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Total Syntheses of (−)-Hanishin, (−)-Longmide B, and (−)-Longmide B Methyl Ester *via* a Novel Preparation of *N*-Substituted Pyrrole-2-Carboxylates

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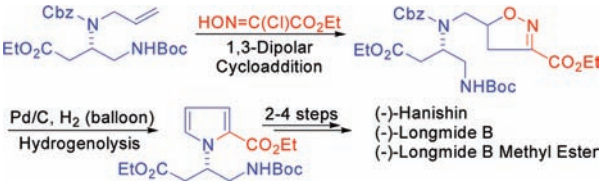
ABSTRACT



A novel preparation of *N*-substituted pyrrole-2-carboxylates has been developed based upon 1,3-dipolar cycloaddition and a conventional hydrogenolysis. By using this method as the key step, total syntheses of natural alkaloids (−)-hanishin, (−)-longmide B, and (−)-longmide B methyl ester were accomplished in the highest overall yields, respectively.

Pyrrole-2-carboxylic acid derivatives are a large family of natural alkaloids.[1] Most brominated pyrrole-2-carboxamides were isolated from marine sponges, such as (−)-hanishin (**1**),[2] (−)-longmide B (**2**),[3] and (−)-longmide B methyl ester (**3**)[4] (Figure 1). These alkaloids not only have a novel chiral dihydropyrrolo[1,2-*a*]pyrazin-1-one skeleton but also showed biologically important properties. For example, (−)-hanishin (**1**) was cytotoxic toward NSCLC-N6 human nonsmall-cell-lung carcinoma (IC_{50} 9.7 μg/mL); (−)-longmide B (**2**) displayed activity against African trypanosome (IC_{50} 1.53 μ/mL); and (±)-longmide B methyl ester (**3**) exhibited cytotoxic activity against P-388 lymphocytic leukemia cells (ED_{50} 30 μg/mL), respectively. Therefore, they are highly attractive targets for the total synthesis.

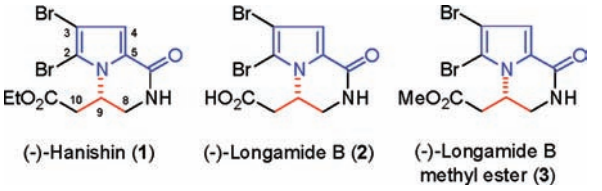


Figure 1. Three bioactive brominated pyrrole-2-carboxamides.

The first racemic total syntheses of **1**−**3** were accomplished a year after (−)-hanishin (**1**) was first isolated.[5] Thereafter a number of enantioselective total syntheses were reported via chiral pool[6] and asymmetric catalysis[7] strategies. These reported routes clearly indicated that efficient total syntheses of **1**−**3** must resolve two major

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issues: (a) efficient construction of the pyrrole-2-carboxylate skeleton; (b) efficient introduction of the chiral C−N bond. Herein, we would like to report a highly practical route for the total synthesis of **1**−**3**, in which a novel method for pyrrole synthesis has been established and the enantiopure *N*-substituted pyrrole-2-carboxylate is constructed conveniently.

In the total syntheses of natural alkaloids containing a structure of dihydro-pyrrolo[1,2-*a*]pyrazin-1-one, chiral *N*-substituted pyrrole-2-carboxylates serve as important precursors. Therefore, many imaginative methods have been developed for their preparation, such as through the use of intramolecular S_N2 reactions of chiral secondary chlorides,[8] the Mitsunobu reaction of chiral secondary alcohols,[9] asymmetric intramolecular *N*-Michael addition,[10] or asymmetric allylic alkylation.[7,11] However, these methods usually afford enantioenriched or diastereoenriched products and satisfactory results are only obtained in a few cases. Therefore, to obtain enantiopure products, traditional Paal−Knorr pyrrole synthesis has been used for this purpose. As shown in Figure 2, Paal−Knorr pyrrole synthesis uses **4a** or **4b** as 1,4-diketone precursors and can directly yield enantiopure products in one step,[12] but the methods are limited by the exceedingly difficult preparation of **4a** or **4b**.[13] The commercially available 2,5-dimethoxytetrahydrofuran (**4c**) could give enantiopure *N*-substituted pyrroles smoothly, but many steps are required for introduction of the 2-carboxylate groups (with low efficiency).[6,14] Thus, there is a great need to develop a more efficient and general protocol for the synthesis of enantiopure *N*-substituted pyrrole-2-carboxylates on a laboratory scale.

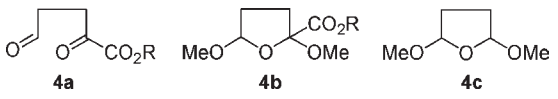
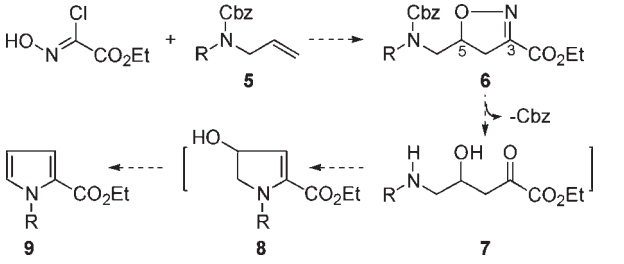


Figure 2. Three precursors in Paal−Knorr pyrrole synthesis.

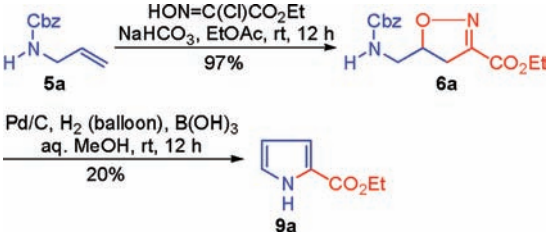
In our recent work, the catalytic hydrogenolysis of 3-substituted 2-isoxazolines was employed as the key step in the total synthesis of various natural alkaloids.[15] When 3-alkyl-2-isoxazolines are hydrogenolyzed in acidic aqueous MeOH, a β-hydroxy ketone is obtained[16] and Raney-Ni or Pd/C are used as catalysts. Based on these experiments, we proposed a novel method for the preparation of *N*-substituted pyrrole-2-carboxylates shown in Scheme 1. Initially, ethyl 2-chloro-2-(hydroxyimino)acetate (HON=C(Cl)CO_2Et) and *N*-Cbz-allylamine (**5**) would react in a 1,3-dipolar cycloaddition to yield 5-aminomethyl-2-isoxazoline-3-carboxylate (**6**). Then, the hydrogenolysis of **6** would give a cyclization product **8** by an intramolecular attack of the amine on the ketone in **7**, due to the ketone being activated by its α-carboxylate group. Finally, the intermediate **8** would be aromatized to yield the expected product **9**.

Scheme 1. A Proposed Novel Method for the Preparation of *N*-Substituted Pyrrole-2-carboxylates



Thus, *N*-Cbz-allylamine **5a** (R = H) was employed as a model substrate and the Cbz-group would play two roles. First, it could activate the amine group to allow efficient and chemoselective *N*-allylation for easy preparation of the analogues (R ≠ H) of **5a**. Second, it could be removed by catalytic hydrogenolysis to unmask an NH_2 group. As shown in Scheme 2, **5a** smoothly underwent a cycloaddition with HON=C(Cl)CO_2Et to give desired **6a** in 97% yield. To our delight, instead of the expected intermediate **8a**, the hydrogenolysis of **6a** directly gave ethyl pyrrole-2-carboxylate (**9a**) as the final product in 20% yield.

Scheme 2. A Two-Step Preparation of Pyrrole-2-carboxylate (**9a**)



Since **7a** (R = H) and **8a** (R = H) were the intermediates in the conversion of **6a** to **9a** and their formation and

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(9) Laha, J. K.; Cuny, G. D. *J. Org. Chem.* **2011**, *76*, 8477–8482.
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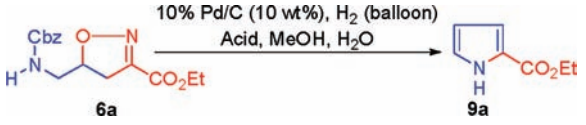
reaction would be influenced by acid,[16] we evaluated different acid additives in the reaction. As shown in Table 1, aq. HCl and aq. H_2SO_4 were better acid reagents than $B(OH)_3$ (entries 1−3) and HOAc gave the best results (entry 4). When **6a** was hydrogenolyzed at 40 °C, **9a** was obtained in 95% yield after 3 h (entry 5) and higher temperatures were not necessary (entry 6). The results in entries 7−9 proved that both MeOH and H_2O were essential and a 5:1 ratio was the best combination.

Table 1. Effects of Solvents, Acids, and Temperatures on the Hydrogenolysis of **6a**

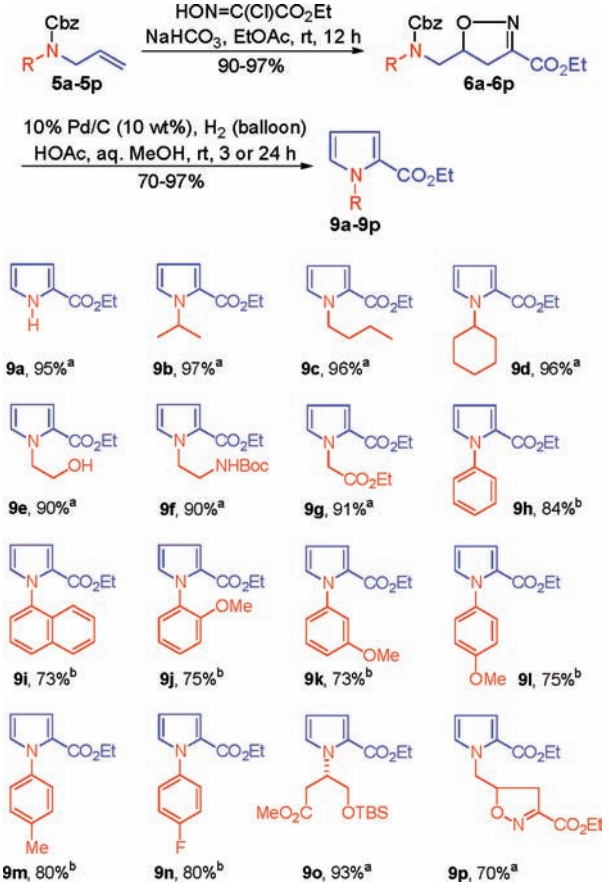


entry	solvent	acid	temp (°C)	time (h)	yield of **9a** (%)[a]
1	MeOH/H_2O (5:1)	$B(OH)_3$	25	12	20
2	MeOH/H_2O (5:1)	aq. HCl	25	12	38
3	MeOH/H_2O (5:1)	aq. H_2SO_4	25	12	43
4	MeOH/H_2O (5:1)	HOAc	25	12	67
5	**MeOH/H_2O (5:1)**	**HOAc**	**40**	**3**	**95**
6	MeOH/H_2O (5:1)	HOAc	60	3	72
7	MeOH/H_2O (1:1)	HOAc	40	12	90
8	MeOH	HOAc	40	12	trace
9	H_2O	HOAc	40	12	trace

[a] The isolated yields were obtained.

To test the scope of this method, different *N*-substituted *N*-Cbz-allylamines (**6b**−**6p**) were prepared in 90−97% yield. As shown in Scheme 3, under the standard hydrogenolytic conditions, all the substrates **6a**−**6g** gave the corresponding pyrroles **9a**−**9g** in excellent yield. Among them, the conversion of **6e** into **9e** was especially important because any 2-aminoethanol or 3-aminopropan-1-ol without protection of the hydroxyl group could not be converted into the corresponding *N*-(2-hydroxyethyl)pyrrole or *N*-(3-hydroxypropyl)pyrrole by Paal−Knorr pyrrole synthesis. Due to the weak nucleophilic ability of aromatic amines, the conversions of **6h**−**6n** to **9h**−**9n** needed longer reaction times (24 h) and gave moderate to good yields. As was expected, the enantiopure *N*-substituted pyrrole-2-carboxylate **9o** was obtained in 93% yield from the corresponding chiral 2-isoxazoline **6o**,[17] which was not the case by any *N*-alkylation methods. It was interesting to observe that one isoxazoline ring in *N*,*N*-bis(2-isoxazoline-3-carboxylate) **6p** was cleaved to give **9p** in 70% yield and the other one stayed intact under these conditions.

Scheme 3. *N*-Substituted Pyrrole-2-carboxylates **9a**−**9p** Prepared



[a] Reaction time was 3 h. [b] Reaction time was 24 h.

Thus, a novel preparation of *N*-substituted pyrrole-2-carboxylates (**9**) was established by the conventional hydrogenolysis of 5-aminomethyl-2-isoxazoline-3-carboxylates (**6**). This transformation in fact was a one-pot five-step process that included deprotection of *N*-Cbz, cleavage of the N−O bond, hydrolysis of imine to the ketone, intramolecular attack of the amino group on a ketone, and aromatization by loss of two H_2O molecules. By using enantiopure amines as substrates, the enantiopure *N*-substituted pyrrole-2-carboxylates can be prepared conveniently.

Then, the new method was employed in the total synthesis of (−)-hanishin (**1**), (−)-longmide B (**2**), and (−)-longmide B methyl ester (**3**). According to the routine

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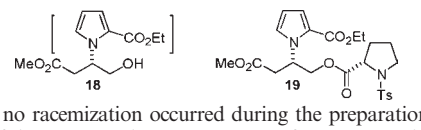
(16) (a) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024–4026. (b) Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1982**, *104*, 4023–4024.

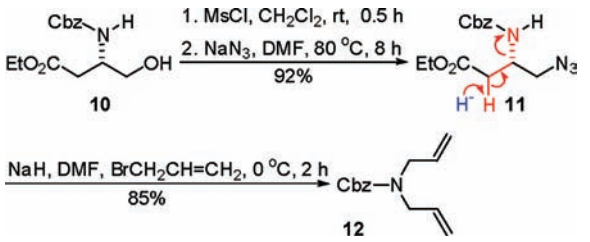
(17) After the TBS protective group in **9o** was removed, the produced alcohol compound **18** was acylated by (*S*)-l-[(4-methylphenyl)-sulphonyl]-2-pyrrolidinecarbonyl chloride to give the corresponding diastereomeric ester **19** in 94% yield as a single product (determined by the spectra of ^1H and ^{13}C NMR) (see Supporting Information).



Deductively, no racemization occurred during the preparation and transformations of the compounds **6o**, **9o**, or **18**. In fact, no racemization of the enantiopure *N*-substituted pyrrole-2-carboxylates was reported in published articles to date.[6,12a,14a−14d]

procedure, the commercially available (*S*)-ethyl 3-(*N*-Cbz-amino)-4-hydroxybutanate (**10**) was initially converted into the corresponding azide **11** in one pot. However, NaH-promoted *N*-allylation of **11** gave a *N,N*-diallyl product **12** instead of the expected product **13**, accompanied by cleavage of the C−N bond. As shown in Scheme 4, it may be caused by a NaH-promoted *retro*-Michael addition through an intramolecular E1cB elimination mechanism.

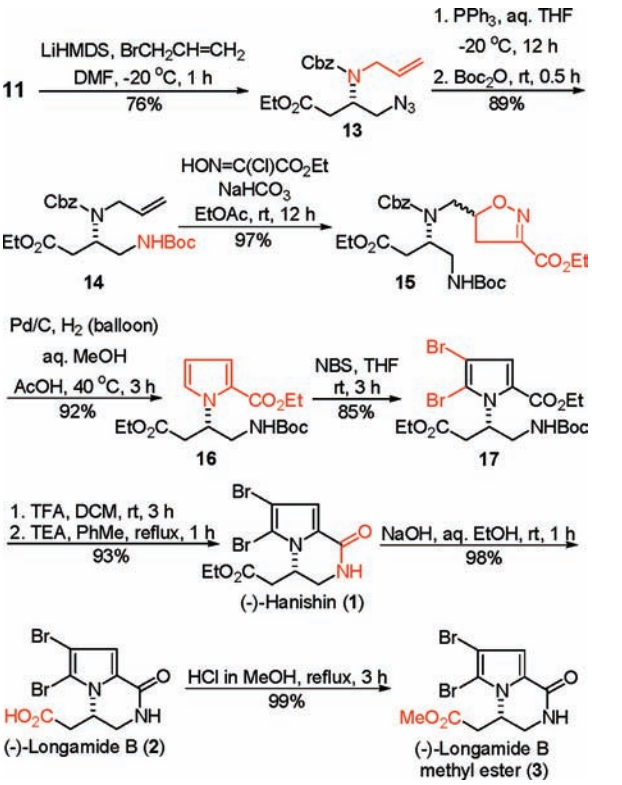
Scheme 4. NaH-Promoted *retro*-Michael Addition



Thus, the relatively weak base LiHMDS was employed and the *N*-allylic product **13** was obtained in moderate yield (Scheme 5). Then **13** was converted into the key precursor **14** by reduction of its azide with PPh_3 followed by *N*-Boc protection in one pot. As was expected, the 1,3-dipolar cycloaddition between **14** and HON=C(Cl)CO_2Et gave 2-isoxazoline **15** as a mixture of diastereoisomers (1:1) in excellent yield under mild conditions (the diastereoisomers would produce the same product in the next step). When the suspension of **15** and Pd/C (10 wt %) in aqueous MeOH and HOAc was stirred for 3 h at 40 °C under a hydrogen atmosphere (balloon), the *N*-substituted pyrrole-2-carboxylate **16** was obtained in 92% yield. According to the literature method,[6] **16** was regioselectively brominated using 2 equiv of NBS to yield the 4,5-dibromopyrrole **17** in 85% yield.

Since intermediate **17** has two different carboxylates, its amidization may generate a mixture of γ-lactam and δ-lactam. Luckily, when the *N*-deprotected product of **17** was heated at reflux in toluene for 1 h in the presence of Et_3N, (−)-hanishin (**1**) was obtained as the sole product in 93% yield. Experiments proved that the weak base Et_3N and nonpolar toluene were essential for this high chemoselectivity. By simple saponification of **1** in solution of NaOH in aqueous EtOH, (−)-longmide B (**2**) was obtained in 98% yield. After **2** was treated with the solution of HCl in MeOH for 2 h, it took an esterification to give (−)-longmide B methyl ester (**3**) in almost quantitative yield. Thus, the total syntheses of natural alkaloids (−)-hanishin (**1**), (−)-longmide B (**2**), and (−)-longmide B methyl ester (**3**) were accomplished in 7, 8, and 9 steps (from the starting material **10**) in 44%, 43%, and 43% overall yield, respectively.

Scheme 5



In conclusion, chiral *N*-substituted pyrrole-2-carboxylates are important precursors in the synthesis of alkaloids containing the structure of dihydropyrrolo[1,2-*a*]pyrazin-1-one. However, Paal−Knorr pyrrole synthesis usually shows low efficiency and chemoselectivity, while other methods normally afford enantioenriched or diastereoenriched products. In this article, a novel preparation of *N*-substituted pyrrole-2-carboxylates has been developed and applied in the total synthesis of several natural products. Further works will be reported in due course.

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Supporting Information Available. Experiments, characterization, ^1H and ^{13}C NMR spectra for products intermediates **6a**−**p**, **9a**−**p**, **11**, **13**−**17**, **19**, and the alkaloids **1**−**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.