H, H_{cis}); 7.27 and 7.53 (AA′BB′system, 2d, J=7.8 Hz, $4H_{arom}$). (*Ss,S*)-**9** (59%): ^{1}H NMR δ 0.87 (t, J=7.3 Hz, 3H); 1.54–1.65 (m, 2H); 2.39 (s, 3H); 2.92 (d, J=3.5 Hz, 1H, OH); 4.05 (m, 1H); 5.83 (s, 1H, H_{trans}); 6.05 (s, 1H, H_{cis}); 7.31 and 7.54 (AA′BB′ system, 2d, J=7.8 Hz, $4H_{arom}$).

*4.6. Synthesis of (*R*)-2-*p*-tolysulfanylpent-3-en-2-ol **7***

A solution of (*Ss,R*)-**9** (448 mg; 2 mmol), $CF_3SO_3SiMe_2tBu$ (700 μL; 3 mmol) and 2,6-lutidine (465 μL; 4 mmol) in dichloromethane (2 mL) was stirred for 2 h at ambient temperature. The reaction mixture was then poured into water (2 mL) and the resulting suspension extracted with petroleum ether (3×6 mL). The organic extracts were combined, dried and concentrated to give the corresponding silylether (693 mg; 95%) as a colorless liquid. ^{1}H NMR data shown that no purification was necessary. $[\alpha]_D$ +43

(*c* 0.5, ethanol). IR (film): 3050, 2954, 2929, 1621, 1471, 1081 cm^{-1}. ^1H NMR δ −0.31 (s, 3H); −0.16 (s, 3H); 0.79–0.87 (s+t, J=7.5 Hz, 12H); 1.47–1.60 (m, 2H); 2.40 (s, 3H); 4.08 (t, J=5.3 Hz, 1H); 5.89 (s, 1H, H_{trans}); 6.05 (s, 1H, H_{cis}); 7.27 and 7.51 (AA′BB′ system, 2d, J=8 Hz, $4H_{arom}$). ^{13}C NMR δ −5.30 (q); −5.23 (q); 9.04 (q); 17.97 (s); 21.34 (q); 25.61 (q); 31.43 (t); 70.07 (d); 118.53 (t); 125.26 (2d); 129.76 (2d); 139.43 (s); 141.58 (s); 156.81 (s).

To a stirred suspension of P_2I_4 (1.076 g; 1.9 mmol) in ether (25 mL) was added a solution of silylether (647 mg; 1.9 mmol) in ether (25 mL) containing pyridine (1.9 mL). The mixture was then stirred for 1 h at room temperature, quenched by addition of water (15 mL) and extracted with ether (3×30 mL). The combined ether layers were successively washed with 10% HCl (10 mL); 5% H_2SO_3 solution and brine. Drying ($MgSO_4$) and concentration in vacuo gave the sulfide silylether (490 mg; 80%) as a colorless liquid. $[\alpha]_D$ −50.3 (*c* 0.5, ethanol). IR (film): 3023, 2958, 2929, 1604, 1095, 1018 cm^{-1}. ^1H NMR δ 0.026 (s, 3H); 0.043 (s, 3H); 0.88 (t, J=7.4 Hz, 3H); 0.91 (s, 9H); 1.65–1.77 (m, 2H); 2.35 (s, 3H); 4.10 (t, J=5.7 Hz, 1H); 4.74 (d, J=0.68 Hz, 1H, H_{trans}); 5.32 (d, J=0.68 Hz, 1H, H_{cis}); 7.14 and 7.33 (AA′BB′ system, 2d, J=8 Hz, $4H_{arom}$). ^{13}C NMR δ −5.08 (q); −4.73 (q); 9.38 (q); 18.24 (s); 21.16 (q); 25.82 (q); 30.06 (t); 75.99 (d); 110.48 (t); 128.99 (d); 129.91 (d); 134.06 (s); 138.05 (s); 149.83 (s).

Tetrabutylammonium fluoride (3 mL, 1 molar in THF) was added to a solution of sulfide silylether (480 mg; 1.49 mmol) in THF (6 mL) at 0°C. After 2 h at room temperature, the solvent was removed under reduced pressure and the residue purified by chromatography (eluent: ether:petroleum ether, 2:8) to give (*R*)-**7** as a colorless liquid. (*R*)-**7**: $[\alpha]_D$ −100 (c 0.5, ethanol). IR (film): 3363, 3035, 2958, 2857, 1608, 1492, 1095 cm^{-1}. ^1H NMR δ 0.93 (t, J=7.4 Hz, 3H); 1.69 (dq, J=7.4 and 6.4 Hz, 1H); 1.78 (dq, J=7.4 and 6.4 Hz, 1H); 1.85 (d, J=4.8 Hz, 1H, OH); 2.33 (s, 3H); 4.12 (q, J=6.4 Hz, 1H); 4.79 (s, 1H, H_{trans}); 5.34 (s, 1H, H_{cis}); 7.13 and 7.33 (AA′BB′ system, 2d, J=8 Hz, $4H_{arom}$). ^{13}C NMR δ 9.74 (q); 21.09 (q); 28.88 (t); 75.91 (d); 111.31 (t); 128.41 (s); 130.01 (d); 133.86 (d); 138.25 (s); 149.58 (s).

*4.7. (*S*s,2*R,R*) and (*S*s,2*S,R*)-1-(6-Methyl-5-*p*-tolylsulfinyl-3-*p*-tolylsulfanyl-3,4-dihydro-2*H*-pyran-2-yl)-propan-1-ols **11***

A solution of (*Ss*)-**1** (160 mg; 0.77 mmol) and (*R*)-**7** (157 mg; 0.75 mmol) in dichloromethane (10 mL) was refluxed for 5 days. After cooling and concentration under reduced pressure, the residue was purified by chromatography on silica gel (eluent: ether:petroleum ether, 2:8; 5:5 then pure ether) to afford (*Ss*,2*S*,*R*)-**11** (137 mg; 44%) as a colorless oil and (*Ss*,2*R*,*R*)-**11** (66 mg; 21%) as a white solid. Calcd for $C_{23}H_{29}O_3S_2$ [M+H]: 417.1558; found: 417.1556. IR (film): 3388, 3052, 1648, 1492, 1087 cm^{-1}. (*Ss*,2*S*,*R*)-**11**: $[\alpha]_D$ +275 (*c* 0.58, ethanol). ^1H NMR δ 0.96 (t, J=7.4 Hz, 3H); 1.36–1.46 (m, 2H); 1.61–1.72 (m, 2H); 2.00 (ddd, J=14.7, 6.5 and 2 Hz, 1H); 2.21 (s, 3H); 2.38 (s, 3H); 2.41 (s, 3H); 2.56–2.66 (m, 1H); 2.66 (s, 1H, OH); 3.39 (d, J=9.8 Hz, 1H); 7.17–7.37 and 7.30–7.41 (AA′BB′ systems, 4d, J=8 Hz, $8H_{arom}$). ^{13}C NMR δ 11.23 (q); 13.85 (t); 17.68 (q); 21.18 (q); 21.22 (q); 22.89 (t); 24.22 (t); 73.98 (d); 93.24 (s); 115.60 (s); 124.17 (d, 2CHAr); 124.41 (s); 129.62 (d, 2CHAr); 129.66 (d, 2CHAr); 137.00 (d, 2CHAr); 139.66 (s); 139.97 (s); 140.35 (s); 154.86 (s). (*Ss*,2*R*,*R*)-**11**: m.p. 108–112°C (ether). $[\alpha]_D$ −429 (*c* 0.55, ethanol). ^1H NMR δ 0.94 (t, J=7.4 Hz, 3H); 1.19–1.40 (m, 1H); 1.69–1.81 (m, 2H); 2.00–2.05 (m, 2H); 2.14 (td, J=12.9 and 6.2 Hz, 1H); 2.28 (s, 3H); 2.34 (s, 3H); 2.37 (s, 3H); 2.37–2.45 (m, 1H); 3.42 (d, J=10 Hz, 1H); 7.11–7.28 and 7.21–7.48 (AA′BB′ systems, 4d, J=8 Hz, $8H_{arom}$). ^{13}C NMR δ 11.23 (q); 12.23 (t); 17.57 (q); 21.16 (q); 21.22 (q); 23.28 (t); 23.57 (t); 75.55 (d); 91.88 (s); 114.69 (s); 124.45 (d, 2CHAr); 125.14 (s); 129.50 (d, 2CHAr); 129.62 (d, 2CHAr); 136.46 (d, 2CHAr); 138.93 (s); 139.42(s); 140.24 (s); 155.89 (s).

4.8. (Ss,1S,4S,5S,7R)-7-Ethyl-5-methyl-1-p-tolylsulfanyl-4-p-tolylsulfinyl-6,8-dioxabicyclo[3.2.1]-octane **6**

A solution of (*Ss*,2*S*,*R*)-**11** (100 mg; 0.24 mmol) and *p*-toluene sulfonic acid (11.5 mg; 0.06 mmol) in dichloromethane (12 mL) was stirred at ambient temperature for 12 h. After evaporation of the solvent in vacuo, the residue was purified by chromatography (eluent: ether:petroleum ether, 2:8 and then 4:6) to give (*Ss*,1*S*,4*S*,5*S*,7*R*)-**6** (90 mg, 90%) as a white solid. $[\alpha]_D$ +55 (*c* 0.5, ethanol). M.p. 131–132°C (ether). IR (KBr): 3004, 2989, 2925, 1492, 1380, 1203, 1047, 995, 808, 493 cm^{-1}. ^1H NMR δ 1.02 (t, J=7.3 Hz, 3H); 1.37 (dd, J=13.5 and 5.9 Hz, 1H); 1.56–1.63 (m, 1H); 1.71 (s, 3H); 1.72–1.81 (m, 1H); 1.90–1.99 (m, 1H); 2.06 (dd, J=14.7 and 6.3 Hz, 1H); 2.18 (td, J=13.5 and 6.3 Hz, 1H); 2.31 (s, 3H); 2.35 (s, 3H); 2.55 (d, J=6 Hz, 1H); 3.96 (dd, J=9.6 and 3 Hz, 1H); 7.13–7.37 and 7.24–7.47 (AA′BB′ systems, 4d, J=8 Hz, $8H_{arom}$). ^{13}C NMR δ 10.21 (q); 16.65 (t); 21.21 (q); 21.28 (q); 24.49 (q); 25.37 (t); 31.91 (t); 66.82 (d); 83.44 (d); 93.23 (s); 107.82 (s); 123.89 (d, 2CHAr); 126.35 (s); 129.64 (d, 2CHAr); 129.85 (d, 2CHAr); 134.99 (d, 2CHAr); 138.67 (s); 141.00 (s); 141.70 (s). MS (EI, 70 eV): *m/z* (%)=417 (M+1, 2), 416 (M^+, 5), 399 (12), 339 (25), 277 (13), 218 (26), 189 (14), 165 (15), 153 (11), 124 (28), 123 (29), 111 (34), 95 (100), 91 (50).

4.9. (1S,5S,7R)-7-Ethyl-5-methyl-1-p-tolylsulfanyl-6,8-dioxabicyclo[3.2.1]octane **12**

A solution of (*Ss*,1*S*,4*S*,5*S*,7*R*)-**6** (188 mg; 0.45 mmol) in freshly distilled benzene (6 mL) was mixed with tri-*n*-butyltin hydride (306 μL; 2 equiv.) and a catalytic amount of azobisisobutyronitrile (AIBN, 2 mg) and refluxed over 48 h. After cooling and concentration under reduced pressure, the residue was purified by chromatography on silica gel (eluent: petroleum ether) to give (1*S*,5*S*,7*R*)-**12** (90 mg; 72%) as a colorless oil. $[\alpha]_D$ −132 (*c* 0.7, ethanol). Calcd for $C_{16}H_{21}O_2S$ [M+H]: 277.1262; found: 277.1255. IR (neat): 3040, 2923, 2875, 1643, 1492, 1386, 1241, 1201, 1128, 1070, 1020, 991, 872, 812 cm^{-1}. ^1H NMR δ 1.04 (t, J=7.3 Hz, 3H); 1.59 (s, 3H); 1.65–1.83 (m, 2*S*); 1.92 (ddd, J=17.8, 4.3 and 1.6 Hz, 1H); 2.33 (s, 3H); 2.50 (ddd, J=17.8, 2.3 and 2.3 Hz, 1H); 3.92 (dd, J=9.7 and 3.4 Hz); 5.63 (ddd, J=9.4, 4.3 and 2.4 Hz, 1H); 5.76 (ddd, J=9.4, 2.4 and 1.8 Hz, 1H); 7.12–7.48 (AA′BB′ systems, 4d, J=8.2 Hz, $4H_{arom}$). ^{13}C NMR δ 11.02 (t); 21.20 (t); 21.48 (q); 24.67 (q); 38.39 (t); 84.38 (d); 90.88 (s); 103.46 (s); 125.95 (d); 128.78 (d); 131.08 (d); 135.32 (s); 135.45 (d); 138.70 (s).

4.10. exo-(1R,5S,7R)-(7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]oct-3-ene **13**

A solution of (1*S*,5*S*,7*R*)-**12** (81 mg; 0.29 mmol) in freshly distilled benzene (1 mL) was mixed with tri-*n*-butyltin hydride (195 μL; 0.72 mmol) and a solution of azobisisobutyronitrile (1% in benzene, 200 μL). The mixture was degassed with a stream of argon for 30 min and then placed into a preheated oil bath (90–100°C). The solution was heated at 80°C for 4 days. Removal of the solvent and column chromatography of the residue (eluent: petroleum ether) afforded pure *exo*-(1*R*,5*S*,7*R*)-**13** (19 mg; 42%) as a colorless liquid. $[\alpha]_D$ −88 (*c* 0.5, $CHCl_3$) (lit.[21]: $[\alpha]_D$ −90.5 (*c* 0.95, $CHCl_3$); $[\alpha]_D$ −71 (*c* 2.5, ether)). IR (neat): 3060, 2980, 1640, 1425, 1395, 1380, 1255, 1200, 1150, 1130, 1115 cm^{-1}. ^1H NMR δ 0.94 (t, J=7.5 Hz, 3H); 1.53 (s, 3H); 1.55–1.65 (m, 2H); 1.85 (ddd, J=17.9, 4.3 and 1.8 Hz, 1H); 2.64 (dddd, J=17.9, 4.4, 2.3 and 2.3 Hz); 3.79 (td, J=6.3 and 1.6 Hz, 1H); 4.24 (m, 1H); 5.71 (dddd, J=9.5, 4.4, 2.2 and 1.8 Hz); 5.82 (ddd, J=9.6, 2.3 and 1.8 Hz, 1H). MS (EI, 70 eV): *m/z* (%)=154 (M^+, 1.89); 137 (1.4); 125 (8); 111 (20); 95 (34); 83 (17); 67 (13); 57 (18); 43 (100).

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