Stereoselective Cyclopropanation of 2-[(*S*)-(4-Methylphenyl)sulfinyl]-cyclopent-2-en-1-one with Sulfur Ylides and α-Halo Carbanions

Preliminary Communication

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Dedicated to Professor *Rolf Huisgen* on the occasion of his 85th birthday

The cyclopropanation of the title compound (*S*)-**2** with various sulfur ylides has been examined. The reaction with methylenesulfonium ylides gave the corresponding cyclopropanes **4** with low diastereoselectivity. The formation of the second product **5** arising from the subsequent methylenation of the C=O group was also observed. A clean cyclopropanation of (*S*)-**2** took place with ethyl (dimethylsulfanylidene)acetate affording the cyclopropanes **6**, with high π-facial selectivity, but low *endo*/*exo* ratio. A high *endo*/*exo* selectivity, but low π-facial selectivity was observed in the reaction of (*S*)-**2** with (2-ethoxy-2-oxoethyl)(diphenyl)sulfonium tetrafluoroborate. The use of α-bromoacetate carbanion as the cyclopropanation reagent resulted in the formation of **6** with very high facial and *endo*/*exo*-selectivity. In a proposed explanation of the stereochemical outcome of the cyclopropanations investigated, the ground-state conformation of the sulfoxide **2** and the transition-state structure of the initial addition step were taken into account.

The cyclopropane ring occurs as a basic structural unit in a great variety of biologically active natural and synthetic products (for a general review on cyclopropanes, see [1]). Due to large inherent strain in this smallest cycloalkane, cyclopropanes serve as versatile synthetic intermediates in the synthesis of structurally more complex cycloalkanes and acyclic compounds that are formed by the cleavage of the three-membered ring [2]. In the last two decades, an increasing importance of the cyclopropane ring compounds in diverse areas of organic chemistry and biology has led to a rapid development of new and efficient methods for the preparation of cyclopropane compounds, especially those in enantiomerically pure forms (for recent reviews, see [3]).

As a part of our program aimed at the synthesis of new biologically active cyclopropanephosphonic acid derivatives, we have investigated the diastereoselective

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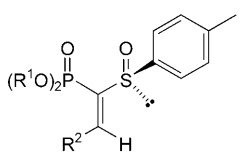
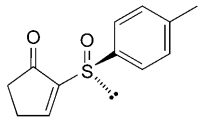
cyclopropanation reaction of enantiomerically pure α-phosphorylvinyl sulfoxides **1** with sulfur ylides and diazoalkanes [4][5]. A very high or full diastereoselectivity observed in these cyclopropanation reactions has been attributed to the differentiation of the π-faces induced by the (4-methylphenyl)sulfinyl group as a chiral auxiliary [6]. The asymmetric cyclopropanation reaction of the vinyl sulfoxides **1a** and **1b** was a key reaction in the synthesis of enantiomerically pure [(1*R*,2*R*,3*R*)-2-amino-3-phenylcyclopropyl]phosphonic acid [7], a constrained analogue of the $GABA_B$ antagonist phaclofen (PHAC), and cyclopropylphosphonate analogues of nucleotides [8].

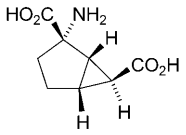
Pursuing our interest in asymmetric cyclopropanation mediated by a chiral sulfinyl auxiliary (for a recent paper, see [9]), we turned our attention to 2-[(*S*)-(4-methylphenyl)sulfinyl]cyclopent-2-en-1-one (**2**) as a new chiral substrate for the cyclopropanation reaction. This reagent has been successfully used by *Posner* as *Michael* acceptor with a variety of nucleophiles and as dienophile in *Diels–Alder* cycloadditions [10]. In both reactions, a high degree of asymmetric induction has been observed. The main reason to study the asymmetric cyclopropanation of (*S*)-**2** (or (*R*)-**2**) was our hope to develop a new short approach to the synthesis of (+)-(1*S*,2*S*,5*R*,6*S*)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid ((+)-**3**, LY354740)[2]), a potent and selective agonist for a glutamate receptor involved in the mammalian central nervous system. Here, we wish to disclose the results of the cyclopropanation reactions of (*S*)-**2** with sulfur ylides and α-halo carbanions as well as to rationalize the stereochemical outcome of the reactions investigated.



(*S*)-**1a** R^1 = Et, R^2 = H
(*S*)-**1b** R^1 = Me, R^2 = Ph



(*S*)-**2**



(+)-**3** (LY354740)

Initially, the reactivity of (*S*)-**2** towards simple methylenesulfonium ylides was examined (*Scheme 1* and *Table 1*). Thus, when (*S*)-**2** was treated with an excess of dimethyl(oxo)sulfonium methylide in DMSO at room temperature, the reaction afforded the expected cyclopropane **4** as a mixture of two diastereoisomers in a 1:1 ratio together with the main product **5** arising from the subsequent methylene group transfer to the C=O group in **4**. The use of equimolar amounts of both reagents led to a mixture of **4** and **5** in equal amounts. The same reaction carried out in the presence of $ZnCl_2$ gave the diastereoisomeric cyclopropanes **4** (dr = 3:7) without concomitant formation of **5**. Similarly, the use of diphenylsulfonium methylide in the reaction with (*S*)-**2** resulted in the preponderant formation of the diastereoisomeric cyclopropanes **4**, though with very low diastereoselectivity (dr = 11:7), accompanied by only small amounts (10%) of the undesired product **5**.

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[2]) For the asymmetric synthesis of (+)-**3** based on the cyclopropanation reaction of the protected (−)-4,5-dihydroxycyclopent-2-en-1-one see [11].

Scheme 1. *Cyclopropanation of 2-[(S)-(4-Methylphenyl)sulfinyl]cyclopent-2-en-1-one* (**2**) *with Methylenesulfonium Ylides* (see *Table 1*)

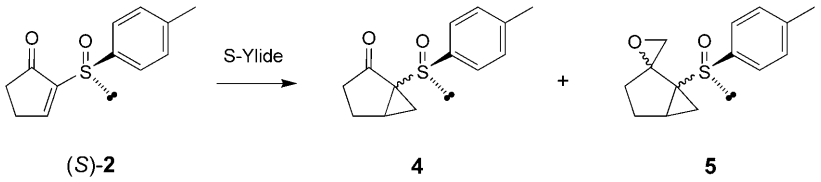


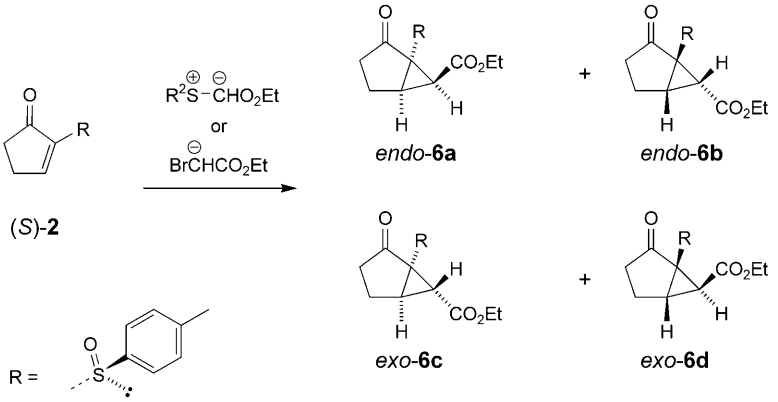
Table 1. *Selected Results of the Cyclopropanation of Compound* **2** *with Methylenesulfonium Ylides*

Condition	Total yield (**4**+**5**)	**4**/**5**	Diastereoisomer ratio of **4**
$Me_2S^{\oplus}(O)CH_2^{\ominus}$, DMSO (2 equiv.)	78	2:3	1:3
$Me_2S^{\oplus}(O)CH_2^{\ominus}$, DMSO (1.1 equiv.)	58	1:1	1:1
$Me_2S^{\oplus}(O)CH_2^{\ominus}$, THF, $ZnCl_2$ (1.1 equiv.)	62	1:0	3:7[b])
$Ph_2S^{\oplus}CH_3BF_4^{\ominus}$, DBU, DME (1.2 equiv.)	86	10:1	11:7

[a]) The diastereoisomeric ratios were determined by integral values of the cyclopropyl *endo* proton at C(6) in the ^{1}H-NMR spectra. [b]) This mixture was separated, and the pure diastereoisomers of **4**, $[\alpha]_D = +131.1$ (acetone) and $[\alpha]_D = -16.3$ (acetone), were isolated and characterized spectroscopically. The determination of their absolute configurations is currently in progress.

Having in mind the main purpose of the present work, *i.e.*, the synthesis of (+)-**3**, the reaction of (*S*)-**2** with ethyl (dimethylsulfanylidene)acetate (EDSA) was next investigated. It was found that the corresponding cyclopropanation product **6** was exclusively formed and that the stereochemical outcome of this reaction was dependent on the nature of the ylide component (*Scheme 2* and *Table 2*).

Scheme 2. *Cyclopropanation of Compound* **2** *with Sulfur Ylides and α-Bromoacetate Carbanion*



When a CH_2Cl_2 solution of (*S*)-**2** was treated at 0° for 1 h with the freshly and separately prepared EDSA [12], the cyclopropanation product **6** was obtained in 72% yield as a mixture of four diastereoisomers **6a**–**d**. They were easily separated by column chromatography and fully characterized. Based on the coupling constants between H–C(5) and H–C(6) ($^3J(5, 6)$) in ^{1}H-NMR spectra, the *endo*/*exo*

Table 2. *Selected Results of the Cyclopropanation of Compound* **2** *with Sulfur Ylides and α-Bromoacetate Carbanion*

Entry	Condition[a])	Yield [%] of **6**	Diastereoisomer ratio				Selectivity	
			endo-**6a**	*endo*-**6b**	*exo*-**6c**	*exo*-**6d**	π-Facial	*endo*/*exo*
1	$Me_2S^{\oplus}C^{\ominus}HCO_2Et$, CH_2Cl_2	72	31	7	50	12	81 : 19	38 : 62
2	$(Me_2S^{\oplus}CH_2CO_2Et)Br^{\ominus}$, DBU, CH_2Cl_2	83	29	5	56	10	85 : 15	34 : 66
3	$(Me_2S^{\oplus}CH_2CO_2Et)Br^{\ominus}$, DBU, CH_2Cl_2, $ZnBr_2$[b])	70	26	8	53	13	79 : 21	34 : 66
4	$(Me_2S^{\oplus}CH_2CO_2Et)Br^{\ominus}$, DBU, THF, $ZnBr_2$[b])	80	26.5	7	52.5	14	79 : 21	33.5 : 66.5
5	$(Ph_2S^{\oplus}CH_2CO_2Et)BF_4^{\ominus}$, DBU, CH_2Cl_2	73	46	42	9	3	55 : 45	88 : 12
6	$BrCH_2CO_2Et$, LDA, THF[c])	66	85.5	5	7.5	2	93 : 7	90.5 : 9.5
7	$BrCH_2CO_2Et$, LDA, THF, $ZnBr_2$[b])[c])	78	85	4	8	3	93 : 7	89 : 11
8	$BrCH_2CO_2Et$, LDA, THF, $ZnBr_2$[c])[d])	75	85.5	4	7.5	3	93 : 7	89.5 : 10.5

[a]) A 1.1 equimolar excess of ylide or α-bromo carbanion in respect to (*S*)-**2** was used. [b]) Equimolar amounts of $ZnBr_2$ were used. [c]) The carbanion of α-bromoacetate was generated at −78° with LDA and then added to (*S*)-**2** at this temperature. [d]) Two equimolar amounts of $ZnBr_2$ were used.

configuration was assigned to the diastereoisomers of **6**. Since it is greater for **6a** and **6b** (9.3 Hz) than that for **6c** and **6d** (4.9 Hz), it is reasonable to ascribe the *endo* configuration to the former diastereoisomeric pair, and *exo* to the latter.

It turned out that **6a**, $[\alpha]_D = +31.3$ (acetone), one of the two major diastereoisomers formed in this reaction (*Table 2*, *Entry 1*), was crystalline (m.p. 111–112°). Therefore, it was subjected to an X-ray crystal-structure analysis[3]) which allowed us to establish its absolute configuration as (1*S*,5*R*,6*R*,S_S) (see *Figure*). In accord with

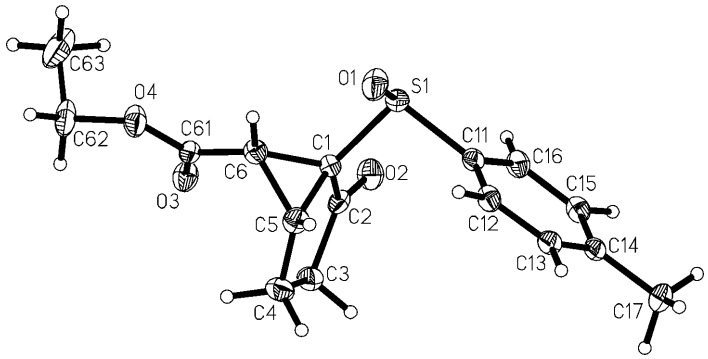
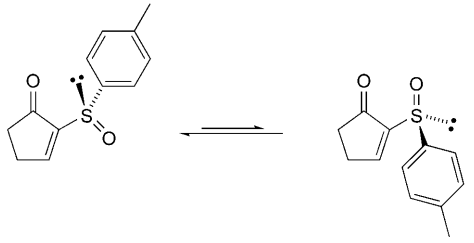


Figure. *X-Ray crystal structure of (1S,5R,6R)-1-[(S)-(4-methylphenyl)sulfinyl]-2-oxobicyclo[3.1.0]hexane-6-carboxylate* (*endo*-**6a**). Thermal ellipsoids are shown at the 50% probability level.

[3]) CCDC-224400 contains the crystallographic data for this paper. These data can be obtained, free of charge, *via* www.ccdc.cam.ac.uk/data_request/cif (or from the *Cambridge Crystallographic Data Centre*, 12 Union Read, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Posner's concept of conformational equilibrium of the cyclopentenone sulfoxide **2** shown in *Scheme 3* and his rationale for asymmetric conjugate addition of nucleophiles [10], the cyclopropanation with EDSA occurs apparently *via* the non-chelated s-*cis* form from the less-hindered π-face occupied by the sulfur lone electron pair leading to the major diastereoisomers **6a** and **6c**, both having the same (1*S*,5*R*) configuration of the ring junction and differing in the absolute configuration at C(6).

Scheme 3. *Two Ground-State Conformations of Compound* **2**



In order to improve facial or *endo*/*exo* selectivity, the cyclopropanation of (*S*)-**2** with EDSA was further investigated under different reaction conditions. However, the use of the ylide generated *in situ* from (2-ethoxy-2-oxoethyl)(dimethyl)sulfonium bromide with DBU ('1,8-diazabicyclo[5.4.0]undec-7-ene') gave the cyclopropanes **6a**–**d** in almost the same ratio (*Table 2*, *Entry 2*) as in the experiment with the preformed ylide (*Table 2*, *Entry 1*). Similarly, when the reaction was carried out in the presence of $ZnBr_2$, the cyclopropanes **6a** and **6c** were again formed as major diastereoisomers, indicating that, in contrast to our expectations, the cyclopropanation occurred in a non-chelated mode[4]) (*Table 2*, *Entries 3* and *4*). Furthermore, treatment of (*S*)-**2** with (2-ethoxy-2-oxoethyl)(diphenyl)sulfonium tetrafluoroborate in the presence of DBU afforded a mixture of **6a**–**d** with quite high *endo*/*exo* selectivity but with very low facial stereoselectivity (*Table 2*, *Entry 5*).

Lastly, it was gratifying to find that both facial and *endo*/*exo* selectivity were much better when in the reaction with (*S*)-**2** instead of a sulfur ylide α-bromoacetate carbanion was used as a nucleophile inducing ring closure (*Table 2*, *Entry 6*). Interestingly, also in this case the addition of $ZnBr_2$ to (*S*)-**2** before α-bromo carbanion did not change the stereochemical outcome of the cyclopropanation reaction (*Table 2*, *Entries 7* and *8*).

An inspection of the results in *Table 2* indicates that the cyclopropanation of (*S*)-**2** with EDSA and α-bromoacetate carbanion occurs with a high π-facial diastereoselectivity *via* the more-abundant non-chelated ground-state conformation s-*cis*-**2**. The only exception is the reaction with (2-ethoxy-2-oxoethyl)(diphenyl)sulfonium tetra-

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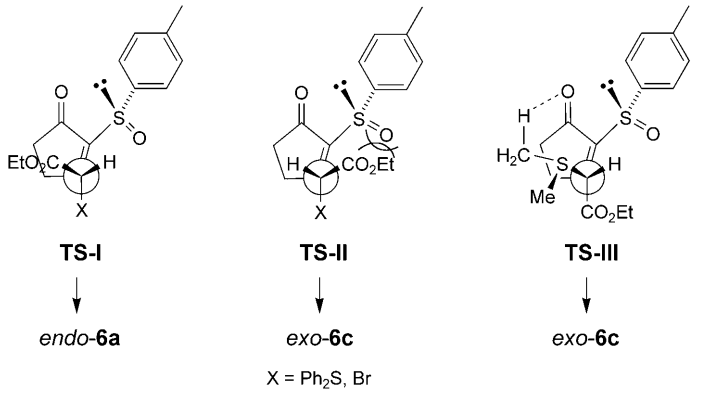
[4]) Asymmetric *Michael* addition of *tert*-butyl or methyl α-lithioacetate to (*R*)-**2** in the presence of $ZnBr_2$ occurs also in a non-chelate mode [13].

fluoroborate. Most probably, this relatively stable and bulky ylide readily reacts with the more-reactive chelated conformer s-*trans*-**2**. To rationalize the *endo*/*exo* selectivity it is useful to consider the transition-state geometry of the initial addition step of the sulfur ylide or α-bromo carbanion to the C=C bond of (*S*)-**2** (*Scheme 4*). By assuming the antiperiplanar arrangement of the diphenylsulfonium or bromine moiety with respect to C(2) of the cyclopentenone ring, the transition state **TS-I** yielding *endo*-**6a** would be more favored than **TS-II** due to steric repulsion interactions of the ethoxycarbonyl and sulfinyl groups in the latter. However, for the addition of EDSA to (*S*)-**2** it is reasonable to assume the transition state **TS-III**, leading to *exo*-**6c**, with a *gauche* arrangement of the dimethylsulfonium function with respect to the *endocyclic* double bond[5]). Such a geometry of **TS-III** may be stabilized by a week H-bond between the positively charged methyl group and the carbonyl O-atom as shown in *Scheme 4*.

Scheme 4. *Possible Transition States for the First Step of the Cyclopropanation Reaction*



In summary, we have shown that the cyclopropanation of 2-[(*S*)-(4-methylphenyl)sulfinyl]cyclopent-2-en-1-one (**2**) with sulfur ylides and α-bromoacetate carbanion proceeds efficiently and with a high degree of stereocontrol at the newly generated stereocenters. The best facial and *endo*/*exo* selectivity was observed in the reaction of (*S*)-**2** with the α-bromoacetate carbanion. The asymmetric synthesis of (+)-(1*S*,2*S*,5*R*,6*S*)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (**3**) based on the cyclopropanation reaction of (*R*)-**2** with α-bromoacetate carbanion is under current study.

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5) A similar explanation has been proposed by us to explain the *exo*-selectivity observed in the cyclopropanation of (5*S*)-5-ethoxy-3-[(*S*)-(4-methylphenyl)sulfinyl]furan-2(5*H*)-one with dimethylsulfonium ylides [9].

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Received March 17, 2005