Preparation and Alkylation of *N*-t-Butyldimethylsilyl-3-trimethylsilyloxyazetidin-2-one

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The title β-lactam (**6**) is prepared in three steps from commercially available 2-azetidinone (**9**) (50% overall yield) and can be efficiently alkylated with a variety of electrophiles.

The lethal chlorotic action of tabtoxinine-β-lactam (**1**),[1] the active constituent of tabtoxin[1,2] (wildfire toxin) is a well established consequence of the potent and irreversible inactivation of glutamine synthetase (GS).[2,3] Utilizing glutamate, ammonia, and ATP as substrates, GS initially phosphorylates glutamate affording an enzyme bound carboxylate-phosphate anhydride (**2**).[3] Nucleophilic attack by enzyme bound ammonia on (**2**) presumably gives rise to a tetrahedral intermediate (**3**) which subsequently collapses liberating glutamine, P_i, and ADP. The 3-hydroxy-azetidin-2-one unit in (**1**) represents an efficient carboxylate mimic and when engaged with the enzyme, (**1**) is phosphorylated yielding a tightly bound analogue (**4**) [or (**5**)] of the acyl-phosphate intermediate.[1] By analogy with GS, other pharmacologically significant enzymes, which act as carboxylate kinases, may potentially be inactivated through thoughtful design of modified substrates incorporating this 3-hydroxy-β-lactam unit.[4] Direct introduc-

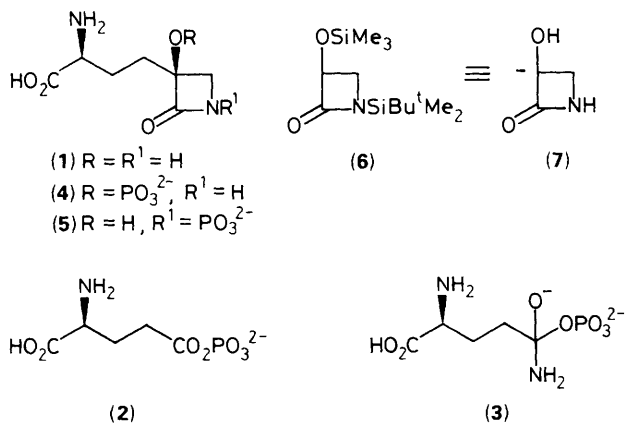
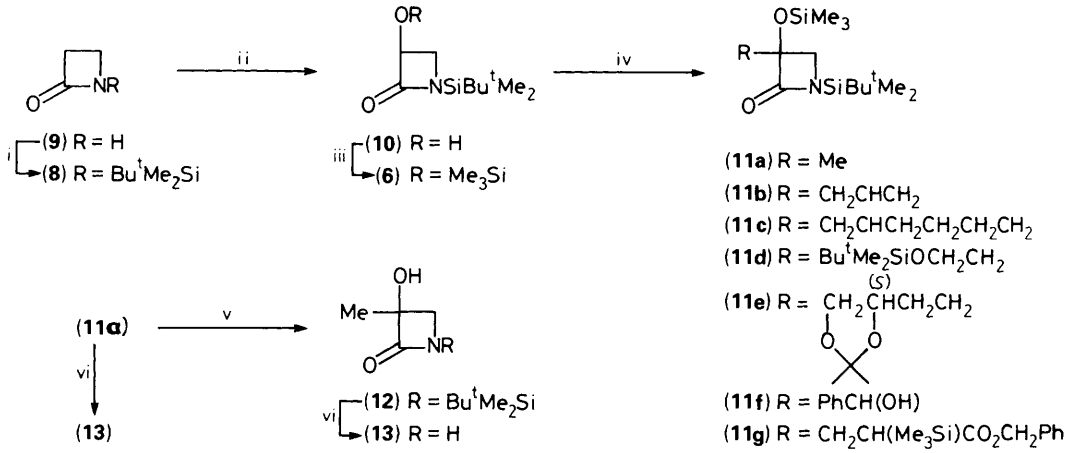


Figure 1

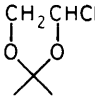


Scheme 1. *Reagents and conditions*: i, see ref. 6; ii, LDA, −78 °C, then MoOPH; iii, Me_3SiCl, Et_3N, CH_2Cl_2; iv, LDA, −78 °C then 1.5 equiv. electrophile, −78 → 0 °C, Table 1; v, 9:1 MeOH, HOAc; vi, Bu^n_4NF; HOAc, THF.

tion of such a structural unit would therefore be most useful.[4,5,6] As a general solution to this problem, we investigated the synthesis and alkylation of *N*-t-butyl-dimethylsilyl-3-trimethylsilyloxyazetidin-2-one (**6**) and herein report the utility of (**6**) as a 3-hydroxy-β-lactam enolate equivalent (**7**).

N-t-Butyldimethylsilylazetidin-2-one (**8**) was prepared as previously described[6] from commercially available (Aldrich) 2-azetidinone (**9**) (78% yield; Scheme 1). Deprotonation of β-lactam (**8**) [1.2 equiv. lithium di-isopropylamide (LDA), tetrahydrofuran (THF), −78 °C, 30 min] and hydroxylation with the Vedejs molybdenum peroxide reagent MoOPH[7] (1.5 equiv., −78 → 25 °C, 30 min) gave 3-hydroxy-β-lactam (**10**) as a white solid† [68%; m.p. 52—55 °C; ^{1}H n.m.r. ($CDCl_3$) δ 4.95 (m, H-3), 3.49 (t, *J* 5.5 Hz, H-4), 3.19 (dd, *J* 5.5, 2.5 Hz, H-4′)]. Treating (**10**) with chlorotrimethylsilane‡ (1.2 equiv. Me_3SiCl, 1.5 equiv. Et_3N, CH_2Cl_2, 25 °C, 1 h) afforded the title β-lactam (**6**) [97%, b.p. 150 °C (Kugelrohr, 1.0 mmHg); ^{1}H n.m.r. ($CDCl_3$) δ 4.88 (dd, *J* 5.2, 2.5 Hz, H-3)].

Table 1. Reaction of the lithium enolate of (**6**) with selected electrophiles.

Electrophile[a]	Product	% Yield[b]
MeI	(**11a**)	73
CH_2CHCH_2Br	(**11b**)	85
$CH_2CHCH_2CH_2CH_2CH_2Br$	(**11c**)	52
$Bu^tMe_2SiOCH_2CH_2I$	(**11d**)	83
	(**11e**)	72
PhCHO	(**11f**)	65
$CH_2C(Me_3Si)CO_2CH_2Ph$	(**11g**)	70[c]

[a] Anion reacted with 1.5 equiv. of the electrophile, see text. [b] Isolated yield. [c] 3:1 mixture of diastereoisomers.

† All new compounds exhibited physical and spectroscopic properties consistent with their structure.

‡ 3-Hydroxyazetidin-2-one (**10**) reacted with $PhCH_2OCH_2Cl$ under standard conditions affording the corresponding 3-benzyloxymethyl ether (68%). This ether was alkylated with MeI (64%). Use of this protecting group permits sequential *N*- then *O*-deprotection.

Alkylation of β-lactam (**6**) proved straightforward. Thus, deprotonation of (**6**) using LDA (1.1 equiv., THF, −78 °C, 30 min) was adequate to generate the colourless anion which upon addition of MeI (1.5 equiv., −78 °C → 0 °C, 30 min) provided *C*-methylated β-lactam (**11a**) (73%, Scheme 1, Table 1). The lithium anion derived from (**6**) reacted with other electrophiles including other alkyl halides, aldehydes, and Michael acceptors to give β-lactams (**11b**) through (**11g**) in 50—85% isolated yields (Table 1). Sequential removal of the silyl protecting groups in β-lactams (**11a—11g**) was accomplished [*e.g.*, (**11a**) → (**12**) → (**13**); 70%; Scheme 1] by mild acid treatment (1:9 HOAc · · · MeOH, 25 °C, 12 h; *O*-desilylation) followed by fluoride anion (1.2 equiv. each Bu^n_4NF and HOAc, 25 °C, 15 min; *N*-desilylation). Simultaneous fluoride mediated *N*- and *O*-desilylation was also possible [2.5 equiv. each Bu^n_4NF and HOAc, 25 °C, 15 min; (**11a**) → (**13**); 90%].‡

Application of this chemistry to the design and synthesis of novel enzyme inhibitors will be forthcoming.

One of us (C-S. L.) is a postdoctoral fellow at Smith Kline & French.

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