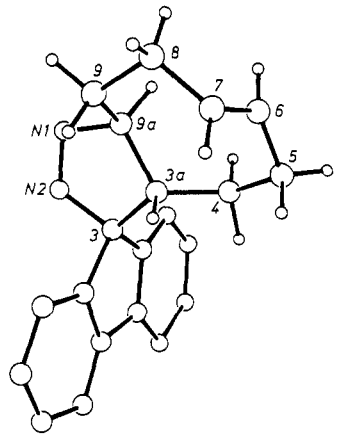

Figure 1. Structure of the diazofluorene adduct **10** of (*E*,*E*)-1,5-cyclooctadiene (one enantiomer). Bond lengths and angles of eight-membered ring: 3a–4 154.5, 4–5 154.8, 5–6 148.6, 6–7 132.3, 7–8 148.7, 8–9 155.3, 9–9a 153.9, 9a–3a 156.0 pm; 3a–4–5 115.0°, 4–5–6 106.4°, 5–6–7 123.1°, 6–7–8 122.4°, 7–8–9 106.1, 8–9–9a 114.2°, 9–9a–3a 119.4°.

adducts were separated in each case. From the structure proof of **1a** given below, we deduce that in all four cases we were dealing with 1:1 mixed crystals of diastereoisomers, this foiling potential distinction of derivatives of **1a** and **1b** by their ^{13}C NMR spectra.

After the failure of the "number game" we resorted to X-ray analysis of a crystalline monoadduct of **1**. The structure of the diazofluorene adduct **10** (Figure 1),[10] colorless monoclinic prisms, reveals provenance from the twist form **1a**. The angle of 69.4° between the 6,7- and 3a,9a-bond (Figure 1) indicates that the monoadduct is still fixed in a twist conformation. Not only the 1,2-bond of (*E*)-cyclooctene but also the 5,6-bond[11] is sterically constrained; force field calculations[3b] show a preference of the "crown" (here twist) over the chair form by 4.0 kcal mol^{-1} and $\Delta H^{\ddagger}$ = 11.6 kcal mol^{-1} for the "jump rope rotation" at the 5,6-bond. The corresponding rotation of the 3a,9a-bond in **10** is blocked by the annelated pyrazoline ring.

The dihedral angle (5–6–7–8) at the trans double bond of **10** is 136.3°, as compared with 137.7° found for (*E*)-cycloocten-3-yl 3,5-dinitrobenzoate (X-ray)[12] and 136.0° for gaseous (*E*)-cyclooctene (electron diffraction).[13] Out-of-plane bending (χ = 24.0°, 28.1°) and torsion (17.7°) in **10** participate to a similar extent in the deformation of the double bond as in the other models.

The ^1H NMR spectrum of **1a** in $CDCl_3$ at 0 °C shows two broad signals at δ 2.0–2.9 and 4.8–5.2 in the ratio 2:1. Irradiation at δ 2.45 furnishes a sharp singlet at δ 5.05, demonstrating the equivalence of the four vinyl Hs. Two ^{13}C NMR signals at δ 32.3 and 141.1 confirm the symmetry. The following δ_C values ($CDCl_3$) and (in brackets) $J(^{13}C–H)$ of the olefinic C atoms of cyclooctenes and 1,5-cyclooctadienes suggest a relation with ring strain: (*Z*) 130.1 (154.0), (*E*) 132.8 (151), (*Z*,*Z*) 128.6 (152.7), (*E*,*Z*) 136.0, (*E*,*E*) 141.1 (146 Hz). Strain energies according to force-field MM1:[2,14] (*Z*) 5.3, (*E*) 13.1, (*Z*,*Z*) 8.3, (*E*,*E*) 20.3 kcal mol^{-1}.

(10) $C_{21}H_{20}N_2$, monoclinic, $P2_1/c$, a = 13.797 (3) Å, b = 16.173 (4) Å, c = 15.687 (4) Å, β = 109.42 (2)°, V = 3301 Å^3, Z = 8 (pair of enantiomers in asymmetric unit), D_{calcd} = 1.21 g·cm^{-3}, μ = 0.66 cm^{-1}, Mo Kα, colorless prisms, 0.15 × 0.21 × 0.30 mm, Syntex P3 diffractometer graphite monochromator; $2 < 2\theta < 45°$, ω-scan, 2–29.3°/min; correction for intensity variation of check reflexion (3%). 4926 data collected, 4316 unique and 3275 observed ($I \geq 2\sigma(I)$). Direct methods solution, blocked cascade refinement, all non-hydrogen atoms anisotropic, hydrogen atoms refined with fixed isotropic U approximately 1.2U_{eq} of corresponding carbon atom. R_F = 0.0819, R_{wF} = 0.0674, highest difference map peak = 0.248 e/Å^3, number of refined parameters 529; ratio data/parameters 6.2. Comparable bond lengths and bond angles of the two species can be considered as equivalent within the 3σ criterion, but numerical values for the molecule depicted in Figure 1 match more closely standard values than those for the other isomer.

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(15) Atomic coordinates found in the supplementary material are also deposited at the Cambridge Crystallographic Data Center.

Acknowledgment. We thank Dr. D. Männig for assistance in the X-ray work and express our gratitude to the Fonds der Chemischen Industrie for support.

Supplementary Material Available: Tables of atomic coordinates,[15] bond distances, bond angles, parameters of anisotropic temperature factors, and hydrogen coordinates (6 pages); table of calculated and observed structure factors (20 pages). Ordering information is given on any current masthead page.

1,2-Asymmetric Rearrangements in Chiral Sulfinylcyclopropane Systems: Asymmetric Synthesis of α,α-Disubstituted Cyclobutanones

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Creation of asymmetric quaternary carbon atoms[1] is one of the most important problems for the enantioselective synthesis[2] of natural products such as steroids, terpenoids, and alkaloids. We wish to communicate a potentially valuable method for enantioselective creation of quaternary carbons by thermal 1,2-asymmetric rearrangements in cyclopropane systems possessing a chiral sulfinyl group on the rings.

The thermal rearrangements in cyclopropane systems have received much attention in recent years for the preparation of various kinds of synthetically valuable compounds;[3] however, no work has been reported on asymmetric rearrangements in such systems. This paper presents the first example of asymmetric induction in thermal rearrangements of cyclopropane systems affected by the chirality of optically active sulfoxides.

Addition of the α-carbanion of (R_S)-(+)-*p*-toluenesulfinylcyclopropane (**1**) (100% ee),[4] generated by treatment of (R_S)-(+)-**1** with *n*-butyllithium, to acetophenone (**2a**) at −20 °C for 4 h afforded (S_S)-**3a** in 78% yield (ratio of the diastereomers, 3:2). When (S_S)-**3a** obtained was heated in refluxing benzene for 3.5 h in the presence of a catalytic amount of *p*-toluenesulfonic acid, it underwent a 1,2-asymmetric rearrangement to give (S_S,4*R*)-**4a** in 88% yield. Reduction of the sulfoxide in (S_S,4*R*)-**4a** was carried out by treatment with acetyl chloride[5] in dichloromethane at room temperature for 2 h, affording (*R*)-(−)-**5a** ($[\alpha]^{25}_D$ −14.7° (*c* 2.0, EtOH)) in 78% yield. Isolation of the diastereomers of **3a** was successfully accomplished by careful preparative thick-layer chromatography over silica gel ($CHCl_3$–EtOH 25:1). The same sequences of each diastereomer of **3a** were carried out by heating in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid and treatment with acetyl chloride under the same conditions to give (*R*)-(−)-**5a** having the same optical rotation as described above. Hydrolysis of the enol thioether (*R*)-(−)-**5a** obtained was performed by treatment with titanium(IV) chloride (3 equiv)–lead hydroxide (3 equiv)–H_2O (6 equiv)[6] in acetonitrile at room temperature for 18 h to produce (*R*)-(−)-2-methyl-2-

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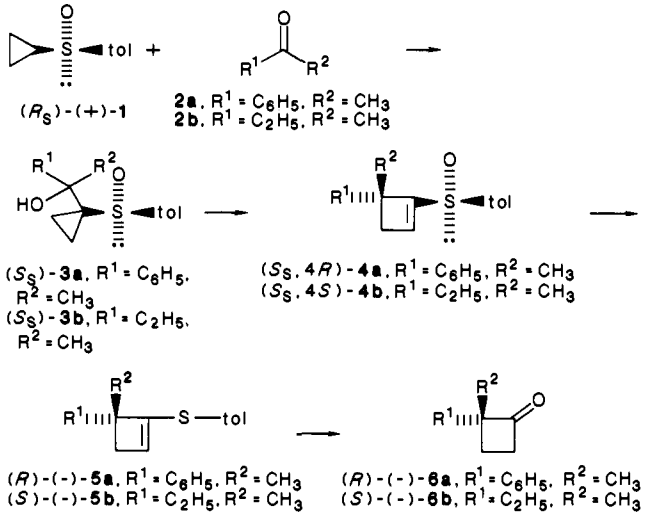
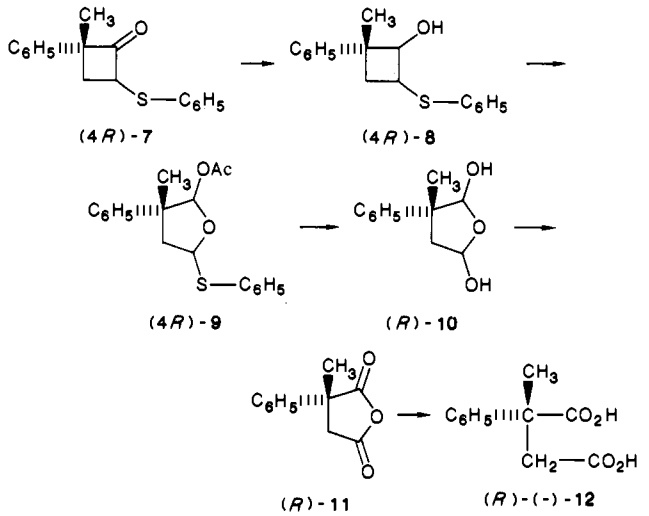
Scheme I



Scheme II



phenylcyclobutanone (**6a**) ($[\alpha]^{20}_D$ −9.6° (*c* 3.0, EtOH)) in 86% yield (Scheme I).

The absolute configuration and the enantiomeric excess of the product **6a** were determined as (*R*)-(−)-**6a** and 94.0% ee by chemical correlation of (−)-**6a** with (*R*)-(−)-2-methyl-2-phenylsuccinic acid (**12**) of known configuration[7] as follows. Sulfenylation of the ketone (−)-**6a** obtained above with diphenyl disulfide followed by sodium borohydride reduction of **7** produced an α-phenylthio alcohol **8**. Alcohol **8** upon treatment with lead tetraacetate in toluene–acetic acid (4:1) at 0 °C for 8 h underwent an oxidative cleavage[8] to give a thioacetal acetate **9**. Hydrolysis of this acetate **9** with potassium hydroxide in methanol at room temperature gave a hemiacetal **10**. Oxidation of this hemiacetal **10** with chromic acid in aqueous sulfuric acid–acetone at 0 °C produced 2-methyl-2-phenylsuccinic anhydride (**11**), which upon hydrolysis with potassium hydroxide in refluxing methanol gave (*R*)-(−)-**12** ($[\alpha]^{20}_D$ −18.8° (*c* 3.5, EtOH), 94.0% ee)[7] (Scheme II). The reaction sequences starting with ethyl methyl ketone (**2b**) were successfully executed in the same way.

Addition of the α-carbanion of (R_S)-(+)-**1** (100% ee)[4] to **2b** gave (S_S)-**3b** in 72% yield (the diastereomers of **3b** (ratio 3:2) were unseparable). The thermal rearrangement of (S_S)-**3b** thus obtained was carried out by treatment with *p*-toluenesulfonic acid in refluxing benzene for 3.5 h to furnish a cyclobutene derivative (S_S)-**4b** in 65% yield. Reduction of the sulfoxide (S_S)-**4b** with acetyl chloride followed by hydrolysis of the enol thioether (−)-**5b**

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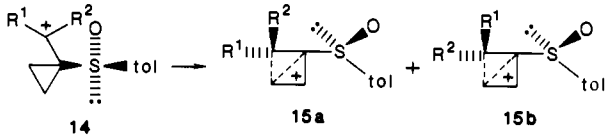
Scheme III



produced (*S*)-(−)-2-ethyl-2-methylcyclobutanone (**6b**). The absolute configuration and the enantiomeric excess of the product **6b** were determined as (S)-(−)-**6b** and 73.3% ee by transformation of **6b** into 4-methyl-4-hexanolactone (**13**) of known configuration;[9] Baeyer–Villiger oxidation of (−)-**6b** (H_2O_2–NaOH in aqueous methanol) followed by lactonization by heating in refluxing benzene with a catalytic amount of *p*-toluenesulfonic acid led to (*S*)-(−)-**13** ($[\alpha]^{23}_D$ − 6.3° (*c* 3.0, $CHCl_3$), 73.3% ee).[9]

On the basis of the above experimental results, the asymmetric inductions in these thermal 1,2-rearrangements of **3a,b** to **4a,b** were determined to give 94.0% and 73.3% optical yields, respectively.

From these stereochemical results, the mechanistic pathway for this asymmetric induction would be represented as follows. In the acid-catalyzed thermolysis, the carbonium ion **14** would be formed initially. The 1,2-migration of a carbon–carbon bond of the cyclopropane ring would occur via a transition state **15**, and a new asymmetry would be induced at this stage. The degree of asymmetric induction would depend on the difference between the thermodynamical stability of **15a** and **15b**, that is, on the difference of the steric interference between R^1 or R^2 and the lone pair or the oxygen atom of the chiral sulfoxide (Scheme III).

The easy access to the starting chiral sulfoxide and the high degree of asymmetric induction in this thermal rearrangement represent a potentially great advantage for the construction of asymmetric quaternary carbons. Furthermore, this method provides a facile entry to chiral cyclobutane derivatives, which have usually been hard to access.

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Biosynthesis of the Modified Peptide Antibiotic Nosiheptide in *Streptomyces actuosus*

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Nosiheptide (**1**),[1,2] a metabolite of *Streptomyces actuosus*, is a member of a broader class of highly modified, sulfur-rich peptide antibiotics, which also includes thiostrepton,[3] micrococcin,[4] the thiopeptins,[5] and several other compounds. Compound **1** inhibits protein synthesis in Gram-positive bacteria by binding to the 50S ribosomal subunit;[6] it is used as an animal-feed additive to increase weight gains.[7] Nosiheptide contains several structural elements

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