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Enantioselective 1,3-Dipolar Cycloadditions of Diazoacetates with Electron-Deficient Olefins

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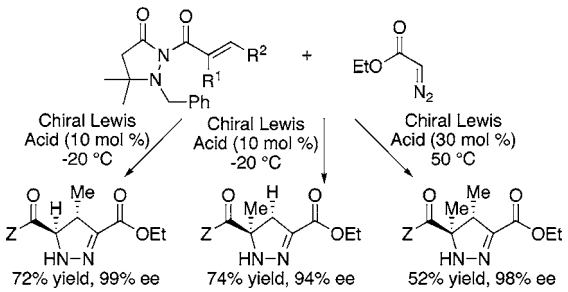
ABSTRACT



A general strategy for highly enantioselective 1,3-dipolar cycloaddition of diazoesters to β-substituted, α-substituted, and α,β-disubstituted α,β-unsaturated pyrazolidinone imides is described. Cycloadditions utilizing less reactive α,β-disubstituted dipolarophiles require elevated reaction temperatures, but still provide the corresponding pyrazolines with excellent enantioselectivities. Finally, an efficient synthesis of (–)-manzacidin A employing this cycloaddition methodology as a key step is illustrated.

Cycloadditions of nitrogen-containing dipoles with olefinic dipolarophiles continue to be attractive for the synthesis of a variety of heterocycles.[1] Over the past decade, highly enantioselective cycloadditions of nitrones, azomethine ylides, azomethine imines, nitrile oxides, and nitrile imines have been reported.[2] In comparison, asymmetric 1,3-dipolar cycloadditions of diazoalkanes and diazoesters are less prominent. Only in the past decade have highly diastereoselective examples been illustrated,[3] while we are aware of only two highly enantioselective variants to date. Kanemasa and Kanai reported the first enantioselective, chiral Lewis acid-catalyzed cycloadditions of trimethylsilyldiazomethane to β-alkyl-substituted, α,β-unsaturated oxazolidinone imides.[4] Subsequently, Maruoka and co-workers developed a titanium BINOLate-catalyzed cycloaddition of diazoesters with α,β-unsaturated aldehydes, which was applied in a very efficient synthesis of (−)-manzacidin A.[5] The pyrazolines prepared in this work were isolated in moderate to good yields with

(1) For a comprehensive review of 1,3-dipolar cycloadditions, see: *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley and Sons: Hoboken, NJ, 2003. For recent reviews of asymmetric 1,3-dipolar cycloadditions, see: (a) Pellissier, H. *Tetrahedron* **2007**, *63*, in press. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

(2) For recent examples, see the following and references therein: (a) Evans, D. A.; Song, H.-J.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 3351. (b) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 11926. (c) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* ***2006****, 45, 1979.* (d) Cabrera, S.; Gómez Arrayás, R.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394. (e) Suga, H.; Funya, A.; Kakehi, A. *Org. Lett.* **2007**, *9*, 97. (f) Chen, W.; Yuan, X.-H.; Li, R.; Du, W.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Adv. Synth. Catal.* **2006**, *348*, 1818. (g) Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778. (h) Sibi, M. P.; Ma, Z.; Itoh, K.; Prabagaran, N.; Jasperse, C. P. *Org. Lett.* **2005**, *7*, 2349. (i) Sibi, M. P.; Itoh, K.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 5366. (j) Sibi, M. P.; Stanley, L. M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 8276.

(3) For selected diastereoselective examples, see: (a) Mish, M. R.; Guerra, F. M.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 8379. (b) Whitlock, G. A.; Carreira, E. M. *J. Org. Chem.* **1997**, *62*, 7916. (c) Muray, E.; Alvarez-Larena, A.; Piniella, J. F.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2000**, *65*, 388. (d) García Ruano, J. L.; Fraile, A.; Gonzalez, G.; Martín, M. R.; Clemente, F. R.; Gordillo, R. *J. Org. Chem.* **2003**, *68*, 6522. (e) García Ruano, J. L.; Peromingo, T. M.; Alonso, M.; Fraile, A.; Martín, M. R.; Titio, A. *J. Org. Chem.* **2005**, *70*, 8942.

(4) Kanemasa, S.; Kanai, T. *J. Am. Chem. Soc.* **2000**, *122*, 10710.

(5) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174.

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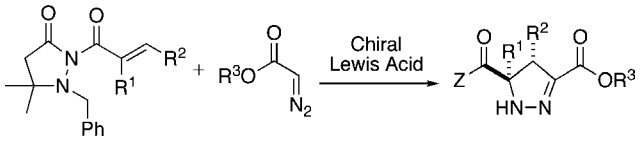
generally high enantioselectivity, but it is important to note the substrate scope is limited to α-substituted acroleins.

Given the limited substrate scope demonstrated in previous enantioselective diazoalkane and diazoacetate 1,3-dipolar cycloadditions as well as the potential for enhanced chemical efficiency in enantioselective cycloadditions of diazoacetates, we became interested in evaluating α,β-unsaturated pyrazolidinone imides as dipolarophiles that might serve to address these issues (Scheme 1).[6] Although the use of α,β-unsaturated pyrazolidinone imides could be regarded as less atom-economical than application of the corresponding α,β-unsaturated aldehydes or esters, α,β-unsaturated pyrazolidinone imides offer a number of noteworthy advantages, especially for less reactive substrates such as cinnamates and tiglates. Advantages include (1) the potential for bidentate coordination of a chiral Lewis acid leading to a well-organized chiral Lewis acid/substrate complex,[7] (2) the ability to provide high enantioselectivities at elevated reaction temperatures (relative to temperatures commonly employed in enantioselective 1,3-dipolar cycloadditions),[2i,6b] and (3) the ability to control rotamer geometry in α-substituted and α,β-disubstituted substrates, for which common auxiliaries such as oxazolidinone perform poorly.[6c]

Scheme 1. Enantioselective 1,3-Dipolar Cycloaddition of Diazoacetates with α,β-Unsaturated Pyrazolidinone Imides

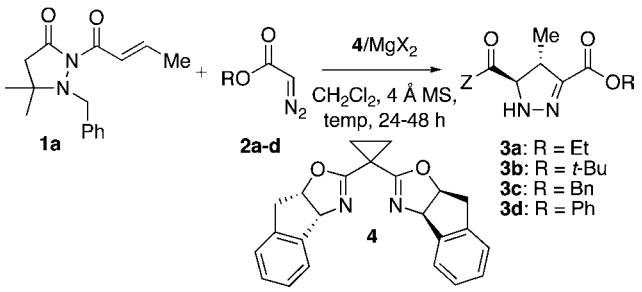


Initial reaction optimization focused on evaluation of $Mg(ClO_4)_2$ in combination with ligand **4** as the chiral Lewis acid. Room temperature cycloaddition of crotonate **1a** with ethyl diazoacetate **2a** in the presence of 30 mol % $Mg(ClO_4)_2$/**4** gave cycloadduct **3a** in excellent yield and moderate enantioselectivity (Table 1, entry 1). Lowering the reaction temperature provided **3a** with increased selectivity (entries 2 and 3); however, a corresponding decrease in reactivity was also observed, most notably at −20 °C. In an attempt to increase reactivity of the chiral Lewis acid, we employed 4 Å MS as a water scavenger. This led to a moderate increase in yield for **3a** (entry 4). Although the increase in reactivity was less than desired, the use of 4 Å MS led to a significiant improvement with regard to the enantioselectivity of the cycloaddition.

(6) For enantioselective dipolar cycloadditions utilizing α,β-unsaturated pyrazolidinone imides, see: (a) Reference 2i. (b) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718. (c) Sibi, M. P.; Stanley, L. M.; Soeta, T. *Adv. Synth. Catal.* **2006**, *348*, 2371.

(7) For additional enantioselective transformations utilizing α,β-unsaturated pyrazolidinone imides as substrates, see: (a) Sibi, M. P.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2001**, *123*, 8444. (b) Sibi, M. P.; Liu, M. *Org. Lett.* **2001**, *3*, 4181. (c) Sibi, M. P.; Prabagaran, N. *Synlett* **2004**, 2421. (d) Nakano, H.; Tsugawa, N.; Fujita, R. *Tetrahedron Lett.* **2005**, *46*, 5677. (e) Nakano, H.; Tsugawa, N.; Takahashi, K.; Okuyama, Y.; Fujita, R. *Tetrahedron* **2006**, *62*, 10879. (f) Sibi, M. P.; Chen, J.; Stanley, L. M. *Synlett* **2007**, 298. (g) Sibi, M. P.; Stanley, L. M.; Nie, X.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2007**, *129*, 395.

Table 1. Optimization of Enantioseletive Diazoacetate 1,3-Dipolar Cycloadditions[a]



entry	R	MgX_2	mol % CLA*	temp (°C)	yield (%)[b]	ee (%)[c]
1[d]	Et	$Mg(ClO_4)_2$	30	rt	93	54
2[d]	Et	$Mg(ClO_4)_2$	30	0	76	84
3[d]	Et	$Mg(ClO_4)_2$	30	−20	38	86
4	Et	$Mg(ClO_4)_2$	30	−20	49	93
5	Et	MgI_2	30	−20	53	97
6	Et	$Mg(NTf_2)_2$	30	−20	72	98
7	Et	$Mg(NTf_2)_2$	20	−20	81	99
8	Et	$Mg(NTf_2)_2$	10	−20	72	99
9	*t*-Bu	$Mg(NTf_2)_2$	10	−20	79	99
10	Bn	$Mg(NTf_2)_2$	10	−20	86	98
11	Ph	$Mg(NTf_2)_2$	10	−20	25	46
12	Ph	$Mg(NTf_2)_2$	10	rt	82	86

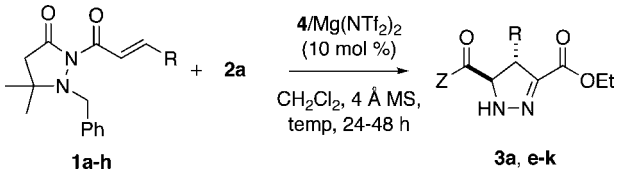
[a] For experimental details see the Supporting Information. [b] Isolated yields. [c] Determined by chiral HPLC. [d] Reaction run in the absence of 4 Å MS.

Unsatisfied with the reactivity provided by $Mg(ClO_4)_2$/**4** in cycloadditions at −20 °C, we chose to evaluate additional Mg(II) salts. Interestingly, when MgI_2/**4** was employed as the chiral Lewis acid, an increase in enantioselectivity was observed, but the isolated yield was only marginally better (entry 5). The best combination of reactivity and enantioselectivity was observed when $Mg(NTf_2)_2$/**4** was employed as the chiral Lewis acid (entries 6−8). In reactions conducted with 30 mol % $Mg(NTf_2)_2$/**4**, **3a** was isolated in 72% yield and 98% ee (entry 6). We were pleased to observe no decrease in reaction efficiency or selectivity upon lowering the catalyst loading to 10 mol % (entry 8).

With optimized conditions in hand, we set out to evaluate diazoacetates bearing additional ester substituents (entries 9−12). Reactions utilizing *tert*-butyl diazoaceate **2b** and benzyl diazoacetate **2c** gave pyrazolines **3b** and **3c** in high yields and excellent enantioselectivities (entries 9 and 10, respectively). Unfortunately, when phenyl diazoacetate was employed as the dipole in reactions at −20 °C, the yield and selectivity were both poor (entry 11). The isolated yield of **3d** could be improved by performing the reaction at room temperature. Interestingly, the enantioselectivity was increased to 86% ee upon raising the reaction temperature. At the present time a clear rationale for the increased selectivity at increased temperature is not apparent; it is, nonetheless, noteworthy.

Attempts to expand the scope of β-substituted dipolarophiles applicable in enantioselective 1,3-dipolar cycloaddition

Table 2. Enantioselective Dipolar Cycloaddition with β-Substituted, α,β-Unsaturated Pyrazolidinone Imides[a]



1a-h **3a, e-k**

entry	substrate	R	temp (°C)	product	yield (%)[b]	ee (%)[c]
1	**1a**	Me	−20	**3a**	72	99
2	**1b**	H	−20	**3e**	75	97
3	**1c**	CO_2t-Bu	−20	**3f**	91	99
4	**1d**	Et	−20	**3g**	32	97
5	**1d**	Et	rt	**3g**	85	99
6	**1e**	*i*-Pr	rt	**3h**	79	98
7	**1f**	CH_2Ph	rt	**3i**	58	95
8	**1g**	$CH_2C_6H_{11}$	rt	**3j**	59	90
9	**1h**	Ph	rt	**3k**	54	90
10[d]	**1h**	Ph	40	**3k**	76	88

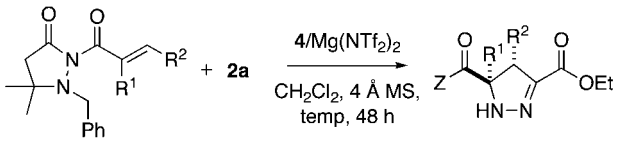
[a] For experimental details see the Supporting Information. [b] Isolated yields. [c] Determined by chiral HPLC. [d] Reactions performed at 40 °C were run in sealed, heavy wall pressure vessels with threaded Teflon bushing.

of ethyl diazoacetate are illustrated in Table 2. In addition to crotonate **1a** (entry 1), cycloadditions utilizing highly reactive dipolarophiles, such as acrylate **1b** and fumarate **1c**, proceed in high yields with excellent enantioselectitivies at −20 °C (entries 2 and 3, respectively). We were quite intrigued by the lack of reactivity when **1d** (R = Et) was employed as the dipolarophile given the minimal increase in steric bulk relative to crotonate **1a** (compare entry 4 with entry 1). This apparent lack of reactivity was easily overcome by performing the reaction at room temperature (entry 5). Surprisingly, the enantioselectivity was once again higher for the reaction conducted at room temperature (compare entry 4 with entry 5). Room temperature cycloadditions also proved optimal for additional dipolarophiles **1e**−**g** bearing aliphatic β-substituents (entries 6−8).

Prior to this work, no examples of enantioselective 1,3-dipolar cycloaddition of diazoalkanes or diazoacetates to β-aryl-subsitituted dipolarophiles have been reported. The lack of successful examples with such substrates likely stems from the increased energy of the LUMO relative to that of β-alkyl-subsitituted dipolarophiles.[8] Given the low temperatures necessary in previous work to obtain high enantioselectivities and minimize byproduct formation, increasing reaction temperature was not a practical option for additional activation of such substrates.[4,5] The high enantioselectivities observed in previous room temperature cycloadditions (entries 5−8) led us to evaluate whether reactions utilizing cinnamate **1h** as the dipolarophile could provide access to 4-phenyl-substituted pyrazoline **3k**. We were quite pleased to isolate pyrazoline **3k** in moderate yield with good enantioselectivity (entry 9). Furthermore, the yield of **3k** could be increased with only minimal erosion of enantioselectivity by conducting the reaction at 40 °C (entry 10).

Encouraged by the good enantioselectivity observed at 40 °C in the cycloaddition of ethyl diazoacetate to cinnamate **1h**, we became interested in determining whether elevated reaction temperatures might allow us to access pyrazoline cycloadducts derived from α,β-disubstituted, α,β-unsaturated pyrazolidinone imides, which had proven completely unreactive in room temperature reactions utilizing 100 mol % chiral Lewis acid. Cycloaddition of **2a** to tiglate **5a** did, however, proceed at 40 °C in the presence of 100 mol % $Mg(NTf_2)_2$/**4** (Table 3, entry 1). Although the isolated yield

Table 3. Enantioselective Dipolar Cycloaddition with α,β-Disubstituted, α,β-Unsaturated Pyrazolidinone Imides[a]



5a or b

6a: R^1 = Me, R^2 = Me
6b: R^1,R^2 = -$(CH_2)_3$-

entry	substrate	R^1	R^2	mol % CLA*	temp (°C)[b]	yield (%)[c]	ee (%)[d]
1	**5a**	Me	Me	100	40	37	95
2	**5a**	Me	Me	50	40	42	95
3	**5a**	Me	Me	50	50	61	99
4	**5a**	Me	Me	30	50	52	98
5	**5b**	$-(CH_2)_3-$		30	50	62	99

[a] For experimental details see the Supporting Information. [b] Reactions performed at 40 °C or higher were run in sealed, heavy wall pressure vessels with threaded Teflon bushing. [c] Isolated yields. [d] Determined by chiral HPLC.

of this cycloaddition was moderate at best, it should be noted that the enantioselectivity was high. Attempts at lowering the loading of chiral Lewis acid had little effect on the outcome of this reaction (entry 2). Interestingly, significant increases in both reaction efficiency and selectivity were observed when the cycloaddition was performed at 50 °C (entry 3). Under optimized conditions pyrazoline **6a** could be isolated in moderate yield with excellent enantioselectivity at 30 mol % chiral Lewis acid loading (entry 4). Bicyclic pyrazoline **6b** was also prepared with excellent enantioselecitivity at elevated temperature (entry 5).

Unfortunately, we were not able to isolate pyrazolines derived from less reactive α,β-disubstituted dipolarophiles (R^1 = Me; R^2 = Et or Ph) at 50 °C.[9] Nevertheless, the selectivities obtained for pyrazolines **6a** and **6b** clearly offer additional evidence of the high levels of rotamer control provided by α,β-disubstituted, α,β-unsaturated pyrazolidi-

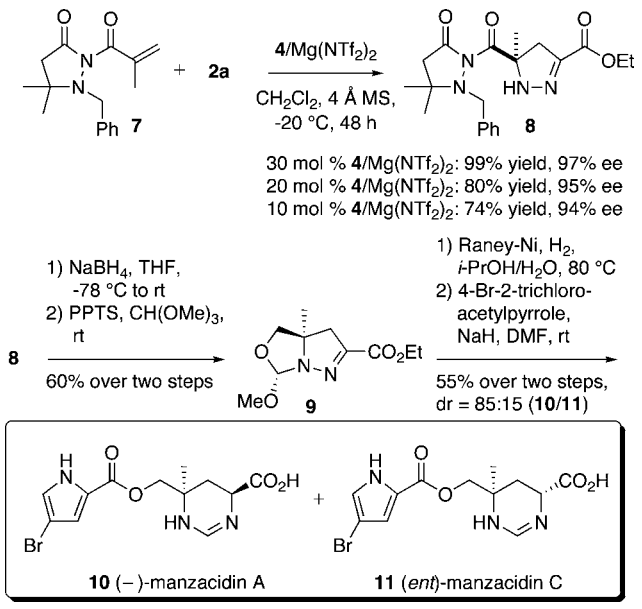
(8) (a) Houk, K. N.; Sims, J.; Duke, R. E., Jr.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287. (b) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301.

(9) Cycloaddition of ethyl diazoacetate to the pyrazolidinone imide derived from *trans*-2-methyl-2-pentenoic acid (R^1 = Me; R^2 = Et) at 60 °C gave the corresponding pyrazoline in low yield and reduced enantioselectivity. Additional increases in reaction temperature led only to increased formation of unidentified byproducts.

none imides, and suggest pyrazolidinone auxiliaries may have significant potential in enantioselective transformations requiring elevated temperatures for enhanced reactivity.

Previous work from our lab,[6c] in combination with the results with α,β-disubstituted dipolarophiles presented above, suggested high levels of enantioselectivity could be achieved for cycloaddition of ethyl diazoacetate to α-methyl acrylate **7** (Scheme 2). We were particularly interested in cycloaddition to **7** as the resulting pyrazoline core has been elegantly elaborated to (−)-manzacidin A by Maruoka and co-workers.[5] Furthermore, we believed our catalyst/dipolarophile system offered the potential to increase the moderate yields previously obtained for this key cycloadduct. Cycloaddition of **3a** to **7** gave 2-pyrazoline **8** in 99% yield with 97% ee in the presence of 30 mol % $Mg(NTf_2)_2$.[10] Enantioselectivity remains high and yields are also good at lower loadings of the chiral Lewis acid. Even with the lower yields observed in reactions run at lower catalyst loadings, these results represent a more efficient means to access this key pyrazoline core.

Scheme 2. Enantioselective Synthesis of (−)-Manzacidin A



Pyrazoline **8** is readily elaborated to a diastereomeric mixture of (−)-manzacidin A and (*ent*)-manzacidin C using Maruoka's previously reported approach (Scheme 2). Compound **8** was reduced to the corresponding amino alcohol, which was subsequently treated with trimethyl orthoformate to give bicycle **9** in 60% yield over two steps. It should be noted that the difficult separation of the intermediate amino alcohol and the cleaved pyrazolidinone need not be performed, as the auxiliary is readily removed after formation of **9**. Treatment of **9** with Raney-nickel/H_2 resulted in the formation of the desired tetrahydropyrimidine core, which was used directly. After esterification with 4-bromo-2-trichloroacetylpyrrole an 85:15 diastereomeric mixture of (−)-mancacidin A (**10**) and (*ent*)-manzacidin C (**11**) was obtained. An analytical sample of mancacidin A was isolated according to the literature procedure, which matched the spectral data for previously reported syntheses[11] and isolation[12] of (−)-manzacidin A. Based on the absolute stereochemistry of (−)-manzacidin A, the absolute configuration of pyrazoline **8** has been assigned as (5*R*).[13]

In conclusion, we have illustrated a method for enantioselective synthesis of 2-pyrazolines via magnesium(II)-catalyzed cycloaddition of diazoesters to α,β-unsaturated pyrazolidinone imides. The methodology allows facile access to enantioenriched pyrazolines derived from β-subsituted, α-substituted, and α,β-disubstituted dipolarophiles, the latter two resulting in pyrazolines bearing quaternary *tert*-alkyl amino stereocenters at the 5-position of the pyrazoline.[14] One such pyrazoline has been elaborated to (−)-manzacidin A in 4 additional steps via a previously reported procedure. Work toward additional applications of chiral pyrazolines in asymmetric synthesis and α,β-unsaturated pyrazolidinone imides in high-temperature enantioselective transformations is ongoing in our laboratory.

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Supporting Information Available: Experimental procedures and characterication data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Reaction of ethyldiazoacetate with oxazolidinone methacrylate under identical conditions gave <5% yield of the adduct.

(11) For additional syntheses of (−)-manzacidin A, see: (a) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. (b) Wehn, P. M.; DuBois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950. (c) Namba, K.; Shinada, T.; Teramoto, T.; Ohfune, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10708.

(12) Kobayashi, J.; Kanda, F.; Ishibashi, M.; Shigemori, H. *J. Org. Chem.* **1991**, *56*, 4574.

(13) Absolute stereochemistry has been tentatively assigned as (4*S*,5*R*) for pyrazolines derived from β-substituted and α,β-disubstituted dipolarophiles based on related stereochemical models, see refs 2i and 2j.

(14) For a review on the total synthesis of natural products containing *tert*-alkylamino stereocenters, see: Kang, S. H.; Kang, S. Y.; Lee, H.-S.; Buglass, A. J. *Chem. Rev.* **2005**, *105*, 4537.