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rel-(1R,4R,5S)-5-HYDROXY-3-OXO-2-AZABICYCLO[2.2.0]HEXANE, A STABLE SYNTHETIC EQUIVALENT OF 4-(2-OXOETHYL)AZETIDIN-2-ONE[1]

Nobuya Katagiri,[a] Masayuki Sato,[a] Toshihiko Naito,[b] Makoto Muto,[a] Toshiyuki Sakamoto,[a] Satoshi Saikawa,[a] and Chikara Kaneko*[a]
Pharmaceutical Institute, Tohoku University,[a] Aobayama, Sendai 980, Japan and Faculty of Pharmaceutical Sciences, Kanazawa University,[b] Takara-machi, Kanazawa 920, Japan

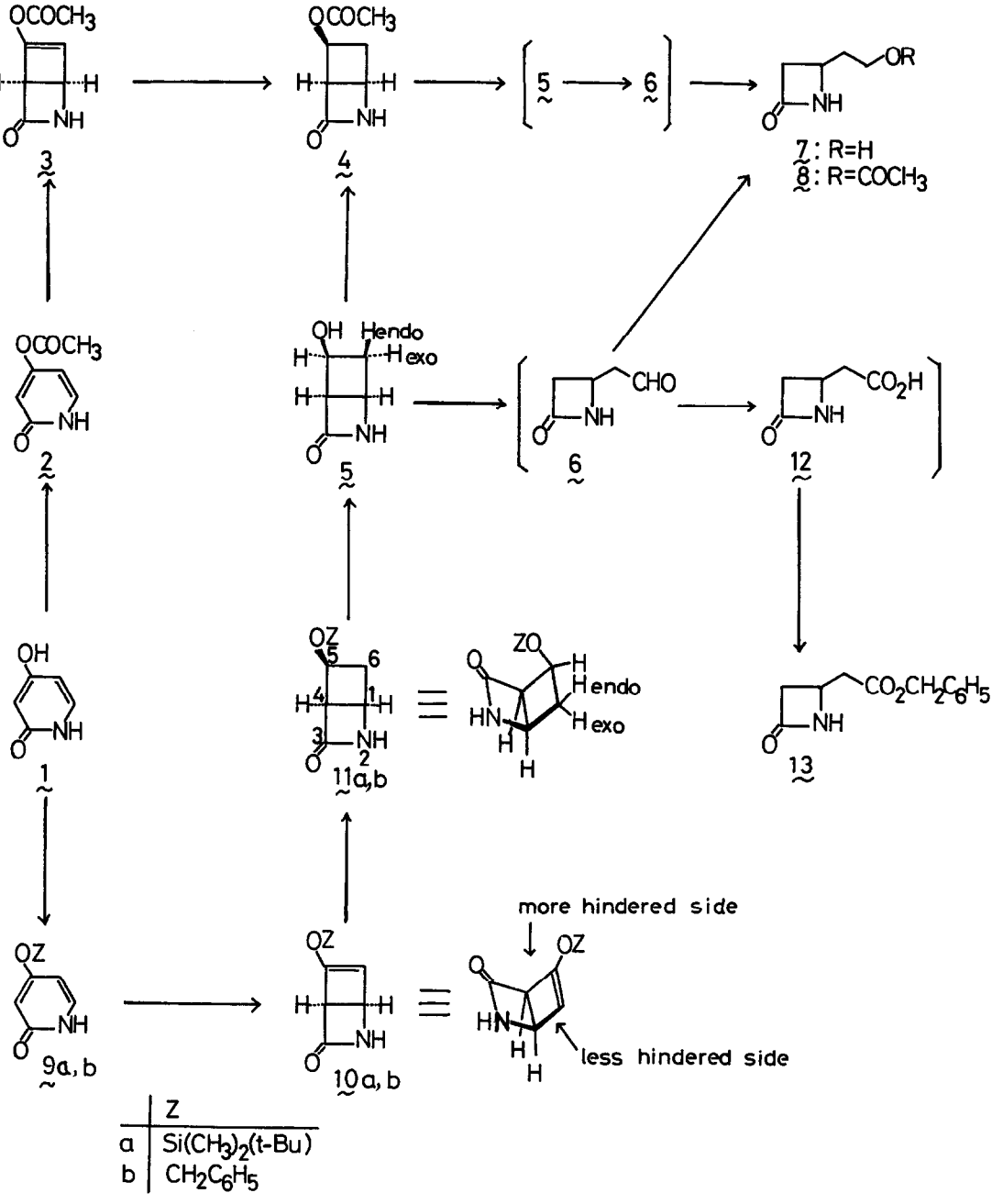
Abstracts: The title compound, a synthetic equivalent of 4-(2-oxoethyl)-azetidin-2-one, has been synthesized as a stable crystalline solid either from 4-(t-butyldimethylsilyloxy)- or 4-benzyloxy-2-pyridone via photopyridone formation, catalytic hydrogenation, and deblocking of the protecting group.

4-(2-Oxoethyl)azetidin-2-one and its 1-substituted derivatives were considered to be versatile synthetic intermediates of the carbapenem nuclei on the basis of previous studies.[2] However, due to their extreme instability, they had to be used immediately as they were formed.[3] Obviously, if some new compound which is stable enough to be stored and behaves exactly like the aldehyde can be prepared, it would not only help to prepare the already known carbapenems, but also facilitate the synthesis of their new analogues. Here, we report the synthesis of rel-(1R,4R,5S)-5-hydroxy-3-oxo-2-azabicyclo[2.2.0]-hexane, a stable crystalline solid, as a synthetic equivalent of 4-(2-oxo-ethyl)azetidin-2-one.

Previously, we reported the synthesis of 4-(2-hydroxyethyl)azetidin-2-one 7 (isolated as its acetate) from 4-acetoxy-2-pyridone 2 via three-step procedure (2→3→4→7): photolysis, catalytic hydrogenation, followed by basic hydrolysis in the presence of sodium borohydride.[4] Though the title compound 5 was surely involved in the above transformation, a facile retro-aldol ring opening of 5 to 4-(2-oxoethyl)azetidin-2-one 6 (which was then reduced in situ to the final product 7) under a basic medium had prevented its isolation. While all attempts to hydrolyze 4 under acidic conditions have failed,[5] the following synthesis of 5 has now been realized using the photopyridones 10a and 10b derived from either 4-(t-butyldimethylsilyloxy)- or 4-benzyloxy-2-pyridone 9a and 9b as key intermediates.[6]

A solution of 4-(t-butyldimethylsilyloxy)-2-pyridone 9a [mp 114°C, softened at 105°C. $\lambda_{max.}$ (Et_2O) 295 nm][7,8] in ether was irradiated[9] by high-pressure mercury lamp (Ushio 450 W, Pyrex filter) to give the photopyridone 10a (mp 65°C)[10] in 51% yield[11] as a sole isolable product. Hydrogenation of the olefinic bond in 10a over palladium on charcoal in MeOH gave a single

stereoisomer 11a (mp 75°C)[12] which was assigned as the endo-configuration, since the coupling constant between the protons of C_4 and C_5 is 8 Hz. As expected, hydrogenation occurs from the less hindered side of the molecule (10a).



Removal of the t-butyldimethylsilyl group of 11a was achieved by Dowex (H^+), TsOH, or CF_3CO_2H in aq. THF at room temperature to give rel-(1R,4R,5S)-5-hydroxy-3-oxo-2-azabicyclo[2.2.0]hexane 5 [mp 116-120°C, $\delta_H(CD_3OD)$: 1.94 (dd, J = 14, 5 Hz, $H_{6\text{-endo}}$), 2.68 (ddd, J = 14, 9, 5 Hz, $H_{6\text{-exo}}$), 3.64-3.78 (m, H_1), 3.82 (dd, J = 9, 3 Hz, H_4), 4.56 (td, J = 9, 5 Hz, H_5)] in ca. 80% yield. This compound is stable either in its crystalline state or in a protic solvent even in the presence of hydrochloric acid at room temperature. This stability in an acidic condition led us a more economical synthesis of 5. Thus, the photopyridone 10b (mp 122-124°C)[6] derived from 4-benzyloxy-2-pyridone 9b[13] was hydrogenated as above to the dihydro compound 11b [mp 105-107°C, $\delta_H(CDCl_3)$: 2.06 (dd, J = 14, 4.5 Hz, $H_{6\text{-endo}}$), 2.52 (ddd, J = 14, 8.5, 4 Hz, $H_{6\text{-exo}}$), 3.55-3.75 (m, H_1), 3.75-4.1 (m, H_4), 4.1-4.5 (m, H_5), 4.3 and 4.7 (each d, J = 10 Hz, CH_2Ph), 6.6 (bs, NH), 7.3 (bs, C_6H_5)] in nearly quantitative yield. Though the catalytic hydrogenation terminated at the dihydro stage (11b) in an alcohol (e.g., MeOH) even under high pressure conditions, catalytic hydrogenation of 11b in MeOH containing 0.3 volume % of conc. HCl at room temperature afforded smoothly the debenzylated product 5 in almost quantitative yield.

Chemical equivalency of 5 to 4-(2-oxoethyl)azetidin-2-one 6 was demonstrated by the following two reactions. Thus, treatment of 5 by 1% K_2CO_3 in MeOH in the presence of an excess of sodium borohydride at room temperature, followed by acetylation (Ac_2O-pyridine) gave 4-(2-acetoxyethyl)azetidin-2-one 8 in nearly quantitative yield. As reported in the previous paper,[4] the same two-step procedure if applied to rel-(1R,4R,5S)-5-acetoxy-3-oxo-2-azabicyclo-[2.2.0]hexane 4 afforded the same acetate 8 in 75% yield. The fact that acetylation (Ac_2O-pyridine) of 5 gave 4 in quantitative yield indicated that both compounds (4 and 5) have the same stereochemistry. In the second example, treatment of 5 by 1% aq. K_2CO_3 in the presence of potassium permanganate (a slight excess of the theoretical amount) at 0°C, followed by benzylation ($PhCH_2Br$/DMF, room temperature) gave 4-benzyloxycarbonylmethyl-azetidin-2-one 13[14] in 66% yield. Probably, base-catalyzed retro-aldol ring opening of 5 to 6, followed by oxidation to 4-carboxymethylazetidin-2-one 12 (potassium salt) may be involved in this transformation.

Since rel-(1R,4R,5S)-5-hydroxy-3-oxo-2-azabicyclo[2.2.0]hexane 5 is a stable crystalline compound and can be synthesized readily from appropriately protected 4-hydroxy-2-pyridones (e.g., 9a and 9b) by three-step, we believe that this compound 5 is a better precursor than 4-(2-oxoethyl)azetidin-2-one for the carbapenem synthesis.

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7. Compound 9a was prepared by the reaction of 1 (1 equiv.) with t-butyldimethylsilyl chloride (1 equiv.) in the presence of imidazole (2.5 equiv.) in N,N-dimethylformamide at room temperature under stirring and recrystallized from n-hexane. Due to its relative instability, the ether extract of 9a from the reaction mixture was immediately used for the photolysis.
8. All new compounds were supported either by elemental analyses or by high-resolution mass spectra.
9. All irradiations (ether for 9a and acetonitrile for 9b) were continued until almost all of the starting 2-pyridones (9a and 9b) were consumed. The reactions were monitored UV spectroscopically and continued until the absorption maxima of 9 (around 300 nm) became almost nil.
10. $\delta_H(CDCl_3)$: 0.22 (s, CH_3x2), 0.93 (s, CH_3x3), 4.20 (bs, H_1 and H_4), 5.08 (bs, H_6), 6.15 (bs, NH). IR ν_{max}: 3425, 1750, 1625, 1615 cm^{-1}.
11. The yield was based on compound 1.
12. $\delta_H(CDCl_3)$: 0.08 (s, CH_3), 0.10 (s, CH_3), 0.88 (s, CH_3x3), 2.01 (dd, J = 14, 4 Hz, $H_{6\text{-endo}}$), 2.64 (ddd, J = 14, 8, 4 Hz, $H_{6\text{-exo}}$), 3.58-3.75 (m, H_1), 3.88 (ddd, J = 8, 2.5, 2.5 Hz, H_4: the signal becomes dd with J = 8 and 2.5 Hz by the addition of D_2O), 4.55 (td, J = 8, 4 Hz, H_5), 6.38 (bs, NH). IR ν_{max}: 3400, 1750 cm^{-1}.
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