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A Practical Synthesis of A Key Intermediate for the Production of β-Lactam Antibiotics.

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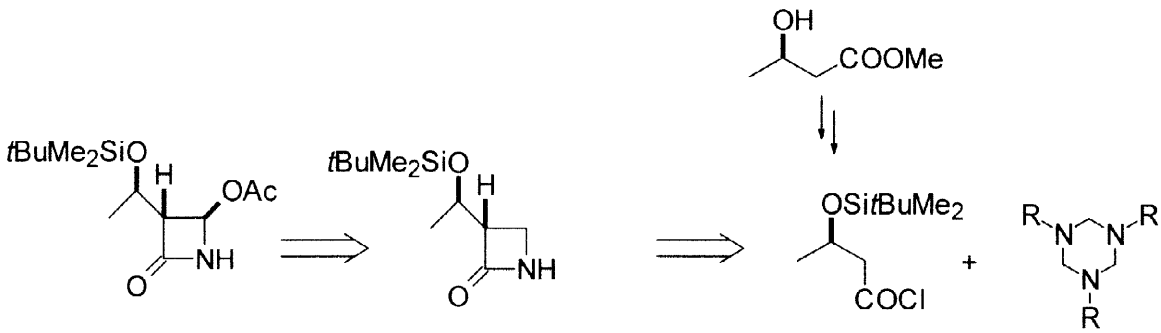
Abstract: *N*-(*p*-methoxyphenyl)-hexahydro-1,3,5-triazine in presence of a Lewis acid and (*R*)-3-(*t*-butyldimethylsilyloxy)butyric acid chloride with Et_3N directly furnish (3*S*,1'*R*)-*N*-*p*-methoxyphenyl-3-(1-*t*-butyldimethylsilyloxy)ethylazetidin-2-one with good diastereoselectivity. This product is transformed into the 4-acetoxy-azetidinone **1**, a key intermediate in the synthesis of β-lactam antibiotics.

The unique chemotherapeutic properties of β-lactam antibiotics continue to attract the attention of the chemical community. Strategies for the stereoselective synthesis of carbapenems, penems, monobactams and tribactams usually rely first on the construction of a monocyclic azetidin-2-one bearing the appropriate functionalities on C-3 and C-4. In this perspective the (3R,4R,1'R)-3-[1-(*t*-butyldimethylsilyloxy)ethyl]-4-acetoxy-azetidin-2-one **1** has been recognized as the most versatile building block.[1] This important intermediate can be obtained through a C-4 oxidation by means of a Ru catalyst,[2] so that the azetidinone **2** can be considered the true target.[3]

As a part of our ongoing studies in the area of C-4 unsubstituted azetidin-2-ones,[4] we report herein a stereocontrolled synthesis of **2** starting from methyl (*R*)-3-hydroxybutyrate[5] and hexahydrotriazine (Scheme 1).



1 **2** **3**

R = *p*-methoxyphenyl-

Scheme 1

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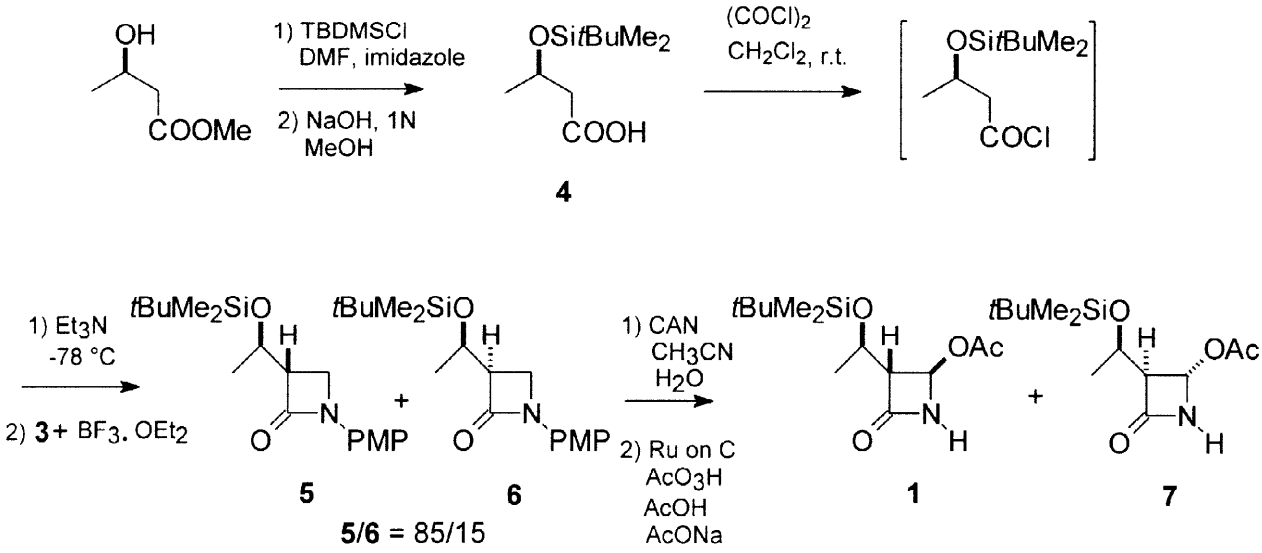
In this approach hexahydro-1,3,5-triazine **3**, easily obtained from an aqueous solution of formaldehyde and *p*-anisidine, acts as a *N*-methyleneamine equivalent. In fact, according to a modified Kamiya procedure,[6] hexahydrotriazines in presence of a Lewis acid react with acid chlorides and triethylamine to afford C-4 unsubstituted β-lactams. As a ketene equivalent we selected a (*R*)-3-hydroxybutyric acid derivative. The protected acid **4** was readily prepared from the chiral methyl (*R*)-3-hydroxybutyrate[7] in two steps (88% overall yield)[8] and then treated with oxalyl chloride at room temperature to produce the corresponding acid chloride. Any attempt to isolate this chloride by distillation gave a mixture of products. The corresponding ketene was then generated *in situ* at -78 °C with triethylamine. To this orange solution was added the purple-red complex between the *N,N,N*-*p*-methoxyphenylhexahydro-1,3,5-triazine **3** and boron trifluoride etherate. The mixture was slowly warmed to room temperature overnight. Chromatographic purification of the crude reaction mixture afforded azetidin-2-ones **5** and **6** in 85/15 ratio (GC analysis) and 60% yield starting from **4** (Scheme 2).[9]

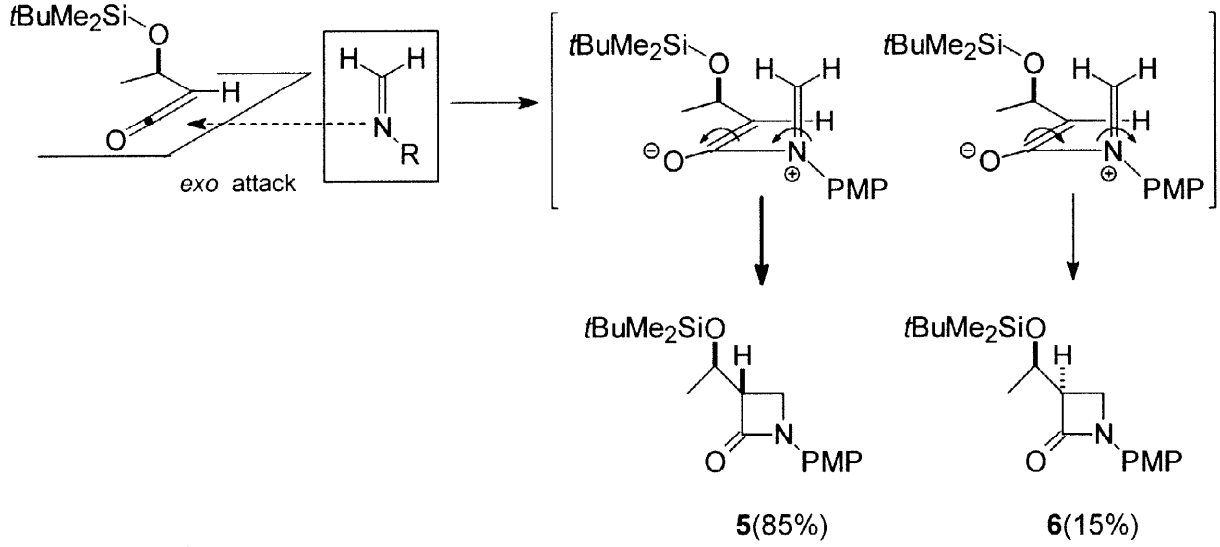


Scheme 2

The absolute configuration of the known products **5** and **6** was determined by spectral comparison and chemical conversion to 4-acetoxy-azetidin-2-ones **1** and **7** according to a previously reported procedure[3b] (oxidative deprotection of the *p*-methoxyphenyl group with ceric ammonium nitrate and C-4 oxidation with Ru on C). The ^{1}H NMR and ^{13}C NMR spectra of the major isomer **1** are identical to those of an authentic sample.[10] Of particular interest is the unexpected stereochemical control that the (*R*)-stereogenic center of the acid chloride exerts on the newly developed C-3 stereocenter of the azetidinone ring. Surprisingly, the diastereofacial selectivity is in favour of the (3*S*,1'*R*)-configuration. It is worth mentioning that the use of the hexahydrotriazine as a formal synthetic equivalent of a formaldimine is crucial for the stereoselectivity of

this cycloaddition. In fact, using (*S*)-3-tri*iso*propylsilyloxybutyric acid chloride in a reaction with α-ketoimines, the (3*S*,1'*S*)-azetidin-2-one thus obtained, required a Mitsunobu inversion reaction to be converted into the biologically active (3*S*, 1'*R*)-product.[11]

The stereochemical outcome observed for our reaction can be rationalized by assuming that the ketene addition to the hexahydrotriazine occurs from the direction opposite to the ketene substituent (denoted *exo*).[12] The bulkiness of the OSi*t*BuMe$_2$ affects the counterclockwise conrotatory ring closure leading to the desired (3*S*,1'*R*)-configuration as major isomer (Scheme 3). The clockwise closure is less favoured because it would require the *O*-*t*-butyldimethylsilyl and the CH_2 groups to pass through each other.



Scheme 3

In conclusion, we report a practical and short synthesis of an important carbapenem intermediate using methyl (*R*)-3-hydroxybutyrate and hexahydro-1,3,5-triazine. The unique stereochemical behaviour of the cycloaddition directly affords the biologically active (3*S*,1'*R*)-configuration of the β-lactam. The use of readily accessible materials allows in few steps easy access to acetoxyazetidinone **1**, an important key intermediate in the β-lactam antibiotic field. An evaluation of the iminic and ketene substituent effect on the stereoselectivity of the cycloaddition, along with optimization of the process, is currently underway.

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5. Methyl (*R*)-3-hydroxy-butyrate is the starting material for the industrial production of **1**: Nakatsuka, T.; Iwata, H.; Tanaka, R.; Imajo, S,; Ishiguro, M.; *J. Chem. Soc., Chem. Comm.* **1991**, 662. Noyori,R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134.
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7. The most convenient methods to obtain the (*R*)-3-hydroxybutyric acid are available either through depolymerization of poly-(*R*)-3-hydroxybutyrate (see: Seebach, D.; Roggo, S.; Zimmermann, J., in: *Stereochemistry of Organic and Biorganic Transformation.* Bartmann, W.; Sharpless, K. B., Eds., Verlag Chemie, Weinheim **1987**, pp. 85-126) or by microbial oxidation: Ohashi, T.; Proc. CHIRAL 90 SYMP., Spring Innovations, Stockport, UK, 1990, pp.65-71.
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9. To a solution of **4** (654 mg, 3 mmol) in CH_2Cl_2 (20 mL) at room temperature, oxalylchloride (4.5 mmol, 0.385 mL) was added. After the mixture was stirred for 3 hours, the temperature was brought to –78 °C and Et_3N (12 mmol, 1.67 mL) was slowly added. The solution became yellow and then orange to confirm that the ketene was formed. After 15 min. at low temperature a solution of *N*-p-methoxyphenyl-hexahydro-1,3,5-triazine (405 mg, 1 mmol) and $BF_3.Et_2O$ (0.380 mL, 3 mmol) previously mixed in CH_2Cl_2 (10 mL) at room temperature, was added dropwise. The mixture was allowed to warm slowly to room temperature overnight. The resulting brown solution was diluted with CH_2Cl_2 and washed with HCl (1 M, 20 mL). The aqueous phase was re-extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were dried and concentrated in vacuo. The residue was purified by chromatography over silica gel (cyclohexane / AcOEt = 8/2) given **5** and **6** in 60% yield. **5**: IR (neat): 1747, 1514, 1246. ^{1}H NMR ($CDCl_3$, 300 MHz): 0.04 (s, 3H); 0.08 (s, 3H); 0.80 (s, 9H); 1.25 (d, 3H, J = 6.3 Hz); 3.27 (ddd, 1H, J = 2.7, J = 5.4 and J = 4.2 Hz); 3.57 (dd, 1H, J = 5.4 and J = 5.3 Hz); 3.64 (dd, 1H, J = 2.7 and J = 5.3 Hz); 3.79 (s, 3H), 4.30 (dq, 1H, J = 4.2 and J = 6.3 Hz); 6.85- 7.31 (4H, m, arom).^{13}C NMR ($CDCl_3$, 75.5 MHz): 165.0; 155.8; 132.2; 117.4; 114.3; 65.2; 56.6; 55.5; 40.3; 25.6; 22.6; 17.8; -4.3; -5.0. **6**: IR (neat): 1747, 1514, 1246. ^{1}H NMR ($CDCl_3$, 300 MHz): 0.08 (s, 6H); 0.82 (s, 9H); 1.35 (d, 3H, J = 6.4 Hz);3.40 (m, 1H); 3.50 (dd, 1H, J = 2.7 and J = 5.3 Hz); 3.56 (dd, 1H, J = 5.4 and J = 5.3 Hz); 3.79 (s, 3H); 4.23 (dq, 1H, J = 4.1 and J = 6.3 Hz); 6.85- 7.31 (m, 4H, arom.). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 164.5; 155.8; 132.1; 117.3; 114.2; 65.7; 56.5; 55.7; 40.6; 25.6; 20.7; 17.8; -4.2; -5.0.
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