ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ

THE PATENT OFFICE OF CYPRUS

ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ **CY1447**
PUBLICATION NUMBER

ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ
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ΗΝΩΜΕΝΟΥ ΒΑΣΙΛΕΙΟΥ
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U1S 1347 C3S

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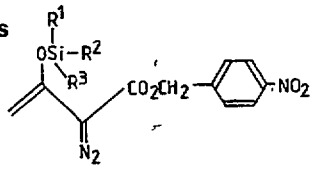
EP 0078026A2

(58) Field of search
C3S

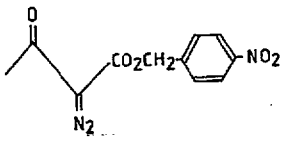
(54) Carbapenum intermediates

(57) The intermediate

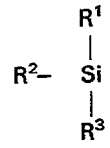


R^1, R^2, R^3 = C_{1-4} alkyl

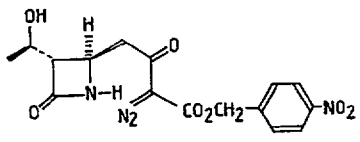
is prepared by the reaction of



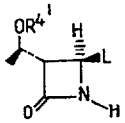
with



and may be used to prepare the known carbapenem intermediate



by reaction with



L = leaving group
$R^{4'}$ = protecting group
e.g. ^{t}Bu Me_2Si- or
(2,4,6 - tri - tert - butylphenoxy) dimethyl silyl.

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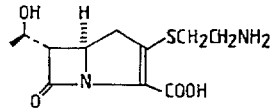
SPECIFICATION

Carbapenen intermediates

The present invention is directed to a new process for producing a key intermediate used in the synthesis of thienamycin and other carbapenem antibiotics.

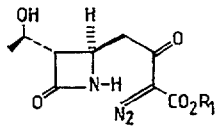
The antibiotic thienamycin of the formula



was originally obtained by fermentation of *Streptomyces cattleya* as described in U.S. Patent 3,950,357. Thienamycin is an exceptionally potent broad-spectrum antibiotic which possesses notable activity against various *Pseudomonas* species, organisms which have been notoriously resistant to β-lactam antibiotics.

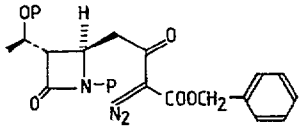
Because of the exceptional biological activity of thienamycin, a large number of derivatives have been prepared. While attempts have been made to synthesize derivatives with various substituents other than hydroxyethyl at the 6-position of the carbapenem ring system, the hydroxyethyl group is still considered the most advantageous 6-substituent for optimum activity.

Since fermentation procedures to prepare thienamycin and derivatives thereof have been unsatisfactory, several total synthesis procedures have been reported in the literature (see, for example, U.S. Patents 4,287,122, 4,269,772, 4,282,148, 4,273,709, 4,290,947 and European Patent Application 7973). While the various synthetic procedures utilize different starting materials, they go through a common diazo intermediate having the formula

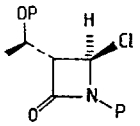


where R_1 represents a conventional carboxyl-protecting group. One of the most preferred carboxyl-protecting groups for intermediate I is the p-nitrobenzyl group which can be readily removed by catalytic hydrogenation after formation of the ultimate carbapenem product.

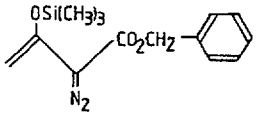
Recently attempts have been made to synthesize intermediate I (and subsequently thienamycin and other carbapenem derivatives) from readily available 6-APA. Karady *et al.*, for example, in *J. Am. Chem. Soc. 103*(22): 6765-6767 (1981) disclose one such process which produces the diazo intermediate of the formula



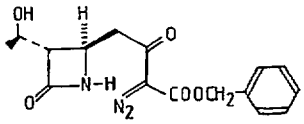
where P is t-butyldimethylsilyl by displacement of the O-protected azetidinone of the formula



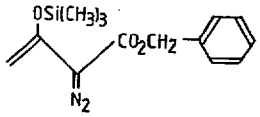
with an enol silyl ether of benzyl 2-diazoacetoacetate having the formula



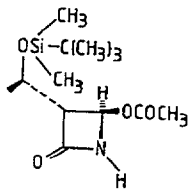
Tetrahedron Lett. 23(22): 2293-2296 (1982) discloses the preparation of the diazo intermediate of the formula



from 4-acetoxy-3-(1-hydroxyethyl)-2-azetidinone by Lewis acid catalyzed alkylation with the corresponding silyl enol ether of the formula

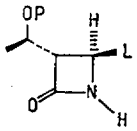


Yoshida *et al.* in *Chem. Pharm. Bull. 29*(10): 2899-2909 (1981) report another synthetic procedure for converting 6-APA to the O-protected azetidinone of the formula



which can be converted to a diazo intermediate of Formula I by the process disclosed in the above-mentioned *Tetrahedron Lett.* reference.

Since the diazo intermediate of Formula I having a p-nitrobenzyl ester protecting group is a preferred carbapenem intermediate, it would be desirable to have a process for converting readily available azetidinone compounds of the general formula



where L is a conventional leaving group such as halo or acetoxy and P is a conventional hydroxyl-protecting group such as triorganosilyl to the corresponding p-nitrobenzyl ester intermediate of Formula I.

Since the Lewis acid catalyzed alkylation of ketones

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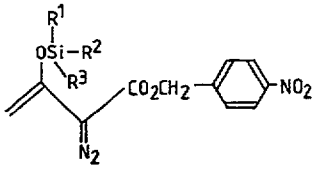
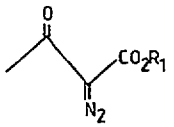
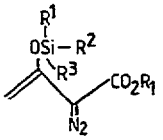
as their silyl enol ethers has been described in the literature (see, for example, *Tetrahedron Lett. 23*(22): 2293-2296, 1982 and also *Tetrahedron Lett. 23*(4): 379-382, 1982), it might be expected that the desired p-nitrobenzyl ester intermediate I or a hydroxy-protected derivative thereof could be prepared by Lewis acid catalyzed alkylation of an appropriate azetidinone compound II with an enol silyl ether of p-nitrobenzyl diazoacetoacetate having the formula



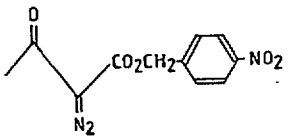
wherein R^1, R^2 and R^3 are each independently C_1-C_4 alkyl. Unfortunately, however, the present inventors have found that the known method of preparing compounds of Formula III does not work when a p-nitrobenzyl protecting group is desired. Thus, the prior art method for preparing enol silyl ethers of diazo-acetoacetates employs silylation of a diazoacetoacetate ester of the formula



wherein R_1 is a carboxyl-protecting group to the enol silyl ether ester

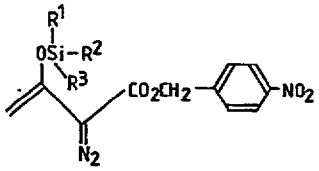


wherein R^1, R^2 and R^3 are each independently C_1-C_4 alkyl by use of a triorganosilyl halide silylating agent in the presence of a strong base, e.g. trimethylchlorosilane with a lithium base such as lithium hexamethyldisilazide. When this prior art silylation procedure is empolyed with the p-nitrobenzyl ester

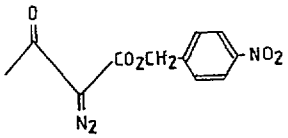


the strong base needed to form the enolate is incompatible with the p-nitrobenzyl ester because of the highly reactive methylene group. Use of weaker organic bases such as trialkylamines with the triorganosilyl halide silylating agent, however, does not produce the desired enol silyl ether.

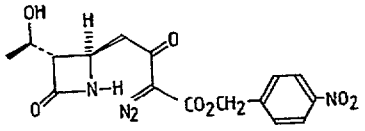
It was the object of the present invention to provide a silylation procedure for producing the p-nitrobenzyl silyl enol ether



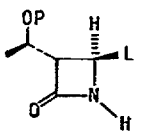
wherein R^1, R^2 and R^3 are each independently C_1-C_4 alkyl from the intermediate



Successful perperation of intermediate III would then allow preparation of the key carbapenem intermediate

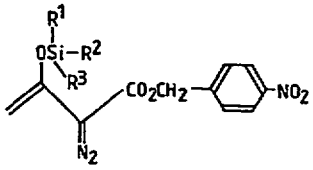


or a hydroxyl-protected derivative thereof by reaction of intermediate III with a suitable O-protected azetidinone of the formula



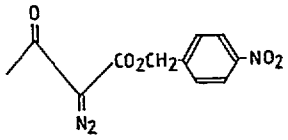
wherein P and L are as defined above followed by removal, if desired, of the hydroxyl-protecting group.

The present invention provides novel carbapenem intermediates having the formula

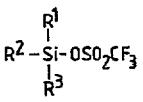


wherein R^1, R^2 and R^3 are each independently C_1-C_4 alkyl.

Also provided by the present invention is a process for the preparation of an intermediate of Formula III which comprises reacting a compound of the formula

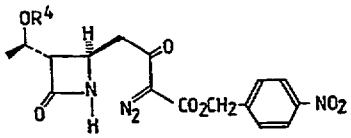


with a silyl triflate of the formula

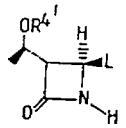


wherein R^1, R^2 and R^3 are each independently C_1-C_4 alkyl in an inert organic solvent and in the presence of an organic base.

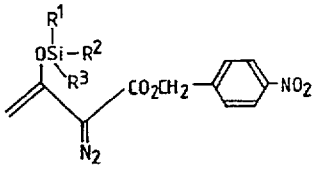
Still further provided by the present invention is a process for the preparation of an intermediate of the formula



wherein R^4 is hydrogen or a conventional hydroxyl-protecting group, which process comprises reacting a compound of the formula

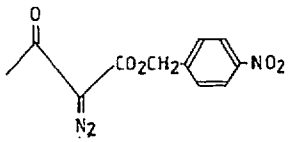


wherein $R^{4'}$ is a conventional hydroxyl-protecting group and L is a conventional leaving group such as acetoxy, propionyloxy, t-butyryloxy or chloro in an inert organic solvent and in the presence of a Lewis acid catalyst with a silyl enol ether of the formula

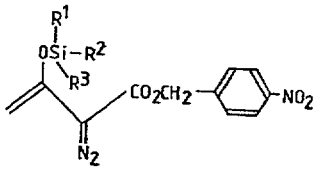


wherein R^1, R^2 and R^3 are each independently C_1-C_4 alkyl.

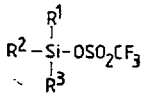
The present invention is based on the unexpected discovery that the p-nitrobenzyl diazoacetoacetate intermediate of the formula



could be successfully converted to the corresponding enol silyl ether intermediate of the formula



wherein R^1, R^2 and R^3 are each independently C_1-C_4 alkyl by reaction of Compound IV with a triorganosilyl triflate silylating agent of the formula



wherein R^1, R^2 and R^3 are as defined above in an inert organic solvent and in the presence of an organic base. Use of the silyl triflate silylating agent instead of the prior art silylchloride reagent allows use of an organic base such as a trialkylamine [e.g. tri(C_1-C_4) alkylamine] instead of the prior art strong bases, thus making it possible to successfully form the desired silyl enol ether intermediate III in high yield despite the presence of the highly reactive methylene group in the p-nitrobenzyl moiety.

The reaction of intermediate IV with the triorganosilyl triflate silylating agent is carried out in an inert organic solvent such as methylene chloride, tetrahydrofuran, carbon tetrachloride, dioxane, dimethoxyethane, diethyl ether or chloroform at a temperature in the range of from about −40°C to about +30°C. Most conveniently the reaction is allowed to take place at a temperature in the range of from about 0-5°C.

The triorganosilyl triflate may be any trialkylsilyl trifuoromethylsulfonate but is preferably a commercially available reagent such as trimethylsilyl trifluoromethylsufonate or *tert*-butyl dimethylsily trifluoromethylsulfonate. The most preferred silylating agent is *tert*-butyl dimethylsilyl trifluoro-methylsulfonate.

Organic amine bases such as diisopropylethylamine, DBU (1,8-diazabicyclo [5.4.0] undec-7-ene), DBN (1,5-diazabicyclo-[4.3.0] non-5-ene) and especially tri (C_1-C_4) alkylamines (e.g. trimethylamine, triethylamine, tributylamine, tripropylamine) are suitable for use with the triorganosilyl triflate silylating agent.

Generally the organic base, triorganosilyl triflate and intermediate IV are reacted in approximately equimolar amounts with the base being used in slight excess. The most preferred molar ratio of intermediate IV: triorganosilyl triflate: base is about 1:1.2:1.4.

The desired silyl enol ether intermediates of general Formula III are formed in high yields by use of the above-described process.

Of the novel intermediates included within the scope of Formula III, the most preferred compounds are those having the trimethylsilyl or *tert*-butyl dimethylsilyl protecting groups.

Once intermediates of Formula III are prepared, they may be used in a further aspect of the present invention to prepare the known diazo intermediate Ia. Thus, intermediate III is reacted with a suitable O-protected azetidinone of the Formula II in an inert organic solvent such as methylene chloride, chloroform, carbon tetrachloride, dioxane, diethyl ether, tetrahydrofuran or dimethoxyethane in the presence of a Lewis acid catalyst such as zinc chloride, zinc iodide, zinc bromide, titanium tetrachloride, magnesium bromide, boron trifluoride, aluminum chloride, stannic chloride or ferric chloride. A preferred solvent is methylene chloride and a preferred catalyst is zinc chloride.

Azetidinone compounds of Formula II are known compounds or may be prepared by known methods. The hydroxyalkyl group of such compounds is protected by a conventional hydroxy-protecting group. While the particular protecting group used is not critical and may be selected from a large number of such groups known in the art, it is preferred to use a triorganosily protecting group such as trimethylsilyl or *tert*-butyl dimethylsilyl since such groups are readily removable by treatment with methanolic HCl or with fluoride ion (e.g. tetra-n-butyl ammonium fluoride/tetrahydrofuran). Other examples of suitable hydroxy-protecting groups include p-nitrobenzyloxycarbonyl which can be removed by catalytic hydrogenation, allyloxycarbonyl which can be removed by $Pd(P\varnothing_3)_4$-catalyzed reaction and 2-trihaloethoxycarbonyl ($-CO_2CH_2CX_3$ where X=Cl or Br) which may be removed by treatment with Zn-acetic acid in methanol. The leaving group L may be any conventional leaving group such as halo (e.g. chloro) or acyloxy (e.g. acetoxy, propionyloxy or t-butyryloxy) but is most preferably acetoxy. Generally it is

preferred to add an excess of the silyl enol ether III to the azetidinone II.

Following the alkylation reaction to form the hydroxyl-protected diazo intermediate, the protecting group may be subsequently removed by known methods so as to provide the desired intermediate Ia. Triorganosilyl protecting groups, as mentioned above, are especially preferred because they may be readily removed without disruption of the remaining portion of the molecule.

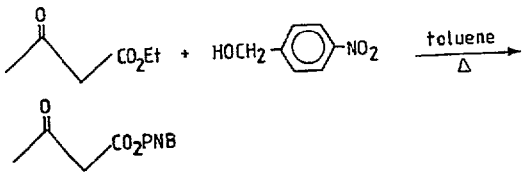
Diazo intermediate Ia may be converted by known methods to thienamycin and various other carbapenem derivatives having useful antibacterial activity.

The following examples illustrate but do not limit the scope of the present invention.

Example 1

Preparation of p-Nitrobenzyl 2-diazo-3-trimethylsilyloxy-3-butenoate

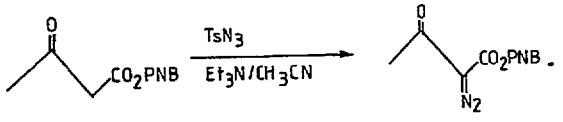
A. *p-Nitrobenzyl acetoacetate*



A mixture of ethyl acetoacetate (140 g, 1.08 mole) and p-nitrobenzyl alcohol (153 g, 1.00 mole; was washed with diethyl ether prior to use) in toluene (1 L) was slowly distilled, 900 ml of the solvent being collected over a period of 15 hours. After cooling, any insoluble material was removed by filtration over Celite, washed with toluene and evaporated *in vacuo* to obtain 280 g of a crude oil. This oil was crystallized at 5°C from diethyl ether (280 ml) to yield 181.55 g (0.766 mole, 76.6% yield) of the title compound as off-white crystals: mp 40°-42°C; ir (film) ν_{max}: 1740 (ester), 1715 (C=0), 1515 and 1345 (NO_2) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 1.98 (s, impurity), 2.32 (3H, s, CH_3), 3.62 (2H, s, -COCH_2CO_2R), 5.08 (s, impurity), 5.28 (2H, s, -CO_2CH_2Ar), 7.53 (2H, "d", *J*=9 Hz, ArH's), and 8.23 ppm (2H, "d", *J*=9 Hz, ArH's); Rf 0.45 (diethyl ether). An analytical sample was obtained by recrystallization from toluene-hexanes: mp 47°-49°C.

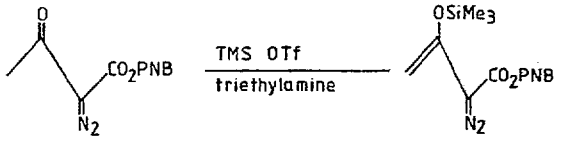
Anal. calc'd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.91 Found: C, 55.59; H, 4.62; N, 5.85.

B. *p-Nitrobenzyl 2-diazo-3-ketobutanoate*



To a solution of p-nitrobenzyl acetoacetate (134.6 g, 0.568 mole) and triethylamine (79.0 ml, 0.568 mole) in CH_3CN (340 ml) was added at 0-5°C under a nitrogen atmosphere p-toluenesulfonyl azide (130 g, 0.639 mole; 97% pure) over a period of 15 minutes. During this period the title compound started precipitating. The cooling bath was removed and the mixture was stirred at room temperature for 3 hours. The mixture was cooled in an ice-bath for 30 minutes and the precipitate was filtered, washed with cold CH_3CN (75 ml) and then cold diethyl ether (200 ml), and dried to yield 135.06 g (0.514 mole, yield 90.4%) of the title compound as pale yellow powder: ^{1}Hmr ($CDCl_3$) δ: 2.50 (3H, s, H_3), 5.38 (2H, s, -CO_2CH_2Ar), 7.53 (2H, "d", *J*=9 Hz, aromatic Hs) and 8.27 ppm (2H, "d", *J*=9 Hz, aromatic Hs); ir (CH_2Cl_2) ν_{max}: 2130 (N_2), 1720 (ester), 1655 (C=O), 1520 and 1350 cm^{-1} (NO_2); Rf 0.65 (ethyl acetate).

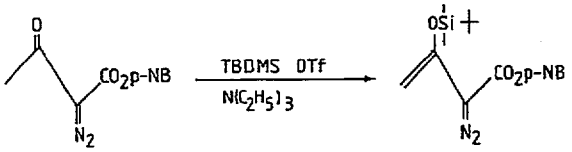
C. *p-Nitrobenzyl 2-diazo-3-trimethylsilyloxy-3-butenoate*



To a suspension of p-nitrobenzyl α-diazoacetoacetate (236 mg, 1 mmole) and triethylamine (0.15 ml, 1.08 mmole) in CH_2Cl_2 (2 ml) was added at 0°-5°C trimethylsilyl trifluoro-methylsulfonate (0.22 ml) under a nitrogen atmosphere and the mixture was stirred for 30 minutes. To this clear yellow solution was added dry hexanes (30 ml) and the reaction mixture was stirred for 10 minutes. After removing the oily deposit, the hexanes solution was evaporated *in vacuo* to yield yellow solid which was redissolved in dry hexanes (50 ml). The insoluble material was filtered over Celite and the filtrate was evaporated *in vacuo* to obtain 277 mg (0.90 mmole, yield 90%) of the title compound as yellow crystals: ir (film ν_{max}: 2100 (N_2), 1705 (ester), 1520 and 1345 cm^{-1} (NO_2); ^{1}Hmr ($CDCl_3$) δ: 0.27 (9H, s, -$SiMe_3$), 4.23 (1H, d, *J*=2 Hz, vinyl proton), 4.93 (1H, d, *J*=2 Hz, vinyl proton), 5.32 (2H, s, -CO_2CH_2Ar), 7.48 (2H, "d", *J*=9 Hz, aromatic protons), and 8.23 ppm (2H, "d", *J*=9 Hz, aromatic protons).

Example 2

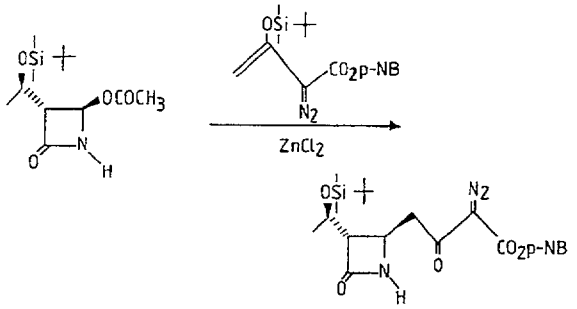
Preparation of p-Nitrobenzyl 2-diazo-3-tert-butyl dimethylsilyloxy-3-butenoate



To a suspension of p-nitrobenzyl α-diazoacetoacetate (26.30 g, 0.10 mole) and triethylamine (14.57 g, 20.00 ml, 0.14 mole) in dry methylene chloride (200 ml) was added at 2°C *tert*-butyl dimethylsilyl trifluoromethylsulfonate (31.72 g, 27.50 ml, 0.12 mole) over a 30 minute period under a nitrogen atmosphere. The mixture was then stirred at 2°C for one hour. The clear orange solution was diluted with methylene chloride (50 ml) and washed with water (3 × 200 ml) and then brine (100 ml), dried (Na_2SO_4) and evaporated, yielding 37.40 g (0.099 mole, yield 99%) of the title compound as a yellow solid: ^{1}Hmr ($CDCl_3$, EM-360A, 60 MHz) δ: 0.26 (6H, s, $Si(CH_3)_2$), 0.96 (9H, s, $SiC(CH_3)_3$), 4.25 (1H, d, *J*=2.5 Hz, 4-H), 4.97 (1H, d, *J*=2.5 Hz, 4-H), 5.32 (2H, s, -CO_2CH_2Ar), 7.48 (2H, "d", J=9.0 Hz, ArH's) and 8.22 ppm (2H, "d", J=9.0 Hz, ArH's); ir (film) ν_{max}: 2090 (N_2), 1694 (ester), 1600 (C=C) and 1344 cm^{-1} (NO_2).

Example 3

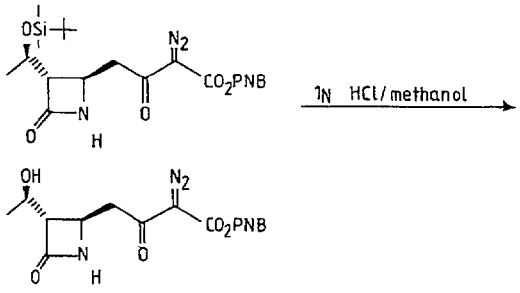
Preparation of (3S, 4R) - 3 - [(1R) - (tert - butyl - dimethylsilyloxy) ethyl] - 4 - [3 - (4 - nitrobenzyloxy) carbonyl - 2 - oxo - 3 - diazopropyl] azetidin - 2 - one



To a suspension of anhydrous zinc chloride (34 mg, 0.25 mmole), in methylene chloride (2 ml) was added a solution of (1'*R*, 3*R*, 4*R*) - 3 - (1' - *tert* - butyldimethylsilyloxyethyl) - 4 - acetoxy - azetidin - 2 - one (144 mg, 0.5 mmole) in methylene chloride (4 ml) followed by solid 4-nitrobenzyl - 2 - diazo - 3 - *tert* - butyldimethyl - silyloxy - 3 - butenoate (350 mg, 0.93 mmole) under a nitrogen atmosphere. The mixture was stirred at room temperature under nitrogen for 4.5 hours. The mixture, diluted with ethyl acetate (50 ml), was washed with saturated sodium bicarbonate (2 × 25 ml) and then brine (30 ml), dried (Na_2SO_4) and evaporated, yielding a crude oily yellow solid which was purified by column chromatography [(SiO_2, 30 g) eluted with methylene chloride : ethyl acetate 4:1] to obtain 198 mg (0.405 mmole, 81%) of the title compound as an oil identical (tlc, ^{1}Hmr) with an authentic sample prepared by a published procedure.

Example 4

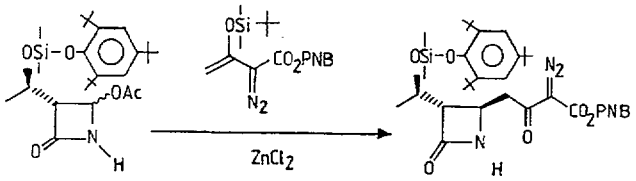
Preparation of (3S, 4R) - 3 - [(1R) - Hydroxyethyl] - 4 - [3 - (4 - nitrobenzyloxy) carbonyl - 2 - oxo - 3 - diazopropyl] azetidin - 2 - one



To a solution of (3*S*, 4*R*) - 3 - [(1*R*) - (*tert* - butyldimethyl - silyloxy) ethyl] - 4 - [3 - (4 - nitrobenzyloxy) carbonyl - 2 - oxo - 3 - diazopropyl] azetidin - 2 - one (72 mg, 0.15 mmole) in methanol (1.0 ml) was added 1 *N* aqueous HCl (0.2 ml) and the mixture was stirred at room temperature for 2 hours by which time tlc (ethyl acetate) indicated that the reaction was completed. During this period the title compound was precipitated. This was filtered and rinsed with cold CH_3OH-H_2O (9:1) and then cold diethyl ether to obtain 43 mg (0.11 mmole, yield 73%) of the title compound as a white solid. The title compound was similarly obtained from (3*S*, 4*R*) - 3 - {(1R) - [(2, 4, 6 - tri - *tert* - butylphenoxy) dimethylsilyloxy] ethyl} - 4 - [3 - (4 - nitrobenzyloxy) - carbonyl - 2 - oxo - 3 - diazopropyl] azetidin - 2 - one.

Example 5

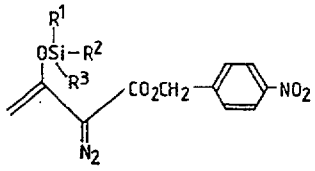
Preparation of (3S, 4R) - 3 - {(1R - [(2, 4, 6 - Tri - tert butylphenoxy) dimethylsilyloxy] ethyl} - 4 - [3 - (4 - nitrobenzyl) oxycarbonyl - 2 - oxo - 3 - diazopropyl] azetidin - 2 - one



The title compound was prepared in 84% yield from (3*R*, 4*R* and 4*S*) - 4 - acetoxy - 3 - {(1*R* - [(2, 4, 6 - tri - *tert* - butylphenoxy) - dimethylsilyloxy] ethyl} - 2 - azetidinone by the method described above for the corresponding t-butyl dimethylsilyl derivative: ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 0.26 (3H, s, SiMe), 0.40 (3H, s, SiMe), 1.27 (9H, s, t-Bu), 1.41 (18H, s, (t-Bu)$_2$), 2.92 (1H, dd, $J_{3\text{-}1'}$= 4.7 Hz, $J_{3\text{-}4}$=2.5 Hz, 3-H), 2.97 (1H, dd, J_{gem}=17.6 Hz, $J_{1''b\text{-}4}$= 9.6 Hz, 1''-H_b), 3.40 (1H, dd, J_{gem}=17.6 Hz, $J_{1''a\text{-}4}$=3.5 Hz, 1''-H_a), 3.98-4.24 (1H, m, 4-H), 4.32-4.57 (1H, m, 1'-H), 5.35 (2H, s, -CO_2CH_2Ar), 5.95 (1H, br s, NH), 7.22 (2H, s, ArH's of the ether), 7.52 (2H, "d", *J*=8.7 Hz, ArH's of the ester) and 8.25 ppm (2H, "d", *J*=8.7 Hz, ArH's of the ester): ir (neat) ν_{max}: 3300 (br, NH), 2137 (-N_2), 1755 (β-lactam), 1720 (ester), 1651 (C=O), 1523 and 1345 cm^{-1} (NO_2).

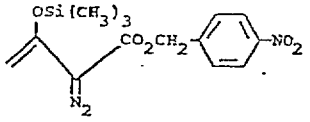
CLAIMS

1. A compound having the formula

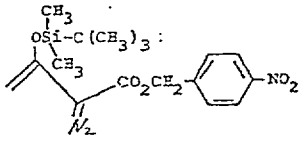


wherein R^1, R^2 and R^3 are each independently C_1-C_4 alkyl.

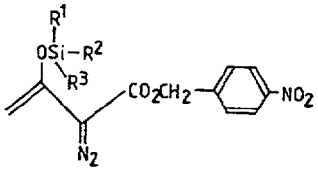
2. A compound according to Claim 1 having the



3. A compound according to Claim 1 having the formula

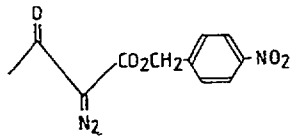


4. A process for the preparation of a compound of the formula

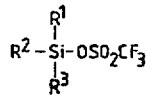


wherein R^1, R^2 and R^3 are each independently C_1-C_4

alkyl, which process comprises reacting a compound of the formula



with a silyl triflate of the formula

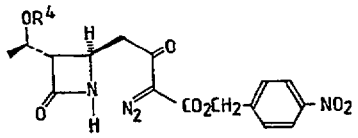


wherein R^1, R^2 and R^3 are as defined above, in an inert organic solvent and in the presence of an organic base.

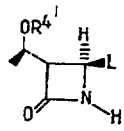
5. The process according to Claim 4 wherein the reaction is carried out at a temperature of from about -40°C to +30°C.

6. The process according to Claim 4 or Claim 5 wherein the organic base is a C_1-C_4 trialkylamine, and the solvent is methylene chloride.

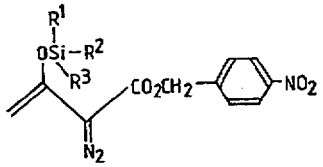
7. A process for the preparation of a compound of the formula



wherein R^4 is hydrogen or a conventional hydroxyl-protecting group, which process comprises reacting a compound of the formula



wherein L is a conventional leaving group and $R^{4'}$ is a conventional hydroxyl-protecting group in an inert organic solvent and in the presence of a Lewis acid catalyst with an enol silyl ether compound of the formula



wherein R^1, R^2 and R^3 are each independently C_1-C_4 alkyl, and, if desired, removing the hydroxyl-protecting group to obtain the corresponding hydroxyethyl intermediate.

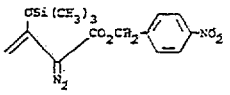
8. The process according to Claim 7 wherein the leaving group L is

9. The process according to Claim 7 or Claim 8 wherein the Lewis acid catalyst is $ZnCl_2$.

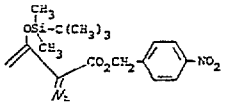
10. The process according to Claim 7, 8 or 9 wherein the solvent is methylene chloride.

11. The process according to Claim 7, 8, 9 or 10 wherein the hydroxyl-protecting group is *tert*-butyldimethylsilyl, trimethylsilyl or (2, 4, 6-tri-*tert*-butylphenoxy) dimethylsilyl.

12. Process according to claim 4, 5 or 6, characterized in that the compound of the following formula is prepared:



13. Process according to claim 4, 5 or 6 characterized in that the compound of the following formula is prepared:



14. A process as claimed in claim 4, substantially as described in the foregoing Example 1 or 2.

15. A process as claimed in claim 7, substantially as described in the foregoing Example 3 or 5 or in the foregoing Examples 3 and 4 taken together.

16. A compound as claimed in claim 1 prepared by a process as claimed in claim 4, 5, 6, 12, 13 or 14.

17. An azetidin-2-one derivative prepared by a process as claimed in any of claims 7 to 11 or claim 15.

18. A compound as claimed in claim 1, 2, 3 or 16, for use in the preparation of thienamycin and other carbapenem antibiotics.

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