Anti-Selective Michael Addition of Thiols and Their Analogues to Nitro Olefins

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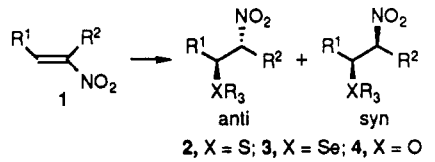
The reaction of nitro olefins with thiolate anions followed by protonation at −78 °C gives anti-β-nitro sulfides. This procedure can be applied to the anti-selective preparation of β-nitro ethers and β-nitro selenides. The reaction of cyclic nitro olefins with aryl thiol gives *cis*-β-nitro sulfide in excellent selectivity. The conjugate addition of alkylaluminum reagents to phenylthio β-nitro olefins followed by protonation at −78 °C also results in selective formation of *anti*-β-nitro sulfides. The anti isomers are also prepared through the deprotonation–protonation procedure at −78 °C from a mixture of *syn*- and *anti*-β-nitro sulfides. The protonation process of the nitronate anion intermediates at −78 °C is important for the occurrence of the high anti selectivity. However, the selectivity is not observed in the conjugate addition of an alkyl group to a simple nitro olefin. This difference in stereoselectivity can be explained on the basis of the differences of the preferable conformations of the nitronate anion intermediates. Theoretical calculations show that the methylthio group on the β-position covers the one side of the nitronate plane effectively to give the anti isomer in a stereoselective way.

The Michael addition reaction is one of the most important methods in organic chemistry. Nitro olefins act as good Michael acceptors owing to the strong electron deficiency of the nitro group.[1] As the nitro group is readily converted into other functional groups such as keto, cyano, and amino groups,[1,2] the Michael addition to nitro olefins has been frequently used in organic synthesis. The stereocontrol of the reaction has been extensively studied by Valentin[3] and Seebach.[4] Recently, the stereoselective methods using tin(II) enolates[5] and crotyltin compounds[6] have also been reported. Heteroatom nucleophiles such as nitrogen, oxygen, sulfur, and phosphorus atom anions act as good nucleophiles for the Michael addition to nitro olefins.[1] For example, the reaction of thiols with nitro olefins readily proceeds in the presence of catalytic amounts of base to give β-nitro sulfides in quantitative yield. However, the products of the reaction usually consist of the two diastereomeric isomers, syn and anti isomers, whose ratios are usually 1:1. To our knowledge, there have been few studies relating to this stereochemical control. In this paper we report three procedures for stereoselective preparation of *anti*-β-nitro sulfides and their homologues. The first procedure is the Michael addition of thiolate anions to nitro olefins followed by protonation at −78 °C.[7] This procedure can be extended to the preparation of *anti*-β-nitro selenides or *anti*-β-nitro ethers.[8,9] The second procedure is conjugate addition of alkyl groups to phenylthio β-nitro olefins. The third procedure is deprotonation–protonation of β-nitro sulfides at −78 °C. The last procedure provides a valuable method to prepare *anti*-β-nitro sulfides, because diastereomeric mixtures of the β-nitro sulfides are readily prepared under the conventional conditions. The anti selectivty of these reactions is explained on the basis of stereoselective protonation to nitronate anion intermediates. As the Michael addition of alkyl anion equivalents to simple nitro olefins proceeds in a nonstereoselective way, the high stereoselectivity requires heteroatom substituents on the β-position of the nitronate anion intermediates. The computational calculation exhibits that the heteroatom substituent covers ideally the one side of the plane of the nitronate anion.

Results

The Reaction of Nitro Olefins with Thiols and Their Homologues. β-Nitro sulfides **2** are readily prepared by the Michael addition of thiols to nitro olefins **1**. The reaction is conventionally carried out in the presence of catalytic amounts of base such as triethylamine. For example, 2-nitro-2-butene (**1a**) reacts with thiophenol smoothly under the conventional conditions to give 2-nitro-3-(phenylthio)butane (**2a**) in 98% yield. However, the product **2a** consists of a mixture of the two diastereoisomers, *syn*-**2a** and *anti*-**2a**, whose ratio is 60:40. In order to improve the stereochemical control of the formation of **2**, we examined the following new procedure, i.e., the reaction of thiolate anion with nitro olefin and subsequent protonation at −78 °C. We call this new procedure method

Scheme I[a]



2, X = S; **3**, X = Se; **4**, X = O

[a] Method A: (i) $R^3X^-M^+$, THF, room temperature; (ii) −78 °C, AcOH, 2 h. Method B: R^3SH, Et_3N (0.1 equiv), CH_3CN, room temperature, 1 h, 90–100% yield.

† Kyoto University.

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Table I. Diastereoselective Michael Addition of Thiols or Their Homologues to Nitro Olefins

run	R^1	R^2	R^3	X	M	time, h	product	yield,[a] %	anti/syn[b] method A	anti/syn[b] method B
1	Me	Me	Ph	S	Li	1	**2a**	75	91/9	40/60
2	Me	Me	Ph	S	K[c]	1	**2a**	73	81/19	
3	Me	Me	Me	S	Na	1	**2b**	64	90/10	
4	Et	Me	Ph	S	Li	1	**2c**	70	87/13	48/52
5	*i*-Pr	Me	Ph	S	Li	1	**2d**	62	32/68	43/57
6	Ph	Me	Ph	S	Li	1	**2e**	70	75/25[d]	34/66
7	Me	Et	Ph	S	Li	1	**2f**	63	91/9	37/63
8	Me	Ph	Ph	S	Li	1	**2g**	79	90/10	24/76
9	Me	Ph	Me	S	Na	1	**2h**	82	95/5	36/64
10	Me	1-cyclohexenyl	Ph	S	Li	1	**2i**	67	96/4	67/33
11	Me	1-cycloheptenyl	Ph	S	Li	1	**2j**	58	92/8	29/71
12	Me	*i*-Pr	Ph	S	Li	1	**2k**	56	57/43	50/50
13	Me	Me	Ph	Se[e]	Na	1	**3a**	68	91/9	
14	Et	Me	Ph	Se[e]	Na	1	**3b**	77	87/13	
15	Me	Me	$PhCH_2$	O	Na	48	**4a**	55	88/12	
16	Et	Me	$PhCH_2$	O	Na	36	**4b**	62	86/14	
17	C_5H_{11}	Me	$PhCH_2$	O	Na	72	**4c**	68	85/15	
18	Me	Ph	$PhCH_2$	O	Na	36	**4d**	73	91/9	
19	Me	Ph	Me	O	Na	12	**4e**	70	95/5	
20	Ph	Me	$PhCH_2$	O	Na	36	**4f**	70	67/33	

[a] Isolated yield by method A. [b] Determined by HPLC analyses. [c] tBuOK was used as a base. [d] Anti/syn ratio was 78/22 in the presence of HMPA. [e] Ethanol was used as a solvent.

Table II. Conjugate Addition of Methyl Group to 5 by Trimethylaluminum

run	R^1	R^2	R^3	compd	yield,[a] %	anti/syn[b]
1	Me	Me	Ph	**2a**	68	88/12
2	Me	Et	Ph	**2f**	41	91/9

[a] Isolated yield. [b] Determined by HPLC analyses.

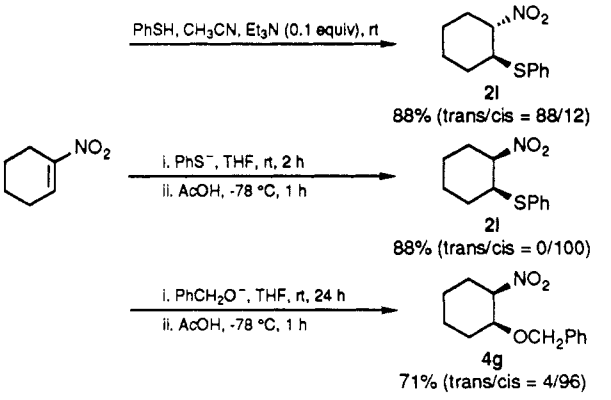
A and the conventional procedure method B (Scheme I). The results are summarized in Table I.

Method A gave *anti*-**2** stereospecifically. For example, **2a** was obtained in 75% yield under these conditions (run 1). To our surprise, the 100-MHz ^1H NMR spectrum of this **2a** showed that the product consisted of almost a single isomer. HPLC analysis showed the anti/syn ratio of **2a** was 91/9. The stereochemistry of the product was assigned to be *anti*-**2a** on comparison with the ^1H NMR spectra of *anti*-**2g** and *anti*-**3a**.

This procedure is also applicable to the stereoselective preparation of β-nitro selenides **3** and β-nitro ethers **4** to give the anti isomers preferentially (runs 13–20). The preparation of **4** needs excess amounts of alkoxide anions and a longer reaction time than the preparation of **2** and **3**, owing to the lower nucleophilicity of alkoxide anions.

Lithium, sodium, and potassium can be used as counter cations (run 1, 2, and 3). Since the changes of the anti/syn ratio are relatively small among them, their influence on the stereoselectivity is not very important. The steric bulkiness of R^3 does not affect the anti selectivity. For example, the anti/syn ratio of **2a** is similar to that of **2b** (runs 1 and 3). This tendency is also observed between runs 8 and 9, or runs 18 and 19. However, R^1 and R^2 groups affect the stereoselectivity. For example, the anti selectivity is usually in the range of 85/15 to 95/5 when R^1 and R^2 are methyl or primary alkyl groups (runs 1, 3, 4, 7, and 13–17). However, when a bulky group such as isopropyl or phenyl is located on the R^1 position, the anti/syn ratios fall to ca. 3:1 to 2:1 (runs 5, 6, and 20). This ratio is not improved very much when THF–HMPA (1:1) is used as a reaction solvent (run 6).[10a,b] It is noteworthy that phenyl, 1-cycloheptenyl, and 1-cyclohexenyl groups in the R^2 position enhance the anti selectivity (runs 8–11, 18, and 19). However, the isopropyl group in the R^2 position gives, a nearly 1:1 mixture of *anti*- and *syn*-**2k** (run 12).

Scheme II



Configurational assignments of **2** were done on the basis of the ^1H NMR downfield shift of the methyl group in the *anti*-**2g** because of the anisotropic effect of the nitro group.[11] The configuration of **3** was revealed to be anti by its conversion of the *Z*-nitro olefin via syn elimination of benzeneselenic acid.[8] The stereochemistry of **4** was assigned by comparison with the literature data after the conversion of **4** into the corresponding β-amino alcohols.[9,10a]

These two procedures provide useful methods for the stereoselective preparation of cyclic *trans*- and *cis*-β-nitro sulfides. For example, the reaction of 1-nitrocyclohexene with thiophenol proceeds under the condition of method B to give 1-nitro-2-(phenylthio)cyclohexane **2l** in 88% yield. *trans*-**2l** is the major isomer of the reaction with an

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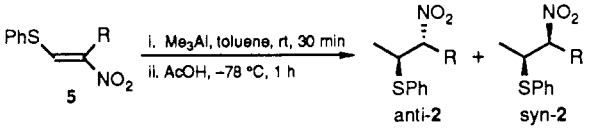
(11) The observed J_{12} of *anti*-**2g** and *syn*-**2g** are 10.8 and 11.4 Hz, respectively. These large coupling constants indicate a dihedral angle of H^1 and H^2 close to 180°. See: Kamimura, A.; Sasatani, H.; Hashimoto, T.; Ono, N. *J. Org. Chem.* **1989**, *54*, 4998.

Table III. Preparation of *anti*-2 via Deprotonation–Protonation Pathway

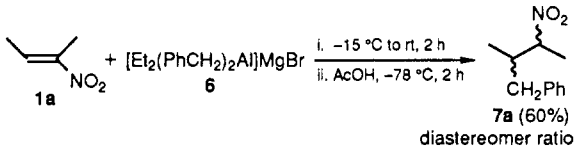
run	compd	R^1	R^2	R^3	X	anti/syn[c] before[a]	anti/syn[c] after[b]
1	**2a**	Me	Me	Ph	S	40/60	88/12
2	**2f**	Me	Et	Ph	S	37/63	89/11
3	**2h**	Me	Ph	Me	S	36/64	89/11
4	**7b**	Me	p-Tol	Me	CH_2	53/47[d]	57/43[d]

[a] The diastereomeric mixtures were prepared by method B or epimerization by triethylamine. [b] Isolated yields are more than 80%. [c] Determined by HPLC. [d] Determined by 250-MHz NMR spectroscopy.

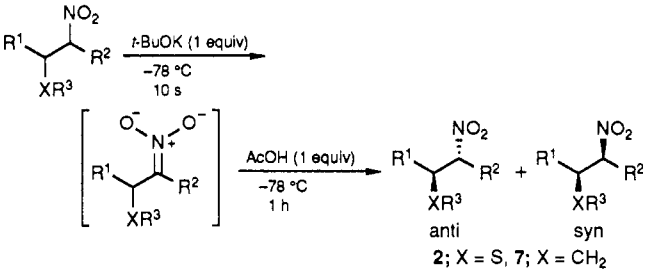
Scheme III



Scheme IV



Scheme V



88/12 trans/cis ratio. On the other hand, exposure of nitrocyclohexene to thiolate anion followed by protonation at −78 °C results in the formation of *cis*-**2l** exclusively. *cis*-β-Nitro ether **4g** was also prepared by the same procedure as the preparation of *cis*-**2l** (Scheme II).

We examined an alternative route for the preparation of **2**, that is, conjugate addition of alkyl group to phenylthio β-nitro olefin.[12] It is interesting whether or not stereoselectivity of this procedure differs from method A. Conjugate addition of a methyl group to phenylthio β-nitro olefins **5** was carried out as shown in Scheme III. The results are summarized in Table II. Trimethylaluminum was used as a methyl donor.[13] Although the yields of **2a** and **2f** are lower than by method A, the reaction proceeded in a stereoselective way. The major products are identical with *anti*-**2a** and *anti*-**2f**. The degree of the stereoselectivity is similar to that of method A. These results suggest that the stereoselectivity should not be determined by the sequence of introduction of substituents.

However, the conjugate addition of alkyl groups to simple nitro olefins proceeds in a nonselective way.[13] For example, the reaction of **1a** with aluminum ate complex **6**[13c] gives 2-methyl-3-nitro-1-phenylbutane **7a** in 60% yield (Scheme IV). **7a** consists of nearly 1:1 mixture of diastereomers.

Deprotonation–Protonation Process of Diastereomeric Mixture of β-Nitro Sulfides. Anti-enriched **2** is also obtained by treatment of **2** with 1 equiv of *t*-BuOK in THF at −78 °C for 5–10 s, followed by the addition of acetic acid at −78 °C (Scheme V). The results are summarized in Table III. The addition of acetic acid must be done as quickly as possible to avoid β-elimination of the thiolate anion. The anti selectivity in this procedure is similar to that in method A. This deprotonation–protonation pathway provides a meaningful method to obtain anti-**2**, because the diastereomeric mixtures of **2** are readily available via conventional Michael addition of thiol. Although this method is effective for the isomerization of methyl sulfide **2h** (run 3), the anti selectivity is not observed when the sulfur atom is replaced by the methylene group (run 4).

Discussion and Computational Results

The anti selectivity of the Michael addition appears when the nucleophiles are oxygen, sulfur, and selenium atom. The conjugate addition of an alkyl group to phenylthio β-nitro olefins also proceeds in an anti-selective way. The deprotonation–protonation procedure gives anti-enhanced products. Since all three procedures exhibit similar stereoselectivity, the step of protonation of the nitronate anion intermediates is thought to determine the stereoselectivity. A remarkable feature of the reaction is that the substituents on the nucleophiles (R^3 in Schemes I and V) do not affect the stereoselectivity. For example, high selectivity is achieved even when a methylthio or a methoxyl group is used as a nucleophile (Table I, runs 3, 9, and 19). On the other hand, the conjugate addition of alkyl groups to simple nitro olefins proceeds in a nonselective way. This tendency is also observed in the deprotonation–protonation procedure. Although the difference of steric effects between benzyl and phenylthio groups should be small, there are large differences on the stereoselectivity of the reaction (Schemes IV and V). These results suggest that the chief determining factor on the selectivity is not steric effects but rather the natures of the atom in the β-position of the nitronate anions. If similar conformations of the nitronate intermediates are preferred both in the sulfur and the methylene cases, it is impossible to explain the difference in selectivity. Thus, the large differences of the stereoselectivity between the sulfur and the methylene groups should be attributed to the differences in the preferred conformation of the nitronate anion intermediates. In Scheme VI three possible conformations of the nitronate anion, A–C, are depicted, which are eclipsed model A[14] and perpendicular models B and C.[15]

If the intermediates prefer conformer A, the relative steric bulkiness between the R^1 group and the R^3X group should play an important roll in the stereoselectivity, be-

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(13) (a) Pecunioso, A.; Menicagli, R. *J. Org. Chem.* **1988**, *53*, 45. (b) Pecunioso, A.; Menicagli, R. *Tetrahedron* **1987**, *43*, 5411. (c) Pecunioso, A.; Menicagli, R. *J. Org. Chem.* **1989**, *54*, 2391.
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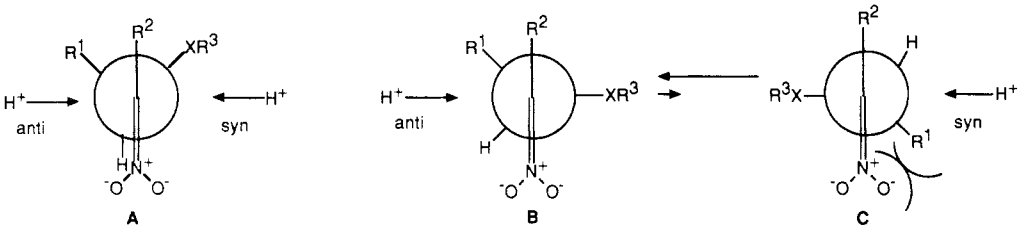
Scheme VI



cause the proton attacks the less hindered side of conformer A preferentially.[14] In other words, slight differences of the R^3 group may lead to significant change of the selectivity. In the case of the X = S, O, and Se, however, our results reveal that the stereoselectivity does not depend on the R^3 group in the range of methyl to phenyl. For example, comparison of runs 8 and 9 in Table I shows that the anti selectivity is similar. Particularly in run 9, high anti selectivity (95/5) is witnessed even though the steric differences between the methylthio group on R^3X and the methyl group on R^1 should be small. It is known that the selectivity from this conformer is lower than our results. For example, the anti selectivity of conjugate addition of butylcopper to methyl crotonate, which is explained by protonation proceeding via conformer A type intermediates, is 73:27.[15] Thus, conformer A should not be the favored conformation for the intermediates with S, O, and Se as the X groups. Conformer B should be preferred over conformer C due to the steric repulsion between R^1 and the nitro group. As the R^3X group covers the one face of the nitronate intermediates effectively, the proton attacks only from the opposite side of the R^3X group. High diastereofacial differentiation is expected from conformer B. The steric effect of the R^3 group in this conformer is not as important as in conformer A. Thus, conformer B is regarded as the favored conformer in the case of X = O, S, and Se. The perpendicular model has also been proposed for other β-heteroatom-substituted enolates such as those with Si or Sn.[16-18] On the other hand, when X is CH_2, the favored conformation of the nitronate anion should be conformer A from analogy with other cases.[15]

In order to ascertain the preferred structure of the intermediates, ab initio molecular orbital (MO) calculations are performed with the GAUSSIAN-80 program.[19] The 3-21G[20] basis set was used for MO calculations, and the geometry of 8 was optimized with the energy gradient method. The stereoviews and optimized parameters are shown in Figure 1. The C^1HNO_2 fragment (the nitro fragment) is almost planer because of the sp^2 hybridization. On the other hand, C_2 has an sp^3 structure. The dihedral angle, N-C^1-C^2-S (=θ), is calculated to be 95.4°, indicating that 8 has the perpendicular conformation (Figure 1, part b). Although the substituents on R^1 and R^2 may change the dihedral angle θ, the geometrical feature will not change. Therefore, the intermediate adopts a structure resembling conformation B. The view from another direction (Figure 1, part a) given a more important feature of the molecular geometry. It is remarkable that the

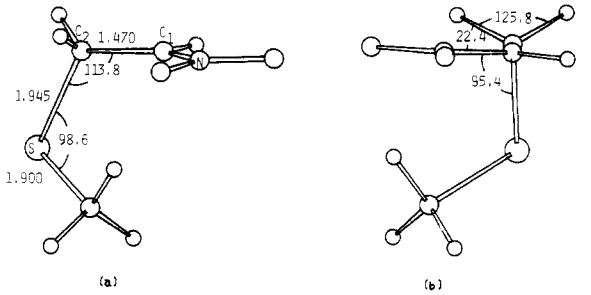


Figure 1. Stereoviews and optimized parameters of the nitronate anion intermediate $CH_3SCH_2CH{=}NO_2^-$ (8).

methyl group takes the cis position to the nitro fragment to cover one side of the nitronate plane very effectively. This is an unexpected structure because the trans conformation is more stable than the cis conformation in usual alkyl chains. The subsequent protonation occurs from the opposite side of the methylthio group to give anti products in a stereoselective way. The detailed analysis will be published elsewhere.[21]

Experimental Section

^1H NMR spectra were recorded on a JEOL-FX-400 spectrometer at 400 MHz, a Hitachi R-250-H spectrometer at 250 MHz, or a JEOL-PS-100 spectrometer at 100 MHz. ^{13}C NMR spectra were recorded on a JEOL-FX-400 or a R-250-H spectrometer. The solvent used was $CDCl_3$ with internal tetramethylsilane as a standard. Infrared spectra were recorded on a Hitachi 285 spectrometer. Mass spectra were recorded on a JEOL-DX-300/JMA-3100 mass spectrometer at 70 eV (EI). High-performance liquid chromatography (HPLC) analyses were carried out on R & D-ODS-5-A (4.6 mm i.d. × 25 cm, YMC Co. Ltd.) or ODS-80T (4.6 mm i.d. × 15 cm, Tosoh Co. Ltd.) with a Tosoh Model CCPE pump and UV-8000 UV detector. Elemental analyses were performed by Microanalytical Center, Kyoto University, and Advanced Instrumentation Center for Chemical Analysis, Ehime University. Nitro olefins were prepared by dehydration of corresponding nitro alcohols.[22] Nitrocyclohexene[23] and phenylthio β-nitro olefin 5[12] were prepared by the previously reported method. 2-Methyl-1-nitro-1-*p*-tolylbutane (**7b**) was prepared by oxidation of the corresponding amine using *m*-CPBA.[24] Trimethylaluminum and diethylaluminum chloride were purchased from Kanto Kagaku Co., Ltd.

Preparation of β-Nitro Sulfides 2. Preparation of 2-Nitro-3-(phenylthio)butane (2a). Method A. To a solution

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(21) There are two possible pathways of the protonation to nitronate anion. One path is the protonation directly on a carbon atom. The other path is the protonation firstly on oxygen atom to give the *aci*-nitro form, which is then protonated on carbon atom. In the latter case, favored conformation of *aci*-nitro form is important because the ultimate stereochemistry is determined by protonation to the *aci*-nitro form. However, our calculation exhibits that the *aci*-nitro form also gives similar geometry as Figure 1. Thus, the same conclusion can be reached in spite of the protonation pathways. See: Hori, K.; Higuchi, S.; Kamimura, A., submitted for publication.
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of thiophenol (1.32 g, 12 mmol) in 20 mL of THF was added butyllithium (1.41 M, 7.8 mL, 11 mmol) at 0 °C, and the mixture was stirred for 30 min. 2-Nitro-2-butene (1.01 g, 10 mmol) was added to this solution, and the mixture was stirred for 1 h at room temperature. The reaction mixture was cooled at −78 °C, 3 mL of acetic acid was added, and the resulting mixture was stirred for 1 h. The solution was poured into water and extracted with ethyl acetate, and the organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The crude product was subjected to column chromatography (silica gel/hexane) to give 1.58 g of **2a** in 75% yield. HPLC analysis showed that **2a** consisted of the mixture of *anti*-**2a** and *syn*-**2a**, whose ratio was 91/9.

Method B. A mixture of thiophenol (1.32 g, 12 mmol), 2-nitro-2-butene (1.01 g, 10 mmol), and triethylamine (0.10 g, 1 mmol) in acetonitrile (10 mL) was stirred for 1 h. The reaction mixture was poured into 1 M HCl and extracted with ethyl acetate, and the organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification by column chromatography gave 2.00 g of **2a** in 95% yield. HPLC analysis showed that this **2a** was consisted of the mixture of *anti*-**2a** and *syn*-**2a**, whose ratio was 40/60.

2-Nitro-3-(phenylthio)butane (2a): oil; (*anti*-**2a**) ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.33 (d, J = 7 Hz, 3 H), 1.66 (d, J = 7 Hz, 3 H), 3.52 (qd, J = 7, 7 Hz, 1 H), 4.20–4.40 (m, 1 H), 7.20–7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 17.0, 18.3, 46.8, 87.0; IR 1550 cm^{-1}; (*syn*-**2a**) ^{1}H NMR ($CDCl_3$) δ 1.27 (d, J = 7 Hz, 3 H), 1.55 (d, J = 7 Hz, 3 H), 3.80 (qd, J = 6, 7 Hz, 1 H), 4.20–4.40 (m, 1 H), 7.20–7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.5, 15.1, 45.3, 85.1. Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63. Found: C, 56.66; H, 6.27; N, 6.50.

The other β-nitro sulfides **2** were prepared by the same way as above.

2-(Methylthio)-3-nitrobutane (2b): oil; anti/syn = 90/10; (*anti*-**2b**) ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.35 (d, J = 7 Hz, 3 H), 1.67 (d, J = 6 Hz, 3 H), 3.14 (quint, J = 7 Hz, 1 H), 4.52 (qd, J = 7, 8 Hz, 1 H); (*syn*-**2b**) ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.29 (J = 7 Hz, 3 H), 1.58 (d, J = 7 Hz, 3 H), 3.25 (quint, J = 7 Hz, 1 H), 4.62 (quint, J = 6 Hz, 1 H); IR 1550 cm^{-1}. Anal. Calcd for $C_5H_{11}NO_2S$: C, 40.25; H, 7.43; N, 9.39. Found: C, 40.39; H, 7.39; N, 9.21.

2-Nitro-3-(phenylthio)pentane (2c): oil; anti/syn = 90/10; (*anti*-**2c**) ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.15 (t, J = 7 Hz, 3 H), 1.66 (d, J = 6 Hz, 3 H), 1.45–1.76 (m, 2 H), 3.41 (ddd, J = 4.6, 7.6, 9.2 Hz, 1 H), 4.60 (quint, J = 6 Hz, 1 H), 7.25–7.45 (m, 5 H); (*syn*-**2c**) ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.16 (t, J = 6 Hz, 3 H), 1.56 (d, J = 6 Hz, 3 H), 1.45–1.76 (m, 2 H), 3.58 (ddd, J = 3.4, 5.5, 10.1 Hz, 1 H), 4.60 (quint, J = 6 Hz, 1 H), 7.20–7.45 (m, 5 H); IR 1550 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22. Found: C, 58.65; H, 6.66; N, 6.16.

2-Methyl-4-nitro-3-(phenylthio)pentane (2d): oil; anti/syn = 74/26; (*anti*-**2d**) ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.99 (d, J = 6.7 Hz, 3 H), 1.12 (d, J = 6.7 Hz, 3 H), 1.63 (d, J = 6.7 Hz, 3 H), 2.13 (d quint, J = 4.3, J = 6.7 Hz, 1 H), 3.48 (dd, J = 4.3, 8.6 Hz, 1 H), 4.70 (dq, J = 8.6, 6.7 Hz, 1 H), 7.26–7.46 (m, 5 H); (*syn*-**2d**) ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.04 (d, J = 6.7 Hz, 3 H), 1.17 (d, J = 6.7 Hz, 3 H), 1.63 (d, J = 6.7 Hz, 3 H), 1.90 (d quint, J = 4.3, 6.7 Hz, 1 H), 3.45 (dd, J = 4.3, 9.2 Hz, 1 H), 4.79 (dq, J = 9.2, 6.7 Hz, 1 H), 7.23–7.46 (m, 5 H); IR 1550 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85. Found: C, 59.90; H, 7.34; N, 6.01.

2-Nitro-1-phenyl-1-(phenylthio)propane (2e): anti/syn = 70/30; (*anti*-**2e**) mp 70–71 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.81 (d, J = 7 Hz, 3 H), 4.55 (d, J = 9.4 Hz, 1 H), 4.98 (dq, J = 9.3, 6.6 Hz, 1 H), 7.20–7.30 (m, 10 H); (*syn*-**2e**) oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.41 (d, J = 7.3 Hz, 3 H), 4.55 (d, J = 9.4 Hz, 1 H), 4.95 (dq, J = 9, 6.6 Hz, 1 H), 7.30–7.50 (m, 10 H); IR 1550 cm^{-1}. Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12. Found: C, 66.11; H, 5.62; N, 4.93.

3-Nitro-2-(phenylthio)pentane (2f): oil; anti/syn = 91/9; (*anti*-**2f**) ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 3 H), 1.33 (d, J = 7.3 Hz, 3 H), 1.94–2.09 (m, 1 H), 2.16–2.30 (m, 1 H), 3.43 (quint, J = 7.3 Hz, 1 H), 4.31 (t, d, J = 9.5 Hz, 2.8 Hz, 1 H), 7.27–7.48 (m, 5 H); (*syn*-**2f**) ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 3 H), 1.32 (d, J = 6.8 Hz, 3 H), 1.96–2.08 (m, 2 H), 3.58 (quint, J = 7.1 Hz, 1 H), 4.26–4.38 (m, 1 H), 7.35–7.64 (m, 5 H); IR 1550 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22. Found: C, 58.99; H, 6.94; N, 6.18.

1-Nitro-1-phenyl-2-(phenylthio)propane (2g): anti/syn = 90/10; (*anti*-**2g**) oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.47 (d, J = 6.6 Hz, 3 H), 4.01 (dq, J = 10.8, 7.2 Hz, 1 H), 5.32 (d, J = 10.8 Hz, 1 H), 7.20–7.50 (m, 10 H); (*syn*-**2g**) mp 112 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.00 (d, J = 7.2 Hz, 3 H), 3.95 (dq, J = 10.8, 6.6 Hz, 1 H), 5.29 (d, J = 11.4 Hz, 1 H), 7.25–7.55 (m, 10 H); IR 1550 cm^{-1}. Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12. Found: C, 66.29; H, 5.48; N, 5.07.

2-(Methylthio)-1-nitro-1-phenylpropane (2h): oil; anti/syn = 95/5; (*anti*-**2h**) ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.45 (d, J = 6.5 Hz, 3 H), 1.75 (s, 3 H), 3.59 (dq, J = 11, 6.9 Hz, 1 H), 5.32 (d, J = 10.9 Hz, 1 H), 7.40–7.57 (m, 5 H); (*syn*-**2h**) ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.10 (d, J = 6.5 Hz, 3 H), 2.18 (s, 3 H), 3.59 (dq, J = 11, 7 Hz, 1 H), 5.35 (d, J = 11 Hz, 1 H), 7.40–7.58 (m, 5 H); IR 1550 cm^{-1}.

1-(1′-Cyclohexenyl)-1-nitro-2-(phenylthio)propane (2i): anti/syn = 96/4; (*anti*-**2i**) mp 82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, J = 6.7 Hz, 3 H), 1.46–1.64 (m, 4 H), 2.02–2.13 (m, 4 H), 3.81 (dq, J = 11.0, 6.7 Hz, 1 H), 4.73 (d, J = 11.0 Hz, 1 H), 6.00–6.02 (m, 1 H), 7.25–7.51 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 18.8, 21.4, 21.9, 23.5, 25.3, 42.1, 98.7, 128.1, 128.8, 130.7, 131.9, 133.8, 133.9; (*syn*-**2i**) mp 86 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (d, J = 7 Hz, 3 H), 1.50–1.66 (m, 4 H), 2.05–2.16 (m, 4 H), 3.68 (dq, J = 11.3, 7 Hz, 1 H), 4.73 (d, J = 11.3 Hz, 1 H), 5.90–5.92 (m, 1 H), 7.30–7.53 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 17.7, 21.4, 22.0, 23.3, 25.2, 43.0, 97.9, 128.6, 128.8, 130.5, 130.6, 133.4, 135.4; IR 1550 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_2S$: C, 65.13; H, 6.78; N, 4.80. Found C, 64.95, H, 6.90; N, 5.05.

1-(1′-Cycloheptenyl)-1-nitro-2-(phenylthio)propane (2j): anti/syn = 92/8; (*anti*-**2j**) oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, J = 6.7 Hz, 3 H), 1.30–1.76 (m, 6 H), 2.04–2.30 (m, 4 H), 3.78 (dq, J = 11, 6.7 Hz, 1 H), 4.73 (d, J = 11 Hz, 1 H), 6.14 (t, J = 6.8 Hz, 1 H), 7.25–7.51 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 19.0, 25.9, 26.2, 27.6, 28.6, 32.0, 42.9, 99.8, 127.5, 128.3, 129.0, 132.1, 134.3, 137.3, 139.0; (*syn*-**2j**) mp 58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, J = 7 Hz, 3 H), 1.31–1.88 (m, 6 H), 2.07–2.23 (m, 4 H), 3.67 (dq, J = 11.3, 7.4 Hz, 1 H), 4.72 (d, J = 11 Hz, 1 H), 6.04 (t, J = 6.4 Hz, 1 H), 7.21–7.51 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 18.3, 25.9, 26.3, 27.3, 28.5, 31.9, 43.3, 99.1, 128.2, 128.7, 129.0, 134.3, 135.5, 138.9; IR 1550 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_2S$: C, 65.94; H, 7.26; N, 4.81. Found: C, 65.95; H, 7.28; N, 4.74.

2-Methyl-3-nitro-4-(phenylthio)pentane (2k): oil; anti/syn = 57/43; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.95–1.08 (m, 6 H), 1.32–1.39 (m, 3 H), 2.24–2.35 (m, 1 H, for *syn*-**2k**), 2.51–2.64 (m, 1 H, for *anti*-**2k**), 3.44–3.60 (m, 1 H), 4.22–4.29 (m, 1 H, for *anti*-**2k**), 4.31–4.38 (m, 1 H, for *syn*-**2k**), 7.27–7.51 (m, 5 H); IR 1550 cm^{-1}.

1-Nitro-2-(phenylthio)cyclohexane (2l): (*trans*-**2l**) oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.20–2.36 (m, 8 H), 3.33 (dt, J = 4.27, 10.98 Hz, 1 H) 4.37 (dt, J = 4.28, 10.5 Hz, 1 H), 7.30–7.56 (m, 5 H); (*cis*-**2l**) oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.22–2.24 (m, 8 H), 3.84 (m, J < 5.5 Hz, 1 H), 4.58 (dt, J = 9.8, 4.28 Hz, 1 H), 7.25–7.50 (m, 5 H); IR 1550 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90. Found: C, 60.43; H, 6.41; N, 6.02.

Preparation of β-Nitro Selenide 3: General Procedure. To a solution of diphenyl diselenide (1 g, 3.2 mmol) in ethanol (20 mL) under an argon atmosphere was added $NaBH_4$ until the solution color turned to colorless.[25] The amount of $NaBH_4$ was about 0.3 g. Nitro olefin (6 mmol) was added to this solution, and the resulting mixture was stirred for 1 h at ambient temperature. The mixture was cooled at −78 °C, acetic acid (1 mL) was added, and the resulting mixture was stirred for an additional 1 h. The reaction mixture was poured into water (50 mL), and ethanol was removed in vacuo. The solution was extracted with ethyl acetate three times, and the organic phase was washed with brine and dried over Na_2SO_4. After filtration and evaporation, the residue was subjected to column chromatography (silica gel, hexane) to give **3**.

2-Nitro-3-(phenylseleno)butane (3a): oil; anti/syn = 90/10; NMR (100 MHz, $CDCl_3$) δ 1.43 (d, J = 7 Hz, 3 H), 1.69 (d, J = 7 Hz, 3 H), 3.51 (m, J = 7 Hz, 1 H), 4.52 (m, J = 7 Hz, 1 H), 7.29–7.60 (m, 5 H); IR 1550 cm^{-1}. Anal. Calcd for $C_{10}H_{13}NO_2Se$:

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C, 46.52; H, 5.07; N, 5.43. Found: C, 46.81; H, 5.06; N, 5.67.

2-Nitro-3-(phenylseleno)pentane (3b): oil; anti/syn = 87/13; NMR (100 MHz, $CDCl_3$) δ 1.13 (t, J = 7 Hz, 3 H), 1.51–1.93 (m, 2 H), 1.68 (d, J = 7 Hz, 3 H), 3.38 (m, J = 7 Hz, 1 H), 4.62 (m, J = 7 Hz, 1 H), 7.24–7.60 (m, 5 H); IR 1550 cm^{-1}.

Preparation of β-Nitro Ethers 4: General Procedure. To the suspension of 60% sodium hydride (1.2 g, 30 mmol) in THF (20 mL) was added alcohol (30 mmol) at 0 °C. After completion of the hydrogen evolution, nitro olefin (10 mmol) was added to the solution and the resulting mixture was stirred for 12–72 h at ambient temperature. To the mixture was added acetic acid (2 mL) at −78 °C, and the mixture was stirred for an additional 1 h. The mixture was poured into water (50 mL), and the usual workup gave the crude product, which was subjected to column chromatography (silica gel, hexane–ethyl acetate, 20:1) to give pure 4.

2-(Benzyloxy)-3-nitrobutane (4a): oil; anti/syn = 88/12; ^1H NMR (250 MHz, $CDCl_3$) δ 1.25 (d, J = 6.1 Hz, 3 H), 1.56 (d, J = 6.7 Hz, 3 H), 4.11 (quint, J = 6.1 Hz, 1 H), 4.48 (d, J = 11.6 Hz, 1 H), 4.59 (d, J = 11.7 Hz, 1 H), 4.42–4.68 (m, 1 H), 7.23–7.41 (m, 5 H); IR 1550, 1060 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.67. Found: C, 63.11; H, 7.35; N, 6.59.

3-(Benzyloxy)-2-nitropentane (4b): oil; anti/syn = 86/14; ^1H NMR (250 MHz, $CDCl_3$) δ 0.98 (t, J = 7.4 Hz, 3 H), 1.55 (d, J = 6.8 Hz, 3 H), 1.46–1.72 (m, 2 H), 3.98 (q, J = 6.8 Hz, 1 H), 4.53 (s, 2 H), 4.53–4.63 (m, 1 H), 7.22–7.51 (m, 5 H); IR 1550 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.53; H, 7.76; N, 6.17.

3-(Benzyloxy)-2-nitrooctane (4c): oil; anti/syn = 85/15; (*anti*-**4c**) ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, J = 6.7 Hz, 3 H), 1.29–1.71 (m, 8 H), 1.55 (d, J = 6.7 Hz, 3 H), 4.01–4.08 (m, 1 H), 4.52 (s, 2 H), 4.55–4.61 (m, 1 H), 7.14–7.41 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 12.844, 14.113, 22.609, 25.197, 31.740, 73.071, 80.078, 84.668, 127.86, 128.39; (*syn*-**4c**) ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, J = 6.7 Hz, 3 H), 1.29–1.71 (m, 8 H), 1.49 (d, J = 6.7 Hz, 3 H), 3.88–3.96 (m, 1 H), 4.52 (s, 2 H), 4.60–4.72 (m, 1 H), 7.14–7.41 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 15.554, 23.976, 29.738, 29.835, 31.935, 72.998, 80.298, 85.717, 127.86, 128.39; IR 1550 cm^{-1}. Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.82; H, 8.96; N, 5.43.

2-(Benzyloxy)-1-nitro-1-phenylpropane (4d): oil; anti/syn = 91/9; ^1H NMR (250 MHz, $CDCl_3$) δ 1.30 (d, J = 6.1 Hz, 3 H), 4.28 (d, J = 11.0 Hz, 1 H), 4.47 (d, J = 11.4 Hz, 1 H), 4.31–4.47 (m, 1 H), 5.36 (d, J = 7.9 Hz, 1 H), 7.02–7.60 (m, 10 H); IR 1550 cm^{-1}. Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.16; H, 6.38; N, 5.18.

2-Methoxy-1-nitro-1-phenylpropane (4e): oil; anti/syn = 95/5; (*anti*-**4e**) ^1H NMR (250 MHz, $CDCl_3$) δ 1.24 (d, J = 6.1 Hz, 3 H), 3.25 (s, 3 H), 4.26 (quint, J = 6.7 Hz, 1 H), 5.32 (d, J = 7.3 Hz, 1 H), 7.26–7.54 (m, 5 H); (*syn*-**4e**) ^1H NMR (250 MHz, $CDCl_3$) δ 0.97 (d, J = 6.8 Hz, 3 H), 3.41 (s, 3 H), 4.29 (dq, J = 10.8, 6.1 Hz, 1 H), 5.29 (d, J = 10.4 Hz, 1 H), 7.26–7.52 (m, 5 H); IR 1550 cm^{-1}.

1-(Benzyloxy)-2-nitro-1-phenylpropane (4f): oil; anti/syn = 67/33; ^1H NMR (250 MHz, $CDCl_3$) δ 1.24 (d, J = 6.7 Hz, 3 H, for *syn*-**4f**), 1.56 (d, J = 6.7 Hz, 3 H, for *anti*-**4f**), 4.21–5.11 (m, 4 H), 7.16–7.62 (m, 10 H); IR 1550 cm^{-1}. Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.20; H, 6.35; N, 5.01.

***cis*-1-(Benzyloxy)-2-nitrocyclohexane (4g)**: oil; trans/cis = 4/96; ^1H NMR (250 MHz, $CDCl_3$) δ 1.20–1.64 (m, 4 H), 1.84–2.36 (m, 4 H), 4.28 (dd, J = 3.0, 4.3 Hz, 1 H), 4.31–4.37 (m, 1 H), 4.43 (d, J = 11.6 Hz, 1 H), 4.56 (d, J = 11.6 Hz, 1 H), 7.18–7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 19.2, 23.6, 24.3, 28.3, 71.3, 74.8, 85.7, 127.49, 127.66, 128.32. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.11; H, 7.32; N, 5.99.

The Reaction of Phenylthio β-Nitro Olefin 5 and Trimethylaluminum. To a solution of trimethylaluminum (8 mmol) in toluene (5 mL) was added 2-(phenylthio)-1-nitropropene (395 mg, 2.03 mmol) at room temperature, and the solution was stirred for 6 h. The reaction mixture was cooled at −78 °C, and acetic acid (5 mL) was added at the same temperature. After being stirred for an additional 1 h, the mixture was poured into water and the aqueous layer was extracted with ethyl acetate three times. The organic layer was combined, washed with brine, and dried over Na_2SO_4. The solvent was removed in vacuo, and the crude product was subjected to column chromatography (silica gal/hexane) to give **2a** in 64% yield (273 mg). The anti/syn ratio was 88/12 (HPLC analysis). **2f** was prepared in the same way. The anti/syn was 91/9 (HPLC analysis).

Preparation of 2-Methyl-3-nitro-1-phenylbutane (7a). To an ether solution (20 mL) of benzylmagnesium bromide, which was prepared in situ from benzyl bromide (2.045 g, 12.0 mmol) and magnesium (308 mg, 12.8 mmol), was added diethylaluminum chloride (5 mL, 1 M hexane solution) at 0 °C, and the resulting mixture was stirred for 4 h at room temperature. 2-Nitro-2-propene (472 mg, 4.6 mmol) was added to the mixture at −15 °C, and the mixture was stirred for 2 h. The reaction mixture was cooled at −78 °C, and a THF solution of acetic acid (1 M, 30 mL) was added. The mixture was stirred and allowed to warm up to room temperature for 2 h. The reaction mixture was poured into water. After usual workup and purification by column chromatography (silica gel, hexane–ethyl acetate, 20:1), **7a** was obtained in 60% yield as oil: diastereomer ratio = 54/46 (HPLC); ^1H NMR (250 MHz, $CDCl_3$) δ 0.89 (d, J = 6.1 Hz, 3 H, for minor isomer), 0.92 (d, J = 6.7 Hz, 3 H, for major isomer), 1.51 (d, J = 6.7 Hz, 3 H, for minor isomer), 1.55 (d, J = 6.7 Hz, 3 H, for major isomer), 1.88–2.86 (m, 3 H), 4.45–4.57 (m, 1 H)8 7.15–7.33 (m, 5 H); IR 1550 cm^{-1}.

Preparation of *anti*-2 via Deprotonation–Protonation Procedure. General Procedure. To a solution of *t*-BuOK (1 equiv) in THF was added **2** at −78 °C, and the mixture was quenched by acetic acid (2 mL) after 5–10 s. The resulting solution was stirred for 1 h and poured into water. After usual workup and purification by column chromatography (silica gel, hexane–ethyl acetate, 20:1), *anti*-**2** was obtained in 80–90%.

Deprotonation–Protonation Procedure of 7b. To a solution of *t*-BuOK (136 mg, 1.21 mmol) th THF (10 mL) was added **7b** (216 mg, 1.04 mmol) at −78 °C, and the resulting mixture was stirred for 1 min. Acetic acid (3 mL) was added at −78 °C, and the solution was allowed to be warmed to room temperature for 3 h. The solution was poured into water. After usual workup and purification by column chromatography (silica gel, hexane–ethyl acetate, 20:1), **7b** was obtained in 71% yield. Anti/syn ratio was determined by 250-MHz NMR: (*anti*-**7b**) ^1H NMR (250 MHz, $CDCl_3$) δ 0.82 (t, J = 6.7 Hz, 3 H), 1.06 (d, J = 6.1 Hz, 3 H), 1.16–1.62 (m, 2 H), 2.36 (s, 3 H), 2.39–2.61 (m, 1 H), 5.11 (d, J = 10.9 Hz, 1 H), 7.19 (d, J = 8 Hz, 2 H), 7.37 (d, J = 8 Hz, 2 H); (*syn*-**7b**) ^1H NMR (250 MHz, $CDCl_3$) δ 0.71 (d, J = 6.7 Hz, 3 H), 0.98 (t, J = 7.3 Hz, 3 H), 1.16–1.62 (m, 2 H), 2.36 (s, 3 H), 2.39–2.61 (m, 1 H), 5.12 (d, J = 11.6 Hz, 1 H), 7.19 (d, J = 8 Hz, 2 H), 7.37 (d, J = 8 Hz, 2 H).

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