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Formal Synthesis of Belactosin A and Hormaomycin via a Diastereoselective Intramolecular Cyclopropanation of an α-Nitro Diazoester

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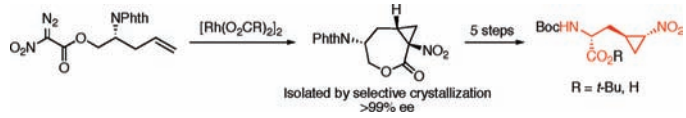
ABSTRACT



An efficient and convenient methodology for the synthesis of the 3-(*trans*-2-aminocyclopropyl) alanine and 3-(*trans*-2-nitrocyclopropyl) alanine moieties found in the core of belactosin A and hormaomycin, respectively, is reported. By using an enantioenriched substituted α-nitro diazoester in a diastereoselective intramolecular cyclopropanation reaction, the *trans*-nitrocyclopropyl alanine moiety can be obtained efficiently in five steps from the initial α-nitrocyclopropyl lactone unit, thus achieving the synthesis of the cyclopropane core of the two natural products.

Nature displays a wide range of chemical diversity through a variety of architecturally complex molecules. Among these designs, the unique structure of the cyclopropane subunit is common to many compounds of biological and pharmacological relevance. As such, there have been significant efforts toward the synthesis of functionalized cyclopropanes as well as their applications in synthesis.[1,2]

Belactosin A (**1**, Figure 1) is a naturally occurring molecule demonstrating moderate antitumor activity against cell-cycle progression at the G2/M phase.[3] Additionally, hormaomycin (**2**), produced by the strain W384 *Streptomyces griseoflavus*, has a direct impact on the secondary metabolite proliferation of certain micro-organisms.[4] These two unusual compounds are both structurally related, as they contain 3-(*trans*-2-aminocyclopropyl) alanine [(A*c*P)Ala, **3**][5] and 3-(*trans*-2-nitrocyclopropyl) alanine [(N*c*P)Ala, **4**][5a,6] as part of their central core (Figure 1). Furthermore, current investigations of the biological activities of belactosin A (**1**) and hormaomycin (**2**) derivatives illustrate the importance of more efficient enantioselective methods to synthesize these cyclopropyl subunits.[6]

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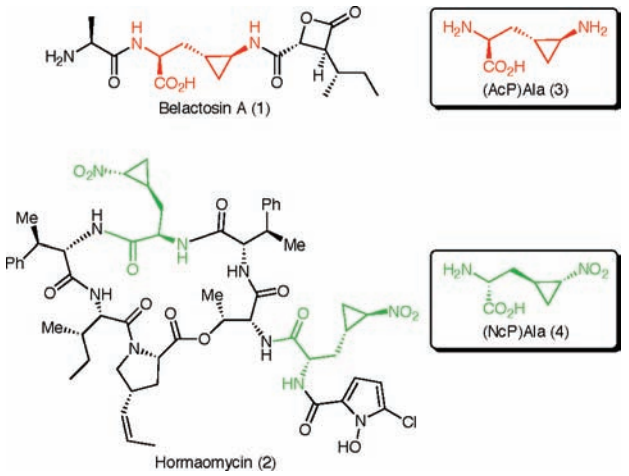


Figure 1. Belactosin A (**1**), hormaomycin (**2**), and their subunits (A*c*P)Ala (**3**) and (N*c*P)Ala (**4**).

Many elegant approaches have been designed to prepare (A*c*P)Ala (**3**) and (N*c*P)Ala (**4**) while investigating the total synthesis of natural products **1** and **2**.[5,7] Despite the proximity of the three stereogenic centers present on amino-acids **3** and **4**, two asymmetric processes are usually required to obtain the desired cyclopropane as a single stereoisomer.[8] Thus, the diastereoselective synthesis of these fragments from one defined stereogenic center remains a synthetic challenge.[2,5f]

Among the multiple methods to synthesize enantiopure cyclopropanes, diastereoselective intramolecular cyclopropanation reactions continue to be extremely efficient, as the formation of the bicycle generally occurs with good stereocontrol. Although a few examples using this approach have been reported, their application in total synthesis remains scarce, likely due to the low yields generally associated with the reaction.[9] Herein we report an elaboration of (A*c*P)Ala (**3**) and (N*c*P)Ala (**4**) using a diastereoselective intramolecular cyclopropanation reaction. This represents a convenient formal synthesis of both belactosin A and hormaomycin natural products.

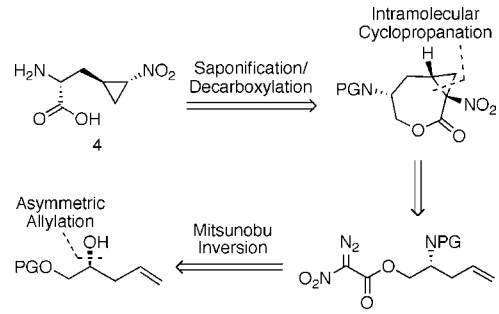
We envisioned that the preparation of **4** could be achieved via a stereoselective one-pot saponification /decarboxylation/ protonation[9a] sequence from an amino-substituted N*c*P lactone after oxidation of the primary alcohol (Scheme 1).

(7) For the synthesis of **2** and **4**, see: (a) Zindel, J.; de Meijere, A. *J. Org. Chem.* **1995**, *60*, 2968–2973. (b) Zlatopolskiy, B. D.; Loscha, K.; Alvermann, P.; Kozhushkov, S. I.; Nikolaev, S. V.; Zeeck, A.; de Meijere, A. *Chem.—Eur. J.* **2004**, *10*, 4708–4717. For structural stereogenic elucidations of **1** and **2**, see: (c) Kozhushkov, S. I.; Zlatopolskiy, B. D.; Brandl, M.; Alvermann, P.; Radzom, M.; Geers, B.; de Meijere, A.; Zeeck, A. *Eur. J. Org. Chem.* **2005**, 854–863. (d) Reinscheid, U. M.; Ziatopolskiy, B. D.; Griesinger, C.; Zeeck, A.; de Meijere, A. *Chem.—Eur. J.* **2005**, *11*, 2929–2945.

(8) de Meijere et al. have reported an elegant synthesis of **4** using the separation of two diastereoisomers obtained from an asymmetric alkylation reaction on a racemic mixture of nitrocyclopropanes: ref 7b.

(9) (a) Moriarty, R. M.; May, E. J.; Guo, L.; Prakash, O. *Tetrahedron Lett.* **1998**, *39*, 765–766. (b) Honma, M.; Takeda, H.; Takano, M.; Nakada, M. *Synlett* **2009**, 1695–1712. For an example in total synthesis, see: (c) Campbell, M. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 10370–10371.

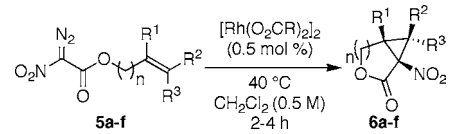
Scheme 1. Retrosynthesis of (N*c*P)Ala (**4**)



The nitrocyclopropane synthesis would involve a diastereoselective intramolecular cyclopropanation reaction (ICR) as the key step of the sequence. Finally, the stereogenic center of the α-nitro diazoester compound would arise from an asymmetric allylation reaction. By applying this approach, we anticipated that high diastereoselectivities could be obtained from a suitably protected chiral homoallylic amine.

In the past 10 years, our group has developed various methodologies for stereoselective cyclopropanation reactions using either diazo or iodonium ylide derivatives of α-nitro ester compounds.[10] Hence, to expand on this methodology, we considered the formation of 5- to 7-membered ring lactones bearing an N*c*P unit as a viable starting point for the synthesis of **4**. With this in mind, we envisioned a series of suitable substrates prepared by a Rh-catalyzed ICR. As illustrated in Table 1, rhodium *bis*(1-adamantate) dimer

Table 1. Scope of Rh-Catalyzed Intramolecular Cyclopropanation Reaction



entry	*n*	R^1	R^2	R^3	$[Rh(O_2CR)_2]_2$	product	yield[a] (%)
1	1	Me	H	H	$[Rh(OAc)_2]_2$	**6a**	20
2	1	Me	H	H	$[Rh(OPiv)_2]_2$	**6a**	79
3	1	Me	H	H	$[Rh(OAd)_2]_2$	**6a**	82
4	1	H	H	H	$[Rh(OAd)_2]_2$	**6b**	20
5	1	H	Me	Me	$[Rh(OAd)_2]_2$	**6c**	50
6	2	Me	H	H	$[Rh(OAd)_2]_2$	**6d**	80
7	3	Me	H	H	$[Rh(OAd)_2]_2$	**6e**	95
8	3	H	H	H	$[Rh(OAd)_2]_2$	**6f**	65

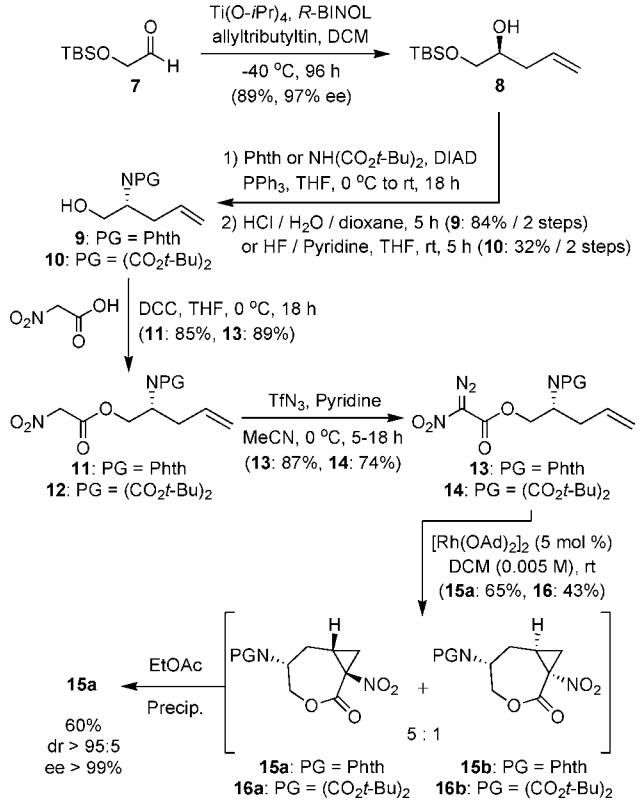
[a] Isolated yield.

catalyst gave the best results, as was previously reported.[9c] The yields were quite dependent on the alkene substitution for allylic substrates, as more electron-rich alkenes (entries 3−5) gave improved results relative to allyl α-nitro diazoacetate, which afforded only 20% yield of **6b** (entry 4).[11] The influence of the ring size in ICR was also briefly studied

with α-diazo esters **5d**−**5f** (entries 6−8). Interestingly, by increasing the number of methylene bridging units present in the ring of the N*c*P lactone formed, good to excellent yields were obtained for 6- and 7-membered ring lactones **6e** and **6f** (entries 7 and 8). It is noteworthy that only one diastereoisomer was observed in all the cases studied. With these results in hand, we decided to exploit a 7-membered ring N*c*P lactone as a direct precursor for the generation of **4**, as it already contained all the carbon units required in the target molecule.

To begin the synthesis, the enantioenriched homoallylic alcohol **8** was synthesized from the aldehyde **7** using a modified Keck asymmetric allylation reaction (Scheme 2).[12]

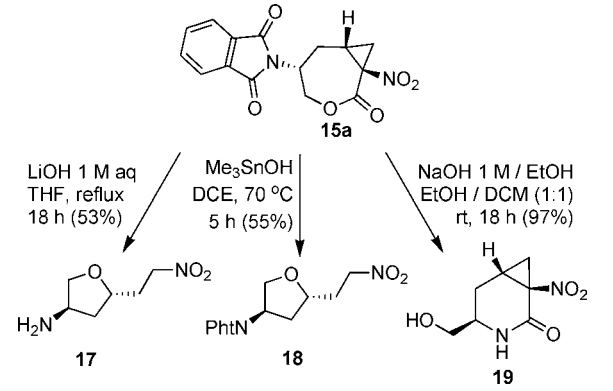
Scheme 2. Synthesis of N*c*P Lactones **15** and **16**



Performing the reaction at −40 °C and over 4 days afforded alcohol **8** in 89% yield and 97% ee on a multigram scale. The introduction of various protected homoallylic amines was accomplished using a Mitsunobu inversion. A subsequent esterification[13] and diazo transfer reaction afforded phthalimidoyl diazoester **13**[14] and di-*tert*-butylcarbamate **14** in four steps (63% and 21% overall yields, respectively). With diazo **13** and **14** in hand, we tested the optimal ICR conditions (see Table 1), which gave N*c*P lactones **15** and **16** in low yields. After further optimization, it was found that performing the reaction at room temperature and using more diluted reaction conditions could afford **15** and **16** in 65 and 43% yield, respectively, with 5:1 dr in favor of the expected *trans* isomer in both cases.[15] Interestingly, lactone **15a** could be purified through a simple precipitation upon adding EtOAc to the crude reaction mixture. A single enantio- and diastereoisomer was isolated in 60% yield, making the phthalimide protected amine route more attractive than that via the bis(Boc) analog.

With these results in hand, we pursued the synthesis of N*c*P **4** by submitting lactone **15a** to a saponification/decarboxylation/protonation sequence.[9a] Disappointingly, only the product resulting from the cleavage of the phthalimide protecting group was observed. Many basic and acidic conditions were then studied, providing either recovery of the starting material or formation of side products **17**, **18**,[16] or **19** (Scheme 3). Presumably, these products arose from the partial deprotection of the amine group followed by an intramolecular lactam ring-opening/decarboxylation sequence. Interestingly, by using only one equivalent of NaOH at room temperature in conjunction with a longer reaction time, the lactam **19** was obtained in quantitative yield. We thus decided to take advantage of **19** as an appropriate precursor of **4**, since other attempts failed to preserve the N*c*P unit. However, further attempts to hydrolyze **19** into the desired N*c*P derivative proved unproductive. As a

Scheme 3. Opening Attempts of Lactone **15a**



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(11) For previously reported reaction on **5a**, see: Snider, B. B.; Che, Q. *Tetrahedron* **2002**, *58*, 7821–7827.

(12) (a) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467–8468. (b) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160–10161. (c) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117–4126.

(13) Sylvain, C.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **1999**, *40*, 875–878.

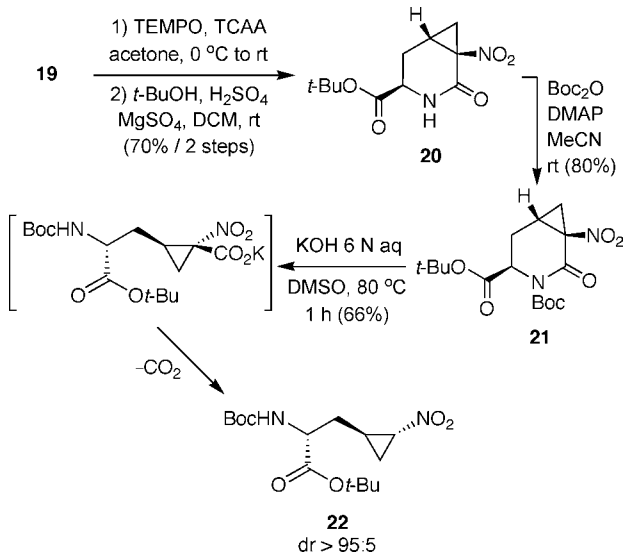
(14) Erosion of the ee (from 97 to 53% ee) for compound **9** was observed in the first unoptimized Mitsunobu reaction attempts.

(15) -NSuc. and -OTBS substituted diazoesters generated poor diastereoselectivities (3:1 and 1:1, respectively) along with moderate yields. Iodonium ylide cyclopropanation of **11** afforded **15a** in 51% yield.

(16) See Supporting Information for NOESY experiment on the relative configurations of **18** and X-Ray details of **19**.

carboxylic acid is needed at the C-4 position in the target compound (Scheme 4), we considered that oxidation of the primary alcohol into a carboxylic acid at this stage of the synthesis could be advantageous.

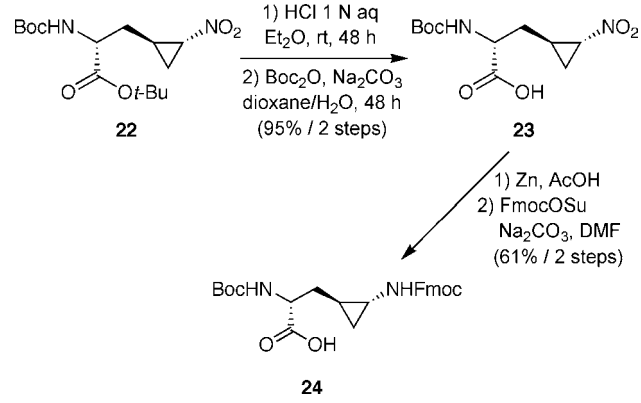
Scheme 4. Synthesis of Protected (N*c*P)Ala **22**



The oxidation of **19** into the corresponding carboxylic acid occurred smoothly using TEMPO/trichloroisocyanuric acid (TCAA) reagents (Scheme 4). The following esterification led to the corresponding *t*-butyl ester **20**[17] in 70% over 2 steps. The activation of the lactam nitrogen via the formation of carbamate **21** was necessary to facilitate the ring-opening of the seven-membered ring in basic conditions. Protection of the lactam nitrogen as a Boc followed by basic treatment led to the corresponding carboxylate that underwent the expected in situ decarboxylation reaction to afford *bis*-protected N*c*P **22**[18] in 66% yield. This last sequence concludes the first asymmetric synthesis of protected **4** using an efficient ICR methodology in an average yield of 13% over 11 steps, which is comparable to already reported syntheses.[19]

Finally, we demonstrated that standard derivatization of **22** (Scheme 5) into the corresponding NHBoc-protected N*c*P **23** and A*c*P **24** could be achieved according to a previously reported procedure.[5c]

Scheme 5. Synthesis of (N*c*P)Ala **23** and (A*c*P)Ala **24**



In summary, we have demonstrated that an intramolecular cyclopropanation reaction can serve as a direct, simple, and efficient methodology in the synthesis of N*c*P and A*c*P units, thus complementing existing reported syntheses of two natural products.

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Note Added after ASAP Publication. There was a change made to the first sentence in the abstract on January 14, 2010.

Supporting Information Available: Experimental procedures, NMR spectra, SFC traces, X-ray structure data for **15a**, **15b**, and **19**, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Ensuing steps to the oxidation of **19** using methylester derivatives afforded the corresponding deprotected acid along with cyclopropane opening by-products.

(18) See Supporting Information for NOESY experiment on the relative configuration of **22**.

(19) References 5b and 7b reported the synthesis of protected (AcP) and (NcP)Ala in 16% yield over 8 steps and 13% yield over 6 steps, respectively.