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Microwave-induced 1,3-dipolar intramolecular cycloadditions of *N*-substituted oximes, nitrones, and azomethine ylides for the chiral synthesis of functionalized nitrogen heterocycles

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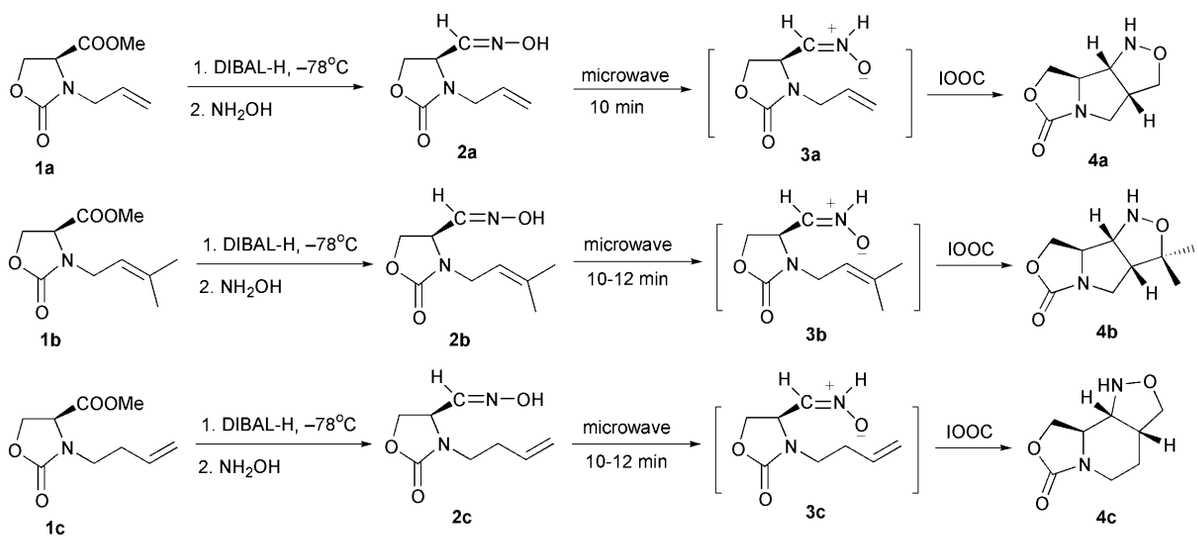
Highly stereoselective intramolecular cycloadditions of unsaturated *N*-substituted oximes, nitrones, and azomethine ylides on the surface of silica gel without a solvent, which have been conducted under microwave irradiation, to produce functionalized tricyclic isoxazolidines fused with a pyrroline or piperidine ring in good yields, are presented.

Introduction

The nitrone cycloaddition reaction with olefins, particularly an intramolecular nitrone cycloaddition reaction (INC), has experienced impressive growth, and finds broad applications in organic synthesis due to the production of their product isoxazolidines, which have a labile N–O bond which is easily converted into various functionalized groups. These sequences have been utilized as a key step for the synthesis of highly functionalized pyrrolidines and piperidines which have been applied to the synthesis of biologically active natural products.[1] However, it is known that a disadvantageous factor of the reaction is that the cycloaddition only takes place at high temperature and after long reaction times.[2] In the past decade, microwave irradiation has been widely used in organic synthesis.[3] However, so far, only a limited number of microwave-assisted 1,3-dipolar intermolecular cycloaddition reactions of nitrilimines and nitrile oxides giving cycloadducts in moderate yields have been reported.[4] Recently, we have investigated the possibility of intramolecular nitrone cycloaddition reaction under microwave irradiation. In this paper, we report our research efforts on the intramolecular cycloaddition reactions of oximes, nitrones, and azomethine ylides derived from L-serine methyl ester on the surface of silica gel without a solvent under microwave irradiation, which result in the chiral preparation of functionalized tricyclic isoxazolidines fused with a pyrrolidine or piperidine ring.

Results and discussion

The five- and six-membered nitrogen heterocycles belong to the largest class of heterocyclic compounds with diverse biological activities.[5] Naturally an intensive effort has been directed towards the development of efficient strategies for their synthesis.[6] The synthesis of substituted chiral pyrrolidines as potential glycosidase inhibitors *via* an intramolecular NH–nitrone cycloaddition reaction (also named an intramolecular oxime–olefin cycloaddition, IOOC) starting from L-serine has recently been reported by Hassner and his colleagues.[7] It has been found that an oxime **2a** undergoes the IOOC reaction, *via* an intermediate **3a**, which requires heating at 170 °C in toluene in a sealed tube for 16 h to form an isoxazolidine **4a**. Very recently, it has been observed that the oxime **2a**, mixed with silica gel and irradiated by microwaves for 15 min, affords the desired isoxazolidine **4a** in 82% yield through the IOOC reaction (Scheme 1). The product **4a** was determined to be consistent with the previously reported compound.[7] Similarly,



Scheme 1

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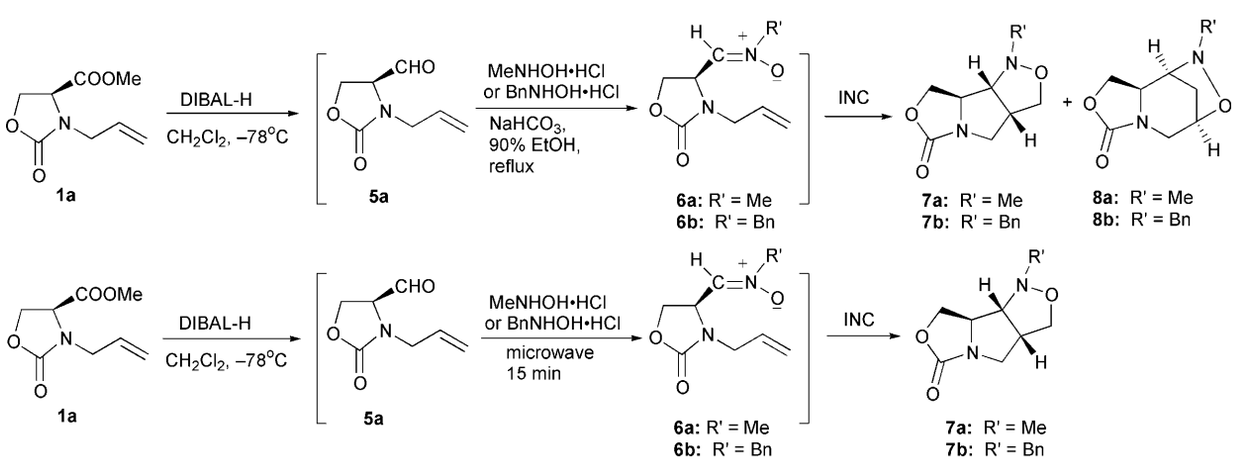
compounds **2b** and **2c**, prepared from L-serine methyl ester according to the previously reported method,[7] were subsequently mixed with silica gel and irradiated by microwaves to produce the intermediates **3b** and **3c**, which *in situ* underwent the IOOC reaction to give the isoxazolidines **4b** (80% yield) and **4c** (77% yield) respectively. The structure and stereochemistry of **4b** and **4c** were unambiguously established by extensive NMR studies involving 2D-NMR experiments. The ^{1}H NMR spectrum of **4b** showed that a coupling J_{HH} 8.5 Hz between H-3a and H-8b accompanied by the smaller coupling J_{HH} 5.1 Hz between H-8a and H-8b suggested the *trans* stereochemistry of H-8a and H-8b, and *cis* stereochemistry of H-8b and H-3a. This tentative assignment was further confirmed by a 4% NOE enhancement between H-3a and H-8b and a 3% NOE enhancement between H-8 and H-8b (Fig. 2). On the other hand, the ^{1}H NMR spectrum of **4c** displayed a coupling J_{HH} 8.8 Hz of H_{ax}-9a to H_{ax}-9b along with a small coupling J_{HH} 4.8 Hz of H_{eq}-3a to H_{ax}-9b, and their NOE data exhibited by arrows in Fig. 2, all indicated that H-3a and H-9b possess a *cis* stereochemistry, and H-9a and H-9b possess a *trans* stereochemistry.

The interesting findings for the IOOC reaction induced by microwave irradiation have prompted us to widely investigate the intramolecular cycloaddition reaction of chiral *N*-substituted nitrones which is induced by microwave irradiation. Usually, the intramolecular nitrone cycloaddition reaction, like the IOOC reaction, can be carried out in a solvent under reflux to give rise to the cycloadducts.[8] For comparison of the intramolecular cycloaddition reaction of *N*-substituted nitrones derived from L-serine methyl ester, which is induced and occurred under different reaction conditions, the process which involves both oxidation and INC reaction of an intermediate **5a** under reflux in alcohol was studied first (Scheme 2).

Reduction of **1a** with an excess of DIBAL-H gave the intermediate **5a**, which on treatment with *N*-methylhydroxylamine generated the corresponding nitrone **6a**, which *in situ* underwent the INC reaction to furnish an isoxazolidine **7a** in 72% yield along with a bridged isoxazolidine **8a** in 10% yield. The NMR data of **7a** displayed high structural correlations to the previously described compound **1a** except that a methyl group was located at the N-atom of the isoxazolidine ring. On the other hand, the NMR data of **8a** showed only one methylene carbon resonance, at δ_C 66.37 (t), and a high-field methylene carbon resonance, at δ_C 26.28 (t), together with two proton resonances, at δ_H 2.32 (ddd, *J* 12.6, 6 and 4.8 Hz) and δ_H 1.88 (d, *J* 12.6 Hz), these indicated the presence of a piperidine ring. The stereochemistry of **8a** was established by characteristic ^{1}H NMR signals for a six-membered ring, enabling a credible stereochemical assignment for a piperidine ring to be made. The same coupling J_{HH} 4.8 Hz observed for both H-1 to H_{ax}-2 and H-1 to H_{ax}-11, and the coupling J_{HH} 6.0 Hz of H-8 to H_{ax}-11 plus the coupling J_{HH} 4.8 Hz of H-8 to H_{ax}-7, indicated that both H-1 and H-8 possess an equatorial orientation in the piperidine ring, therefore they have a *cis* relationship, which was confirmed by 2D-NOESY of **8a** (Fig. 2). The nitrone **6b**, which was prepared from **5a** by reaction with *N*-benzylhydroxylamine, underwent an *in situ* INC reaction to afford an isoxazolidine **7b** in 64% yield and a bridged isoxazolidine **8b** in 13% yield, which were determined by NMR experiments and 2D-NOESY studies. Formation of the bridged isoxazolidines **8a**,**b** may be rationalized to arise from INC reactions *via* the bridged-ring transition state (*Z*-nitrone) whereas the isoxazolidines **7a**,**b** from the INC reactions arose *via* the fused-ring transition state (*E*-nitrone), respectively. Since *Z*- and *E*-nitrone transition states are known to interconvert under our reaction conditions,[9] we may assume tentatively that the diastereoisomeric ratio depends only on the respective transition-state energies (Fig. 1). The observation of the pyrrolidine derivatives **7**, which were formed highly selectively (≈7 : 1), led to a conclusion that the *E*-nitrone transition state was energetically more favourable.

However, when the intermediate **5a** and *N*-methylhydroxylamine were mixed with silica gel and irradiated by microwaves for 15 min, it provided only the pyrrolidine derivative **7a**, in 82% yield, as the cycloadduct. Similarly, a mixture of **5a**, *N*-benzylhydroxylamine and silica gel was irradiated by microwaves to give only the pyrrolidine derivative **7b**, in 79% yield. These results indicated that the bridged-ring transition states (*Z*-nitrone) for the formation of bridged isoxazolidines were not likely to form under these reaction conditions, probably due to the higher temperature. In order to confirm this hypothesis, a mixture of the intermediate **5a** and *N*-methylhydroxylamine in alcohol was placed in a sealed tube and heated at 120 °C for 6 h. Unfortunately, both products **7a** and **8a**, in an 8 : 1 ratio, were obtained in this reaction. Therefore, it may be proposed



Scheme 2

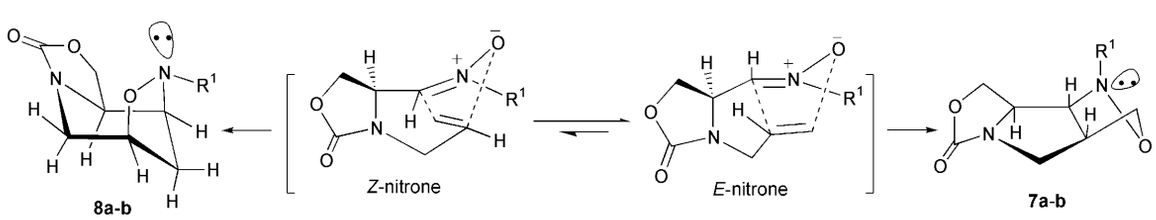


Fig. 1 The transition states for the INC leading to **7** and **8**.

that the selectivity in the microwave-induced reactions results from a faster transformation that leads to the kinetically controlled product.

It is known that azomethine ylides, which can be regarded as nitrones in the INC reaction, are used as the dipoles in the 1,3-dipolar azomethine ylide cycloaddition reactions leading to cycloadducts in high stereoselectivity.[10] For further investigation into the possibility of 1,3-dipolar azomethine ylide cycloaddition reactions irradiated by microwaves, the cycloadditions of two *N*-substituted azomethine ylides **9a**,**b** derived from **1a** were studied (Scheme 3). Non-stabilized azomethine ylides can be generated by direct treatment of aldehydes with *N*-substituted α-amino esters and subsequently trapped smoothly by olefin dipolarophiles. A mixture of the aldehyde **5a** and *N*-methylglycine ethyl ester on the surface of silica gel therefore was irradiated under microwaves for 15 min, generating an azomethine ylide **9a**, which then *in situ* smoothly underwent intramolecular cycloaddition to afford the corresponding cycloadduct **10a** in 79% yield. Similarly, **5a** and *N*-benzylglycine ethyl ester were mixed on the surface of silica gel, followed by irradiation under microwaves for 15 min, leading to ylide **9b**, which underwent intramolecular cycloaddition to furnish the cycloadduct **10b** in 81% yield. The structure and stereochemistry of **10a**,**b** were established by extensive NMR and NOE studies. The most important proof of stereochemistry by NOE is indicated with arrows in Fig. 2.

In conclusion, microwave irradiation effected highly stereoselective 1,3-dipolar intramolecular cycloaddition reactions of *N*-substituted oximes, nitrones, and azomethine ylides on the surface of silica gel without a solvent in a short time leading to the cycloadducts in good yields. Accordingly, we believe that this method will be potentially useful for the chiral synthesis of functionalized nitrogen heterocycles using suitable starting materials.

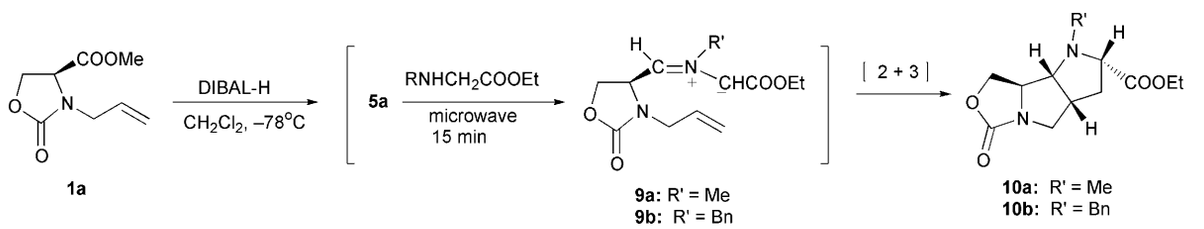
Experimental

^{1}H NMR, ^{13}C NMR, NOE, COSY, NOESY and HMQC spectra were recorded on a Varian Unity INOVA 500 (500 MHz) spectrometer for samples in $CDCl_3$ using $SiMe_4$ (TMS) as internal standard. Optical rotations were recorded on a Horiba SEPA-300 polarimeter. $[a]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. MS and HRMS were measured on a JEOL JMS-700 spectrometer using EI and FAB modes. Diethyl ether was refluxed and distilled from sodium. Dichloromethane was refluxed and distilled from CaH_2 under nitrogen. All commercially available reagents were used without further purification. Chromatography was carried out on Merck silica gel 60 (230–400 mesh). Mps were measured on a micro-melting point apparatus (Yanagimoto) and are uncorrected. All microwave-irradiated reactions were performed in a domestic microwave oven (Koizumi, power source 100 V, 50 Hz; microwave frequency: 2450 MHz) at 750 W in the temperature range 110–120 °C for a certain period of time (specified for each reaction).

General procedure for reduction and oximation of esters 1a–c to aldoximes 2a–c

To a solution of **1a** (1.85 g, 10 mmol) in CH_2Cl_2 (30 ml) cooled to −78 °C under nitrogen was added dropwise DIBAL-H (1.0 M in hexane; 16 ml). After stirring of the mixture at −78 °C for 2 h, methanol (4 ml) was added and then the reaction mixture was partitioned between EtOAc (70 ml) and saturated aq. potassium sodium tartrate (30 ml), followed by addition of $NH_2OH{\cdot}HCl$ (2.09 g, 30 mmol) and NaOH (1.4 g, 35 mmol). The resulting mixture was vigorously stirred at room temperature until all the solids dissolved. The organic layer was separated and the aqueous phase was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to give a residue, which was chromatographed (EtOAc–hexane 4:1 v/v) to give **2a** (1.04 g, 61%) as a white solid, mp 110–112 °C; $[a]_D^{22}$ + 29.3 (*c* 0.05, $CHCl_3$); the major (*E*-form) isomer in mixture: ^{1}H NMR δ 7.86 (br s, 1H), 7.35 (d, *J* 7.2 Hz, 1H), 5.76 (m, 1H), 5.26 (m, 1H), 5.24 (m, 1H), 4.52 (dd, 1H, *J* 9, 8.5 Hz), 4.45 (ddd, *J* 9, 7.2, 5 Hz, 1H), 4.20 (dd, 1H, *J* 8.5, 5 Hz), 4.10 (m, 1H), 3.64 (m, 1H). The minor (*Z*-form) isomer in mixture: ^{1}H NMR δ 8.10 (br s, 1H), 6.91 (d, 1H, *J* 5.5 Hz), 5.79 (m, 1H), 5.27 (m, 2H), 5.01 (ddd, *J* 9, 6, 5.5 Hz, 1H), 4.57 (t, 1H, *J* 9 Hz), 4.14 (dd, 1H, *J* 9, 6 Hz), 4.12 (m, 1H), 3.68 (m, 1H).

2b. Obtained from **1b** in 57% yield as a *white solid* when chromatographed (EtOAc–hexane 4:1 v/v), mp 76–78 °C; $[a]_D^{22}$ +26.1 (*c* 0.02, $CHCl_3$); the major (*E*-form) isomer in mixture: ^{1}H NMR δ 7.84 (br s, 1H), 7.32 (d, 1H, *J* 7.0 Hz), 5.14 (m, 1H), 4.53 (dd, 1H, *J* 9.0, 8.8 Hz), 4.45 (ddd, 1H, *J* 9.0, 7.0, 5.0 Hz), 4.21 (dd, 1H, *J* 8.8, 5.0 Hz), 4.12 (dd, 1H, *J* 15.0, 6.0 Hz), 3.82 (dd, 1H, *J* 15.0, 8.0 Hz), 1.73 (s, 3H), 1.64 (s, 3H); ^{13}C NMR δ 157.48 (s, C=O), 147.60 (d), 139.01 (s), 117.30 (d), 65.40 (t), 54.71 (d), 40.84 (t), 25.70 (q), 17.63 (q). The minor (*Z*-form) isomer in mixture: ^{1}H NMR δ 8.09 (br s, 1H), 6.94 (d, *J* 5.5 Hz, 1H), 5.16 (m, 1H), 4.57 (t, 1H, *J* 9.0 Hz), 4.98 (ddd, 1H, *J* 9.0, 6.0, 5.5 Hz), 4.17 (dd, *J* 9.0, 6.0 Hz, 1H), 4.12 (dd, 1H, *J* 15.0, 6.0 Hz), 3.83 (dd, 1H, *J* 15.0, 8.0 Hz), 1.75 (s, 3H), 1.68 (s, 3H); ^{13}C NMR δ 157.69 (s, C=O), 148.50 (d), 139.14 (s), 117.36 (d), 64.81 (t), 51.00 (d), 42.36 (t), 25.63 (q), 18.25 (q);



Scheme 3

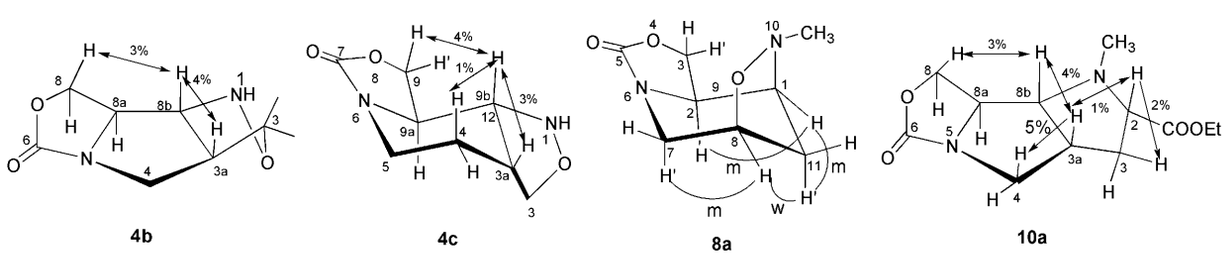


Fig. 2 The key NOE (%) enhancements of **4b**, **4c** and **10a** and NOESY interaction of **8a** (m: medium; w: weak).

HRMS-EI Calc. for $C_9H_{14}N_2O_3$ (*M*), 198.1003. Found: *M*, 198.1006.

2c. Obtained from **1c** in 56% yield as a *white solid* when chromatographed (EtOAc–hexane 4:1 v/v), mp 89–92 °C; $[\alpha]_D^{22}$ +23.4 (*c* 0.1, $CHCl_3$); the major (*E*-form) isomer in mixture: ^{1}H NMR δ 7.83 (br s, 1H), 7.36 (d, 1H, *J* 7.0 Hz), 5.67 (m, 1H), 4.99 (m, 1H), 4.97 (m, 1H), 4.54 (dd, 1H, *J* 9.0, 8.5 Hz), 4.47 (ddd, 1H, *J* 8.5, 7.0, 6.0 Hz), 4.23 (dd, 1H, *J* 9.0, 6.0 Hz), 3.39 (t, 2H, *J* 7.4 Hz), 2.21 (m, 1H), 2.19 (m, 1H); ^{13}C NMR δ 158.20 (s, C=O), 147.20 (d), 134.39 (d), 117.00 (t), 65.32 (t), 54.90 (d), 46.75 (t), 34.29 (t). The minor (*Z*-form) isomer in mixture: ^{1}H NMR δ 8.15 (br s, 1H), 6.90 (d, 1H, *J* 5.6 Hz), 5.64 (m, 1H), 5.07 (ddd, 1H, *J* 9.0, 6.0, 5.6 Hz), 4.97 (m, 2H), 4.61 (dd, 1H, *J* 9.0, 8.8 Hz), 4.15 (dd, 1H, *J* 9.0, 6.0 Hz), 3.37 (m, 2H), 2.24 (m, 1H), 2.18 (m, 1H); ^{13}C NMR δ 158.62 (s, C=O), 147.83 (d), 134.52 (d), 117.65 (t), 65.80 (t), 51.00 (d), 46.23 (t), 33.51 (t); HRMS-EI Calc. for $C_8H_{12}N_2O_3$ (*M*), 184.0847. Found: M^+ 184.0852.

General procedure for IOOC leading to isoxazolidines 4a–c

A mixture of **2a** (0.85 g, 50 mmol) and silica gel (60 PF_{254}; 3 g) was placed on a Pyrex plate with a cover. The Pyrex plate containing the reaction mixture was put in a microwave oven and irradiated for 12 min as required to complete the reaction. The mixture was eluted with EtOAc. After removal of EtOAc, the residue was chromatographed (EtOAc–EtOH 4:1 v/v) to give **4a** (0.7 g, 82%) as a white solid which was identified as being consistent with the previously reported compound.[7] Mp 111–113 °C; $[\alpha]_D^{23}$ −69.7 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 5.22 (s, 1H), 4.58 (dd, 1H, *J* 9.5, 8.0 Hz), 4.34 (dd, *J* 9.5, 3.0 Hz, 1H), 4.17 (dd, 1H, *J* 12.0, 9.0 Hz), 4.00 (dd, 1H, *J* 9.5, 1.2 Hz), 3.96 (dd, *J* 9.0, 6.0 Hz, 1H), 3.76 (ddd, 1H, *J* 8.0, 6.0, 3.0 Hz), 3.51 (dd, 1H, *J* 9.5, 6.5 Hz), 3.32 (ddddd, *J* 9.0, 9.0, 7.0, 6.5, 1.2 Hz, 1H), 2.94 (dd, 1H, *J* 12.0, 7.0 Hz); ^{13}C NMR δ 160.74 (s, C=O), 76.76 (t), 71.64 (d), 67.46 (t), 63.61 (d), 51.65 (t), 49.43 (d).

4b. Obtained from **2b** in 80% yield as a *white solid* following the general procedure when chromatographed (EtOAc–EtOH 4:1 v/v), mp 97–99 °C; $[\alpha]_D^{23}$ −63.2 (*c* 1.3, $CHCl_3$); ^{1}H NMR δ 5.19 (s, 1H), 4.53 (t, 1H, *J* 8.8 Hz), 4.27 (dd, 1H, *J* 8.8, 3.7 Hz), 3.94 (ddd, 1H, *J* 8.8, 5.1, 3.7 Hz), 3.79 (dd, 1H, *J* 12.1, 8.5 Hz), 3.36 (dd, 1H, *J* 8.8, 5.1 Hz), 3.26 (dd, 1H, *J* 12.1, 7.0 Hz), 3.05 (td, 1H, *J* 7.0, 8.5 Hz), 1.34 (s, 3H), 1.28 (s, 3H); ^{13}C NMR δ 161.14 (s, C=O), 81.08 (s), 73.50 (d), 67.25 (t), 65.27 (d), 54.59 (t), 50.11 (d), 29.07 (q), 24.17 (q); HRMS-EI Calc. for $C_9H_{14}N_2O_3$ (*M*), 198.1003. Found: M^+, 198.0998. Calc. for $C_9H_{14}N_2O_3$: C, 54.52; H, 7.12; N, 14.14. Found: C, 54.762; H, 7.34; N, 14.17%.

4c. Obtained from **2c** in 77% yield as a *white solid* following the general procedure when chromatographed (EtOAc–EtOH 4:1 v/v), mp 75–76 °C; $[\alpha]_D^{23}$ −31.3 (*c* 0.7, $CHCl_3$); ^{1}H NMR δ 5.20 (s, 1H), 4.57 (dd, 1H, *J* 9.0, 8.0 Hz), 4.29 (dd, 1H, *J* 9.0, 7.1 Hz), 4.05 (dd, 1H, *J* 9.5, 1.5 Hz), 3.89 (ddd, 1H, *J* 8.8, 8.0, 7.1 Hz), 3.82 (dd, 1H, *J* 8.8, 4.8 Hz), 3.75 (ddd, 1H, *J* 13.6, 11.5, 4.8 Hz), 3.57 (dd, 1H, *J* 9.5, 7.0 Hz), 3.20 (ddd, 1H, *J* 13.6, 4.8, 4.2 Hz), 3.11 (ddddd, *J* 7.0, 4.8, 4.8, 4.2, 1.5 Hz, 1H), 2.08 (m, 1H), 1.74 (m, 1H); ^{13}C NMR δ 161.31 (s, C=O), 74.56 (t), 72.97 (d), 66.52 (t), 62.74 (d), 48.46 (d), 40.18 (t), 31.02 (t); HRMS-EI Calc. for $C_8H_{12}N_2O_3$ (*M*), 184.0847. Found: M^+, 184.0848.

General procedure for reduction of 1a and INC leading to isoxazolidines 7a,b and 8a,b

Method A. To a solution of **1a** (185 mg, 1 mmol) in dry CH_2Cl_2 (7 ml) at −78 °C under nitrogen was added dropwise DIBAL-H (1.0 M in hexane; 1.6 ml). After stirring of the mixture for 2 h at −78 °C, MeOH (0.5 ml) was added. The reaction mixture was warmed to room temperature and then partitioned between EtOAc (10 ml) and saturated aq. potassium sodium tartrate (5 ml). Vigorous stirring was continued until all the solids dissolved. The organic layer was separated, and dried over $MgSO_4$. Evaporation of EtOAc under reduced pressure gave a residue; this, and *N*-methylhydroxylamine hydrochloride (323 mg, 3 mmol), were dissolved in 90% aq. EtOH (8 ml). $NaHCO_3$ (378 mg, 4.5 mmol) was added and the resulting mixture was heated under reflux for 6 h. Removal of EtOH gave a residue, which was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by chromatography (EtOAc–EtOH 8:1 v/v) to give products **7a** (129 mg, 70%) and **8a** (18 mg, 10%) as white solids. **7a**: mp 113–114 °C; $[\alpha]_D^{22}$ −72.5 (*c* 0.07, $CHCl_3$); ^{1}H NMR δ 4.56 (dd, *J* 9.5, 8 Hz, 1H), 4.33 (dd, 1H, *J* 9.5, 2.5 Hz), 4.18 (dd, *J* 12.0, 9.0 Hz, 1H), 4.16 (dd, 1H, *J* 9.5, 6.5 Hz), 3.78 (ddd, 1H, *J* 8.0, 6.5, 2.5 Hz), 3.74 (dd, 1H, *J* 9.5, 2.0 Hz), 3.51 (dd, 1H, *J* 9.0, 6.5 Hz), 3.43 (ddddd, 1H, *J* 9.0, 9.0, 6.5, 6.0, 2.0 Hz), 3.03 (dd, *J* 12.0, 6.0 Hz, 1H), 2.65 (s, 3H); ^{13}C NMR δ 160.69 (C=O), 78.45 (d), 71.11 (t), 67.27 (t), 60.87 (d), 51.96 (t), 47.93 (d), 44.82 (q); MS-EI (*m*/*z*, %) 184 (M^+, 20), 140 (68), 98 (13), 85 (100), 84 (87); HRMS-EI Calc. for $C_8H_{12}N_2O_3$ (*M*), 184.0847. Found: M^+, 184.0849. Calc. for $C_8H_{12}N_2O_3$: C, 52.15; H, 6.57; N, 15.21. Found: C, 52.34; H, 6.72; N, 15.17%). **8a**: mp 81–83 °C; $[\alpha]_D^{22}$ +37.6 (*c* 0.05, $CHCl_3$); ^{1}H NMR δ 4.65 (ddd, 1H, *J* 6.0, 4.8, 4.2 Hz), 4.58 (t, 1H, *J* 9.0 Hz), 4.16 (dd, 1H, *J* 9.0, 7.8 Hz), 3.99 (ddd, 1H, *J* 9.0, 7.8, 4.8 Hz), 3.73 (dd, 1H, *J* 13.8, 4.8 Hz), 3.22 (dd, 1H, *J* 13.8, 4.2 Hz), 3.18 (t, *J* 4.8 Hz, 1H), 2.65 (s, 3H), 2.32 (ddd, 1H, *J* 12.6, 6.0, 4.8 Hz), 1.88 (d, 1H, *J* 12.6 Hz); ^{13}C NMR δ 158.88 (C=O), 73.46 (d), 66.54 (d), 66.37 (t), 57.83 (d), 49.96 (t), 47.38 (q), 26.28 (t); MS-EI (*m*/*z*, %) 184 (M^+, 34), 169 (10), 149 (32), 140 (31), 128 (52), 94 (95), 84 (100); HRMS-EI Calc. for $C_8H_{12}N_2O_3$ (*M*); 184.0847. Found: M^+, 184.0852.

7b. 7b (166 mg, 64%) and **8b** (34 mg, 13%) were obtained as white solids from **3a** and *N*-benzylhydroxylamine hydrochloride following method **A**. Chromatography (EtOAc–hexane 2:1 v/v) gave **7b**: mp 145–146 °C; $[\alpha]_D^{22}$ −69.1 (*c* 0.1, $CHCl_3$); ^{1}H NMR δ 7.29–7.34 (m, 5H), 4.59 (dd, *J* 9.2, 8.0 Hz, 1H), 4.35 (d, 1H, *J* 11.5 Hz), 4.36 (dd, 1H, *J* 9.2, 2.5 Hz), 4.21 (dd, 1H, *J* 12.0, 9.0 Hz), 4.15 (dd, 1H, *J* 9.5, 7.0 Hz), 3.73 (d, 1H, *J* 11.5 Hz), 3.79 (ddd, 1H, *J* 8.0, 6.5, 2.5 Hz), 3.75 (dd, *J* 9.5, 2.0 Hz, 1H), 3.54 (dd, 1H, *J* 9.0, 6.5 Hz), 3.44 (ddddd, 1H, *J* 9.0, 9.0, 7.0, 6.0, 2.0 Hz), 3.07 (dd, 1H, *J* 12.0, 6.0 Hz); ^{13}C NMR δ 160.42 (C=O), 135.48 (s), 129.25 (d), 128.75 (d), 128.17 (d), 77.54 (d), 71.01 (t), 66.35 (t), 62.54 (t), 61.87 (d), 49.96 (t), 47.91 (d); MS-EI (*m*/*z*, %) 260 (M^+, 24), 140 (56), 91 (21), 85 (100), 84 (83); HRMS-EI Calc. for $C_{14}H_{16}N_2O_3$ (*M*), 260.1160. Found: M^+, 260.1164. Calc. for $C_{14}H_{16}N_2O_3$: C, 64.59; H, 6.20; N, 10.77. Found: C, 64.47; H, 6.09; N, 10.72%. **8b**: mp 105–107 °C; $[\alpha]_D^{22}$ +34.5 (*c* 0.04, $CHCl_3$); ^{1}H NMR δ 7.30–7.33 (m, 5H), 4.51 (ddd, *J* 6.0, 5.0, 4.2 Hz, 1H), 4.38 (t, 1H, *J* 9.0 Hz), 4.32 (d, 1H, *J* 12.0 Hz), 4.02 (dd, 1H, *J* 9.0, 7.5 Hz), 3.84 (ddd, 1H, *J* 9.0, 7.5, 4.8 Hz), 3.75 (d, 1H, *J* 12.0 Hz), 3.64 (dd, 1H, *J* 13.6, 5.0 Hz), 3.16 (dd, *J* 13.6, 4.2 Hz, 1H), 3.11 (dd, 1H, *J* 5.0, 4.8 Hz), 2,25 (ddd, 1H, *J* 12.6, 6.0, 5.0 Hz), 1.86 (d, *J* 12.6 Hz, 1H); ^{13}C NMR δ 159.12 (C=O), 135.23 (s), 129.21 (d), 128.87 (d), 128.31 (d), 72.98 (d), 66.46 (d), 66.18 (t), 62.47 (t), 58.03 (d), 50.06 (t), 27.12 (t); MS-EI (*m*/*z*, %) 260 (M^+, 30), 204 (52), 169 (11), 149 (28), 140 (34), 94 (89), 84 (100); HRMS-EI Calc. for $C_{14}H_{16}N_2O_3$ (*M*), 260.1160. Found: M^+, 260.1157.

Method B. To a solution of **1a** (185 mg, 1 mmol) in dry CH_2Cl_2 (7 ml) at −78 °C under nitrogen was added dropwise DIBAL-H (1.0 M in hexane; 1.6 ml). After stirring of the mixture for 2 h at −78 °C, MeOH (0.5 ml) was added. The reaction mixture was warmed to room temperature and then partitioned between EtOAc (10 ml) and saturated aq.

potassium sodium tartrate (5 ml). Vigorous stirring was continued until all the solids dissolved. The organic layer was separated, and dried over $MgSO_4$. Evaporation of EtOAc under reduced pressure gave a residue; this, and *N*-methylhydroxylamine hydrochloride (323 mg, 3 mmol), were dissolved in CH_2Cl_2 (10 ml) followed by the addition of $NaHCO_3$ (504 mg, 6 mmol) and silica gel (60 PF_{254}; 5 g). The resulting mixture was carefully mixed, and evaporated by a rotary vacuum evaporator. The reaction mixture was placed in a Pyrex plate with a cover and then irradiated in a microwave oven for 15 min to complete the reaction. The mixture was eluted with EtOAc. After removal of EtOAc, the residue was chromatographed (EtOAc–EtOH 8 : 1 v/v) to give only the isoxazolidine **7a** (151 mg, 82%), which was consistent with the previously described compound.

7b. Obtained in 79% yield from **3a** and *N*-benzylhydroxylamine hydrochloride following method **B**. Chromatography (EtOAc–hexane 2 : 1 v/v) gave **7b** consistent with the previously described compound.

Reduction of 1a and INC in sealed tube leading to isoxazolidines 7a and 8a

The crude aldehyde (116 mg, 0.75 mmol), prepared following the above reduction procedure, and *N*-methylhydroxylamine hydrochloride (242 mg, 2.25 mmol) were dissolved in 90% aq. EtOH (6 ml). $NaHCO_3$ (283 mg, 3.37 mmol) was added and the mixture was heated in a sealed tube under nitrogen at 120–125 °C for 6 h. Opening the sealed tube and removal of EtOH gave a residue, which was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by chromatography (EtOAc–EtOH 8 : 1 v/v) to give products **7a** (99 mg, 72%) and **8a** (15 mg, 11%).

General procedure for reduction of 1a and [2 + 3]cycloaddition leading to cycloadducts 10a,b

To a solution of **1a** (185 mg, 1 mmol) in dry CH_2Cl_2 (7 ml) at −78 °C under nitrogen was added dropwise DIBAL-H (1.0 M in hexane; 1.6 ml). After stirring of the mixture for 2 h at −78 °C, MeOH (0.5 ml) was added. The reaction mixture was warmed at room temperature and then partitioned between EtOAc (10 ml) and saturated aq. potassium sodium tartrate (5 ml). Vigorous stirring was continued until all the solids dissolved. The organic layer was separated, and dried over $MgSO_4$. Evaporation of EtOAc under reduced pressure gave a residue, and this and sarcosine ethyl ester (176 mg, 1.5 mmol) were dissolved in CH_2Cl_2 (5 ml) followed by addition of silica gel (60 PF_{254}; 3 g). The resulting mixture was carefully mixed, and evaporated by rotary vacuum evaporator. The reaction mixture was placed on a Pyrex plate with a cover and then irradiated in a microwave oven for 15 min to complete the reaction. The mixture was eluted with EtOAc. After removal of EtOAc, the residue was chromatographed (EtOAc–hexane 2 : 1 v/v) to give product **10a** (200 mg, 79%) as a *white solid*, mp 123–125 °C; $[\alpha]_D^{22}$ −21.4 (*c* 0.8, $CHCl_3$); ^{1}H NMR δ 4.57 (dd, 1H, *J* 8.0, 3.0 Hz), 4.53 (t, 1H, *J* 8.8 Hz), 4.17 (dd, *J* 8.8, 3.7 Hz, 1H), 4.14 (q, 2H, *J* 7.0 Hz), 3.94 (ddd, 1H, *J* 8.8, 5.5, 3.7 Hz), 3.79 (dd, *J* 12.1, 7.0 Hz, 1H), 3.36 (dd, 1H, *J* 9.0, 5.5 Hz), 3.26 (dd, 1H, *J* 12.1, 8.5 Hz), 3.01 (ddddd, *J* 9.0, 8.5, 7.0, 6.5, 2.0 Hz, 1H), 2.76 (ddd, 1H, *J* 9.5, 8.0, 6.5 Hz), 2.67 (s, 3H), 2.44 (ddd, 1H, *J* 9.5, 3.0, 2.0 Hz), 1.29 (t, *J* 7.0 Hz, 3H); ^{13}C NMR δ 170.54 (s, C=O), 160.75 (s, C=O), 76.72 (d), 67.43 (t), 61.20 (d), 59.45 (t), 56.24 (d), 50.97 (t), 46.84 (d), 43.79 (q), 28.45 (t), 15.14 (q); MS-FAB (*m*/*z*, %) 255 (MH^+, 56), 254 (M^+, 43); HRMS-FAB Calc. for $C_{12}H_{18}N_2O_4$ + H (MH^+), 255.1344. Found: *m*/*z*, 255.1350. Calc. for $C_{12}H_{18}N_2O_4$: C, 56.66; H, 7.14; N, 11.02. Found: C, 56.42; H, 6.91; N, 10.89%.

10b. Obtained in 81% yield as a white solid from **1a** and *N*-benzylglycine ethyl ester following the general procedure. Chromatography (EtOAc–hexane 2 : 1 v/v) gave **10b**, mp 162–164 °C; $[\alpha]_D^{22}$ −24.9 (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 7.30–7.35 (m, 5H), 4.62 (dd, 1H, *J* 8.5, 2.5 Hz), 4.40 (dd, 1H, *J* 9.0, 8.5 Hz), 4.34 (d, 1H, *J* 11.5 Hz), 4.19 (dd, 1H, *J* 9.0, 2.5 Hz), 4.16 (q, 2H, *J* 7.0 Hz), 3.98 (dd, *J* 12.0, 8.8 Hz, 1H), 3.75 (d, 1H, *J* 11.5 Hz), 3.72 (ddd, 1H, *J* 8.5, 6.0, 2.5 Hz), 3.41 (dd, 1H, *J* 9.0, 6.0 Hz), 3.07 (dd, 1H, *J* 12.0, 6.5 Hz), 2.97 (ddddd, 1H, *J* 9.0, 8.8, 7.0, 6.5, 2.0 Hz), 2.72 (ddd, *J* 9.5, 8.5, 2.5 Hz, 1H), 2.38 (ddd, 1H, *J* 9.5, 2.5, 2.0 Hz), 1.30 (t, 3H, *J* 7.0 Hz); ^{13}C NMR δ 170.34 (s, C=O), 160.37 (s, C=O), 135.40 (s), 129.17 (d), 128.69 (d), 128.21 (d), 77.92 (d), 66.54 (t), 62.46 (t), 61.94 (d), 59.02 (t), 55.48 (d), 50.17 (t), 48.02 (d), 28.57 (t), 14.95 (q); MS-FAB (*m*/*z*, %) 331 (MH^+, 67), 330 (M^+, 36), 329 (M^+ − 1, 42); HRMS-FAB Calc. for $C_{18}H_{22}N_2O_4$ + H (MH^+), 331.165. Found: *m*/*z*, 331.1658.

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References

1 For recent reviews: (*a*) J. J. Tufariello, in *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley, New York, 1984, pp. 83–168; (*b*) A. Padwa and A. M. Schoffstall, *Advances in Cycloaddition*, ed. D. Curran, JAI Press, Greenwich, CT, 1990, pp. 2–28; (*c*) S. E. Denmark and A. Thorarsensen, *Chem. Rev.*, 1996, **96**, 137 and references cited therein; (*d*) W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, ed. J. E. Baldwin and P. D. Magnus, Tetrahedron Organic Chemistry Series, Pergamon Press, Oxford, 1990, vol. 8, pp. 296–313.

2 (*a*) A. Hassner and R. Maurya, *Tetrahedron Lett.*, 1989, **30**, 2289; (*b*) A. Hassner, R. Maurya, A. Padwa and W. H. Bullock, *J. Org. Chem.*, 1991, **56**, 2775; (*c*) A. Hassner, R. Maurya, O. Friedman, H. E. Gottlieb, A. Padwa and D. Austin, *J. Org. Chem.*, 1993, **58**, 4539; (*d*) M. Noguchi, H. Okada, S. Nishimura, Y. Yamagata, S. Takamura, M. Tanaka, A. Kakeihi and H. Yamamoto, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 185.

3 (*a*) A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault and D. Math, *Synthesis*, 1998, 1213; (*b*) S. Kasmi, J. Hamelin and H. Benhaoua, *Tetrahedron Lett.*, 1998, **39**, 8093; (*c*) P. M. Bendale and B. M. Khadilkar, *Synth. Commun.*, 2000, **30**, 1713; (*d*) M. Gianotti, G. Martelli, G. Spunta, E. Campana, M. Panunzio and M. Mendozza, *Synth. Commun.*, 2000, **30**, 1725.

4 H. Kaddar, J. Hamelin and H. Benhaoua, *J. Chem. Res.* (*S*), 1999, 718.

5 (*a*) R. J. Bernacki and W. Korytnyk, *Cancer Metastatis Rev.*, 1985, **4**, 81; (*b*) G. Casiraghi and F. Zanardi, *Chem. Rev.*, 1995, **95**, 1677; (*c*) Y. Chen and P. Vogel, *J. Org. Chem.*, 1994, **59**, 2487; (*d*) K. Koide, M. E. Bunnage, L. G. Paloma, J. R. Kanter, S. S. Taylor, L. L. Brunton and K. C. Nicolaou, *Chem. Biol.*, 1995, **2**, 601.

6 (*a*) G. W. J. Feelt and P. W. Smith, *Tetrahedron Lett.*, 1985, **26**, 1469; (*b*) H. Setoi, J, H. Kayakiri, H. Tekeno and M. Hashimoto, *Chem. Pharm. Bull.*, 1987, **35**, 3995; (*c*) D. K. Thompson, C. N. Hubert and R. H. Wightman, *Tetrahedron*, 1993, **49**, 3827; (*d*) S. E. Denmark and L. R. Marcin, *J. Org. Chem.*, 1993, **58**, 3857; (*e*) M. S. Vissor, N. M. Heron, M. T. Didiuk, J. F. Sagal and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1996, **118**, 4291; (*f*) K. Asano, T. Hakogi, S. Iwama and S. Katsumura, *Chem. Commun.*, 1999, 41.

7 (*a*) E. Falb, Y. Bechor, A. Nudelman, A. Hassner, A. Albeck and H. E. Gottlieb, *J. Org. Chem.*, 1999, **64**, 498; (*b*) A. Hassner, E. Falb, A. Nudelman, A. Albeck and H. E. Gottlieb, *Tetrahedron Lett.*, 1994, **35**, 2397.

8 (*a*) T. K. M. Shing, D. A. Elsey and J. G. Gillhouley, *J. Chem. Soc.*, *Chem. Commun,*, 1989, 1281; (*b*) T. K. M. Shing, C. H. Wong and T. Yip, *Tetrahedron: Asymmetry*, 1996, **7**, 1323; (*c*) B. Alcaide, J. M. Alonso, M. F. Aly, E. Saez, M. P. Martinez-Alcazar and F. Hernandez-Cano, *Tetrahedron Lett.*, 1999, **40**, 5391.

9 (*a*) T. K. M. Shing, W. C. Fung and C. H. Wong, *J. Chem. Soc.*, *Chem. Commun.*, 1994, 449; (*b*) Y. Inoue, J. Hara and H. Kakisawa, *Chem. Lett.*, 1980, 1407.

10 M. Nyerges, L. Gajdics, A. Szollosy and L. Toke, *Synlett*, 1999, 111.