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Stereoselective Synthesis of 1-Nitrobicyclo[3.1.0]hexanes and Fused Isoxazoline-*N*-oxides from Primary Nitro Compounds

Akio Kamimura,*[,†] Ryota Takeuchi,[†] Kosuke Ikeda,[†] Takaaki Moriyama,[†] and Michinori Sumimoto[‡]

[†]Department of Applied Molecular Bioscience, Graduate School of Medicine, Yamaguchi University, Ube 755-8611, Japan

[‡]Department of Material Chemistry, Graduate School of Science and Engineering, Yamaguchi University, Ube 755-8611, Japan

Supporting Information

ABSTRACT: The one-step preparation of 1-nitrobicyclo[3.1.0]hexane and bicycloisoxazoline-*N*-oxide was readily achieved from conjugate adducts of nitro alkenes and allylmalonates by treatment with Ag_2O and iodine under basic conditions. We observed that when a primary alkyl group was present at the *β*-position of the nitro group, bicyclo[3.1.0]hexane was preferentially formed, whereas if a secondary alkyl group occupied that position, isoxazoline-*N*-oxide was predominantly produced. High *cis*-selectivity was observed for the formation of cyclopentane units for both reactions. An iodomethyl adduct, considered an intermediate of the cyclization, was isolated, and its conversion to isoxazoline-*N*-oxide was successfully achieved. The isoxazoline-*N*-oxide underwent 1,3-dipolar cycloaddition with alkenes to yield tricycloheterocyclic compounds, which were readily converted to spirolactam in good yield by reductive cleavage of N−O bonds using Raney-Ni. On the other hand, 1,3-dipolar cycloaddition of the isoxazoline-*N*-oxide to terminal alkynes yielded tricyclic aziridines stereoselectively.

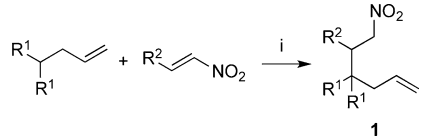
INTRODUCTION

Recently, domino reactions have been attracting attention in the field of organic synthesis because they provide a convenient and economical method to prepare desired organic molecules.[1] Domino reactions afford two or more bonds continuously under single reaction conditions, and the latter bond formation occurs as a result of the former bond formation reaction. Therefore, it reduces the experimental manipulation and enhances synthetic efficiency. Cyclopropanes are recognized as an important class of organic compounds because of their unique biological activities. Preparation of fused cyclopropanes has been of interest because they exhibit interesting biological activity. The total synthesis of fused cyclopropanes such as indolizomycin,[2] trovafloxacin,[3] duocarmycin, and CC-1065[4] has been achieved. To prepare these structures, the Kulinkovich reaction, in which low valence titanium plays an important role, provides a useful method.[5,6] Recently, we discovered a new synthetic method to prepare fused cyclopropanes by a one-pot reaction from primary nitro compounds, which underwent a domino process involving single electron oxidation of the *α*-nitro anion, radical cyclization, and an intramolecular S_N2 reaction.[7] Using this strategy, aza- and oxa-bicyclo[3.1.0]-hexanes were prepared in a highly stereoselective manner. The precursors of the reaction were readily prepared by the conjugate addition reaction of amides or alkoxides to nitro alkenes. Thus, this method provided a convenient way to synthesize these compounds. In order to enhance the synthetic utilities of this methodology, we examined the reaction for the conjugate adducts of nitroalkenes with carbon nucleophiles such as malonate derivatives. It was previously reported that a similar process of primary nitro compounds driven by CAN gave isoxazoline-*N*-oxides exclusively.[8] In this paper, we describe the details of the cyclopropanation of malonate-derived precursors and the preparation of 1-nitrobicyclo[3.1.0]-hexanes stereoselectively. The chemoselectivity of the isoxazoline-*N*-oxide/cyclopropane depended on the substituent at the adjacent position of the nitro group. During the investigation, we observed that the formation of bicyclic isoxazoline-*N*-oxide occurred through *O*-alkylation of the nitronate anion of an iodomethyl intermediate rather than through *C*-alkylation.[9] A convenient method to prepare tricycloheterocyclic compounds via 1,3-dipolar cycloaddition of the isoxazoline-*N*-oxides to alkenes or alkynes is also demonstrated.[10]

RESULTS AND DISCUSSION

Cyclization precursors **1** were prepared by the conjugate addition of allylmalonate derivatives to nitro alkenes (Scheme 1). The results are summarized in Table 1.

Scheme 1[a]



1

[a]Reagents and conditions: (i) *t*-BuOK, THF, −30 °C.

The conjugate addition occurred smoothly in the presence of *t*-BuOK as a base to give the desired precursors **1a**−**1l** in good yields. For example, the conjugate addition of dimethyl

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Table 1. Preparation of Cyclization Precursors

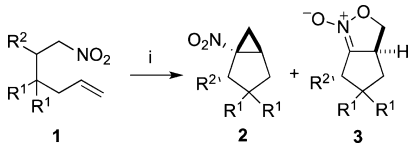
entry	R^1	R^2	1	yield (%)[a]
1	CO_2Me	Et	**1a**	88
2	CO_2Me	*n*Pr	**1b**	92
3	CO_2Me	*i*Pr	**1c**	98
4	CO_2Me	*n*-C_4H_9	**1d**	100
5	CO_2Me	*n*-C_5H_{11}	**1e**	94
6	CO_2Me	*n*-C_6H_{13}	**1f**	94
7	CO_2Me	*c*-C_6H_{11}	**1g**	98
8	CO_2Me	Ph	**1h**	51
9	CO_2Et	Et	**1i**	91
10	CO_2Et	*i*Pr	**1j**	89
11	CO_2Et	*n*-C_5H_{11}	**1k**	93
12	CN	*n*-C_5H_{11}	**1l**	89

[a]Isolated yields.

allylmalonate to 1-nitrobutene proceeded smoothly in the presence of *t*-BuOK, providing compound **1a** in 88% yield (Table 1, entry 1). The procedure was easily performed, and most of compounds **1** were isolated in almost quantitative yields.

We then examined the cyclopropanation of **1**. Treatment of **1** with Ag_2O and iodine in the presence of DBU resulted in a smooth consumption of **1**, and the desired bicyclo[3.1.0]hexane **2** was isolated in good yields (Scheme 2). The results are summarized in Table 2.

Scheme 2[a]



[a]Reagents and conditions: (i) DBU (1.2 equiv), Ag_2O (2.0 equiv), I_2, (2.0 equiv), THF, rt, 4h.

Table 2. Cyclopropanation or Nitrone Formation of Nitro Compounds 1

entry	R^1	R^2	1	2; yield (%)[a]	3; yield (%)[a]
1	CO_2Me	Et	**1a**	**2a**; 72 (1/99)[b]	**3a**; 23 (1/99)[c]
2	CO_2Me	*n*Pr	**1b**	**2b**; 60 (1/99)[b]	**3b**; 19 (1/99)[c]
3	CO_2Me	*i*Pr	**1c**	**2c**; 16 (1/99)[b]	**3c**; 80 (1/99)[c]
4	CO_2Me	*n*-C_4H_9	**1d**	**2d**; 61 (1/99)[b]	**3d**; 25 (1/99)[c]
5	CO_2Me	*n*-C_5H_{11}	**1e**	**2e**; 51 (1/99)[b]	**3e**; 17 (1/99)[c]
6	CO_2Me	*n*-C_6H_{13}	**1f**	**2f**; 60 (1/99)[b]	**3f**; 12 (1/99)[c]
7	CO_2Me	*c*-C_6H_{11}	**1g**	**2g**; 16 (1/99)[b]	**3g**; 66 (1/99)[c]
8	CO_2Me	Ph	**1h**	**2h**; 58 (16/84)[b]	**3h**; 0
9	CO_2Et	Et	**1i**	**2i**; 66 (1/99)[c]	**3i**; 22 (1/99)[c]
10	CO_2Et	*i*Pr	**1j**	**2j**; 31 (1/99)[c]	**3j**; 54 (1/99)[c]
11	CO_2Et	*n*-C_5H_{11}	**1k**	**2k**; 64 (1/99)[c]	**3k**; 19 (1/99)[c]
12	CN	*n*-C_5H_{11}	**1l**	**2l**; 21 (5/95)[b]	**3l**; 7 (1/99)[c]

[a]Isolated yields, *cis*/*trans* ratios. [b]Determined by GC analyses. [c]Determined by NMR.

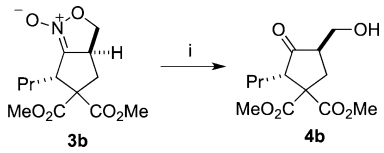
For example, primary nitro compound **1a** underwent the reaction smoothly to give 1-nitrobicyclo[3.1.0]hexane **2a** in 72% yield, accompanied by a side product of isoxazoline-*N*-oxide **3a** in 23% yield (Table 2, entry 1). Isolated **2a** contained only one diastereomer, indicating that the stereoselectivity of the cyclopropanation was very high. The side product **3a** exhibited a characteristic peak at approximately 120 ppm in ^{13}C NMR and 1660 cm^{-1} in IR spectra, both of which suggested that the side product **3a** contained a C═N double bond in an isoxazoline ring. Compound **3a** was somewhat less stable because it decomposed during recrystallization in an alcoholic solvent. The structure was confirmed by the result that compound **3** underwent the 1,3-dipolar cycloaddition to give tricyclic compounds (vide infra). The side product **3a** also contained only single diastereomer and was formed stereoselectively.

Nitro compounds such as **1b**, **1d**, **1e**, **1f**, **1i**, and **1k**, in which a nonbulky primary alkyl substituent occupies the R^2 position, afforded similar results; cyclopropanes **2** were isolated as the main products, and side products **3** were obtained in approximately 20% yields (Table 2, entries 2, 4, 5, 6, 9, and 11). These products consisted of single diastereomers, indicating that the transformation occurred in a highly stereoselective manner. Compound **1h**, which possesses an aromatic substituent at the R^2 position, also gave the corresponding cyclopropane **2h** in moderate yield but with a lower stereoselectivity than that of the other compounds that contain nonbulky groups at the R^2 position (Table 2, entry 8). On the other hand, isoxazoline-*N*-oxide **3** was formed as the major product when the nitro compounds **1c**, **1g**, and **1j**, all of which attached a bulky secondary alkyl group at the R^2 position, were treated under the same reaction conditions, although the formation of bicyclo[3.1.0]hexane **2c**, **2g**, and **2j** in small amounts was observed (Table 2, entries 3, 7, and 10). Using a malononitrile precursor **1l** gave the corresponding **2l** and **3l**; however, the yields remained in a low level (Table 2, entry 12).

The stereochemistry of bicyclo[3.1.0]hexane **2** was determined by X-ray crystallographic analyses. Compound **2d**, which was isolated as a single isomer, gave a good crystal, which verified the configuration unambiguously. Other compounds **2** exhibited NMR patterns similar to those of compound **2d**. X-ray crystallographic analysis for **2h** clearly indicated a fused cyclopropane structure with an identical configuration.

Isoxazoline-*N*-oxide **3** was readily converted to corresponding hydroxylketone without epimerization at chiral centers. For example, treatment of **3b** with an aqueous HCl in MeOH gave **4b** in 50% yield as a single diastereomeric isomer (Scheme 3).

Scheme 3[a]



[a]Reagents and conditions: (i) 1 M HCl, MeOH, rt, 48 h, 50%.

The present transformation was modified to a one-pot reaction procedure (Scheme 4). For example, dimethyl allylmalonate and 1-nitroheptene were mixed together in the presence of *t*-BuOK in THF, and the mixture was stirred overnight at −30 °C. Then, Ag_2O, I_2, and DBU were added to the mixture at room temperature, promoting the cyclization reaction to give **2e** and **3e** in 42 and 22% yields, respectively. The product ratio of **2** and **3** varied slightly compared to that of the products obtained from the two-step preparation of **2** and **3**. There was nearly no loss in the yield by combining the two steps; therefore, the compounds were obtained rapidly and effectively.

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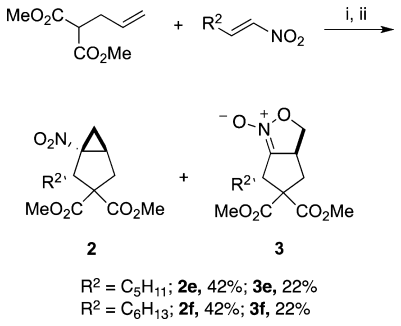
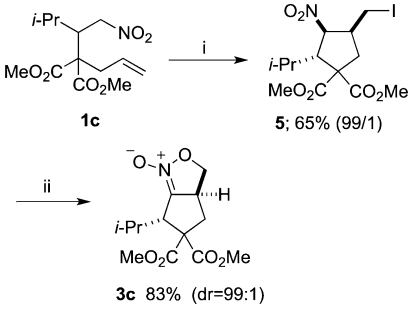
Scheme 4[a]



[a]Reagents and conditions: (i) *t*-BuOK, THF, −30°C, 2 h; (ii) DBU (1.2 equiv), Ag_2O (2.0 equiv), I_2 (1.7 equiv), THF, rt, 3 h.

Surprisingly, when compound **1c** was treated with wet THF under similar conditions, iodomethylcyclopentane **5** was isolated in 65% yield (Scheme 5); compound **3c** was not

Scheme 5[a]

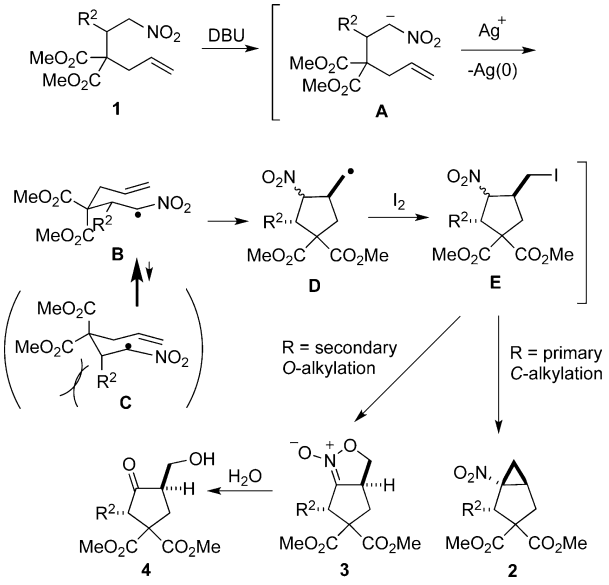


[a]Reagents and conditions: (i) DBU (1.2 equiv), Ag_2O (2.0 equiv), I_2 (2.0 equiv), THF−H_2O (10−0.2 mL); (ii) DBU, THF, rt, 3 h.

detected in the reaction mixture. The reaction progressed in a highly stereoselective manner to yield a single diastereomer of **5** in 99/1 ratio. Compound **5** was stable and provided a good crystal suitable for X-ray crystallographic analysis, which unambiguously revealed the configuration of **5** (Scheme 5). This compound was considered as an intermediate of the present cyclization that would yield a cyclopropane or isoxazoline-*N*-oxide. Compound **5** was converted to isoxazoline-*N*-oxide **3c** by treatment with DBU, obtained in 83% yield. This result clearly indicated that the intramolecular S_N2 reaction by the *O*-anion of the nitronate dominantly occurred to yield **3c**. Although we attempted to isolate a corresponding iodomethyl intermediate from precursors **1** containing a primary alkyl group at the R^2 position, the desired iodomethyl compounds were not isolated or observed in the reaction mixture.

Combining all the results obtained so far, we propose the reaction pathway shown in Scheme 6. Initially, precursor **1** is deprotonated in the presence of DBU to give nitronate anion **A**, which is immediately oxidized by silver oxide to yield α-nitro radical **B**.[11] Radical **B** attacks the terminal carbon−carbon double bond to give a primary alkyl radical **D**. During the cyclization process, the two conformations **B** and **C** are possible. Because the R^2 group at the C2 position occupies a pseudoequatorial position in conformer **B** and a pseudoaxial position in conformer **C**, conformer **B** is favored over conformer **C**, and radical cyclization dominantly occurs through

Scheme 6



conformer **B** to give radical **D** stereoselectively. The primary radical in **D** must be trapped by iodine to give iodomethyl intermediate **E**. When R^2 is a nonbulky primary alkyl group or an aryl group, an intramolecular S_N2 reaction by C-alkylation occurred to give cyclopropane **2**. On the other hand, with a bulky secondary alkyl substituent at the R^2 position, *O*-alkylation occurs dominantly to give isoxazoline-*N*-oxide **3** or its hydrolyzed product **4**.

The differences between the *C*-alkylation and *O*-alkylation reactions from **E** were not clear; therefore, we performed calculations for compounds **2a**, **2c**, **3a**, and **3c**. Geometry optimization was performed using the MP2 method. Relative energies were estimated from an MP4(SDQ) calculation on the optimized structures. These calculations were performed with the Gaussian 03 program.[12] For C, N, and O atoms, the 6-311+G(2d) basis sets were employed in these calculations, whereas for H atoms, the 6-31G basis set was used. Figure 1

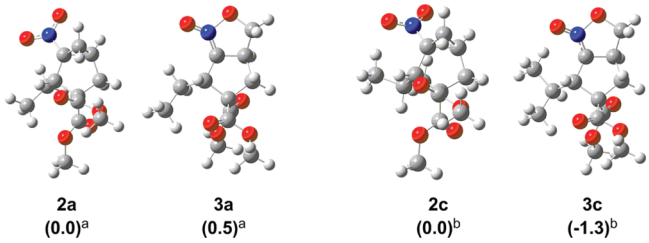


Figure 1. MP2 optimized structures of **2a**, **3a**, **2c**, and **3c**. The relative energies (kcal/mol) calculated with the MP4(SDQ) method are in parentheses. (a) Relative energy to **2a**. (b) Relative energy to **2c**.

shows the optimized structures and their relative energies. A comparison of the energies reveals that **2a** is more stable than **3a** by 0.5 kcal/mol, while **3c** is more stable than **2c** by 1.3 kcal/mol. Therefore, when a bulky secondary alkyl group was substituted at the R^2 position, the *O*-alkylated product was more thermodynamically stable than cyclopropane. On the contrary, the cyclopropane adduct is more favorable than isoxazoline-*N*-oxide when a nonbulky primary alkyl group occupies the R^2 position. This can be one of the reasons for the

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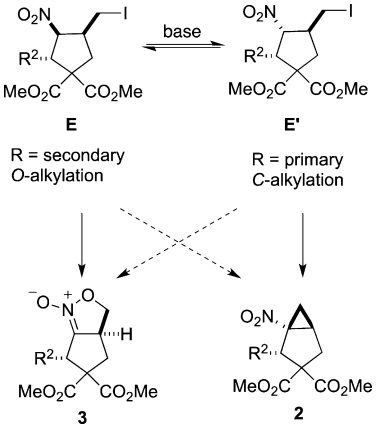
reaction undergoing *O*-alkylation or *C*-alkylation depending on the substituent pattern in the substrate.

Alternatively, the following reaction pathway may be possible (Scheme 7): intermediate **E** easily epimerizes under basic

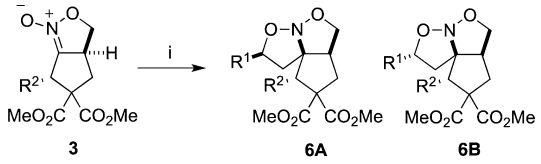
Scheme 7



conditions to give its epimer **E**′. The thermodynamic stability of the intermediates depends on the bulkiness of R^2. For example, a bulky substituent at the R^2 position causes steric repulsion of the nitro group and prefers intermediate **E** that has *trans* configuration between the nitro group and the R^2 group. As a result, the configuration between the nitro group and the iodomethyl group becomes *cis*, and *O*-alkylation should be preferred, giving isoxazoline-*N*-oxide **3**. On the other hand, intermediate **E**′ contains *trans* configuration between the nitro and the iodomethyl group, which enables the intramolecular S_N2 reaction by the C-nucleophile to give cyclopropane **2**. An investigation of the reason to explain the difference in selectivity between *C*-alkylation and *O*-alkylation is in progress in our laboratory.

Isoxazoline-*N*-oxides **3** are considered to be cyclic nitrones. These compounds serve as good dipoles for 1,3-dipolar cycloaddition,[10] which has been frequently used in organic synthesis.[13,14] To enhance the synthetic utility of the present methodology, we examined the 1,3-dipolar cycloaddition of **3** with various alkenes (Scheme 8).

Scheme 8[a]



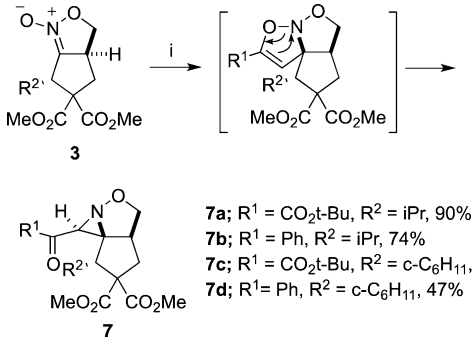
6a; R^2 = CO_2Me, R^2 = iPr, 98% (**A**:**B** = 67:33)
6b; R^1 = CO_2t-Bu, R^2 = iPr, 90% (**A**:**B** = 61:39)
6c; R^1 = CN, R^2 = iPr, 98% (**A**:**B** = 60:40)
6d; R^1 = CO_2Me, R^2 = c-C_6H_{11}, 85% (**A**:**B** = 62:38)
6e; R^1 = CO_2t-Bu, R^2 = c-C_6H_{11}, 89% (**A**:**B** = 57:43)
6f; R^1 = CN, R^2 = c-C_6H_{11}, 89% (**A**:**B** = 60:40)
6g; R^1 = CO_2Me, R^2 = Pr, 72% (**A**:**B** = 46:54)

[a]Reagents and conditions: (i) CH_2=CHR^1, toluene, 80 °C, 12 h.

Heating the mixture of **3c** and methyl acrylate at 80 °C afforded the corresponding tricyclic dipolar adduct **6a** in 98% yield. Compound **6a** contained two diastereomers **6aA** and **6aB**, which were readily separated by chromatographic treatment. The configurations of **6aA**, **6eA**, and **6eB** were determined by X-ray crystallographic analyses. The cycloaddition also occurred with acrylonitrile to give **6c** and **6f** in 98 and 89% yield, respectively. Although the stereoselectivity ratio of the reaction was approximately 6:4, the treatment provided an easy three-step preparation of multicyclic heterocyclic compounds **6** from nitro alkenes and active methylene compounds.

When alkynes were used as dipolarophiles, polycyclic aziridines **7** were prepared (Scheme 9). For instance, when

Scheme 9[a]



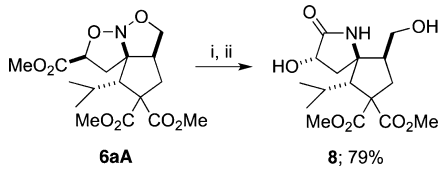
7a; R^1 = CO_2t-Bu, R^2 = iPr, 90%
7b; R^1 = Ph, R^2 = iPr, 74%
7c; R^1 = CO_2t-Bu, R^2 = c-C_6H_{11}, 76%
7d; R^1= Ph, R^2 = c-C_6H_{11}, 47%

[a]Reagents and conditions: (i) CH≡CR^1, toluene, 80 °C, 9 h.

3c was treated with *tert*-butyl acetylenecarboxylate, an azirinoisoxazole **7a** was obtained in 90% yield. Compound **7d** was formed as a single isomer, and its structure was confirmed by X-ray crystallographic analysis. The results clearly showed that good regio- and stereoselectivity were achieved during cycloaddition. This formation of aziridine can be due to the rearrangement of the cycloadduct intermediate, which was reported by Seebach.[15] Other alkynes also underwent the cycloaddition and rearrangement reaction to give aziridinoisoxazole **7** in good yield in a highly regio- and stereoselective manner.

The two isoxazolidine parts of compound **6** were reductively cleaved using Raney-Ni. Starting with **6aA**, the amino group formed through the reduction attacked the ester group to form spirolactam **8** in 79% yield in a single diastereomer (Scheme 10).

Scheme 10[a]



[a]Reagents and conditions: (i) Raney-Ni, H_2, MeOH, rt, 24 h; (ii) reflux, MeOH, 24 h.

In conclusion, treatment of nitro compounds with a combination use of base, Ag_2O, and iodine constitutes a new simple method for the transformation to give multicyclic compounds in a stereoselective manner. The present method employed a simple manipulation, and complicated heterocyclic units were readily prepared from nitro alkenes and active methylene compounds in three steps. Because cyclic adducts such as fused cyclopropane and isoxazoline-*N*-oxide prepared by this method are regarded as potentially useful for the

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synthesis of heterocyclic compounds, this method provides an effective method for the construction of multiheterocyclic compounds.

EXPERIMENTAL SECTION

Preparation of Dimethyl 2-Allyl-2-(1-nitrobutan-2-yl)-malonate (1a). General Procedure. Under nitrogen atmosphere, *t*-BuOK (476.2 mg, 4.24 mmol) was added to a solution of dimethyl 2-allylmalonate (884.5 mg, 5.14 mmol) in dry THF (35 mL) at room temperature. The reaction mixture was cooled to −35 °C, and a solution of (*E*)-1-nitrobut-1-ene (784.9 mg, 7.76 mmol) in dry THF (3 mL) was added to the solution. The reaction mixture was stirred for 1 h at −35 °C. Saturated aqueous NH_4Cl (50 mL) was added, and THF was removed under reduced pressure. The aqueous residue was extracted with EtOAc (60 mL × 3). The organic phase was dried over Na_2SO_4. After filtration and concentration, the crude product was purified by flash chromatography (silica gel/ethyl acetate−hexane 3:1) to give **1a** in 88% yield (1242.0 mg). Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (dddd, J = 18.8, 9.1, 6.6, 1.2 Hz, 1 H), 5.14 (d, J = 10.5 Hz, 1 H), 5.13 (d, J = 17.6 Hz, 1 H), 4.74 (ddd, J = 14.4, 3.2, 0.6 Hz, 1 H), 4.35 (ddd, J = 14.4, 7.0, 1.1 Hz, 1 H), 3.74 (s, 3 H), 3.71 (s, 3 H), 2.95 (dtd, J = 6.7, 3.2, 2.3 Hz, 1 H), 2.78 (ddd, J = 14.5, 6.6, 1.2 Hz, 1 H), 2.65 (ddd, J = 14.6, 8.1, 0.8 Hz, 1 H), 1.69−1.60 (m, 1 H), 1.33−1.22 (m, 1 H), 0.93 (td, J = 7.5, 1.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 170.1, 170.0, 169.9, 132.0, 119.3, 119.3, 77.3, 60.5, 52.4, 52.4, 52.4, 52.3, 41.0, 37.8, 37.8, 22.3, 22.3, 11.0, 11.0. Anal. Calcd. for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.54; H, 6.92; N, 5.23.

Dimethyl 2-Allyl-2-(1-nitropentan-2-yl)malonate (1b). Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80−5.70 (m, 1 H), 5.13 (d, J = 10.7 Hz, 2 H), 5.13 (d, J = 17.5 Hz, 2 H), 4.75 (dd, J = 14.5, 3.4 Hz, 1 H), 4.32 (dd, J = 14.4, 6.6 Hz, 1 H), 3.75 (s, 3 H), 3.71 (s, 3 H), 3.01 (dd, J = 9.3, 5.9 Hz, 1 H), 2.78 (dd, J = 14.5, 6.5 Hz, 1 H), 2.64 (dd, J = 14.5, 8.1 Hz, 1 H), 1.54−1.45 (m, 1 H), 1.40−1.17 (m, 3 H), 0.90 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 170.3, 132.2, 119.6, 78.1, 61.0, 52.7, 52.6, 39.8, 38.2, 32.1, 20.2, 14.1; HRMS (FAB M + H) m/z 288.1448. Calcd for $C_{13}H_{22}NO_6$ 288.1447.

Dimethyl 2-Allyl-2-(3-methyl-1-nitrobutan-2-yl)malonate (1c). Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (dddd, J = 16.6, 10.4, 8.5, 6.2 Hz, 1 H), 5.13 (d, J = 18.5 Hz, 1 H), 5.12 (d, J = 9.3 Hz, 1 H), 4.71 (dd, J = 14.9, 3.1 Hz, 1 H), 4.47 (dd, J = 14.9, 6.9 Hz, 1 H), 3.74 (s, 3 H), 3.70 (s, 3 H), 3.16 (dt, J = 6.7, 2.8 Hz, 1 H), 2.83 (dd, J = 14.5, 6.2 Hz, 1 H), 2.66 (dd, J = 14.5, 8.5 Hz, 1 H), 2.19−1.97 (m, 1 H), 0.95 (d, J = 7.1 Hz, 3 H), 0.75 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 170.7, 132.1, 119.8, 74.2, 60.6, 52.7, 52.7, 44.4, 38.4, 26.5, 22.7, 16.5. Anal. Calcd. for $C_{13}H_{21}NO_6$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.02; H, 7.15; N, 4.93.

Dimethyl 2-Allyl-2-(1-nitrohexan-2-yl)malonate (1d). Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (dddd, J = 11.0, 9.1, 8.2, 7.4 Hz, 1 H), 5.13 (d, J = 10.5 Hz, 1 H), 5.12 (d, J = 16.7 Hz, 1 H), 4.74 (dd, J = 14.4, 3.5 Hz, 1 H), 4.32 (dd, J = 14.4, 6.6 Hz, 1 H), 3.74 (s, 3 H), 3.71 (s, 3 H), 2.99 (ddt, J = 9.7, 6.6, 3.3 Hz, 1 H), 2.77 (dd, J = 14.5, 6.7 Hz, 1 H), 2.64 (dd, J = 14.5, 8.2 Hz, 1 H), 1.62−1.16 (m, 6 H), 0.86 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 170.3, 132.2, 119.7, 78.1, 61.1, 52.7, 52.6, 40.1, 38.3, 29.7, 29.2, 22.8, 13.9; HRMS (ESI M + H) m/z 302.1604. Calcd for $C_{14}H_{24}NO_6$ 302.1604.

Dimethyl 2-Allyl-2-(1-nitroheptan-2-yl)malonate (1e). Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (dddd, J = 17.0, 10.7, 8.1, 6.6 Hz, 1 H), 5.13 (d, J = 10.3 Hz, 1 H), 5.13 (d, J = 17.0 Hz, 1 H), 4.75 (dd, J = 14.4, 3.5 Hz, 1 H), 4.33 (dd, J = 14.4, 6.6 Hz, 1 H), 3.74 (s, 3 H), 3.71 (s, 3 H), 3.00 (ddd, J = 9.7, 6.6, 3.4 Hz, 1 H), 2.77 (dd, J = 14.5, 6.5 Hz, 1 H), 2.64 (dd, J = 14.5, 8.1 Hz, 1 H), 1.61−1.13 (m, 8 H), 0.86 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 170.4, 132.2, 119.7, 78.1, 61.0, 52.6, 52.6, 40.1, 38.2, 31.8, 29.8, 26.6, 22.3, 13.9; HRMS (FAB M + H) m/z 316.1755. Calcd for $C_{15}H_{26}NO_6$ 316.1760.

Dimethyl 2-Allyl-2-(1-nitrooctan-2-yl)malonate (1f). Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (dddd, J = 12.7, 8.4, 7.4, 1.6 Hz, 1 H), 5.13 (d, J = 10.0 Hz, 1 H), 5.12 (d, J = 17.5 Hz, 1 H), 4.74 (ddd, J = 14.4, 3.4, 1.3 Hz, 1 H), 4.32 (ddd, J = 14.4, 6.6, 1.6 Hz, 1 H), 3.74 (s, 3 H), 3.70 (s, 3 H), 3.02−2.95 (m, 1 H), 2.77 (ddd, J = 14.4, 6.5, 1.0 Hz, 1 H), 2.64 (dd, J = 14.5, 8.1 Hz, 1 H), 1.68−1.15 (m, 10 H), 0.86 (t, J = 6.3 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 170.3, 132.2, 119.7, 78.1, 61.1, 52.7, 52.6, 40.2, 38.3, 31.6, 30.0, 29.4, 27.0, 22.6, 14.1; HRMS (ESI M + H) m/z 330.1904. Calcd for $C_{16}H_{28}NO_6$ 330.1917.

Dimethyl 2-Allyl-2-(1-cyclohexyl-2-nitroethyl)malonate (1g). Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (dddd, J = 12.2, 9.8, 7.2, 1.3 Hz, 1 H), 5.14 (d, J = 9.9 Hz, 1H), 5.13 (d, J = 17.8 Hz, 1 H), 4.65 (dd, J = 14.8, 2.7 Hz, 1 H), 4.55 (ddd, J = 14.9, 7.5, 1.3 Hz, 1 H), 3.74 (s, 3 H), 3.70 (s, 3 H), 3.10 (d, J = 7.4 Hz, 1 H), 2.83 (ddd, J = 14.4, 6.3, 1.2 Hz, 1 H), 2.66 (dd, J = 14.5, 8.5 Hz, 1 H), 1.80−1.51 (m, 5 H), 1.34−0.92 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 170.7, 132.2, 119.7, 75.0, 60.1, 52.7, 52.7, 44.8, 38.6, 37.4, 33.0, 27.4, 27.1, 26.6, 26.0. Anal. Calcd. for $C_{16}H_{25}NO_6$: C, 58.70; H, 7.70; N, 4.28. Found: C, 58.71; H, 7.55; N, 4.33.

Dimethyl 2-Allyl-2-(2-nitro-1-phenylethyl)malonate (1h). Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.27 (m, 3 H), 7.14−7.07 (m, 2 H), 5.72 (dddd, J = 16.8, 10.2, 8.0, 6.6 Hz, 1 H), 5.14 (dd, J = 10.0, 0.7 Hz, 1 H), 5.05 (ddd, J = 8.0, 3.1, 1.5 Hz, 1 H), 4.98 (dd, J = 13.5, 10.9 Hz, 1 H), 4.19 (dd, J = 10.9, 3.3 Hz, 1 H), 3.81 (d, J = 2.0 Hz, 3 H), 3.75 (s, 3 H), 2.56 (ddt, J = 14.5, 6.5, 1.4 Hz, 1 H), 2.28 (dd, J = 14.5, 8.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 170.1, 134.8, 131.9, 129.0, 128.9, 128.7, 120.1, 78.4, 60.9, 53.0, 52.9, 46.8, 38.6; HRMS (ESI M + H) m/z 322.1292. Calcd for $C_{16}H_{20}NO_6$ 322.1291.

Diethyl 2-Allyl-2-(1-nitrobutan-2-yl)malonate (1i). Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85−5.68 (m, 1 H), 5.20−5.07 (m, 2 H), 4.77 (dd, J = 14.5, 3.1 Hz, 1 H), 4.35 (dd, J = 14.4, 7.1 Hz, 1 H), 4.25−4.14 (m, 4 H), 2.95 (ddd, J = 12.9, 6.8, 3.2 Hz, 1 H), 2.77 (ddt, J = 14.6, 6.6, 1.3 Hz, 1 H), 2.65 (dd, J = 14.6, 8.1 Hz, 1 H), 1.66 (dqd, J = 15.2, 7.6, 3.2 Hz, 1 H), 1.32−1.25 (m, 1 H), 1.28 (t, J = 7.1 Hz, 3 H), 1.24 (t, J = 7.1 Hz, 3 H), 0.93 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 169.9, 132.3, 119.6, 77.9, 61.9, 61.8, 60.7, 41.2, 38.1, 22.8, 14.1, 14.0, 11.5; HRMS (FAB M + H) m/z 302.1603. Calcd for $C_{14}H_{24}NO_6$ 302.1604.

Diethyl 2-Allyl-2-(3-methyl-1-nitrobutan-2-yl)malonate (1j). Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (tdd, J = 14.9, 8.6, 6.2 Hz, 1 H), 5.19−5.08 (m, 2 H), 4.73 (dd, J = 15.0, 2.8 Hz, 1 H), 4.48 (dd, J = 15.0, 7.1 Hz, 1 H), 4.27−4.11 (m, 4 H), 3.16 (dt, J = 7.0, 2.7 Hz, 1 H), 2.82 (dd, J = 14.6, 6.3 Hz, 1 H), 2.67 (dd, J = 14.6, 8.5 Hz, 1 H), 2.11 (dtd, J = 14.0, 6.9, 2.4 Hz, 1 H), 1.29 (t, J = 7.2 Hz, 3 H), 1.23 (t, J = 7.1 Hz, 3 H), 0.94 (d, J = 7.1 Hz, 3H), 0.77 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 170.3, 132.1, 119.7, 74.3, 62.0, 61.8, 60.4, 44.1, 38.3, 26.5, 22.7, 16.6, 14.1, 14; HRMS (ESI M + H) m/z 316.1762. Calcd for $C_{15}H_{26}NO_6$ 316.1760.

Diethyl 2-Allyl-2-(1-nitroheptan-2-yl)malonate (1k). Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83−5.70 (m, 1 H), 5.19−5.06 (m, 2 H), 4.77 (dd, J = 14.4, 3.3 Hz, 1 H), 4.32 (dd, J = 14.4, 6.8 Hz, 1 H), 4.26−4.14 (m, 4 H), 3.04−2.95 (m, 1 H), 2.77 (dd, J = 14.6, 6.6 Hz, 1 H), 2.64 (dd, J = 14.6, 8.1 Hz, 1 H), 1.55−1.50 (m, 1 H), 1.29−1.20 (m, 7 H), 1.28 (t, J = 7.1 Hz, 3 H), 1.24 (t, J = 7.1 Hz, 3 H), 0.86 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 169.9, 132.3, 119.6, 78.4, 61.9, 61.8, 60.8, 39.9, 38.2, 31.9, 30.0, 26.7, 22.5, 14.2, 14.1, 14.0; HRMS (ESI M + H) m/z 344.2062. Calcd for $C_{17}H_{30}NO_6$ 344.2073.

2-Allyl-2-(1-nitroheptan-2-yl)malononitrile (1l). Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (dddd, J = 10.1, 9.7, 7.4, 6.9 Hz, 1 H), 5.49 (d, J = 10.1 Hz, 1 H), 5.45 (d, J = 16.9 Hz, 1 H), 4.65 (dd, J = 14.3, 5.3 Hz, 1 H), 4.53 (dd, J = 14.3, 5.5 Hz, 1 H), 2.87 (td, J = 9.1, 5.3 Hz, 1 H), 2.76−2.67 (m, 1 H), 1.90−1.82 (m, 1 H), 1.68−1.60 (m, 1 H), 1.56−1.21 (m, 9 H), 0.89 (t, J = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 127.8, 124.28, 113.7, 113.6, 75.3, 42.3, 41.7, 39.6, 31.4, 30.1, 29.0, 26.5, 22.5, 14.0; HRMS (ESI M + H) m/z 250.1558. Calcd for $C_{13}H_{20}N_3O_2$ 250.1556.

Preparation of (1*R,2*S**,5*R**)-Dimethyl 2-Ethyl-1-nitrobicyclo[3.1.0]hexane-3,3- dicarboxylate (2a). General Procedure.** Under a nitrogen atmosphere, DBU (0.16 mL, 1.1 mmol)

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was added to a solution of **1a** (234.6 mg, 0.86 mmol) in dry THF (10 mL) at room temperature. Then, Ag_2O (419.4 mg, 1.81 mmol) and iodine (319.5 mg, 1.26 mmol) were added to the solution, and the resulting mixture was stirred for 5 h at room temperature. Solid residue was removed by filtration, and the filtrate was concentrated. The obtained crude product was purified by flash chromatography (silica gel/ethyl acetate−hexane 3:1) to give **2a** in 72% yield (167.1 mg) along with **3a** in 23% (54.0 mg). Colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (s, 3 H), 3.73 (s, 3 H), 3.58 (dd, J = 5.6, 3.4 Hz, 1 H), 2.93 (ddd, J = 14.1, 5.3, 0.9 Hz, 1 H), 2.64 (ddd, J = 10.1, 5.4, 5.0 Hz, 1 H), 2.23 (d, J = 14.2 Hz, 1 H), 1.95 (dqd, J = 15.2, 7.6, 5.7 Hz, 1 H), 1.67 (ddd, J = 9.8, 6.7, 1.1 Hz, 1 H), 1.48 (dqd, J = 15.1, 7.5, 3.4 Hz, 1 H), 1.13 (dd, J = 6.6, 5.7 Hz, 1 H), 0.86 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 168.8, 71.9, 63.6, 53.4, 53.1, 45.3, 33.5, 27.5, 24.6, 21.1, 10.7; IR (neat) ν 1732, 1527, 1244 cm^{-1}; HRMS (ESI M + H) m/z 272.1135. Calcd for $C_{12}H_{18}NO_6$ 272.1134.

Dimethyl 6-Ethyl-3a,4-dihydro-3*H*-cyclopenta[c]isoxazole-5,5(6*H*)-dicarboxylate-*N*-oxide (3a). Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 (dd, J = 9.2, 7.6 Hz, 1 H), 4.37−4.28 (m, 1 H), 4.10 (dd, J = 9.9, 7.6 Hz, 1 H), 3.74 (s, 3 H), 3.71 (s, 3 H), 3.53 (ddd, J = 10.5, 5.1, 2.2 Hz, 1 H), 2.67 (dd, J = 13.4, 7.9 Hz, 1 H), 1.86 (dd, J = 13.5, 8.8 Hz, 1 H), 1.62 (dqd, J = 14.9, 7.5, 5.2 Hz, 1 H), 1.39 (ddq, J = 14.5, 10.5, 7.3 Hz, 1 H), 1.03 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 170.1, 122.0, 72.4, 67.3, 53.2, 52.8, 47.6, 44.1, 37.0, 23.0, 12.8; IR (neat) ν 1732, 1712, 1664 cm^{-1}; HRMS (ESI M − H) m/z 270.0977. Calcd for $C_{12}H_{16}NO_6$ 270.0978.

(1*R,2*S**,5*R**)-Dimethyl 2-Propyl-1-nitrobicyclo[3.1.0]-hexane-3,3-dicarboxylate (2b).** Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (s, 3 H), 3.73 (s, 3 H), 3.54 (dd, J = 5.8, 3.6 Hz, 1 H), 2.90 (ddd, J = 14.1, 5.3, 0.7 Hz, 1 H), 2.60 (dt, J = 10.1, 5.2 Hz, 1 H), 2.20 (d, J = 14.1 Hz, 1 H), 1.81−1.72 (m, 1 H), 1.70 (ddd, J = 9.8, 6.7, 1.0 Hz, 1 H), 1.46−1.22 (m, 2 H), 1.18 (dd, J = 13.6, 6.6 Hz, 1 H), 1.13 (dd, J = 6.6, 5.7 Hz, 1 H), 0.84 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 169.0, 72.3, 63.9, 53.3, 53.0, 44.9, 33.5, 30.3, 27.7, 25.0, 20.0, 14.5; IR (neat) ν 1732, 1529, 1260, 1240 cm^{-1}; HRMS (ESI M + H) m/z 286.1315. Calcd for $C_{13}H_{20}NO_6$ 286.1291.

Dimethyl 6-Propyl-3a,4-dihydro-3*H*-cyclopenta[c]isoxazole-5,5(6*H*)-dicarboxylate-*N*-oxide (3b). Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.66 (dd, J = 9.1, 7.7 Hz, 1 H), 4.44−4.26 (m, 1 H), 4.12 (dd, J = 9.8, 7.5 Hz, 1 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.64 (d, J = 10.7 Hz, 1 H), 2.70 (dd, J = 13.2, 7.8 Hz, 1 H), 1.89 (dd, J = 13.5, 8.7 Hz, 1 H), 1.56−1.43 (m, 2 H), 1.31−1.20 (m, 2 H), 0.93 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 170.1, 122.1, 72.3, 67.3, 53.3, 52.8, 47.6, 42.3, 37.0, 31.8, 21.4, 14.0; IR (neat) ν 2958, 1730, 1712, 1663 cm^{-1}; HRMS (ESI M − H) m/z 284.1154. Calcd for $C_{13}H_{18}NO_6$ 284.1134.

(1*R,2*S**,5*R**)-Dimethyl 2-Isopropyl-1-nitrobicyclo[3.1.0]-hexane-3,3-dicarboxylate (2c).** Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78 (s, 3 H), 3.70 (s, 3 H), 2.97 (ddd, J = 13.5, 6.6, 1.5 Hz, 1 H), 2.85 (d, J = 8.3 Hz, 1 H), 2.49−2.36 (m, 2 H), 2.22 (dd, J = 8.1, 7.3 Hz, 1 H), 1.77 (ddd, J = 13.6, 2.7, 2.0 Hz, 1 H), 1.29 (td, J = 6.3, 1.6 Hz, 1 H), 0.98 (dd, J = 6.8, 2.0 Hz, 3 H), 0.89 (dd, J = 6.7, 2.2 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 169.4, 73.3, 68.3, 58.6, 53.0, 52.9, 37.9, 31.5, 30.8, 27.9, 21.4, 21.2; IR (neat) ν 1730, 1527, 1250 cm^{-1}; HRMS (ESI M + H) m/z 286.1315. Calcd for $C_{13}H_{20}NO_6$ 286.1291.

Dimethyl 6-Isopropyl-3a,4-dihydro-3*H*-cyclopenta[c]-isoxazole-5,5(6*H*)-dicarboxylate-*N*-oxide (3c). Pale yellow solid: mp 103.9−105.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.65 (dd, J = 9.2, 7.6 Hz, 1 H), 4.29 (dtd, J = 17.3, 8.2, 2.2 Hz, 1 H), 4.09 (dd, J = 9.9, 7.6 Hz, 1 H), 3.74 (s, 6 H), 3.52 (dd, J = 5.3, 2.2 Hz, 1 H), 2.72 (dd, J = 13.5, 8.2 Hz, 1 H), 1.94 (tt, J = 13.4, 6.7 Hz, 1 H), 1.86 (dd, J = 13.5, 8.4 Hz, 1 H), 1.08 (d, J = 6.7 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 170.1, 121.4, 72.3, 67.0, 53.3, 53.0, 49.6, 48.5, 37.5, 29.7, 23.1, 20.1; IR (CH_2Cl_2) ν 2953, 1726, 1654 cm^{-1}; HRMS (ESI M − H) m/z 284.1136. Calcd for $C_{13}H_{18}NO_6$ 284.1134.

(1*R,2*S**,5*R**)-Dimethyl 2-Butyl-1-nitrobicyclo[3.1.0]hexane-3,3-dicarboxylate (2d).** White solid: mp 64.9−66.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (s, 3 H), 3.73 (s, 3 H), 3.58−3.54 (m, 1 H), 2.92 (dd, J = 14.1, 5.4 Hz, 1 H), 2.62 (dt, J = 10.8, 5.5 Hz, 1 H), 2.21 (d, J = 14.2 Hz, 1 H), 1.80 (dtd, J = 16.4, 10.4, 4.5 Hz, 1 H), 1.69 (dd, J = 9.7, 6.8 Hz, 1 H), 1.42 (dddd, J = 9.9, 8.4, 4.5, 1.0 Hz, 1 H), 1.32 (qd, J = 12.4, 5.8 Hz, 1 H), 1.22 (dq, J = 14.9, 7.3 Hz, 2 H), 1.12 (t, J = 5.5 Hz, 1 H), 1.16−1.04 (m, 1 H), 0.83 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 168.7, 72.1, 63.6, 53.2, 52.9, 44.5, 33.2, 28.4, 27.6, 27.5, 24.7, 22.9, 13.6; IR (neat) ν 1735, 1529, 1363 cm^{-1}; HRMS (ESI M + H) m/z 300.1454. Calcd for $C_{14}H_{22}NO_6$ 300.1447.

Dimethyl 6-Butyl-3a,4-dihydro-3*H*-cyclopenta[c]isoxazole-5,5(6*H*)-dicarboxylate-*N*-oxide (3d). Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.66 (dd, J = 9.2, 7.6 Hz, 1 H), 4.34 (tdd, J = 10.2, 8.9, 2.2 Hz, 1 H), 4.18−4.06 (m, 1 H), 3.77 (s, 3 H), 3.74 (s, 3 H), 3.63 (ddd, J = 10.2, 4.9, 2.0 Hz, 1 H), 2.70 (dd, J = 13.5, 8.0 Hz, 1 H), 1.89 (dd, J = 13.5, 8.6 Hz, 1 H), 1.69−1.20 (m, 6 H), 0.88 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 170.0, 122.1, 72.3, 67.3, 53.3, 52.8, 47.5, 42.5, 36.9, 30.1, 29.3 22.6, 13.9; IR (neat) ν 1732, 1710, 1667 cm^{-1}; HRMS (ESI M + H) m/z 300.1449. Calcd for $C_{14}H_{22}NO_6$ 300.1447.

(1*R,2*S**,5*R**)-Dimethyl 2-Pentyl-1-nitrobicyclo[3.1.0]-hexane-3,3-dicarboxylate (2e).** Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (s, 3 H), 3.72 (s, 3 H), 3.54 (dd, J = 5.8, 3.7 Hz, 1 H), 2.95−2.87 (m, 1 H), 2.61 (dt, J = 6.2, 5.5 Hz, 1 H), 2.20 (d, J = 14.1 Hz, 1 H), 1.77 (dddd, J = 14.7, 11.6, 5.8, 4.4 Hz, 1 H), 1.69 (ddd, J = 9.8, 6.7, 1.0 Hz, 1 H), 1.43 (dddd, J = 14.9, 11.3, 5.1, 3.8 Hz, 1 H), 1.39−1.30 (m, 1 H), 1.28−1.09 (m, 5 H), 1.12 (dd, J = 6.7, 5.6 Hz, 1 H), 0.84 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 168.9, 72.2, 63.7, 53.4, 53.0, 44.7, 33.4, 32.1, 28.0, 27.6, 26.1, 24.9, 22.3, 14.0; IR (neat) ν 1732, 1529, 1248 cm^{-1}; HRMS (ESI M + H) m/z 314.1588. Calcd for $C_{15}H_{24}NO_6$ 314.1604.

Dimethyl 6-Pentyl-3a,4-dihydro-3*H*-cyclopenta[c]isoxazole-5,5(6*H*)-dicarboxylate-*N*-oxide (3e). Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.66 (dd, J = 9.2, 7.6 Hz, 1 H), 4.34 (tdd, J = 10.2, 8.9, 2.2 Hz, 1 H), 4.12 (dd, J = 9.9, 7.7 Hz, 1 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.63 (ddd, J = 10.4, 5.0, 2.0 Hz, 1 H), 2.71 (ddd, J = 13.4, 8.0, 0.4 Hz, 1 H), 1.89 (dd, J = 13.5, 8.6 Hz, 1 H), 1.59−1.22 (m, 8H), 0.87 (t, J = 6.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 170.0, 122.0, 72.3, 67.3, 53.3, 52.8, 47.5, 42.5, 36.9, 31.7, 29.6, 27.7, 22.5, 14.1; IR (neat) ν 2950, 1732, 1710, 1667 cm^{-1}; HRMS (ESI M − H) m/z 312.1454. Calcd for $C_{15}H_{22}NO_6$ 312.1447.

(1*R,2*S**,5*R**)-Dimethyl 2-Hexyl-1-nitrobicyclo[3.1.0]-hexane-3,3-dicarboxylate (2f).** Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (s, 3 H), 3.73 (s, 3 H), 3.55 (dd, J = 5.8, 3.6 Hz, 1 H), 2.91 (ddd, J = 14.1, 5.3, 0.8 Hz, 1 H), 2.61 (ddd, J = 6.1, 5.4, 2.7 Hz, 1 H), 2.21 (d, J = 14.2, 1 H), 1.78 (dddd, J = 14.7, 11.8, 5.8, 4.4 Hz, 1 H), 1.69 (dd, J = 9.8, 6.7 Hz, 1 H), 1.42 (dddd, J = 14.8, 11.4, 4.9, 3.7 Hz, 1 H), 1.37−1.16 (m, 8 H), 1.12 (dd, J = 6.7, 5.6 Hz, 1 H), 0.85 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 168.9, 72.3, 63.9, 53.3, 53.0, 45.0, 33.5, 31.5, 29.7, 28.1, 27.6, 26.6, 25.0, 22.6, 14.1; IR (neat) ν 1732, 1529, 1246 cm^{-1}; HRMS (ESI M + H) m/z 328.1758. Calcd for $C_{16}H_{26}NO_6$ 328.1760.

Dimethyl 6-Hexyl-3a,4-dihydro-3*H*-cyclopenta[c]isoxazole-5,5(6*H*)-dicarboxylate-*N*-oxide (3f). Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.66 (dd, J = 9.2, 7.6 Hz, 1 H), 4.39−4.29 (m, 1 H), 4.11 (dd, J = 10.0, 7.6 Hz, 1 H), 3.77 (s, 3 H), 3.74 (s, 3 H), 3.63 (ddd, J = 10.2, 4.9, 2.2 Hz, 1 H), 2.70 (dd, J = 13.4, 8.0 Hz, 1 H), 1.88 (dd, J = 13.5, 8.6 Hz, 1 H), 1.59−1.11 (m, 10 H), 0.86 (dd, J = 9.9, 4.0 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 170.0, 122.0, 72.3, 67.3, 53.3, 52.8, 47.5, 42.5, 36.9, 31.7, 29.6, 29.2, 28.0, 22.6, 14.1; IR (neat) ν 2955, 1732, 1670 cm^{-1}; HRMS (ESI M − H) m/z 326.1599. Calcd for $C_{16}H_{24}NO_6$ 326.1604.

(1*R,2*S**,5*R**)-Dimethyl 2-Cyclohexyl-1-nitrobicyclo[3.1.0]-hexane-3,3-dicarboxylate (2g).** White solid: mp 107.4−108.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (s, 3 H), 3.70 (s, 3 H), 2.98 (dd, J = 13.3, 7.5 Hz, 1 H), 2.74 (d, J = 9.2 Hz, 1 H), 2.41−2.32 (m, 2 H), 2.14 (qt, J = 11.9, 3.0 Hz, 1 H), 1.78 (d, J = 12.5 Hz, 1 H), 1.74−1.60 (m, 4 H), 1.51 (d, J = 12.6 Hz, 1 H), 1.34 (t, J = 4.9 Hz, 1 H), 1.27−0.93 (m, 5 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 169.6, 73.2,

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69.2, 59.2, 53.0, 52.9, 38.6, 37.9, 32.5, 32.3, 32.3, 31.9, 26.7, 26.4, 26.2; IR ($CHCl_3$) ν 1732, 1527 cm^{-1}. Anal. Calcd. for $C_{16}H_{23}NO_6$: C, 59.06; H, 7.13; N, 4.31. Found: C, 59.17; H, 7.21; N, 4.31.

Dimethyl 6-Cyclohexyl-3a,4-dihydro-3*H*-cyclopenta[c]-isoxazole-5,5(6*H*)-dicarboxylate-*N*-oxide (3g). Pale yellow solid: mp 115.0−116.0 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 4.64 (ddd, J = 7.9, 7.0, 1.8 Hz, 1 H), 4.29 (p, J = 8.5 Hz, 1 H), 4.14−4.04 (m, 1 H), 3.78 (s, 6 H), 3.55−3.45 (m, 1 H), 2.70 (ddd, J = 13.4, 8.1, 1.7 Hz, 1 H), 1.84 (ddd, J = 13.4, 8.6, 1.1 Hz, 1 H), 1.78 (d, J = 13.4 Hz, 1 H), 1.71 (d, J = 10.4 Hz, 2 H), 1.62−1.49 (m, 3 H), 1.38−1.00 (m, 5 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 170.3, 121.6, 72.2, 67.0, 53.3, 52.9, 48.9, 48.7, 39.6, 37.7, 33.5, 30.7, 26.6, 26.4, 25.9; IR (CH_2Cl_2) ν 2928, 1732, 1661 cm^{-1}; HRMS (ESI M − H) m/z 324.1429. Calcd for $C_{16}H_{22}NO_6$ 324.1447.

(1*R,2*S**,5*R**)-Dimethyl 2-Phenyl-1-nitrobicyclo[3.1.0]-hexane-3,3-dicarboxylate (2h).** White solid: mp 162.2−163.0 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31−7.14 (m, 5 H), 4.83 (s, 1 H), 3.78 (s, 3 H), 3.25 (ddd, J = 14.5, 5.1, 1.1 Hz, 1 H), 3.18 (s, 3 H), 2.95 (dt, J = 9.8, 5.3 Hz, 1 H), 2.39 (d, J = 14.6 Hz, 1 H), 1.76 (ddd, J = 9.8, 6.8, 1.3 Hz, 1 H), 1.35 (dd, J = 6.6, 5.7 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 167.4, 136.4, 128.6, 128.1, 73.0, 64.4, 53.6, 52.7, 50.6, 32.0, 27.7, 22.8; IR ($CHCl_3$) ν 1732, 1701, 1532, 1248 cm^{-1}. Anal. Calcd. for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39. Found: C, 59.96; H, 5.32; N, 4.29.

(1*R,2*S**,5*R**)-Diethyl 2-Ethyl-1-nitrobicyclo[3.1.0]hexane-3,3-dicarboxylate (2i).** Pale yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 4.33−4.09 (m, 4 H), 3.58 (dd, J = 5.5, 3.4 Hz, 1 H), 2.91 (ddd, J = 14.1, 5.3, 1.0 Hz, 1 H), 2.63 (dt, J = 10.1, 5.2 Hz, 1 H), 2.21 (d, J = 14.2 Hz, 1 H), 1.97 (dqd, J = 15.2, 7.6, 5.5 Hz, 1 H), 1.64 (ddd, J = 9.8, 6.6, 1.1 Hz, 1 H), 1.51 (dqd, J = 15.1, 7.6, 3.4 Hz, 1 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.24 (t, J = 7.1 Hz, 3 H), 1.17 (dd, J = 6.6, 5.6 Hz, 1 H), 0.86 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 168.4, 72.0, 63.7, 62.3, 62.2, 44.9, 33.4, 27.5, 24.5, 21.0, 14.1, 14.0, 10.7; IR (neat) ν 1730, 1529, 1363 cm^{-1}; HRMS (FAB M + H) m/z 300.1450. Calcd for $C_{14}H_{22}NO_6$ 300.1447.

Diethyl 6-Ethyl-3a,4-dihydro-3*H*-cyclopenta[c]isoxazole-5,5(6*H*)-dicarboxylate-*N*-oxide (3i). Pale yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 4.66 (dd, J = 9.2, 7.6 Hz, 1 H), 4.38−4.29 (m, 1 H), 4.29−4.14 (m, 4 H), 4.12 (dd, J = 10.1, 7.6 Hz, 1 H), 3.56 (ddd, J = 10.4, 5.2, 2.2 Hz, 1 H), 2.69 (dd, J = 13.4, 8.0 Hz, 1 H), 1.86 (dd, J = 13.5, 8.6 Hz, 1 H), 1.73−1.61 (m, 1 H), 1.50−1.36 (m, 1 H), 1.26 (t, J = 7.2 Hz, 6 H), 1.06 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 169.6, 122.2, 72.4, 67.4, 62.2, 62.0, 47.6, 44.0, 36.9, 22.9, 14.1, 14.0, 12.8; IR (neat) ν 2980, 1726, 1713, 1667 cm^{-1}; HRMS (ESI M − H) m/z 298.1284. Calcd for $C_{14}H_{20}NO_6$ 298.1291.

(1*R,2*S**,5*R**)-Diethyl 2-Isopropyl-1-nitrobicyclo[3.1.0]-hexane-3,3-dicarboxylate (2j).** Pale yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 4.35−4.07 (m, 4 H), 2.99 (dd, J = 13.5, 6.6 Hz, 1H), 2.90 (d, J = 8.0 Hz, 1H), 2.48 (td, J = 13.7, 6.8 Hz, 1 H), 2.45−2.37 (m, 1 H), 2.20 (dd, J = 9.9, 6.4 Hz, 1 H), 1.78 (dd, J = 13.5, 1.9 Hz, 1 H), 1.31−1.28 (m, 1 H), 1.29 (t, J = 7.1 Hz, 3 H), 1.24 (t, J = 7.1 Hz, 3 H), 1.02 (d, J = 6.8 Hz, 3 H), 0.92 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 169.1, 73.3, 68.3, 62.0, 61.9, 58.0, 37.7, 31.3, 30.5, 28.0, 21.4, 21.3, 14.0; IR ($CHCl_3$) ν 1728, 1529, 1361, 1246 cm^{-1}; HRMS (ESI M − H) m/z 312.1457. Calcd for $C_{15}H_{22}NO_6$ 312.1447.

Diethyl 6-Isopropyl-3a,4-dihydro-3*H*-cyclopenta[c]-isoxazole-5,5(6*H*)-dicarboxylate-*N*-oxide (3j). White solid: mp 53.3−54.2 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 4.66 (dd, J = 9.1, 7.6 Hz, 1 H), 4.33−4.25 (m, 1 H), 4.23 (q, J = 7.1 Hz, 2 H), 4.19 (q, J = 7.1 Hz, 2 H), 4.10 (dd, J = 10.0, 7.6 Hz, 1 H), 3.53 (dd, J = 5.2, 2.0 Hz, 1 H), 2.73 (dd, J = 13.5, 8.2 Hz, 1 H), 2.00 (dqd, J = 13.3, 6.7, 1.2 Hz, 1 H), 1.86 (dd, J = 13.6, 8.2 Hz, 1 H), 1.27 (t, J = 7.1 Hz, 3 H), 1.26 (t, J = 7.1 Hz, 3 H), 1.11 (d, J = 6.7 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 169.8, 121.5, 72.4, 67.1, 62.2, 62.1, 49.5, 48.5, 37.4, 29.6, 23.2, 20.2, 14.1, 14.0; IR (CH_2Cl_2) ν 2980, 1726, 1712, 1658 cm^{-1}; HRMS (ESI M − H) m/z 312.1444. Calcd for $C_{15}H_{22}NO_6$ 312.1447.

(1*R,2*S**,5*R**)-Diethyl 2-Pentyl-1-nitrobicyclo[3.1.0]hexane-3,3-dicarboxylate (2k).** Colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 4.27−4.10 (m, 4 H), 3.55 (dd, J = 5.5, 3.7 Hz, 1 H), 2.90 (dd, J = 14.1, 5.3 Hz, 1 H), 2.61 (dd, J = 10.0, 5.3 Hz, 1 H), 2.19 (d, J = 14.0 Hz, 1 H), 1.87−1.71 (m, 1 H), 1.66 (dd, J = 9.7, 6.8 Hz, 1 H), 1.51−1.30 (m, 2 H), 1.28−1.10 (m, 6 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.24 (t, J = 7.0 Hz, 3 H), 1.16 (t, J = 6.3 Hz, 1 H), 0.84 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 168.5, 72.4, 63.9, 62.2, 62.1, 44.5, 33.4, 32.2, 28.1, 27.6, 26.2, 24.9, 22.4, 14.1, 14.0, 13.9; IR (neat) ν 1730, 1531, 1244 cm^{-1}; HRMS (ESI M − H) m/z 340.1768. Calcd for $C_{17}H_{26}NO_6$ 340.1760.

Diethyl 6-Pentyl-3a,4-dihydro-3*H*-cyclopenta[c]isoxazole-5,5(6*H*)-dicarboxylate-*N*-oxide (3k). Pale yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 4.65 (dd, J = 9.2, 7.6 Hz, 1 H), 4.31 (tdd, J = 10.1, 8.2, 2.0 Hz, 1 H), 4.26−4.14 (m, 4 H), 4.09 (dd, J = 10.1, 7.6 Hz, 1 H), 3.60 (ddd, J = 10.1, 4.9, 2.1 Hz, 1 H), 2.69 (dd, J = 13.5, 8.1 Hz, 1 H), 1.86 (dd, J = 13.6, 8.4 Hz, 1 H), 1.64−1.17 (m, 10 H), 1.25 (t, J = 7.1 Hz, 6 H), 0.85 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 169.5, 122.3, 72.4, 67.3, 62.2, 62.0, 47.4, 42.4, 36.7, 31.7, 29.5, 27.7, 22.5, 14.1, 14.0; IR (neat) ν 1931, 1726, 1667 cm^{-1}; HRMS (ESI M − H) m/z 340.1765. Calcd for $C_{17}H_{26}NO_6$ 340.1760.

(1*R,2*S**,5*R**)-1-Nitro-2-pentylbicyclo[3.1.0]hexane-3,3-dicarbonitrile (2l).** Pale yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 3.22 (dd, J = 5.8, 3.7 Hz, 1 H), 2.88−2.82 (m, 1 H), 2.82 (dd, J = 16.7, 4.9 Hz, 1 H), 2.53 (d, J = 13.1 Hz, 1 H), 2.13−1.95 (m, 2 H), 1.92 (dd, J = 7.3, 5.5 Hz, 1 H), 1.48−1.19 (m, 7 H), 0.87 (dd, J = 9.8, 4.2 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 116.6, 113.2, 71.6, 49.5, 49.5, 38.2, 31.6, 29.2, 27.7, 25.8, 24.9, 22.2, 14.0; IR ($CHCl_3$) ν 2251, 1533, 1359 cm^{-1}; HRMS (FAB M + H) m/z 248.1400. Calcd for $C_{13}H_{18}N_3O_2$ 248.1399.

(3a*S,6*S**)-6-Pentyl-3a,4-dihydro-3*H*-cyclopenta[c]-isoxazole-5,5(6*H*)-dicarbonitril-*N*-oxide (3l).** White solid: mp 98.4−99.7 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 4.78 (dd, J = 8.9, 8.0 Hz, 1 H), 4.36 (dd, J = 9.5, 7.9 Hz, 1 H), 4.33−4.20 (m, 1 H), 3.43 (td, J = 7.8, 2.8 Hz, 1 H), 2.85 (dd, J = 12.7, 6.5 Hz, 1 H), 2.36 (ddd, J = 12.4, 10.5, 1.8 Hz, 1 H), 2.06−1.93 (m, 1H), 1.87 (dddd, J = 13.9, 10.1, 8.4, 5.7 Hz, 1 H), 1.65−1.52 (m, 2 H), 1.46−1.26 (m, 4 H), 0.91 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 117.7, 114.3, 112.8, 71.1, 46.8, 46.6, 42.3, 41.4, 31.3, 30.2, 27.0, 22.3, 14.0; IR ($CHCl_3$) ν 2931, 2251, 1706, 1668 cm^{-1}; HRMS (ESI M − H) m/z 246.1254. Calcd for $C_{13}H_{16}N_3O_2$ 246.1243.

One-Pot Preparation of (1*R,2*S**,5*R**)-Dimethyl 2-Pentyl-1-nitrobicyclo[3.1.0]-hexane-3,3-dicarboxylate (2e).** A solution of dimethyl 2-allylmalonate (353.5 mg, 2.05 mmol) in dry THF (1 mL) was added to *t*-BuOK (237.6 mg, 2.12 mmol) in dry THF (20 mL). 1-Nitro-1-heptene (441.3 mg, 3.08 mmol) was added to the solution at −30 °C, and the reaction mixture was stirred at room temperature for 4 h. DBU (0.35 mL, 2.34 mmol), Ag_2O (958.6 mg, 4.14 mmol), and iodine (843.9 mg, 3.32 mmol) were added to the solution in this order. The resulting reaction mixture was stirred at room temperature for 3 h. The precipitate was removed via filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel/ethyl acetate−hexane 3:1) to give **2e** in 42% yield (272.2 mg) along with **3e** in 22% yield (141.4 mg).

Conversion of 3b into 4b. A solution of **3b** (91.7 mg, 0.32 mmol) was solved in MeOH (20 mL), and 1 M HCl (0.6 mL) was added. The solution was allowed to stand at room temperature for two days. MeOH was removed in vacuo, and the residue was purified by flash chromatography (silica gel/ethyl acetate−hexane 3:1) to give **4b** in 50% yield (42.4 mg). Pale yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 3.89 (dd, J = 10.9, 4.4 Hz, 1 H), 3.76 (s, 3 H), 3.70 (s, 3 H), 3.63 (dd, J = 10.9, 5.0 Hz, 1 H), 2.76 (dddd, J = 10.5, 9.2, 4.7, 1.1 Hz, 1 H), 2.71−2.62 (m, 2 H), 2.46−2.17 (br, 1 H), 2.11 (dd, J = 13.4, 10.7 Hz, 1 H), 1.69−1.49 (m, 2 H), 1.48−1.30 (m, 2 H), 0.88 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 217.3, 171.5, 171.1, 61.6, 59.3, 55.6, 52.9, 52.6, 48.8, 31.9, 29.2, 21.3, 14.1; IR ($CHCl_3$) ν 3587−3259, 2958, 2875, 1728 cm^{-1}; HRMS (FAB M + H) m/z 273.1334. Calcd for $C_{13}H_{21}O_6$ 273.1338.

Preparation of Dimethyl 4-(iodomethyl)-2-isopropyl-3-nitrocyclopentane-1,1-dicarboxylate (5). Under nitrogen atmosphere, DBU (182.7 mg, 1.20 mmol) in dry THF (1 mL) was added to a solution of **1c** (284.2 mg, 0.99 mmol) in dry THF (15 mL) and

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water (0.2 mL) at room temperature. Then, Ag_2O (469.7 mg, 2.03 mmol) and iodine (512.1 mg, 2.02 mmol) were added to the solution, and the resulting mixture was stirred for 1 h at room temperature. Solid residue was removed via filtration, and the filtrate was concentrated. The obtained crude product was purified by flash chromatography (silica gel/ethyl acetate−hexane 3:1) to give **5** in 65% yield (264.9 mg). Pale yellow solid: mp 67−68 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.92 (dd, J = 8.2, 5.7 Hz, 1 H), 3.72 (s, 3 H), 3.69 (s, 3 H), 3.40 (dd, J = 6.6, 5.8 Hz, 1 H), 3.16−3.06 (m, 1 H), 3.03 (dd, J = 10.0, 6.6 Hz, 1 H), 2.89 (dd, J = 9.9, 9.1 Hz, 1 H), 2.71 (dd, J = 13.1, 6.3 Hz, 1 H), 2.05 (t, J = 12.9 Hz, 1 H), 2.00 (dd, J = 13.5, 6.8 Hz, 1 H), 0.91 (d, J = 6.8 Hz, 3 H), 0.79 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 170.9, 91.7, 61.3, 57.8, 53.1, 52.9, 45.5, 41.6, 28.8, 22.7, 19.1; IR ($CHCl_3$) ν 1735, 1550, 1365 cm^{-1}; HRMS (FAB M + H) m/z 414.0419. Calcd for $C_{13}H_{21}INO_6$ 414.0414.

Conversion of 5 to 3c. Under nitrogen atmosphere, DBU (34.4 mg, 0.23 mmol) in dry THF (1 mL) was added to a solution of **5** (68.2 mg, 0.17 mmol) in dry THF (7 mL) at room temperature, and the reaction mixture was stirred for 3 h. Then, 1 M aqueous HCl (20 mL) was added, and the resulting solution was extracted with EtOAc (50 mL × 3). The organic phase was washed with brine (20 mL × 1) and dried over Na_2SO_4. After filtration, concentration in vacuo afforded crude product, which was purified by flash chromatography (silica gel/ethyl acetate−hexane 3:1) to give **3c** in 83% yield (39.2 mg).

1,3-Dipolar Cycloaddition of 4c to Methyl Acrylate. (6a*S,9*S**,9a*R**)-Trimethyl 9-Isopropyldihydro-1*H*-cyclopenta-[c]isoxazolo[2,3-b]isoxazole-2,8,8(2*H*,6*H*,9*H*)-tricarboxylate (6a). General Procedure.** Under a nitrogen atmosphere, a mixture of **4c** (102.4 mg, 0.36 mmol) and methyl acrylate (2 mL) in dry toluene (2 mL) was heated at refluxing temperature for 3 h. After cooling and concentration in vacuo, the crude product was purified by flash chromatography (silica gel/ethyl acetate−hexane 3:1) to give **6a** in 98% yield (130.0 mg). 2*S**-**6aA** (major) and 2*R**-**6aB** (minor) were carefully separated by chromatography. **6aA**. Colorless solid: mp 138.8−139.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 (dd, J = 10.8, 5.6 Hz, 1 H), 4.19 (dd, J = 9.1, 6.5 Hz, 1 H), 3.86 (d, J = 9.2 Hz, 1 H), 3.80 (s, 3 H), 3.77 (s, 3 H), 3.71 (s, 3 H), 2.81 (dd, J = 12.3, 8.5 Hz, 1 H), 2.72 (dd, J = 15.7, 9.1 Hz, 1 H), 2.58 (t, J = 11.3 Hz, 2 H), 2.26 (dd, J = 12.8, 5.7 Hz, 1 H), 2.07−1.98 (m, 1 H), 1.71 (dd, J = 12.2, 10.1 Hz, 1 H), 1.05 (d, J = 6.5 Hz, 3 H), 0.98 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 170.8, 170.2, 89.5, 77.6, 75.5, 63.4, 57.2, 52.8, 52.7, 52.6, 51.3, 41.3, 38.1, 27.9, 22.0, 21.6. Anal. Calcd. for $C_{17}H_{25}NO_8$: C, 54.98; H, 6.79; N, 3.77. Found: C, 54.93; H, 6.90; N, 3.74. **6aB**. Colorless solid: mp 125.4−126.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (dd, J = 9.8, 4.0 Hz, 1 H), 4.53 (dd, J = 8.7, 6.6 Hz, 1 H), 3.82 (dd, J = 8.7, 1.1 Hz, 1 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.71 (s, 3 H), 2.86−2.75 (m, 2 H), 2.71 (dt, J = 15.3, 4.9 Hz, 1 H), 2.44 (d, J = 11.0 Hz, 1 H), 2.30 (dd, J = 13.6, 4.0 Hz, 1 H), 2.10 (qd, J = 13.0, 6.5 Hz, 1 H), 1.70 (dd, J = 12.4, 9.6 Hz, 1 H), 1.03 (d, J = 6.5 Hz, 3 H), 0.97 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 171.1, 170.8, 88.9, 75.7, 74.8, 63.3, 58.0, 52.8, 52.6, 52.5, 51.4, 41.6, 36.5, 28.0, 27.9, 22.3, 21.8. Anal. Calcd. for $C_{17}H_{25}NO_8$: C, 54.98; H, 6.79; N, 3.77. Found: C, 55.06; H, 6.87; N, 3.82.

(6a*S,9*S**,9a*R**)-2-*tert*-Butyl 8,8-Dimethyl 9-Isopropyldihydro-1*H*-cyclopenta-[c]isoxazolo[2,3-b]isoxazole-2,8,8-(2*H*,6*H*,9*H*)-tricarboxylate (6b): 6bA.** Colorless solid: mp 113.6−114.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.58 (dd, J = 10.4, 6.0 Hz, 1 H), 4.16 (dd, J = 8.8, 6.8 Hz, 1 H), 3.83 (d, J = 9.2 Hz, 1 H), 3.79 (d, J = 1.1 Hz, 3 H), 3.71 (d, J = 1.1 Hz, 3 H), 2.78 (dd, J = 12.3, 8.4 Hz, 1 H), 2.70 (dd, J = 15.7, 9.1 Hz, 1 H), 2.60−2.48 (m, 2 H), 2.17 (dd, J = 12.6, 5.4 Hz, 1 H), 2.04 (tt, J = 12.7, 6.4 Hz, 1 H), 1.70 (dd, J = 12.2, 10.2 Hz, 1 H), 1.46 (d, J = 1.0 Hz, 9 H), 1.06 (d, J = 6.5 Hz, 3 H), 0.97 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 170.9, 168.8, 89.4, 82.6, 78.8, 75.3, 63.4, 57.2, 52.8, 52.6, 51.6, 41.3, 38.1, 28.0, 27.9, 22.0, 21.64. Anal. Calcd. for $C_{20}H_{31}NO_8$: C, 58.10; H, 7.56; N, 3.39. Found: C, 58.03; H, 7.60; N, 3.45. **6bB**. Colorless solid: mp 121.2−122.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (dd, J = 8.5, 6.6 Hz, 1 H), 4.45 (dd, J = 9.8, 3.9 Hz, 1 H), 3.80 (d, J = 9.6 Hz, 1 H), 3.79 (s, 3 H), 3.70 (s, 3 H), 2.78 (dd, J = 12.0, 8.9 Hz, 1 H), 2.76 (dd, J = 12.9, 9.5 Hz, 1 H), 2.70 (dd, J = 15.8, 8.9 Hz, 1 H), 2.42 (d, J = 11.0 Hz, 1 H), 2.22 (dd, J = 13.5, 3.9 Hz, 1 H), 2.11 (ddd, J = 17.7, 12.9, 6.3 Hz, 1 H), 1.69 (dd, J = 12.3, 9.6 Hz, 1 H), 1.47 (s, 9 H), 1.02 (d, J = 6.5 Hz, 3 H), 0.97 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 170.7, 169.7, 88.8, 82.5, 75.6, 75.3, 63.3, 58.0, 52.7, 52.5, 51.2, 41.5, 36.4, 28.0, 27.9, 22.3, 21.8. Anal. Calcd. for $C_{20}H_{31}NO_8$: C, 58.10; H, 7.56; N, 3.39. Found: C, 58.04; H, 7.60; N, 3.32.

(6a*S,9*S**,9a*R**) Dimethyl 2-Cyano-9-isopropyltetrahydro-1*H*-cyclopenta[c]-isoxazolo[2,3-b]isoxazole-8,8(2*H*)-dicarboxylate (6c). 6cA.** Colorless solid: mp 186.6−187.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.86 (dd, J = 9.9, 6.2 Hz, 1 H), 4.18 (dd, J = 9.3, 6.7 Hz, 1 H), 3.87 (d, J = 9.2 Hz, 1 H), 3.79 (s, 3 H), 3.71 (s, 3 H), 2.81 (dd, J = 11.3, 7.2 Hz, 1 H), 2.77 (dd, J = 11.7, 8.6 Hz, 1 H), 2.68 (dd, J = 15.4, 8.6 Hz, 1 H), 2.52 (d, J = 11.1 Hz, 1 H), 2.44 (dd, J = 13.0, 6.2 Hz, 1 H), 2.08−1.98 (m, 1 H), 1.70 (dd, J = 12.6, 9.9 Hz, 1 H), 1.06 (d, J = 6.5 Hz, 3 H), 0.98 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 170.8, 116.6, 89.6, 76.0, 65.6, 63.3, 57.2, 52.9, 52.8, 50.9, 41.4, 39.3, 27.9, 22.1, 21.6. Anal. Calcd. for $C_{16}H_{22}N_2O_6$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.70; H, 6.58; N, 8.27. **6cB**. Colorless solid: mp 105.8−106.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.91 (d, J = 9.0 Hz, 1 H), 4.48 (dd, J = 9.5, 6.6 Hz, 1 H), 4.00 (d, J = 9.5 Hz, 1 H), 3.81 (s, 3 H), 3.72 (s, 3 H), 2.98 (td, J = 8.9, 7.4 Hz, 1 H), 2.91 (dd, J = 13.7, 9.3 Hz, 1 H), 2.85 (dd, J = 12.6, 8.6 Hz, 1 H), 2.50 (d, J = 11.1 Hz, 1 H), 2.35 (d, J = 13.7 Hz, 1 H), 2.08 (ddd, J = 17.3, 12.9, 6.4 Hz, 1 H), 1.77 (dd, J = 12.6, 10.1 Hz, 1 H), 0.99 (d, J = 6.9 Hz, 3 H), 0.97 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 170.6, 117.6, 89.2, 76.7, 65.3, 63.1, 57.5, 52.9, 52.8, 50.4, 41.7, 38.3, 27.6, 22.0, 21.5. Anal. Calcd. for $C_{16}H_{22}N_2O_6$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.79; H, 6.60; N, 8.25.

(6a*S,9*S**,9a*R**)-Trimethyl 9-Cyclohexyldihydro-1*H*-cyclopenta[c]isoxazolo[2,3-b]-isoxazole-2,8,8(2*H*,6*H*,9*H*)-tricarboxylate (6d): 6dA.** Colorless solid: mp 133.8−134.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (ddd, J = 10.5, 5.7, 1.9 Hz, 1 H), 4.17 (t, J = 8.8 Hz, 1 H), 3.84 (d, J = 9.4 Hz, 1 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.70 (s, 3 H), 2.80 (dd, J = 11.4, 9.3 Hz, 1 H), 2.70 (dd, J = 16.3, 7.9 Hz, 1 H), 2.63 (d, J = 11.0 Hz, 1 H), 2.53 (t, J = 11.4 Hz, 1 H), 2.25 (dd, J = 12.0, 4.9 Hz, 1 H), 1.94 (d, J = 13.6 Hz, 1 H), 1.80−1.53 (m, 6H), 1.26−0.91 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 170.7, 170.2, 89.5, 77.6, 75.4, 62.9, 56.0, 52.9, 52.8, 52.7, 51.4, 41.3, 38.2, 37.7, 32.1, 31.5, 26.9, 26.3, 26.2. Anal. Calcd. for $C_{20}H_{29}NO_8$: C, 58.38; H, 7.10; N, 3.40. Found: C, 58.21; H, 7.17; N, 3.41. **6dB**. Colorless solid: mp 115.6−116.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (dd, J = 9.9, 3.8 Hz, 1 H), 4.51 (dd, J = 8.7, 6.7 Hz, 1 H), 3.80 (d, J = 7.0 Hz, 1 H), 3.80 (s, 3 H), 3.77 (s, 3 H), 3.71 (s, 3 H), 2.83−2.73 (m, 2 H), 2.69 (dd, J = 15.2, 8.6 Hz, 1 H), 2.53 (d, J = 10.9 Hz, 1 H), 2.30 (dd, J = 13.5, 3.8 Hz, 1 H), 1.89 (d, J = 13.7 Hz, 1 H), 1.79−1.59 (m, 5H), 1.30−0.92 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 171.2, 170.7, 88.8, 75.6, 74.9, 62.8, 56.8, 52.8, 52.7, 52.6, 51.3, 41.6, 37.8, 36.5, 32.3, 31.6, 26.9, 26.3, 26.2. Anal. Calcd. for $C_{20}H_{29}NO_8$: C, 58.38; H, 7.10; N, 3.40. Found: C, 58.35; H, 7.18; N, 3.39.

(6a*S,9*S**,9a*R**) 2-*tert*-Butyl 8,8-Dimethyl 9-Cyclohexyldihydro-1*H*-cyclopenta-[c]isoxazolo[2,3-b]isoxazole-2,8,8-(2*H*,6*H*,9*H*)-tricarboxylate (6e). 6eA.** Colorless solid: mp 197.8−198.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.58 (dd, J = 10.8, 5.6 Hz, 1 H), 4.16 (dd, J = 9.2, 6.4 Hz, 1 H), 3.82 (d, J = 9.2 Hz, 1 H), 3.80 (s, 3 H), 3.71 (s, 3 H), 2.78 (dd, J = 12.3, 8.4 Hz, 1 H), 2.68 (dd, J = 15.8, 9.1 Hz, 1 H), 2.64 (d, J = 11.1 Hz, 1 H), 2.49 (dd, J = 12.6, 11.0 Hz, 1 H), 2.18 (dd, J = 12.7, 5.6 Hz, 1 H), 2.00 (d, J = 14.2 Hz, 1 H), 1.82−1.61 (m, 6 H), 1.46 (s, 9 H), 1.28−1.09 (m, 3 H), 1.07−0.94 (m, 2 H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 170.8, 168.8, 89.3, 82.6, 78.9, 75.2, 62.9, 56.0, 52.8, 52.7, 51.7, 41.3, 38.3, 37.8, 32.0, 31.5, 28.0, 26.9, 26.3, 26.3. Anal. Calcd. for $C_{23}H_{35}NO_8$: C, 60.91; H, 7.78; N, 3.09. Found: C, 60.92; H, 7.84; N, 3.12. **6eB**. Colorless solid: mp 150.9−151.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (dd, J = 8.6, 6.7 Hz, 1 H), 4.45 (dd, J = 10.0, 3.7 Hz, 1 H), 3.80 (s, 3H), 3.79 (d, J = 8.8 Hz, 1 H), 3.71 (s, 3 H), 2.82−2.70 (m, 2 H), 2.69 (dd, J = 15.2, 8.6 Hz, 1 H), 2.51 (d, J = 10.9 Hz, 1 H), 2.23 (dd, J = 13.5, 3.6 Hz, 1 H), 1.90 (d, J = 13.9 Hz, 1 H), 1.79−1.61 (m, 6 H), 1.49−1.45 (m, 9 H), 1.26−0.92 (m, 5 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 170.7, 169.8, 88.8, 82.5, 75.5, 75.4, 62.8, 56.8, 52.8, 52.6, 51.1, 41.6, 37.8,

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36.4, 32.3, 31.6, 28.0, 26.9, 26.3, 26.2. Anal. Calcd. for $C_{23}H_{35}NO_8$: C, 60.91; H, 7.78; N, 3.09. Found: C, 60.88; H, 7.89; N, 3.15.

(6a*S,9*S**,9a*R**) Dimethyl 2-Cyano-9-cyclohexyltetrahydro-1*H*-cyclopenta[c]-isoxazolo[2,3-b]isoxazole-8,8(2*H*)-dicarboxylate (6f). 6fA.** Colorless solid: mp 182.2−183.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.85 (dd, J = 10.0, 6.0 Hz, 1 H), 4.17 (dd, J = 9.3, 6.7 Hz, 1 H), 3.88 (d, J = 9.0 Hz, 1 H), 3.83−3.79 (m, 3 H), 3.72 (s, 3 H), 2.81 (dd, J = 12.5, 8.6 Hz, 1 H), 2.74 (dd, J = 13.0, 10.0 Hz, 1 H), 2.68 (dd, J = 15.5, 8.8 Hz, 1 H), 2.62 (d, J = 11.0 Hz, 1 H), 2.43 (dd, J = 13.0, 6.1 Hz, 1 H), 1.97 (d, J = 13.9 Hz, 1 H), 1.85−1.61 (m, 6 H), 1.29−0.93 (m, 5 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 170.8, 116.5, 89.6, 75.9, 65.7, 62.8, 56.0, 53.0, 52.9, 50.9, 41.4, 39.4, 37.8, 32.2, 31.5, 26.8, 26.3, 26.2. Anal. Calcd. for $C_{19}H_{26}N_2O_6$: C, 60.30; H, 6.93; N, 7.40. Found: C, 60.37; H, 7.03; N, 7.48. **6fB**. Colorless solid: mp 118.6−119.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.91 (d, J = 9.2 Hz, 1 H), 4.47 (dd, J = 8.7, 7.4 Hz, 1 H), 3.99 (d, J = 9.5 Hz, 1 H), 3.81 (s, 3 H), 3.72 (s, 3 H), 2.97 (dd, J = 16.7, 8.5 Hz, 1 H), 2.91−2.81 (m, 2 H), 2.58 (d, J = 10.9 Hz, 1 H), 2.34 (d, J = 13.7 Hz, 1 H), 1.86−1.59 (m, 7 H), 1.33−0.91 (m, 5 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 170.6, 117.6, 89.1, 76.6, 65.4, 62.6, 56.3, 53.0, 52.9, 50.4, 41.8, 38.3, 37.5, 32.2, 31.3, 26.8, 26.3, 26.2. Anal. Calcd. for $C_{19}H_{26}N_2O_6$: C, 60.30; H, 6.93; N, 7.40. Found: C, 60.02; H, 6.98; N, 7.21.

(6a*S,9*S**,9a*R**)-Trimethyl 9-Propyldihydro-1*H*-cyclopenta[c]isoxazolo[2,3-b]-isoxazole-2,8,8(2*H*,6*H*,9*H*)-tricarboxylate (6g). 6gA.** Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75 (dd, J = 9.3, 6.9 Hz, 1 H), 4.22 (dd, J = 9.2, 6.6 Hz, 1 H), 3.84 (d, J = 9.2 Hz, 1 H), 3.77 (s, 3 H), 3.74 (s, 3 H), 3.72 (s, 3 H), 2.92 (dd, J = 15.2, 8.7 Hz, 1 H), 2.73 (dd, J = 4.0, 10.0 Hz, 1 H), 2.72 (dd, J = 8.9, 12.9 Hz, 1 H), 2.47 (d, J = 6.5 Hz, 1 H), 2.46 (d, J = 10.0 Hz, 1 H), 1.81−1.70 (m, 1 H), 1.65 (dd, J = 13.2, 9.5 Hz, 1 H), 1.52−1.41 (m, 1 H), 1.41−1.32 (m, 1 H), 1.31−1.22 (m, 1 H), 0.92 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 170.7, 170.4, 90.0, 77.6, 76.1, 63.7, 52.7, 52.7, 52.5, 51.2, 49.5, 40.2, 37.8, 29.9, 20.7, 14.2; HRMS (ESI M + H) m/z 372.1660. Calcd for $C_{17}H_{26}NO_8$ 372.1658. **6gB**. Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.57 (dd, J = 8.7, 6.6 Hz, 1 H), 4.54 (dd, J = 9.3, 4.3 Hz, 1 H), 3.81 (dd, J = 8.8, 1.2 Hz, 1 H), 3.76 (s, 3 H), 3.73 (s, 3 H), 3.71 (s, 3 H), 2.85 (ddd, J = 15.7, 9.0, 1.3 Hz, 1 H), 2.72 (dd, J = 13.4, 9.3 Hz, 1 H), 2.68 (dd, J = 13.1, 8.8 Hz, 1 H), 2.59 (dd, J = 9.4, 4.7 Hz, 1 H), 2.43 (dd, J = 13.6, 4.5 Hz, 1 H), 1.82−1.73 (m, 1 H), 1.66 (dd, J = 13.2, 9.2 Hz, 1 H), 1.49−1.39 (m, 1 H), 1.39−1.29 (m, 2 H), 0.92 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 171.0, 170.9, 89.2, 76.3, 74.6, 63.6, 52.7, 52.6, 52.4, 51.1, 50.7, 40.3, 36.5, 29.9, 20.9, 14.3; HRMS (ESI M + H) m/z 372.1653. Calcd for $C_{17}H_{26}NO_8$ 372.1658.

1,3-Dipolar Cycloaddition of 4c to Methyl Propiorate. (7*S,7a*R**) Dimethyl 1-(2-(*tert*-Butoxy)-2-oxoacetyl)-7-isopropyltetrahydroazirino[1,2-b]cyclopenta[c]-isoxazole-6,6(1*H*)-dicarboxylate (7a). General Procedure.** Under a nitrogen atmosphere, a mixture of **4c** (328.3 mg, 1.15 mmol), MS4A (500 mg), and methyl propiorate (0.8 mL) in dry toluene (4 mL) was heated at refluxing temperature for 19 h. After cooling, filtration, and concentration in vacuo, the crude product was purified by flash chromatography (silica gel/ethyl acetate−hexane 5:1) to give **7a** in 90% yield (427.4 mg). Pale yellow solid: mp 92.8−93.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 (dd, J = 13.5, 7.4 Hz, 1 H), 3.94−3.87 (m, 1 H), 3.75 (s, 3 H), 3.70 (s, 3H), 3.73−3.65 (m, 1 H), 3.45−3.34 (m, 1 H), 2.89−2.76 (m, 2 H), 2.30 (d, J = 14.5 Hz, 1 H), 1.78−1.69 (m, 1 H), 1.51 (s, 9 H), 0.98 (d, J = 6.9 Hz, 3 H), 0.91 (d, J = 6.7 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.7, 171.3, 169.5, 159.5, 84.7, 83.3, 71.7, 64.6, 53.3, 52.9, 52.8, 52.6, 43.5, 36.8, 28.7, 27.8, 22.9, 19.4. Anal. Calcd. for $C_{20}H_{29}NO_8$: C, 58.38; H, 7.10; N, 3.40. Found: C, 58.44; H, 7.14; N, 3.43.

(7*S,7a*R**) Dimethyl 1-Benzoyl-7-isopropyltetrahydroazirino[1,2-b]cyclopenta[c]-isoxazole-6,6(1*H*)-dicarboxylate (7b).** White solid: mp 128.3−129.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, J = 8.3 Hz, 2 H), 7.57 (t, J = 7.4 Hz, 1 H), 7.46 (dd, J = 11.1, 4.3 Hz, 2 H), 4.13 (t, J = 8.3 Hz, 1 H), 3.86 (dt, J = 9.5, 4.7 Hz, 1 H), 3.79 (s, 3 H), 3.74 (s, 3 H), 3.71 (dd, J = 4.4, 1.5 Hz, 1 H), 3.70 (s, 1 H), 3.69 (d, J = 7.9 Hz, 1 H), 2.99−2.90 (m, 1 H), 2.36 (dd, J = 14.6, 2.0 Hz, 1 H), 1.78 (dtd, J = 13.9, 7.0, 3.6 Hz, 1 H), 1.07 (d, J = 6.9 Hz, 3 H), 1.00 (d, J = 7.0 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.3, 171.6, 169.8, 136.6, 134.0, 129.1, 128.8, 82.2, 67.9, 64.2, 55.2, 53.3, 53.2, 52.9, 43.2, 36.8, 29.1, 23.2, 19.4. Anal. Calcd. for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.50; N, 3.62. Found: C, 65.16; H, 6.60; N, 3.66.

(7*S,7a*R**)-Dimethyl 1-(2-(*tert*-Butoxy)-2-oxoacetyl)-7-cyclohexyltetrahydro-azirino[1,2-b]cyclopenta[c]isoxazole-6,6(1*H*)-dicarboxylate (7c).** Colorless solid: mp 95.3−97.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 (t, J = 8.3 Hz, 1 H), 3.80 (s, 1 H), 3.67 (t, J = 7.7 Hz, 1 H), 3.66 (s, 3 H), 3.61 (s, 3 H), 3.25 (q, J = 8.8 Hz, 1 H), 2.70 (d, J = 9.5 Hz, 1 H), 2.67 (dd, J = 6.5, 2.8 Hz, 1 H), 2.23 (dd, J = 14.4, 2.3 Hz, 1 H), 1.65−1.38 (m, 5 H), 1.43 (s, 9 H), 1.28−0.87 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.7, 171.3, 169.5, 159.4, 84.7, 83.4, 72.1, 64.7, 53.3, 52.9, 52.8, 52.6, 43.4, 39.4, 37.2, 33.1, 30.3, 27.8, 27.3, 26.8, 26.1; HRMS (ESI M + H) m/z 452.2267. Calcd for $C_{23}H_{34}NO_8$ 452.2284.

(7*S,7a*R**) Dimethyl 1-Benzoyl-7-cyclohexyltetrahydro-azirino[1,2-b]cyclopenta[c]-isoxazole-6,6(1*H*)-dicarboxylate (7d).** White solid: mp 142.2−143.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (dd, J = 8.2, 1.5 Hz, 2 H), 7.59 (td, J = 7.2, 1.3 Hz, 1 H), 7.48 (t, J = 7.0 Hz, 2 H), 4.13 (t, J = 8.3 Hz, 1 H), 3.80 (s, 3H), 3.93−3.64 (m, 3 H), 3.76 (s, 3 H), 2.93 (ddd, J = 14.4, 9.5, 1.8 Hz, 1 H), 2.87 (s, 1 H), 2.38 (d, J = 14.4 Hz, 1 H), 1.89−1.43 (m, 6H), 1.45−0.97 (m, 5 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.3, 171.5, 169.8, 136.6, 134.0, 129.1, 128.8, 82.2, 68.0, 64.3, 55.3, 53.3, 53.2, 52.9, 43.2, 39.8, 37.2, 33.6, 30.1, 27.3, 26.9, 26.1. Anal. Calcd. for $C_{24}H_{29}NO_6$: C, 67.43; H, 6.84; N, 3.28. Found: C, 67.55; H, 7.02; N, 3.29.

Preparation of (3*S,5*R**,6*S**,9*S**)-Dimethyl 3-Hydroxy-9-(hydroxymethyl)-6-isopropyl-2-oxo-1-azaspiro[4.4]nonane-7,7-dicarboxylate 8.** This conversion was performed according to a method discussed in the literature.[11] Raney Ni (1.5341 g) was added to an aqueous solution of NaOH (1.2298 g in 15 mL of water), and the resulting suspension was heated at 50 °C for 50 min. Saturated $NaHCO_3$ (5 mL) was added, and black precipitate was washed with water (40 mL) eight times and with MeOH (40 mL) for four times. The catalyst was added to MeOH solution of **6aA** (107.0 mg, 0.29 mmol, 15 mL) under a hydrogen atmosphere, and the reaction mixture was stirred vigorously for 24 h. Then, the reaction mixture was heated at refluxing temperature for 24 h under a nitrogen atmosphere. Raney Ni was filtered through a Celite pad and rinsed with MeOH. The filtrate was concentrated, and the residue was purified by flash chromatography (silica gel, hexane−EtOAc (20:1) then MeOH) to give **8** in 79% yield (78.6 mg). White solid: mp 155.0−156.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (br, 1 H), 5.06 (br, 1 H), 4.20 (d, J = 18.0 Hz, 1 H), 3.77 (s, 3 H), 3.71 (s, 3 H), 3.48 (br, 1 H), 2.66 (dd, J = 14.5, 8.4 Hz, 1 H), 2.51 (dd, J = 12.7, 7.6 Hz, 1 H), 2.43 (d, J = 10.6 Hz, 1 H), 2.38−2.29 (m, 1 H), 2.27−2.15 (m, 1 H), 1.89 (dd, J = 12.7, 10.8 Hz, 1 H), 1.69 (dd, J = 14.6, 2.2 Hz, 1 H), 1.20 (br, 1 H), 0.94 (d, J = 6.4 Hz, 3 H), 0.86 (t, J = 5.7 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.9, 173.3, 171.0, 70.5, 67.8, 61.8, 60.8, 60.8, 53.0, 52.6, 51.0, 40.6, 37.3, 27.4, 22.8, 22.6; HRMS (ESI M + H) m/z 344.1709. Calcd for $C_{16}H_{26}NO_7$ 344.1709.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectroscopic charts and preparation methods for compounds **1**, **2**, **3**, **4**, **5**, **6**, **7**, and **8** and X-ray crystallographic data for **2d**, **2h**, **5**, **6aA**, **6eA**, **6eB**, and **7d**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ak10@yamaguchi-u.ac.jp.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For a review of tandem reactions, see: (a) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (c) Bunce, R. A. *Tetrahedron* **1995**, *48*, 13103. (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (e) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006.

(2) (a) Groaning, M. D.; Meyers, A. I. *Tetrahedron Lett.* **1999**, *40*, 4639. (b) Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1993**, *115*, 30.

(3) (a) Gooding, B. B.; Jones, R. N. *Antimicrob. Agents Chemother.* **1993**, *37*, 349. (b) Khan, A. A.; Araujo, F. G.; Brighty, K. E.; Gootz, T. D.; Remington, J. S. *Antimicrob. Agents Chemother.* **1999**, *43*, 1783. (c) Norris, T.; Braish, T. F.; Butters, M.; DeVries, K. M.; Hawkins, J. M.; Massett, S. S.; Rose, P. R.; Santafianos, D.; Sklavounos, C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1615.

(4) For review, see: Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A. *Chem. Rev.* **1997**, *97*, 787.

(5) (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789. (b) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835. (c) Bertus, P.; Szymoniak, J. *Synlett* **2007**, 1346.

(6) (a) Esposito, A.; Piras, P. P.; Ramazzotti, D.; Taddei, M. *Org. Lett.* **2001**, *3*, 3273. (b) de Meijere, A.; Williams, C. M.; Kourdioukov, A.; Sviridov, S. V.; Chaplinski, V.; Kordes, M.; Savchenko, A. I.; Stratmann, C.; Noltemeyer, M. *Chem.—Eur. J.* **2002**, *8*, 3789. (c) Caroche, C.; Bertus, P.; Szymoniak, J. *Tetrahedron Lett.* **2003**, *44*, 2485. (d) Faler, C. A.; Cao, B.; Joullié, M. M. *Heterocycles* **2006**, *67*, 519. (e) Gensini, M.; de Meijere, A. *Chem.—Eur. J.* **2004**, *10*, 785. (f) Cao, B.; Xiao, D.; Joullié, M. M. *Org. Lett.* **1999**, *1*, 1799. (g) Gensini, M.; Kozhushkov, S. I.; Yufit, D. S.; Howard, J. A. K.; Es-Sayed, M.; de Meijere, A. *Eur. J. Org. Chem.* **2002**, 2499.

(7) (c) Kamimura, A.; Kadowaki, A.; Yoshida, T.; Takeuchi, R.; Uno, H. *Chem.—Eur. J.* **2009**, *16*, 10330. For other similar cyclopropanation reactions, see: (a) Snider, B. B.; Che, Q. *Tetrahedron* **2002**, *58*, 7821. (b) Asahi, K.; Nishino, H. *Synthesis* **2009**, 409.

(8) So far, one-pot nitrone formation was reported. See: (a) Arai, N.; Narasaka, K. *Chem. Lett.* **1995**, 987. (b) Arai, N.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2525.

(9) Kanemasa, S.; Yoshimiya, T.; Wada, E. *Tetrahedron Lett.* **1998**, *39*, 8869.

(10) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. Denmark, S. E.; Schnute, M. E.; Senanayake, C. B. W. *J. Org. Chem.* **1993**, *58*, 1859. Denmark, S. E.; Schnute, M. E.; Marcin, L. R.; Thorarensen, A. *J. Org. Chem.* **1995**, *60*, 3205. Denmark, S. E.; Thorarensen, A. *J. Am. Chem. Soc.* **1997**, *119*, 127. Denmark, S. E.; Hurd, A. R.; Sacha, H. J. *J. Org. Chem.* **1997**, *62*, 1668. Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675. Denmark, S. E.; Guagnano, V.; Dixon, J. A.; Stolle, A. *J. Org. Chem.* **1997**, *62*, 4610. Denmark, S. E.; Dixon, J. A. *J. Org. Chem.* **1998**, *63*, 6167. Creech, G. S.; Kwon, O. *J. Am. Chem. Soc.* **2010**, *132*, 8876.

(11) Kornblum, N.; Singh, H. K.; Kelly, W. J. *J. Org. Chem.* **1983**, *48*, 332.

(12) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision D.02; Gaussian, Inc.: Wallingford, CT, 2004.

(13) Feuer, H. *Nitrile Oxides, Nitrones, And Nitronates in Organic Synthesis*, 2nd ed.; Wiley-Interscience: New York, 2008.

(14) Recently, one-pot nitrone cycloaddition from nitroalkenes was reported: Creech, G. S.; Kwon, O. *J. Am. Chem. Soc.* **2010**, *132*, 8876.

(15) Seebach, D.; Lyaplkalo, I. M.; Dahinden, R. *Helv. Chim. Acta* **1999**, *82*, 1828.