Thermal Hetero [3 + 2] Cycloaddition of Dipolar Trimethylenemethane to *O*-Alkyloximes. Straightforward Synthetic Routes to Substituted Pyrrolidines and Prolines

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Thermal hetero [3 + 2] cycloaddition reaction of a dipolar trimethylenemethane **2** with an *O*-alkyloxime produces a substituted pyrrolidine. Thus, heating of a mixture of an alkylidenecyclopropane **1** an *anti*-*O*-alkyloxime **3** proceeds smoothly in good yield to give a substituted pyrrolidine **4** bearing a ketene acetal group in its 3-position, which upon hydrolysis under mild conditions gives a 3-alkoxycarbonylpyrrolidine **5** in quantitative yield. On the other hand, the cycloaddition to a *syn*-oxime is extremely slow. The cycloaddition reaction can be achieved by starting with nearly equimolar quantities of the two starting materials, and the reaction is quite insensitive to the choice of solvent and to the presence of oxygen and water. In the reaction of a substituted methylenecyclopropane **1** (R ≠ H), the reaction may take place with high regio- and stereoselectivity, which is in consonance with the concerted nature of the cycloaddition reaction. The present synthesis represents one of the rare examples of the imine-based route to pyrrolidines, which have been much less explored than the 1,3-dipolar cycloaddition route using olefin and azomethine ylide.

Pyrrolidines are among the most common structures in biologically active natural products, and the diversity of their biological functions as well as their structure has stimulated efforts for the rapid and controlled synthesis of this class of compounds.[1] Among various synthetic strategies, concerted cycloadditions, as represented by the Diels−Alder reaction, possesses a number of ideal properties, because the reaction may take place with orbital-controlled stereochemistry and with high "atom economy",[2] starting with neutral reactants without recourse to the use of any extraneous reagent. Because of such merits, intensive efforts have been focused on a hetero [3 + 2] cycloaddition reaction in the synthesis of pyrrolidines.[3] An approach to pyrrolidines based on the [3 + 2] cycloaddition reaction reveals two possibilities. One involves a 1,3-dipolar cycloaddition of an azomethine ylide to an olefin which has frequently been studied[4] (Scheme 1, route a), and the other involves an all-carbon 1,3-dipole with an imine (route b). The latter route has long been unsuccessful because of the low reactivity of imines in cycloadditions as well as the scarcity of appropriate 1,3-dipoles.

Although trimethylenemethane (TMM)[5] and its equivalent[6] are seemingly the most promising three-carbon units for realization of route b, the cycloaddition reaction of alkyl-substituted diradical TMM species to C=N double bonds has proved to be a poor synthetic reaction.[7] A metal-mediated approach with a Trost-type TMM precursor and an electron-deficient imine offered a solution to this problem.[8,9] Our discovery of a thermal cycloaddition of a singlet dipolar TMM species **2**[10] to an olefin[11] as well as a carbonyl compound[12] led us to examine the reaction to a C=N double bond. Since the cycloaddition of the TMM species to an electron-deficient

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(1) *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI Press Inc: Greenwich, 1990; Vol. 1. Pichon, M. *Tetrahedron: Asymmetry* **1996**, *7*, 927. Ishibashi, H.; Sato, T.; Ikeda, M. *J. Synth. Org. Chem., Jpn.* **1995**, *53*, 85. Hirai, Y.; Momose, T. *J. Synth. Org. Chem., Jpn.* **1993**, *51*, 25. Hudlicky, T.; Seoane, G.; Price, J. D.; Gadamasetti, K. G. *Synlett* **1990**, 433.

(2) Trost, B. M. *Science* **1991**, *254*, 1471.

(3) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987. Weinreb, S. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 401. Waldmann, H. *Synthesis* **1994**, 535.

(4) Lown, J. W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. 1, p 653. Vedejs, E. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press Inc: Greenwich, 1990; Vol. 1, p 33. Padwa, A.; Schoffstall, A. M. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press Inc: Greenwich, 1990; Vol. 2, p 1. Tominaga, Y.; Hojo, M.; Hosomi, A. *J. Synth. Org. Chem., Jpn.* **1992**, *50*, 48.

(5) (a) Dowd, P. *Acc. Chem. Res.* **1972**, *5*, 242. (b) Berson, J. A. *Acc. Chem. Res.* **1978**, *11*, 486. (c) Little, R. D. *Chem. Rev.* **1986**, *86*, 875.

(6) Chan, D. M. T. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 271. Binger, P.; Büch, H. M. In *Small Ring Compounds in Organic Synthesis II*, de Meijire, A., Ed.; Springer-Verlag: Berlin, 1987; p 77. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1.

(7) Little, R. D.; Bode, H.; Stone, K. J.; Wallquist, O.; Dannecker, R. *J. Org. Chem.* **1985**, *50*, 2401. This situation has a similarity to the ineffectiveness of the thermal Diels−Alder reactions with carbonyl compounds.

(8) Jones, M. D., Kemmitt, R. D. *J. Chem. Soc., Chem. Commun.* **1986**, 1201. Trost, B. M., Marrs, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 6636. Trost, B. M.; Matelich, M. C. *J. Am. Chem. Soc.* **1991**, *113*, 9007. Trost, B. M.; Parquette, J. R.; Nübling, C. *Tetrahedron Lett.* **1995**, *36*, 2917.

(9) Addition/cyclization of a bifunctional allylic reagent represents a strategic surrogate of the TMM cycloaddition reactions. For a recent example, see: Trost, B. M.; Bonk, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 1778. van der Heide, T. A. J.; van der Bann, J. L.; de Kimpe, V.; Bickelhaupt, F.; Klumpp, G. W. *Tetrahedron Lett.* **1993**, *34*, 3309.

(10) Nakamura, E.; Yamago, S.; Ejiri, S.; Dorigo, A. E.; Morokuma, K. *J. Am. Chem. Soc.* **1991**, *113*, 3183.

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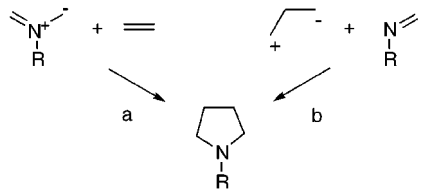
Scheme 1

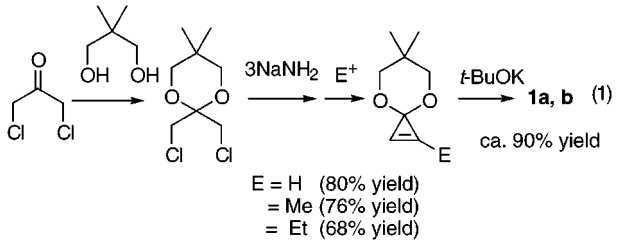


olefin takes place through a concerted transition state to afford a substituted cyclopentane with high stereocontrol,[11] it was particularly interesting to see whether this would also be the case in the hetero [3 + 2] cycloaddition reactions.

We report in this paper the cycloaddition reactions of the dipolar TMM species to *O*-alkyloximes; this represents the first synthetically viable construction of pyrrolidine skeletons by thermal hetero [3 + 2] cycloaddition of free TMM species. The cycloaddition reaction is effected simply by heating an equimolar mixture of an alkylidenecyclopropane **1** and an appropriate *O*-alkyloxime and proceeded with high levels of regio-, stereo-, and periselectivity with suitable choice of substituents (Scheme 2). The cycloaddition reaction affords ketene-acetal-substituted pyrrolidines as primary cycloadducts, which upon hydrolysis gives pyrrolidine carboxylic acid esters. This reaction enjoys the full advantages of concerted cycloaddition process as to the stereocontrol as well as to the atom economy, therefore making a unique and useful synthetic entry to pyrrolidines.

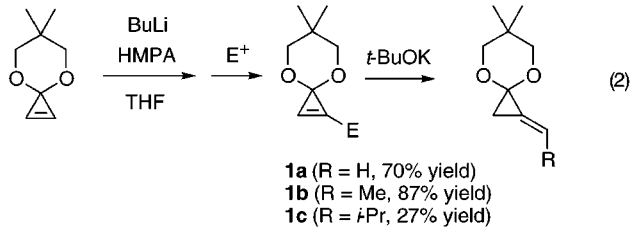
Results

Preparation of Alkylidenecyclopropanone Acetals. Alkylidenecyclopropanone acetals are readily available on a large scale (0.1−0.5 mol scale) in two or three steps from 1,3-dichloroacetone (see the Experimental Section). In the first approach (eq 1), the ketone is



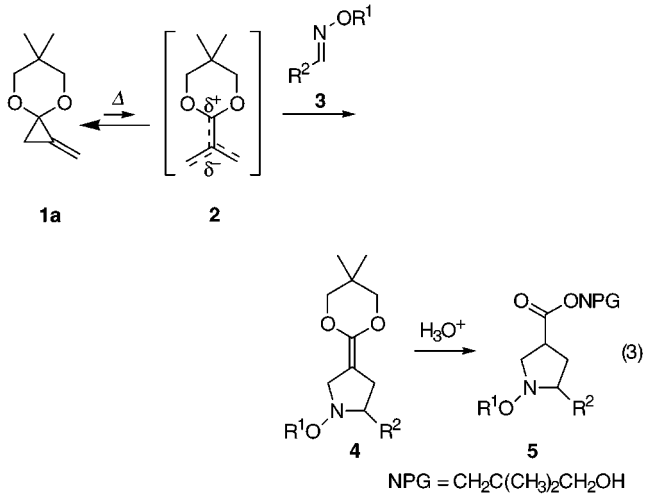
first converted to the corresponding neopentyl glycol acetal. The acetal is treated with 3 equiv of sodium amide (cyclization and in situ deprotonation of the resulting cyclopropenone acetal to generate a 2-sodiocyclopropenone acetal) and then with an alkyl iodide to obtain methyl- and ethyl-substituted cyclopropenone acetals in ca. 80% overall yield. Base-catalyzed isomerization of the alkylated cyclopropene to the less strained alkylidenecyclopropane completes the synthesis of the target molecule **1**.

In another approach (eq 2), a purified unsubstituted cyclopropenone acetal (available in 0.3−1.0-mol scale and stable in a freezer)[13] is deprotonated with BuLi in the



presence of HMPA, which stabilizes the lithiocyclopropenone acetal, and then alkylated with an alkyl halide. This method is suitable for the preparation of **1c**. The merits of the use of neopentyl glycol include its simple NMR signal pattern, the low cost of the diol, and the synthetically viable rate of TMM formation. For methylenecyclopropanes corresponding to **1a** derived from 1,3-propanediol and 2,4-pentanediol in stead of neopentyl glycol, the TMM formation is several times faster, making these precursors rather unstable for synthetic use.

Cycloaddition to *O*-Alkyloximes. In view of the low electrophilicity of imines, it was not unexpected that attempted reaction of a dipolar TMM **2** with benzaldehyde *N*-phenyl imine did not give the desired [3 + 2] cycloaddition product.[14] We were, however, pleasantly surprised by the finding that *O*-alkyloximes take part in the cycloaddition (eq 3). The following procedure il-



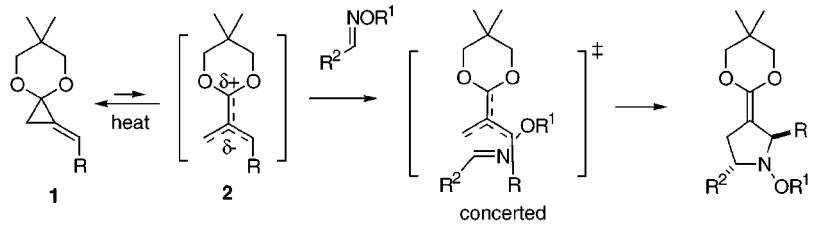
lustrates the new pyrrolidine synthesis. A neat mixture of methylenecyclopropane **1a** (4.81 g, 1.20 equiv relative to the benzyloxime) and methyl glyoxylate *O*-benzyloxime (5.01 g, anti:syn = 93:7) was heated under air (or nitrogen) for 4 h at 100 °C. ^{1}H NMR analysis of aliquots of the cooled reaction mixture indicated high-yield formation of the ketene acetal **4A** ($R^1 = CH_2Ph$, $R^2 = CO_2Me$), which was hydrolyzed in aqueous HCl/THF mixture at room temperature. Purification through a silica gel column afforded **5A** (7.67 g, 89%; cis:trans = 71:29). The

(11) (a) Yamago, S.; Nakamura, E. *J. Am. Chem. Soc.* **1989**, *111*, 7285. (b) Ejiri, S.; Yamago, S.; Nakamura, E. *J. Am. Chem. Soc.* **1992**, *114*, 8707. (c) Yamago, S.; Ejiri, S,; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **1993**, *115*, 5344. (d) Yamago, S.; Ejiri, S.; Nakamura, E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2154. (e) For applications in fullerene science including synthesis of ^{14}C labeled derivatives, see: Prato, M.; Suzuki, T.; Foroudian, H.; Li, Q.; Khemani, K.; Wudl, F.; Leonetti, J.; Little, R. D.; White, T.; Rickborn, B.; Yamago, S.; Nakamura, E. *J. Am. Chem. Soc.* **1993,** *115*, 1594; Yamago, S.; Nakamura, E. *Chem. Lett.* **1996**, 395. Yamago, S.; Tokuyama, H.; Nakamura, E.; Kikuchi, K.; Kananishi, S.; Sueki, K.; Nakahara, H.; Enomoto, S.; Ambe, F. *Chem. Biol.* **1995**, *2*, 385.

(12) Yamago, S.; Nakamura, E. *J. Org. Chem.* **1990**, *55*, 5553.

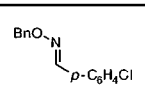
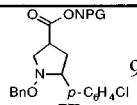
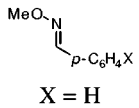
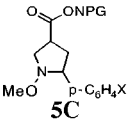
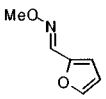
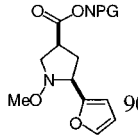
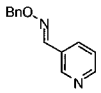
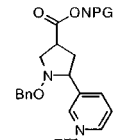
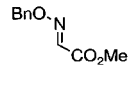
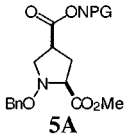
(13)) Isaka, M.; Ejiri, S.; Nakamura, E. *Tetrahedron* **1992**, *48*, 2045−2057.

Scheme 2



a: R = H, **b**: R = Me,
c: R = *i*-Pr

Table 1. Cycloaddition of Methylenecyclopropane 1a with *O*-Alkyloxime 3[a]

entry	oxime	temp[b] °C	time h	5[c]	%yield[d]
1		100	31	 **5B**	99 (90) [98]
2		120-130	36	 **5C**	70
3	X = H	80	24		{76}
4	X = OMe	80	24	**5D**	{70}
5		100	85	 **5E**	90 (92) [58]
6		100	29	 **5F**	66
7		80	1.5	 **5A**	79 [89]

[a] The reactions were carried out by using **1a** (1.2 equiv) and an *O*-alkyloxime **3** (>90% anti) in CH_3CN or CD_3CN (1.5 M solution of the oxime ether) at the indicated temperature unless otherwise noted; The initial product **4** was hydrolyzed to **5**. Conditions other than the above are (C_3H_7CN), {CH_2Cl_2 at 10 kbar pressure}, and [no solvent]. [b] Bath temperature. [c] Hydrolyzed product. NPG = $CH_2C(CH_3)_2CH_2OH$. [d] The yields are based on analytically pure isolated products. The product was a 60:40−70:30 mixture of cis and trans stereoisomers. The cis stereochemistry was determined for the product in entries 5 and 7 by NOE experiments.

reaction selectively afforded pyrrolidine **4**. This reaction does not require the use of solvent and tolerates various aprotic solvents (hydrocarbon, haloalkane, nitrile, DMSO). However, an alkylnitrile solvent was used routinely since the TMM generation takes place smoothly in a polar solvent.[10] The reaction does not necessarily require rigorous exclusion of moisture or air and does not appear to suffer very much from the presence of organic impurity either.

The reaction of the parent methylenecyclopropane **1a** has been examined for various *anti*-*O*-alkyloximes (Table 1). Thus, the reaction of a near equimolar mixture of **1a** and *p*-chlorobenzaldehyde *O*-benzyloxime at 100 °C afforded the corresponding pyrrolidine **5B** ($R^1 = CH_2Ph$, $R^2 = p\text{-}ClC_6H_4$, entry 1) in 99% yield after treatment of the ketene acetal product **4B** with 10% aqueous HCl in THF. The ketene acetal product was identified by ^1H and ^{13}C NMR in the experiments carried out in CD_3CN. Benzaldehyde *O*-methoxime also reacted with the parent cyclopropane **1a** to give **5C** (R^1 = Me, R^2 = Ph) in 70% yield, but more slowly than *p*-chlorobenzaldehyde *O*-benzyloxime, requiring higher temperature (120−130 °C, entry 2). Under high-pressure conditions (10 kbar, at 80 °C in CH_2Cl_2),[15] the reaction proceeded faster and gave **5C** in 76% yield after hydrolysis (entry 3). The reaction with the less electrophilic *p*-anisaldehyde *O*-methoxime proceeded only under high pressure (ca. 10 kbar) to give the cycloadduct **5D** (R^1 = Me, $R^2 = p\text{-}MeOC_6H_4$) in 70% yield (entry 4). Reactions of *O*-alkyloximes derived from heteroaromatic aldehydes also took place smoothly (entries 5 and 6). The reaction with 3-pyridinecarboxaldehyde *O*-benzyloxime afforded a 4-substituted nicotine derivative **5F** ($R^1 = CH_2Ph$, R^2 = 3-pyridyl) in good yield (entry 6). The reaction with methyl glyoxylate *O*-benzyloxime, which is more electron-deficient than the above substrates, reacted within 1.5 h at 80 °C (79% yield, entry 7) to provide a new route to proline derivatives. *O*-Alkyloximes derived from aromatic aldehydes reacted smoothly with **1a** around 100 °C, while aliphatic aldehyde alkyloximes are poor substrates: the reaction of **1a** and hexanal *O*-methoxime took place only under high-pressure conditions (10 kbar, 80 °C, 60 h) to afford a complex mixture from which the desired cycloadduct was isolated in low yield. In the above experiments, no attempts were made to control the stereochemistry of the hydrolysis of **4** to **5**, and a 7:3 mixture of diastereomers (cis stereochemistry assigned by NOE experiments in entries 5 and 7) generally formed.

In the above experiments, we noted the significant difference of the reactivity of *anti*- and *syn*-oximes. Syn isomer being obtained as a minor product in *O*-alkyloxime synthesis, we routinely observed that the syn isomer of the oxime was left unreacted.[16] The difference in reactivity was confirmed in experiments using pure stereoisomers: The reaction of **1a** with the pure (>99%) *anti*-*O*-methoxime of 2-furaldehyde in CD_3CN was complete in 85 h to give **4E** (R^1 = Me, R^2 = 2-furyl) at 100 °C (entry 5), while the reaction of the corresponding 98% pure *syn*-*O*-alkyloxime showed very low conversion after 66 h at 100 °C. After 116 h of heating at this temperature, **4e** formed in 13% yield, together with 37% recovery of the *syn*-*O*-alkyloxime. In these experiments, geometric

(14)) The reaction of **1** with *N*-acyl and *N*-tosyl imines gives γ-amino acid derivatives instead of [3 + 2] cycloadduct; to be published.

(15) *Organic High-Pressure Chemsitry*; le Noble, W. J., Ed.; Elsevier: Amsterdam, 1988.

(16) In this respect, *O*-benzyloximes are superior to *O*-methoxime, because the former generally is obtained with higher anti selectivity (9:1) than the latter (7:3) by the reaction of an aldehyde and the corresponding alkoxyamine.

Scheme 3

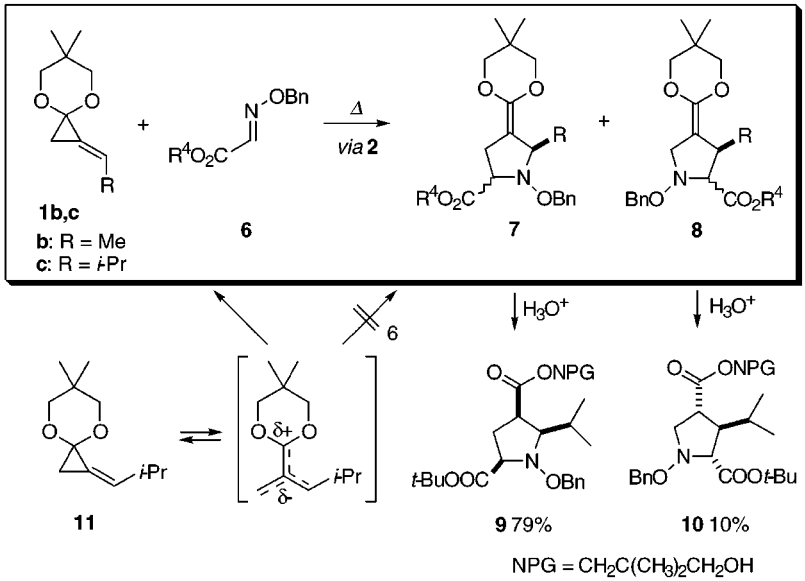


Table 2. Cycloaddition of Methylenecyclopropane 1b and 1c with *O*-Alkyloxime[a]

entry	1, R =	3, R^4 =	reaction time, h[b] (solvent)	% yield[c,d]	**7**:**8**	**9**, *cis*:*trans*[d]	**10**, *cis*:*trans*[d]
1	Me	Me	4	81 (82)	70:30	68:32	51:49
2	Me	*t*-Bu	10	99 (100)	82:12	77:23	43:57
3	*i*-Pr	Me	21	81 (85)	78:22	71:29	4:>96
4	*i*-Pr	Ph_2CH	16.5	71 (79)	83:17	>95:5	7:93
5	*i*-Pr	Ph	4	41 (46)	77:23	52:48	39:61
6	*i*-Pr	2,6-Me_2Ph	8	83 (93)	44:56	93:7	5:>95
7	*i*-Pr	*t*-Bu	17	89 (100)	90:10	>97:3	4:>96
8			21.5 (DMSO-d_6)	96 (99)	91:9	94:6	6:94
9			36 (toluene-d_8)	85 (100)	86:14	>96:4	5:>95
10			18 (none)	83 (95)	84:16	>98:2	7:93
11[e]			30	88 (99)	89:11	>98:2	3:>97
12	*i*-Pr	2,4,6-*t*-Bu_3Ph	40	41 (60)	88:12	94:6	5:>95

[a] The reactions were carried out with pure *anti*-oxime ether. [b] All reactions were carried out at 80 °C in CD_3CN, except in entries 5−7, where the solvent used is indicated in the parentheses. [c] The yields in the parentheses are based on the recovery of **3**. [d] Corresponding to 2,5- and 2,3-stereochemistry for **9** and **10**, respectively. The isomeric ratio was determined by ^1H and ^{13}C NMR. The > mark indicates that the minimum ratio based on the signal/noise ratio. [e] Corresponding methoxime was used.

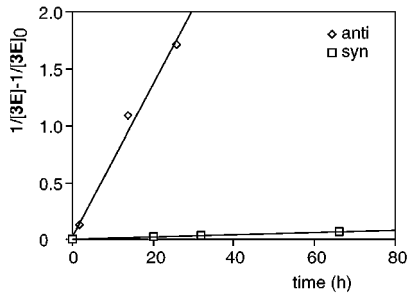


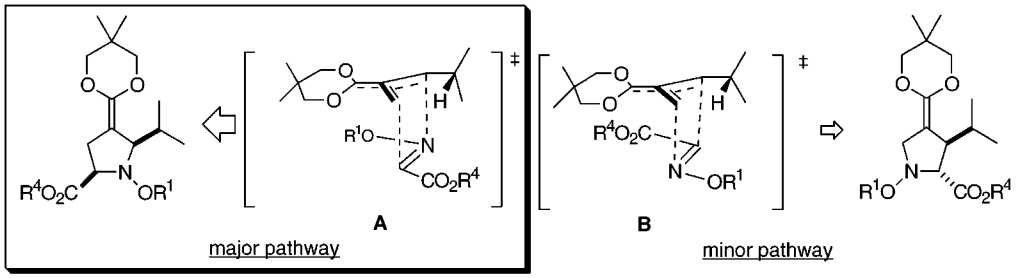
Figure 1. Time course of the cycloaddition. The reaction was carried out in an NMR tube in CD_3CN at 100 ± 5 °C and was monitored by ^1H NMR. Initial concentrations of **3E** (R^1 = Me, R^2 = 2-furyl) and **1a** were 1.5 and 1.8 M, respectively. The decrease of **3E** was proportional to the increase of the cycloadduct **4E** for the observed period. After 80 h, the reaction with the *syn*-oxime rapidly formed an unidentified side product.

isomerization of the *O*-alkyloximes was not observed. Second-order rate constants k for the anti and syn substrates are, thus, obtained as $k_{anti} = 6.7 \times 10^{-2}$ $M^{-1}\cdot s^{-1}$ and $k_{syn} = 1.0 \times 10^{-3}$ $M^{-1}\cdot s^{-1}$ (Figure 1). The anti isomer reacted 67 times faster than the syn isomer.

Regio- and Stereoselectivity. Having established the basic reaction protocol for the parent TMM (i.e., R = H), we next examined the regio- and stereochemistry for the synthesis of substituted pyrrolidines by using substituted TMM **2b** (i.e., R = Me). However, the cycloaddition of the ethylidenecyclopropane **1b** and 2-furaldehyde *O*-methoxime did not take place even after heating at 100 °C for 1 week. *p*-Chloro- and *p*-nitrobenzaldehyde *O*-benzyloxime were also inert to **1b,** presumably due to steric effects of the TMM substituent R.

In contrast, *O*-alkyloximes derived from glyoxalic acid esters **6** were found to react with the substituted TMM (Scheme 3). Thus, a combination of sterically unhindered reactants (substituents on the TMM and the *O*-alkyloxime being a methyl groups; R = R^4 = Me, entry 1, Table 2) afforded a 70:30 mixture of regioisomers **7** and **8**, both of which are 1:1 mixtures as to the relative stereochemistry for the R and CO_2R^4 group. When a bulkier *tert*-butyl group was employed as the R^4 group in the ester moiety, **7**:**8** regioselectivity improved slightly to 82:18 (entry 2). The use of a bulkier *i*-Pr group as the TMM substituent R also improved the regioselectivity (to 78:22) and had a large influence on the cis/trans selectiv-

Scheme 4



ity in the minor regioisomer **8**, improving it to 4:>96 (entry 3). The use of bulkier diphenylmethyl group R^4 on the ester moiety showed only small effects on the regioselectivity but significant effects for the cis/trans selectivity of both **7** and **8** (entry 4). While the use of phenyl ester (R^4 = Ph) increased the reactivity of the *O*-alkyloxime, the cis/trans selectivity was low (entry 5). The 2,6-dimethylphenyl ester of the oxime, on the other hand, gave a near 1:1 mixture of **7** and **8** (entry 6). Finally, the reaction between a sterically hindered TMM and an *O*-alkyloxime (R = *i*-Pr and R^4 = *t*-Bu) took place with excellent selectivities (a 90:10 mixture of **7**:**8**, wherein **7** was >97% pure cis and **8** was >96% trans, entry 7). We found that solvents (toluene, acetonitrile, DMSO, and no solvent, entries 7−10) exert very small effects on the selectivities. The use of the very bulky 2,4,6-tri-*tert*-butylphenyl groups as the R^4 group also resulted in high regioselectivity and cis/trans selectivity, while the reaction slowed. Hydrolysis of the ketene acetal **7** and **8** in entry 7 with 1:9 1 M HCl/THF at room-temperature took place with high diastereoselectivity to give the trisubstituted pyrrolidines **9** and **10** both as a single isomer in 79% and 10% isolated yield, respectively (Scheme 3).

The reactivity of the *Z*-TMM precursor **11** with the *O*-benzyloxime **6** (R^4 = *t*-Bu) was examined next to find that **11** is extremely unreactive (100 °C, <8 h, CD_3CN). The reluctance of the (*Z*)-alkylidene cyclopropanone acetal to generate the TMM and the rapid isomerization of this TMM to the more stable *E*-isomer were noted previously.[10] After 8 h of heating, **11** was found to isomerize, to some extent, to its *E*-isomer **1c,** and then the *O*-benzyloxime **6** started to be consumed. After 43 h, the reaction afforded the cycloadducts (**7** and **8**) of the same isomeric distribution as obtained in the reaction of **1c**. The results indicated that the *Z*-TMM species which forms upon thermolysis did not react with **6** but underwent isomerization to the *E*-isomer **2c**, which then afforded **1c** as well as **7** and **8**.

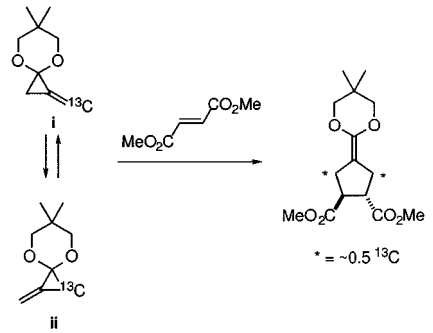
Discussion

We have developed a rapid synthesis of substituted pyrrolidines by the thermal hetero [3 + 2] cycloaddition of dipolar TMMs with *O*-alkyloximes. The reaction does not require any extraneous reagents (including solvent) other than the two reactants, the methylenecyclopropane **1** and a nearly equimolar amount of an *O*-alkyloxime. The success of the current reaction rests on the reversible generation of the singlet TMM species **2** from **1**.[10] TMM **2** generated in a minute quantity reacts either with the C=N compound or, when there is no C=N compound available, goes back to the cyclopropane precursor,[17] and hence few side reactions take place. The cycloaddition of the TMM to a C=N double bond is faster than the reaction with triplet molecular oxygen due to the singlet nature of **2**, and hence rigorous exclusion of oxygen was not necessary.[10]

The reaction rate of the present cycloaddition show marked dependence on the stereochemistry of the C=N double bond. An *anti*-oxime reacts ca. 70 times faster than the corresponding *syn*-oxime, and on the basis of Huisgen's criteria,[18] this rate difference provides strong evidence of concerted character of the cycloaddition.,[19−22]

The observed rate enhancement at high pressure is also consistent with the ordered transition state of the present cycloaddition reaction. As we have already shown by theoretical analysis and experiments on the cycloaddition with electron deficient olefins,[10,11b] the dipolar TMM shows its 4π nucleophilic character in its planar conformation (cf. Scheme 4). Therefore, we sug-

(17) Degenerated isomerization of **1** by way of **2** is usually faster than the cycloaddition to external unsaturated bonds. In the ^{13}C labeled experiments, the methylene-labeled methylenecyclopropane **i** isomerized to the cyclopropane labeled **ii** prior to the cycloaddition, even when the reactive dimethyl fumarate was used as an acceptor. See also ref 10.



(18) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633. See also: Trost, B. M.; Miller, M. L. *J. Am. Chem. Soc.* **1988**, *110*, 3687.

(19) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633.

(20) See for a single electron-transfer pathway of the TMM cycloaddition: Yamago, S.; Ejiri, S.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **1993**, *115*, 5344.

(21) While Huisgen experimentally defined the minimum anti/syn rate difference (k_{anti}/k_{syn}) for the concerted 1,3-dipolar cycloaddition as 2.6, studies on the cycloaddition of metalated TMM addition with olefins by Trost revealed a stepwise reaction whose rate difference k_{anti}/k_{syn} larger than 2.6 and suggested the importance of the magnitude of the difference. See: Trost, B. M.; Miller, M. L. *J. Am. Chem. Soc.* **1988**, *110*, 3687. Whatever the threshold may be, the 67-fold rate difference in the present cycloaddition is a clear indication of the concertedness of the cycloaddition.

(22) The stereospecificity of the C=N cannot be certified in the presence example. Though the stereospecificity of cycloaddition has been considered to be a reliable criterion for the concertedness of the cycloaddition, recent studies by Zewail on the retro-Diels−Alder reaction revealed that the time scale of this conventional criteria is too slow to certify the concertedness: Horn, B. A.; Herek, J. L.; Zewail, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 8755.

gest that the stereoselective cycloaddition of the isopropyl-substituted TMM **2c** (R = *i*-Pr) with *anti*-oximes took place mainly via regio- and stereo-defined five-centered transition states schematically represented as **A** (Scheme 4). In these transition states, the oxime substrate bearing a bulky R^4 group is so oriented that it avoids interaction with a methyl group of the *i*-Pr group. The relatively low regiosteering power of the R and R^4 substituents of low steric demand (i.e., methyl) (as well as the lack of solvent effects, Table 2) suggests that neither OR^1 nor CO_2R^4 group acts as an electronic stereochemistry-directing group but rather indicates that the regio- and stereochemistry of the reaction is controlled by the steric bulk of the OR^1 and CO_2R^4 groups. This stands in contrast to the solvent-polarity-sensitive endo selectivity of the same TMM (**2c**) to substituted acrylic acid esters.[11b]

Experimental Section

General. All ^{1}H NMR spectra taken at 270, 400, or 500 MHz and ^{13}C NMR spectra at 67.5, 100, or 125 MHz are reported in ppm (δ). IR spectra are reported in cm^{-1}. GC analysis was performed on a capillary column (0.25 mm i.d. × 25 m) coated with HR-1. Recycle preparative HPLC was performed on a Japan Analytical Industry LC-908 machine equipped with GPC columns (JAIGEL 1H and 2H) using $CHCl_3$ as eluent.

Materials. Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Ethereal solvents were distilled from benzophenone ketyl immediately under nitrogen before use. MeCN, EtCN, CH_2Cl_2 were distilled successively from P_2O_5 and K_2CO_3 and stored over molecular sieves.

Preparation of 1-Ethyl-2,2-bis(chloromethyl)-5,5-dimethyl-1,3-dioxane. A mixture of 1,3-dichloroacetone (152 g, 1.20 mol, an irritant), neopentyl glycol (138 g, 1.32 mol), *p*-toluenesulfonic acid (4.6 g, 0.024 mol), and benzene (100 mL) was refluxed for 19 h in a 500-mL round-bottomed flask equipped with a Dean−Stark trap and a condenser for azeotropic removal of water. After completion of the formation of H_2O, the solution was partitioned between hexane (500 mL) and saturated $NaHCO_3$ (200 mL). The organic phase was washed with water (100 mL) and saturated NaCl (100 mL), dried over $MgSO_4$, and concentrated on a rotary evaporator. Distillation of the residue yielded, after about 5 g of forerun, 249 g (97%) of the title compound as a colorless oil (bp 99−100 °C, 3.5 mmHg). The product was spectroscopically pure. Spectral properties: IR (neat) cm^{-1} 2950, 2860, 1105, 1025, 770; ^{1}H NMR (270 MHz, $CDCl_3$) 1.00 (s, 6H), 3.57 (s, 4H), 3.80 (s, 4H).

Preparation of 1-Ethyl-6,6-dimethyl-4,7-dioxaspiro-[2,5]oct-1-ene and 6,6-Dimethyl-4,7-dioxaspiro[2,5]oct-1-ene (One-Pot Cyclization−Alkylation Procedure). A solution of sodium amide in liquid ammonia was prepared according to a procedure previously described.[23] An oven-dried 2000-mL three-necked, round-bottomed flask was equipped with a mechanical stirrer, a nitrogen gas inlet, and a dry ice/acetone condenser protected with a drying tube containing potassium hydroxide pellets. The flask was flushed with nitrogen and was placed in a dry ice/acetone bath. The nitrogen source was replaced with a hose connected to a cylinder of ammonia. Gaseous ammonia was introduced to the flask to collect ca. 400 mL of liquid NH_3 and gentle stirring was started. The gas inlet was replaced with a glass stopper and the dry ice/acetone bath was replaced with a −35 °C bath (electronic temperature control or a dry ice/trichloroethylene bath). Crystals of $Fe(NO_3)_3 \cdot 9H_2O$ (0.3 g) were added through the stoppered neck. To the resulting orange solution was added a small (about 5 mm) cube of sodium. The solution was stirred until the blue color disappeared. [Gentle stirring (e.g., 120 rpm) is recommended to avoid loss of the amide base which may stick to the upper part of the glass flask. This was found to be a good practice to achieve the most accurate base/substrate molar ratio.] Pieces of sodium (total 21.44 g, 0.930 mol) were then added over 25 min. After 20 min, the solution became a dark gray suspension with white precipitate. The cooling bath was replaced with a dry ice/acetone bath, and the gas inlet was replaced with a pressure-equalized dropping funnel containing a solution of the 2,2-bis-(chloromethyl)-5,5-dimethyl-1,3-dioxane (63.93 g, 0.300 mol) in 150 mL of dry Et_2O. This solution was added dropwise to the slurry of sodium amide in liquid NH_3 over 1 h. The dropping funnel was rinsed with 20 mL of dry Et_2O. The cooling bath was removed, and the mixture was stirred for 3 h. The flask was cooled again with a dry ice/acetone bath. After 10 min, a solution of fleshly distilled ethyl bromide (34.32 g, 0.315 mol) in 80 mL of dry Et_2O was added during 1.5 h through the dropping funnel.[8,9] The funnel was rinsed with 20 mL of dry ether. After stirring for 15 min, the cooling bath was removed and the solution was stirred for 1 h. The mixture was cooled with a dry ice/acetone bath again and solid NH_4Cl (20.24 g, 0.378 mol) was added in several portions during 5 min. The dry ice condenser was removed and ammonia was allowed to evaporate through the open neck. The cooling bath was changed to a water bath (ca. 30 °C), and a 1:1 mixture of dry Et_2O and dry pentane (400 mL) was added through the dropping funnel during 10 min. The water bath temperature was maintained between 25 and 30 °C. After most of ammonia was allowed to evaporate in a period of 1.5−2 h, the ethereal solution was filtered by suction through a pad of Hyflo Super Cell to remove the inorganic salts. The filter cake was washed three times with 80 mL of Et_2O. The combined filtrate was concentrated under reduced pressure (30−40 mmHg, 25 °C), and the residue was distilled through a 15-cm vacuum-jacketed Vigreux column to yield the title compound as a colorless oil (34.28 g, 68%; bp 50−52 °C, 1 mmHg). [To obtain a good yield, it is most important to carry out the distillation quickly (<25 min), but with the bath temperature below 100 °C.] IR (neat) cm^{-1} 2950, 1730 (w), 1280, 1070, 1020; ^{1}H NMR (270 MHz, $CDCl_3$) 1.01 (s, 3H), 1.05 (s, 3H), 1.22 (t, J = 7.3 Hz, 3H), 2.55 (dq, J = 7.3, 1.2 Hz, 2H), 3.61 (d, J = 10.3 Hz, 2H), 3.63 (d, J = 10.3 Hz, 2H), 7.32 (t, J = 1.2 Hz, 1H). When ethyl bromide was replaced with solid NH_4Cl (3∼4 equiv added to 1-ethyl-2,2-bis(chloromethyl)-5,5-dimethyl-1,3-dioxane very carefully in many portions), an unsubstituted cyclopropenone acetal was obtained after distillation in the same manner in 70−85% yield on a 0.3−1 mol scale.

Preparation of Alkylidenecyclopropanes: 6,6-Dimethyl-4,8-dioxa-1-methylenespiro[2.5]octane (1a) (Deprotonation−Alkylation Procedure). To a solution of 8.41 g of 6,6-dimethyl-4,8-dioxaspiro[2.5]oct-1-ene[24] (60.0 mmol) and 10.75 g of HMPA (60.0 mmol) in 60.0 mL of THF was added 36.8 mL of BuLi (1.6 M in hexane) at −78 °C under nitrogen, and the resulting solution was stirred for 30 min at this temperature. To this solution was added 9.37 g of iodomethane (66.0 mmol) during 15 min, the reaction mixture was gradually warmed to room temperature during 1 h and was quenched by addition of saturated NH_4Cl during 5 min. The aqueous layer was extracted with ether, and the combined organic extracts were washed with saturated $NaHCO_3$ and saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo to afford an oily product (10.30 g). To a solution of the crude product in 10.3 mL of ether was slowly added a solution of 1.35 g of potassium *tert*-butoxide (12.0 mmol) and 2.80 g of DMSO (36.0 mmol) in 10.0 mL of ether at 0 °C under nitrogen. After the solution was stirred for 2 h at room temperature, the reaction mixture was quenched by addition of saturated NH_4Cl. The aqueous phase was extracted with ether, and the

(23) Hancock, E. M.; Cope, A. C. *Organic Synthesis;* Wiley: New York, 1955; Collect. Vol. 3, p 219.

(24) Isaka, M.; Matsuzawa, S.; Yamago, S.; Ejiri, S.; Miyachi, Y.; Nakamura, E. *J. Org. Chem.* **1989**, *54*, 4727. Isaka, M.; Ejiri, S.; Nakamura, E. *Tetrahedron* **1992**, *48*, 2045.

combined extracts were washed with saturated $NaHCO_3$ and saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo to afford an oily product (8.90 g). Purification on silica gel (89 g, elution with 4% ether/pentane) followed by distillation under reduced pressure (bp 72−73 °C/18 mmHg) afforded 6.46 g of the title compound **1a** (70% yield). IR (neat) 3150(w), 1270, 1255, 1245, 1150, 1140, 1070, 1030, 1015, 970, 905; ^{1}H NMR ($CDCl_3$, 270 MHz) 1.04 (s, 3H), 1.06 (s, 3H), 1.62 (dd, J = 3.1, 2.4 Hz, 2H), 3.63 (s, 4H), 5.45 (t, J = 2.4 Hz, 1H), 5.81 (t, J = 3.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) 18.47 (t), 22.25 (q), 22.34 (q), 30.84 (s), 76.78 (t, two overlapping signals) 84.70 (s), 105.67 (t), 134.63 (s). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.02; H, 9.25.

6,6-Dimethyl-4,8-dioxa-1-ethylidenespiro[2.5]octane (1b). To a solution of 7.99 g of 6,6-dimethyl-4,8-dioxaspiro-[2.5]oct-1-ene (57.0 mmol) and 32.25 g of HMPA (180.0 mmol) in 90.0 mL of THF was added 37.0 mL of BuLi (1.54 M hexane solution) at −72 °C under nitrogen, and the resulting solution was stirred for 15 min at this temperature. To this was added a solution of 10.61 g of ethyl iodide (68.0 mmol) in 30.0 mL of THF through a cannula at −55 to −50 °C over 20 min under nitrogen. After stirring for 1 h at this temperature, the solution was gradually warmed to room temperature during 1 h and was quenched by addition of 20.0 mL of saturated NH_4Cl and 10.0 mL of water. The aqueous layer was extracted with ether, the combined organic extracts were washed with saturated NaCl and dried over Na_2SO_4, and the solvent was removed to afford an oil (15.80 g). To a solution of the crude product in 90.0 mL of ether were added 1.28 g of potassium *tert*-butoxide (11.4 mmol) and 2.67 g of DMSO (34.2 mmol) in 10.0 mL of ether at 0 °C under nitrogen. After being stirred for 15 min at this temperature, the solution was quenched by addition of saturated NH_4Cl. The aqueous layer was extracted with ether, the combined organic extracts were washed with saturated NaCl and dried over Na_2SO_4, and the solvent was removed to afford product. Purification on silica gel (120 g, elution with 5% ethyl acetate/hexane) afforded 8.37 g of the ethylidenecyclopropanone acetal **1b** as a white solid (49.8 mmol, 87% yield, a 88:12 mixture of *E*- and *Z*-isomers). Recrystallization from hexane (−20 °C) afforded the pure *E*-isomer. The mother liquor was concentrated, and the resulting mixture was subjected to recycling preparative HPLC to obtain the pure *Z*-isomer. The geometry of the olefins was assigned on the basis of the high-field shift (steric compression effect) of the cyclopropane methylene carbon cis to the methyl group in each isomer and was finally confirmed by X-ray crystallographic analysis of the *E*-isomer.[25] IR (neat, determined for a 88:12 mixture) 1265, 1250, 1145, 1130, 1115, 1080, 1055, 1040, 1010. Anal. (determined for a 88:12 mixture) Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.24; H, 9.29. ***(E)*-6,6-Dimethyl-4,8-dioxa-1-ethylidenespiro[2.5]-octane (*E*-1b):** ^{1}H NMR (270 MHz, $CDCl_3$) 1.01 (s, 3H), 1.09 (s, 3H), 1.51 (dq, J = 3.1, 2.2 Hz, 2H), 1.84 (dt, J = 6.4, 2.2 Hz, 3H), 3.60 (d, J = 10.0 Hz, 2H), 3.63 (d, J = 10.0 Hz, 2H), 6.28 (tq, J = 6.4, 3.1 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) 16.69 (t), 17.30 (q), 22.46 (q), 22.67 (q), 31.01 (s), 76.90 (t, two overlapping signals), 85.53 (s), 116.91 (d), 126.22 (s). ***(Z)*-6,6-Dimethyl-4,8-dioxa-1-ethylidenespiro[2.5]octane (*Z*-1b):** ^{1}H NMR (270 MHz, $CDCl_3$) 0.96 (s, 3H), 1.17 (s, 3H), 1.51 (dq, J = 2.7, 2.5 Hz, 2H), 1.95 (dt, J = 7.0, 2.7 Hz, 3H), 3.64 (s, 4H), 5.83 (tq, J = 7.0, 2.5 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) 18.26 (t), 18.32 (q), 22.49 (q), 22.76 (q), 30.98 (s), 76.78 (t, two overlapping signals), 85.65 (s), 117.94 (d), 125.70 (s).

6,6-Dimethyl-4,8-dioxa-1-isobutylidenespiro[2.5]-octane (1c and 11). To a solution of 14.02 g of 6,6-dimethyl-4,8-dioxaspiro[2.5]oct-1-ene (100.0 mmol) and 45.32 g of HMPA (250.0 mmol) in 150.0 mL of THF was added 66.0 mL of BuLi (1.67 M hexane solution) at −72 °C under nitrogen, and the resulting solution was stirred for 30 min at this temperature. To this was added a solution of 22.39 g of isobutyl iodide (121.6 mmol) in 30.0 mL of THF through a dropping funnel at −70 °C over 20 min under nitrogen. After stirring for 1 h at this temperature, the solution was warmed to −50 °C and then room temperature after 1.5 h, and the solution was stirred for 19 h at this temperature. After the solution was quenched by addition of 20.0 mL of buffer (pH = 4.01) and 20.0 mL of water, the mixture was added in 20.0 mL of ether and was separated. The aqueous layer was extracted with ether, and the combined organic extracts were washed with saturated $NaHCO_3$ and saturated NaCl and dried over Na_2SO_4. The solvent was removed to afford an oily product (16.29 g). The crude product was purified by chromatography with silica gel (490 g, elution with 4% ethyl acetate/hexane) to afford the 5,5-dimethyl-3,7-dioxa-1-isobutylspiro[2.5]oct-1-ene in 29% yield (5.78 g). To a solution of 1.96 g of 5,5-dimethyl-3,7-dioxa-1-isobutylspiro[2.5]oct-1-ene (10.0 mmol) in 30.0 mL of ether was added 227 mg of potassium *tert*-butoxide (2.0 mmol) in 2.50 mL of DMSO and ether (1:2 v/v) at −23 °C under nitrogen. After being stirred for 15 min at this temperature, the solution was warmed to 0 °C and stirred for 1 h. Then the solution was quenched by addition of saturated NH_4Cl. The aqueous layer was extracted with ether, the combined organic extracts were washed with saturated NaCl and dried over Na_2SO_4, and the solvent was removed to afford an oily product. Purification on silica gel (97 g, elution with 3% ethyl acetate/hexane) afforded 1.79 g of the isobutylidenecyclopropanone acetal **1c** and **11** as a colorless oil (9.1 mmol, 91% yield, a 89:11 mixture of **1c** and **11**). The diastereomers were separated by recycling HPLC. The overall yield was over 26%. ***(E)*-6,6-Dimethyl-4,8-dioxa-1-isobutylidenespiro[2.5]octane (1c):** IR (neat) 2958, 2904, 2870, 2362, 1774, 1745, 1468, 1394, 1363, 1350, 1250, 1130, 1074, 1026, 852, 760; ^{1}H NMR (400 MHz, $CDCl_3$) 1.00 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.09 (d, J = 6.4 Hz, 6H, CH_3), 1.59 (br s, 2H, CH_2), 2.51 (dq, J = 7.0, 6.4 Hz, 1H, CH_3CH), 3.61 (s, 2H, OCH_2), 3.62 (s, 2H, OCH_2), 6.19 (dt, J = 7.0, 3.6 Hz, 1H, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$) 17.89 (CH_2), 21.93 (CH_3, 2C), 22.28 (CH_3), 22.47 (CH_3), 30.71-(CH_3CH), 76.67 (OCH_2, 2C), 84.00 (OC), 122.68 (CH=*C*), 128.13 (C=*C*H). ***(Z)*-6,6-Dimethyl-4,8-dioxa-1-isobutylidenespiro[2.5]octane (11):** IR (neat) 3851, 2958, 2870, 2360, 2341, 1778, 1469, 1412, 1394, 1362, 1348, 1215, 1128, 1070, 1038, 1003; ^{1}H NMR (400 MHz, $CDCl_3$) 0.84 (s, 3H, CH_3), 1.12 (d, J = 6.4 Hz, 6H, CH_3), 1.44 (t, J = 3.0 Hz, 2H, CH_2), 2.45−2.60 (m, 1H, CH_3CH), 3.62 (dd, J = 10.2, 9.0 Hz, 4H, OCH_2), 5.82−5.88 (m, 1H, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$) 17.16 (CH_2), 21.73 (CH_3, 2 C), 22.01 (CH_3), 22.82 (CH_3), 30.88 (CH_3C), 31,41 (CH_3CH), 76.20 (OCH_2, 2C), 85.43 (OC), 121.99 (*C*=CH), 131.02 (C=*C*H).

Preparation of Alkyloximes (3): Methyl Glyoxylate *O*-Benzyloxime. To a suspension of 18.01 g of dimethyl tartrate (200.0 mmol) in 390.0 mL of ether was added 55.77 g of $HIO_4 \cdot 2H_2O$ (244.7 mmol) for 15 min at 0 °C under nitrogen, and resulting suspension was stirred for 25 min at this temperature and then allowed to warm to room temperature. The suspension was stirred with 15.50 g of dried, powdered molecular sieve (4A) for 25 min. The reaction mixture was passed through a Celite pad, and the filtrate was concentrated in vacuo and was distilled over 4.20 g of P_2O_5 at 50−70 °C (28.5−30.0 mmHg) to afford an oily product. To a suspension of 32.00 g of $BnONH_2 \cdot HCl$ (200.5 mmol) and 23.73 g of pyridine (300.0 mmol) in 100.0 mL of CH_2Cl_2 was added a solution of the oily product in 20.00 mL of CH_2Cl_2 through a cannula over 10 min at room temperature under nitrogen. After being stirred for 1 h, the mixture was added 50.0 mL of water. The aqueous layer was extracted with ether, and the combined organic extracts were washed with saturated NaCl and dried over $MgSO_4$, and the solvent was removed to afford a crude product. Purification on silica gel (406 g, elution with 9% ethyl acetate/hexane) afforded 33.42 g of the title compound as a colorless oil (173.0 mmol, 87% yield, a 93:7 mixture of anti and syn isomer). The diastereomer mixture was subjected to recycling preparative HPLC to obtain the pure *anti*-isomer. Anal. (determined for a 93:7 mixture) Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.36; H, 5.87; N, 7.42. *anti*-isomer: IR (neat) 3064, 3033, 2952, 2885, 1724, 1600,

(25) Takenaka, Y.; Ejiri, S.; Yamago, S.; Nakamura, E.; Ohashi, Y. Manuscript in preparation.

1496, 1454, 1439, 1369, 1327, 1273, 1207, 1182, 1047, 1001, 924, 868, 760, 735, 698, 615, 536, 492; ^{1}H NMR (400 MHz, $CDCl_3$) 3.84 (s, 3H, CO_2CH_3), 5.28 (s, 2H, OCH_2Ph), 7.38 (s, 5H, C_6H_5), 7.52 (s, 1H, N=CH); ^{13}C NMR (100 MHz, $CDCl_3$) 52.53 (CH3), 78.15 (OCH_2Ph), 128.52 (CH), 128 55 (CH, 2C), 128.87 (CH, 2C), 140.88 (N=CH).

***anti-tert*-Butyl Glyoxylate *O*-Benzyloxime.** To 100.0 mL of ^{t}BuOH was added 375.0 mL of BuLi (1.60 M hexane solution) over 35 min at 0 °C under nitrogen, and the resulting solution was stirred for 30 min at this temperature. The solution was added a solution of 45.89 g of fumaryl chloride (300.0 mmol) in 130.0 mL of ether through a dropping funnel at room temperature for 1.5 h. The solution became brown. After being stirred for 5 h, the solution was quenched by addition of 120.0 mL of water. The combined organic extracts were washed with saturated $NaHCO_3$ and saturated NaCl and dried over Na_2SO_4, and the solvent was removed to afford brown crystals. Recrystallization from hexane afforded di-*tert*-butyl fumarate (46.24 g, 202.5 mmol, 68% yield). To a solution of 11.40 g of di-*tert*-butyl fumarate (49.9 mmol) and 0.50 mL of pyridine in 50.00 mL of CH_2Cl_2 was bubbled with O_3 in O_2 at −23 °C for 4.5 h. Excess O_3 was removed by passing O_2 through the solution. To the solution was added 6.21 g of dimethyl sulfide (100.0 mmol) and the mixture was warmed to room temperature. The solvent was removed to afford an oily product (14.40 g). To a suspension 15.96 g of $BnONH_2$·HCl (100.0 mmol) and 11.07 g of pyridine (139.9 mmol) in 90.0 mL of CH_2Cl_2 was added a solution of the crude oil in 20.0 mL of CH_2Cl_2 through a cannula over 15 min at room temperature under nitrogen. After being stirred 2.5 h, to the mixture was added 50.0 mL of water. The aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were washed with saturated NaCl and dried over $MgSO_4$, and the solvent was removed to afford a crude product (25.37 g). Purification on silica gel (150 g, elution with 8% ethyl acetate/hexane) afforded 14.02 g of the title compound as a colorless oil (59.6 mmol, 60% yield). The overall yield of three steps was 41%. IR (neat) 2979, 2935, 1738, 1714, 1599, 1477, 1456, 1394, 1369, 1336, 1279, 1259, 1214, 1159, 1047, 1026, 972, 922, 843, 781, 737, 698; ^{1}H NMR (400 MHz, $CDCl_3$) 1.52 (s, 9H, CH_3), 5.27 (s, 2H, OCH_2), 7.35 (br s, 5H, C_6H_5), 7.47 (s, 1H, CH=N); ^{13}C NMR (100 MHz, $CDCl_3$) 27.97 (CH_3, 3C), 77.81 (OCH_2), 82.65 ($OC(CH_3)_3$), 128.37 (CH), 128.52 (CH, 2C), 128.57 (CH, 2C), 136.16 (C), 142.40 (N=CH), 160.98 (C=O). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.31; H, 7.35; N, 5.93.

Cycloaddition Reaction of Methylenecyclopropane (1a) and Oxime Ethers: 1-Benzyloxy-2-(4′-chlorophenyl)-4-(2,2-dimethyl-3-hydroxypropoxycarbonyl)pyrrolidine (5B). A solution of **1a** (185 mg, 1.2 mmol) and *p*-chlorobenzaldehyde *O*-benzyloxime (246 mg, 1.0 mmol, >99.8% anti) in CD_3CN (0.23 mL) in a sealed NMR tube was heated for 31 h at 100 °C. The reaction mixture was treated with 10% aqueous HCl (1.0 N) in THF (1.0 mL) and stirred for 25 min. After usual workup (addition of saturated $NaHCO_3$, extraction with ether, washing organic extracts with saturated NaCl, drying over Na_2SO_4, and concentration in vacuo), purification of the resulting crude mixture by chromatography with silica gel (14 g, elution with 40% ethyl acetate in hexane) afforded the title compound **5B** in 99% yield (415 mg) as a 64:36 diastereomeric mixture. These diastereomers were separated by preparative recycle HPLC for characterization. **Major diastereomer of 5B**: IR (neat) 3450, 1724, 1496, 1373, 1188, 1092, 1050, 1019, 701; ^{1}H NMR (400 MHz, $CDCl_3$) 0.91 (s, 6H, CH_3), 2.00 (br dt, J = 12.7, 9.3 Hz, 1H, CH_2), 2.26 (br s, 1H, OH), 2.46 (ddd, J = 12.7, 8.8, 5.4 Hz, 1H, CH_2), 3.03−3.18 (m, 2H, $CHCO_2$, NCH_2), 3.28 (s, 2H, CH_2OH), 3.61 (dd, J = 8.8, 7.8 Hz, 1H, NCH_2), 3.93 (d, J = 11.2 Hz, 1H, CO_2CH_2), 3.98 (d, J = 11.2 Hz, 1H, CO_2CH_2), 4.01 (dd, J = 9.3, 8.8 Hz, 1H, NCH), 4.41 (d, J = 11.2 Hz, 1H, OCH_2), 4.46 (d, J = 11.2 Hz, 1H, OCH_2), 7.06−7.16 (m, 2H, C_6H_5), 7.19−7.27 (m, 3H, C_6H_5), 7.28 (d, J = 8.3 Hz, 2H, *p*-ClC_6H_4), 7.33 (d, J = 8.3 Hz, 2H, *p*-ClC_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$) 21.39 (CH_3, 2C), 33.24 (CH_2), 36.39 (C), 39.09 ($CHCO_2$), 58.39 (NCH_2), 68.07 (CH_2OH), 69.70 (CO_2CH_2), 70.18 (NCH), 75.73 (OCH_2), 127.69 (CH), 128.12 (CH, 2C), 128.34 (CH, 2C), 128.52 (CH, 2C), 129.14 (CH, 2C), 133.05 (C), 137.37 (C), 139.07 (C), 174.76 (C=O). Anal. Calcd for $C_{23}H_{28}NO_4Cl$: C, 66.10; H, 6.75; N, 3.35. Found: C, 65.99; H, 6.67; N, 3.16. **Minor diastereomer of 5B**: IR (neat) 3430, 1735, 1492, 1370, 1192, 1091, 1050, 1017, 728, 700; ^{1}H NMR (400 MHz, $CDCl_3$) 0.90 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 2.06−2.22 (m, 1 H, CH_2), 2.20 (br s, 1H, OH), 2.36−2.48 (m, 1H, CH_2), 3.04−3.18 (m, 2H, $CHCO_2$, NCH_2), 3.26 (s, 2H, CH_2OH), 3.57−3.66 (m, 1H, NCH_2), 3.94 (dd, J = 9.8, 8.8 Hz, 1H, NCH), 3.95 (d, J = 10.7 Hz, 1H, CO_2CH_2), 3.99 (d, J = 10.7 Hz, 1H, CO_2CH_2), 4.42 (d, J = 11.2 Hz, 1H, OCH_2), 4.49 (d, J = 11.2 Hz, 1H, OCH_2), 7.08−7.16 (m, 2H, Ph), 7.20−7.27 (m, 3H, Ph), 7.28 (d, J = 9.1 Hz, 2H, *p*-ClC_6H_4), 7.35 (d, J = 9.1 Hz, 2H, *p*-ClC_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$) 21.44 (CH_3, 2C), 33.54 (CH_2), 36.47 (C), 39.48 ($CHCO_2$), 58.74 (NCH_2), 68.16 (CH_2OH), 69.81 (CO_2CH_2), 70.90 (NCH), 75.87 (OCH_2), 127.73 (CH), 128.16 (CH, 2C), 128.38 (CH, 2C), 128.64 (CH, 2C), 129.17 (CH, 2C), 133.08 (C), 137.39 (C), 139.29 (C), 174.78 (C=O). Anal. Calcd for $C_{23}H_{28}NO_4Cl$: C, 66.10; H, 6.75; N, 3.35. Found: C, 66.14; H, 7.13; N, 3.26.

Cycloaddition of 1a with *p*-Chlorobenzaldehyde *O*-Benzyloxime in C_3H_7CN. A solution of **1a** (0.79 g, 5.09 mmol) and *p*-chlorobenzaldehyde *O*-benzyloxime (1.02 g, 4.15 mmol, >99.8% anti) in C_3H_7CN (0.95 mL) was heated for 30 h at 100 °C under nitrogen. The reaction mixture was treated with 10% aqueous HCl (1.0 N) in THF (2.0 mL) and stirred for 35 min. After the usual workup, purification of the resulting crude mixture by chromatography with silica gel (102 g, elution with 25% and 40% ethyl acetate in hexane) afforded **5B** in 90% yield (1.56 g) as a 72:28 diastereomeric mixture.

Cycloaddition of 1a with *p*-Chlorobenzaldehyde *O*-Benzyloxime without Solvent. A mixture of **1a** (0.79 g, 5.09 mmol) and *p*-chlorobenzaldehyde *O*-benzyloxime (1.02 g, 4.15 mmol, >99.8% anti) was heated for 46 h at 100 °C under nitrogen. The reaction mixture was treated with 10% aqueous HCl (1 N) in THF (2 mL) and stirred for 30 min. After usual workup, purification of the resulting crude mixture by chromatography with silica gel (100 g, elution with 25% and 40% ethyl acetate in hexane) afforded **5B** in 98% yield (1.70 g) as a 73:27 diastereomeric mixture.

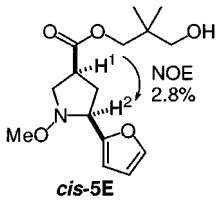
4-(2,2-Dimethyl-3-hydroxypropoxycarbonyl)-1-methoxy-2-phenylpyrrolidine (5C). A solution of **1a** (555 mg, 3.6 mmol) and benzaldehyde *O*-methyloxime (406 mg, 3.0 mmol, 98% anti) in CH_2Cl_2 (0.9 mL) was heated at 80 °C under 10 kbar for 21 h. The crude mixture was treated with 10% v/v water in THF (2.0 mL) and acetic acid (50 mL) for 30 min at room temperature. Solvent was removed, and the resulting crude material was purified by chromatography with silica gel (20 g, elution with 30% ethyl acetate in hexane) to afford the title compound (**5C**) in 76% yield (700 mg) as a 70:30 mixture of two diastereomers. The diastereomers were separated by recycling HPLC for characterization. **Major diastereomer of 5C**: IR (neat) 3440, 1735, 1142, 1060, 703; ^{1}H NMR (500 MHz, $CDCl_3$) 0.93 (s, 6H, CH_3), 2.12−2.23 (m, 1H, CH_2), 2.42 (br s, 1H, OH), 2.46 (ddd, J = 13.3, 9.6, 7.8 Hz, 1H, CH_2), 3.09 (dd, J = 10.5, 9.1 Hz, 1H, CH_2N), 3.11−3.20 (m, 1H, $CHCO_2$), 3.31 (s, 2H, CH_2OH), 3.35 (s, 3H, OCH_3), 3.76 (dd, J = 10.5, 3.7 Hz, 1H, CH_2N), 3.93 (dd, J = 10.1, 7.8 Hz, 1H, CHN), 3.97 (d, J = 11.0 Hz, 1H, CH_2O), 4.01 (d, J = 11.0 Hz, 1H, CH_2O), 7.23−7.29 (m, 1H, C_6H_5), 7.31−7.36 (m, 2H, C_6H_5), 7.42−7.46 (m, 2H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$) 21.41 (CH_3, 2C), 33.82 (CH_2), 36.44 (C), 39.51 ($CHCO_2$), 57.32 (CH_2N), 61.05 (OCH_3), 68.15 (CH_2OH), 69.82 (CH_2O), 71.38 (CHN), 127.36 (CH), 127.53 (CH, 2C), 128.24 (CH, 2C), 140.68 (C), 174.89 (C=O). Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.22; H, 8.48; N, 4.44. **Minor diastereomer of 5C**: IR (neat) 3440, 1732, 1182, 1055, 1021, 700; ^{1}H NMR (400 MHz, $CDCl_3$) 0.94 (s, 6H, CH_3), 2.07 (br dd, J = 23.0, 10.3 Hz, 1H, CH_2), 2.29 (br s, 1H, OH), 2.51 (ddd, J = 13.2, 8.3, 4.9 Hz, 1H, CH_2), 3.08 (dd, J = 19.0, 10.3 Hz, 1H, CH_2N), 3.13−3.23 (m, 1H, $CHCO_2$), 3.31 (s, 2H, CH_2OH), 3.35 (s, 3H, OCH_3), 3.76 (dd, J = 10.3, 7.8 Hz, 1H, CH_2N), 3.96 (d, J = 11.2 Hz, 1H, CH_2O), 3.94−4.03 (m, 1H, CHN), 4.01 (d, J = 11.2 Hz, 1H, CH_2O), 7.24−7.31 (m, 1H, C_6H_5), 7.31−7.38 (m, 2H, C_6H_5),

7.40−7.46 (m, 2H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$) 21.43 (CH_3, 2C), 33.35 (CH_2), 36.46 (C), 39.20 (*C*HCO_2), 57.83 (CH_2N), 61.07 (OCH_3), 68.11 (CH_2OH), 69.68 (CH_2O), 70.67 (CHN), 127.38 (CH), 127.53 (CH, 2C), 128.27 (CH, 2 C), 140.57 (C), 175.00 (C=O). Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.28; H, 8.50; N, 4.43.

4-(2,2-Dimethyl-3-hydroxypropoxycarbonyl)-1-methoxy-2-(4′-methoxyphenyl)pyrrolidine (5D). A solution of **1a** (432 mg, 2.8 mmol) and *p*-anisaldehyde *O*-methyloxime (413 mg, 2.5 mmol, >99% anti) in of CH_2Cl_2 (0.8 mL) was heated at 80 °C under 10 kbar for 24 h. The crude mixture was treated with 10% v/v water in THF (2.0 mL) and acetic acid (50 mL) for 30 min at room temperature, and purification by chromatography with silica gel (20 g, elution with 40% ethyl acetate in hexane) afforded the title compound (**5D**) in 70% yield (590 mg) as a 70:30 mixture of two diastereomers. The diastereomers were separated by recycling HPLC. **Major diastereomer of 5D**: IR (neat) 3450, 1732, 1615, 1516, 1248, 1178, 1057, 1038, 830, 735; ^{1}H NMR (400 MHz, $CDCl_3$), 0.93 (s, 6H, CH_3), 2.17 (br s 1H, C*H*$_2$), 2.42 (ddd, J = 13.2, 9.8, 7.3 Hz, 1H, C*H*$_2$), 2.55 (br s, 1H, OH), 3.07 (dd, J = 10.3, 9.3 Hz, 1H, C*H*$_2$N), 3.10−3.19 (m, 1H, $CHCO_2$), 3.32 (br s, 2H, C*H*$_2$-OH), 3.33 (s, 3H, OCH_3), 3.75 (dd, J = 10.3, 3.4 Hz, 1H, C*H*$_2$N), 3.79 (s, 3H, OCH_3), 3.87 (dd, J = 9.8, 7.8 Hz, 1H, CHN), 3.97 (d, J = 11.2 Hz, 1H, C*H*$_2$O), 4.01 (d, J = 11.2 Hz, 1H, C*H*$_2$O), 6.87 (d, 2H, J = 8.8 Hz, C_6H_4), 7.35 (d, 2H, J = 8.8 Hz, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$) 21.38 (CH_3, 2C), 33.57 (CH_2), 36.38 (C), 39.43 (*C*HCO_2), 55.10 (OCH_3), 57.20 (CH_2N), 61.01 (OCH_3), 68.10 (CH_2OH), 69.78 (CH_2O), 70.77 (CHN), 113.57 (CH, 2C), 128.65 (CH, 2C), 132.49 (C), 158.84 (C), 174.89 (C=O). Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 64.29; H, 7.89; N, 4.00. **Minor diastereomer of 5D**: IR (neat) 3440, 1732, 1612, 1513, 1245, 1175, 1052, 1038, 829, 732; ^{1}H NMR (400 MHz, $CDCl_3$) 0.93 (s, 6H, CH_3), 2.06 (br q, J = 11.2 Hz, 1H, C*H*$_2$), 2.31 (br s, 1H, OH), 2.46 (ddd, J = 13.2, 7.8, 4.4 Hz, 1H, C*H*$_2$), 3.05 (dd, J = 9.8, 9.6 Hz, 1H, C*H*$_2$N), 3.15−3.22 (m, 1H, $CHCO_2$), 3.31 (br s, 2H, C*H*$_2$OH), 3.32 (s, 3H, OCH_3), 3.73 (dd, J = 10.3, 8.3 Hz, 1H, C*H*$_2$N), 3.80 (s, 3H, OCH_3), 3.92−4.00 (m, 1H, CHN), 3.95 (d, J = 10.7 Hz, 1H, C*H*$_2$O), 4.01 (d, J = 10.7 Hz, 1H, C*H*$_2$O), 6.88 (d, J = 8.8 Hz, 2H, C_6H_4), 7.33 (d, J = 8.8 H, 2H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$) 21.42 (CH_3, 2C), 33.20 (CH_2), 36.45 (C), 39.16 (*C*HCO_2), 55.17 (OCH_3), 57.80 (CH_2N), 61.07 (OCH_3), 68.10 (CH_2OH), 69.67 (CH_2O), 70.13 (CHN), 113.63 (CH, 2C), 128.69 (CH, 2C), 132.39 (C), 158.90 (C), 175.08 (C=O). Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 63.89; H, 8.24; N, 4.02.

4-(2,2-Dimethyl-3-hydroxypropoxycarbonyl)-1-methoxy-2-(2′-furyl)pyrrolidine (5E). A solution of **1a** (152 mg, 1.0 mmol) and 2-furaldehyde *O*-methyloxime (109 mg, 0.87 mmol) in CD_3CN (0.34 mL) in a sealed NMR tube was heated for 85 h at 100 °C. To the mixture was added water (0.5 mL) and silica gel (0.5 g), and the slurry was stirred for 1 h. Purification by chromatography with silica gel (3.8 g, elution with 40% ethyl acetate in hexane) afforded the title compound **5E** in 90% yield (234 mg) as a 60:40 diastereomeric mixture. These diastereomers were separated by preparative recycle HPLC for characterization. An NOE experiment revealed that the major isomer had cis stereochemistry (see below). ***cis*-5E**: IR (neat) 3450, 1732, 1193, 1065, 1011, 738; ^{1}H NMR (400 MHz, $CDCl_3$) 0.93 (s, 6H, CH_3), 2.39−2.52 (m, 2H, C*H*$_2$), 2.53 (br s, 1H, OH), 3.19−3.30 (m, 2H, C*H*$_2$N, $CHCO_2$), 3.30 (br s, 2H, C*H*$_2$OH), 3.42 (br s, 3H, OCH_3), 3.47−3.57 (m, 1H, C*H*$_2$N), 3.96 (d, J = 11.2 Hz, 1H, C*H*$_2$O), 4.00 (d, J = 11.2 Hz, 1H, C*H*$_2$O), 4.21 (t, J = 8.1 Hz, 1H, CHN), 6.29−6.35 (m, 2H, CH), 7.37−7.40 (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) 21.38 (CH_3, 2C), 30.32 (CH_2), 36.38 (C), 40.81 (*C*HCO_2), 57.78 (CH_2N), 60.57 (OCH_3), 65.15 (CH_2OH), 68.02 (CH_2O), 69.75 (CHN), 107.51 (CH), 110.15 (CH), 142.08 (CH), 153.16 (C), 174.67 (C=O). Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.30; H, 8.07; N, 4.66.

The stereochemistry was assigned according to differential NOE experiments. Irradiation of H^1 resulted in an NOE enhancement of 2.8% at H^2, indicating a cis orientation of H^1 and H^2.



***cis*-5E**

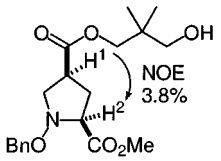
***trans*-5E**: IR (neat) 3460, 1730, 1182, 1053, 1020, 932; ^{1}H NMR (400 MHz, $CDCl_3$) 0.93 (s, 6H, CH_3), 2.28−2.44 (m, 1H, C*H*$_2$), 2.41 (br s, 1H, OH), 2.44−2.55 (m, 1H, C*H*$_2$), 3.17 (dd, J = 7.8, 7.3 Hz, 1H, C*H*$_2$N), 3.18−3.27 (m, 1H, $CHCO_2$), 3.31 (br s, 2H, C*H*$_2$OH), 3.37 (s, 3H, OCH_3), 3.63 (dd, J = 10.2, 7.3 Hz, 1H, C*H*$_2$N), 3.95 (d, J = 10.7 Hz, 1H, C*H*$_2$O), 4.01 (d, J = 10.7 Hz, 1H, C*H*$_2$O), 4.20 (t, J = 8.3 Hz, 1H, CHN), 6.28 (d, J = 2.9 Hz, 1H, CH), 6.34 (dd, J = 2.9, 1.7 H, 1H, CH), 7.39−7.42 (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) 21.40 (CH_3, 2C), 29.87 (CH_2), 36.43 (C), 40.10 (*C*HCO_2), 58.22 (CH_2N), 60.78 (OCH_3), 64.44 (CH_2OH), 68.02 (CH_2O), 69.71 (CHN), 107.68 (CH), 110.17 (CH), 142.10 (CH), 152.76 (C), 174.92 (C=O). Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.29; H, 7.99; N, 4.60.

1-Benzyloxy-4-(2,2-dimethyl-3-hydroxypropoxycarbonyl)-2-(3′-pyridyl)pyrrolidine (5F). A solution of **1a** (101.8 mg, 0.66 mmol) and 3-pyridinecarbaldehyde *O*-benzyloxime (127.4 mg, 0.60 mmol, 97.4% anti) in CD_3CN (0.23 mL) in a sealed NMR tube was heated for 29 h at 100 °C. After solvent was removed, purification by chromatography with silica gel (14 g, elution with 40% ethyl acetate in hexane) afforded the title compound (**5F**) in 66% yield (151.1 mg) as a 70:30 diastereomeric mixture. Spectra were taken for a 7:3 mixtures of the isomers. IR (neat) 3350, 1735, 1372, 1192, 1057, 1030, 735, 700; ^{1}H NMR (400 MHz, $CDCl_3$) 0.92 (s, 4.2H, $(CH_3)_2$), 0.93 (s, 1.8H, $(CH_3)_2$), 1.98−2.12 (m, 0.3H, C*H*$_2$), 2.12−2.26 (m, 0.7H, C*H*$_2$), 2.40−2.57 (m, 1H, C*H*$_2$), 3.07−3.22 (m, 2H, $CHCO_2$, NC*H*$_2$), 3.30 (s, 1.4H, C*H*$_2$OH), 3.33 (s, 0.6H, C*H*$_2$OH), 3.48 (br s, OH), 3.62−3.70 (m, 1H, NC*H*$_2$), 3.93−4.04 (m, 3H, CO_2CH_2, NCH), 4.42 (d, J = 11.2 Hz, 0.7H, OC*H*$_2$Ph), 4.39−4.50 (m, 0.6H, OC*H*$_2$Ph), 4.49 (d, J = 11.2 Hz, 0.7H, OC*H*$_2$-Ph), 7.06−7.14 (m, 1H, Py), 7.20−7.32 (m, 5H, C_6H_5), 7.71 (br d, J = 6.4 Hz, 0.3H, Py), 7.77 (br d, J = 7.8 Hz, 0.7H, Py), 8.57 (br s, 1H, Py), 8.64 (br s, 1H, Py); ^{13}C NMR (100 MHz, $CDCl_3$) 21.42 (CH_3, 2C), 32.97 (CH_2, 0.3C), 33.16 (CH_2, 0.7C), 36.36 (C, 1C), 39.18 (CH, 0.3C), 39.57 (CH, 0.7C), 58.07 (NCH_2, 0.7C), 58.46 (NCH_2, 0.3C), 67.97 (CH_2OH, 1C), 68.46 (NCH, 0.3C), 68.94 (NCH, 0.7C), 69.83 (*C*H_2OCO, 0.3C), 69.89 (CH_2-OCO, 0.7C), 75.74 (CH_2O, 0.3C), 75.80 (CH_2O, 0.7C), 123.58 (CH, 0.3C), 123.69 (CH, 0.7C), 127.78 (CH, 1C), 128.13 (CH, 2C), 128.54 (CH, 0.6C), 128.61 (CH, 1.4C), 135.67 (CH, 0.3C), 135.79 (CH, 0.7C), 136.63 (C, 0.3C), 136.74 (C, 0.7C), 137.10 (C, 1C), 148.18 (CH, 0.7C), 148.36 (CH, 0.3C), 148.95 (CH, 0.7C), 149.08 (CH, 0.3C), 174.40 (C=O, 0.7C), 174.48 (C=O, 0.3C). Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.72; H, 7.34; N, 7.29. Found: C, 68.92; H, 7.30; N, 7.23.

1-Benzyloxy-4-(2,2-dimethyl-3-hydroxypropoxycarbonyl)-2-methoxycarbonylpyrrolidine (5A). A solution of **1a** (185 mg, 1.20 mmol) and methyl glyoxylate *O*-benzyloxime (193 mg, 1.00 mmol, 91% anti) in CD_3CN (0.31 mL) in a sealed NMR tube was heated for 1.5 h at 80 °C. The reaction mixture was treated with water (10 mL) and silica gel (100 mg) for 1 h at room temperature and the silica gel was removed. Purification by chromatography with silica gel (12 g, elution with 43% ethyl acetate in hexane) afforded the title compound (**5A**) in 79% yield (289 mg) as a 73:27 diastereomeric mixture. The diastereomers were separated by preparative recycling HPLC for characterization. An NOE experiment revealed that the major isomer had cis stereochemistry (see below). ***cis*-5A**: IR (neat) 3440, 1738, 1202, 1051; ^{1}H NMR (400 MHz, $CDCl_3$) 0.89 (s, 6H, CH_3), 2.24 (br s, 1H, OH), 2.31−2.50 (m, 2H, C*H*$_2$), 3.12−3.24 (m, 1H, C*H*CO_2), 3.27 (br s, 2H, C*H*$_2$OH), 3.30 (dd, J = 11.7, 8.3 Hz, 1H, NC*H*$_2$), 3.52 (dd, J = 11.7, 6.3 Hz, 1H, NC*H*$_2$), 3.73 (s, 3H, OCH_3), 3.90 (dd, J = 8.3, 8.3 Hz, 1H, C*H*CO_2), 3.94 (d, J = 2.4 Hz, 2H, CO_2CH_2), 4.77 (s, 2H, OCH_2), 7.26−7.39 (m, 5H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$)

21.43 (CH_3, 2C), 29.57 (CH_2), 36.41 (C), 41.08 (*C*HCO_2), 52.19 (OCH_3), 58.90 (CH_2N), 68.01 (CH_2OH), 69.56 (CHN), 69.77 (CO_2CH_2), 75.59 (OCH_2), 127.91 (*p*-Ph), 128.29 (*o*-Ph, 2C), 128.68 (*m*-Ph, 2C), 137.09 (ipso-Ph), 171.62 (C=O), 174.00 (C=O). Anal. Calcd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.15; H, 7.39; N, 3.62.

The stereochemistry was assigned according to differential NOE experiments. Irradiation of H^1 resulted in an NOE enhancement of 3.8% at H^2, indicating a cis orientation of H^1 and H^2.



***cis*-5A**

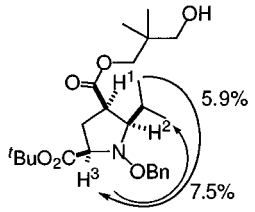
***trans*-5A**: IR (neat) 3400, 1739, 1240, 1182, 1053; ^{1}H NMR (400 MHz, $CDCl_3$) 0.89 (s, 6H, CH_3), 2.12 (br s, 1H, OH), 2.18−2.33 (m, 1H, CH_2), 2.43−2.56 (m, 1H, CH_2), 3.10−3.25 (m, 2H, NCH_2CHCO_2), 4.10 (m, 3H, NCH, CO_2CH_2), 4.78 (s, 2H, OCH_2), 7.26−7.39 (m, 5H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$) 21.39 (CH_3, 2C), 28.90 (CH_2), 36.40 (C), 40.35 (*C*HCO_2), 52.11 (OCH_3), 58.97 (CH_2N), 68.06 (CH_2OH), 68.92 (CHN), 69.80 (CO_2CH_2), 75.67 (OCH_2), 127.88 (*p*-Ph), 128.26 (*o*-Ph, 2C), 128.61 (*m*-Ph, 2C), 137.17 (ipso-Ph), 171.55 (C=O), 174.29 (C=O). Anal. Calcd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.63; H, 7.60; N, 3.82.

Cycloaddition of 1a with Methyl Glyoxylate *O*-Benzyloxime under Dry Air without Solvent. A mixture of **1a** (4.81 g, 31 mmol) and methyl glyoxylate *O*-benzyloxime (5.01 g, anti:syn = 93:7, 25.9 mmol) was heated for 4 h at 100 °C. After ^{1}H NMR analysis of the reaction mixture indicated near quantitative formation of the ketene acetal,the reaction mixture was treated with 10% aqueous HCl (1.0 N) in THF (5.0 mL) and stirred for 1 h. After usual workup, purification by chromatography with silica gel (100 g, elution with 8% and 45% ethyl acetate in hexane) afforded cycloadduct **5A** in 89% yield (8.40 g, 23.0 mmol) as a 71:29 diastereomeric mixture.

Cycloaddition of 1c with Glyoxalic Acid *tert*-Butyl Ester *O*-Benzyloxime. 1-Benzyloxy-*cis*-4-(2,2-dimethyl-3-hydroxypropoxycarbonyl)-*cis*-5-isopropyl-*r*-2-*tert*-methoxycarbonylpyrrolidine (*cis*-9). A solution of **1c** (177 mg, 0.9 mmol) and glyoxalic acid *tert*-butyl ester *O*-benzyloxime **3** (176 mg, 0.75 mmol, >99% anti) in CD_3CN (0.35 mL) in a sealed NMR tube was heated for 17 h at 100 °C. The reaction mixture was treated with 10% aqueous HCl (1.0 N) in THF (2.0 mL) and stirred for 5 min. After usual workup (addition of saturated $NaHCO_3$, extraction with ether, washing organic extracts with saturated NaCl, drying over Na_2SO_4, and concentration in vacuo), purification by chromatography with silica gel (22 g, elution with 24% and 30% ethyl acetate in hexane) afforded the titled compound (*cis*-**9**) and 1-benzyloxy-*cis*-4-(2,2-dimethyl-3-hydroxypropoxycarbonyl)-*trans*-3-isopropyl-*r*-2-*tert*-methoxycarbonylpyrrolidine (*trans*-**10**) in 79% (266 mg) and 10% (34 mg) yields. The ratio of diastereomers (***cis*-9**:***trans*-9** and ***cis*-10**:***trans*-10**) was determined by ^{1}H NMR and ^{13}C NMR. NOE experiments revealed that **9** had 2,4-cis and 2,5-cis stereochemistry, and that **10** was 2,3-trans and 2,4-cis stereochemisty.

***cis*-9**: IR (neat) 3523 (OH), 2962, 2873, 1732 (C=O), 1456, 1369, 1257, 1225, 1157, 1052, 912, 847, 735, 698, 528; ^{1}H NMR (400 MHz, $CDCl_3$) 0.92 (s, 6H, CCH_3), 0.93 (d, J = 8.0 Hz, 3H, $CHCH_3$), 1.00 (d, J = 8.0 Hz, 3H, $CHCH_3$), 1.49 (s, 9H, $OCCH_3$), 2.00 (dq, J = 8.0, 8.0 Hz, 1H, CH_3CH), 2.10 (ddd, J = 13.0, 10.0, 10.0 Hz, 1H, CH_2), 2.27 (ddd, J = 13.0, 8.0, 5.0 Hz, 1H, CH_2), 2.78 (ddd, J = 10.0, 8.0, 5.0 Hz, 1H, $CHCO_2$), 3.30 (dd, J = 8.0, 4.0 Hz, 3H, NC*H*, CH_2OH), 3.83 (dd, J = 10.0, 8.0 Hz, 1H, $NCHCO_2$), 3.93 (s, 2H, CO_2CH_2), 4.78 (d, J = 11 Hz, 1H, OCH_2Ph), 4.95 (d, J = 11 Hz, 1H, OCH_2Ph), 7.25−7.35 (m, 5H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$) 16.98 (CH_3), 19.67 (CH_3), 21.50 (CH_3, 2C), 28.03 (CH_3, 3C), 29.12 (CH_3CH), 30.06 (CH_2), 36.47 (CH_3C), 40.81 (*C*HCO_2), 68.08 (CH_2OH), 69.41 (*NC*HCO_2), 69.83 (CO_2CH_2), 75.94 (NCH), 76.51 (OCH_2), 81.19 ($OCCH_3$), 127.84 (CH), 128.28(CH, 2C), 128.59 (CH, 2C), 137.17 (C), 171.31 (CO_2), 175.54 (CO_2). Anal. Calcd for $C_{25}H_{39}NO_6$: C, 66.79; H, 8.74; N, 3.12. Found: C, 66.55; H, 8.44; N, 3.35.

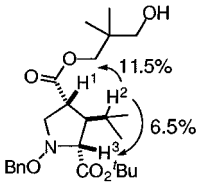
The stereochemistry was assigned according to differential NOE experiments. Irradiation of H^1 resulted in an NOE enhancement of 5.9% at H^3 and irradiation of H^3 resulted in an NOE enhancement of 7.5% at H^2, indicating a cis orientation of H^1, H^2, and H^3.



***cis*-9**

1-Benzyloxy-*cis*-4-(2,2-dimethyl-3-hydroxypropoxycarbonyl)-*trans*-5-isopropyl-*r*-2-*tert*-methoxycarbonylpyrrolidine (*trans*-10): IR (neat) 3510, 2962, 2873, 1732 (C=O), 1473, 1456, 1392, 1369, 1255, 1155, 1054, 847, 748, 698; ^{1}H NMR (400 MHz, $CDCl_3$) 0.91 (s, 6H, CCH_3), 0.93 (d, J = 6.8 Hz, 3H, $CHCH_3$), 0.95 (d, J = 6.8 Hz, 3H, $CHCH_3$), 1.48 (s, 9H, $OCCH_3$), 1.81 (dq, J = 6.8, 6.8 Hz, 1H, CH_3CH), 2.52 (m, 1H, CH_3CHCH), 2.90 (dd, J = 8.0, 5.0 Hz, 1H, *C*HCO_2), 3.23 (dd, J = 11.5, 8.0 Hz, 1H, CH_2), 3.28 (s, 2H, CH_2OH), 3.48 (dd, J = 11.5, 8.0 Hz, 1H, CH_2), 3.52 (d, J = 6.8 Hz, 1H, *NC*HCO_2), 3.94 (s, 2H, CO_2CH_2), 4.74 (s, 2H, OCH_2Ph), 7.25−7.35 (m, 5H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$) 20.44 ($CHCH_3$), 20.51 ($CHCH_3$), 21.53 (CCH_3, 2 C), 27.97 ($OCCH_3$, 3 C), 31.57 (CH_3CH), 36.46 (CH_3C), 44.20 (CH_3CHCH), 45.56 (*C*HCO_2), 59.54 (CH_2), 68.11 (CH_2OH), 69.83 (CO_2CH_2), 74.13 (*NC*HCO_2), 75.48 (OCH_2Ph), 81.30 ($OCCH_3$), 127.84 (CH), 128.26 (CH, 2C), 128.59 (CH, 2C), 137.28 (C), 171.17 (CO_2), 175.57 (CO_2). Anal. Calcd for $C_{25}H_{39}NO_6$: C, 66.79; H, 8.74; N, 3.12. Found: C, 66.56; H, 8.49; N, 3.40.

The stereochemistry was assigned according to differential NOE experiments. Irradiation of H^2 resulted in an NOE enhancement of 11.5% and 6.5% at H^1 and H^3, indicating a trans orientation of H^1, H^2, and H^3.



***trans*-10**

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