Tetrahedron Letters 52 (2011) 5349–5351

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereoselective synthesis of functionalized pyroglutamates

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ARTICLE INFO

Article history:
Received 7 July 2011
Revised 1 August 2011
Accepted 3 August 2011
Available online 11 August 2011

Keywords:
Pyroglutamates (γ-carboxy-γ-lactams)
Threonine
Oxazoles
Substrate controlled alkylation
Baylis–Hillman bromides/acetates

ABSTRACT

Novel stereoselective synthesis of α-methylene-β-substituted pyroglutamates, and α-alkylidene-pyroglutamates has been achieved via substrate controlled asymmetric alkylation of L-threonine derived oxazole with Baylis–Hillman reaction based allyl bromides and acetates, respectively. The synthesized compounds were evaluated for their proteasome inhibition and cytotoxicity on multiple myeloma cells.

1. Introduction

Five-membered nitrogen containing heterocyclic structural units such as pyroglutamates (γ-carboxy-γ-lactams) are important structural motifs that serve as valuable synthons in the preparation of several types of complex natural products and heterocycles.[1] Recently, several pyroglutamate containing natural products such as lactacystin **1**, omuralide **2**, salinosporamides **3**, cinnabaramides A–G **4**, etc. (Fig. 1) have been isolated from terrestrial strain of *Streptomyces* sp. and marine actinomycete *Salinispora tropica*.[2] Several of these molecules were found to exhibit potent anti-cancer, anti-microbial, and other important medicinal properties.[2] Owing to the importance of pyroglutamates in medicinal and materials chemistry, a general methodology for facile synthesis of highly substituted chiral pyroglutamates is highly desirable. Recently, we reported a diastereoselective methodology for the synthesis of pyroglutamates starting from chlorobenzaldehyde imines of racemic α-amino acids.[3] In this Letter, we report the enantioselective synthesis of functionalized pyroglutamates starting from L-threonine derived oxazole.

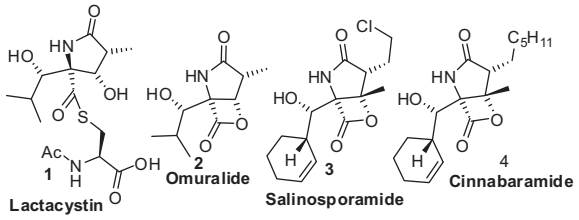
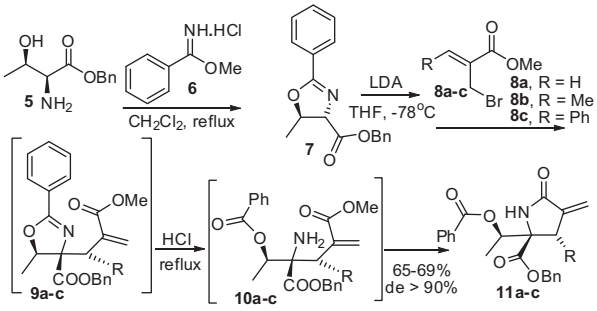


Figure 1. Pyroglutamate based natural products.



Scheme 1. Preparation of α-methylene-β-substituted pyroglutamates.

2. Results and discussion

We envisaged that the alkylation[4] of threonine oxazole **7** with ester containing allylic bromides or acetates obtained via Baylis–Hillman (BH) alcohols should provide functionalized pyroglutamates in one step. The required oxazole **7** was synthesized by

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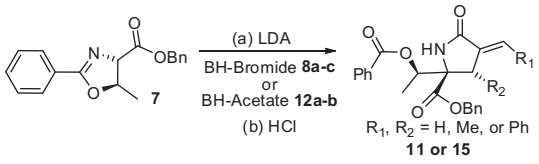
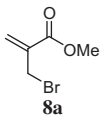
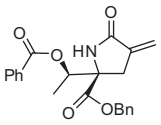
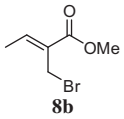
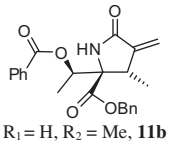
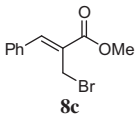
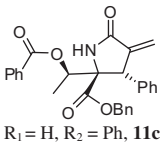
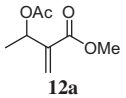
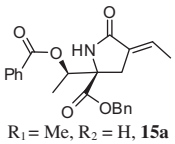
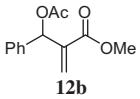
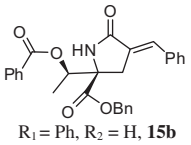
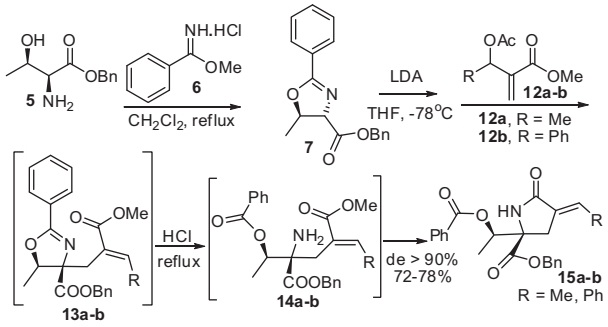
doi:10.1016/j.tetlet.2011.08.029

Table 1
Alkylation of oxazole **7** with BH bromides/acetates[8]



#	Bromide/acetate	Product	Yield
1	 **8a**	 $R_1 = R_2 = H$, **11a**	65
2	 **8b**	 $R_1 = H$, $R_2 = Me$, **11b**	67
3	 **8c**	 $R_1 = H$, $R_2 = Ph$, **11c**	69
4	 **12a**	 $R_1 = Me$, $R_2 = H$, **15a**	72[a]
5	 **12b**	 $R_1 = Ph$, $R_2 = H$, **15b**	78

[a] The (*Z*)-diastereomer was also obtained as the minor isomer (~10%) for pyroglutamate **15a**.



Scheme 2. Preparation of α-alkylidene pyroglutamates.

the reaction of threonine benzyl ester **5** with methyl benzimidate **6** in refluxing CH_2Cl_2. We chose bromides and acetates derived from BH alcohols obtained via the reaction of formaldehyde, acetaldehyde, and benzaldehyde with methyl acrylate.[5] Alkylation of oxazole **7** with methyl bromomethylacrylate **8a** followed by acidic work up provided pyroglutamate **11a** in good yield (Scheme 1). The proton NMR analysis of the crude material revealed the formation of predominantly one diastereomer. The reaction took place in highly stereoselective fashion and the alkylation proceeded from the less hindered face of the enolate to provide pyroglutamate **11a** as the major diastereomer (>90% de). Similarly, the alkylation of **7** with BH bromides **8b–c** obtained from acetaldehyde and benzaldehyde, respectively, proceeded in highly selective manner and β-methyl/phenyl pyroglutamates **11b–c** were obtained as the major isomers (Table 1). The relative stereochemistry was ascertained via single crystal X-ray analysis of the β-phenylpyroglutamate **11c** (Fig. 2).

We then extended the methodology towards the synthesis of α-alkylidine/arylidene pyroglutamates via the alkylation of **7** with allylic acetates **12a–b**. The reaction took place smoothly in S_N2' fashion, and the products **15a–b** were obtained in good yield and diastereoselectivity (Scheme 2 and Table 1).

All of the pyroglutamate natural products described in Figure 1 are potent proteasome inhibiting anti-cancer agents. Since the synthesized molecules described in Schemes 1 and 2 have the core pyroglutamate moiety, we evaluated the biological efficacy of

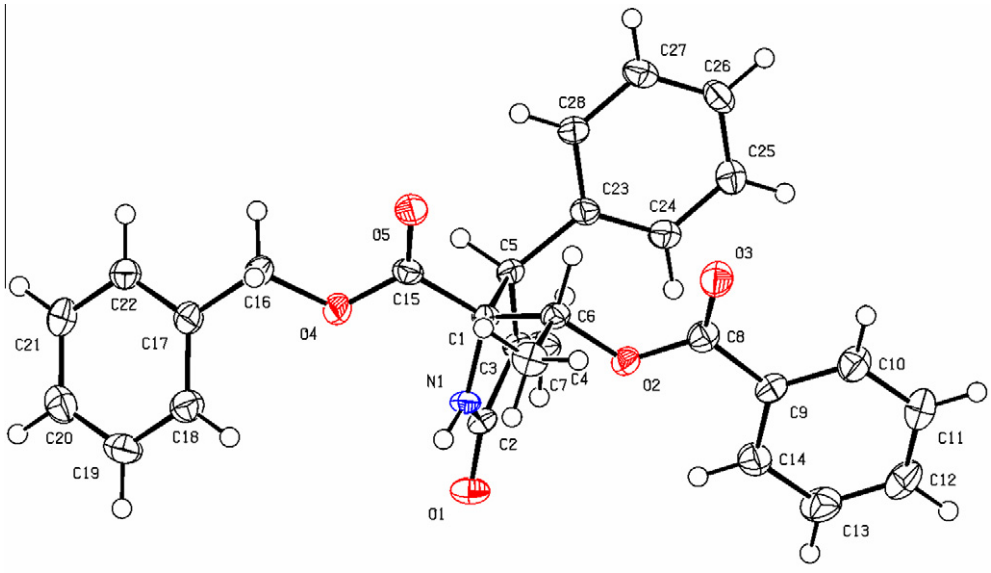


Figure 2. X-ray crystal structure of **11c**.

these analogs as potential proteasome inhibitors. Unfortunately, none of these molecules showed any significant enzyme inhibition activity[6] or cytotoxicity against multiple myeloma (RPMI-8226) cancer cell lines[7] even at 50 μM concentration.

3. Conclusions

In conclusion, we have carried out a highly diastereoselective alkylation of threonine based oxazoline with Baylis–Hillman-derived allyl bromides. Upon acidic hydrolysis, α-methylene-β-alkyl/aryl-γ-carboxy-γ-lactams with α-hydroxyethyl side chain were obtained in enantiomerically pure form. The oxazoline upon alkylation with Baylis–Hillman reaction derived allylic acetates proceeded smoothly with allylic rearrangement to provide α-alkylidine/arylidene-γ-carboxy-γ-lactams in highly stereoselective fashion. Owing to the importance of pyroglutamates in various fields and the scarcity of synthetic procedures coupled with the versatility of BH chemistry make the current methodologies highly important.

Acknowledgments

We thank the Departments of Chemistry and Biochemistry, University of Minnesota Duluth and Rowan University for the funding. Partial support for this work was also provided by research grants from the University of Minnesota Academic Health Center Faculty Development Grant (V.R.M.), Whiteside Institute for Clinical Research (V.R.M.), and Rowan University Non-Salary Financial Support Grants (NSFSG) (S.C.J.). We thank Dr. Victor G. Young, Jr. (University of Minnesota X-ray Crystallographic Laboratory) for providing the crystal structure.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.029.

References and notes

1. (a) Najera, C.; Yus, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2245–2303; (b) Smith, M. B. *Alkaloids: Chemical and Biological Perspectives* **1998**, *12*, 229–287; (c) Benoit, R.; Pascal, C.; Dominique, F.; Francois, S. *Trends Heterocycl. Chem.* **1991**, *2*, 155–204; (d) Poulsen, T. B.; Dickmeiss, G.; Overgaard, J.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4687–4690; (e) Schmidt, C.; Kazmaier, U. *Org. Biomol. Chem.* **2008**, *6*, 4643–4648; (f) Buller, M. J.; Gilley, C. B.; Nguyen, B.; Olshansky, L.; Fraga, B.; Kobayashi, Y. *Synlett* **2008**, 2244–2248; (g) Gilley, C. B.; Buller, M. J.; Kobayashi, Y. *Synlett* **2008**, 2249–2252; (h) Sun, P.-P.; Chang, M.-Y.; Chiang, M. Y.; Chang, N. C. *Org. Lett.* **2003**, *5*, 1761–1763.
2. (a) Guilder, T. A. M.; Moore, B. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9346–9367; (b) Shibasaki, M.; Kanai, M.; Fukuda, N. *Chem. Asian J.* **2007**, *2*, 20–38; (c) Stadler, M.; Bitzer, J.; Bartschmid, A. M.; Muller, H.; Buchholz, J. B.; Gantner, F.; Tichy, H. V.; Reinemer, P.; Bacon, K. B. *J. Nat. Prod.* **2007**, *70*, 246–252; (d) Masse, C. E.; Morgan, A. J.; Adams, J.; Panek, J. S. *Eur. J. Org. Chem.* **2000**, 2513–2528.
3. Tekkam, S.; Alam, M. A.; Jonnalagadda, S. C.; Mereddy, V. R. *Chem. Commun.* **2011**, 3219–3221.
4. (a) Seebach, D.; Aebi, J. D. *Tetrahedron Lett.* **1983**, *24*, 3311–3314; (b) Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1592–1604; (c) Corey, E. J.; Choi, S. *Tetrahedron Lett.* **1993**, *34*, 6969–6972; (d) Becker, M. H.; Chua, P.; Downham, R.; Douglas, C. J.; Garg, N. K.; Hiebert, S.; Jaroch, S.; Matsuoka, R. T.; Middleton, J. A.; Ng, F. W.; Overman, L. E. *J. Am. Chem. Soc.* **2007**, *129*, 11987–12002.
5. (a) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447–5674; (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev* **2003**, *103*, 811.
6. All the synthesized pyroglutamates **11a–c** and **15a–b** were tested for their ability to inhibit human erythrocyte 20S proteasome (Enzo Life Sciences) in 100 μl real-time FRET assays employing the Suc-LLVY-AMC fluorogenic peptide substrate in ½ volume white 96-well plates. Release of free AMC by proteolytic activity was monitored on Molecular Devices M5 plate reader with excitation and emission wavelengths of 360 and 460 nm, respectively. Inhibition assays at multiple compound concentrations were done in triplicate and averaged. However, none of the compounds showed significant inhibition at 50 μM concentration.
7. RPMI-8226 multiple myeloma cancer cells were plated in 96 well plates and allowed to adhere for 72 h. Cells were then treated with each compound (50 μM) or with DMSO alone for 24 h. MTS assay was used for determining the number of remaining viable cells after exposure to compounds. 20 μl of MTS was added to 100 μl culture medium in each well. After incubation at 37 °C for 3 h, absorbance was measured using an ELISA plate reader. All the compounds tested under these conditions proved to be non-toxic at 50 μM.
8. *Representative procedure for the preparation of functionalized pyroglutamates*: To a solution of LDA (30 ml, 2 M in THF/heptane/ethyl benzene) in THF (140 ml) was added threonine oxazoline (10 g, 33.9 mmol) drop wise at −78 °C. After 1 h, bromide **8a** (8.9 g, 50 mmol) was added and stirred for 6 h at −78 °C. The reaction was quenched with 3 M HCl and extracted with ethyl acetate, washed with brine, and concentrated in vacuo. The crude product was refluxed in THF and 3 M HCl for 1 h. The reaction was worked up with $NaHCO_3$ and ethyl acetate, dried ($MgSO_4$), concentrated in vacuo, and purified by silica gel column chromatography to get the lactam **11a** (8.36 g, 65% yield). ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.89–7.87 (m, 2H), 7.55 (m, 1H), 7.39–7.36 (m, 7H), 7.25 (br s, 1H), 6.00 (dd, J = 2.5, 3.0 Hz, 1H), 5.45 (q, J = 6 Hz, 1H), 5.31–5.33 (m, 1H), 5.29 (d, J = 12.5 Hz, 1H), 5.21 (d, J = 12.5 Hz, 1H), 3.19 (ddd, J = 2.5, 3.0, 17.5 Hz, 1H), 3.00 (ddd, J = 2.5, 3.0, 17.5 Hz, 1H), 1.31 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 169.7, 165.7, 137.4, 134.9, 133.6, 130.0, 129.5, 129.0, 128.9, 128.7, 128.6, 117.4, 73.8, 68.4, 65.7, 34.2, 15.2; ESI-MS: 402 $[M+Na]^+$, 380 $[(M+H)^+$, 100%], 362 $[(M+H-H_2O)^+]$; HRMS (ESI) m/z: calcd for $C_{22}H_{21}NO_5$ $[M+Na]^+$: 402.1334, found 402.1318.