N-Methylative aziridine ring opening and asymmetric synthesis of MeBmt

Yongeun Kim, Doo-Ha Yoon, Hyun-Joon Ha, Kyung Yeon Kang, Won Koo Lee

Department of Chemistry and Protein Research Center for Bio-Industry, Hankuk University of Foreign Studies, Yongin, Kyunggi-Do 449-719, Republic of Korea

Department of Chemistry, Sogang University, Seoul 121-742, Republic of Korea

Article info

Article history:
Received 5 July 2011
Revised 4 August 2011
Accepted 8 August 2011
Available online 7 September 2011

Keywords:
MeBmt
Asymmetric synthesis
Aziridine
Ring opening
Crotylation

MeBmt (1) was isolated from the fungus Tolypocladium inflatum with a cyclic undecapeptide cyclosporine possessing immunosuppressive activity. The structure of MeBmt as a nonproteogenic unusual amino acid features \(\gamma\)-alkyl-\(\beta\)-hydroxy-\(\alpha\)-methylamino acid with three contiguous stereocenters and a \(\beta,\gamma\)-trans double bond. Though MeBmt itself does not have biological activity, structural modification of MeBmt in cyclosporine affects its immunosupressant activity to a great extend. There is rich literature detailing the synthesis of MeBmt based on asymmetric reactions and chiral building blocks including sugars and amino acid. However all synthetic methods except one required monomethylation of amine at a certain stage. Recently we have developed the \(N\)-methylative aziridine ring opening reaction with various nucleophiles to afford \(N\)-methylated \(\alpha\)- or \(\beta\)-amino compounds. Applying this methodology allows us to give an easy access for the asymmetric synthesis of MeBmt including orthogonally protected MeBmt as a synthetic intermediate which is valuable for the further biological studies.

Our synthetic plan stems from two key reactions (Scheme 1); the addition of crotylboronate of aziridine-2-carboxaldehyde to give rise to the methyl groups at \(\gamma\)-position with the extension of the backbone and the subsequent \(N\)-methylative aziridine ring opening reaction. Aziridine-2-carboxaldehyde (2) considered as a synthetic surrogate of aminoaldehyde shows better stereoselectivity in most of nucleophilic carbonyl addition reactions with better stability under strong base compared to the most of other aminoaldehydes and their synthetic surrogates including the Garner's aldehyde. Thereby chiral aziridine-2-carboxaldehyde, readily available from commercial source, was used as a starting substrate. Addition of (E)-crotylboronate was planned to put three more carbons to the aziridine-2-carboxaldehyde with the hydroxyl group and the methyl branch formed at C3 and C4 in MeBmt with the expectation of high stereoselectivity. Another key reaction, \(N\)-methylative aziridine ring opening, from 3 to 4 at a certain stage may generate \(N\)-methyl amino alcohol which are essential functional groups toward the target molecule. The synthetic plan including those two key reactions would afford us a facile route for the preparation of MeBmt not only as in its naked but as in its orthogonally protected form.

Scheme 1.
This synthesis was initiated from the addition reaction of crotylboronate to aziridine-2-carboxaldehyde (2). The reaction of (S,S)-diisopropyl tartrate (E)-crotylboronate with (2R)-aziridine-2-carboxaldehyde (2) provided anti-favored crotylation product, (1R,2R)-2-methyl-1-[(R)-1-phenylethyl]aziridin-2-yl]but-3-en-1-ol (3), without detection of any other isomers in 87% yield (Scheme 2).

The secondary alcohol in 3 was protected with benzylbromide and sodium hydride to provide 1-benzyloxy-2-methyl-3-butenyloxirane (4). A regioselective N-methylative ring opening reaction of the unactivated aziridine proceeded with methyl trifluoromethansulfonate and an acetate nucleophile. After the successful formation of N-methyl aziridinium ion by N-methylation with methyl trifluoromethansulfonate we tried (n-Bu)₃NOAc as an acetate source with an advantage of good solubility in organic solvent to yield two regioisomers of the ring-opened products (5) and (6) with the ratio of 71:29 in 51% yield, which were readily separable by silica gel chromatography (Scheme 2). We tried to improve the regioselectivity and the reaction yield by changing the sources of acetate nucleophiles including NaOAc, CsOAc, and AgOAc. Eventually, we found that CsOAc was the best to show the selectivity as 87:13 in favor of the expected product 5 in 69% yield.

The successful introduction of all three stereocenters with the N-methyl group is followed by the extension of two more carbons with (E)-olefin between C6 and C7 of backbone and the oxidation of the primary alcohol to the corresponding carboxylic acid. Extension of the backbone chain by two more carbons from the ring-opened product 5 was achieved by the olefination of the aldehyde (8) which was acquired from hydration of the olefin to the primary alcohol (7) followed by oxidation. To furnish 7 from 5 through hydromethylation and oxidation protocol, Wilkinson’ catalyst procedure with catecholborane⁶ and oxidative workup was the best in a 78% yield. The Swern oxidation of the resulting primary alcohol 7 with dimethyl sulfoxide and oxaly chloride afforded the aldehyde 8 in 90% yield. The reaction of aldehyde 8 with 5-(ethoxysulfonyl)-1-phenyl-1H-tetrazole⁹ in the presence of KHMSD in THF provided the (E)-olefin 9 with the removal of acetate in 89% yield. The enantimERICally pure amino acid protected by two benzyl groups at the nitrogen and oxygen was prepared from the primary alcohol 9 through oxidation with pyridinium dichromate (PDC) in dimethylformamide (DMF). Subsequent removal of two benzyl groups was accomplished in the presence of sodium and liquid ammonia in THF to afford the target molecule MeBmt (1) in 61% yield (Scheme 2).

In conclusion an asymmetric synthesis of MeBmt, an unusual amino acid constituent of cyclosporine A, was achieved from aziridine-(2R)-carboxaldehyde through seven chemical steps including highly stereoselective addition of (E)-crotylboronate and N-methylative aziridine-ring opening in 20% overall yield.

Acknowledgments

This work was supported by National Research Foundation (NRF) (Basic Science Research Program, 2010-0008424 and the Center for Bioactive Molecular Hybrids to H.-J.H.) and the HUFS (NRF) (Basic Science Research Program, 2010-0008424 and the Center for Bioactive Molecular Hybrids to H.-J.H.) and the HUFS (NRF) (Basic Science Research Program, 2010-0008424 and the Center for Bioactive Molecular Hybrids to H.-J.H.). W.K.L. also acknowledges the financial support from KRF-2010-0005538 and KRF-2009-0081956.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.048.

References and notes
