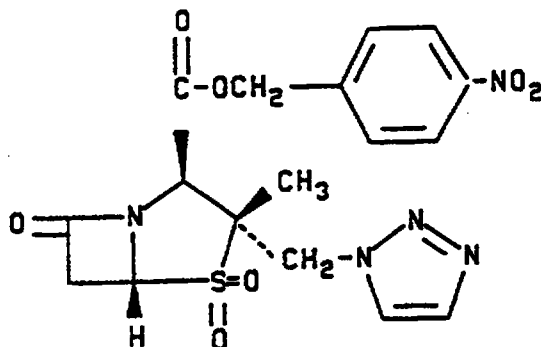


Description

SUMMARY OF THE INVENTION

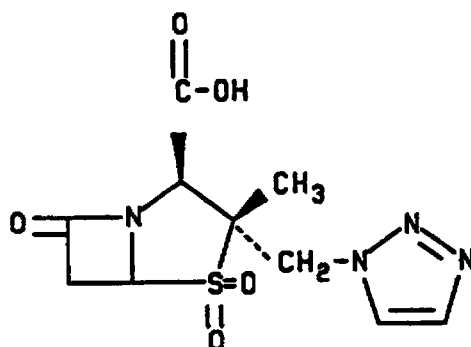
5 This invention is concerned with an improved process for producing the intermediate [2S-(2 α ,3 β ,5 α)]-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, (4-nitrophenyl)methyl ester, 4,4-dioxide, having the structure



20 The improvement resides in an increased yield (60%) and purity (90%), the elimination of two steps in the heretofor known synthesis and allows isolation directly from the reaction mixture without resorting to chromatography.

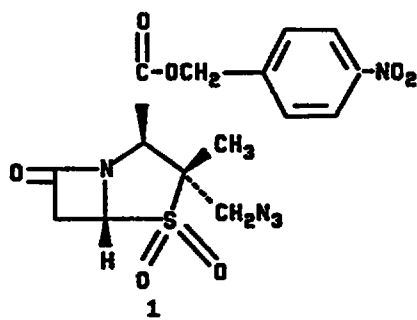
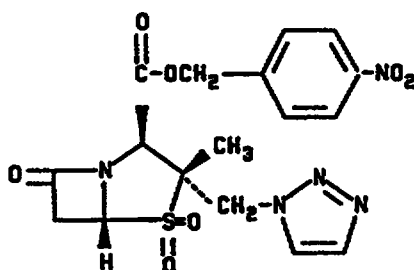
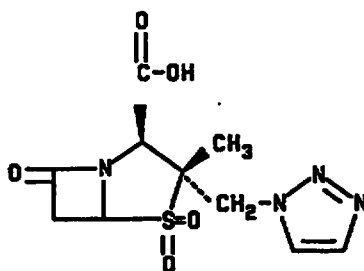
25 In a known reaction described in EP-A-0097446 strenuous conditions are involved and the product is isolated by column chromatography.

The above described intermediate is then used to produce the biologically active β -lactamase inhibitor [2S-(2 α ,3 β ,5 α)]-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 4,4-dioxide having the formula



45 DESCRIPTION OF THE INVENTION

The process improvement which is the subject of this invention is described by the following reaction scheme and description:

123

According to the above reaction azidopenamsulfone 1 is dissolved in vinyl propionate containing 4-methoxyphenol and this solution is reacted dropwise with a solution of bis(trimethylsilyl)acetamide and 4-methoxyphenol in toluene at 70-80°C followed by reaction at 95-100°C for about 24 hours and filtration and cooling to produce the intermediated [2S-(2 α ,3 β ,5 α ,)]-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, (4-nitrophenyl)methyl ester, 4,4-dioxide, 2 having 90% purity and in 60% yield.

The intermediate 2 is then hydrogenated over 5% palladium on carbon in ethyl acetate/water, containing sodium bicarbonate, followed by acidification with a mineral acid, giving the desired β -lactamase inhibitor 3.

Example 1

[2S-(2 α ,3 β ,5 α)]-3-Methyl-7-oxo-3-(1H-1,2,3-
triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]-
heptane-2-carboxylic acid, (4-nitrophenyl)-
methyl ester 4,4-dioxide

An ethyl acetate solution containing 84 g of azidopenamsulfone was evaporated to dryness, then added to 1865 ml of vinyl propionate containing 4 g of 4-methoxyphenol and stirred for 1 hour. The solution was filtered and the filtrate added dropwise over 3.5 hours to a solution comprised of 1324 ml of toluene, 84 ml (66.8 g) of bis(trimethylsilyl)acetamide and 4 g of 4-methoxyphenol at 70-80 °C. When addition was complete the reaction temperature was raised to 95-100 °C and maintained for 24 hours. The reaction was then cooled to room temperature, combined with 11 g of hydrous magnesium silicate, stirred for 20 minutes and then filtered through a bed of 33 g of hydrous magnesium silicate. The filtrate was rotoevaporated, collecting 2500 ml of distillate. The filtrate was stirred at room temperature for 12 hours, then cooled to 0-5 °C for 2 hours and the resulting solid collected, washed with heptane and dried, giving 50 g of the desired intermediate with a purity of 90%.

Claims

1. A process for producing the compound [2S-(2 α ,3 β ,5 α)]-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylic acid, (4-nitrophenyl)methyl ester, 4,4-dioxide, which comprises reacting a solution of azidopenamsulfone, 4-methoxyphenol and vinylpropionate with a solution of bis(trimethylsilyl)acetamide and 4-methoxyphenol in toluene at 80-100 °C for 18-30 hours followed by filtering the resulting solution and cooling the filtrate to 0-10 °C.

Patentansprüche

1. Verfahren zur Herstellung der Verbindung [2S-(2 α ,3 β ,5 α)]-3-Methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptan-2-carbonsäure, -(4-Nitrophenyl)methylester, -4,4-Dioxid, das umfaßt die Umsetzung einer Lösung von Azidopentamsulfon, 4-Methoxyphenol und Vinylpropionat mit einer Lösung von Bis(trimethylsilyl)acetamid und 4-Methoxyphenol in Toluol bei 80 bis 100 °C für 18 bis 30 Stunden, gefolgt von Filtration der entstandenen Lösung und Abkühlen des Filtrats auf 0 bis 10 °C.

Revendications

1. Procédé de production du composé 4,4-dioxyde de [2S-(2 α ,3 β ,5 α)]-3-méthyl-7-oxo-3-(1H-1,2,3-triazol-1-ylméthyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate de (4-nitrophényl)méthyle, qui comprend la réaction d'une solution d'azidopenamsulfone, de 4-méthoxyphénol et de propionate de vinyle avec une solution de bis(triméthylsilyl)acétamide et de 4-méthoxyphénol dans le toluène à 80-100 °C pendant 18-30 h puis la filtration de la solution résultante et le refroidissement du filtrat à 0-10 °C.

Example 1

[2S-(2 α ,3 β ,5 α)]-3-Methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, (4-nitrophenyl)-methyl ester 4,4-dioxide

An ethyl acetate solution containing 84 g of azidopenamsulfone was evaporated to dryness, then added to 1865 ml of vinyl propionate containing 4 g of 4-methoxyphenol and stirred for 1 hour. The solution was filtered and the filtrate added dropwise over 3.5 hours to a solution comprised of 1324 ml of toluene, 84 ml (66.8 g) of bis(trimethylsilyl)acetamide and 4 g of 4-methoxyphenol at 70-80 °C. When addition was complete the reaction temperature was raised to 95-100 °C and maintained for 24 hours. The reaction was then cooled to room temperature, combined with 11 g of hydrous magnesium silicate, stirred for 20 minutes and then filtered through a bed of 33 g of hydrous magnesium silicate. The filtrate was rotoevaporated, collecting 2500 ml of distillate. The filtrate was stirred at room temperature for 12 hours, then cooled to 0-5 °C for 2 hours and the resulting solid collected, washed with heptane and dried, giving 50 g of the desired intermediate with a purity of 90%.

Claims

1. A process for producing the compound [2S-(2 α ,3 β ,5 α)]-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, (4-nitrophenyl)methyl ester, 4,4-dioxide, which comprises reacting a solution of azidopenamsulfone, 4-methoxyphenol and vinylpropionate with a solution of bis(trimethylsilyl)acetamide and 4-methoxyphenol in toluene at 80-100 °C for 18-30 hours followed by filtering the resulting solution and cooling the filtrate to 0-10 °C.

Patentansprüche

1. Verfahren zur Herstellung der Verbindung [2S-(2 α ,3 β ,5 α)]-3-Methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptan-2-carbonsäure, -(4-Nitrophenyl)methylester, -4,4-Dioxid, das umfaßt die Umsetzung einer Lösung von Azidopenamsulfon, 4-Methoxyphenol und Vinylpropionat mit einer Lösung von Bis(trimethylsilyl)acetamid und 4-Methoxyphenol in Toluol bei 80 bis 100 °C für 18 bis 30 Stunden, gefolgt von Filtration der entstandenen Lösung und Abkühlen des Filtrats auf 0 bis 10 °C.

Revendications

1. Procédé de production du composé 4,4-dioxyde de [2S-(2 α ,3 β ,5 α)]-3-méthyl-7-oxo-3-(1H-1,2,3-triazol-1-ylméthyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate de (4-nitrophényl)méthyle, qui comprend la réaction d'une solution d'azidopenamsulfone, de 4-méthoxyphénol et de propionate de vinyle avec une solution de bis(triméthylsilyl)acétamide et de 4-méthoxyphénol dans le toluène à 80-100 °C pendant 18-30 h puis la filtration de la solution résultante et le refroidissement du filtrat à 0-10 °C.

