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A PRACTICAL SYNTHESIS OF 3-[(1*R*)-1-*t*-BUTYLDIMETHYLSILYLOXYETHYL]-4-[(2*R*)-4-HALO-3-OXO-2-BUTYL]AZETIDINONE, A VERSATILE INTERMEDIATE FOR CARBAPENEM ANTIBIOTICS

Chunhua Yang* and Nobuyoshi Yasuda

Department of Process Research, Merck Research Laboratories, Merck & Co., Inc., P.O. Box 2000, Rahway, New Jersey 07065

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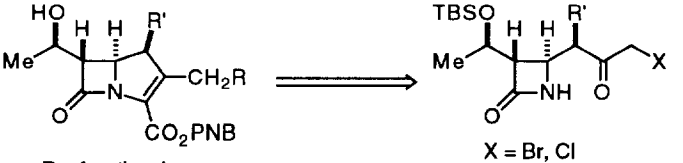
Abstract: A key intermediate for 2-(functionalized-methyl)-1-β-methylcarbapenems, 3-[(1*R*)-1-*t*-butyldimethylsilyloxyethyl]-4-[(2*R*)-4-halo-3-oxo-2-butyl]azetidinone, was prepared efficiently from a commercially available carboxylic acid in 3 steps.

Recently, 2-functionalized-methyl carbapenems **1b** have received attention because of their important biological activities,[1] including potency against Methicillin-resistant *Staphylococcus aureus*.[2] It has also been found that similar carbapenems bearing a β-methyl substituent at C-1 exhibit greater chemical and metabolic stability than their des-methyl analogs.[3] Compounds **2a** were identified as a versatile intermediates toward the preparation of **1a**. Several workers have reported the utility of 4-(halomethylcarbonyl-1-ethyl)-2-azetidinones **2b** in the preparation of compounds **1b**.[1b,4] An efficient synthesis of compounds **2a** and **2b**, however, has yet to be reported. To date all syntheses of **2b** have been either lengthy, low yielding and/or required the use of hazardous reagents such as diazomethane.[4]



R = functional group
1a R'=Me
1b R'=H

X = Br, Cl
2a R'=Me
2b R'=H

Here we report an efficient and practical route to 3-[(1*R*)-1-*t*-butyldimethylsilyloxyethyl]-4-[(2*R*)-4-halo-3-oxo-2-butyl]azetidinone **2c** and **2d** from commercially available carboxylic acid **3** in 3 steps.

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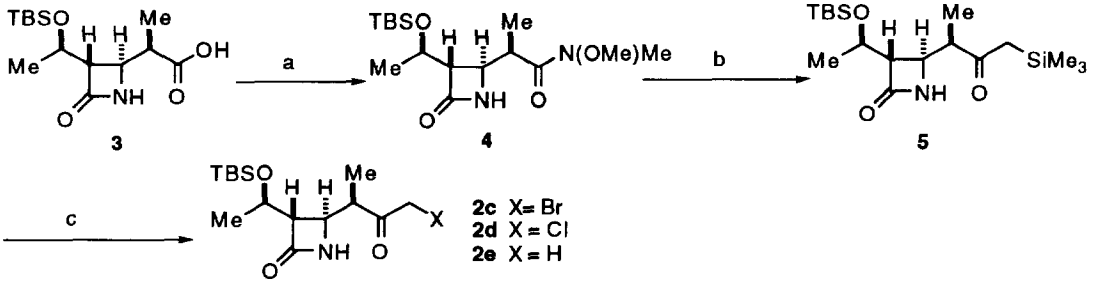

(a) HN(OMe)Me•HCl, HOBt, EDC•HCl, NEt_3, CH_2Cl_2/H_2O, 22 °C, 24 h 98% (b) i. THF, Me_3SiCH_2Li 1 *M* in hexanes, -45 °C to -10°C then aged 20 min. ii. 2 *M* AcOH in THF at -45 °C, then pH7 phosphate buffer, 84% (c) for **2c**: i. THF, 2 *M* Br_2 in CH_2Cl_2, -35 °C to -5 °C, 20 min. ii. pH7 phosphate buffer, then wash with 0.1 *M* NaS_2O_3, 98%. for **2d**: i. THF, 2 *M* sulfuryl chloride in CH_2Cl_2, -30 °C, 20 min. ii. pH7 phosphate buffer, then wash with 0.1 *M* NaS_2O_3, 77%

Treatment of carboxylic acid **3** with 1-hydroxybenzotriazole hydrate (HOBT) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC•HCl) provided **4**, which was readily crystallized from ethyl acetate and hexane.[5] Weinnreb amide **4**[6] reacted smoothly with Me_3SiCH_2Li. Unexpectedly a typical aqueous quench with saturated NH_4Cl promoted desilylation yielding primarily the methylketone **2e**.[7] This desilylation was prevented by using a nonaqueous quench of anhydrous AcOH in THF. Trimethysilylketone **5** proved to be quite labile to silica gel, however trituration of the crude product with hexane provided **5** as a colorless crystalline solid. Addition of bromine or sulfuryl chloride to **5** provided **2c** and **2d**, respectively, as crystalline solids.[8] These compounds proved useful for the preparation of biologically active carbapenems which will be reported in due course.

In summary, carboxylic acid **3** can be converted efficiently in three steps to **2c** and **2d**, which are the key intermediates for preparation of certain carbapenem antibiotics.

References and Notes

1. (a) Nishi, K.; Imuta, M.; Kimura, Y.; Miwa, H. *J. Antibiot.* **1995**, *48*, 1481. (b) Schmitt, S. M.; Salzmann, T. N.; Shih, D. H.; Christensen, B. G. *J. Antibiot.* **1988**, *41*, 780 and references cited therein. (c) Ona, H.; Uyeo, S.; Fukao, T.; Doi, M.; Yoshida, T. *Chem. Pharm. Bull.* **1985**, *33*, 4382. (d) Narukawa, Y.; Nishi, K.; Onoue H. *Tetrahedron* **1997**, *53*, 539. (e) Imuta, M.; Itani, H.; Hishi, K.; Ona, H.; Uyeo, S.; Kimura, Y. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2199.
2. (a) Imuta, M.; Itani, H.; Ona, H.; Konoike, T.; Uyeo, S.; Kimura, Y.; Miwa, H.; Matsuura, S.; Yoshida, T.*Chem. Pharm. Bull.* **1991**, *39*, 672 and references cited therein. (b) Arnould, J. C.; Illingworth, R. N.; Nichols, W. W.; Wilson, R. G. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2449.
3. (a) Fukasawa, M.; Sumita, Y.; Harabe, E. T.; Tanio, T.; Nouda, H.; Kohzuki, T.; Okuda, T.; Matsumura, H.; Sunagawa, M. *Antimicrob. Agents Chemother.* **1992**, *36*, 1577. (b) Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29.
4. Ueda, Y.; Maynard, C. *Tetrahedron Lett.* **1988**, *29*, 5197 and references cited therein.
5. Ho, G.-J.; Mathre D. J. *J. Org. Chem.* **1995**, *60*, 2271.
6. All compounds were characterized by ^1H NMR and ^{13}C NMR spectra.
7. Demuth, M. *Helv. Chim. Acta* **1978**, *61*, 3136.
8. Benneche, T.; Christiansen, M.; Undheim, K. *Acta Chem Scand.* **1986**, *B40*, 700.