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Stereoselective synthesis of belactosin C and its derivatives using a catalytic proline catalyzed crossed-aldol reaction☆

G. Kumaraswamy* and B. Markondaiah

Organic Division III, Fine Chemicals Laboratory, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Abstract—A highly practical and concise stereoselective total synthesis of belactosin C and synthetic variants was achieved using an *S*-proline catalyzed crossed-aldol reaction as the key step.

Many natural products possessing the 2-oxetanone (β-lactone) moiety exhibit biological activity such as antibiotic, antitumour and antiobesity.[1] Prominent natural molecules bearing a 2-oxetanone ring include anisatin, a potent vegetal poison and the antibiotic 1233A.[2] A significant number of natural 2-oxetanones with interesting biological activity have been identified and synthesized.[3] Recent additions to this family are belactosins A and C (Fig. 1) which inhibit the 20s proteasome in vitro ($IC_{50} = 0.4$ μM, chymotrypsin-like activity) in a yeast based assay of Streptomycin metabolites.[4]

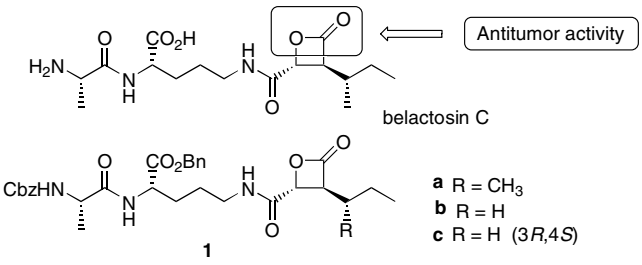

Figure 1.

The basic structure of the belactosins consists of a *trans*-β-lactone moiety attached to an ornithine–alanine amino acid dipeptide unit. Degradation studies suggested that the β-lactone moiety is responsible for the antiproliferative activity. Two total syntheses of belactosins A and C and their analogues have been previously reported.[5] Recently, we developed a stereocontrolled route to belactosin C via an Oppolzer aldol reaction as the key step using a sultam chiral auxiliary.[6] Despite these synthetic methods, there is still a need for an alternative efficient synthetic route for belactosin C and new derivatives in order to further investigate β-lactones and their efficacy towards cancer and other diseases (Fig. 1). We envisioned that belactosin C could be readily accessed by an *S*-proline catalyzed crossed-aldol reaction to install the two stereocentres of the *trans*-β-lactone in a highly diastereo and enantioselective manner.[7] The retrosynthetic approach to belactosin C and derivatives are shown in Scheme 1.

In this Letter we report a concise and a highly stereoselective synthetic route to belactosin C wherein the chirality is derived from catalytic *S*-proline. Our synthesis began with a 10 mol % *S*-proline catalyzed crossed-aldol reaction between 3-(*S*)-methylvaleraldehyde **6a**, derived from L-isoleucine **8** and glyceraldehyde acetonide **7**,[8] which in turn was prepared from D-mannitol. After initial trials, the reaction was carried out with 10 mol % of *S*-proline and 1 equiv of **6a** and 2 equiv of **7** in dry DMF at 4 °C, stirring for 48 h led to aldol product **5a**. Due to the capricious nature of **5a**,[9] it was subjected to oxidation using sodium chlorite and sodium dihydrogen orthophosphate. The resulting β-hydroxy acid was lactonized with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl) to give β-lactone acetonide **4a** in 46% overall yield from **6a**.

Keywords: *S*-Proline; Belactosin C; β-Lactone; Ornithine–alanine; Proliferative activity.

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* Corresponding author. Tel.: +91 40 27193275; fax: +91 40 27160387; e-mail addresses: gkswamy@iictnet.org; gkswamy_iict@yahoo.co.in

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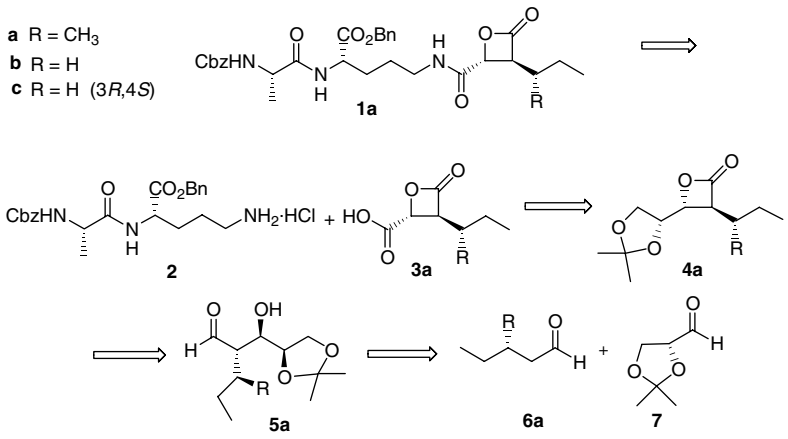
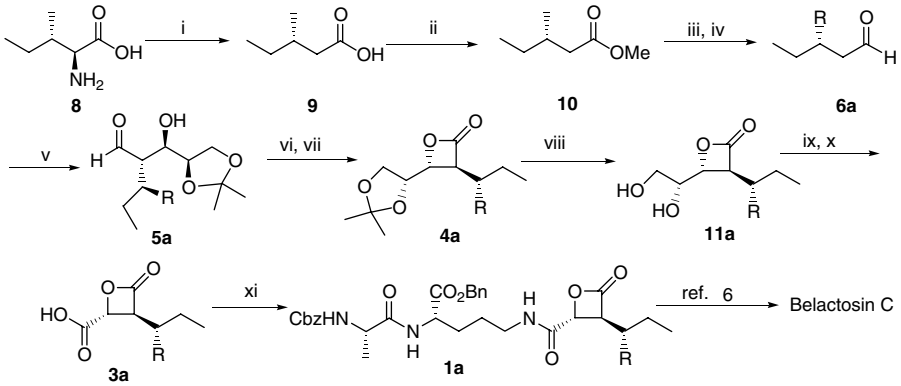


Scheme 1.



Scheme 2. Reagents and conditions: (i) $NaNO_2$, HBr, 0 °C–rt, 12 h; Zn, H_2SO_4, 0 °C–rt, 12 h (65% yield); (ii) dry MeOH, H_2SO_4, reflux, 12 h (70% yield); (iii) $LiAlH_4$, Et_2O, rt, 3 h; (iv) PCC, DCM, rt, 1 h (59% yield over two steps); (v) **7**, *S*-proline (10 mol %), DMF, addition of **6a** via syringe pump over 24 h; then 48 h, 4 °C; (vi) $NaClO_2$, 20% $NaH_2PO_4{\cdot}2H_2O$, *t*-BuOH, 0 °C–rt, 4 h; (vii) BOPCl, Et_3N, DCM, 23 °C, 1 h (46% overall yield from **6a**); (viii) 1 N HCl:THF (1:1) 0 °C–rt, 3 h (95% yield); (ix) $NaIO_4$, 1,4-dioxane:H_2O (1:2), 20 °C, 3 h; (x) $NaClO_2$, 20% $NaH_2PO_4{\cdot}2H_2O$, *t*-BuOH, 0 °C–rt, 4 h (83% yield over two steps); and (xi) **2**, DCC, HOBt, EtOAc:H_2O (1:1) rt, 1 h (50% yield).

β-Lactone acetonide **4a** was subjected to hydrolysis with 1 N HCl:THF (1:1) at 0 °C to rt, for 4 h to give β-lactone diol **11a** in 95% yield. Diol **11a** was subjected to oxidative cleavage using sodium metaperiodate in 1,4-dioxane:H_2O (1:2) to give a crude aldehyde which was further oxidized with chlorite/dihydrogen orthophosphate to afford β-lactone carboxylic acid **3a** in an 83% yield over the two steps.[10] β-Lactone carboxylic acid **3a** was coupled with dipeptide **2**[11] which resulted cleanly in fully protected belactosin C **1a** in an 18% overall yield from aldol **5a**, (Scheme 2).

Belactosin C derivative **1b** was synthesized using valeraldehyde **6b** (R = H) and glyceraldehyde acetonide **7** followed by the same sequence of steps as used in Scheme 2 in an overall yield of 20%. In the same way, diastereomer **1c**[12] was prepared using *R*-proline instead of *S*-proline in an overall yield of 19%. The analytical data of **1a** and **1b** were in full agreement with the reported data.[6]

In conclusion, we have developed a catalytic route for the total synthesis of belactosin C and derivatives. Significantly, the chirality of the β-lactone moiety was installed with inexpensive reagents. Application of this novel methodology to synthesize various substituted β-lactones in order to study their activity profiles is under progress.

Acknowledgements

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Supplementary data

Experimental procedures, spectral data and copies of spectra for compounds **1c**, **3c** and **4a–c** can be found in the Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.059.

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8. Aldehydes containing an α-methine carbon (CHR_3) adjacent to the carbonyl do not under go homo-dimerization when exposed to the catalyst as the kinetic inaccessibility of the α-methine proton and thermodynamic instability of the corresponding enamine effectively prohibit nucleophile formation.
9. β-Hydroxyaldehydes such as **5a** were reported to undergo oligomerization, elimination and other decomposition reactions. For recent documented examples, see: (a) Chemler, S. R.; Roush, W. R. *J. Org. Chem.* **2003**, *68*, 1319–1333; (b) Lautens, M.; Stammers, T. A. *Synthesis* **2002**, 1933–2012.
10. (a) Efforts to estimate the level of diastereoselectivity of **5a** were not successful. Presumably, the minor diastereomer formed during the *S*-proline catalyzed aldol reaction was removed in the subsequent purification of **4a**; (b) The diastereo and enantioselectivity of aldol product **5a** was determined on the basis of β-lactone carboxylic acids **3a** and **3b** reported in our previous work.[6] The optical rotation of compound **3c**, was similar in magnitude but opposite in sign to that of **3b** ($[\alpha]_D^{25}$ +13.8 (*c* 0.05, $CHCl_3$); lit.[6] ($[\alpha]_D^{25}$ −10.5 (*c* 1, $CHCl_3$).
11. For the preparation of dipeptide unit **2**, see Ref. 6.
12. Selected data: Compound **1c**: $[\alpha]_D^{25}$ −11.5 (*c* 0.0125, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.27–7.30 (m, 10H), 5.67 (d, $J = 8.0$ Hz, NH), 5.12 (d, $J = 8.0$ Hz, 2H), 5.03 (s, 2H), 4.50–4.60 (m, 1H), 4.43–4.49 (m, 1H), 4.42 (d, $J = 4.4$ Hz, 1H), 3.40–3.50 (m, 1H), 3.20–3.29 (m, 1H), 2.95–3.08 (m, 1H), 1.66–1.82 (m, 4H), 1.36–1.41 (m, 4H), 1.35 (d, $J = 6.8$ Hz, 3H), 0.94 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz) δ: 172.3, 171.5, 169.5, 167.9, 156.0, 136.1, 135.0, 128.6, 128.5, 128.4, 128.3, 128.1, 127.9, 72.8, 67.3, 67.0, 57.4, 51.7, 51.1, 38.4, 29.9, 29.1, 25.1, 19.8, 18.3, 13.4; IR (KBr): 3316, 2933, 1825, 1731, 1652, 1534, 1447, 1238, 1178, 1072, 905, 738, 661. MS (LC): *m*/*z* 590 $[M+Na]^+$. Compound **4a**: $[\alpha]_D^{25}$ −28.6 (*c* 0.025, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.23 (ddd, $J = 2.2$, 6.8, 9.0 Hz, 1H), 4.19 (dd, $J = 2.2$, 3.7 Hz, 1H), 4.08 (dd, $J = 6.8$, 8.3 Hz, 1H), 3.87 (dd, $J = 6.8$, 8.3 Hz, 1H), 3.49 (dd, $J = 3.7$, 8.3 Hz, 1H), 1.85–1.95 (m, 1H), 1.58–1.70 (m, 1H), 1.41 (s, 3H), 1.37 (s, 3H), 1.23–1.33 (m, 1H), 1.00 (d, $J = 6.8$ Hz, 3H), 0.95 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz): δ 170.0, 110.2, 74.8, 73.0, 65.0, 57.9, 33.3, 26.7, 25.7, 25.4, 16.5, 10.9; IR (KBr): 2962, 2875, 1828, 1460, 1378, 1214, 1114, 1066, 895; MS (LC): *m*/*z* 251 $[M+Na]^+$. Compound **11a**: $[\alpha]_D^{25}$ −38.5 (*c* 0.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.33 (dd, $J = 3.9$, 8.1 Hz, 1H), 3.68–3.80 (m, 3H), 3.53 (dd, $J = 4.3$, 8.3 Hz, 1H), 2.94 (br s, 1H), 2.30 (br s, 1H), 1.89–1.99 (m, 1H), 1.60–1.70 (m, 1H), 1.20–1.33 (m, 1H), 1.05 (d, $J = 6.6$ Hz, 3H), 0.96 (t, $J = 7.4$ Hz, 3H); IR (KBr): 3382, 2963, 1813, 1459, 1293, 1114, 1014, 877. MS (LC): *m*/*z* 211 $[M+Na]^+$.