Asymmetric Dipolar Cycloaddition of Nitrile Oxides to the α,β-Unsaturated Esters Bearing an Imidazolidine Chiral Controller at the β-Position

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(Received June 26, 1991)

Some α,β-unsaturated esters bearing an imidazolidine chiral controller at the β-position were employed in the asymmetric cycloaddition to nitrile oxides. Regio- and diastereoselectivities were both poor when the chiral controller was a perhydropyrrolo[1,2-*c*]imidazol-3-yl auxiliary, while the reaction of the esters bearing a C_2-symmetric imidazolidine chiral controller was exclusively regioselective or diastereoselective depending upon the nature of *N*-substituent. The transition state was briefly discussed.

Nitrile oxide is one of the 1,3-dipoles with high synthetic potential[1] because 1) their ready cycloadditions with a wide variety of dipolarophiles (electron-deficient, eletron-rich, and nonactivated types) produce 2-isoxazolines or isoxazoles bearing various functional groups, 2) these cycloadditions take place in excellent yields in a highly stereospecific and often regioselective manner, 3) the 2-isoxazolines and isoxazoles can be converted to a variety of synthetically useful functional building blocks such as β-hydroxy ketones, β-amino alcohols, α,β-unsaturated ketones, and so on.

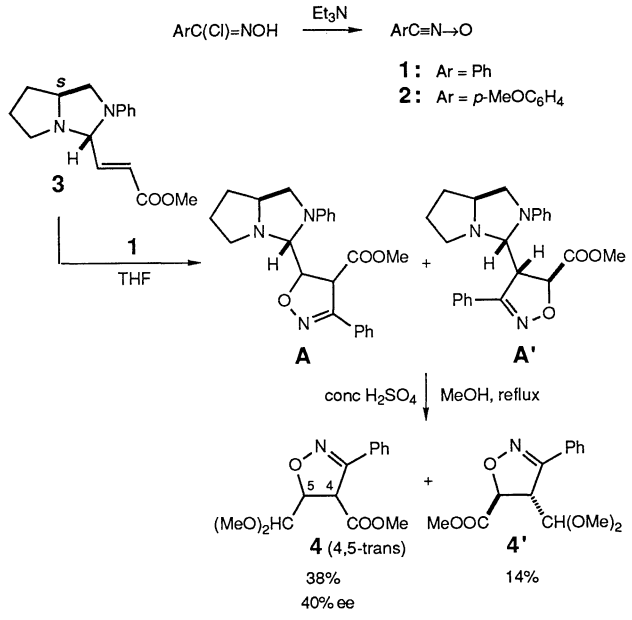
This is why the researches directing to the development of asymmetric versions of nitrile oxide cycloaddition are now enthusiastically under way. Since there are so far few reported examples for the catalyzed nitrile oxide cycloaddition, the diastereoselective reaction by the use of chiral dipolarophiles is the only effective way to establish the asymmetric reaction. The acrylates and crotonates derived from readily available simple chiral alcohols have shown low diastereoselectivities in the cycloaddition with nitrile oxides.[2] Several recent reports presented the highly diastereoselective asymmetric cycloaddition of nitrile oxides employing the Oppolzer's sultam[3] or the chiral auxiliary derived from the Kemp's triacid.[4] However, the auxiliary-controlled asymmetric cycloaddition of nitrile oxides is still of current interest.

We have recently developed the highly diastereoselective asymmetric cycloaddition of azomethine ylide with the α,β-unsaturated esters bearing a 2-imidazolidinyl or 2-oxazolidinyl chiral controller at the β-position.[5] In the present paper, these chiral α,β-unsaturated esters were successfully applied to the asymmetric cycloaddition of nitrile oxides.

Results and Discussion

Diastereoselectivity and Regioselectivity. Reaction of benzonitrile oxide (**1**) with the α,β-unsaturated ester **3**[5a,b] bearing the (3*R*,7a*S*)-2-phenylperhydropyrrolo[1,2-*c*]imidazol-3-yl chiral controller at the β-position, in tetrahydrofuran (THF) at room temperature, produced a mixture of two regioisomeric cycloadducts **A** and **A'**, where **1** had been generated from benzohydroximoyl chloride and triethylamine (Scheme 1). The cycloadduct mixture **A** and **A'** was converted into the acetal mixture **4** and **4'** by treatment with refluxing methanol in the presence of concentrated sulfuric acid because separation of **A** and **A'** from each other or from the dimer of **1** through column chromatography was unsuccessful. The resulting acetals **4** (38%) and **4'** (14%) were separated from each other by column chromatography on silica gel (Table 1).

The relative stereochemistry and regiochemistry of **4** and **4'** were unambiguously determined by ^{1}H NMR analysis. The observed small coupling constants for J_{4-5} (4.4 Hz for both **4** and **4'**) indicated the trans relationship of H-4 and H-5. Based on the chemical shifts as well as the coupling patterns of H-4 and H-5, their regiochemistry was confirmed (the 4-ester **4**: δ=4.43

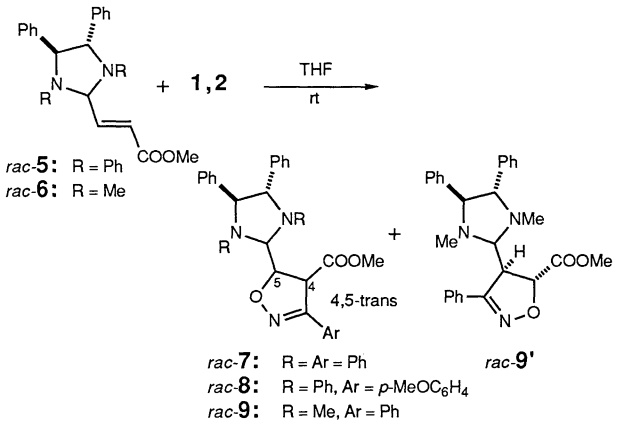


Scheme 1.

Table 1. Dipolar Cycloaddition of Benzonitrile Oxides to the α,β-Unsaturated Esters Bearing an Aminal Type Chiral Controller at the β-Position[a)]

Entry	Dipolarophile	ArCNO (equiv)	Time/h	Product (yield/%)[b)]	Selectivity (ds)[c)]
1	**3**	**1** (2)	24	**4** (38)+**4′** (14)	**4** 70:30[d)] **4′** Single
2	**5**	**1** (2)	16	**7** (52)[e)]	**7** 74:26
3	**5**	**1** (8)	57	**7** (71)	**7** 76:24
4	**5**	**2** (2)	24	**8** (64)	**8** 70:30
5	**6**	**1** (5)	23	**9** (29)+**9′** (10)	**9** Single **9′** Single
6	**6**	**1** (10)	24	**9** (34)+**9′** (16)	**9** Single **9′** Single

a) All reactions were performed in THF at room temperature. Nitrile oxides **1**, **2** were generated from the corresponding hydroximoyl chlorides and triethylamine. b) Isolated yield. c) Determined by ^{1}H NMR spectrum. d) Determined by HPLC (column: Chiral pack OD). e) Recovered **5**: 39%.



Scheme 2.

(d, H-4) and 5.01 (dd, H-5); the 5-ester **4′**: 4.29 (dd, H-4) and 5.32 (d, H-5)).

The major product **4** showed a positive optical rotation ($[\alpha]_D^{24}$=+65.9° (*c* 0.73, $CHCl_3$)) and its enantiomeric excess was determined to be 40% ee by the analysis on a high performance liquid chromatography (HPLC) using a chiral column (Daicel, Chiral pack OD). The absolute configuration of the major enantiomer of **4** was assigned to be 4*S*,5*S* by comparison of the optical rotation with that of the authentic derivative as discussed below. The minor product **4′** was found to be optically pure on the basis of the chiral HPLC analysis, whose optical rotation was recorded as $[\alpha]_D^{22}$=+133.5° (*c* 0.37, $CHCl_3$).

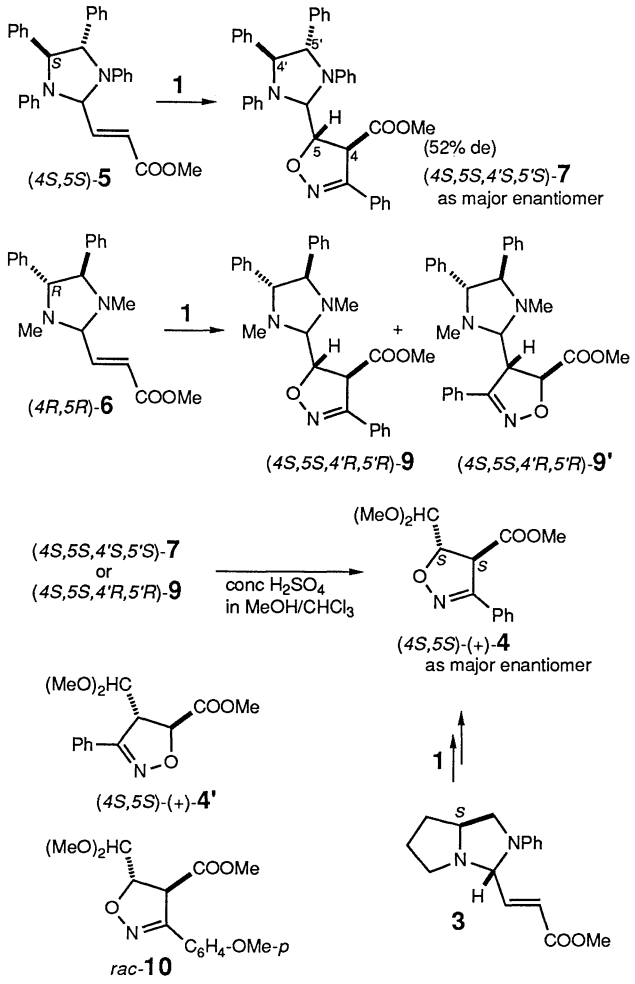
The α,β-unsaturated ester *rac*-**5**[5c)] bearing the 1,3,4,5-tetraphenyl-2-imidazolidinyl chiral controller at the β-position, hereafter referred to as the *N*-phenyl-substituted ester, was applied to the cycloaddition with nitrile oxide **1** at room temperature (Scheme 2). This reaction proceeded in an absolutely regioselective manner to produce a mixture of two diastereomeric 2-isoxazoline-4-carboxylates *rac*-**7** in 52% yield as the sole regioisomer (Table 1, Entry 2). This exclusively high regioselectivity was surprising because the nitrile oxide cycloaddition with α,β-unsaturated ester bearing a β-alkyl substituent is usually very poor in regioselectivity.[1a)] It is found that steric factor may be responsible for this exclusive selectivity, as mentioned later in the discussion of transition state. The diastereoselectivity of the reaction forming *rac*-**7** was only 74:26 (by ^{1}H NMR).

Since the starting α,β-unsaturated ester *rac*-**5** was partly recovered (39% yield) in the above reaction using 2-equivalents of **1**, a large excess amount of nitrile oxide **1** (8 equivalents) was used and *rac*-**7** was obtained in 71% yield (ds 76:24). A similar result was obtained in the reaction of *rac*-**5** with *p*-methoxybenzonitrile oxide **2** (Entry 4).

The reaction of **1** with the α,β-unsaturated ester *rac*-**6**[5c)] bearing the 1,3-dimethyl-4,5-diphenyl-2-imidazolidinyl chiral controller at the β-position, hereafter referred to as the *N*-methyl-substituted ester, made a striking contrast against the aforementioned reaction using the *N*-phenyl-substituted ester *rac*-**5**. Although both yield and regioselectivity were poor (the 2-isoxazoline-4-carboxylate isomer *rac*-**9**: 29%; the 2-isoxazoline-5-carboxylate one *rac*-**9′**: 10%), these regioisomers *rac*-**9** and *rac*-**9′**, separated from each other through silica-gel column chromatography, were found to be both absolutely pure diastereomers (Scheme 2 and Table 1, Entry 5).

Assignment of Absolute Configurations. The 76:24 diastereomeric mixture of **7** obtained from **1** and the optically pure (4*S*,5*S*)-(−)-**5** was treated with methanol in chloroform together with concentrated sulfuric acid to give **4** (a 75:25 mixture of enantiomers by chiral HPLC, $[\alpha]_D^{24}$=+82.8° (*c* 0.61, $CHCl_3$)) in quantitative yield (Scheme 3). The major enantiomer of so obtained 2-isoxazoline-4-carboxylate **4** was found to be identical with the major enantiomer derived from the cycloadduct **A** (Scheme 1). As a result, the same diastereotopic faces of the α,β-unsaturated ester moiety of **3** and (4*S*,5*S*)-(−)-**5** were preferred by nitrile oxide **1**.

On the other hand, the cycloadducts (+)-**9** and (+)-**9′**, obtained as the sole diastereomers from **1** and the optically pure (4*R*,5*R*)-(+)-**6**, were similarly transformed to (+)-**4** and (+)-**4′** in 73% and 96% yields, respectively.



Scheme 3.

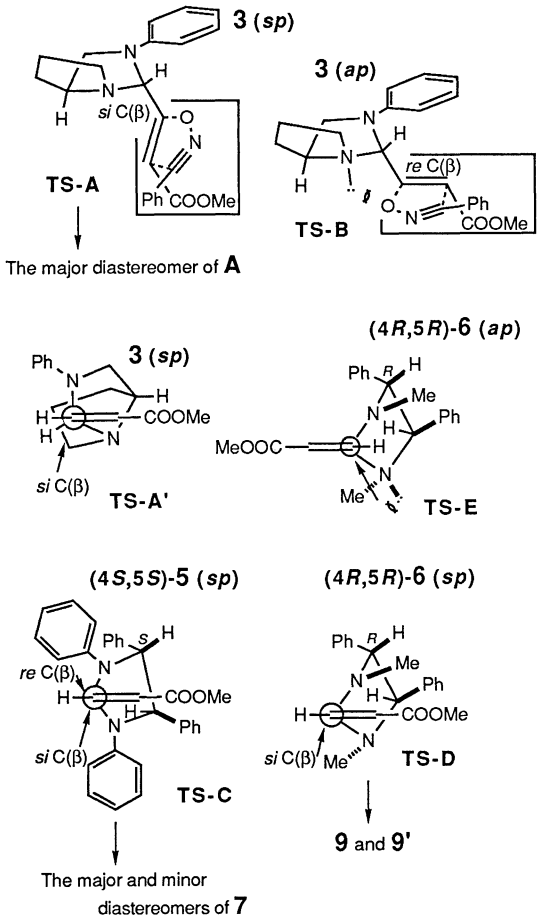


Fig. 1. Transition states for the cycloaddition of nitrile oxide **1** to **3**, **5**, or **6**.

The absolute configurations of the 2-isoxazoline-4-carboxylate skeleton of cycloadducts **A**, **7**, and **9** derived from the optically pure α,β-unsaturated esters **3**, (4*S*,5*S*)-(−)-**5**, and (4*R*,5*R*)-(+)-**6** were definitely assigned on the basis of the X-ray crystallography of *rac*-**9** and the optical rotations of 2-isoxazoline-4-carboxylates **4** derived from them. Thus, the 2-isoxazoline-4-carboxylate regioisomer *rac*-**9** derived from *rac*-**6** was assigned to be 4*RS*,5*RS*,4'*RS*,5'*SR* relative stereochemistry by X-ray crystallography. Accordingly, the 2-isoxazoline-4-carboxylate (+)-**4**, derived from *N*-methyl-substituted ester (4*R*,5*R*)-(+)-**6** via the optically pure (+)-**9**, was determined to be the 4*S*,5*S* enantiomer; the 2-isoxazoline-4-carboxylate (+)-**4**, produced as the major diastereomer from *N*-phenyl-substituted ester (4*S*,5*S*)-(−)-**5** via **7**, has the 4*S*,5*S* configuration.

Transition State. It is now clear, in the cycloaddition of nitrile oxide **1** with the α,β-unsaturated esters **5** and **6** bearing a C_2-symmetric 2-imidazolidinyl chiral controller, that the different diastereotopic faces were predominantly selected between *N*-phenyl-substituted ester **5** and *N*-methyl-substituted one **6**. The degree of diastereoselectivity also depended upon the nature of *N*-substituents of the chiral controller.

The result that the *si* C(β)-face attack of **1** to the α,β-unsaturated ester moiety of **3** was the major reaction path is explained as follows. Although the *re* C(β)-face of the thermodynamically more stable antiperiplanar conformer **3** (*ap*) is sterically open to the attack by **1**, the electrostatic repulsion working between the negative oxygen atom of **1** and the unshared electron pair at the bridgehead nitrogen of **3** would disfavor this approach (**TS-B**, Fig. 1). Accordingly, the *si* C(β)-face attack to the thermodynamically less stable synperiplanar conformer of **3** became the major approach (**TS-A**). Since the terminal oxygen atom of **1** is not so bulky, the occurrence of competitive attack of the *re* C(β)-face of **3** (*sp*) reducing the diastereoselectivity is not surprising. The partial contribution of the *re* C(β)-face attack in **TS-B** would be also a reason for the poor diastereoselectivity.

Another explanation is possible by application of the Kozikowski's "antiperiplanar effect" rule[6] or the Houk's "inside alkoxy effect" rule.[7] Three substituents are attaching to C-3 of the imidazolidine ring of **3**, a phenyl-substituted nitrogen, a bridgehead nitrogen, and a

hydrogen. The anilino type nitrogen is the bulkiest so that it occupies anti position according to the Houk's rule. The second bulky bridgehead nitrogen is inside and the smallest hydrogen is outside positions (**TS-A'**). Therefore, the nitrile oxide cycloaddition has occurred more favorably at the *si* C(β)-face.

Absolute configurations of the regioisomeric 2-isoxazoline-5-carboxylate cycloadduct **A'** and (+)-**9'** could not be assigned on the basis of spectral data and chemical conversion. In the transition state producing the cycloadduct **A'** nitrile oxide **1** has to access to the α,β-unsaturated ester moiety of **3** with the bulky phenyl substituent directing toward the bulky chiral auxiliary. As a result the only possible attack of **1** may have been at the *si* C(β)-face of **3** (*sp*) conformer, the 2-isoxazoline-5-carboxylate ring of (+)-**4'** derived from the minor regioisomers **A'** and (+)-**9'** being tentatively assigned to be 4*S*,5*S* enantiomer.

As previously reported,[5c] the perhydroimidazole ring of the *N*-phenyl-substituted ester **5** is almost flat in solution and both phenyl planes lie in the same plane as the imidazolidine ring. Since these *N*-phenyl substituents become serious steric obstacles to the approach of **1** in the transition state through which the corresponding 2-isoxazoline-5-carboxylate regioisomer is produced, the reaction of **1** with **5** produced 2-isoxazoline-4-carboxylate **7** as the exclusively regioselective cycloadduct. In **TS-C**, where two identical nitrogen substituents are located at C-2 of the imidazolidine ring of (4*S*,5*S*)-**5**, the *si* C(β)-face attack by **1** seems to be a little more favored than the *re* C(β)-face attack. The 76:24 ratio of observed diastereoselectivity is reasonable.

On the other hand, the *re* C(β)-face attack of **1** to the synperiplanar conformer of *N*-methyl-substituted ester (4*R*,5*R*)-**6** (*sp*) was totally inhibited by the top-lying *N*-methyl substituent so that the *si* C(β)-face attacks of **1** leading to (4*S*,5*S*,4'*R*,5'*R*)-**9** and (4*S*,5*S*,4'*R*,5'*R*)-**9'** became the only observed reaction (**TS-D**). Participation of the thermodynamically more stable antiperiplanar conformer **6** (*ap*) was again disfavored because of the aforementioned electrostatic repulsion (**TS-E**).

Experimental

General. Melting points were recorded on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were taken with JASCO IRA-1 and A-702 spectrometers. ^{1}H and ^{13}C NMR spectra were recorded with Hitachi R-40 (^{1}H NMR: 90 MHz) and GSX-270 (270 MHz for ^{1}H NMR and 67.94 MHz for ^{13}C NMR) instruments. Chemical shifts are reported in parts per million downfield (δ) from internal tetramethylsilane. Mass spectra and high resolution mass spectra (HRMS) were recorded with a JEOL-01SG-2 spectrometer operating at an ionization energy of 70 eV. Elemental analyses were performed with a Hitachi 026 CHN analyzer. Optical rotations were recorded with a Horiba SEPA-200 polarimeter. The X-ray diffraction data were collected with graphite-monochromatized Mo $K\alpha$ radiation (λ=0.71069). Structure analyses were performed with a TEXSAN system.[8] The structure was solved by the MITHRIL[9] direct method and defined by full-matrix least squares. For preparative column chromatography, Wakogel C-200, Wako C-300, and Merck Silica gel 60 were employed. Flash chromatography was performed with an Eyera EF-10 apparatus on a 20×180 mm column packed with 0.04—0.063 mm silica gel 60.

Reaction of 1 with 3 Followed by Acetal Exchange Leading to 4 and 4'. To a solution of Et_3N (0.101 g, 1 mmol) in dry THF (4 ml) were added benzohydroximoyl chloride (0.156 g, 1 mmol) and **3** (0.136 g, 0.5 mmol) in that order. The mixture was stirred for 24 h, poured into saturated aqueous NaCl (100 ml), and extracted with Et_2O (30 ml×3). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue (0.26 g) was dissolved in MeOH (10 ml) containing concentrated H_2SO_4 (1 ml). The mixture was refluxed for 24 h, neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (30 ml×3). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was chromatographed (silica gel) with hexane–EtOAc (4:1 v/v) to give **4** (0.054 g, 38%) and **4'** (0.019 g, 14%). The major product **4** was found to be a 70:30 mixture of 4*S*,5*S* and 4*R*,5*R* enantiomers (HPLC, Daicel, Chiral pack OD, hexane–isopropyl alcohol (9:1 v/v) as an eluent, $[\alpha]_D^{24}$=+65.9° (*c* 0.73, $CHCl_3$)).

Methyl *trans*-5-Dimethoxymethyl-3-phenyl-2-isoxazoline-4-carboxylate (4): Colorless liquid; IR (neat) 2935, 1736, 1432, 1336, 1260, 1192, 1124, 1064, 892, and 756 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.47, 3.49 (each 3H, each s, 2×OMe), 3.70 (3H, s, COOMe), 4.43 (1H, d, $J_{4\text{-}5}$=4.4 Hz, H-4), 4.58 (1H, d, $J_{CH\text{-}5}$=5.5 Hz, 5-CH), 5.01 (1H, dd, $J_{5\text{-}4}$=5.5 and $J_{5\text{-}CH}$=4.4 Hz, H-5), 7.39—7.43, and 7.69—7.76 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=53.00 (C-4), 54.18, 55.55, 56.54 (2×OMe and COOMe), 85.38 (C-5), 103.65 (5-CH), 127.09, 128.25, 128.74, 130.33 (each Ph), 154.38 (C-3), and 169.76 (COOMe); MS *m*/*z* (rel intensity, %) 279 (M^+, 2), 76 (3), 75 (base peak). HRMS Found: *m*/*z* 279.1103. Calcd for $C_{14}H_{17}NO_5$: M, 279.1107.

Methyl *trans*-4-Dimethoxymethyl-3-phenyl-2-isoxazoline-5-carboxylate (4'): Colorless liquid; IR (neat) 3919, 1728, 1427, 1332, 1192, 1108, 1060, 880, 756, and 684 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.32, 3.37 (each 3H, each s, 2×OMe), 3.80 (3H, s, COOMe), 4.29 (1H, t, $J_{4\text{-}5}$=$J_{4\text{-}CH}$=4.4 Hz, H-4), 4.55 (1H, d, $J_{CH\text{-}4}$=4.4 Hz, 4-CH), 5.32 (1H, d, $J_{5\text{-}4}$=4.4 Hz, H-5), and 7.40–7.75 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=52.89 (C-4), 55.62, 55.75, 55.98 (2×OMe, COOMe), 79.75 (C-5), 102.95 (4-CH), 127.44, 128.36, 128.75, 130.36 (each Ph), 156.14 (C-3), and 170.87 (COOMe); MS *m*/*z* (rel intensity, %) 279 (M^+, 6), 160 (4), 76 (3), and 75 (base peak). Found: C, 60.36; H, 6.08; N, 5.11%. Calcd for $C_{14}H_{17}NO_5$: C, 60.19; H, 6.14; N, 5.02%.

Reaction of 1 with *rac*-5 Leading to *rac*-7. Triethylamine (0.14 ml, 1 mmol) was added dropwise to a solution of benzohydroximoyl chloride (0.156 g, 1 mmol) in THF (8 ml) under nitrogen at room temperature. After 5 min, the solution of *rac*-**5** (0.458 g, 1 mmol) in THF (2 ml) was added. The mixture was stirred at room temperature for 16 h, poured into saturated aqueous NH_4Cl, and then extracted with Et_2O (20 ml×3). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue (0.367 g) was chromatographed (silica gel) with hexane–EtOAc (3:1 v/v) to give *rac*-**7** (0.15 g, 52%) and *rac*-**5** (0.09 g, 39%). Compound *rac*-**7** was found to be a 74:26 mixture of (4*RS*,5*RS*,4'*RS*,5'*RS*)-**7** and

(4*RS*,5*RS*,4′*SR*,5′*SR*)-**7** (by ^{1}H NMR).

From a similar reaction of **1** with optically pure (4*S*,5*S*)-**5**, a 76:24 diastereomeric mixture of (4*S*,5*S*,4′*S*,5′*S*)-**7** and (4*R*,5*R*,4′*S*,5′*S*)-**7** was obtained (by ^{1}H NMR).

Methyl *trans*-3-Phenyl-5-(*trans*-1,3,4,5-tetraphenylperhydro-2-imidazolyl)-2-isoxazoline-4-carboxylate (*rac*-**7**, a 74:26 mixture of two diastereomers): Colorless prisms (MeOH); mp 97—101 °C; IR(KBr) 3000, 1732, 1589, 1491, 1252, 984, 872, 744, and 684 cm^{-1}; ^{1}H NMR ($CDCl_3$) (4*RS*,5*RS*,4′*RS*,5′*RS*)-**7**: δ=3.63 (3H, s, COOMe), 4.67 (2H, d, J_{4-5}=$J_{4'-5'}$=8.1 Hz, H-4 and H-4′), 5.06 (1H, d, $J_{5'-4'}$=8.1 Hz, H-5′), 5.52 (1H, dd, J_{5-4}=8.1 and $J_{5-2'}$=3.3 Hz, H-5), 6.16 (1H, d, $J_{2'-5}$=3.3Hz, H-2′), 6.63—7.55 (25H, m, 5×Ph); (4*RS*,5*RS*,4′*SR*,5′*SR*)-**7**: δ=3.53 (3H, s, COOMe), 4.73 (1H, d, $J_{4'-5'}$=8.1 Hz, H-4′), 4.84 (1H, d, J_{4-5}=6.2 Hz, H-4), 5.02 (1H, d, $J_{5'-4}$=8.1 Hz, H-5′), 5.54 (1H, dd, J_{5-4}=6.2 and $J_{5-2'}$=2.7 Hz, H-5), and 6.14 (1H, d, $J_{2'-5}$=2.7 Hz, H-2′). Other signals are overlapping with those of (4*RS*,5*RS*,4′*SR*,5′*SR*)-**7**. ^{13}C NMR ($CDCl_3$) (4*RS*,5*RS*,4′*RS*,5′*RS*)-**7**: δ=52.97 (C-4), 55.71 (COOMe), 70.58 (C-5), 75.10, 80.92 (C-4′ and C-5′), 87.47 (C-2′), 114.90, 119.41, 120.27, 120.85, 126.48, 126.68, 126.85, 127.02, 127.66, 127.75, 127.86, 128.55, 128.88, 129.25, 130.15, 138.74, 139.88, 143.13, 147.89 (each Ph), 154.53 (C-3), and 169.70 (COOMe); (4*RS*,5*RS*,4′*SR*,5′*SR*)-**7**: δ=52.83 (C-4), 69.64 (C-5), 74.44, 80.92 (C-4′ and C-5′), 88.02 (C-2′), 114.77, 119.26, 120.54, 120.74, 130.19, 138.51, 139.43, 142.59, 147.48 (each Ph), 154.28 (C-3), and 169.34 (COOMe). Other signals are overlapping with those of (4*RS*,5*RS*,4′*SR*,5′*SR*)-**7**. MS (20 eV) *m*/*z* (rel intensity, %) 548 (M^+—MeO, 0.2), 377 (4), 376 (30), 375 (base peak), 279 (2), 220 (1), 195 (1), 194 (2), 180 (4), and 103 (1). Found: C, 78.59; H, 5.86; N, 7.10%. Calcd for $C_{38}H_{33}N_3O_3$: C, 78.73; H, 5.74; N, 7.25%.

Reaction of 2 with *rac*-5 Leading to *rac*-8. Triethylamine (0.14 ml, 1 mmol) was added dropwise to a solution of *p*-methoxybenzohydroximoyl chloride (0.186 g, 1 mmol) in THF (4 ml) under nitrogen at 0 °C. After 5 min, the solution of *rac*-**5** (0.23 g, 0.5 mmol) in THF (2 ml) was added. The mixture was stirred at room temperature for 24 h, poured into saturated aqueous NH_4Cl, and then extracted with Et_2O (20 ml×3). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue (0.396 g) was chromatographed (silica gel) with hexane–EtOAc (10:1 v/v) to give *rac*-**8** (0.194 g, 64%). Compound *rac*-**8** was assigned, by analogy with **7**, to be a 70:30 mixture of (4*RS*,5*RS*,4′*RS*,5′*RS*)-**8** and (4*RS*,5*RS*,4′*SR*,5′*SR*)-**8** (by ^{1}H NMR).

Methyl *trans*-3-(*p*-Methoxyphenyl)-5-(*trans*-1,3,4,5-tetraphenylperhydro-2-imidazolyl)-2-isoxazoline-4-carboxylate (*rac*-**8**, a 70:30 mixture of two diastereomers): Colorless prisms (MeOH); mp 92—94 °C; IR (KBr) 2850, 1700, 1568, 1476, 1232, 875, 820, 732, and 680 cm^{-1}, ^{1}H NMR ($CDCl_3$) major diastereomer: δ=3.61 (3H, s, COOMe), 3.76 (3H, s, OMe), 4.63 (2H, d, $J_{4'-5'}$=7.7 Hz, H-4′), 4.66 (1H, d, J_{4-5}=8.4 Hz, H-4), 5.06 (1H, d, $J_{5'-4'}$=7.7 Hz, H-5′), 5.49 (1H, dd, J_{5-4}=8.4 and $J_{5-2'}$=2.7 Hz, H-5), 6.15 (1H, d, $J_{2'-5}$=2.7 Hz, H-2′), and 6.66—7.50 (24H, m, Ar); minor diastereomer: δ=3.51 (3H, s, COOMe), 3.77 (3H, s, OMe), 4.73 (1H, d, $J_{4'-5'}$=7.7 Hz, H-4′), 4.82 (1H, d, J_{4-5}=5.9 Hz, H-4), and 5.01 (1H, d, $J_{5'-4'}$=7.7 Hz, H-5′). Other signals are overlapping with those of the major diastereomer. ^{13}C NMR ($CDCl_3$) major diastereomer: δ=52.94 (C-4), 55.26, 55.97 (OMe and COOMe), 70.54 (C-5), 75.09 and 79.93 (C-4′ and C-5′), 87.20 (C-2′), 113.99, 114.87, 120.31, 120.74, 120.85, 126.71, 127.64, 127.74, 127.89, 128.43, 128.57, 128.74, 128.87, 129.08, 129.23, 138.77, 139.92, 143.19, 147.91 (each Ar), 154.06 (C-3), 161.06 (Ar), and 169.83 (COOMe); minor diastereomer: δ=52.80 (C-4), 69.62 (C-5), 74.44 and 80.95 (C-4′ and C-5′), 87.72 (C-2′), 113.93, 114.76, 119.32, 138.54, 139.48, 142.63, and 147.54 (each Ar), 153.80 (C-3), 161.12 (Ar), and 169.47 (COOMe). Other signals are overlapping with those of the major diastereomer. MS (20 eV) *m*/*z* (rel intensity, %) 607 (M^+—2, 0.2), 376 (32), 375 (base peak), 233 (10), 196 (13), and 180 (25). Found: C, 76.69; H, 5.95; N, 6.76%. Calcd for $C_{39}H_{35}N_3O_4$: C, 76.82; H, 5.79; N, 6.89%.

Reaction of 1 with *rac*-6 Leading to *rac*-9 and *rac*-9′. Triethylamine (0.35 ml, 2.5 mmol) was added dropwise to a solution of benzohydroximoyl chloride (0.389 g, 2.5 mmol) in THF (8 ml) under nitrogen at room temperature. After 5 min, the solution of *rac*-**6** (0.168 g, 0.5 mmol) in THF (2 ml) was added. The mixture was stirred at room temperature for 23 h, poured into saturated aqueous NH_4Cl, and then extracted with Et_2O (20 ml×3). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue (0.455 g) was chromatographed (silica gel) with hexane–EtOAc (20:1 v/v) to give *rac*-**9** (0.066 g, 29%) and *rac*-**9′** (0.023 g, 10%).

From a similar reaction of **1** with optically pure (4*R*,5*R*)-**6**, (4*S*,5*S*,4′*R*,5′*R*)-**9** and (4*S*,5*S*,4′*R*,5′*R*)-**9′** were obtained. Optical rotations of these (4*S*,5*S*,4′*R*,5′*R*)-**9** and (4*S*,5*S*,4′*R*,5′*R*)-**9′** were recorded as $[\alpha]_D^{22}$=+59.8 ° (*c* 2.22, $CHCl_3$) and $[\alpha]_D^{23}$=+104.9 ° (*c* 0.67, $CHCl_3$), respectively.

Methyl *trans*-5-(*trans*-1,3-Dimethyl-4,5-diphenylperhydro-2-imidazolyl)-3-phenyl-2-isoxazoline-4-carboxylate (*rac*-**9**): Colorless prisms (MeOH); mp 139—139.5 °C; IR (KBr) 2729, 1656, 1416, 1228, 1112, 952, 880, and 736 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.30, 2.50 (each 3H, each s, 2×NMe), 3.64 (1H, d, $J_{4'-5'}$=8.1 Hz, H-4′), 3.74 (3H, s, COOMe), 3.80 (1H, d, $J_{5'-4}$=8.1 Hz, H-5′), 4.25 (1H, d, $J_{2'-5}$=4.4 Hz, H-2′), 4.94 (1H, d, J_{4-5}=6.2 Hz, H-4), 5.35 (1H, dd, J_{5-4}=6.2 and $J_{5-2'}$=4.4 Hz, H-5), 6.95—7.31, 7.42—7.47, and 7.80—7.84 (each 10H, 3H, and 2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=33.61, 42.14 (2×NMe), 52.89 (C-4), 55.35 (COOMe), 75.25, 78.54 (C-4′ and C-5′), 84.13 (C-2′), 87.76 (C-5), 126.98, 127.30, 127.84, 128.03, 128.32, 128.45, 128.69, 128.81, 130.28, 138.38, 139.48 (each Ph), 154.55 (C-3), and 170.45 (COOMe); MS (20 eV) *m*/*z* (rel intensity, %) 424 (M^+—MeO, 0.4), 253 (2), 252 (20), 251 (base peak), 180 (2), and 103 (2). Found: C, 74.16; H, 6.44; N, 9.24%. Calcd for $C_{28}H_{29}N_3O_3$: C, 73.82; H, 6.42; N, 9.22%.

Methyl *trans*-4-(*trans*-1,3-Dimethyl-4,5-diphenylperhydro-2-imidazolyl)-3-phenyl-2-isoxazoline-5-carboxylate (*rac*-9′): Colorless liquid; IR (neat) 3700, 2800, 2340, 1720, 1445, 1200, 1020, 875, 760, and 670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.18, 2.37 (each 3H, each s, 2×NMe), 3.63 (1H, d, $J_{4'-5'}$=8.1 Hz, H-4′), 3.82 (3H, s, COOMe), 3.95 (1H, d, $J_{5'-4'}$=8.1 Hz, H-5′), 4.46 (1H, d, $J_{5'-4'}$=1.5 Hz, H-2′), 4.56 (1H, dd, J_{4-5}=4.0 and $J_{4-2'}$=1.5 Hz, H-4), 5.73 (1H, d, J_{5-4}=4.0 Hz, H-5), 7.10—7.32, 7.43—7.49, and 7.77—7.82 (each, 10H, 3H, and 2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=33.55, 40.17 (2×NMe), 52.73 (C-4), 55.84 (COOMe), 75.20, 78.28 (C-4′ and C-5′), 80.67 (C-2′), 82.32 (C-5), 127.15, 127.35, 127.45, 127.84, 128.35, 128.51, 129.08, 130.42, 139.26, 139.32 (each Ph), 157.23 (C-3), and 171.57 (COOMe); Found: C, 73.98; H, 6.39; N, 9.20%. Calcd for $C_{28}H_{29}N_3O_3$: C, 73.82; H, 6.42; N, 9.22%.

X-Ray Structure Analysis of *rac*-9. A single crystal grown from MeOH had space group $P2_1/n$, a=9.13 (5), b=28.39 (1), and c=10.08 (1) Å, β=107.9 (2) °, V=2488 (1) Å^3, Z=4. The

final R factor was 0.051 for 1421 observed reflections.[10]

Removal of the Chiral Auxiliary from 7, 9, and 9′ Leading to 4 and 4′. A) **From 7:** Concentrated H_2SO_4 (0.5 ml) was added to a solution of (4*S*,5*S*,4′*S*,5′*S*)-**7** (a 76:24 diastereomeric mixture, 0.048 g, 0.083 mmol) in MeOH (3 ml) and $CHCl_3$ (2 ml). After heating under reflux for 20 h, the mixture was neutralized with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (20 ml×3). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue (0.041 g) was chromatographed (silica gel) with hexane–EtOAc (3:1 v/v) to give a mixture of (4*S*,5*S*)-(+)-**4** and (4*R*,5*R*)-(−)-**4** (0.023 g, 100%, a 75:25 mixture of enantiomers by HPLC using Daicel, Chiral pack OD). $[\alpha]_D^{23}$=+82.8° (*c* 0.61, $CHCl_3$).

B) **From 9:** Concentrated H_2SO_4 (0.5 ml) was added to a solution of (4*S*,5*S*,4′*R*,5′*R*)-**9** (0.089 g, 0.195 mmol) in MeOH (5 ml) and $CHCl_3$ (3 ml). After heating under reflux for 19 h, the mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with Et_2O (40 ml×3). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue (0.094 g) was chromatographed (silica gel) with hexane–EtOAc (3:1 v/v) to give (4*S*,5*S*)-(+)-**4** (0.04 g, 73%, a single enantiomer by HPLC using Daicel, Chiral pack OD, $[\alpha]_D^{22}$=+166.8° (*c* 1.90, $CHCl_3$).

C) **From 9′**: Concentrated H_2SO_4 (0.5 ml) was added to a solution of (4*S*,5*S*,4′*R*,5′*R*)-**9′** (0.091 g, 0.2 mmol) in MeOH (5 ml) and $CHCl_3$ (3 ml). After heating under reflux for 10 h, the mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with Et_2O (30 ml×3). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue (0.093 g) was chromatographed (silica gel) with hexane–EtOAc (5:1 v/v) to give (4*S*,5*S*)-(+)-**4′** (0.054 g, 96%, a single enantiomer by HPLC using Daicel, Chiral pack OD). $[\alpha]_D^{22}$=+133.5° (*c* 0.37, $CHCl_3$).

Conversion of *rac*-8 to *rac*-10. Concentrated H_2SO_4 (0.2 ml) was added to a solution of *rac*-**8** (0.051 g, 0.084 mmol) in MeOH (3 ml) and $CHCl_3$ (2 ml). After heating under reflux for 4 h, the mixture was neutralized with saturated aqueous $NaHCO_3$, and extracted with Et_2O (40 ml×2). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue (0.056 g) was chromatographed (silica gel) with hexane–EtOAc (3:1 v/v) to give *rac*-**10** (0.016 g, 64%). From the subsequent fractions *rac*-**8** (0.018 g, 35%) and *dl*-1,2-dianilino-1,2-diphenylethane (0.02 g, 65%) were obtained.

Methyl *trans*-5-Dimethoxymethyl-3-(*p*-methoxyphenyl)-2-isoxazoline-4-carboxylate (*rac*-**10**): Colorless needles (MeOH); mp 97.5—98 °C; ^{1}H NMR ($CDCl_3$) δ=3.46, 3.49 (each 3H, each s, 2×OMe), 3.71 (3H, s, COOMe), 3.83 (3H, s, *p*-OMe), 4.41 (1H, d, $J_{CH\text{-}5}$=4.8 Hz, 5-CH), 4.54 (1H, d, $J_{4\text{-}5}$= 5.1 Hz, H-4), 4.98 (1H, dd, $J_{5\text{-}4}$=5.1 and $J_{5\text{-}CH}$=4.8 Hz, H-5), 6.81, and 7.68 (each 2H, each d, Ar); ^{13}C NMR ($CDCl_3$) δ=52.99 (4-C), 54.47, 55.35, 55.53, 56.46 (2×OMe, *p*-OMe, and COOMe), 85.08 (C-5), 103.67 (5-CH), 114.16, 120.69, 128.68, 153.90 (each Ar), 161.23 (C-3), and 169.86 (COOMe); MS *m*/*z* (rel intensity, %) 309 (M^+, 8) and 75 (base peak). Found: C, 58.50; H, 6.29; N, 4.54%. Calcd for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19; N, 4.53%.

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