

Communications

Bromination/Hydrolytic Fragmentation Reactions of α,β -Unsaturated *N*-Boc Lactams for the Synthesis of ω -Amino-trisubstituted (*E*)-Vinyl Bromides

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Received September 21, 2009, Accepted October 6, 2009

Key Words: Bromination, Decarboxylation, Fragmentation, α,β -Unsaturated lactam

Trisubstituted (*E*)-halo alkenes are important synthetic building blocks frequently employed in the synthesis of many natural products including scyphostatin,^{1a} octalactin,^{1b} phomactins,^{1c} borrelidin,^{1d} apoptolidin,^{1e} FK901464,^{1f} phorbaxazole A,^{1g} fostriecin,^{1h} taxifolial A,¹ⁱ kendomycin,^{1j} tedanolide^{1k} and deoxytedanolide.^{1l} We have previously developed and reported the bromination/hydrolytic fragmentation reactions of lactones **1** to trisubstituted (*E*)-vinyl bromides **3**.² As a scalable alternative

to the conventional methods, this new strategy was successfully applied to the gram-scale synthesis of enantiomerically pure trisubstituted (*E*)-vinyl bromide (-)-**5** used as the C₈-C₁₁ fragment in the total synthesis of tedanolide (Scheme 1).²

In the reaction sequence, the putative intermediate **2c** undergoes a C-C bond rotation for anti-coplanar alignment of the departing carboxylate and bromide groups before the elimination reaction, thus generating (*E*)-vinyl bromides in a highly stereoselective manner.³

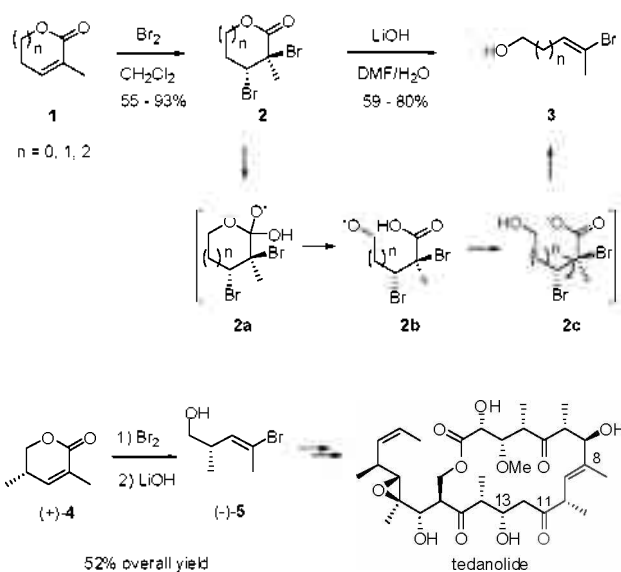
Noticing the potential utility of ω -amino-trisubstituted (*E*)-vinyl bromides (*vide infra*) for the synthesis of indolizidine and quinolizidine type alkaloid natural products,⁴ we decided to apply the above bromination/hydrolytic fragmentation protocol to α,β -unsaturated lactam system. To this end, a short array of α,β -unsaturated *N*-Boc lactams **12a** - **12d** were prepared from the corresponding ω -amino aldehydes by following the literature procedures.⁵ Subsequent bromination reactions gave rise to *trans*-dibromides **13a** - **13d** (75 ~ 85% yield),⁶ setting the stage for the ensuing hydrolytic fragmentation reactions. When treated with LiOH in aqueous DMF at rt, dibromides **13a** - **13d** readily underwent the fragmentation reactions to provide the corresponding ω -amino-(*E*)-vinyl bromides **14a** - **14d**, at a rate much faster than lactone dibromides **1** (Scheme 2).⁷

In summary, the bromination/hydrolytic fragmentation reactions on α,β -unsaturated *N*-Boc lactams furnished various previously unknown ω -amino-trisubstituted (*E*)-vinyl bromides,⁸ in a stereoselective manner and good overall yields. Their utility towards the synthesis of indolizidine and quinolizidine type alkaloid natural products are currently under investigation.

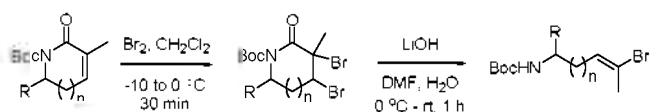
Acknowledgments. This work was supported by the research fund of Hanyang University (HY-2007). NTT acknowledges the BK-21 Program.

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Scheme 1. Bromination/hydrolytic fragmentation reactions of lactones to trisubstituted (*E*)-vinyl bromides and application to the multi-gram synthesis of (-)-**5**.



12a (n = 0, R = H)	13a (n = 0, R = H), 75%	14a (n = 0, R = H), 69%
12b (n = 1, R = H)	13b (n = 1, R = H), 85%	14b (n = 1, R = H), 78%
12c (n = 2, R = H)	13c (n = 2, R = H), 72%	14c (n = 2, R = H), 73%
12d (n = 1, R = Me)	13d (n = 1, R = Me), 77%	14d (n = 1, R = Me), 81%

Scheme 2. Bromination/hydrolytic fragmentation reactions of *N*-Boc lactams **12a** - **12d**.

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 6. Typical procedure: To a solution of *N*-Boc lactam **12b** (500 mg, 2.4 mmol) in CH₂Cl₂ (2.0 mL) was added 4.0 mL of Br₂ in CH₂Cl₂ (2 M) over 10 min at -10 °C. After 30 min, the reaction mixture was poured into a beaker containing 30 mL of sat. NaHSO₃(aq) and ice with aid of EtOAc (caution: the quenching process is quite exothermic). The organic layer was separated, washed with brine, concentrated and chromatographed (hexane/EtOAc = 7/1) to give **13b** (746 mg, 85% yield) as white solids.
 7. Typical procedure: To a flask charged with dibromide **13b** (400 mg, 1.1 mmol) were added 3.0 mL of DMF/H₂O (4:1) and LiOH·H₂O (140 mg, 3.0 equiv) at 0 °C. The reaction mixture was then warmed to rt. After 1 h, the reaction mixture was directly chromatographed (hexane/EtOAc = 5/1) to furnish **14b** (222 mg, 78% yield) as a colorless liquid.
 8. Free amine of **14b** was reported as an inseparable mixture with (*Z*)-isomer. Nugent, B. M.; Williams, A. L.; Prabhakaran, E. N.; Johnston, J. N. *Tetrahedron* **2003**, *59*, 8877.