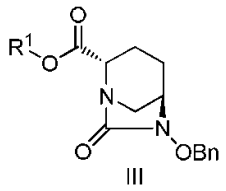
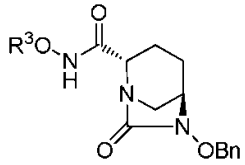
CLAIMS

1. A process for producing a compound represented by Formula (VII), comprising: reacting a compound represented by the following Formula (III):



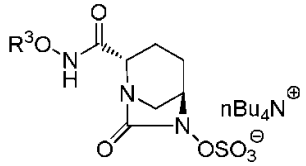
III

with a compound: R^3ONH_2 to obtain a compound represented by the following Formula (IV):



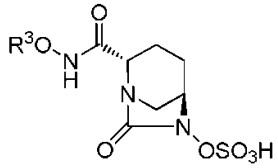
IV

treating with a palladium carbon catalyst under a hydrogen atmosphere, simultaneously or consecutively subjecting to a sulfation reaction using sulfur trioxide-trimethylamine complex in the presence of a catalytic amount of base in an aqueous alcohol-based solvent and treating with tetrabutylammonium hydrogensulfate to obtain a compound represented by the following Formula (VI):



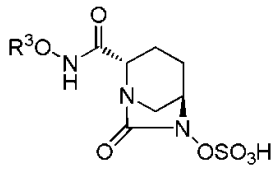
VI

followed by, in a case where the $R^3ONHC(=O)$- side chain has a protecting group, removing the protecting group with an acid, and precipitating a crude product by adding a poor solvent to the reaction solution to obtain a crude compound represented by the following Formula (VII-CR):



VII-CR

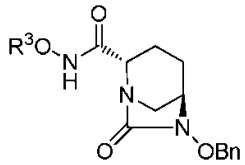
followed by alternately adding the crude compound represented by Formula (VII-CR) and ice-cold buffer to obtain a solution having a pH of 4 to 5.5, concentrating after desalting with a synthetic adsorbent as necessary, adjusting the temperature, seeding as necessary and crystallizing by adding a poor solvent to produce the compound represented by the following Formula (VII):



VII

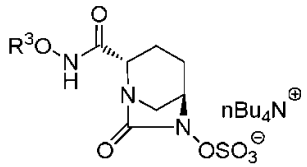
in each of the above formulas, OBn is benzyloxy, R^1 is 2,5-dioxopyrrolidin-1-yl, 1,3-dioxo-3a,-4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl, 1,3-dioxohexahydro-1H-isoindol-2(3H)-yl, or 3,5-dioxo-4-azatricyclo[5.2.1.$0^{2.6}$]dec-8-en-4-yl, R^3 is C_{1-6} alkyl or heterocyclyl or may be modified with 0 to 5 R^4 and R^4 may be consecutively substituted whereby, R^4 is C_{1-6} alkyl, heterocyclyl, $R^5(R^6)N$- or a protecting group, and R^5 and R^6 each independently is hydrogen or C_{1-6} alkyl or together form heterocyclyl and R^3, R^5 and R^6 can undergo ring closure at an arbitrary position.

2. A process for producing a compound represented by Formula (VI), comprising treating a compound represented by the following Formula (IV):



IV

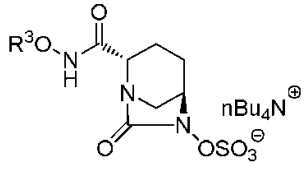
with a palladium carbon catalyst under a hydrogen atmosphere, simultaneously or consecutively subjecting to a sulfation reaction using sulfur trioxide-trimethylamine complex in the presence of a catalytic amount of base in a hydrous solvent, and treating with tetrabutylammonium hydrogen-sulfate to produce the compound represented by the following Formula (VI):



VI

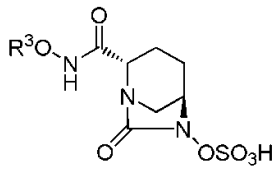
in each of the above formulas, R^3 and OBn are same as described in claim 1.

3. A process for producing a crude compound represented by Formula (VII-CR), comprising: in a case where the R^3ONHC(=O)- side chain has a protecting group, removing the protecting group with an acid from a compound represented by the following Formula (VI):



VI

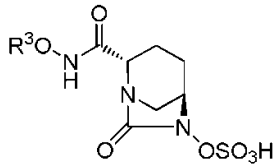
followed by adding an ester-based poor solvent to the reaction solution to precipitate a crude product and produce the crude compound represented by the following Formula (VII-CR):



VII-CR

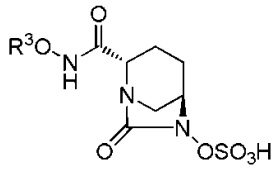
in each of the above formulas, R^3 is same as described in claim 1.

4. A process for producing a compound represented by Formula (VII), comprising: alternately adding a crude compound represented by the following Formula (VII-CR):



VII-CR

and an ice-cold buffer to obtain a solution having a pH of 4 to 5.5, concentrating after desalting with a synthetic adsorbent as necessary, adjusting the temperature, seeding as necessary and crystallizing by adding an alcohol-based poor solvent to produce the compound represented by the following Formula (VII):



VII

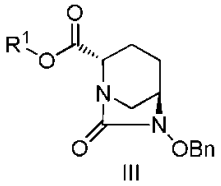
in each of the above formulas, R^3 is same as described in claim 1.

5. The process according to any one of claims 1 to 4, wherein R^3 in Formulas (IV), (VI), (VII-CR) and (VII) is selected from:

2-(tert-butoxycarbonylamino)ethyl;
2-aminoethyl;
2-((tert-butoxycarbonyl)(methyl)amino)ethyl;
2-(methylamino)ethyl;
2-((tert-butoxycarbonyl)(isopropyl)amino)ethyl;
2-(isopropylamino)ethyl;
2-(dimethylamino)ethyl;
(2S)-2-((tert-butoxycarbonyl)amino)propyl;
(2S)-2-(amino)propyl;
(2R)-2-((tert-butoxycarbonyl)amino)propyl;
(2R)-2-(amino)propyl;
3-((tert-butoxycarbonyl)amino)propyl;
3-(amino)propyl;
(2S)-tert-butoxycarbonylazetidin-2-ylmethyl;

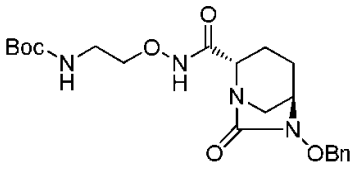
(2S)-azetidin-2-ylmethyl;
(2R)-tert-butoxycarbonylpyrrolidin-2-ylmethyl;
(2R)-pyrrolidin-2-ylmethyl;
(3R)-tert-butoxycarbonylpiperidin-3-ylmethyl;
(3R)-piperidin-3-ylmethyl;
(3S)-tert-butoxycarbonylpyrrolidin-3-yl;
(3S)-pyrrolidin-3-yl;
1-(tert-butoxycarbonyl)azetidin-3-yl; and
azetidin-3-yl.

6. A process for producing a compound represented by Formula (VII-1), comprising: reacting a compound represented by the following Formula (III):



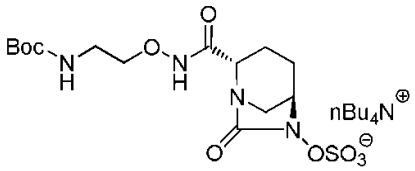
III

with tert-butyl 2-(aminooxy)ethylcarbamate in the presence of a base to obtain a compound represented by the following Formula (IV-1):



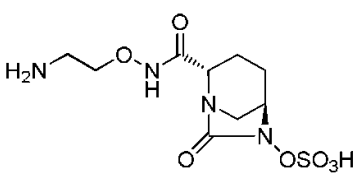
IV-1

followed by treating with a palladium carbon catalyst under a hydrogen atmosphere, simultaneously or consecutively subjecting to a sulfation reaction using sulfur trioxide-trimethylamine complex in the presence of a catalytic amount of base in a hydrous solvent, and treating with terabutyl-ammonium hydrogensulfate to obtain a compound represented by Formula (VI-1):



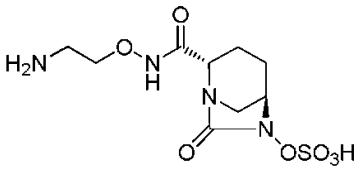
VI-1

followed by removing the tert-butoxycarbonyl (Boc) group with trifluoroacetic acid and dropping ethyl acetate into the reaction solution to precipitate a crude product and obtain a crude compound represented by the following Formula (VII-1-CR):



VII-1-CR

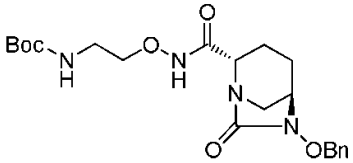
followed by alternately adding the crude compound represented by Formula (VII-1-CR) and an ice-cold phosphate buffer to obtain a solution having a pH of 4 to 5.5, concentrating after desalting with a synthetic adsorbent as necessary, adjusting the temperature, seeding as necessary and adding isopropanol to crystallize and produce the compound represented by the following Formula (VII-1):



VII-1

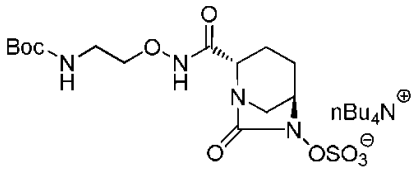
in each of the above formulas, R^1 and OBn are same as described in claim 1.

7. A process for producing a compound represented by Formula (VI-1), comprising: treating a compound represented by the following Formula (IV-1):



IV-1

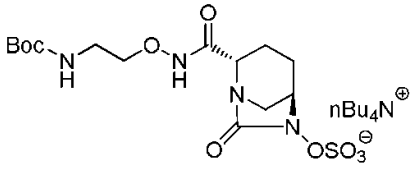
with a palladium carbon catalyst under a hydrogen atmosphere, simultaneously or consecutively subjecting to a sulfation reaction using sulfur trioxide-trimethylamine complex in the presence of a catalytic amount of a base in a hydrous solvent, and treating with tetrabutylammonium hydrogen-sulfate to produce the compound represented by the following Formula (VI-1):



VI-1

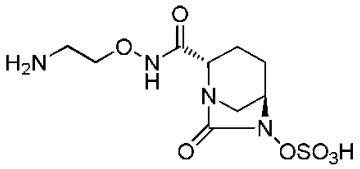
in each of the above formulas, OBn is same as described in claim 1.

8. A process for producing a crude compound represented by Formula (VII-1-CR), comprising: removing the tert-butoxycarbonyl (Boc) group with trifluoroacetic acid from a compound represented by the following Formula (VI-1):



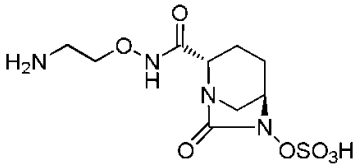
VI-1

followed by dropping ethyl acetate into the reaction solution to precipitate a crude product and produce the crude compound represented by the following Formula (VII-1-CR):



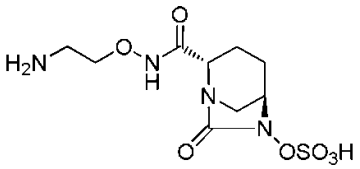
VII-1-CR

9. A process for producing a compound represented by Formula (VII-1), comprising: alternately adding a crude compound represented by the following Formula (VII-1-CR):



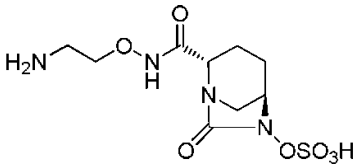
VII-1-CR

and an ice-cold phosphate buffer to obtain a solution having a pH of 4 to 5.5, concentrating after desalting with a synthetic adsorbent as necessary, and adjusting the temperature followed by seeding as necessary and adding isopropanol to crystallize and produce the compound represented by the following Formula (VII-1):



VII-1

10. A crystalline form I of a compound represented by Formula (VII-1):



VII-1

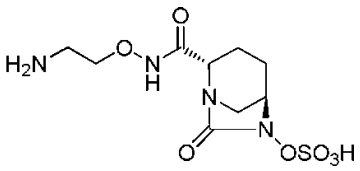
having characteristic peaks appearing at lattice spacing (d) of 7.34, 5.66, 5.53, 5.30, 5.02, 4.66, 4.37, 4.28, 4.06, 3.68, 3.62, 3.47, 3.36, 3.30, 3.16, 3.11, 3.03, 2.99 and 2.50 Å in the powder X-ray diffraction pattern.

11. A process for producing the crystalline form I according to claim 10, comprising: dissolving the crude compound of claim 10 in a phosphate buffer, adjusting the pH of the buffer and diluting with water, adjusting the temperature of a solution of the compound represented by the Formula (VII-1) between 20 to 25 °C, seeding with a crystalline form I and stirring, followed by further adding isopropanol.

12. A use of the crystalline form I according to claim 10 for producing a pharmaceutical composition optionally comprising a pharmaceutically acceptable carrier.

13. A use of the crystalline form I according to claim 10 for producing a pharmaceutical composition comprising a β-lactam antibiotic selected from the group consisting of ampicillin, amoxicillin, piperacillin, ticarcillin, flomoxef, cefotaxime, ceftriaxone, ceftazidime, cefepime, ceftaroline, ceftolozane, imipenem, meropenem, biapenem, doripenem, ertapenem and aztreonam, and optionally a pharmaceutically acceptable carrier.

14. A crystalline form II of a compound represented by Formula (VII-1):



VII-1

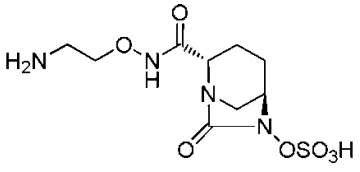
having characteristic peaks appearing at lattice spacing (d) of 9.46, 5.62, 5.23, 5.10, 5.00, 4.91, 4.67, 4.45, 4.29, 3.96, 3.78, 3.71, 3.52, 3.24, 3.18, 3.10, 3.02, 2.88, 2.81, 2.77, 2.67, 2.50 and 2.45 Å in the powder X-ray diffraction pattern.

15. A process for producing the crystalline form II according to claim 14, comprising: dissolving the crude compound of claim 14 in a phosphate buffer solution at 10 °C or less, adjusting the pH of the buffer and diluting with water, adjusting the temperature of a solution of the compound represented by the Formula (VII-1) between 10 to 15 °C, adding isopropanol and stirring.

16. A use of the crystalline form II according to claim 14 for producing a pharmaceutical composition optionally comprising a pharmaceutically acceptable carrier.

17. A use of the crystalline form II according to claim 14 for producing a pharmaceutical composition comprising a β-lactam antibiotic selected from the group consisting of ampicillin, amoxicillin, piperacillin, ticarcillin, flomoxef, cefotaxime, ceftriaxone, ceftazidime, cefepime, ceftaroline, ceftolozane, imipenem, meropenem, biapenem, doripenem, ertapenem and aztreonam, and optionally a pharmaceutically acceptable carrier.

18. A crystalline form III of a compound represented by Formula (VII-1):



VII-1

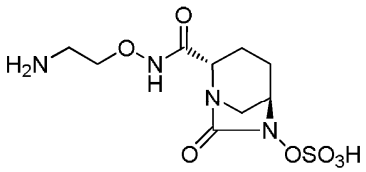
having characteristic peaks appearing at lattice spacing (d) of 8.32, 6.10, 5.98, 5.51, 5.16, 5.07, 4.85, 4.70, 4.61, 4.35, 4.20, 4.06, 4.00, 3.95, 3.77, 3.73, 3.65, 3.42, 3.39, 3.36, 3.26, 3.23, 3.13, 3.09, 2.99, 2.81 and 2.52 Å in the powder X-ray diffraction pattern.

19. A process for producing the crystalline form III according to claim 18, comprising: dissolving the crude compound of claim 18 in a phosphate buffer solution at 10 °C or less, adjusting the pH of the buffer, adjusting the temperature of a solution of the compound represented by the Formula (VII-1) between 20 to 25 °C, seeding with a crystalline form III, adding isopropanol and stirring.

20. A use of the crystalline form III according to claim 18 for producing a pharmaceutical composition optionally comprising a pharmaceutically acceptable carrier.

21. A use of the crystalline form III according to claim 18 for producing a pharmaceutical composition comprising a β-lactam antibiotic selected from the group consisting of ampicillin, amoxicillin, piperacillin, ticarcillin, flomoxef, cefotaxime, ceftriaxone, ceftazidime, cefepime, ceftaroline, ceftolozane, imipenem, meropenem, biapenem, doripenem, ertapenem and aztreonam, and optionally a pharmaceutically acceptable carrier.

22. A crystalline form IV of a compound represented by Formula (VII-1):



VII-1

having characteristic peaks appearing at lattice spacing (d) of 7.88, 6.41, 5.20, 4.67, 4.50, 4.02, 3.81, 3.75, 3.70, 3.62, 3.38, 3.23, 3.20, and 2.74 Å in the powder X-ray diffraction pattern.

23. A process for producing the crystalline form IV according to claim 22, comprising: dissolving the crystalline form III of claim 18 in water, adjusting the temperature of a solution of the compound represented by the Formula (VII-1) between 20 to 25 °C, adding methanol, and stirring.

24. A process for producing the crystalline form IV according to claim 22, comprising: stirring the crystalline form I, II or III according to claim 10, 14 or 18 in methanol, ethanol or isopropanol.

25. A use of the crystalline form IV according to claim 22 for producing a pharmaceutical composition optionally comprising a pharmaceutically acceptable carrier.

26. A use of the crystalline form IV according to claim 22 for producing a pharmaceutical composition comprising a β-lactam antibiotic selected from the group consisting of ampicillin, amoxicillin, piperacillin, ticarcillin, flomoxef, cefotaxime, ceftriaxone, ceftazidime, cefepime, ceftaroline, ceftolozane, imipenem, meropenem, biapenem, doripenem, ertapenem and aztreonam, and optionally a pharmaceutically acceptable carrier.

27. A use of a mixture of the crystalline forms I, II, III or IV according to claim 10, 14, 18 or 22 for producing a pharmaceutical composition optionally comprising a pharmaceutically acceptable carrier.

28. A use of a mixture of the crystalline forms I, II, III or IV according to claim 10, 14, 18 or 22 for producing a pharmaceutical composition comprising a β-lactam antibiotic selected from the group consisting of ampicillin, amoxicillin, piperacillin, ticarcillin, flomoxef, cefotaxime, ceftriaxone, ceftazidime, cefepime, ceftaroline, ceftolozane, imipenem, meropenem, biapenem, doripenem, ertapenem and aztreonam, and optionally a pharmaceutically acceptable carrier.