

STEREOCONTROLLED ASYMMETRIC SYNTHESIS OF OPTICALLY ACTIVE ACYL-CYCLOPROPANE DERIVATIVES BY MICHAEL ADDITIONS OF BROMOMALONATE TO CHIRAL α -ACYLVINYLIC SULFOXIDES

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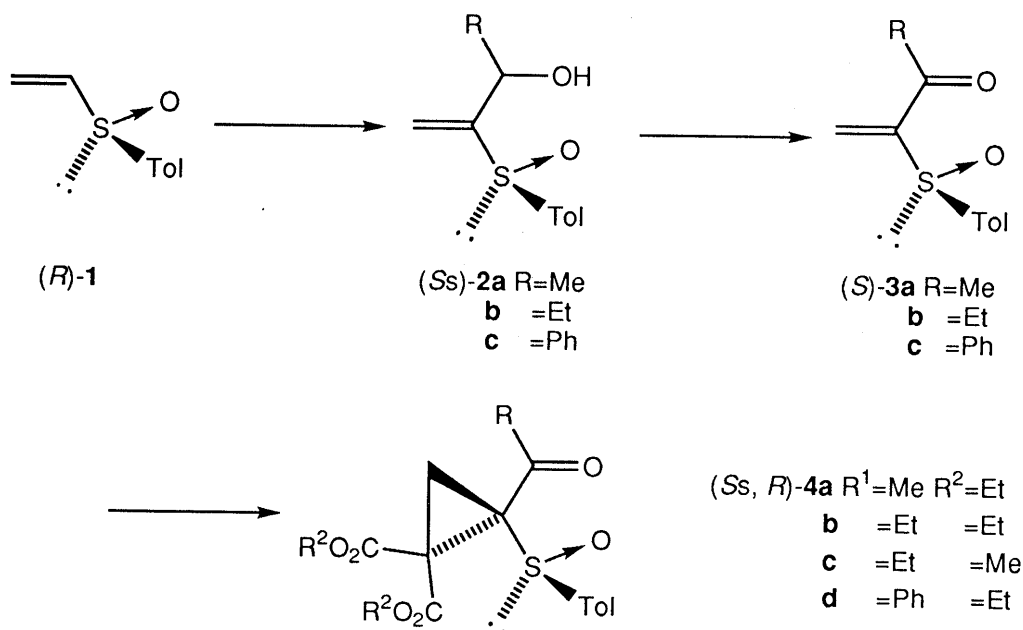
Michael addition of bromomalonate carbanions to chiral α -acylvinylic sulfoxides and the subsequent intramolecular alkylation yielded optically active acylcyclopropane derivatives with high enantiomeric excess. Stereochemistry of the product was determined by chemical correlation to a compound of known absolute configuration. The mechanism for the asymmetric induction is deduced on the basis of the stereochemical results obtained.

KEYWORDS optically active acylcyclopropane derivative; chiral α -acylvinylic sulfoxide; asymmetric synthesis; Michael addition; intramolecular asymmetric alkylation

Cyclopropane rings have received much attention for their chemical characteristics¹⁾ and have been widely used for the construction of three-carbon units in organic molecules *via* the fragmentation of cyclopropane rings by means of many kinds of methods such as thermal rearrangements,²⁾ oxidative and reductive ring fissions, electrophilic and nucleophilic additions, irradiations, transition metal-catalyzed reactions, and free radical reactions.³⁾

We have taken much interest in asymmetric rearrangements of chiral cyclopropane derivatives and successfully achieved thermal⁴⁾ and transition metal-catalyzed asymmetric rearrangements of chiral cyclopropane derivatives.⁵⁾ Therefore, it is quite important for us to develop a new method for preparing optically active cyclopropane derivatives⁶⁾ with high enantioselectivity. The precedent asymmetric synthesis of cyclopropane derivatives⁷⁾ has been based mainly on asymmetric cyclopropanation of olefins with carbenes in the presence of chiral ligands.⁸⁾ We wish to report herein the stereochemistry of stereocontrolled asymmetric synthesis of cyclopropane derivatives with chiral sulfinyl groups as chiral sources.

Optically active α -acylvinylic sulfoxides were readily obtainable from (*R*)-*p*-tolyl vinyl sulfoxide (**1**), which was prepared by the reaction of (–)-menthyl (*S*)-*p*-toluenesulfinate with vinylmagnesium bromide.⁹⁾ Treatment of (*R*)-**1** with lithium diisopropylamide followed by addition of acetaldehyde produced (*Ss*)-3-hydroxy-1-buten-2-yl *p*-tolyl sulfoxide (**2a**),



oxidation of which with Jones reagent gave (*S*)-3-oxo-1-buten-2-yl p-tolyl sulfoxide (**3a**) in 42% yield. The reaction of the α -carbanion of (*R*)-**1** with propionaldehyde or benzaldehyde and the subsequent oxidations of the resulting alcohols (*Ss*)-**2b,c** with Jones reagent gave (*S*)-**3b,c** in 58% yield.

Treatment of diethyl bromomalonate with sodium hydride in THF at 0°C and the subsequent reaction of the resulting sodium bromomalonate with (*S*)-**3a** at 0°C for 15 h gave (*Ss, R*)-**4a** in 45% chemical and 67% optical yields. The same reaction in DME at room temperature for 12 h produced (*Ss, R*)-**4a** in 42% chemical and 77% optical yields. Use of sec-butyllithium instead of sodium hydride in the above reaction in THF produced (*Ss, R*)-**4a** in 30% chemical and 82% optical yields. The reaction of (*S*)-**3b** with diethyl bromomalonate sodium enolate in THF at room temperature for 16 h gave (*Ss, R*)-**4b** in 50% chemical and 72% optical yields. Similarly, the reaction of (*S*)-**3b** with dimethyl bromomalonate lithium enolate in DME at 0°C for 16 h afforded (*Ss, R*)-**4c** in 54% chemical and 74% optical yields. The same reaction was carried out in the presence of 1.1 eq of zinc bromide under the same reaction conditions to give the same result as obtained above under the conditions without zinc bromide. However, the above reaction in the presence of HMPA gave (*Ss, R*)-**4c** with less enantioselectivity (47%). This indicates that the conformational fixation of the substrate by chelation to the metal cation employed would play an important role for the presentation of the high enantioselectivity. The reaction of (*S*)-**3c** with diethyl bromomalonate sodium or lithium enolate gave (*Ss, R*)-**4d** in 80 or 84% optical yield. The results are summarized in Table I. The diastereomeric excess of the products **4a-d** was determined by the NMR (270 MHz) spectral analysis. The optical yields of the reactions were calculated on the basis of the enantiomeric excess of the starting sulfoxides (*S*)-**3a-c** employed and the diastereomeric excess of the products (*Ss, R*)-**4a-d** obtained.

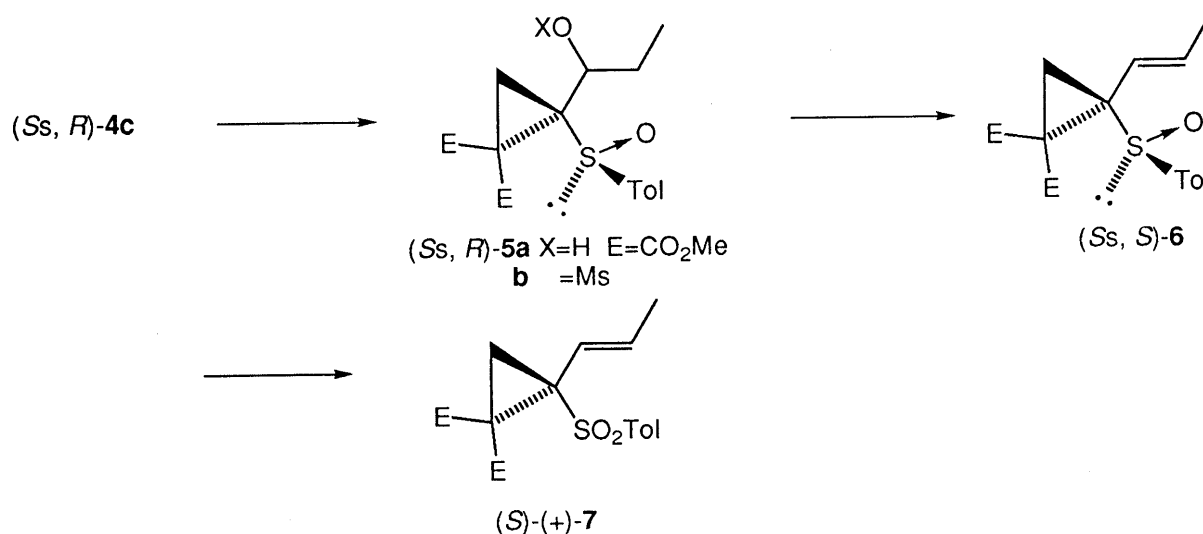
Table I. Asymmetric Synthesis of Chiral Acylcyclopropane Derivatives (*Ss, R*)-**4a-d** by Michael Addition of Bromomalonate to Chiral Vinylic Sulfoxides (*S*)-**3a-c**^{a)}

3	e.e.(%) of 3 ^{b)}	Base	Solvent	Reaction temp.(°C)	Reaction time(h)	Product 4	Yield of 4 (%)	d.e.(%) of (<i>Ss, R</i>)- 4 ^{c)}	Optical yield(%) of (<i>Ss, R</i>)- 4
3a	90	NaH	THF	0	15	4a	45	60	67
3a	90	NaH	DME	r.t.	12	4a	42	70	77
3a	89	sec-BuLi	THF	0	12	4a	30	73	82
3b	87	NaH	THF	r.t.	16	4b	50	63	72
3b	88	sec-BuLi	DME	0	16	4c	54	65	74
3b	88	sec-BuLi	DME/HMPA (10:1)	0	16	4c	55	42	47
3b	88	sec-BuLi	DME/ZnBr ₂ (1.1 equiv.)	0	16	4c	54	65	74
3c	89	NaH	THF	r.t.	24	4d	55	71	80
3c	89	sec-BuLi	THF	0	18	4d	50	75	84

a) Bromomalonate carbanion, prepared from diethyl or dimethyl bromomalonate (1.2 eq) and sodium hydride or sec-butyllithium (1.2 eq), was reacted with (*S*)-**3a-c**.

b) The enantiomeric excess (e.e.) of **3a-c** was determined on the basis of the e.e. of (*R*)-**1** used.

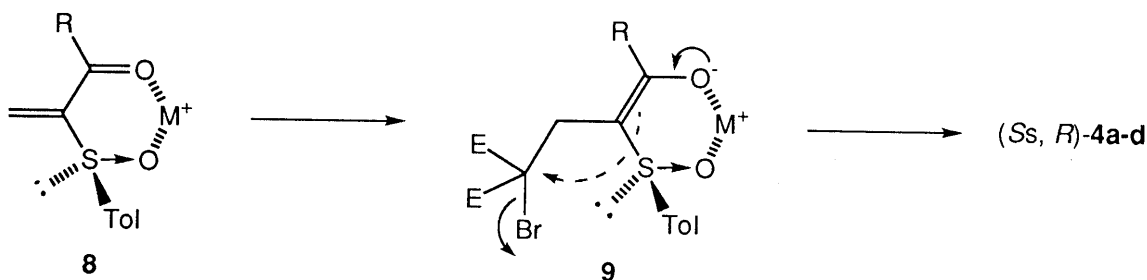
c) The diastereomeric excess (d.e.) of (*Ss, R*)-**4** was determined by the NMR spectral analysis.



The absolute configuration of the newly created asymmetric carbon center on the cyclopropane ring in (Ss)-**4c** obtained above was determined as follows. The NaBH₄ reduction of the ketone in (Ss)-**4c** and the subsequent mesylation of the alcohol (Ss)-**5a** followed by treatment of the mesylate (Ss)-**5b** with DBU gave (Ss, S)-**6**. Oxidation of the sulfinyl group in (Ss, S)-**6b** with *m*-CPBA afforded a sulfone, (S)-(+)-**7**. The absolute configuration of this sulfone **7** was determined by us by chemical correlation to trimethyl (*R*)-1,1,2-cyclopropanetricarboxylate of known absolute configuration,¹⁰ which will be published in due course. Thus, the absolute configuration of the newly created asymmetric carbon center in (Ss)-**4c** obtained from (S)-**3b** was determined as (*R*)-configuration. Based on this stereochemical result, the absolute configurations of the other newly created asymmetric carbon centers in (Ss)-**4a, b** and **d** would be deduced as (*R*)-configuration.

The mechanism for this asymmetric cyclopropanation is presented on the basis of the stereochemical results obtained above, as follows. The carbanion of bromomalonate reacted to the chiral vinyl sulfoxide (S)-**3** from the sterically less crowded lone pair side of the chiral sulfinyl substituent in the transition state **8** conformationally stereocontrolled by the chelation of the oxygen atoms of the carbonyl and sulfinyl groups to the metal cation,¹¹ and intramolecular alkylation would occur from the downward lone pair side of the chiral sulfinyl group, as depicted in **9**, leading to (Ss, *R*)-**4**. Serious different effects of the metal cation species used on the asymmetric induction could not be observed. However, conformational stereocontrol was not attainable in the presence of HMPA in the above reactions, presumably because of destruction of the chelation by the liberation of the metal cation from the chelate with HMPA.

Thus, this stereocontrolled reaction of chiral α -acylvinyl sulfoxides with bromomalonate carbanions provides a novel and readily available synthetic way to optically active acylcyclopropane derivatives with high enantiomeric excess.



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