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Enantioselective 1,3-Dipolar Cycloaddition Reaction between Diazoacetates and α-Substituted Acroleins: Total Synthesis of Manzacidin A

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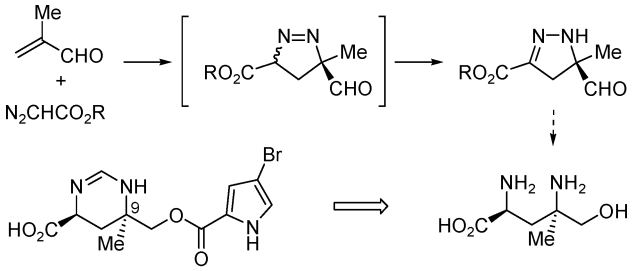
Diazoalkanes have been widely utilized in 1,3-dipolar cycloaddition reactions with various olefins to construct synthetically useful pyrazolines and pyrazoles, which are easily derivatized to various types of nitrogen-containing molecules.[1] The asymmetric variants of this transformation were previously effected by a chiral auxiliary-based approach using, for example, camphor sultam-derived dipolarophiles.[1−4] To the best of our knowledge, only one successful example has been recently reported of chiral Lewis acid-catalyzed enantioselective 1,3-dipolar cycloaddition of diazoalkanes with 3-(2-alkenoyl)-2-oxazolidinones as a bidentate dipolarophile.[5,6] In this context, we are interested in the possibility of developing the unprecedented enantioselective 1,3-dipolar cycloaddition of readily available substrates with broad applicability, such as diazoacetates and monodentate α-substituted acroleins. Here, we wish to report such an asymmetric transformation by using certain chiral titanium BINOLate Lewis acids, one of which has recently been found to effectively catalyze the enantioselective 1,3-dipolar cycloaddition between acrolein and nitrones.[7] The resulting highly functionalized pyrazolines with a quaternary stereogenic center can be transformed by reduction into the pharmacologically intriguing 1,3-diamino carboxylic acids.[8] Indeed, the utility of this methodology is illustrated by the expedient synthesis of manzacidin A (Scheme 1).

Scheme 1



1a manzacidin A
1b manzacidin C (C9 epimer)

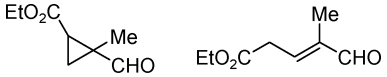
We first examined the reaction between ethyl diazoacetate and methacrolein in CH_2Cl_2, as shown in Table 1. When the reaction was carried out under thermal conditions, the desired cycloadduct, 2-pyrazoline **3a**, was obtained in 16% yield, with concomitant formation of the diastereomixture of cyclopropanes **4** (37%) and ethyl 4-formyl-3-pentenoate **5** (11%) (entry 1).[9] We then investigated the possibility of using titanium BINOLates[10] as a chiral Lewis acid catalyst for this reaction. Unfortunately, the reaction using 10 mol % of (*S*)-BINOL/$Ti(OPr^i)_4$ (1:1 molar ratio) complex (**2a**) at 0 °C gave a complex mixture through nitrogen extrusion (entry 2). However, this problem was circumvented by lowering the temperature to −40 °C, and consequently, 2-pyrazoline **3a** was obtained in moderate yield with high enantioselectivity (entry 3). Moreover, the use of other titanium BINOLates, such as (*S*)-BINOL/$Ti(OPr^i)_4$ (2:1 molar ratio) complex (**2b**)[11] and bis{((*S*)-binaphthoxy)(isopropoxy)titanium} oxide (**2c**),[12] resulted in both improved yields and enantioselectivities (entries 4 and 5).[13] In the case of *tert*-butyl diazoacetate, the rate enhancement was observed, although the yield of **3b** remained moderate (entries 6 and 7).

Table 1. Enantioselective 1,3-Dipolar Cycloaddition between Alkyl Diazoacetates and Methacrolein[a]

3a (R^1 = Et)
3b (R^1 = *t*-Bu)

entry	R^1	catalyst (mol %)	conditions (°C, h)	yield (%)[b]	ee (%)[c]
1	Et	−	rt, 40	16	
2	Et	**2a** (10)	0, 1	−	
3	Et	**2a** (10)	−40, 4	42	88
4	Et	**2b** (10)	−40, 2	54	90
5	Et	**2c** (5)	−40, 3	52	95
6	*t*-Bu	**2b** (10)	−40, 1	52	91
7	*t*-Bu	**2c** (5)	−40, 1	43	94

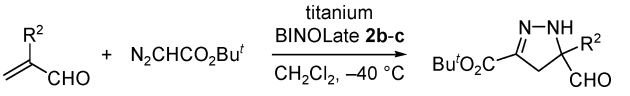
[a] Reactions were performed with methacrolein (1.0 mmol) and alkyl diazoacetates (1.5 mmol) in the presence of a chiral titanium catalyst in CH_2Cl_2. [b] Isolated yield. [c] Determined by chiral HPLC analysis after reduction of the aldehyde.



4 **5**

To evaluate the substrate scope of this methodology, we investigated the enantioselective 1,3-dipolar cycloadditions of various α-substituted acroleins and *tert*-butyl diazoacetate. As shown in Table 2, titanium BINOLates **2b** and **2c** could be applied to a reasonable range of olefinic substrates and provided corre-

Table 2. Enantioselective 1,3-Dipolar Cycloaddition between *tert*-Butyl Diazoacetate and α-Substituted Acroleins[a]



entry	R^2	catalyst (mol %)	time (h)	yield (%)[b]	ee (%)[c]
1	Me	**2b** (10)	1	52	91[d]
2	Me	**2c** (5)	1	43	94[d]
3	Et	**2b** (10)	3	63	83
4	Et	**2c** (5)	3	48	84
5	$BnOCH_2CH_2$	**2b** (10)	1	81	80
6	$PhCH_2CH_2$	**2b** (10)	4	63	82
7	*i*-Pr	**2b** (10)	3	82	92
8	Cy	**2b** (10)	5	77	94
9	Cy	**2c** (5)	5	75	94

[a] Reactions were performed with α-substituted acroleins (1.0 mmol) and *tert*-butyl diazoacetate (1.5 mmol) in the presence of a chiral titanium catalyst in CH_2Cl_2. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Determined by chiral HPLC analysis after reduction of the aldehyde.

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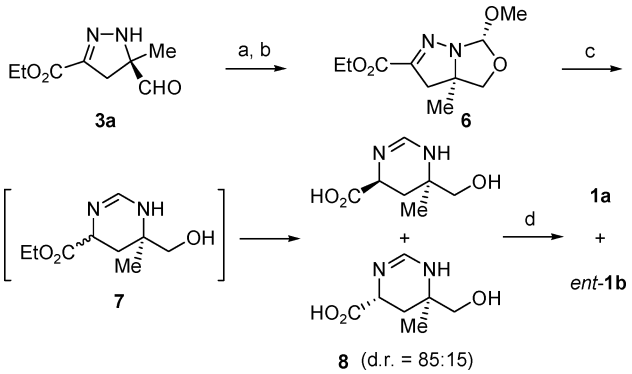
Scheme 2. Total Synthesis of Manzacidin A[a]



[a] Conditions: (a) $NaBH_4$, EtOAc, 73%; (b) PPTS, $HC(OMe)_3$, 89%; (c) Raney-Ni, H_2, ^{i}PrOH/H_2O; (d) 4-bromo-2-trichloroacetylpyrrole, NaH, DMF, 50% (two steps).

sponding 2-pyrazolines in fairly good yields with high to excellent enantioselectivities. Considering the other possible reaction pathways, such as 1,2- and 1,4-addition of *tert*-butyl diazoacetate to α-substituted acroleins,[14] in addition to the cyclopropanation,[15] the yield of 1,3-dipolar cycloaddition products is quite remarkable.

The synthetic utility of the present reaction was further demonstrated by the total synthesis of a bromopyrrole alkaloid manzacidin A,[16] which was isolated from the Okinawan sponge *Hymeniacidon* sp.[17] Manzacidins have the tetrahydropyrimidine ring containing an asymmetric tetrasubstituted carbon center and have been proposed to be generated from formic acid and an unusual amino acid, γ-amino-δ-hydroxyleucine. Thus, we commenced the work with the optically enriched 2-pyrazoline **3a**, which was envisioned as a suitable precursor for the preparation of such an unusual amino acid (Scheme 2).

The synthesis of manzacidin A began with reduction of the formyl group of 2-pyrazoline **3a**, followed by treatment with methyl orthoformate, which can be incorporated into the tetrahydropyrimidine ring as the amidine carbon in the following step. The resulting bicyclic compound **6** was then treated with Raney-nickel to give tetrahydropyrimidine **8** as a result of several reactions involving hydrolysis of the formamide acetal, reduction of the C═N double bond, the reductive cleavage of the N−N bond, formation of the cyclic amidine, and hydrolysis of the ester. The stereochemical outcome can be explained by the epimerization of ester **7** and the following preferential hydrolysis via lactonization rather than by the diastereoselective hydrogenation of the starting 2-pyrazoline. Finally, esterification of tetrahydropyrimidine **8** according to the reported procedure[15a] gave manzacidin A, which was identical in spectral data to naturally occurring manzacidin A.

In summary, we have developed an enantioselective 1,3-dipolar cycloaddition reaction between diazoacetates and α-substituted acroleins, which gives 2-pyrazolines with an asymmetric tetrasubstituted carbon center. This methodology was successfully applied to the short synthesis of manzacidin A in five steps, starting from commercially available methacrolein and ethyl diazoacetate without tedious protection and deprotection steps. Further applications of this catalytic asymmetric transformation and synthetic utilities of the formed 2-pyrazoline will be reported in due course.

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Supporting Information Available: Experimental details and characterization data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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