A New Synthesis of 1-t-Butyldimethylsilyl-3-acetyl-4-carboxyazetidin-2-one

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A practical stereoselective synthesis of the title compound (**1**) *via* titanium tetrachloride mediated alkylation of the silyl enol ether of ethyl acetoacetate is described.

Recently Reider and Grabowski[1] reported a synthesis of thienamicyn, starting from L-aspartic acid, which includes the title compound (**1**) as a key intermediate. In that synthesis the introduction of the hydroxyethyl side chain was *via* the enolate anion of the 3-unsubstituted azetidinone (**2**). Since the aldol condensation of (**2**) with acetaldehyde afforded a mixture of stereoisomeric alcohols, it proved to be necessary to oxidize the mixture to the corresponding methyl ketone which was then stereoselectively reduced to the alcohol having the natural configuration by means of di-isopropylaminoborane–magnesium trifluoroacetate.

In this communication we describe a convenient synthesis of the racemic form of (**1**)† starting from the silyl enol ether of ethyl acetoacetate (**3**) and (**4**),[2] which involves the direct introduction of the acetyl substituent in the first step of the synthesis (Scheme 1).

Treatment of equimolar amounts of (**3**) and (**4**) in methylene chloride with titanium tetrachloride (1 equiv., 1.5 h, 0 °C; 12 h at room temperature; quenching with $NaHCO_3$ at 0 °C) gave in 79% yield a 4 : 1 mixture of the two diastereoisomers of (**5**). The mixture of the two diastereoisomers was then converted in 73% yield into the dioxolanes (**6**) using an excess of ethylene glycol in benzene in the presence of Amberlist A-15H as an acidic catalyst (12 h, 80 °C, Dean–Stark apparatus). Subsequent reaction of (**6**) with hydrazine acetate in ethanol (1 equiv., 50 °C, 40 h)[3] afforded in 85% yield the corresponding mixture of diastereoisomeric amines (**7**). Cyclization of (**7**) with triethylaluminium in boiling toluene[4] (2 h) afforded (**8**) as the *trans* isomer in 70% yield after chromatography on silica gel. The *trans* relationship of the C-3, C-4 substituents on the β-lactam ring was determined by $J_{3,4}$ in [$^2H_6$]acetone (^{1}H n.m.r.). In fact the *trans* substituted system shows $J_{3,4}$ in a range of 1.5—2.9 Hz in analogy with the values reported in the literature.[5]

After protection of the N–H bond of the β-lactam by silylation with t-butyldimethylsilyl chloride in *N,N*-dimethylformamide (DMF), the styryl group was oxidatively removed with sodium periodate in aqueous acetone in the presence of a catalytic amount of ruthenium oxide[6] (2.5 h, room temp.) to give the carboxylic acid (**10**) in 45% yield starting from (**8**). Finally the dioxolane protecting group was removed by hydrolysis with hydrochloric acid (1 M) in acetone (7 h, room temp.) to give the title compound (**1**) in 60% yield.

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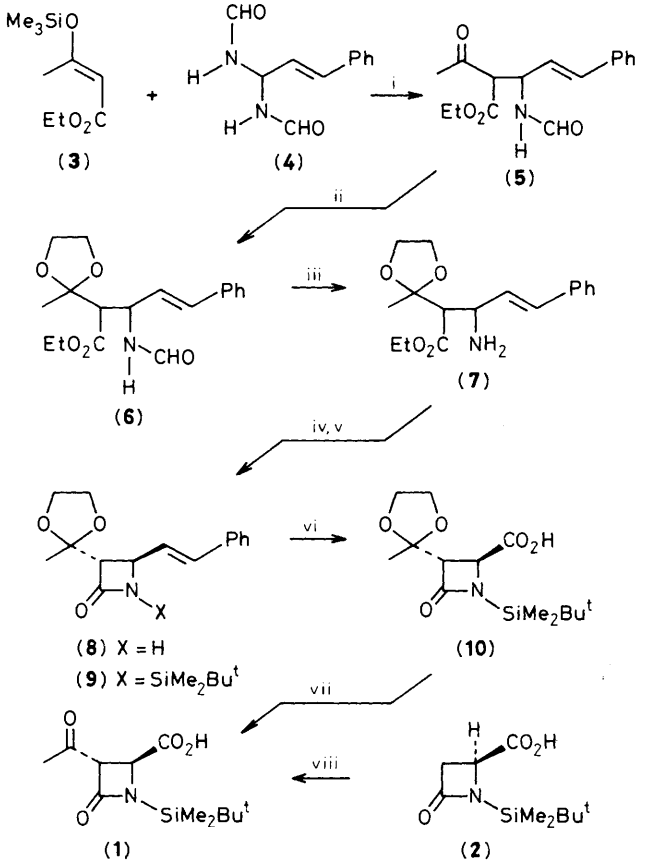

Scheme 1. *Reagents and conditions*: i, $TiCl_4$, CH_2Cl_2; ii, $HOCH_2$-CH_2OH, Amberlist A-15H; iii, NH_2NH_2, AcOH; iv, $AlEt_3$, toluene; v, Bu^tMe_2SiCl, Et_3N, DMF; vi, RuO_2, $NaIO_4$, acetone, H_2O; vii, 1 M HCl, acetone; viii, ref. 1.

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† All chiral substances were produced as racemic mixtures: a single enantiomer is shown for simplicity. Yields are reported for isolated chromatographically pure products and have not been optimized. ^{1}H and ^{13}C n.m.r., i.r., and mass spectra were entirely consistent with the assigned structures and satisfactory combustion analyses were obtained.

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