Total Synthesis of (−)-Belactosin C (I) and Derivatives via Double Diastereoselective Tandem Mukaiyama Aldol Lactonizations

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Total Synthesis of (−)-Belactosin C and Derivatives via Double Diastereoselective Tandem Mukaiyama Aldol Lactonizations

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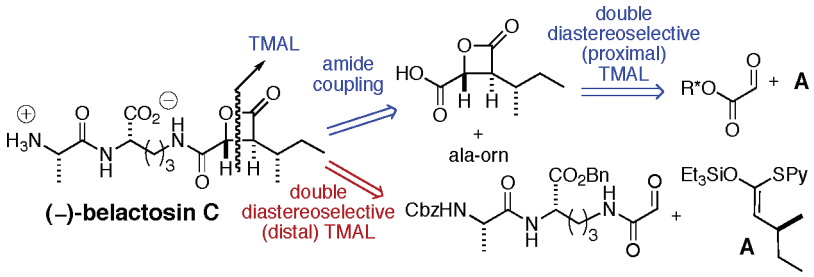
ABSTRACT



The enantioselective synthesis of (−)-belactosin C and derivatives was accomplished in a concise manner employing the tandem, Mukaiyama aldol-lactonizaton (TMAL) process. One approach involved a distal double diastereoselective TMAL reaction with a dipeptide glyoxamide, whereas a second approach involved amide coupling of a dipeptide with a β-lactone carboxylic acid, obtained via the TMAL process employing a chiral silyl ketene acetal. Notable improvements in diastereoselectivity were achieved in a proximal double diastereoselective TMAL process.

The recently isolated bacterial metabolites, belactosins A−C from a fermentation broth of *Streptomyces* sp. UCK14, uniquely contain a β-lactone dipeptide motif and exhibit anticancer activities[1] subsequently attributed to regulation of the ubiquitin-proteasome pathway through inhibition of the 20S proteasome (Figure 1).[2] Belactosins A and C possess the greatest inhibitory activity toward the chymotrypsin activity of the rabbit 20S proteasome (IC_{50} = 0.21 μM), whereas belactosin B which lacks the β-lactone moiety shows greatly reduced activity (>10 μM). In addition, degradation studies of belactosin A suggested that the β-lactone moiety was indeed responsible for the observed antiproliferative activity.[2] A benzyl ester derivative, KF33955, which is presumably more cell permeable, exhibited increased growth inhibitory activity than belactosins A and C (IC_{50} = 0.46 μM vs 51 and 200 μM, respectively) toward HeLa S3 cells. A recent X-ray study of *N*-CBz-*O*-Bn homobelactosin C bound to the yeast 20S proteasome showed that the N-terminal γ-threonine residue in the catalytic pocket of the proteasome is acylated by the β-lactone moiety and that the orientation of binding differs from another β-lactone-containing proteasome inhibitor, omuralide.[3]

As part of a program to develop concise and diastereoselective routes to β-lactones, we developed the tandem Mukaiyama aldol-lactonization (TMAL) process which allows access to both *cis*- and *trans*-β-lactones depending on the Lewis acid employed (Figure 2).[4] We and others[5] have

(1) (a) Mizukami, T.; Asai, A.; Yamashita, Y.; Katahira, R.; Hasegawa, A.; Ochiai, K.; Akinaga, S. U.S. Patent 5 663 298, 1997; *Chem. Abstr.* **1997**, *126*, 79. (b) Asai, A.; Hasegawa, A.; Ochiai, K.; Yamashita, Y.; Mizukami, T. *J. Antibiot.* **2000**, *53*, 81. (c) Yamaguchi, H.; Asai, A.; Mizukami, T.; Yamashita, Y.; Akinaga, S.; Ikeda, S.-i.; Kanda, Y. EP Patent 1 166 781 A1, 2000; *Chem. Abstr.* **2000**, *133*, 751.

(2) Asai, A.; Tsujita, T.; Sharma, S. V.; Yamashita, Y.; Akinaga, S.; Funakoshi, M.; Kobayashi, H.; Mizukami, T.; Asahi-machi, M.-S. *Biochem. Pharmacol.* **2004**, *67*, 227.

(3) Groll, M.; Larionov, O. V.; Huber, R.; De Meijere, A. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 4576.

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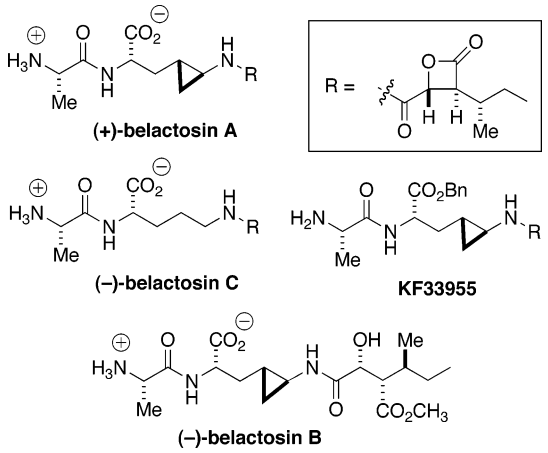


Figure 1. Structures of belactosins A−C and a more potent derivative, KF33955.

used this method to prepare various β-lactones including natural products such as (−)-panclicin D,[4a,c] tetrahydrolipstatin/orlistat,[5a,6] (−)-grandinolide,[7] and okinonellin B,[8] the latter two targets being accessed via β-lactone intermediates obtained by the TMAL process.

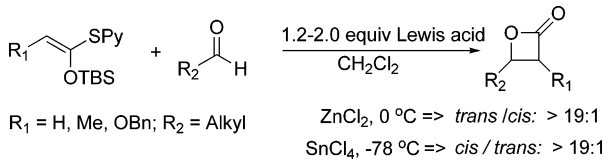


Figure 2. Tandem Mukaiyama aldol-lactonization (TMAL) process leading to *cis*- and *trans*-β-lactones.

To date, three total syntheses of the belactosins and analogues have been reported[9] along with several studies regarding fragment syntheses.[10] In general, these syntheses require multiple steps to construct the key β-lactone nucleus involving a late-stage lactonization step. We were attracted to the possibility of direct construction of belactosin and derivatives via the TMAL process using a chiral silyl ketene acetal and the required glyoxamide dipeptide (strategy A, Figure 3). This would enable rapid SAR studies of these

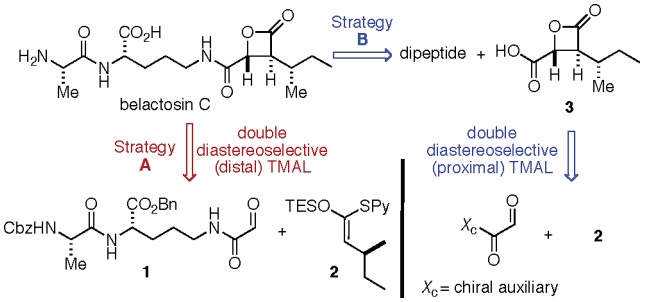
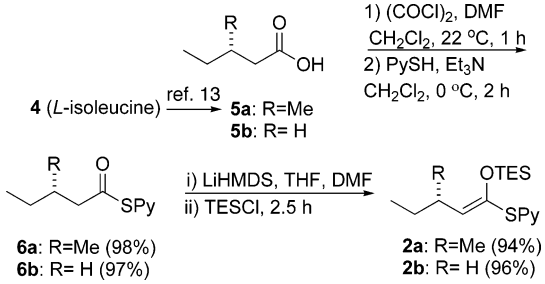


Figure 3. Strategies toward belactosin C employing double diastereoselective TMAL processes.

enzyme inhibitors toward the proteasome and possibly other cellular proteins. However, although this reaction would constitute a double diastereoselective process, a high degree of diastereoselectivity was not assured given the distance between stereogenic centers. Therefore, an alternative strategy would employ chiral glyoxamides[11] bearing cleavable chiral auxiliaries expected to impart higher diastereoselectivity via double diastereodifferentiation due to the greater proximity of the resident stereogenic centers (strategy B, Figure 3). The resulting β-lactone carboxylic acid **3** and simpler β-lactone acids could then be coupled to the protected *orn-ala* dipeptide and other peptides for structure−activity studies. Herein, we disclose our synthesis of belactosin C and derivatives employing these two synthetic strategies.

The synthesis of the required chiral silyl ketene acetal **2a** commenced with the known hydrodeamination[12] of L-isoleucine (**4**) with hydroxylamine-*O*-sulfonic acid followed by conversion to the thioester **6a** via the acid chloride (Scheme 1).[13] Conversion to the silyl ketene acetal (*E*/*Z*, ∼9:1) was accomplished using procedures described previously.[4] An identical route was employed to prepare the achiral silyl ketene acetal **2b**.

Scheme 1. Synthesis of the Ketene Acetal **2**



(4) (a) Yang, H. W.; Romo, D. *J. Org. Chem.*, **1997**, *62*, 4. (b) Yang, H. W.; Zhao, C.; Romo, D. *Tetrahedron* **1997**, *53*, 16471. (c) Wang, Y.; Zhao, C.; Romo, D. *Org. Lett.* **1999**, *1*, 1197.

(5) (a) Dollinger, L. M.; Howell, A. R. *J. Org. Chem.* **1996**, *61*, 7248. (b) Yin, J.; Yang, X. B.; Chen, Z. X.; Zhang, Y. H. *Chin. Chem. Lett.* **2005**, *16*, 1448.

(6) Ma, G.; Zancanella, M.; Oyola, Y.; Richardson, R. D.; Smith, J. W.; Romo, D. *Org. Lett.* **2006**, *8*, 4497.

(7) Zemribo, R.; Champ, M. S.; Romo, D. *Synlett* **1996**, 278.

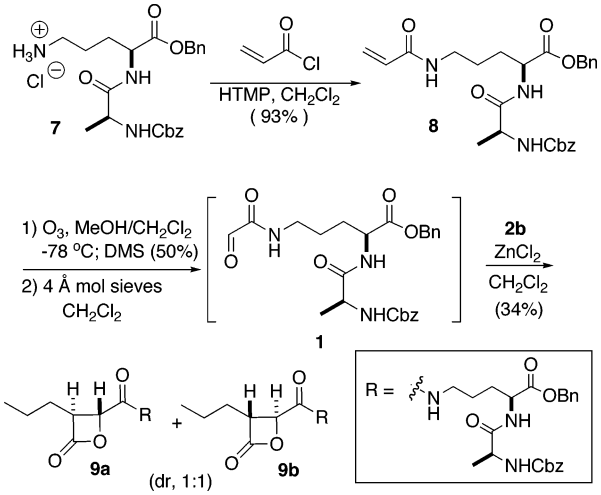
(8) Schmitz, W. D.; Messerschmidt, B.; Romo, D. *J. Org. Chem.* **1998**, *63*, 2058.

(9) (a) Armstrong, A.; Scutt, J. N. *Chem. Commun.* **2004**, *5*, 510. (b) Arionov, O. V.; de Meijere, A. *Org. Lett.* **2004**, *6*, 2153. (c) Kumaraswamy, G.; Padmaja, M.; Markondaiah, B.; Jena, N.; Sridhar, B.; Kiran, M. U. *J. Org. Chem.* **2006**, *71*, 337.

(10) (a) Begis, G.; Sheppard, T. D.; Cladingboel, D. E.; Motherwell, W. B.; Tocher, D. A. *Synthesis* **2005**, *19*, 3186. (b) Larionov, O. V.; Kozhushkov, S. I.; Brandl, M.; de Meijere, A. *Mendeleev Commun.* **2003**, *5*, 199. (c) Jain, R. P.; Vederas, J. C. *Org. Lett.* **2003**, *5*, 4669. (d) Armstrong, A.; Scutt, J. *Org. Lett.* **2003**, *5*, 2331. (e) Brandl, M.; Kozhushkov, S.; Loscha, K.; Kokoreva, O.; Yufit, D.; Howard, J.; de Meijere, A. *Synlett* **2000**, 1741.

The glyoxamide substrate **1** was prepared in two steps from the known protected dipeptide, *O*-Bn-orn-*N*-Cbz-ala **7** (Scheme 2).[9b] Acylation with acryloyl chloride provided

Scheme 2. Synthesis of the Glyoxamide Dipeptide **1** and TMAL Reaction with Achiral Ketene Acetal **2b**



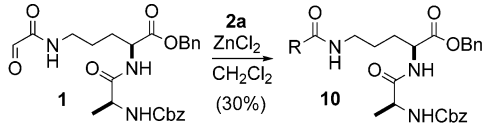
amide **8** which was converted via ozonolysis to a mixture of the desired glyoxamide **1** and its corresponding hydrate following purification by flash column chromatography. Stirring the mixture with 4 Å molecular sieves enabled dehydration to deliver the desired glyoxamide **1** suitable for the subsequent TMAL process.

With chiral and achiral ketene acetals **2a**/**b** and glyoxamide dipeptide **1** in hand, we first set out to study the inherent diastereoselectivity, if any, imparted by the dipeptide on the configuration of the β-lactone generated. On the basis of previous studies of the $ZnCl_2$-mediated TMAL process, we expected exclusive formation of *trans*-β-lactone. Indeed, treatment of aldehyde **1** with ketene acetal **2b** under standard TMAL conditions gave exclusively *trans*-β-lactones **9a**/**9b** albeit in low yield. On the basis of ^{13}C NMR, the ratio of diastereomers **9a**/**9b** was ~1:1. As expected, the stereogenic centers of the dipeptide are too distal to have any impact on the diastereoselectivity.

However, when chiral ketene acetal **2a** was employed, this led to the formation of four diastereomers including *cis*-β-lactones with a slight preference for *trans*-diastereomers (Table 1). In this case, the stereogenic center of the ketene acetal clearly does impact the diastereoselectivity but not in a favorable manner. After careful purification, the *cis*-(**10a**/**10b**) and *trans*-(**10c**/**10d**) diastereomers could be separated; however, the two *trans*-diastereomers were inseparable.

We next studied the TMAL reactions of glyoxylate esters including those bearing a chiral auxiliary, which could be readily deprotected and then coupled to a number of

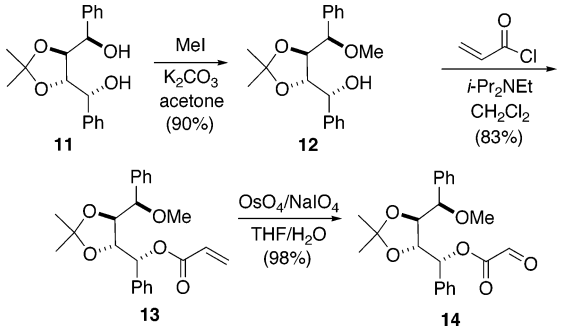
Table 1. Double Diastereoselective TMAL Reaction with Aldehyde **1** and Chiral Ketene Acetal **2a**: Synthesis of Belactosin C



stereochem.	R	ratio	$J_{3,4}$ (Hz)	$J_{1',3}$ (Hz)
C3-epimer	**10a**	1	6.5	10.0
C4-epimer	**10b**	1	6.5	10.0
belactosin C	**10c**	1.5	4.5	8.0
C3,4-epimer	**10d**	2	4.5	8.0

dipeptides. Although several chiral glyoxylates are known,[11] we elected to study a variant of the known tartrate-derived auxiliaries that would be more readily synthesized and deprotected by hydrogenolysis, a requirement for the somewhat labile β-lactone moiety that would be generated.[14] The synthesis commenced with known diol **11**, available in four steps from (−)-L-dimethyl tartrate.[15] Monomethylation of diol **11** proceeded efficiently, and subsequent acylation with acryloyl chloride gave acrylate **13**. Oxidative cleavage of the double bond in acrylate **13** provided chiral glyoxylate **14** (Scheme 3).

Scheme 3. Synthesis of Chiral Glyoxamide **14**



Application of the TMAL process to chiral glyoxylate **14** delivered an equimolar mixture of *cis*- and *trans*-β-lactones

(11) For a review describing the use of chiral glyoxals in synthesis, see: Whitesell, J. *Chem. Rev.* **1992**, *92*, 953.

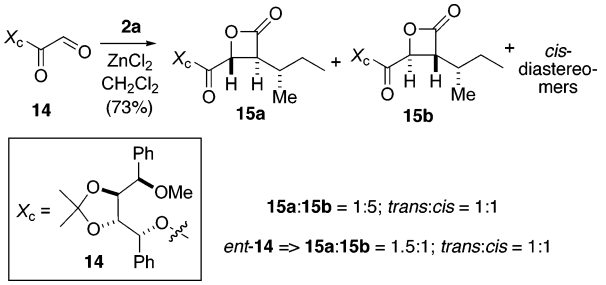
(12) Doldouras, G. A.; Kollonitsch, J. *J. Am. Chem. Soc.* **1978**, *100*, 341.

(13) For the synthesis of a related phenylthio ketene acetal, see ref 9b.

(14) β-Lactone benzyl esters were previously utilized by Yamaguchi and co-workers in this context. See ref 1c.

(15) Prasad, K. R.; Chandrakumar, A. *Synthesis* **2006**, 2159.

Scheme 4. TMAL Reaction with Chiral Glyoxamide **13**



in 73% yield; however, greater selectivity for one *trans*-diastereomer was obtained (**15a**/**15b** = 1:5, Scheme 4). Furthermore, the purification was greatly simplified by the presence of the chiral auxiliary enabling separation of the *trans*-diastereomers by simple column chromatography.

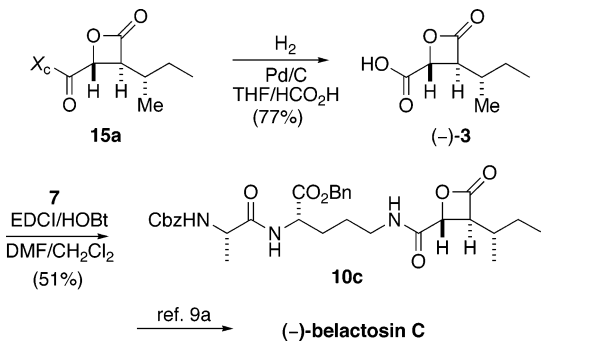
To determine if this was the matched or mismatched series with a desire to improve the diastereoselectivity for the required *trans*-diastereomer, the enantiomeric glyoxylate ester *ent*-**14** was prepared (not shown)[16] and utilized in the TMAL reaction. However, this proved to be the mismatched case as the diastereoselectivity of **15a**/**15b** decreased to 1.5:1 (Scheme 4).

Cleavage of the chiral auxiliary by hydrogenolysis of ester **15a** gave β-lactone acid (−)-**3**, which could be correlated to the same compound reported by Kumaraswamy et al. ($[\alpha]_D$ −3.1; lit. ($[\alpha]_D$ −3.0).[9c] Subsequent coupling with protected dipeptide **7** generated protected belactosin C **10c**, and deprotection by the method of Armstrong[9a] gave belactosin C in diastereomerically pure form; spectral data correlated well with those previously reported (Scheme 5).[1a]

In summary, the TMAL process enabled a concise synthesis of (−)-belactosin C and derivatives employing double diastereoselective processes with chiral ketene acetals and a dipeptide glyoxamide or a novel tartrate-derived chiral

(16) See Supporting Information for details.

Scheme 5. Coupling of β-Lactone Acid **16** and Dipeptide **7**: Synthesis of (−)-Belactosin C



glyoxylate. This strategy is unique in that the pharmacophoric β-lactone moiety of these proteasome inhibitors is constructed in a single step via the TMAL process leading to concise approaches to these novel proteasome inhibitors. Further biological evaluation of these and other belactosin derivatives including diastereomers and structural derivatives is underway and will be reported in due course.[17]

Acknowledgment. We thank the NSF (CHE-0416260) for support of these investigations. The NSF (CHE-0077917) also provided funds for purchase of NMR instrumentation. We thank Prof. John A. Porco (Boston University) for initially bringing these natural products to our attention.

Supporting Information Available: Selected experimental procedures and characterization data (including ^{1}H and ^{13}C NMR spectra) for **2a**, **6a**, **8**, **9**, **12**, **13**, **15a**, and **15b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070275K

(17) Another synthesis of belactosin C appeared while this manuscript was under review. See: Kumaraswamy, G.; Markondaiah, B. *Tetrahedron Lett.* **2007**, *48*, 1707.