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(54) Title: BETA-LACTAM-CANNABINOID CONJUGATE MOLECULES

(57) Abstract: This disclosure provides multifunctional conjugate molecules in which at least one β -lactam antibiotic is covalently attached to a cannabinoid by means of a linker. The disclosed conjugate molecules are designed to deliver therapeutic benefits as intact molecules, with release of the cannabinoid upon binding of the β -lactam antibiotic to its target conveying further therapeutic benefits, and can be used to treat bacterial infections and other disorders.



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BETA-LACTAM-CANNABINOID CONJUGATE MOLECULES

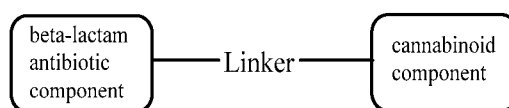
[01] Each reference cited in this disclosure is incorporated by reference herein in its entirety.

TECHNICAL FIELD

[02] This disclosure relates generally to multifunctional therapeutics.

DETAILED DESCRIPTION

[03] This disclosure describes multifunctional conjugate molecules comprising a β -lactam antibiotic component and a cannabinoid component covalently attached by a linker:



[04] In contrast to traditional prodrugs, embodiments of the disclosed conjugate molecules are designed to deliver more than one therapeutic benefit via more than one mechanism of action; this is achieved when the covalent binding of the β -lactam antibiotic component to its target enables the release of the cannabinoid at or near the site of the β -lactam's therapeutic action, where the released cannabinoid can then effect a second therapeutic benefit. That is, these conjugate molecules are designed to deliver the therapeutic benefits of each of their components. In other embodiments, the therapeutic agent component and the cannabinoid component are released to provide their respective therapeutic benefits via functionality of the linker.

[05] For example, the formation of reactive oxygen species (ROS) is a by-product of the normal process of respiration in an oxygen-rich environment (Storz & Imlay, Curr. Opin. Microbiol. 2, 188-94, 1999). There is significant evidence in the literature for the role endogenous ROS plays in mutagenesis, as well as its contribution to the mutational burden experienced by microbes during periods of oxidative stress (reviewed in Dwyer *et al.*, Curr. Opin. Microbiol. 12, 482-89, 2009). In fact, bacteria have evolved several enzymatic mechanisms to combat ROS toxicity (Imlay, Ann. Rev. Biochem. 77, 755-76, 2008).

[06] ROS are generated intracellularly and include superoxide ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and highly-destructive hydroxyl radicals ($OH^{\bullet}$). The species $O_2^{\bullet -}$ and H_2O_2 can be enzymatically eradicated by the activity of superoxide dismutases and catalases/peroxidases, respectively.

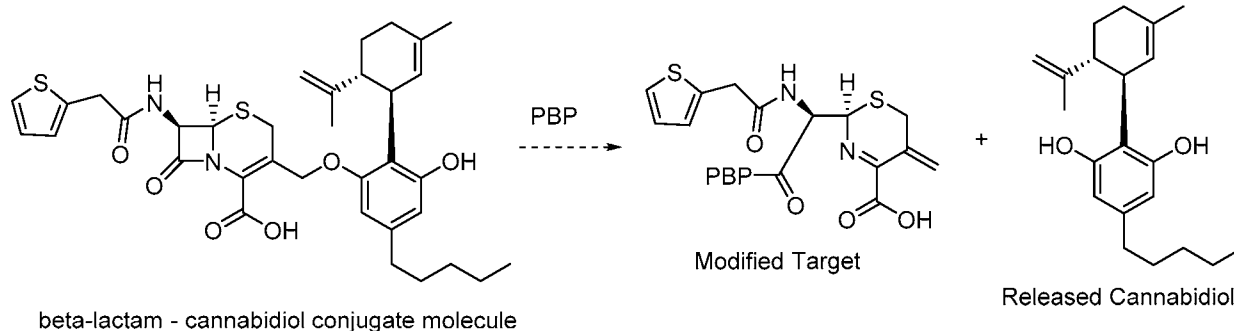
[07] Excess intracellular levels of ROS cause damage to proteins, nucleic acids, lipids, membranes, and organelles, which can lead to activation of cell death processes such as apoptosis. Apoptosis is a tightly regulated and highly conserved process of cell death during which a cell undergoes self-destruction (Kerr *et al.*, Br. J. Cancer 26, 239-57, 1972). Apoptosis can be triggered by a variety of extrinsic and intrinsic signals, including ROS (reviewed in Redza-Dutordoir & Averill-Bates, Biochem. Biophys. Acta 1863, 2977-92, 2016). Exposure to xenobiotics such as antibiotics and chemotherapeutic drugs can also trigger apoptosis, and is often mediated by ROS.

[08] All classes of bactericidal antibiotics, regardless of their specific target, promote the generation of lethal hydroxyl radicals in both Gram-negative and Gram-positive bacteria (Kohanski *et al.*, Cell 130, 797-810, 2007).

[09] Cannabinoids, too, have demonstrated their ability to promote ROS production. Cannabidiol (CBD) is a non-toxic and non-psychoactive cannabinoid that has been shown to have anti-tumor activity in multiple cancer types (Massi *et al.*, J. Pharmacol. Exp. Ther. 308, 838-45, e-pub 2003). CBD has been reported to inhibit human GBM viability in culture, an effect that was reversed in the presence of the ROS scavenger α -tocopherol/vitamin E (Velasco *et al.*, 2012).

[10] CBD-dependent production of ROS has been shown to accompany a reduction in glutathione (Massi *et al.*, Cell. Mol. Sci. 63, 2057-66, 2006), an important anti-oxidant that prevents damage to cellular components by ROS. The source of CBD-dependent stress in part originated in the mitochondria and led to activation of multiple caspases involved in intrinsic and extrinsic pathways of apoptosis.

[11] Cannabigerol (CBG) is another non-psychoactive cannabinoid that interacts with specific targets involved in carcinogenesis and has shown potent anti-tumor activity (Guindon & Hohmann, Br. J. Pharmacol. 163, 1447-63, 2011). Mechanistically, CBG, similar to CBD, appears to influence the inflammatory microenvironment (Mantovani *et al.*, Nature 454, 436-44, 2008; Solinas *et al.*, Cancer Metastasis Rev. 29, 243-48, 2010) and exert pro-apoptotic effects by selectively increasing ROS production (Borrelli *et al.*, Carcinogenesis 35, 2787-97, 2014). Using cannabidiol as an example of the cannabinoid and cephalosporin as an example of a β -lactam antibiotic, this approach is illustrated in the schematic below, in which the conjugate molecule contains a cephalosporin component and a cannabidiol component and in which the antibiotic's target is a penicillin binding protein (PBP):



Conjugate Molecules

[12] In some embodiments, conjugate molecules comprise a β -lactam antibiotic component and a cannabinoid component attached by means of a linker which is covalently attached at one end to the β -lactam antibiotic component and at the other end to a hydroxy group of the cannabinoid component. In some embodiments, the hydroxy group is an “aromatic hydroxy group;” *i.e.*, a hydroxy group bonded directly to an aromatic hydrocarbon. In some embodiments, the hydroxy group is an “aliphatic hydroxy group;” *i.e.*, a hydroxy group bound to a carbon that is not part of an aromatic ring.

[13] In some embodiments, conjugate molecules contain only one β -lactam antibiotic component. In other embodiments, when the cannabinoid component has two or more hydroxy groups, conjugate molecules can contain two or more β -lactam antibiotic components, each attached to one of the two or more hydroxy groups by means of a linker. In such embodiments, the two or more linkers can be the same or different. Independently, the two or more β -lactam antibiotic components can be the same or different. Also independently, the two or more hydroxy groups can be aliphatic or the two hydroxy groups can be aromatic, or, for example, a first hydroxy group can be aliphatic and a second hydroxy group can be aromatic.

[14] Conjugate molecules can have one or more centers of asymmetry and can therefore be prepared either as a mixture of isomers (*e.g.*, a racemic or diastomeric mixture) or in an enantiomerically or diastomerically pure form. Such forms include, but are not limited to, diastereomers, enantiomers, and atropisomers. Conjugate molecules can also include alkenes and can therefore be prepared either as a mixture of double bond isomers or independently as either an E or Z isomer. Isotopic variants of conjugate molecules can also be prepared.

[15] Conjugate molecules can form salts. “Pharmaceutically acceptable salts” are those salts which retain at least some of the biological activity of the free (non-salt) compound and which can be administered as drugs or pharmaceuticals to an individual. Such salts, for example,

include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, oxalic acid, propionic acid, succinic acid, maleic acid, tartaric acid and the like; (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth metal ion, or an aluminum ion; or coordinates with an organic base. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. Further examples of pharmaceutically acceptable salts include those listed in Berge *et al.*, *Pharmaceutical Salts*, *J. Pharm. Sci.* 1977 Jan; 66(1):1-19.

Definitions

[16] The following definitions apply to the descriptions of the “Therapeutic Agent Component(s)” and “Linkers” in the sections below and to the descriptions of “Group One Substituents” and “Group Two Substituents.”

[17] “C1-C3 linear or branched alkyl” means “methyl, ethyl, propyl, and isopropyl.”

[18] “C1-C8 linear or branched alkyl” means “methyl, ethyl, C3, C4, C5, C6, C7, and C8 linear alkyl and C3, C4, C5, C6, C7, and C8 branched alkyl.”

[19] “C1-C3 linear or branched heteroalkyl” means “a linear or branched heteroalkyl containing 1, 2, or 3 carbon atoms.”

[20] “C1-C8 linear or branched heteroalkyl” means “each of a C1, C2, C3, C4, C5, C6, C7, and C8 linear heteroalkyl and C1, C2, C3, C4, C5, C6, C7, and C8 branched heteroalkyl.”

[21] “C1-C6 linear or branched alkoxy” means “a linear or branched alkoxy containing 1, 2, 3, 4, 5, or 6 carbon atoms.”

[22] “C1-C6 linear or branched alkylamino” means “a linear or branched alkylamino containing 1, 2, 3, 4, 5, or 6 carbon atoms.”

[23] “C1-C6 linear or branched dialkylamino” means “each linear or branched dialkylamino in which each alkyl independently contains 1, 2, 3, 4, 5, or 6 carbon atoms.”

[24] “6- 10-membered aromatic” means “each of a 6-, 7-, 8-, 9-, and 10-membered aromatic.”

[25] “5- to 10-membered heteroaromatic” means “each of a 6-, 7-, 8-, 9-, and 10-membered heteroaromatic.”

[26] “3- to 9-membered cycloheteroalkyl” means “each of a 3-, 4-, 5-, 6-, 7-, 8-, and 9-membered cycloheteroalkyl.”

[27] “C3-C6 cycloalkyl” means “C3, C4, C5, and C6 cycloalkyl.”

[28] “Halide” means “Cl, Br, and I.”

[29] “Group One Substituents” is a group of substituents consisting of:

- (a) –OH;
- (b) –NH₂;
- (c) =O;
- (d) =S;
- (e) =NR₇, where R₇ is H or is C1-C3 linear or branched alkyl or C1-C3 linear or branched heteroalkyl comprising an O, N, or S atom;
- (f) –C(O)OR₄, wherein R₄ is H or C1-C3 linear or branched alkyl;
- (g) –C(O)NR₅R₆, wherein R₅ and R₆ independently are H or C1-C6 linear or branched alkyl;
- (h) halide;
- (i) C1-C6 linear or branched alkoxyl;
- (j) C1-C6 linear or branched alkylamino;
- (k) C1-C6 linear or branched dialkylamino;
- (l) 6- to 10-membered aromatic, optionally substituted with 1, 2, 3, or 4 substituents independently selected from
 - (i) phenyl;
 - (ii) halide;
 - (iii) cyano;
 - (iv) C1-C6 linear or branched alkyl, optionally substituted with
 - (1) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 - (2) 1, 2, or 3 substituents independently selected from the Group Two Substituents; and
 - (v) C1-C6 linear or branched heteroalkyl containing 1, 2, or 3 atoms independently selected from O, N, and S and optionally substituted with
 - (1) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 - (2) 1, 2, or 3 substituents independently selected from the Group Two Substituents;

(m) 5- to 10-membered heteroaromatic, optionally substituted with 1, 2, 3, or 4 substituents independently selected from

- (i) phenyl;
- (ii) halide;
- (iii) cyano;
- (iv) C1-C6 linear or branched alkyl, optionally substituted with
 - (1) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 - (2) 1, 2, or 3 substituents independently selected from the Group Two Substituents; and
- (v) C1-C6 linear or branched heteroalkyl containing 1, 2, or 3 atoms independently selected from O, N, and S and optionally substituted with
 - (1) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 - (2) 1, 2, or 3 substituents independently selected from the Group Two Substituents;

(n) 3- to 9-membered cycloheteroalkyl having 1, 2, or 3 heteroatoms independently selected from O, N, and S, optionally substituted with 1, 2, 3, or 4 substituents independently selected from

- (i) phenyl;
- (ii) halide;
- (iii) cyano;
- (iv) C1-C6 linear or branched alkyl, optionally substituted with
 - (1) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 - (2) 1, 2, or 3 substituents independently selected from the Group Two Substituents; and
- (v) C1-C6 linear or branched heteroalkyl containing 1, 2, or 3 atoms independently selected from O, N, and S and optionally substituted with
 - (1) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 - (2) 1, 2, or 3 substituents independently selected from the Group Two Substituents; and

(o) C3-C6 cycloalkyl, optionally substituted with 1, 2, 3, or 4 substituents independently selected from

- (i) phenyl;
- (ii) halide;
- (iii) cyano;
- (iv) C1-C6 linear or branched alkyl, optionally substituted with
 - (1) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 - (2) 1, 2, or 3 substituents independently selected from the Group Two Substituents; and
- (v) C1-C6 linear or branched heteroalkyl containing 1, 2, or 3 atoms independently selected from O, N, and S and optionally substituted with

- (1) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
- (2) 1, 2, or 3 substituents independently selected from the Group Two Substituents.

[30] “Group Two Substituents” is a group of substituents consisting of:

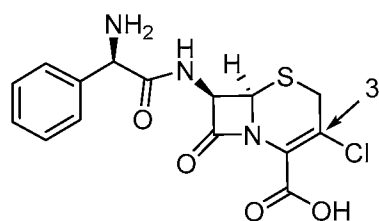
- (a) –OH;
- (b) –NH₂;
- (c) =O;
- (d) =S;
- (e) =NR₇, where R₇ is H or is C1-C3 linear or branched alkyl or C1-C3 linear or branched heteroalkyl comprising an O, N, or S atom;
- (f) –C(O)OR₄, wherein R₄ is H or C1-C3 linear or branched alkyl;
- (g) –C(O)NR₅R₆, wherein R₅ and R₆ independently are H or C1-C6 linear or branched alkyl;
- (h) halide;
- (i) cyano;
- (j) trifluoromethyl;
- (k) C1-C6 linear or branched alkoxy;
- (l) C1-C6 linear or branched alkylamino;
- (m) C1-C6 linear or branched dialkylamino;
- (n) 6- to 10-membered aromatic; and
- (o) 5- to 10-membered heteroaromatic comprising 1, 2, 3, 4, 5, or 6 heteroatoms independently selected from O, N, and S.

β-Lactam Antibiotic Component(s)

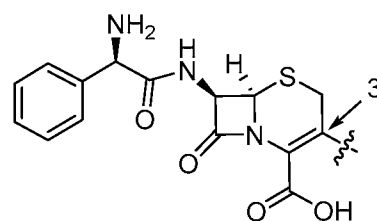
[31] A “β-lactam antibiotic” as used in this disclosure is molecule that contains a 4-membered lactam ring (β-lactam) and that has antibacterial activity. A “β-lactam antibiotic component” as used in this disclosure is that portion of the β-lactam antibiotic that is present in the conjugate molecule and covalently attached to the linker. A number of β-lactam antibiotics can be used to provide the β-lactam antibiotic component of a conjugate molecule.

Cephems and Carbacephems

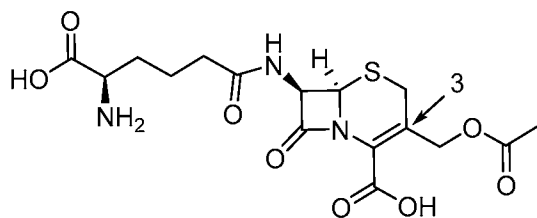
[32] In some embodiments, the β-lactam antibiotic component is a cephem component. As used in this disclosure, a “cephem component” is a cephem in which the substituent ordinarily present at the 3 position of the molecule is not present, as illustrated below:



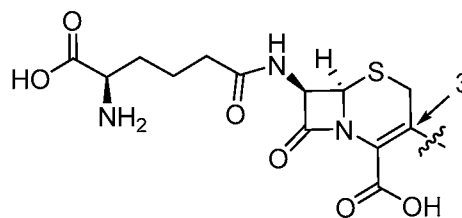
cephaclor



cephaclor component



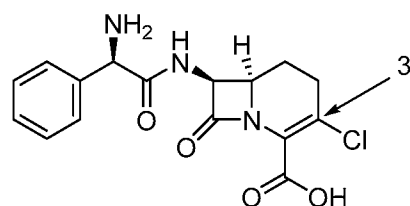
cephalosporin



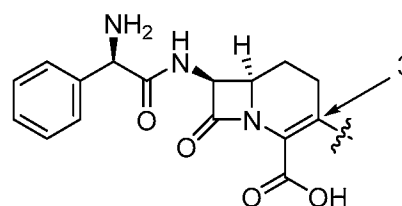
cephalosporin component

[33] A cephem component can be provided by any of a variety of cephems including, but not limited to, cefazolin, cephalexin, cefadroxil, cefapirin, cefazedone, cefazaflur, cefradine, cefroxadine, ceftezole, cefaloglycin, cephacetrile, cefalonium, cefaloridine, cefalotin, cefatrizine, cefaclor, cefotetan, cephamycin, cefoxitin, cefprozil, cefuorixime, cefuroxime axetil, cefamandole, cefminox, cefonicid, ceforanide, cefotiam, cefbuperazone, cefuzonam, cefmetazole, cefixime, ceftriaxone, ceftazidime, cefoperazone, cefdinir, cefcapene, cefdaloxime, ceftizoxime, cefminoxime, cefotaxime, cefpiramide, cefpodoxime, ceftibuten, cefditoren, cefetamet, cefodizime, cefpimizole, cefsulodin, ceftaram ceftiolene, flomoxef, latamoxef, cefepime, cefozopran, cefpirome, cefquinome, ceftaroline fosamil, ceftolozane, ceftobiprole, ceftiofur, cefquinome, and cefovecin. See also, for example, U.S. Patent 9,751,894; U.S. Patent 7,696,354; U.S. Patent 6,150,351.

[34] In some embodiments, the β -lactam antibiotic component is a carbacephem component. As used in this disclosure, a “carbacephem component” is a carbacephem in which the substituent ordinarily present at the 3 position of the molecule is not present, as illustrated below:



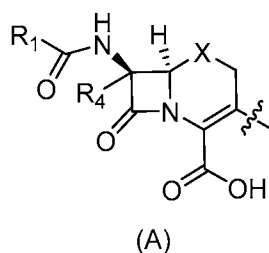
loracarbef



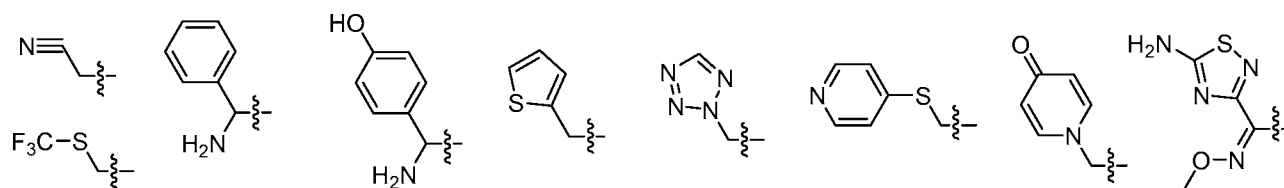
loracarbef component

[35] Carbacephems include, but are not limited to, loracarbef. See also, for example, U.S. Patent 8,445,476, U.S. Patent 4,980,348.

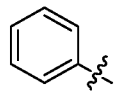
[36] In some embodiments the β -lactam antibiotic component falls within structural Formula (A):



in which X is S, C, or O; R_1 is a side chain of a cephem or a side chain of a carbacephem; and R_4 is H or $-OCH_3$. Cephem side chains include, for example:

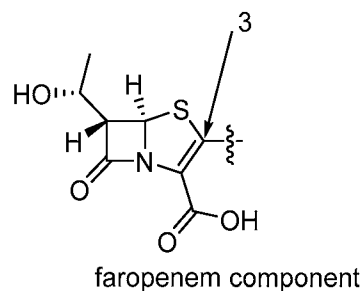
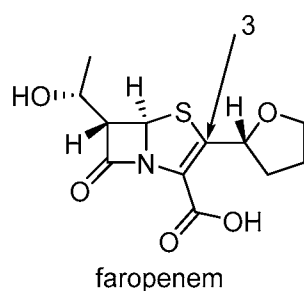


Carbacephem side chains include, for example,



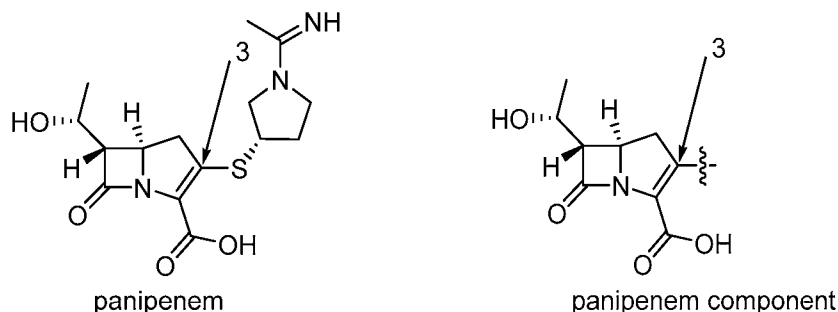
Penems and Carbapenems

[37] In some embodiments, the β -lactam antibiotic component is a penem component. As used in this disclosure, a “penem component” is a penem in which the substituent ordinarily present at the 3 position of the molecule is not present, as illustrated below:



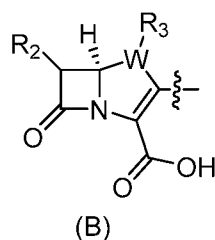
[38] Penems include, but are not limited to, faropenem and ritipenem. See also U.S. Patent 6,271,222; U.S. Patent 5,757,583.

[39] In other embodiments, the β -lactam antibiotic component is a carbapenem component. As used in this disclosure, a “carbapenem component” is a carbapenem in which the substituent ordinarily present at the 3 position of the molecule is not present, as illustrated below:



[40] Carbapenems include, but are not limited to, ertapenem, doripenem, imipenem, meropenem, biapenem, and panipenem. See also U.S. Patent 9,937,151; U.S. Patent 8,318,716.

[41] In some embodiments the β -lactam antibiotic component falls within structural Formula (B):



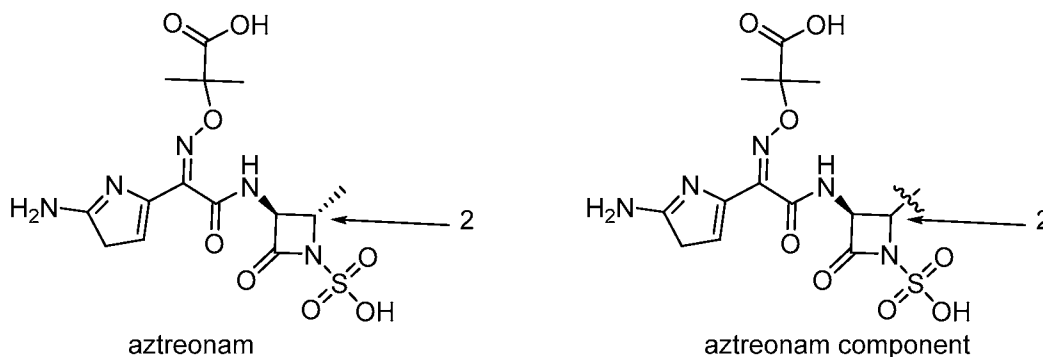
in which W is S or C; R_2 is a side chain of a penem or a side chain of a carbapenem; and, when W is C, R_3 is H, $-\text{CH}_3$, or phenyl, wherein the phenyl is optionally substituted with 1-4 groups selected from the group consisting of halide, trifluoromethyl, C1-C6 linear or branched alkyl optionally substituted with up to nine fluorine atoms, and C1-C6 linear or branched heteroalkyl optionally substituted with up to 9 fluorine atoms.

[42] In some embodiments, the side chain of the penem or carbapenem is .

[43] In some embodiments, R_3 is β -methyl.

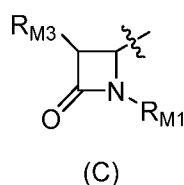
Monobactams

[44] In some embodiments, the β -lactam antibiotic component is a monobactam component. As used in this disclosure, “monobactam component” is a monobactam in which the substituent ordinarily present at the 2 position of the molecule is not present, as illustrated by the example below.

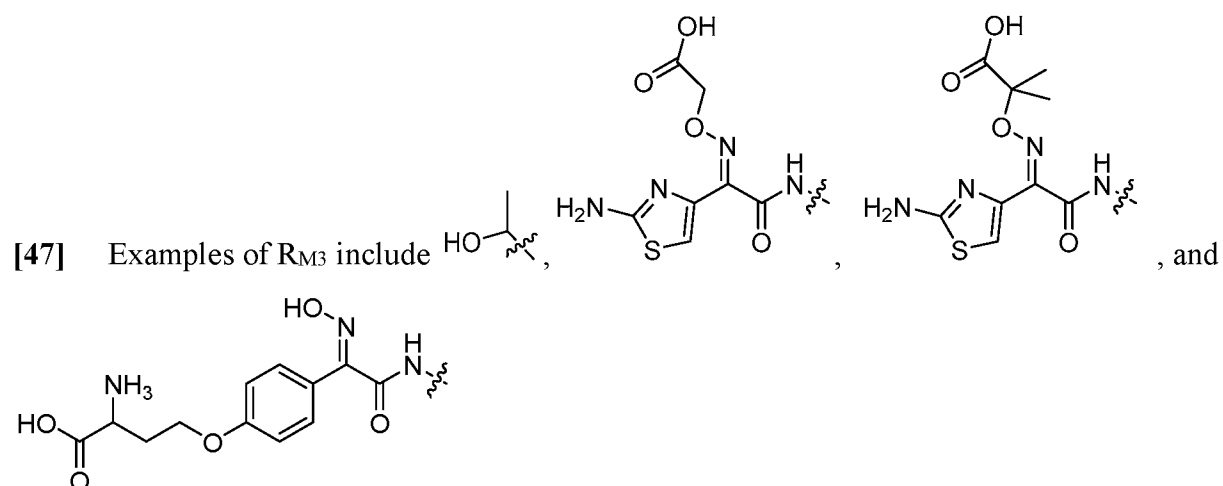


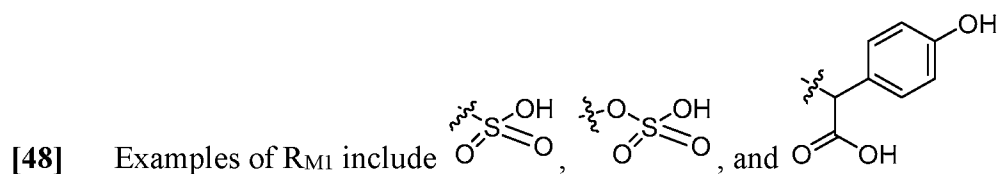
[45] Monobactams include, but are not limited to, aztreonam, tigemonam, carumonam, and nocardicin A. See also, for example, U.S. Patent 9,174,978.

[46] In some embodiments the β -lactam antibiotic component falls within structural Formula (C):



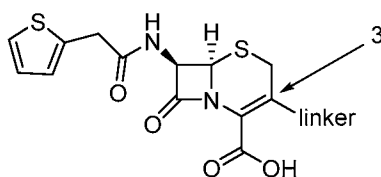
in which R_{M3} is a position 3 monobactam substituent, and R_{M1} is a position 1 monobactam substituent.



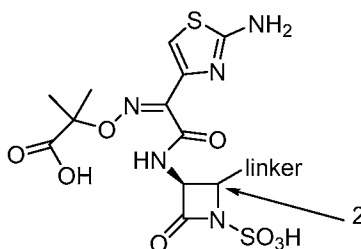


Linkers

[49] Linkers used to connect a β -lactam antibiotic component and a cannabinoid component are typically two to 10 atoms in length and are functionalized to facilitate release of the cannabinoid when the β -lactam antibiotic engages its biological target. When a β -lactam antibiotic component is provided by a cephem, carbacephem, penem, or carbapenem, the linker is covalently attached to the 3 position of the β -lactam antibiotic component; *e.g.*:

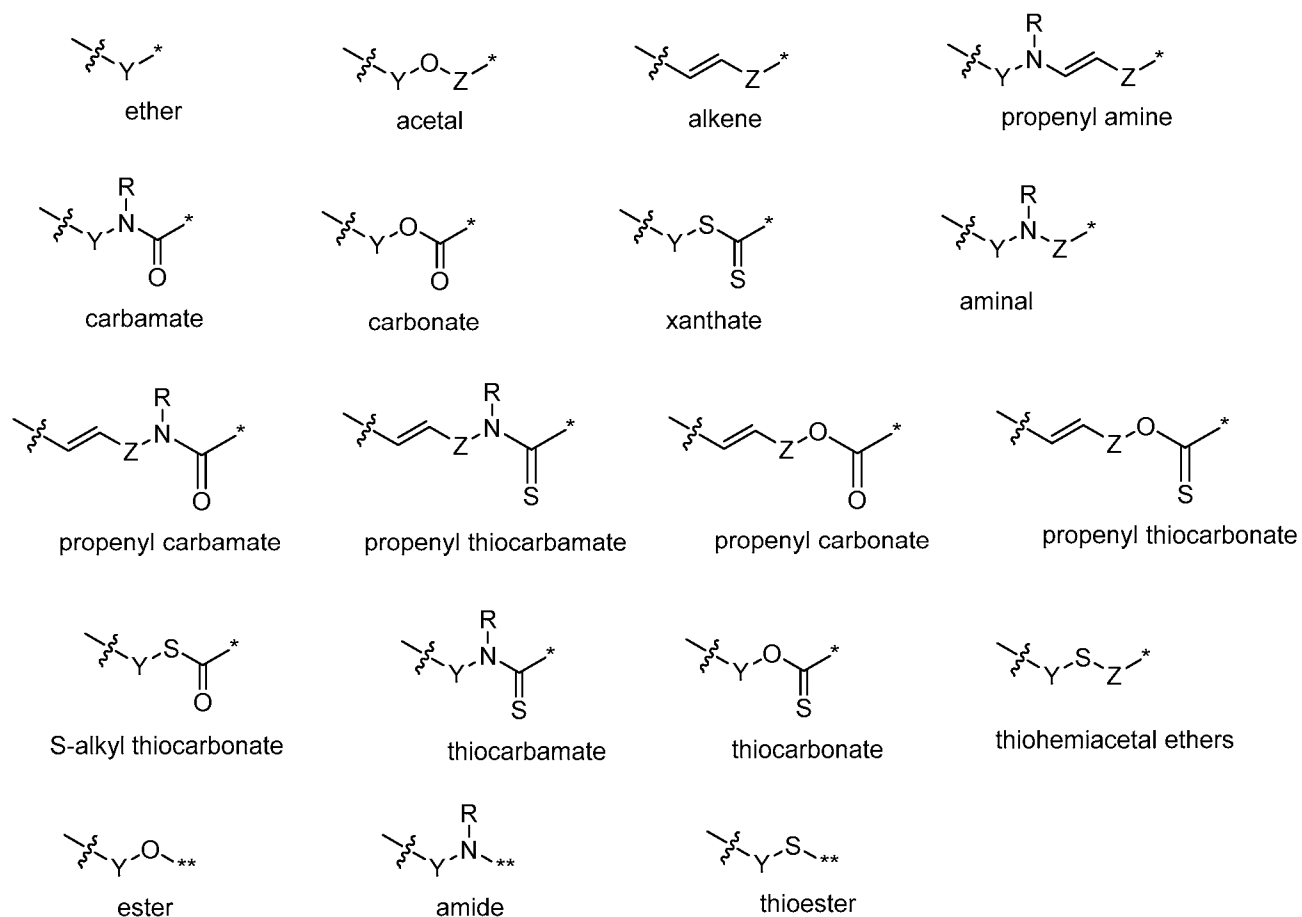


[50] When a β -lactam antibiotic component is provided by a monobactam, the linker is covalently attached to the 2 position of the monobactam component; *e.g.*:



[51] A variety of linkers can be used in the conjugate molecules, including ethers, acetals, alkenes, propenyl amines, carbamates, carbonates, xanthates, amins, propenyl carbamates, propenyl thiocarbamates, propenyl carbonates, propenyl thiocarbonates, S-alkyl thiocarbonates, thiocarbamates, thiocarbonates, and thiohemiacetal ethers.

[52] When a β -lactam antibiotic component is provided by a cephem, carbacephem, penem, or carbapenem, the linker can be selected from the group of linkers shown below (“Group AB Linkers”):



wherein * indicates a site of covalent attachment to the oxygen atom from the OH of a cannabinoid component, ** in cases such as ester, amide, and thioester indicates the site of covalent attachment to the carbon atom of a carbonyl component of a carboxylic acid - bearing cannabinoid component, and marks a bond by which the linker is covalently attached to the β -lactam antibiotic component and wherein

Y is absent or is -CH₂, -CHCH₃, or -CH-phenyl;

Z is CR₁R₂; and

R, R₁ and R₂ independently are selected from the group consisting of:

(a) H;

(b) C1-C8 linear or branched alkyl, optionally substituted with

(1) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or

(2) 1, 2, or 3 substituents independently selected from the Group One Substituents;

(c) C1-C8 linear or branched heteroalkyl containing 1, 2, or 3 heteroatoms independently selected from O, N, and S and optionally substituted with

(1) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or

(2) 1, 2, or 3 substituents independently selected from the Group One Substituents;

(d) phenyl, optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of:

(1) C1-C6 linear or branched alkyl, optionally substituted with

(i) 1, 2, 3, 4, 5, or 6 fluorine atoms; and/or

(ii) 1 or 2 substituents independently selected from the Group Two Substituents; and

(2) C1-C6 linear or branched heteroalkyl containing 1 or 2 heteroatoms independently selected from O, N, and S and optionally substituted with

(i) 1, 2, 3, 4, 5, or 6 fluorine atoms; and/or

(ii) 1 or 2 substituents independently selected from the Group One Substituents;

(e) a 6- to 10-membered aromatic, optionally substituted with 1, 2, 3, or 4 substituents independently selected from the group consisting of:

(1) phenyl;

(2) halide;

(3) cyano;

(4) C1-C6 linear or branched alkyl, optionally substituted with

(i) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or

(ii) 1, 2, or 3 substituents independently selected from the Group Two Substituents, and

(5) C1-C6 linear or branched heteroalkyl containing 1, 2, or 3 atoms independently selected from O, N, and S and optionally substituted with

(i) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or

(ii) 1, 2, or 3 substituents independently selected from the Group

Two Substituents;

(f) 5- to 10-membered heteroaromatic comprising 1, 2, 3, 4, 5, or 6 heteroatoms independently selected from O, N, and S and optionally substituted with 1, 2, 3, or 4 substituents independently selected from

(1) phenyl;

(2) halide;

(3) cyano;

(4) trifluoromethyl;

(5) C1-C6 linear or branched alkyl optionally substituted with

(i) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or

(ii) 1, 2, or 3 substituents independently selected from the Group

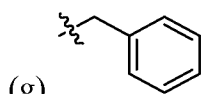
Two Substituents; and

(6) C1-C6 linear or branched heteroalkyl containing 1, 2, or 3 atoms independently selected from O, N, and S and optionally substituted with

(i) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or

(ii) 1, 2, or 3 substituents independently selected from the Group

Two Substituents;



, optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of:

(1) C1-C6 linear or branched alkyl, optionally substituted with

(i) 1, 2, 3, 4, 5, or 6 fluorine atoms; and/or

(ii) 1, 2, or 3 substituents independently selected from the Group

Two Substituents;

(h) 3- to 9-membered cycloheteroalkyl having 1, 2, or 3 heteroatoms independently selected from O, N, and S and optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of:

(1) C1-C6 linear or branched alkyl, optionally substituted with

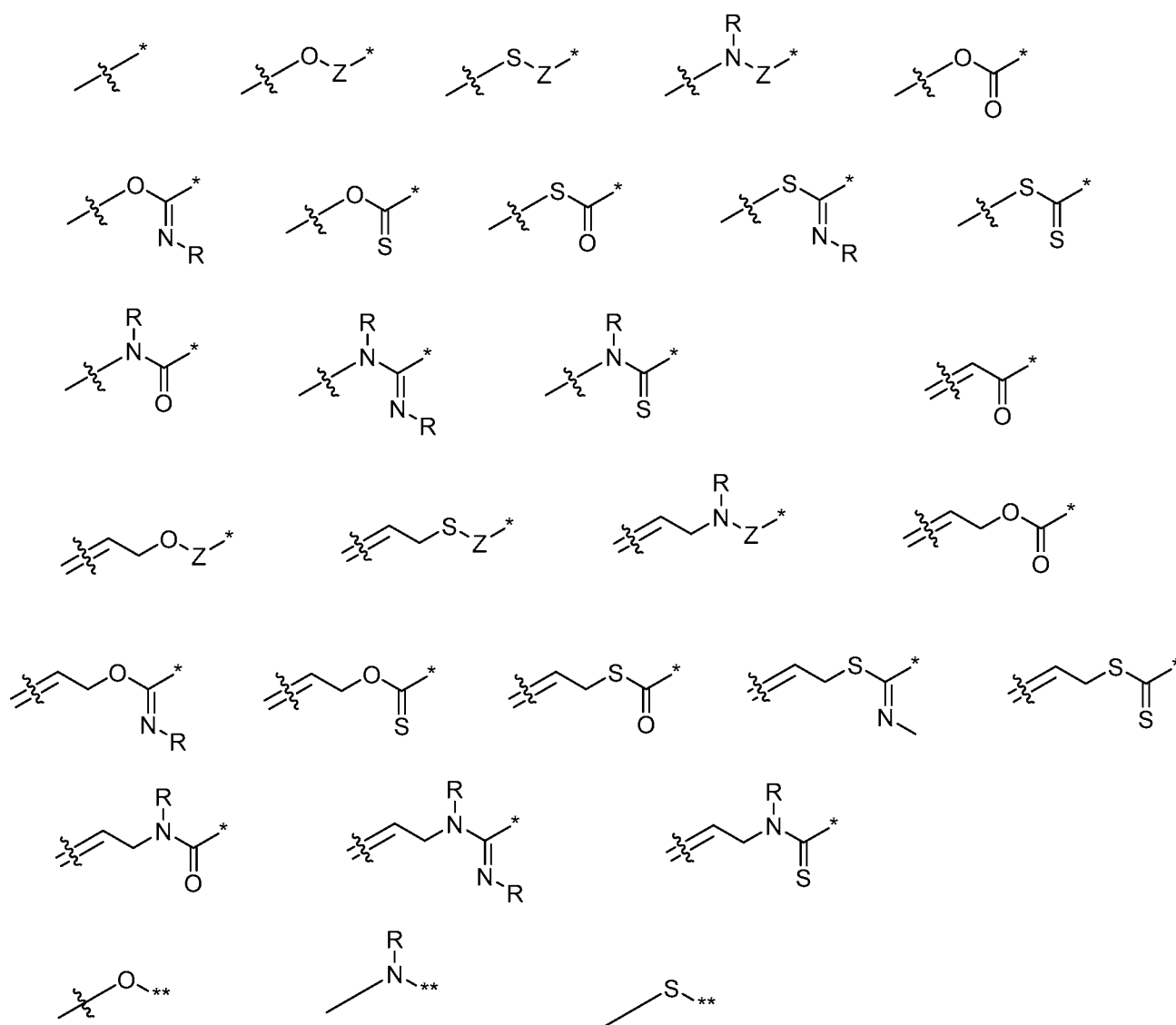
- (i) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 - (ii) 1, 2, or 3 substituents independently selected from the Group Two Substituents,
- (2) C1-C6 linear or branched heteroalkyl, optionally substituted with
- (i) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms and/or
 - (ii) 1, 2, or 3 substituents independently selected from the Group Two Substituents,
- (3) phenyl, optionally substituted with 1, 2, or 3 substituents independently selected from the Group Two Substituents, and
- (4) 5- to 10-membered heteroaromatic, optionally substituted with 1, 2, or 3 substituents independently selected from the Group Two Substituents; and
- (i) C3-C6 cycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from:
- (1) C1-C6 linear or branched alkyl, optionally substituted with
 - (i) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 - (ii) 1, 2, or 3 substituents independently selected from the Group Two Substituents,
 - (2) C1-C6 linear or branched heteroalkyl, optionally substituted with
 - (i) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 - (ii) 1, 2, or 3 substituents independently selected from the Group Two Substituents,
 - (3) phenyl, optionally substituted with 1, 2, or 3 substituents independently selected from Group Two Substituents; and
 - (4) 5- to 10-membered heteroaromatic, optionally substituted with 1, 2, or 3 substituents independently selected from the Group Two Substituents;

OR

R₁ and R₂, together with the atom to which they are attached, form a 3- to 9-membered cycloheteroalkyl having 1, 2, 3, or 4 heteroatoms independently selected from O, S, and N, wherein the cycloheteroalkyl optionally is substituted

with 1, 2, or 3 substituents independently selected from, C1-C6 linear or branched alkyl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms, C1-C6 linear or branched heteroalkyl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms, phenyl optionally substituted with 1, 2, or 3 substituents independently selected from Group Two Substituents, or 5- to 10-membered heteroaromatic optionally substituted with 1, 2, or 3 independently selected from Group Two Substituents

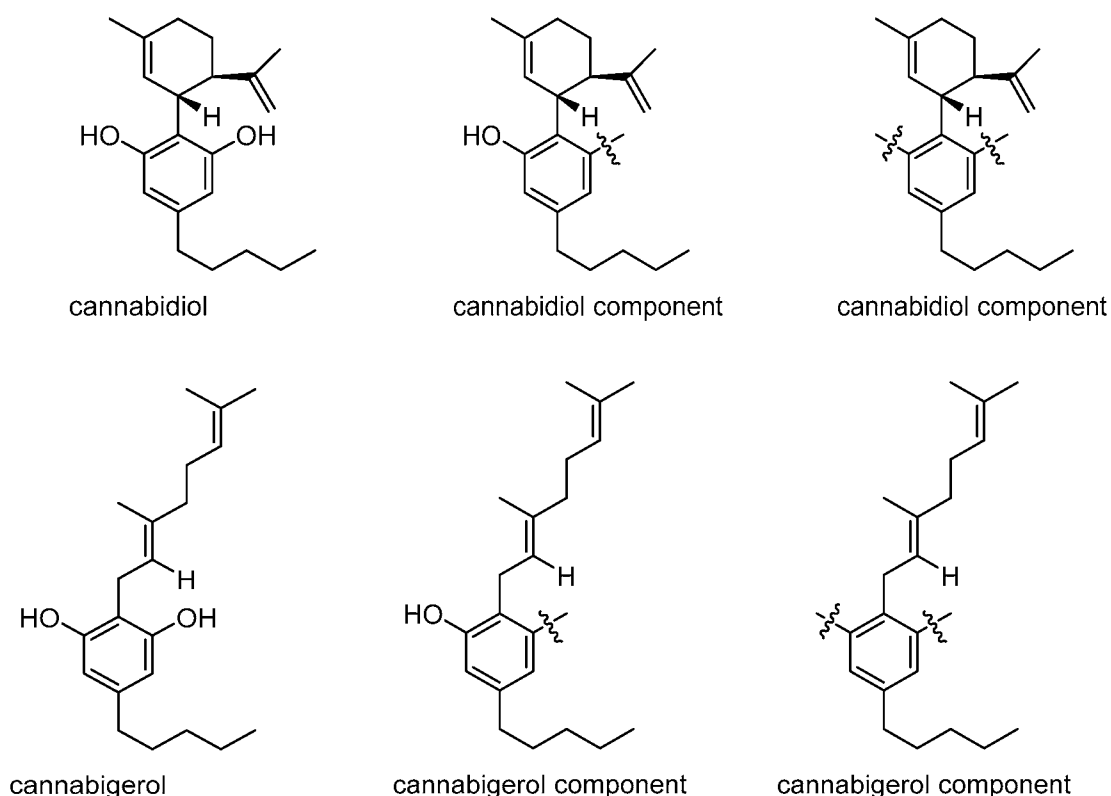
[53] When a β -lactam antibiotic component is provided by a monobactam, the linker by which the β -lactam antibiotic component is covalently attached to the cannabinoid component can be selected from the group of linkers shown below (“Group C Linkers”):



in which *, **, Z, and R are as defined for Group AB linkers.

Cannabinoid Component

[54] A “cannabinoid component” as used in this disclosure is that portion of the cannabinoid that is present in the conjugate molecule and covalently attached to the linker, as shown in the examples below.



[55] The cannabinoid component can be provided by any cannabinoid that contains a hydroxy group to which the linker can be attached. The cannabinoid can be a naturally occurring molecule, either isolated or synthesized, or a modified version of a naturally occurring molecule. See, for example, Morales *et al.*, *Frontiers in Pharmacology* June 2017 review, 1-18.

[56] Examples of cannabinoids include, but are not limited to, cannabigerols, cannabichromenes, cannabidiols, tetrahydrocannabinols, cannabicyclols, cannabielsoins, cannabinols, cannabinodiols, cannabitriols, dehydrocannabifurans, cannabifurans, cannabichromanons, and cannabiripsols.

[57] Examples of cannabigerols include cannabigerolic acid (CBGA), cannabigerolic acid monomethylether (CBGAM), cannabigerol (CBG), cannabigerol monomethylether (CBGM), cannabigerovaric acid (CBGVA), and cannabigerovarin (CBGV).

[58] Examples of cannabichromenes include cannabichromenic acid (CBC), cannabichromene (CBC), cannabichromevarinic acid (CBCVA), and cannabichromevarin (CBCV).

[59] Examples of cannabidiols include cannabidiolic acid (CBDA), cannabidiol (CBD), cannabidiol monomethylether (CBDM), cannabidiol-C₄ (CBD-C₄), cannabidivarinic acid (CBDVA), cannabidivarin (CBDV), and cannabidiorcol (CBD-C₁).

[60] Examples of tetrahydrocannabinols include Δ -9-tetrahydrocannabinolic acid A (THCA-A), Δ -9-tetrahydrocannabinolic acid B (THCA-B), Δ -9-tetrahydrocannabinol (THC), Δ -9-tetrahydrocannabinolic acid-C₄ (THCA-C₄), Δ -9-tetrahydrocannabinol-C₄ (THC-C₄), Δ -9-tetrahydrocannabivarinic acid (THCVA), Δ -9-tetrahydrocannabivarin (THCV), Δ -9-tetrahydrocannabiorcolic acid (THCA-C₁), Δ -9-tetrahydrocannabiorcol (THC-C₁), Δ -7-*cis*-tetrahydrocannabivarin, Δ -8-tetrahydrocannabinolic acid (Δ^8 -THCA), and Δ -8-tetrahydrocannabinol (Δ^8 -THC).

[61] Examples of cannabicyclols include cannabicyclic acid (CBLA), cannabicyclol (CBL), and cannabicyclovarin (CBLV).

[62] Examples of cannabielsoins include cannabielsoic acid A (CBEA-A), cannabielsoic acid B (CBEA-B), and cannabielsoin (CBE).

[63] Examples of cannabinoids and cannabinodiols include cannabinolic acid (CBNA), cannabinol (CBN), cannabinol-C₄ (CBN-C₄), cannabivarin (CBV), cannabinol-C₂ (CBN-C₂), cannabiorcol (CBN-C₁), cannabinodiol (CBND), and cannabinodivarin (CBVD).

[64] Examples of cannabitriols include cannabitriol (CBT), 10-ethoxy-9-hydroxy- Δ -6a-tetrahydrocannabinol, cannabitriolvarin (CBTV), and ethoxy-cannabitriolvarin (CBTVE).

[65] Cannabifurans include dehydrocannabifuran (DCBF) and cannabifuran (CBF).

[66] Examples of other cannabinoids include cannabichromanon (CBCN), 10-oxo- Δ -6a-tetrahydrocannabinol (OTHC), cannabiripsol (CBR), and trihydroxy- Δ -9-tetrahydrocannabinol (triOH-THC).

[67] In some embodiments, the cannabinoid component is provided by cannabidiol.

Conjugate Molecules Comprising Two β -Lactam Antibiotic Components

[68] In some embodiments, in which the cannabinoid component has two hydroxy groups, a second β -lactam antibiotic component can be covalently attached to the second hydroxy group by means of a second linker such that the conjugate molecule contains a first β -lactam antibiotic

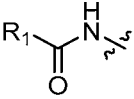
component and a second β -lactam antibiotic component covalently attached to the cannabinoid component by means of a first linker and a second linker, respectively.

[69] In some embodiments, the first β -lactam antibiotic component is a cephem component. In some embodiments, the first β -lactam antibiotic component is a carbacephem component. In some embodiments, the first β -lactam component is a penem component. In some embodiments, the first β -lactam component is a carbapenem component. In some embodiments, the first β -lactam component is a monobactam component. In any of these embodiments, the second β -lactam antibiotic component can be carbapenem component, a cephem component, a carbacephem component, or a monobactam component. That is, the two β -lactam antibiotic components can be the same or different, in any combination.

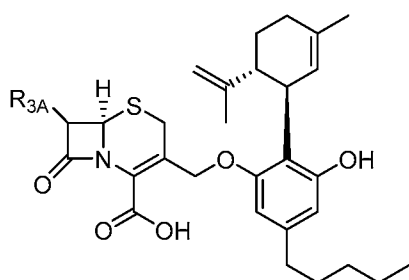
[70] The first and second linkers, too, can be the same or different. In some embodiments, the first and second linkers independently are selected from Group AB linkers. In some embodiments, the first and second linkers independently are selected from Group C linkers. In some embodiments, the first linker is selected from Group AB linkers and the second linker is selected from Group C linkers.

Examples of Conjugate Molecules

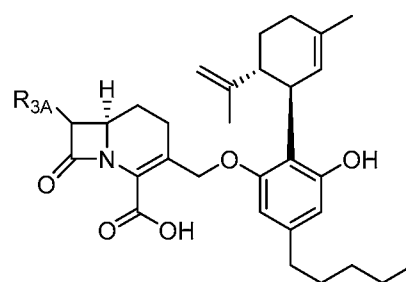
[71] Examples of conjugate molecules comprising cephem, carbacephem, penem, carbapenem, and beta-methyl carbapenem components are shown below. For simplicity, the illustrated cannabinoid component is a cannabidiol component covalently linked to a single β -

lactam antibiotic. In each case, R_{3A} is , in which R_1 is as defined above; and R_{3B} is R_2 as defined above.

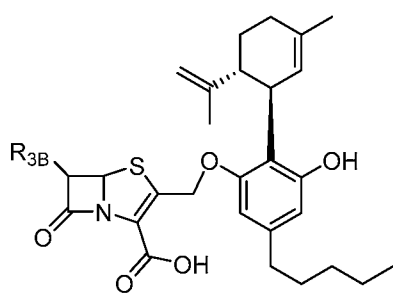
conjugate molecules with ether linkages



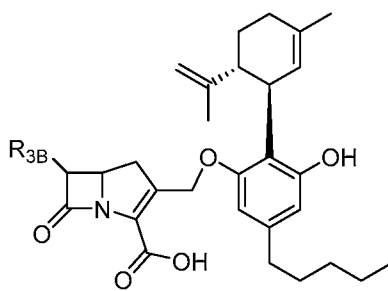
Cephem



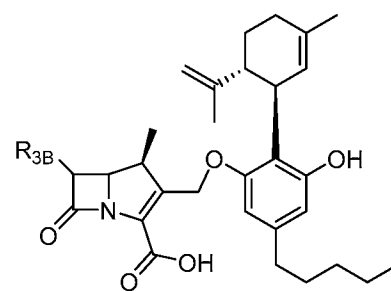
Carbacephem



Penem

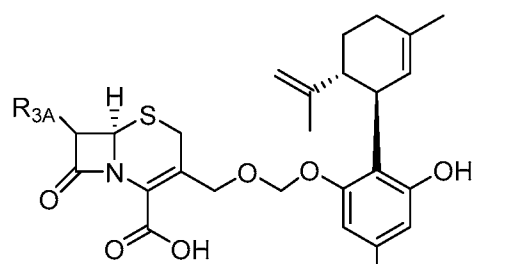


Carbapenem

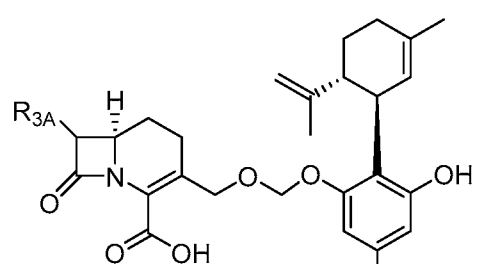


Beta-methyl Carbapenem

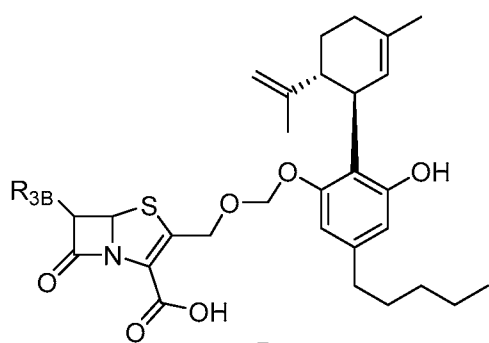
conjugate molecules with acetal linkages



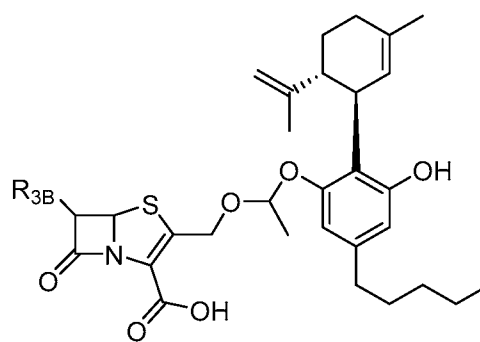
Cephem



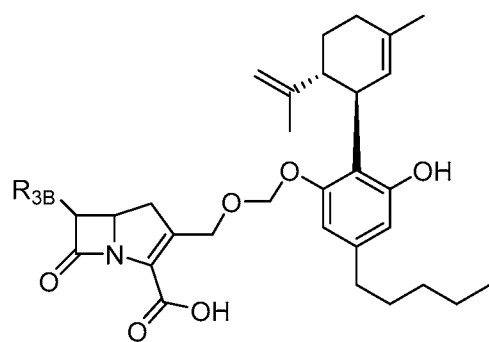
Carbacephem



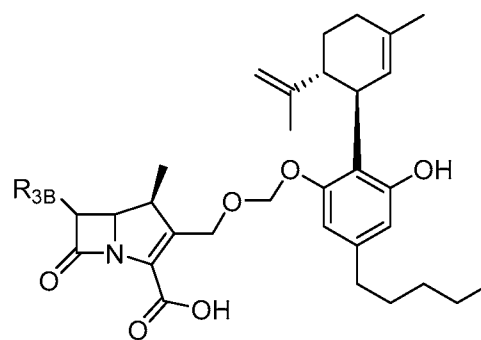
Penem



Penem

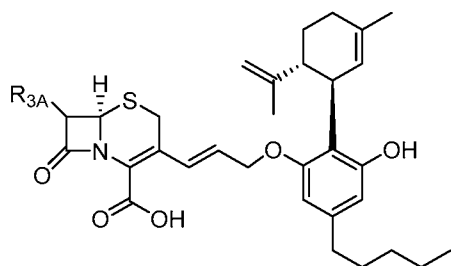


Carbapenem

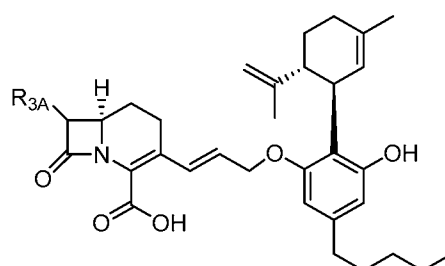


Beta-methyl Carbapenem

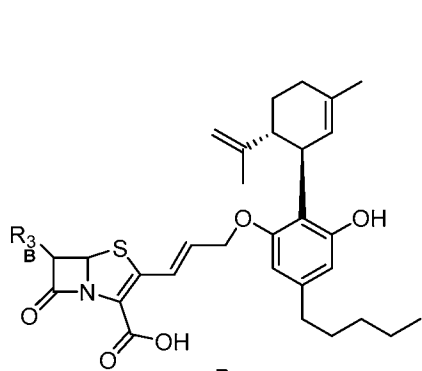
conjugate molecules with alkene linkages



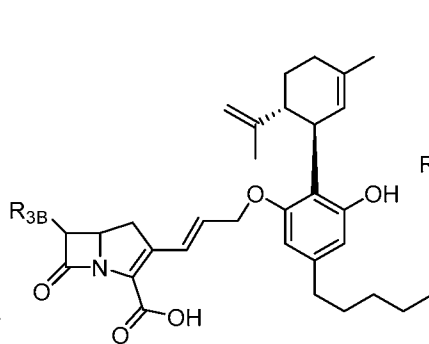
Cephem



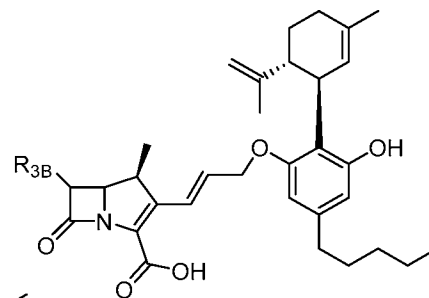
Carbacephem



Penem

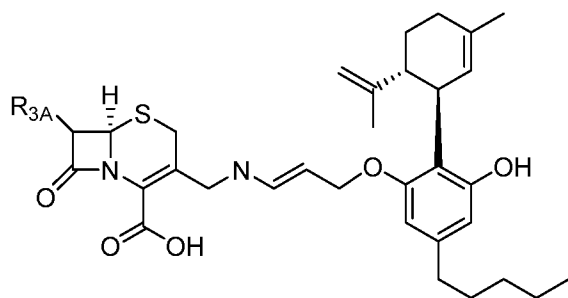


Carbapenem

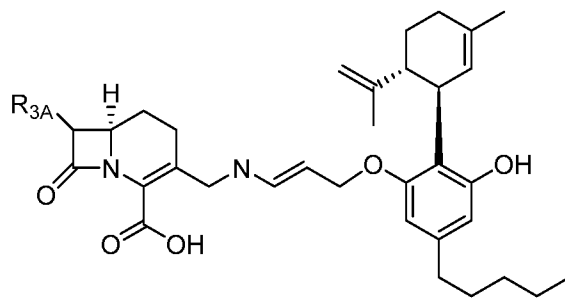


Beta-methyl Carbapenem

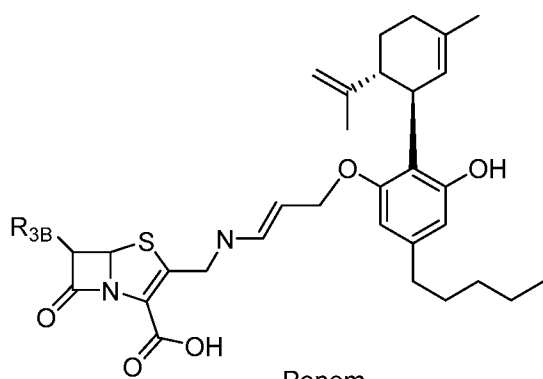
conjugate molecules with propenyl amine linkages



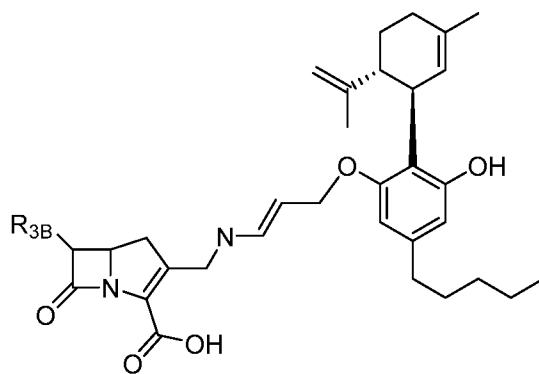
Cephem



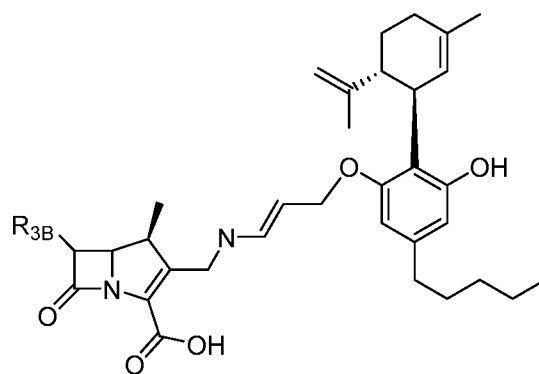
Carbacephem



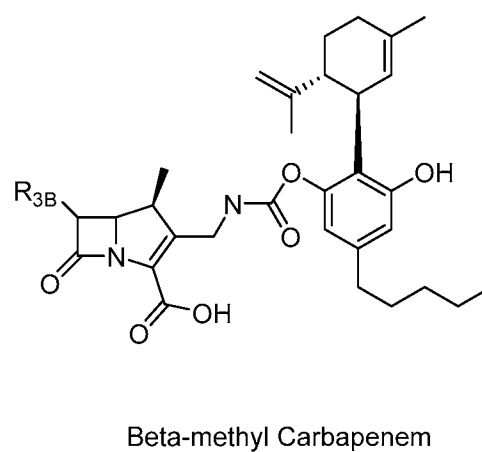
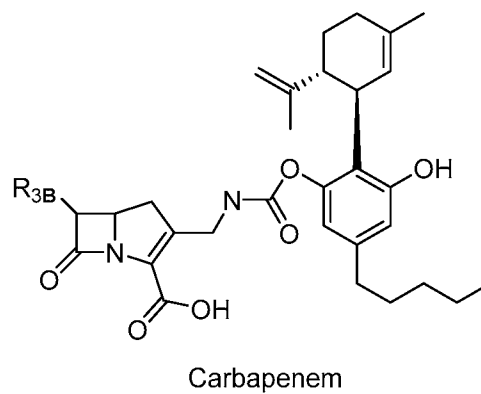
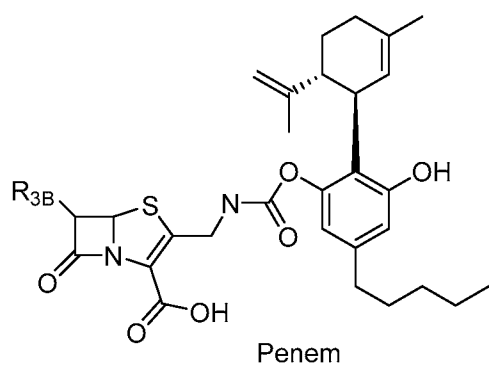
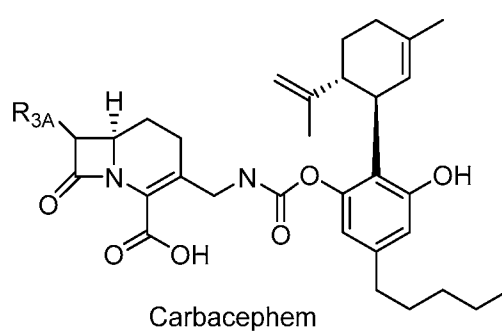
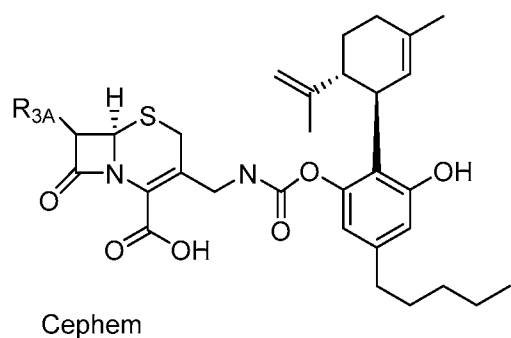
Penem



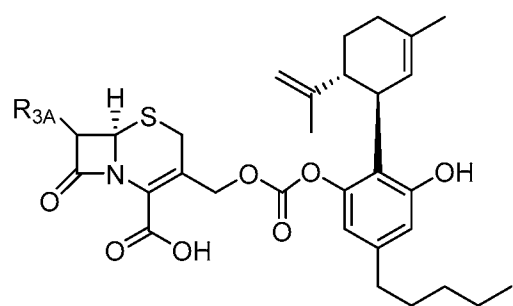
Carbapenem



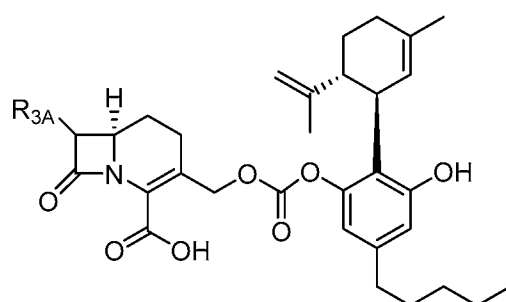
Beta-methyl Carbapenem



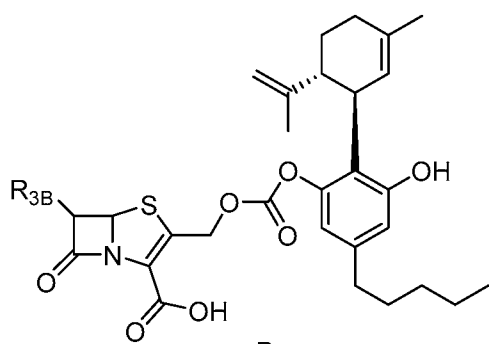
conjugate molecules with carbonate linkages



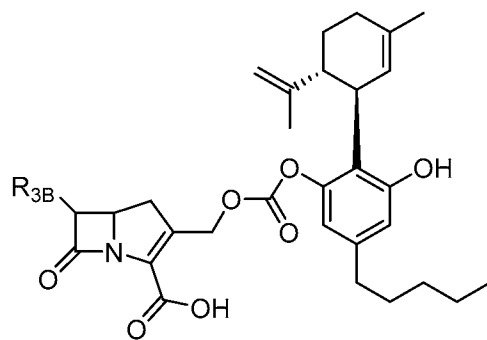
Cephem



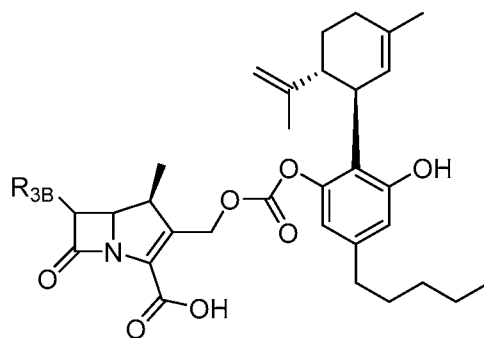
Carbacephem



Penem

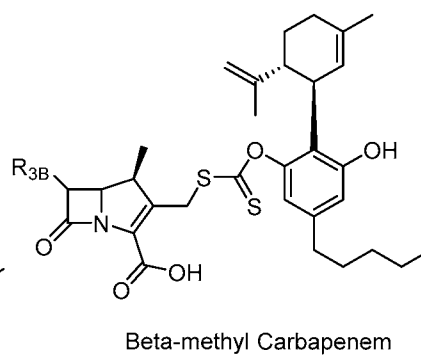
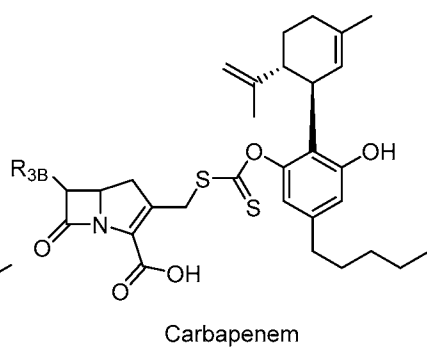
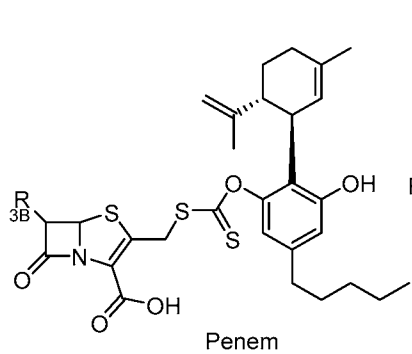
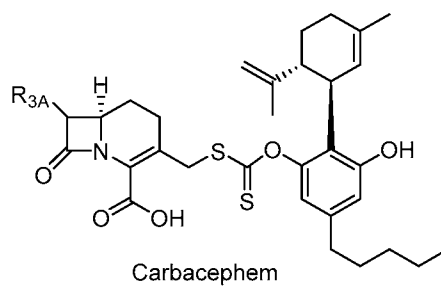
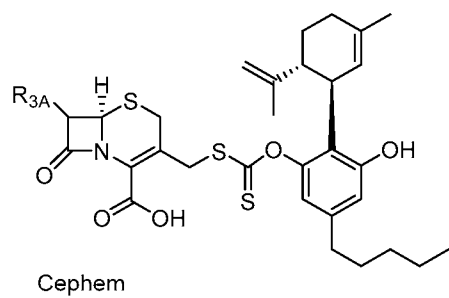


Carbapenem

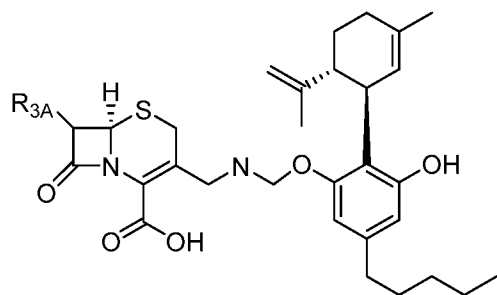


Beta-methyl Carbapenem

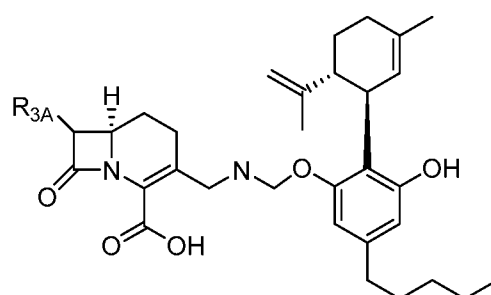
conjugate molecules with xanthate linkages



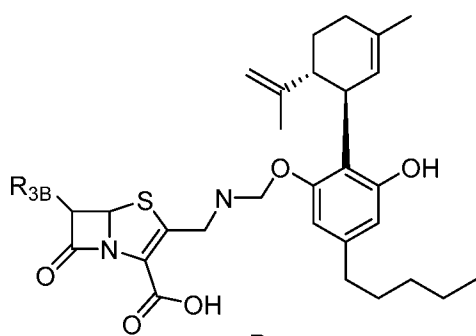
conjugate molecules with amination linkages



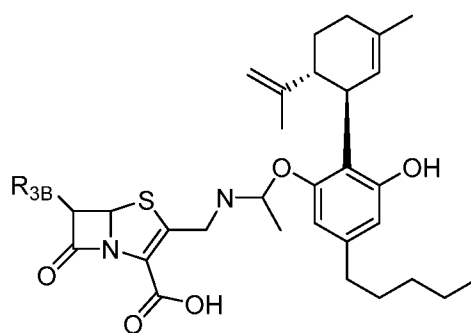
Cephem



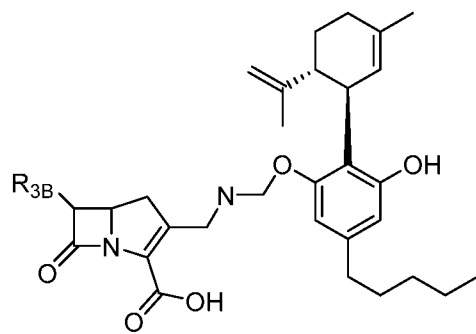
Carbacephem



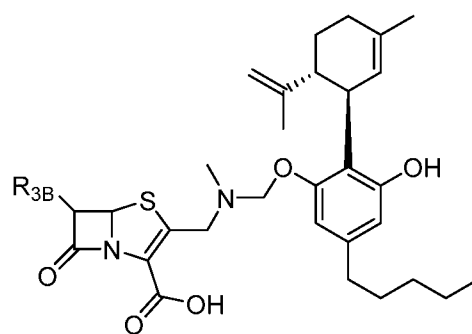
Penem



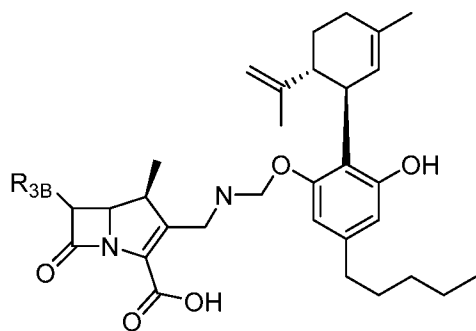
Penem



Carbapenem

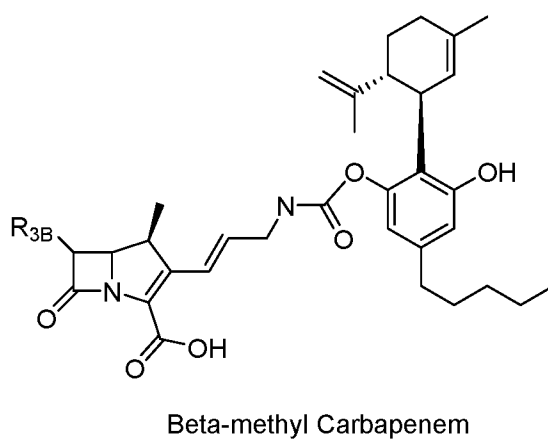
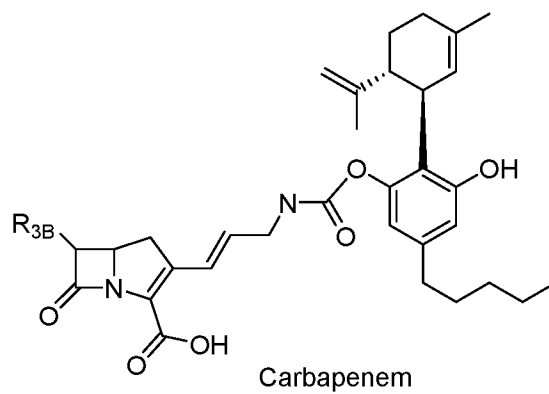
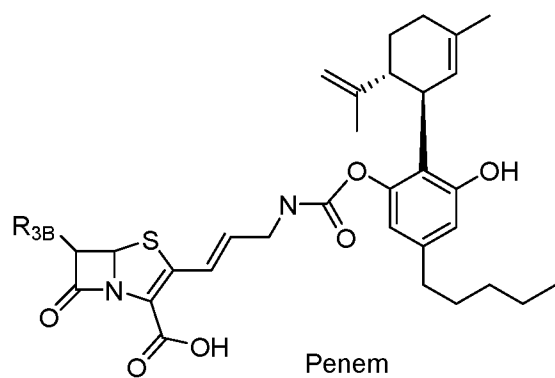
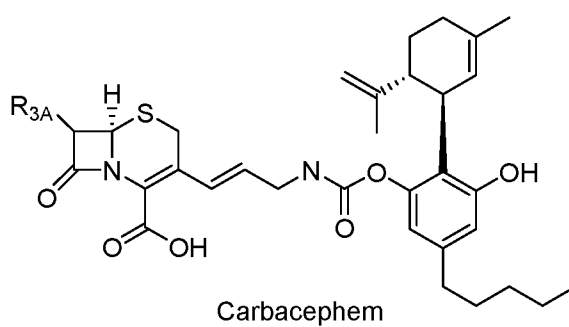
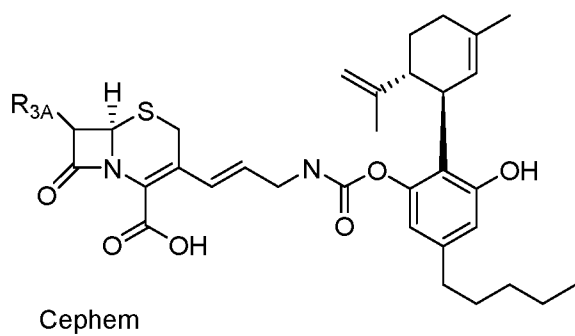


Penem

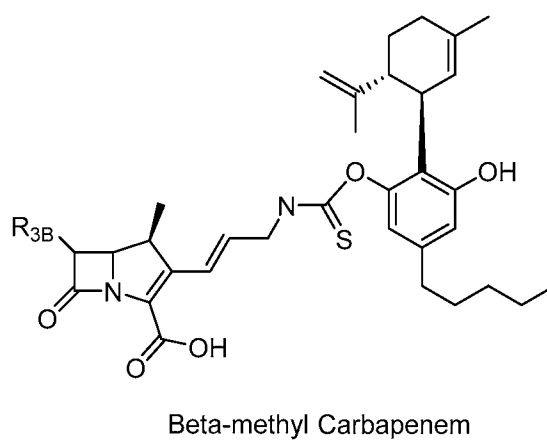
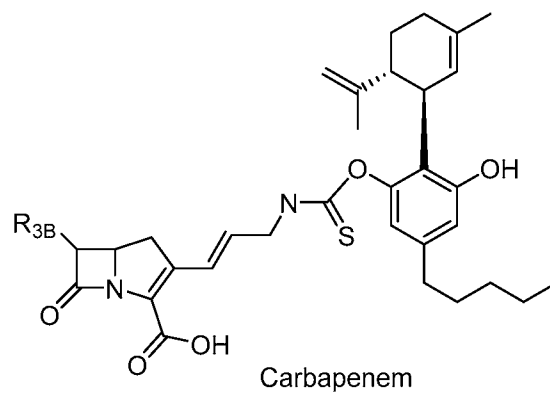
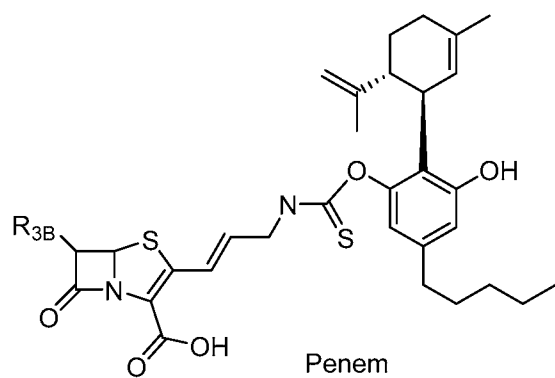
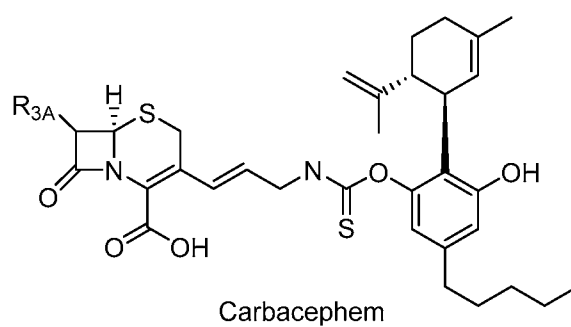
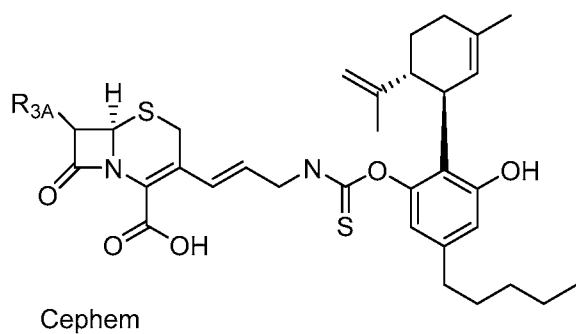


Beta-methyl Carbapenem

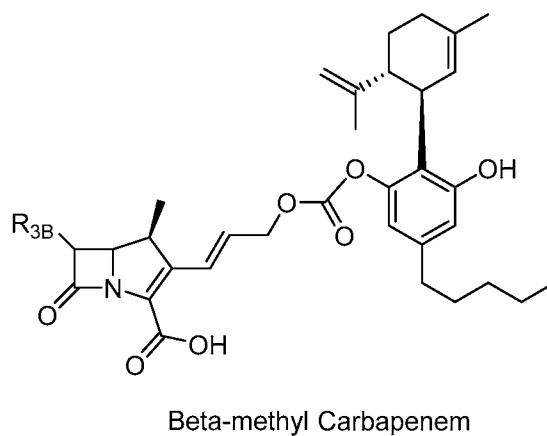
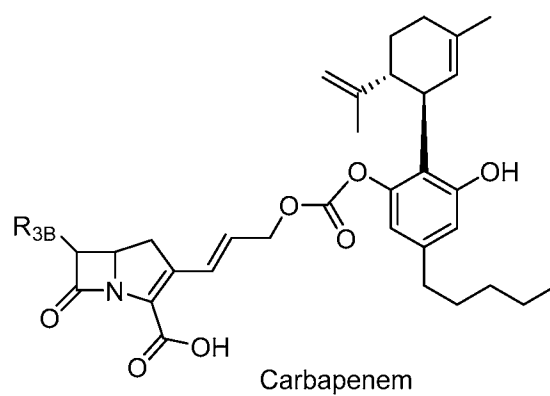
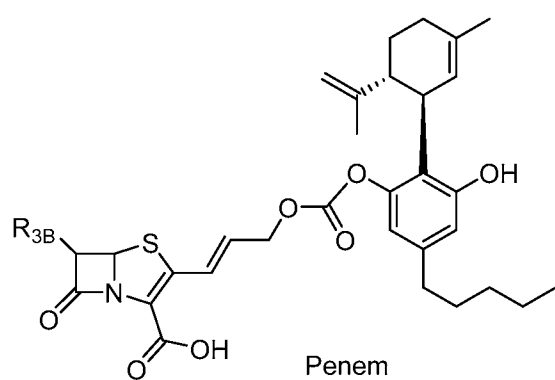
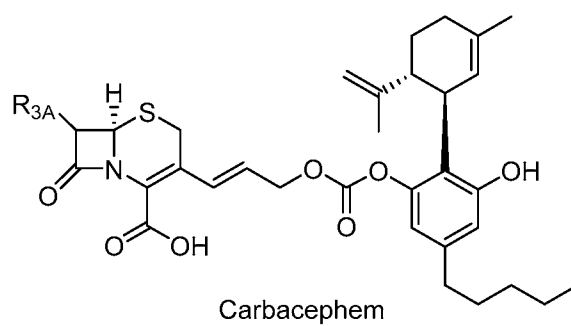
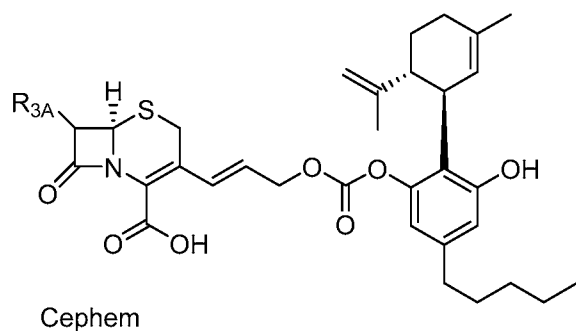
conjugate molecules with propenyl carbamate linkages



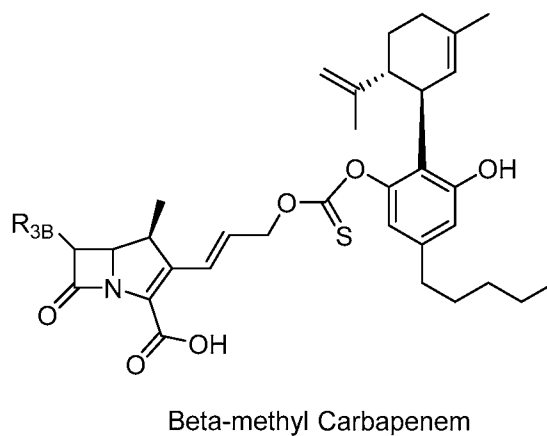
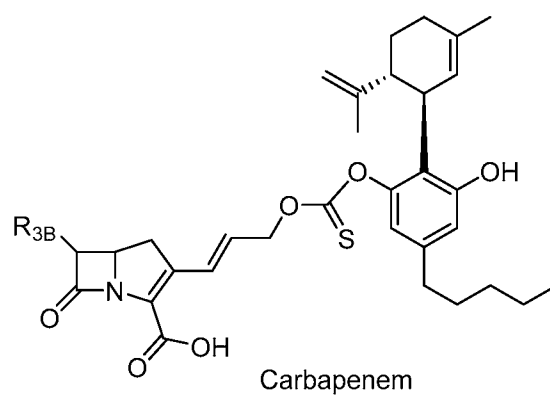
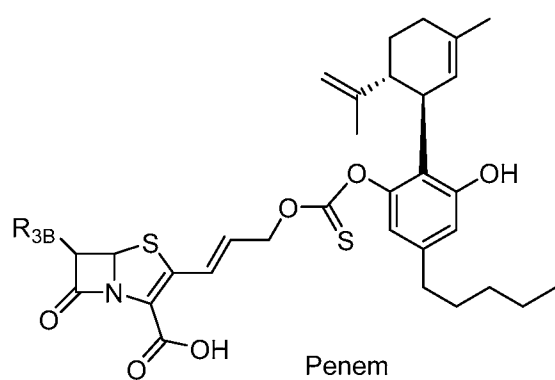
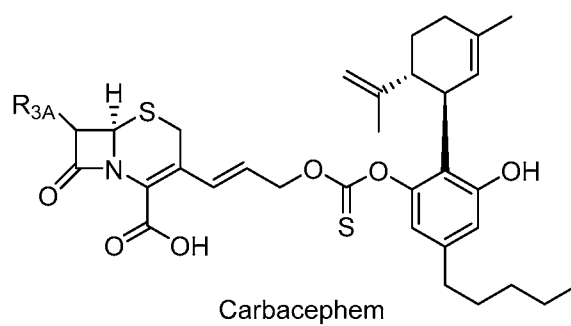
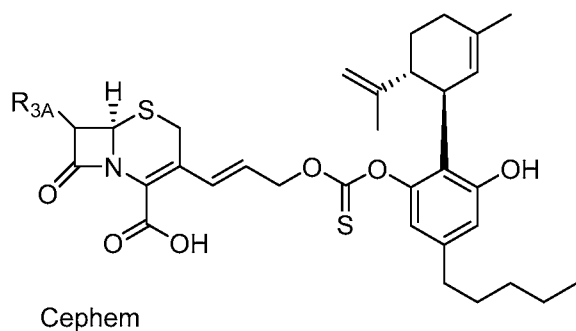
conjugate molecules with propenyl thiocarbamate linkages



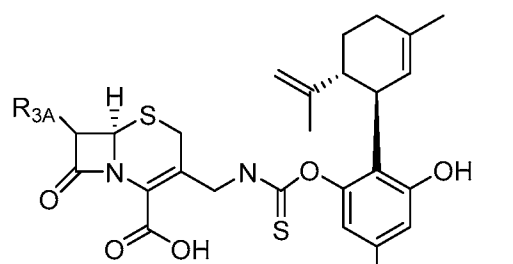
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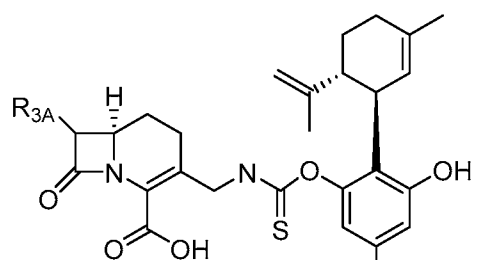
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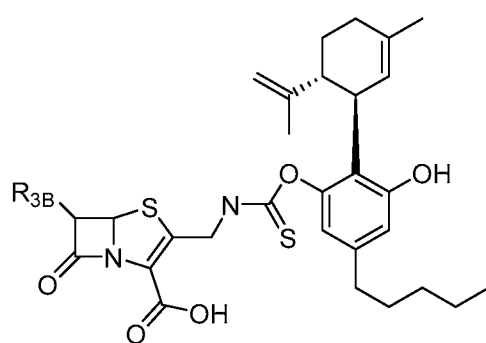
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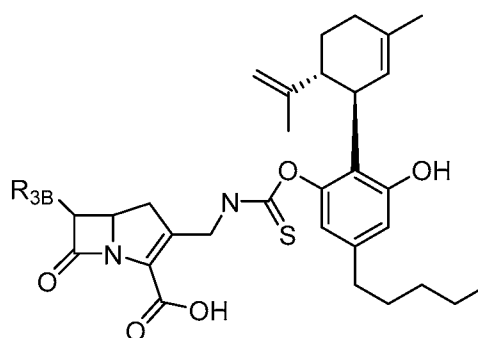
Cephem



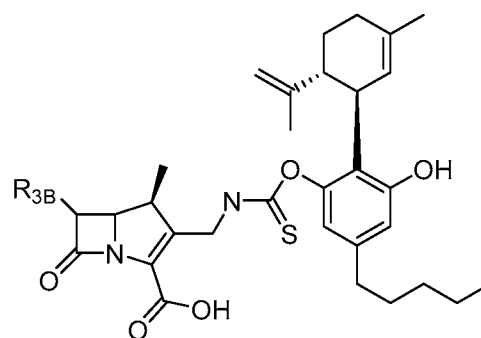
Carbacephem



Penem

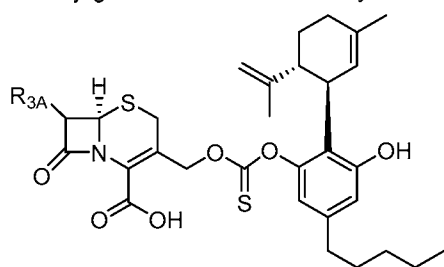


Carbapenem

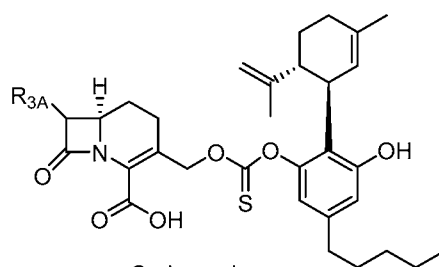


Beta-methyl Carbapenem

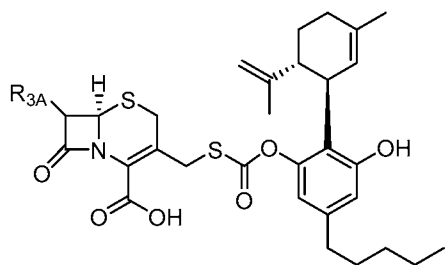
conjugate molecules with S-alkylthiocarbonate linkages



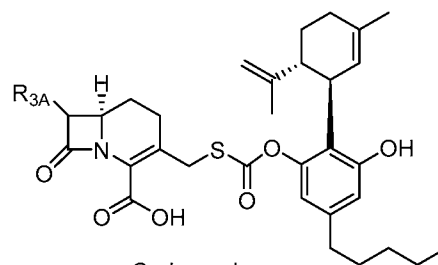
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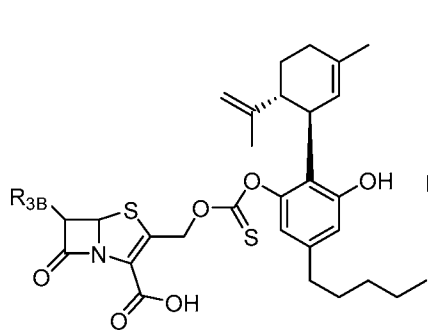
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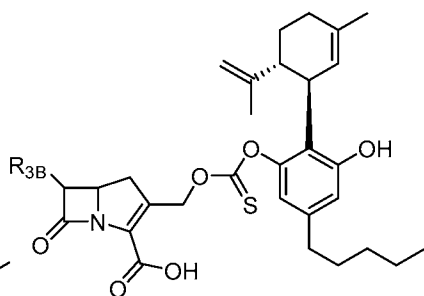
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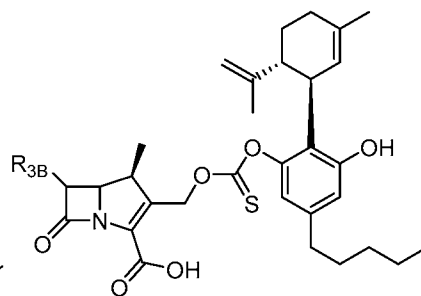
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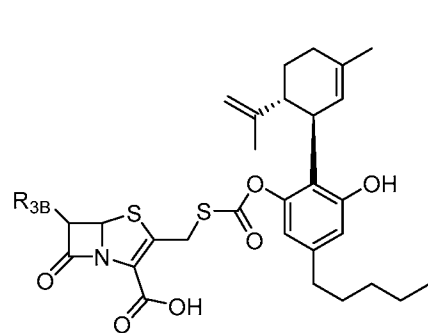
Penem



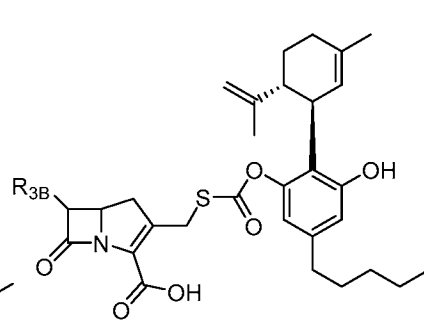
Carbapenem



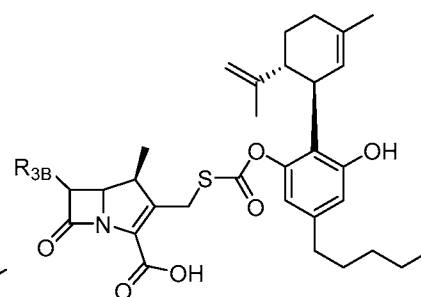
Beta-methyl Carbapenem



Penem

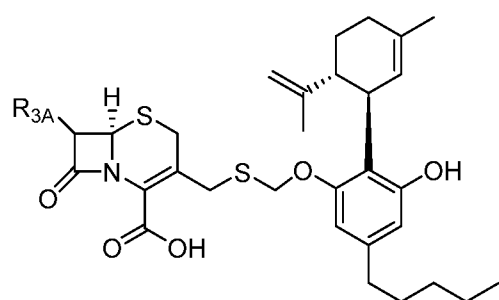


Carbapenem

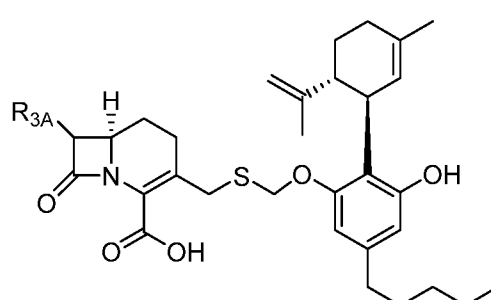


Beta-methyl Carbapenem

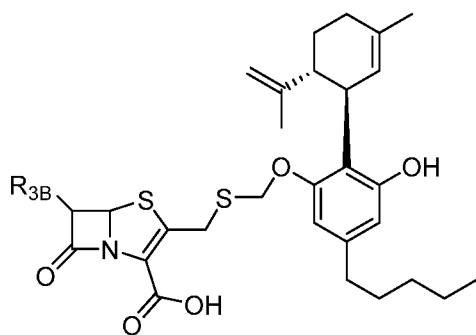
conjugate molecules with thiohemiacetal linkages



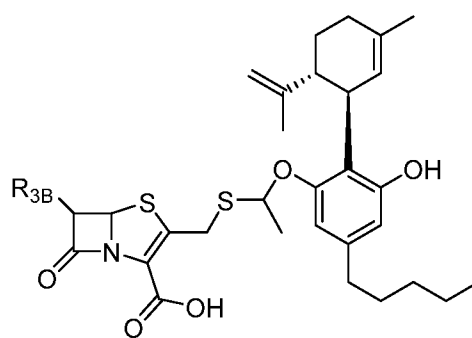
Cephem



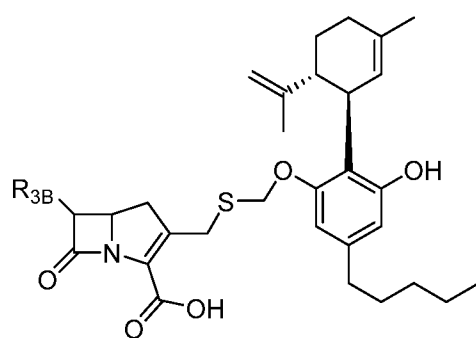
Carbacephem



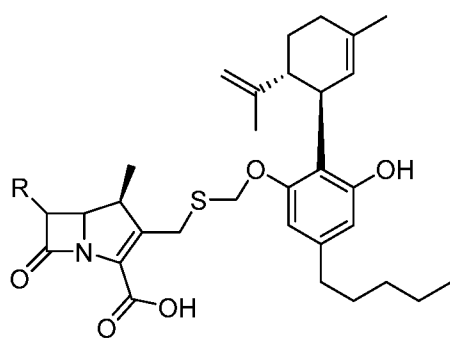
Penem



Penem

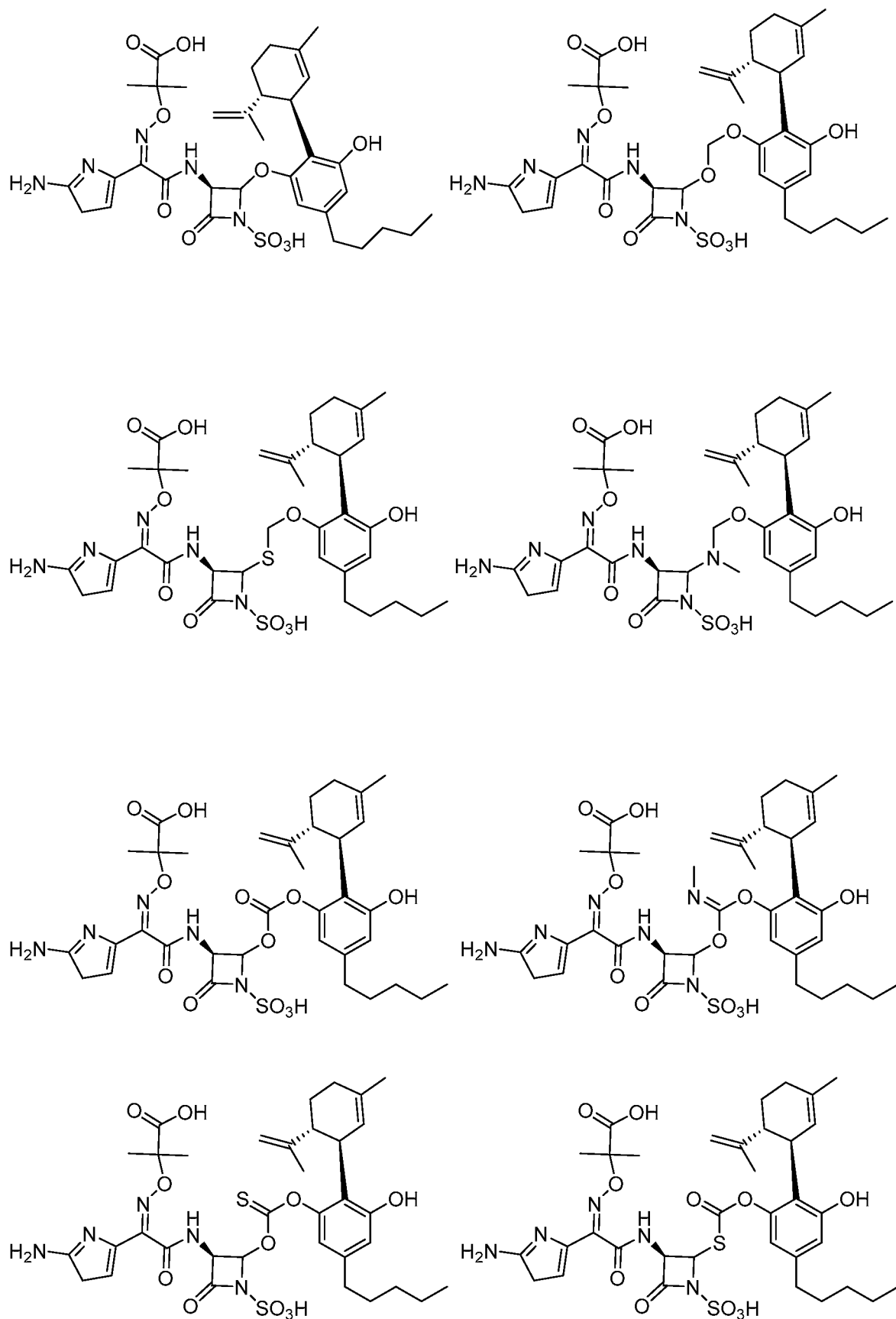


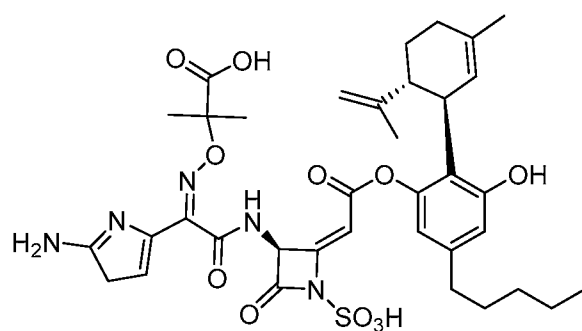
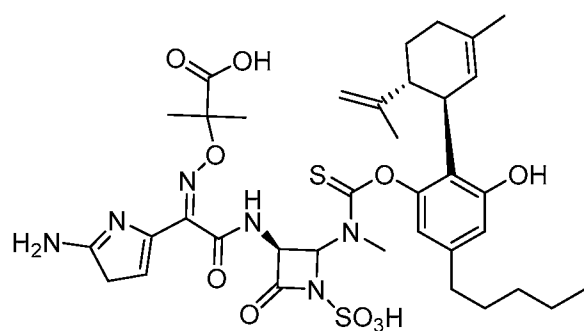
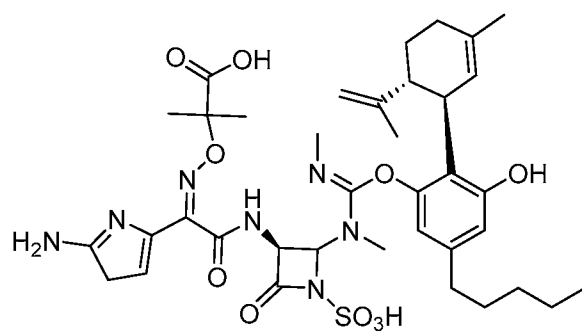
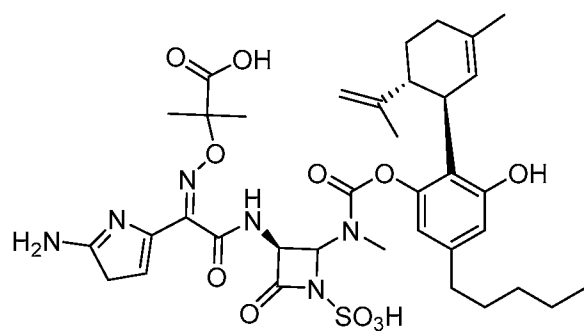
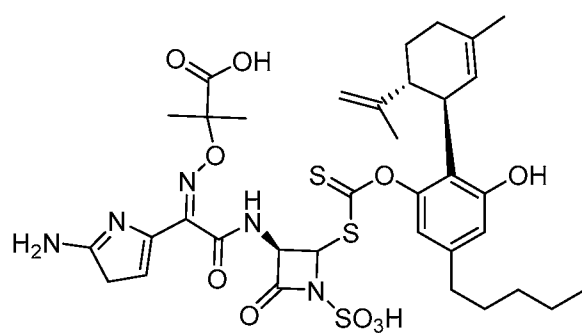
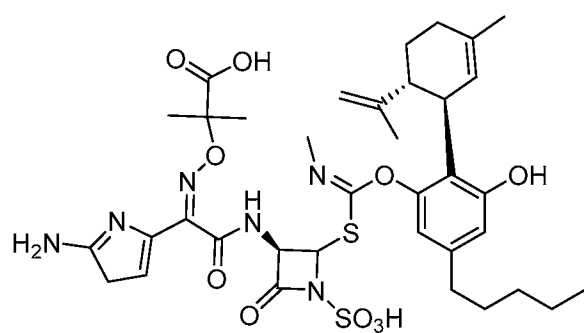
Carbapenem

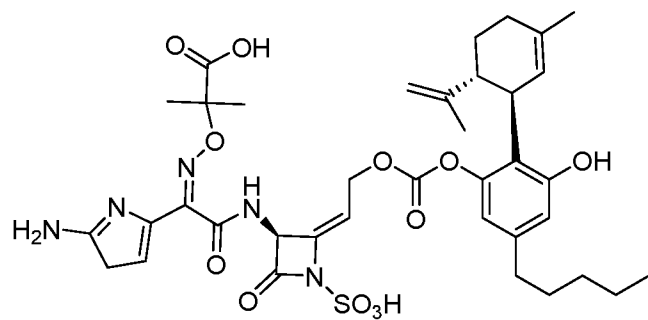
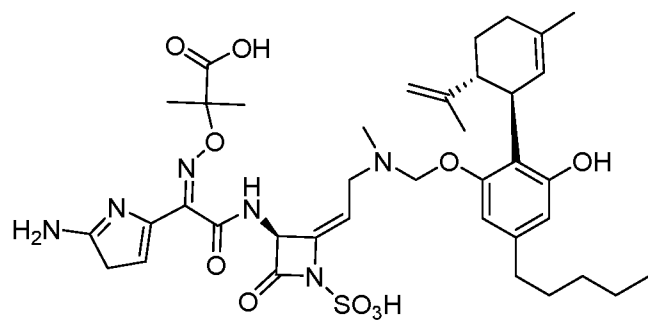
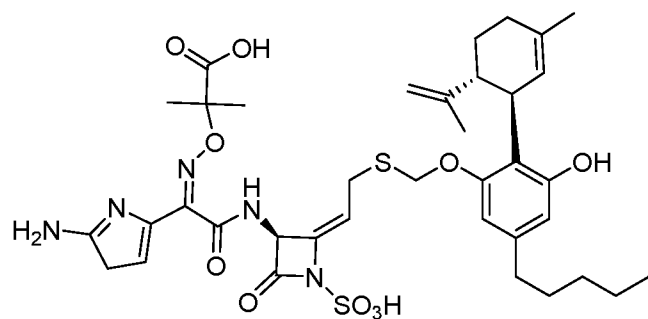
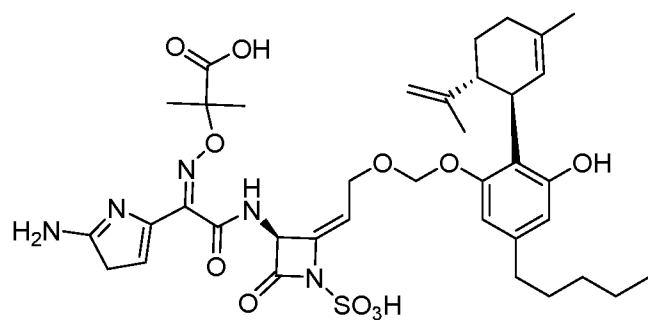


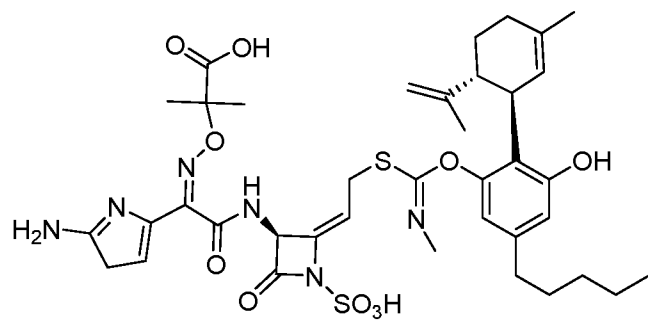
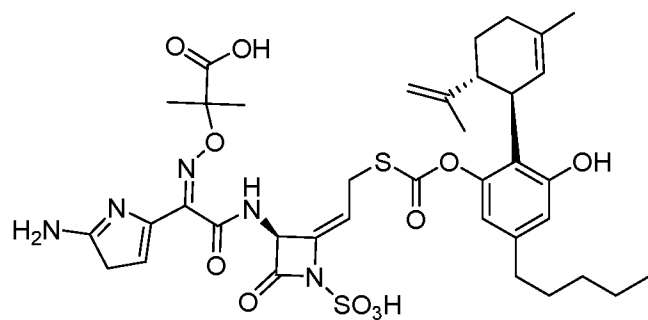
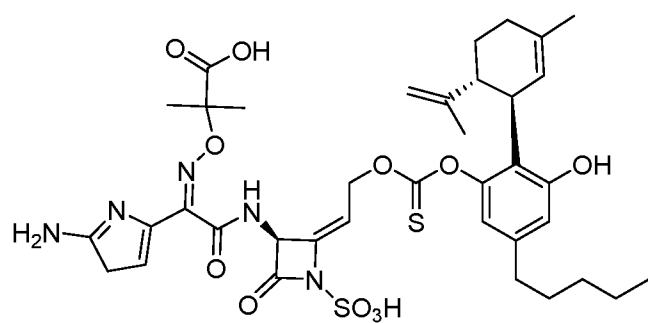
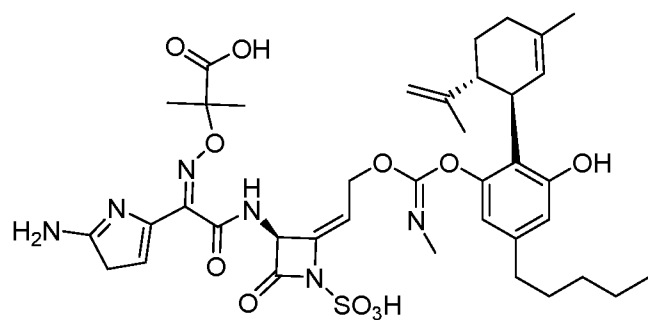
Beta-methyl Carbapenem

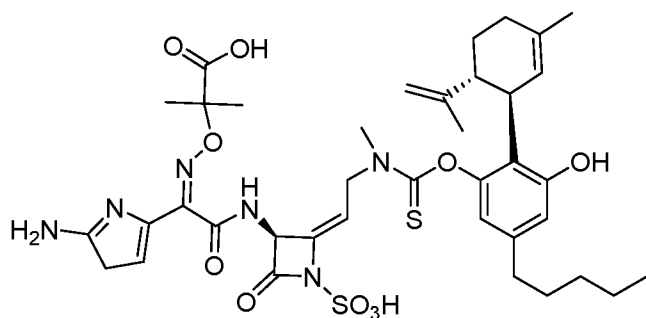
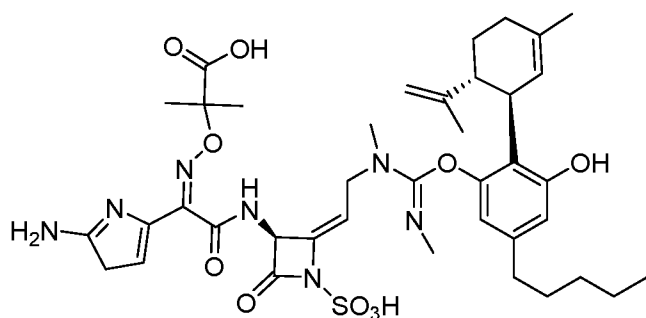
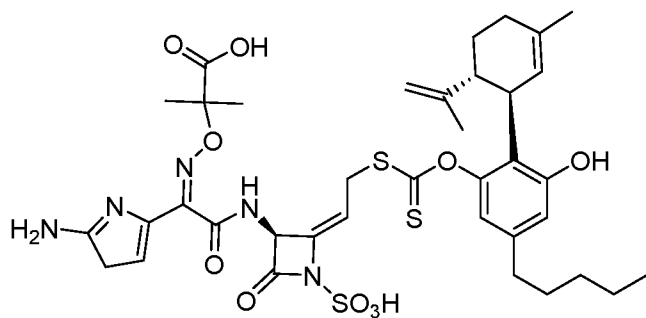
[72] Examples of conjugate molecules comprising a monobactam component are shown below. For simplicity, the cannabinoid component is a cannabidiol component covalently linked to a single aztreonam component.











Pharmaceutical Compositions, Routes of Administration, and Dosages

[73] One or more conjugate molecules, which can be the same or different, can be provided in a pharmaceutical composition together with a pharmaceutically acceptable vehicle. The “pharmaceutically acceptable vehicle” can comprise one or more substances which do not affect the biological activities of the conjugate molecules and, when administered to a patient, do not cause an adverse reaction. Excipients, such as calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, and gelatin can be included. Pharmaceutically acceptable vehicles for liquid compositions include, but are not limited to, water, saline,

polyalkylene glycols (*e.g.*, polyethylene glycol), vegetable oils, and hydrogenated naphthalenes. Controlled release, for example, can be achieved using biocompatible, biodegradable polymers of lactide or copolymers of lactide/glycolide or polyoxyethylene/polyoxypropylene.

[74] Methods of preparing pharmaceutical compositions are well known. Pharmaceutical compositions can be prepared as solids, semi-solids, or liquid forms, such as tablets, capsules, powders, granules, ointments, solutions, suspensions, emulsions, suppositories, injections, inhalants, gels, microspheres, aerosols, and mists. Liquid pharmaceutical compositions can be lyophilized. Lyophilized compositions can be provided in a kit with a suitable liquid, typically water for injection (WFI) for use in reconstituting the composition.

[75] Typical administration routes include, but are not limited to, oral, topical, transdermal, inhalation, parenteral, sublingual, buccal, rectal, vaginal, and intranasal.

[76] The dose of a pharmaceutical composition can be based on the doses typically used for the particular antibiotic(s) which provide the β -lactam antibiotic component(s) of a conjugate molecule. These doses are well known in the art.

[77] In some embodiments, one or more conjugate molecules are co-administered with an inhibitor of β -lactamase (*e.g.*, clavulanic acid, sulbactam, tazobactam). “Co-administration” includes administration together with, before, or after administration of a β -lactamase inhibitor.

Therapeutic Methods

[78] The disclosed conjugate molecules have a variety of therapeutic uses depending on which β -lactam antibiotic component(s) are included in a conjugate molecule. “Treat” as used in this disclosure means reducing or inhibiting the progression of one or more symptoms of the disorder or disease for which the conjugate molecule is administered, such as inflammation or pain.

[79] For example, in addition to treating bacterial infections (including chronic lung infections in cystic fibrosis; *e.g.*, Kirkby *et al.*, Core Evidence 6, 59-66, 2011), β -lactam antibiotics have been proposed for the treatment of type I diabetes (*e.g.*, US 2014/0234282, US 2007/0060561); treatment of cancer (*e.g.*, US 2006/0160787); as neuroprotective compounds (*e.g.*, US 2007/0238717); and as proteasome inhibitors, for treatment of, *e.g.*, Alzheimer's disease, cachexia and muscle-wasting diseases, allergies, and inflammation (in connection with rheumatoid arthritis, scleroderma, rheumatic fever, inflammatory bowel disease, myasthenia gravis, multiple sclerosis, Guillain-Barre syndrome, conjunctiva of the eye, systemic lupus erythematosus, encephalitis, Adult Respiratory Distress Syndrome, psoriasis, emphysema, and muscular dystrophy (*e.g.*, US 2007/0060561).

[80] The disclosed conjugate molecules can be used to treat these and other disorders in the same way the β -lactam antibiotic components of the molecules are used, and these methods are well known. An advantage of conjugate molecules, however, is that the cannabinoid can be delivered directly to the site of infection where it can provide further therapeutic benefits. The therapeutic benefits and potential benefits of cannabinoids are well known. For example, see Dzierzanowski, Cancers 11, 129-41, 2019 (oncology and palliative care); Urits *et al.*, Pain Ther. 8, 41-51, 2019 (pain); Hillen *et al.*, Ther. Adv. Drug Safety 10, 1-23 2019 (neuropsychiatric symptoms in dementia)

[81] In addition, *C. sativa* extracts have microbicidal activity *in vitro* against gram-positive bacteria (*e.g.*, *Bacillus subtilis*, *Bacillus pumilus*, *Staphylococcus aureus*, *Micrococcus flavus*, *Clostridium sporogens*, *Enterococcus faecium*, and *Streptococcus salivarius*); gram-negative bacteria (*e.g.*, *Proteus vulgaris*, *Bordetella bronchioseptica*, *Pectobacterium carotovorum*, and *Pseudomonas savastoni*); and fungi (*e.g.*, *Aspergillus niger*). See Elphick, Gene 399, 65-71, 2007; Wasim *et al.*, J. Pharm. Sci. 8, 29-38, 1995; Nissen *et al.*, Fitoterapia 81, 413-19, 2010; and Hernandez-Cervantes *et al.*, Neuroimmunomodulation 24, 183-99, 2017. See also Appendino *et al.*, J. Nat. Prod. 71, 1427-30, 2008.

EXAMPLES

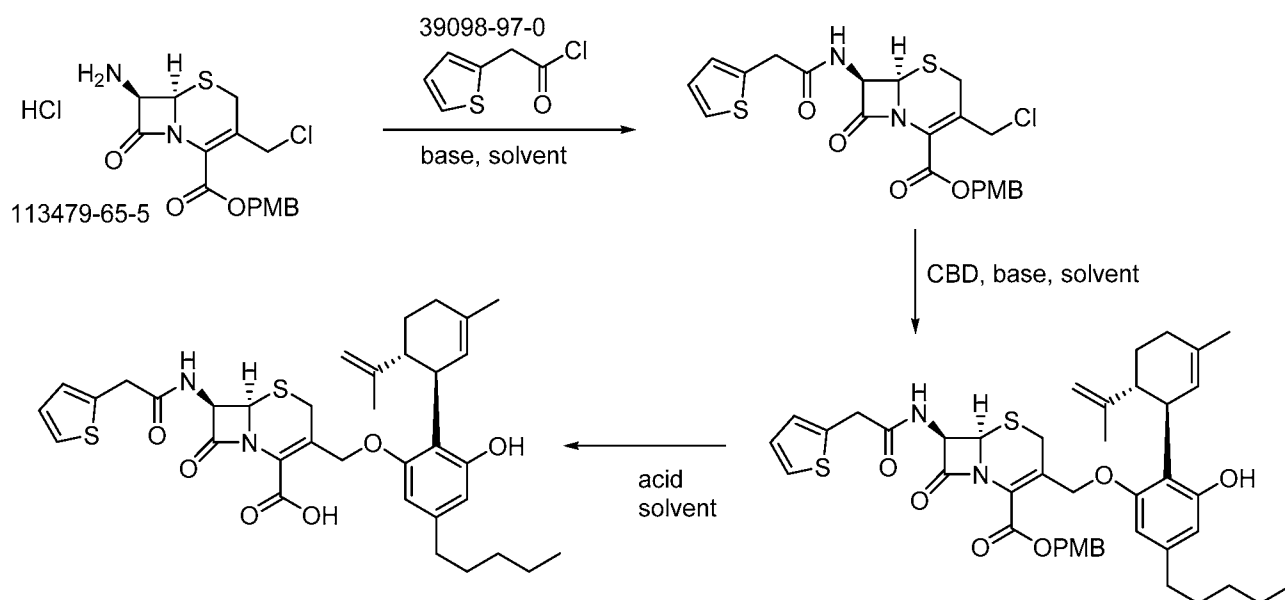
[82] The following synthetic methods are general. They can be used to make these examples or related conjugate molecules using alternative building blocks, intermediates, or reagents. Alternative reagent systems and conditions to achieve desired transformations can be used.

Alternative protecting group strategies can be used. Standard purification techniques can be used at any stage of a synthesis.

Example 1. Ether-linked conjugate molecules

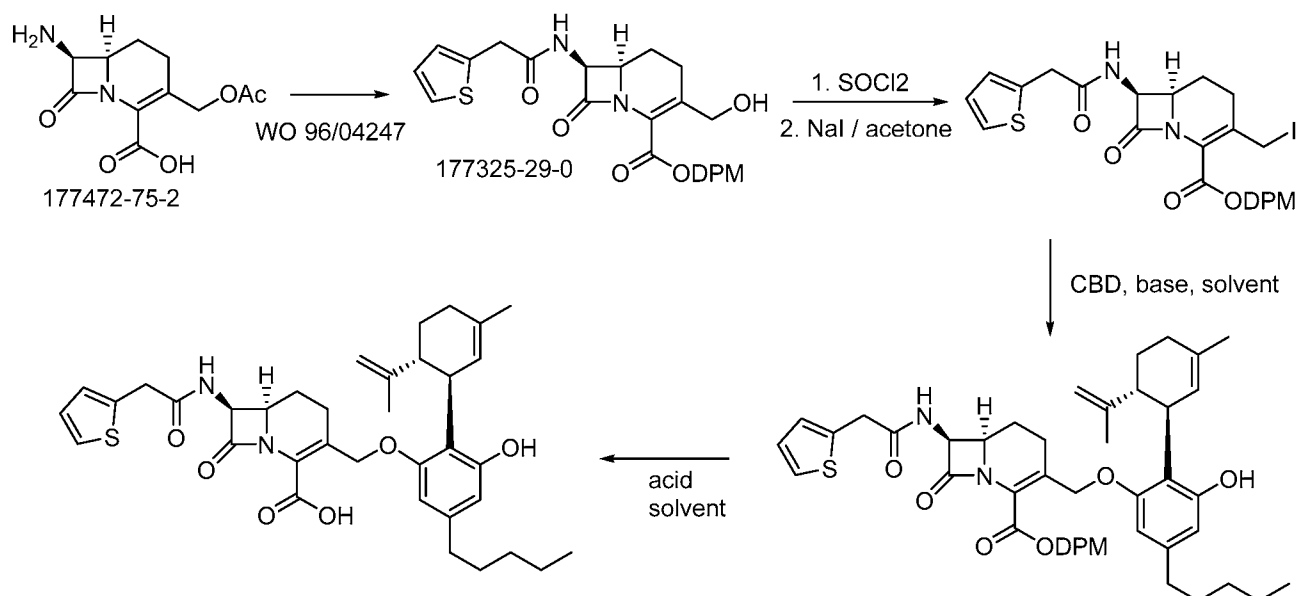
Cephem Conjugate Molecules

[83] Cephem ether linked conjugate molecules are synthesized according to the following Scheme. The CAS numbers for the two key building blocks is shown. Reaction conditions follow standard conditions for amine acylation in the first step to attach the cephem side chain, for alkylation of a phenol group of CBD in the second step with optional use of a catalyst or enhancer such as NaI, followed by standard removal of the p-methoxybenzyl protecting group in the third step to furnish the product.



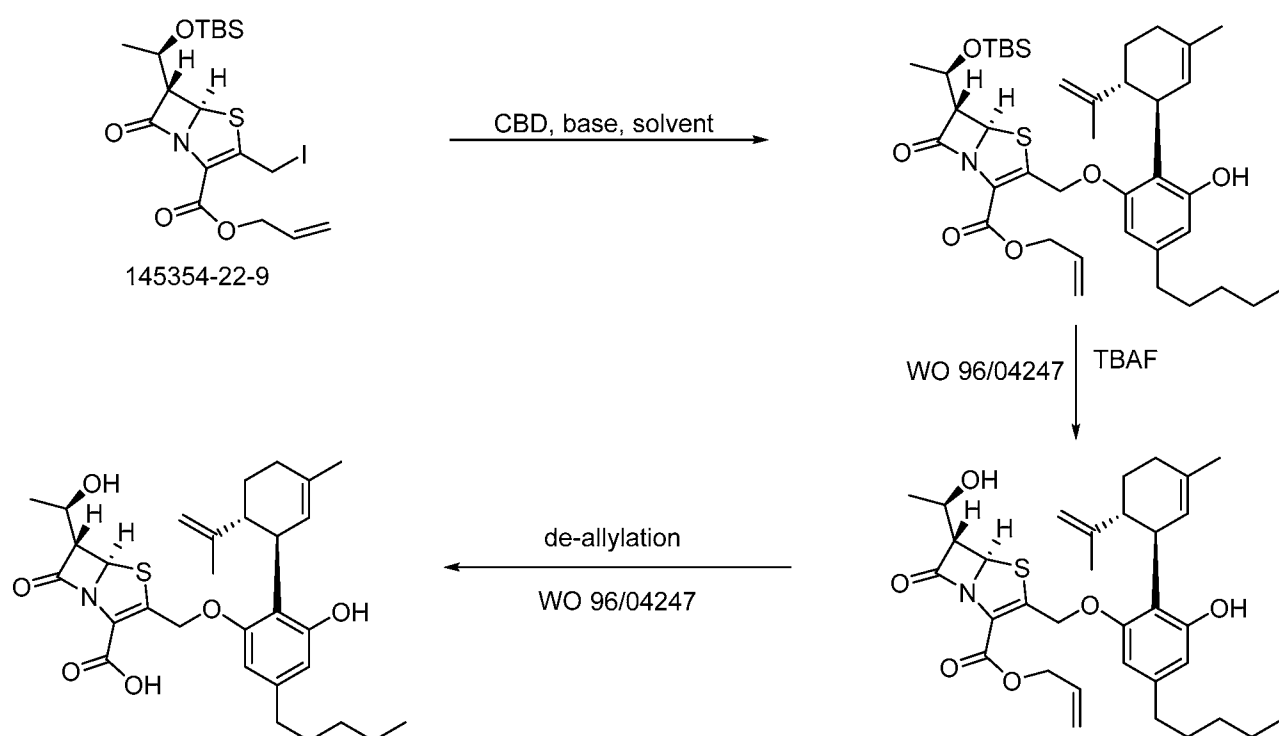
Carbacephem Conjugate Molecules

[84] Carbacephem ether linked conjugate molecules are synthesized according to the following Scheme. The general starting material [177472-75-2] was reported in racemic form as [54296-34-3] (Journal of the American Chemical Society (1974), 96(24), 7584) and is elaborated to the iodide intermediate after installing a side chain of choice using a previously reported process (WO 96/04247). Alkylation of CBD with the iodide followed by deprotection, both steps under standard conditions, provides the desired product.



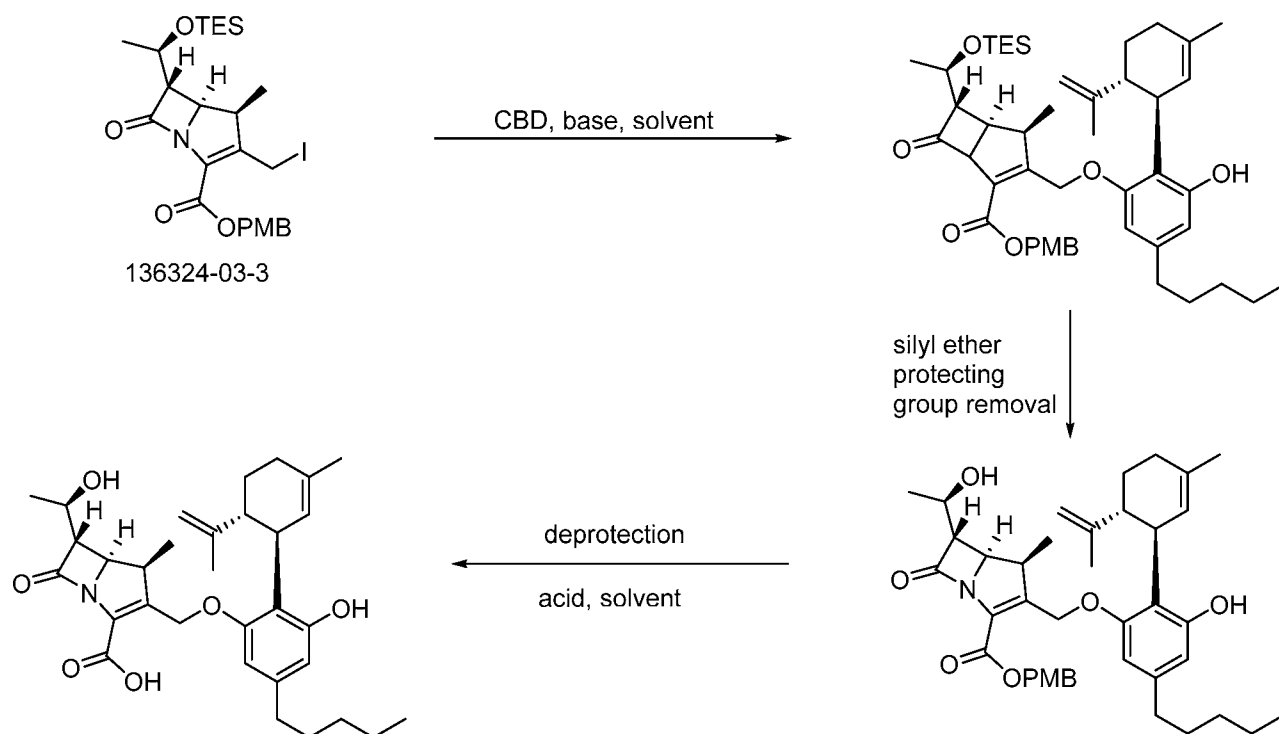
Penem Conjugate Molecules

[85] Penem ether linked conjugate molecules are synthesized according to the following Scheme. The starting material [145354-22-9], prepared as reported (Journal of Organic Chemistry, 58(1), 272-4; 1993), is reacted with CBD under standard alkylating conditions. The silyl ether TBS protecting group is then removed followed by deallylation under known conditions to give the desired product.



Carbapenem Conjugate Molecules

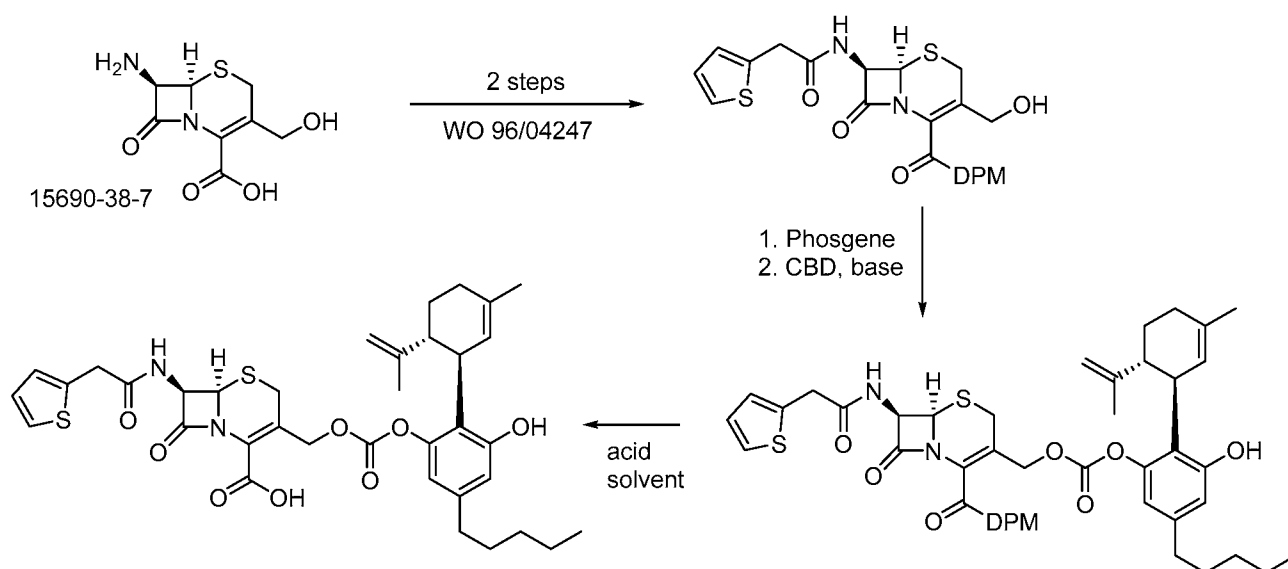
[86] Carbapenem ether linked conjugate molecules are synthesized according to the following Scheme. The starting material [136324-03-3] is reacted with CBD under standard alkylating conditions. The silyl ether TES protecting group is then removed followed by removal of the p-methoxybenzyl ester protecting group under known conditions to give the desired product.



Example 2. Carbonate-linked conjugate molecules

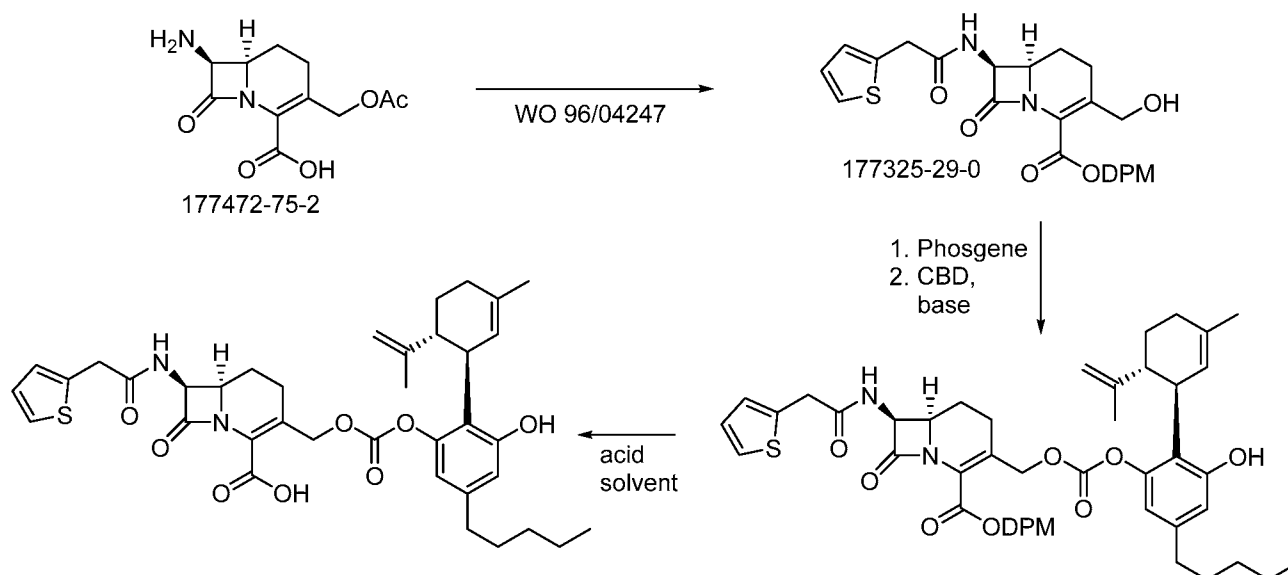
Cephem Conjugate Molecules

[87] Cephem carbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material is acylated with a side chain of choice and then the acid is protected as described previously (WO 96/04247). The resulting alcohol is then treated with phosgene and the adduct reacted with CBD in the presence of base to form the carbonate-linked intermediate, which is then deprotected with acid to deliver the desired product.



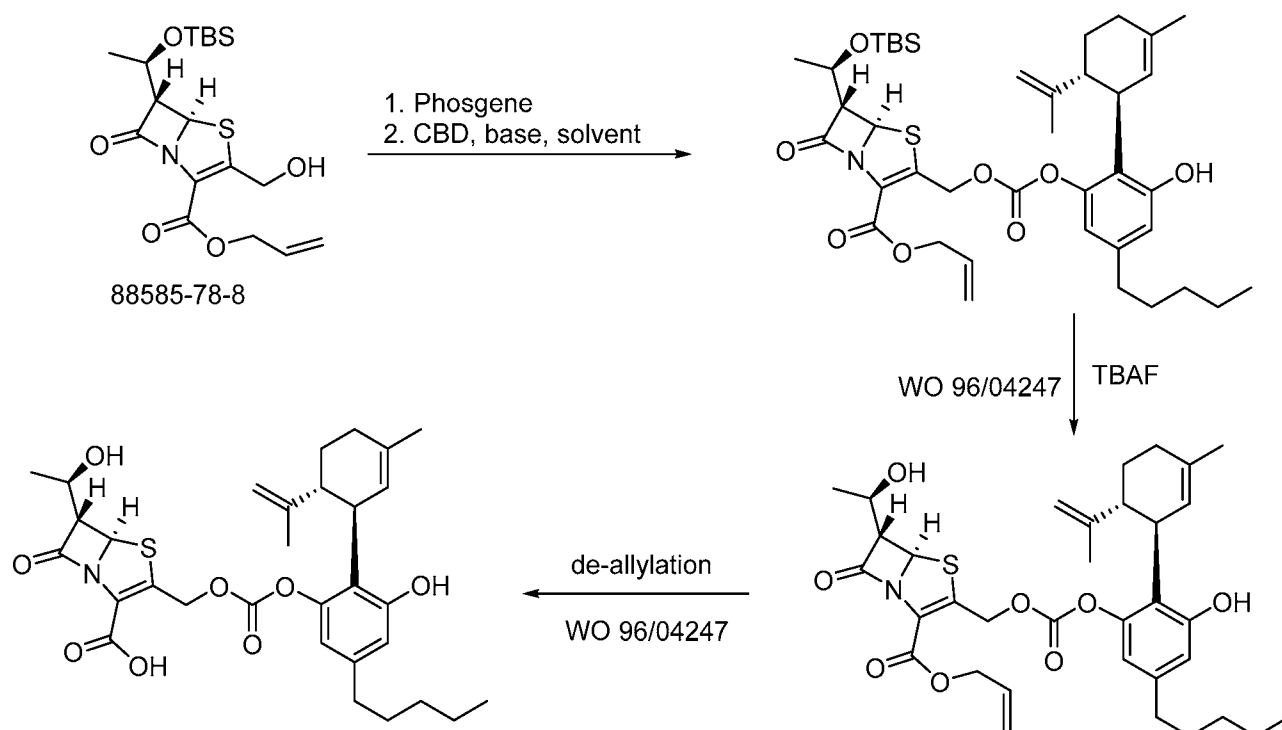
Carbacephem Conjugate Molecules

[88] Carbacephem carbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material is acylated with a side chain of choice and then the acid is protected as described previously (WO 96/04247). The resulting alcohol is then treated with phosgene and the adduct reacted with CBD in the presence of base to form the carbonate-linked intermediate, which is then deprotected with acid to deliver the desired product.



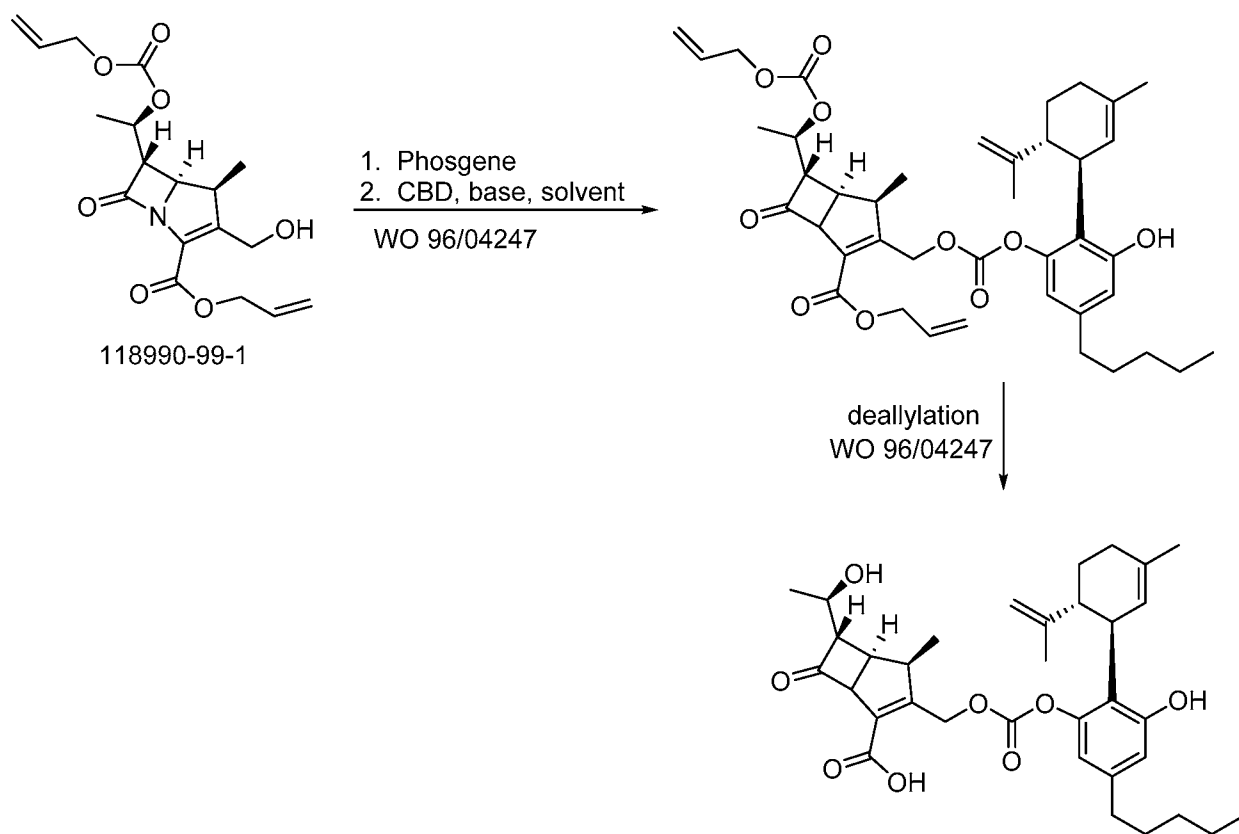
Penem Conjugate Molecules

[89] Penem carbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material [88585-78-8], prepared as reported (U.S. patent 4,631,150), is reacted with phosgene and the intermediate reacted with CBD under standard basic conditions. The silyl ether TBS protecting group is then removed followed by deallylation under known conditions to give the desired product.



Carbapenem Conjugate Molecules

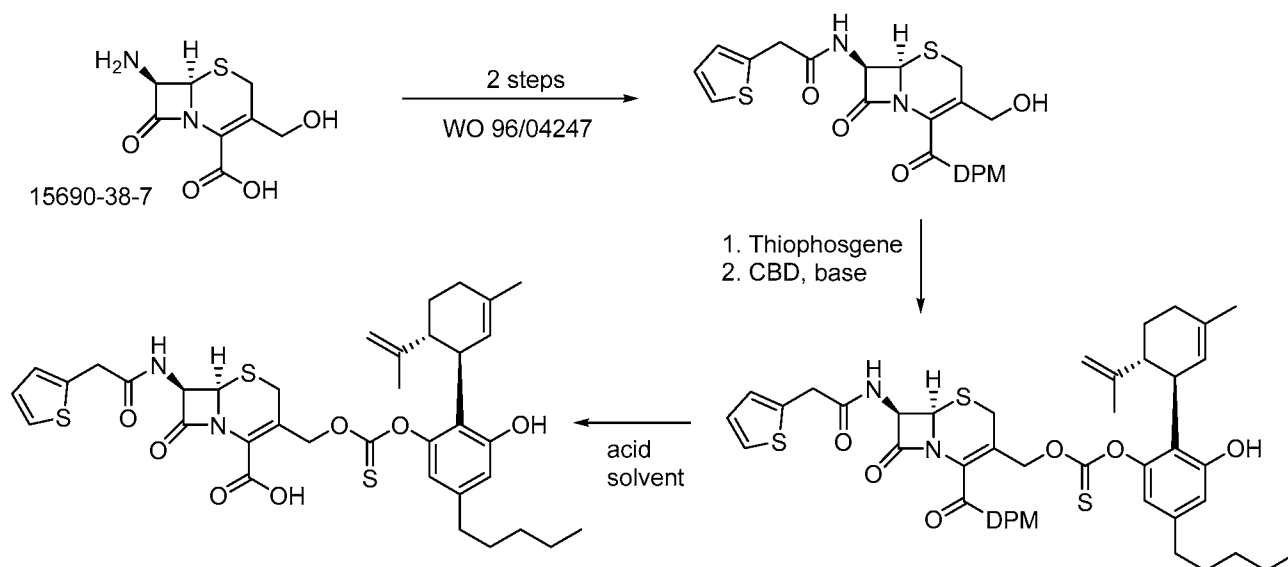
[90] Carbapenem carbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material [118990-99-1], prepared as reported (Journal of Antibiotics (1988), 41(6), 780-7), is reacted with phosgene and the intermediate reacted with CBD under standard basic conditions. Deallylation under known conditions gives the desired product.



Example 3. Thiocarbonate-linked conjugate molecules

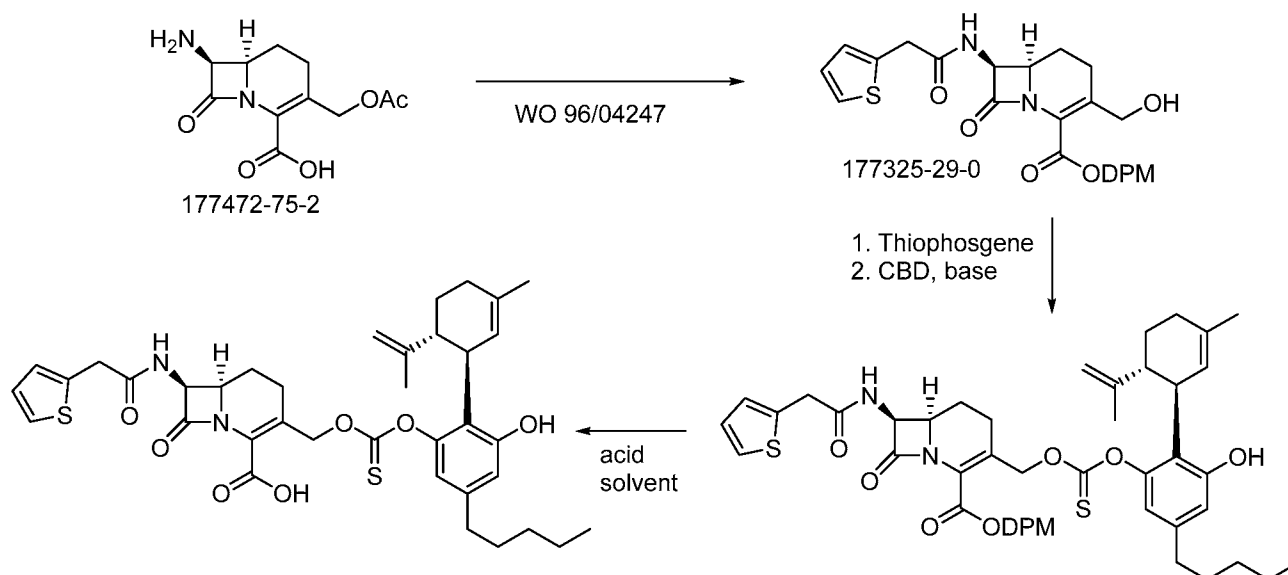
Cephem Conjugate Molecules

[91] Cephem thiocarbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material is acylated with a side chain of choice and then the acid is protected as described previously (WO 96/04247). The resulting alcohol is then treated with thiophosgene and the adduct reacted with CBD in the presence of base to form the thiocarbonate product which is then deprotected with acid to deliver the desired product.



Carbacephem Conjugate Molecules

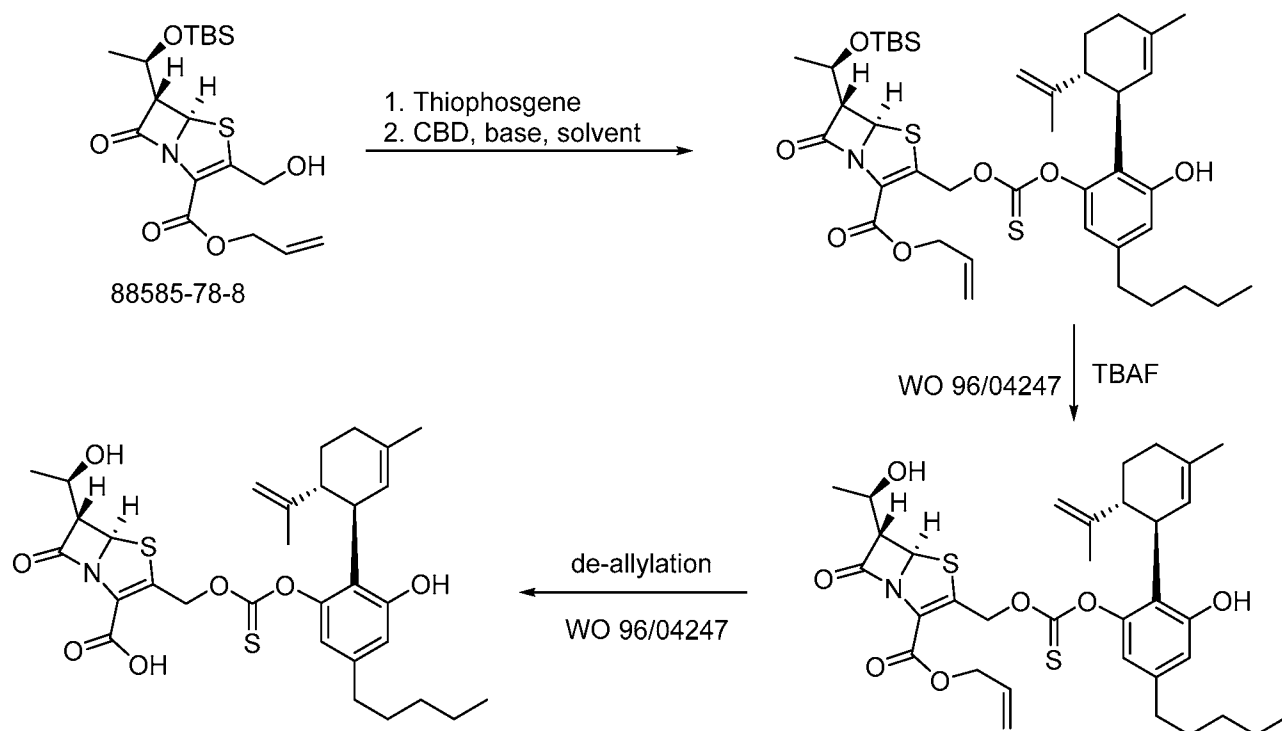
[92] Carbacephem thiocarbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material is acylated with a side chain of choice and then the acid is protected as described previously (WO 96/04247). The resulting alcohol is then treated with thiophosgene and the adduct reacted with CBD in the presence of base to form the thiocarbonate product which is then deprotected with acid to deliver the desired product.



Penem Conjugate Molecules

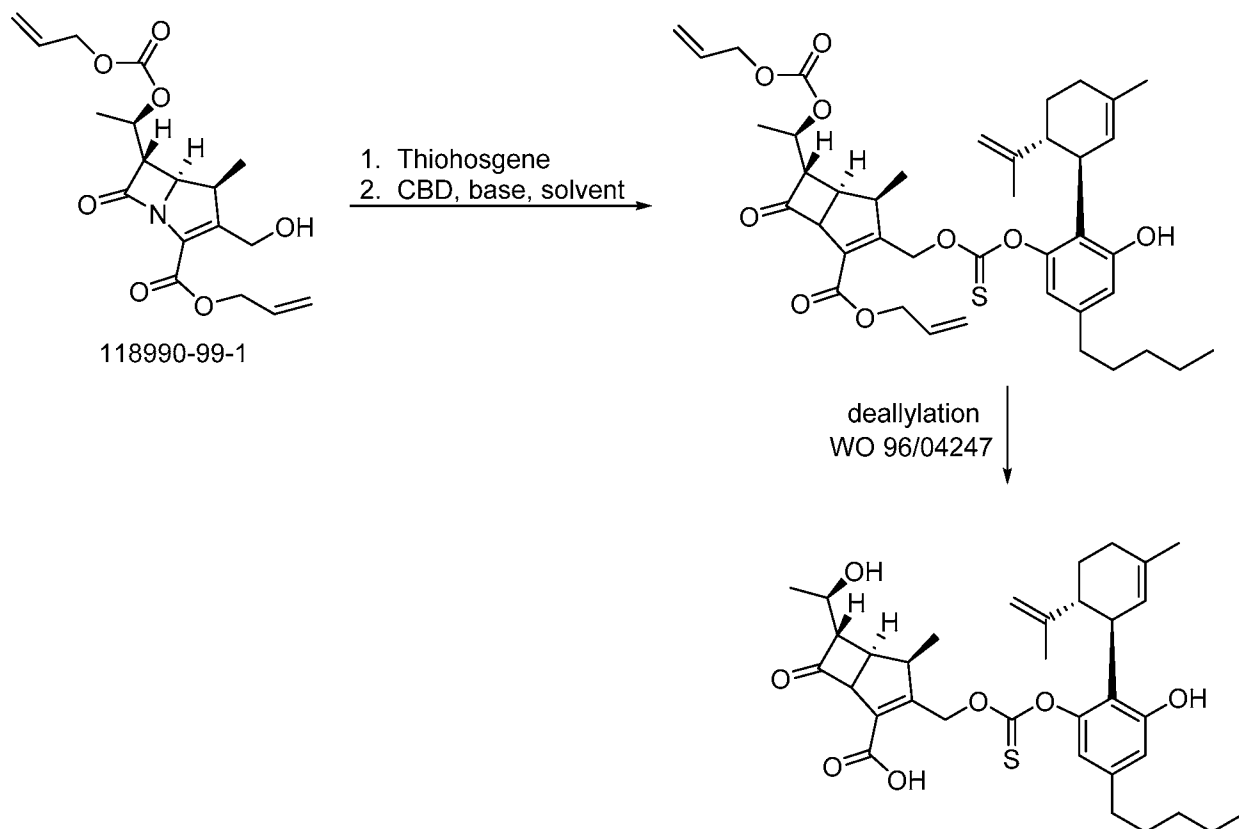
[93] Penem thiocarbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material [88585-78-8], prepared as reported (U.S. patent 4,631,150), is reacted with thiophosgene and the intermediate reacted with CBD under standard

basic conditions. The silyl ether TBS protecting group is then removed followed by deallylation under known conditions to give the desired product.



Carbapenem Conjugate Molecules

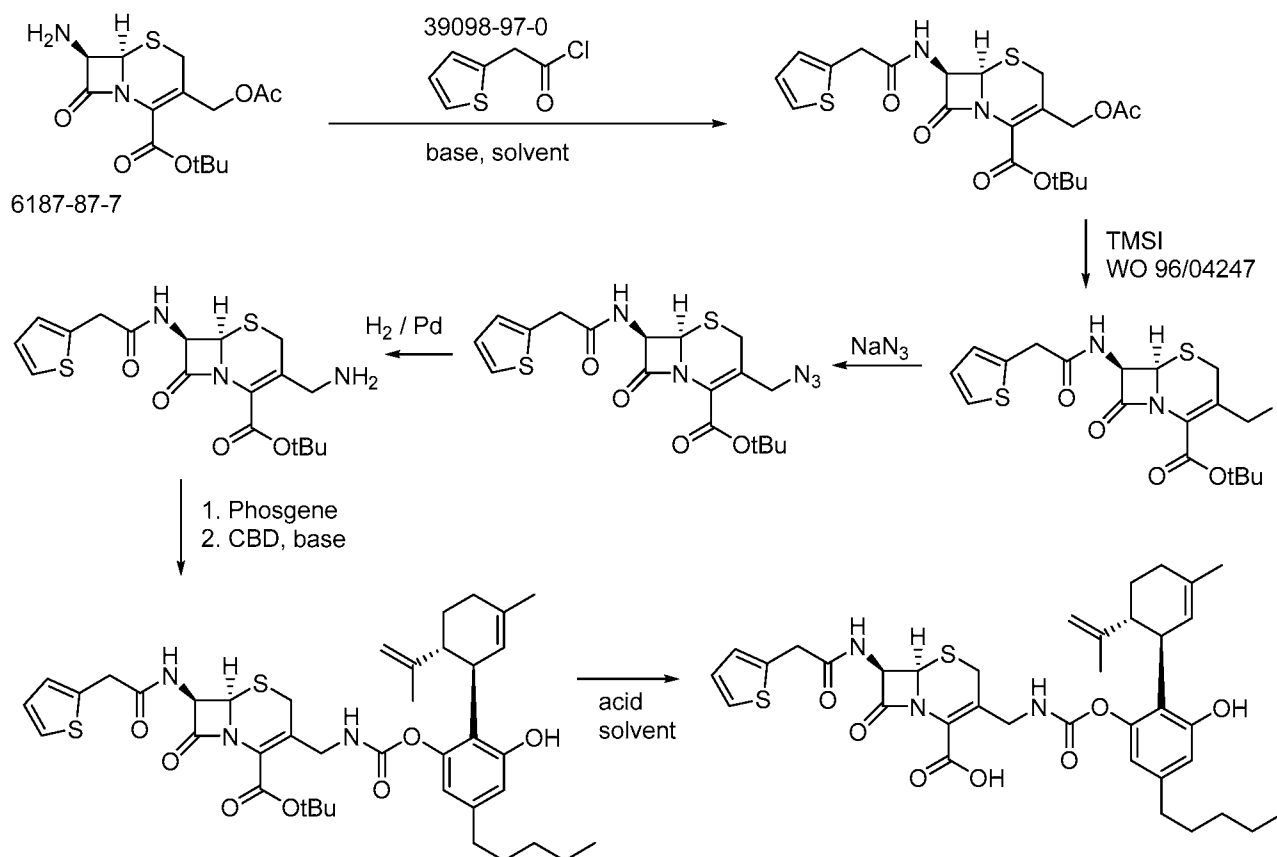
[94] Carbapenem thiocarbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material [118990-99-1], prepared as reported (Journal of Antibiotics (1988), 41(6), 780-7), is reacted with thiophosgene and the intermediate reacted with CBD under standard basic conditions. Deallylation under known conditions gives the desired product.



Example 4. Carbamate-linked conjugate molecules

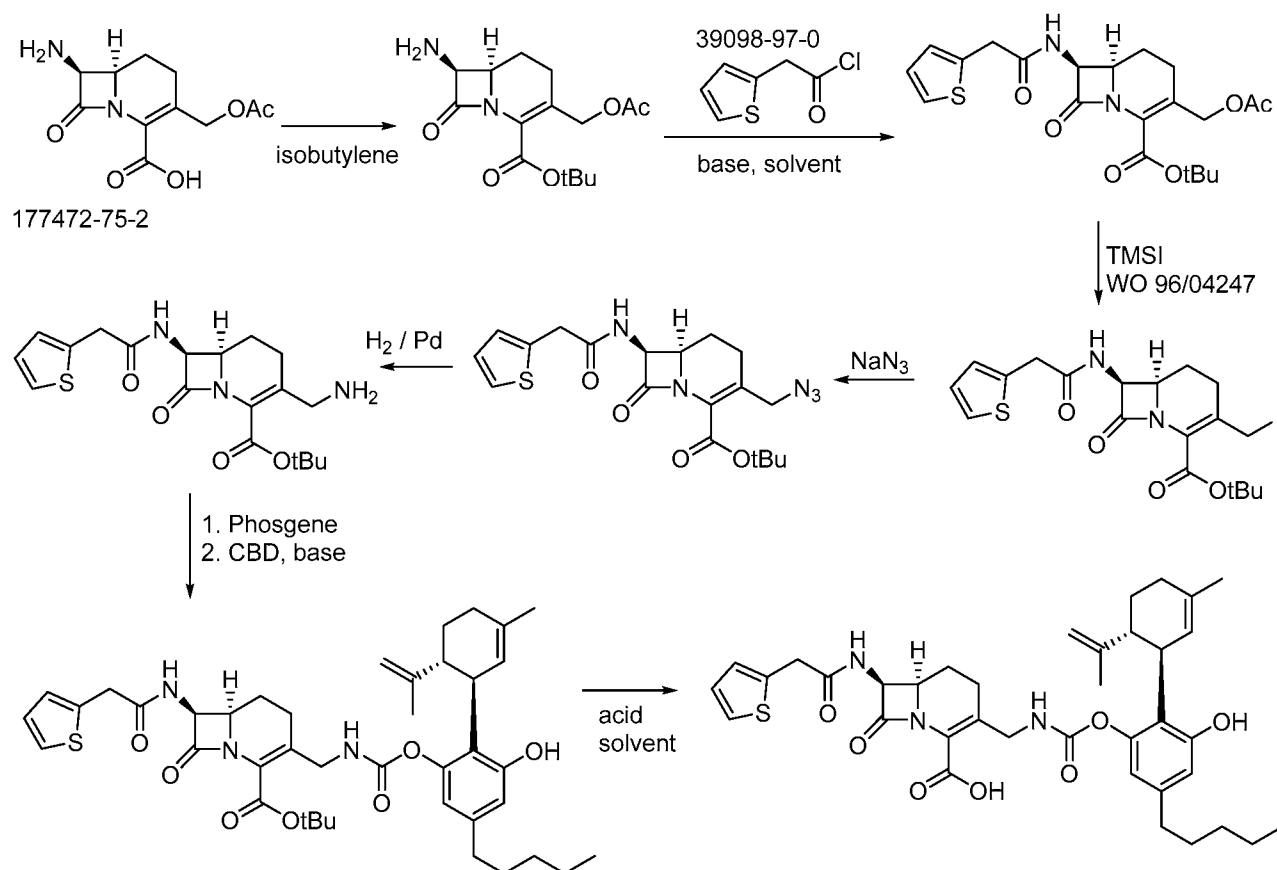
Cephem Conjugate Molecules

[95] Cephem carbamate linked conjugate molecules are synthesized according to the following Scheme. The starting material [6187-87-7] is acylated with a side chain of choice. The acetate group is then converted to the iodide with TMS-I as has been reported for similar molecules (WO 96/04247). The iodide is then converted to the azide which is then reduced to the amine, both steps under standard conditions. Reaction of the amine with phosgene followed by addition of the cannabinoid CBD forms the carbamate linkage. Deprotection of the t-butyl ester under standard conditions gives the desired product.



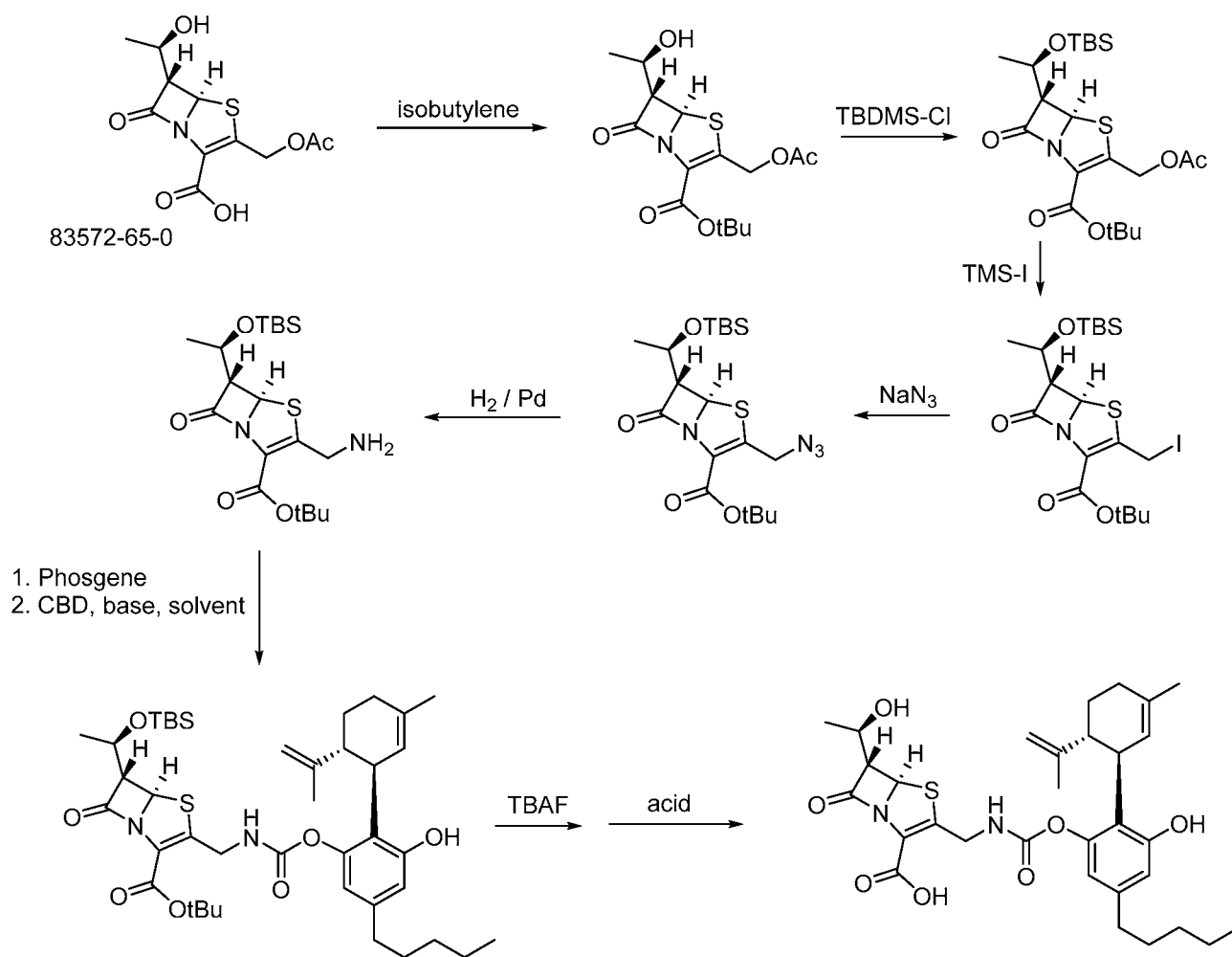
Carbacephem Conjugate Molecules

[96] Carbacephem carbamate linked conjugate molecules are synthesized according to the following Scheme. The starting material [177472-75-2] has been previously described (WO 96/04247; Journal of the American Chemical Society (1974), 96(24), 7584). It is converted to the t-butyl ester under established isobutylene conditions, and then is acylated with a side chain of choice. The acetate group is then converted to the iodide with TMS-I as has been reported for similar molecules (WO 96/04247). The iodide is then converted to the azide which is then reduced to the amine, both steps under standard conditions. Reaction of the amine with phosgene followed by addition of the cannabinoid CBD forms the carbamate linkage. Deprotection of the t-butyl ester under standard conditions gives the desired product.



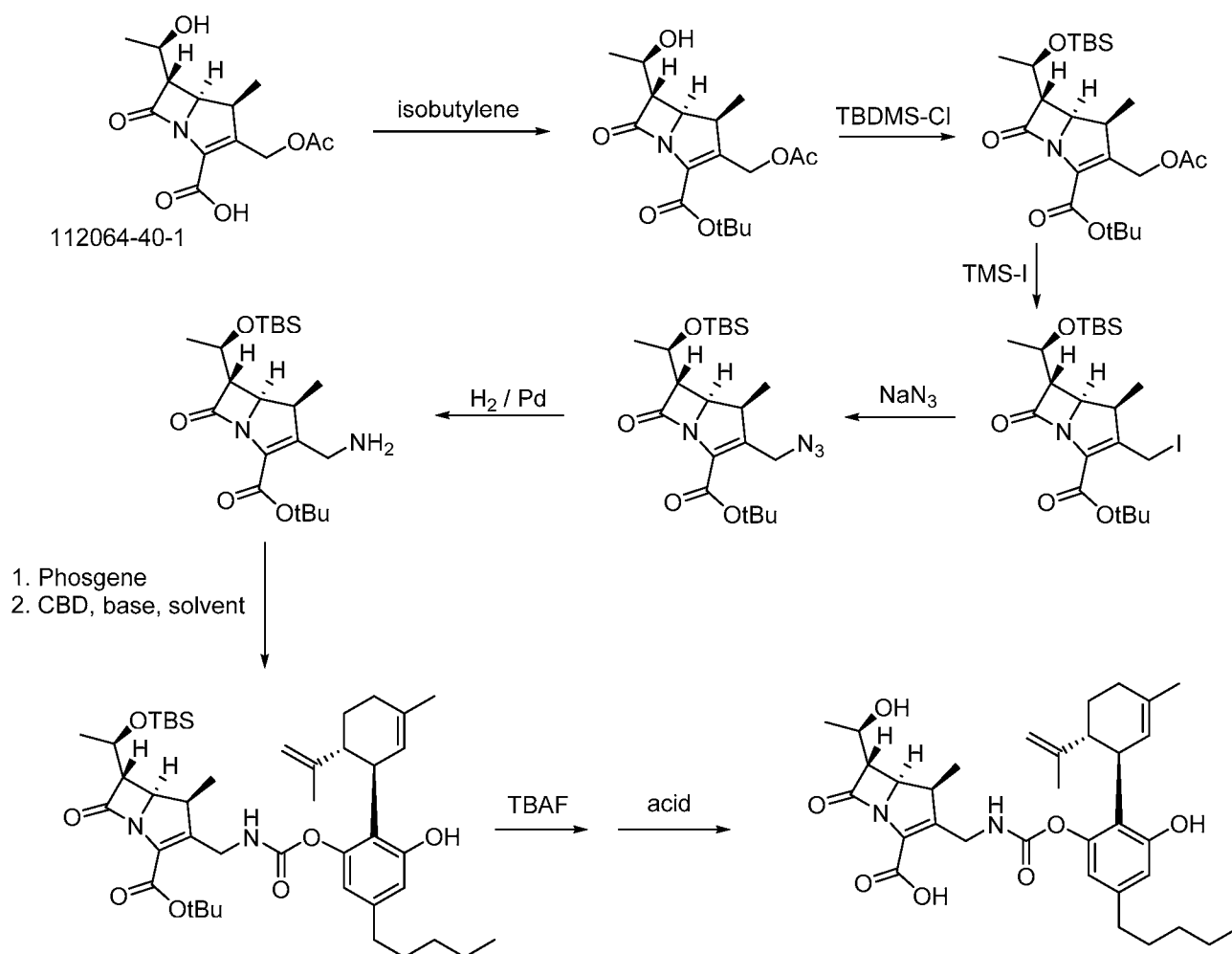
Penem Conjugate Molecules

[97] Penem carbamate linked conjugate molecules are synthesized according to the following Scheme. The starting material [83572-65-0] has been previously described (Journal of Antibiotics (1982), 35(9), 1248-51). It is converted to the t-butyl ester under established isobutylene conditions, and then the hydroxy group is protected as the TBDMS ether. The acetate group is then converted to the iodide with TMS-I as has been reported for similar molecules (WO 96/04247). The iodide is then converted to the azide which is then reduced to the amine, both steps under standard conditions. Reaction of the amine with phosgene followed by addition of the cannabinoid CBD forms the carbamate linkage. Removal of the TBDMS ether and t-butyl ester protecting groups under standard conditions gives the desired product.



Carbapenem Conjugate Molecules

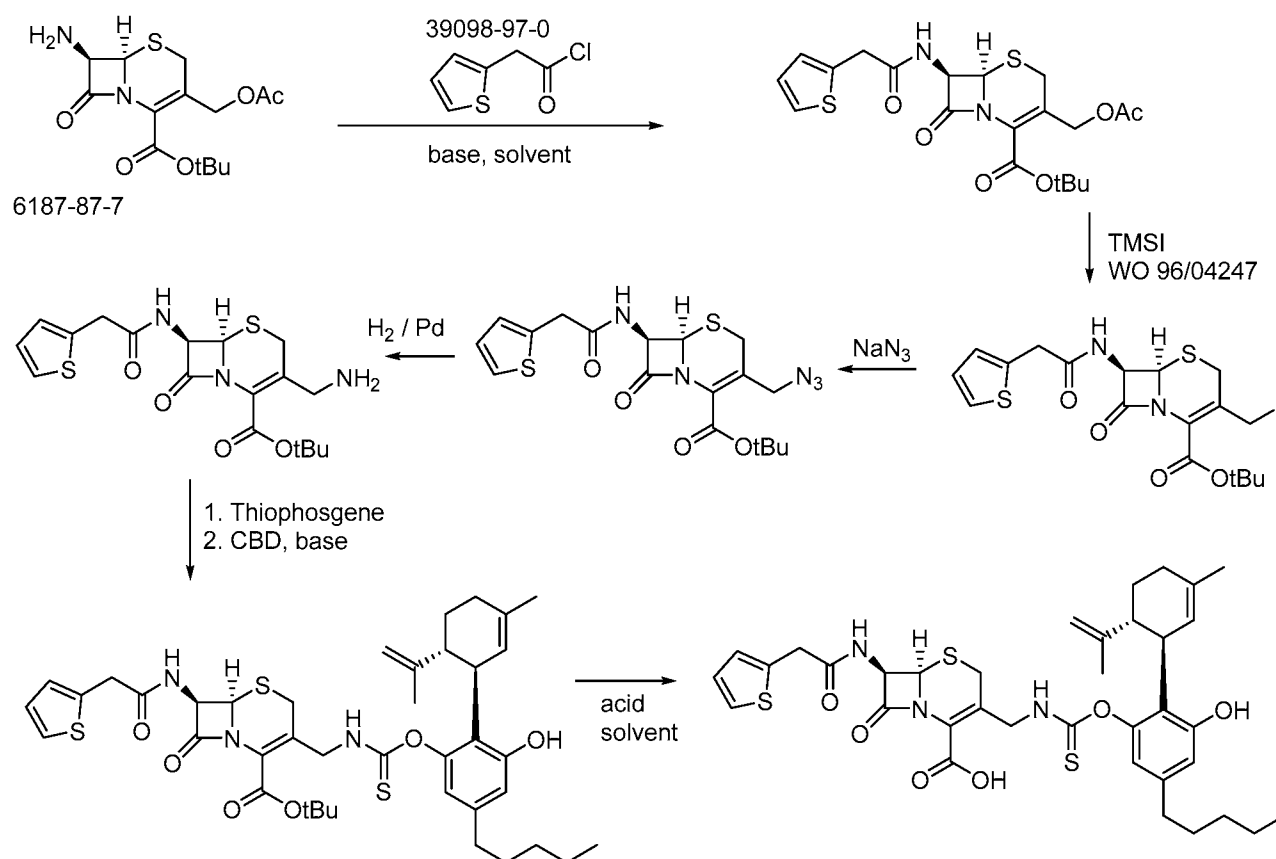
[98] Carbapenem carbamate linked conjugate molecules are synthesized according to the following Scheme. The starting material [112064-40-1] has been previously described (Journal of Antibiotics (1988), 41(6), 780-7). It is converted to the t-butyl ester under established isobutylene conditions, and then the hydroxy group is protected as the TBDMS ether. The acetate group is then converted to the iodide with TMS-I as has been reported for similar molecules (WO 96/04247). The iodide is then converted to the azide which is then reduced to the amine, both steps under standard conditions. Reaction of the amine with phosgene followed by addition of the cannabinoid CBD forms the carbamate linkage. Removal of the TBDMS ether and t-butyl ester protecting groups under standard conditions gives the desired product.



Example 5. Thiocarbamate-linked conjugate molecules

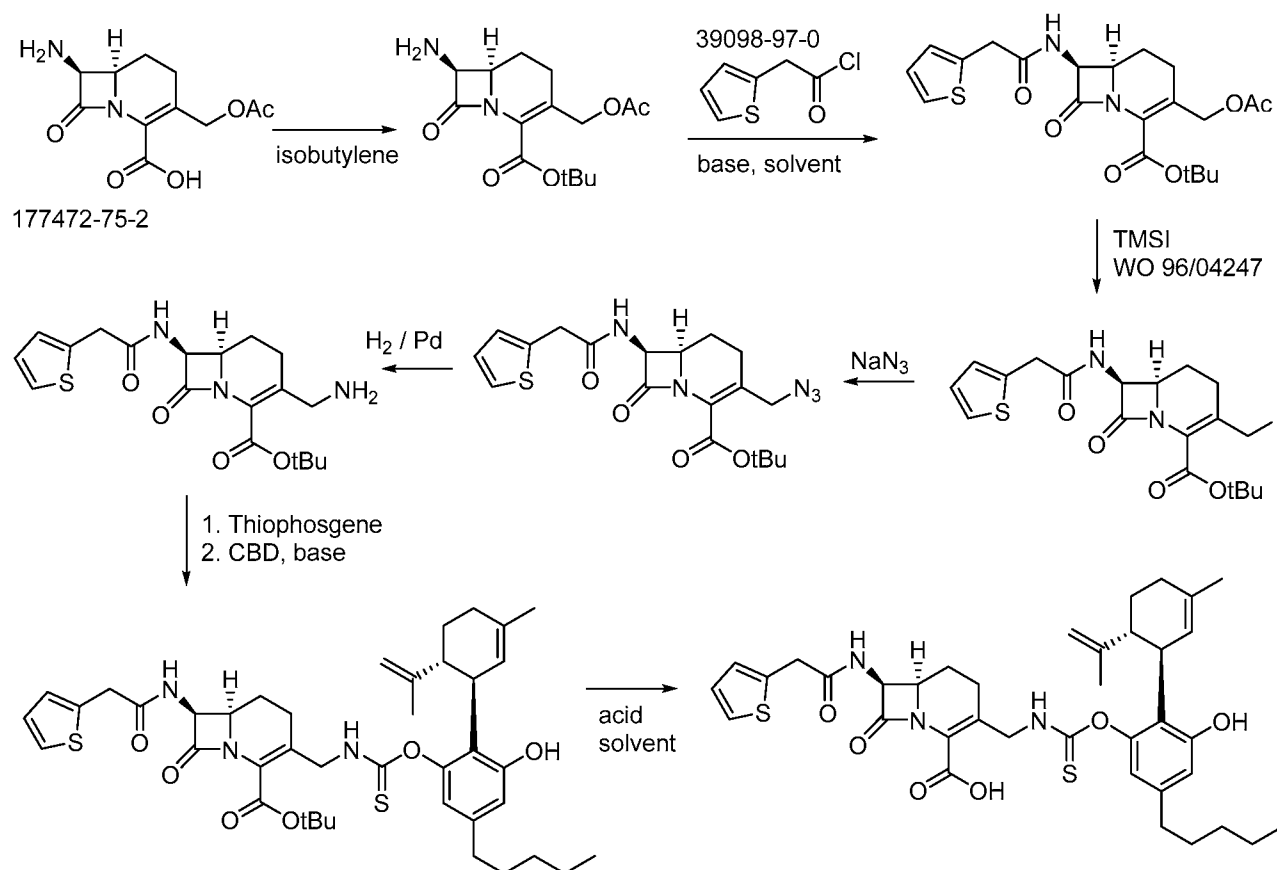
Cephem Conjugate Molecules

[99] Cephem thiocarbamate linked conjugate molecules are synthesized according to the following Scheme. The starting material [6187-87-7] is acylated with a side chain of choice. The acetate group is then converted to the iodide with TMS-I as has been reported for similar molecules (WO 96/04247). The iodide is then converted to the azide which is then reduced to the amine, both steps under standard conditions. Reaction of the amine with thiophosgene followed by addition of the cannabinoid CBD forms the thiocarbamate linkage. Deprotection of the t-butyl ester under standard conditions gives the desired product.



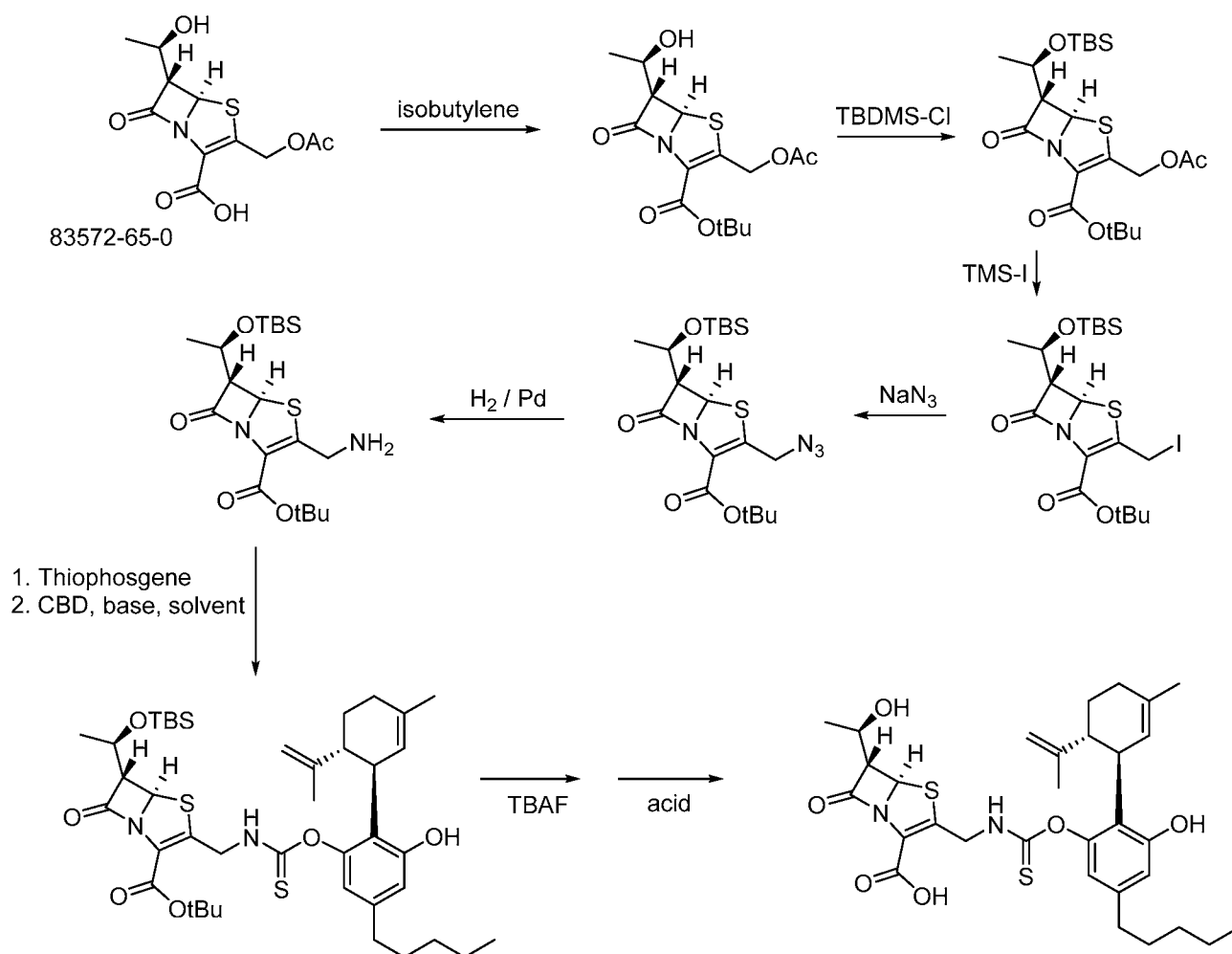
Carbacephem Conjugate Molecules

[100] Carbacephem thiocarbamate linked conjugate molecules are synthesized according to the following Scheme. The starting material [177472-75-2] has been previously described (WO 96/04247; Journal of the American Chemical Society (1974), 96(24), 7584). It is converted to the t-butyl ester under established isobutylene conditions, and then is acylated with a side chain of choice. The acetate group is then converted to the iodide with TMS-I as has been reported for similar molecules (WO 96/04247). The iodide is then converted to the azide which is then reduced to the amine, both steps under standard conditions. Reaction of the amine with thiophosgene followed by addition of the cannabinoid CBD forms the thiocarbamate linkage. Deprotection of the t-butyl ester under standard conditions gives the desired product.



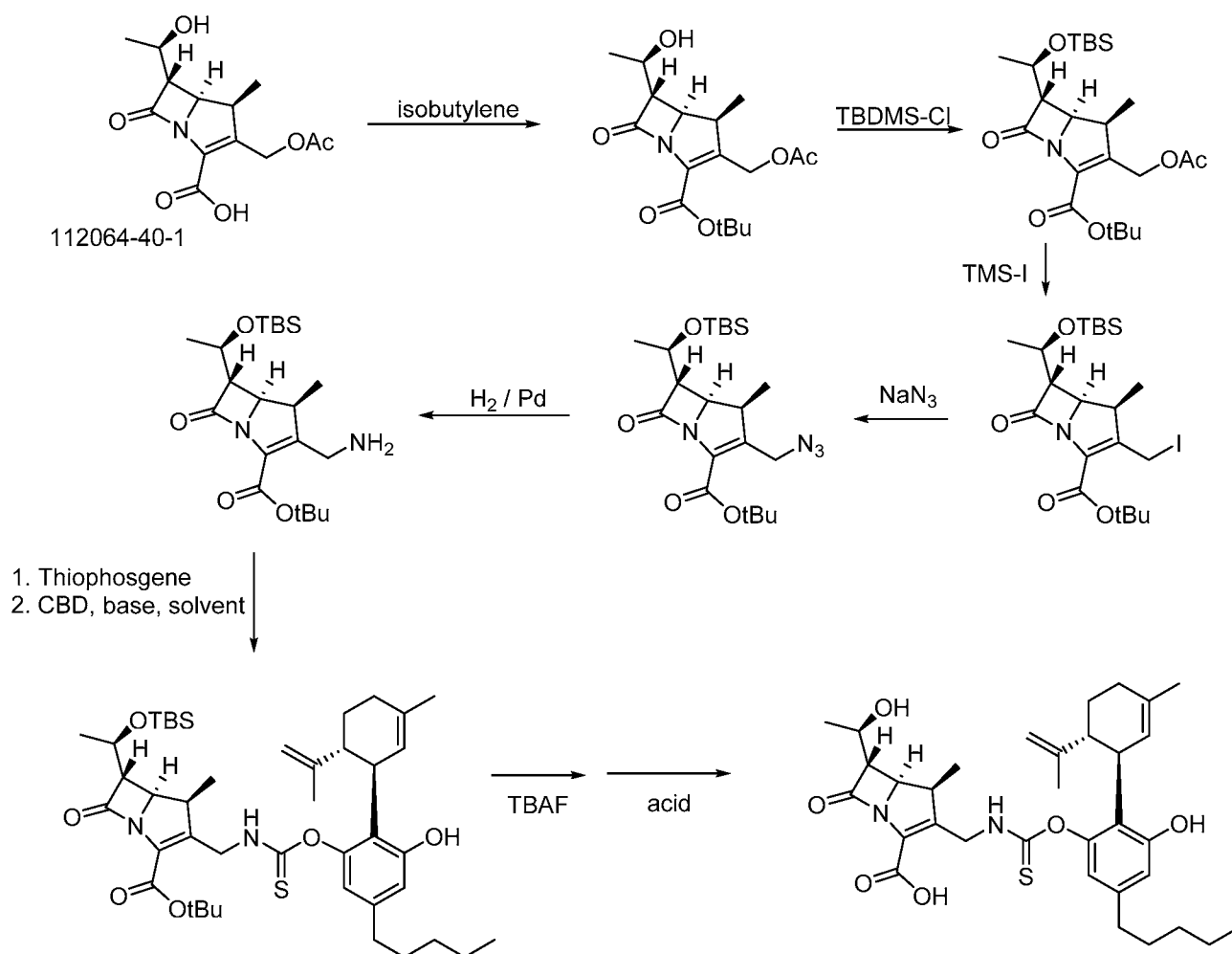
Penem Conjugate Molecules

[101] Penem thiocarbamate linked conjugate molecules are synthesized according to the following Scheme. The starting material [83572-65-0] has been previously described (Journal of Antibiotics (1982), 35(9), 1248-51). It is converted to the t-butyl ester under established isobutylene conditions, and then the hydroxy group is protected as the TBDMS ether. The acetate group is then converted to the iodide with TMS-I as has been reported for similar molecules (WO 96/04247). The iodide is then converted to the azide which is then reduced to the amine, both steps under standard conditions. Reaction of the amine with thiophosgene followed by addition of the cannabinoid CBD forms the thiocarbamate linkage. Removal of the TBDMS ether and t-butyl ester protecting groups under standard conditions gives the desired product.



Carbapenem Conjugate Molecules

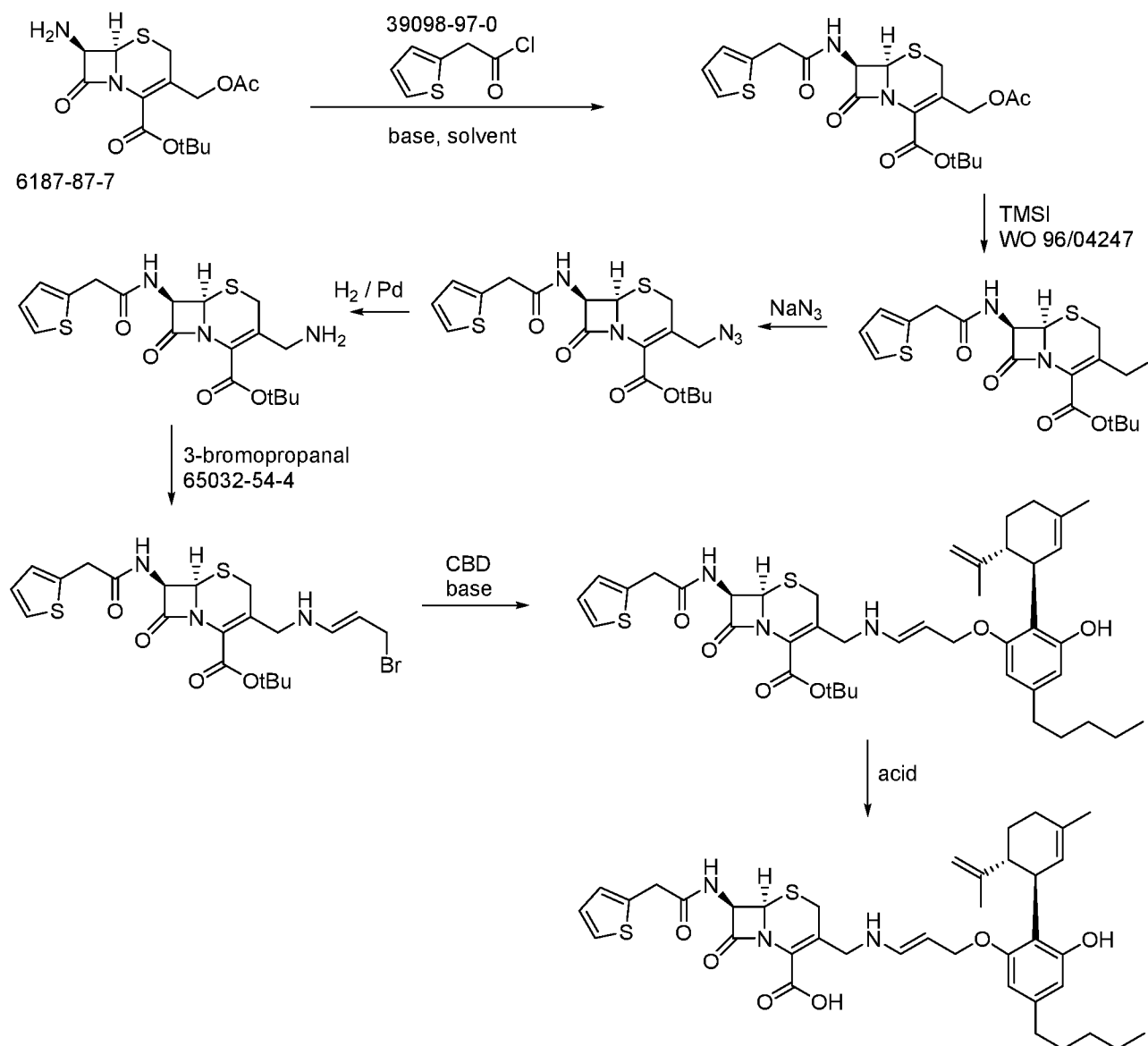
[102] Carbapenem thiocarbamate linked conjugate molecules are synthesized according to the following Scheme. The starting material [112064-40-1] has been previously described (Journal of Antibiotics (1988), 41(6), 780-7). It is converted to the t-butyl ester under established isobutylene conditions, and then the hydroxy group is protected as the TBDMS ether. The acetate group is then converted to the iodide with TMS-I as has been reported for similar molecules (WO 96/04247). The iodide is then converted to the azide which is then reduced to the amine, both steps under standard conditions. Reaction of the amine with thiophosgene followed by addition of the cannabinoid CBD forms the thiocarbamate linkage. Removal of the TBDMS ether and t-butyl ester protecting groups under standard conditions gives the desired product.



Example 6. Propenylamine-linked conjugate molecules

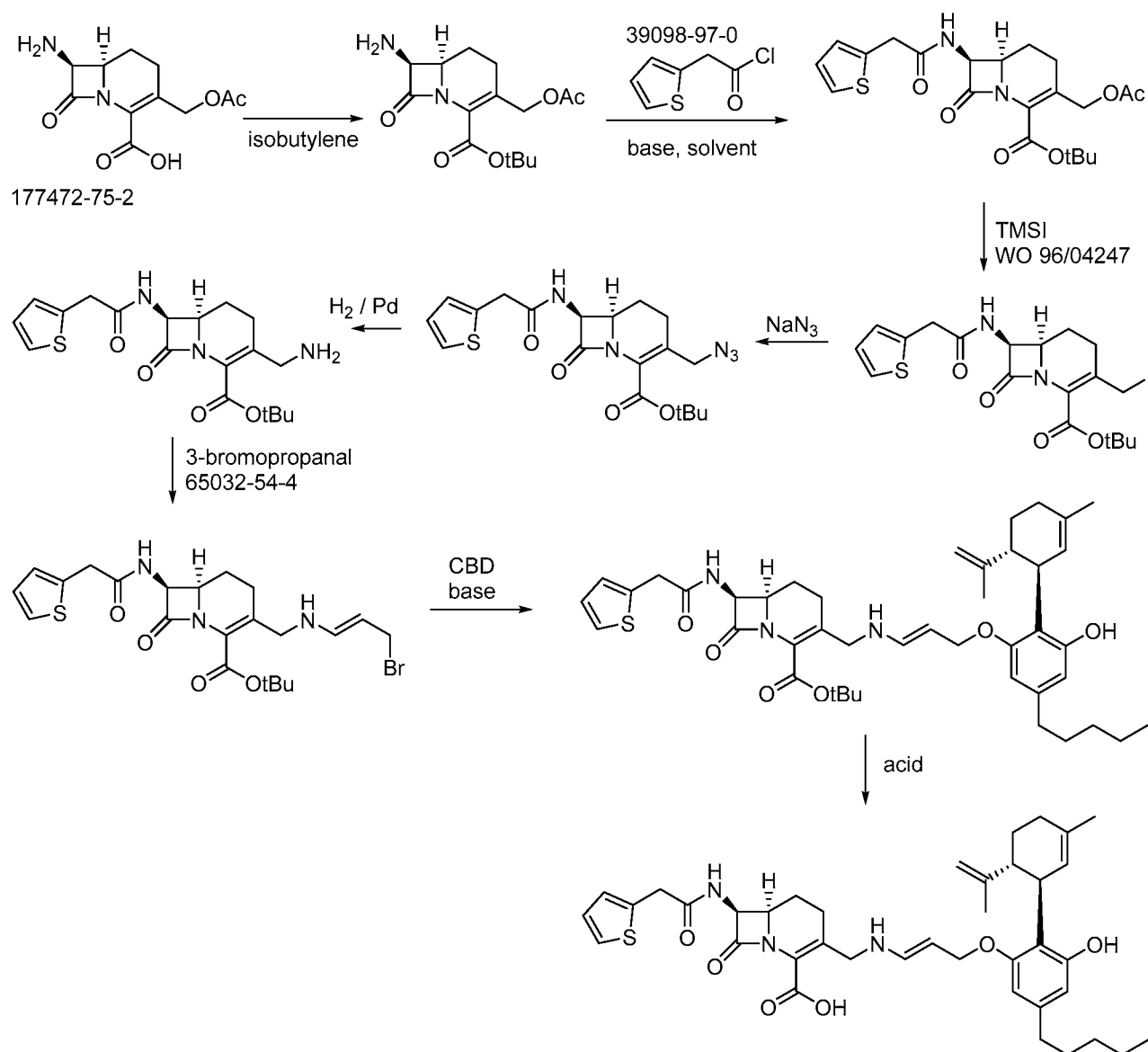
Cephem Conjugate Molecules

[103] Cephem propenylamine linked conjugate molecules are synthesized according to the following Scheme. The starting material [6187-87-7] is acylated with a side chain of choice. The acetate group is then converted to the iodide with TMS-I as has been reported for similar molecules (WO 96/04247). The iodide is then converted to the azide which is then reduced to the amine, both steps under standard conditions. Condensation of the amine with a 3-halopropanal (3-bromo, 65032-54-4) produces the bromopropenyl intermediate which is then used to alkylate the cannabinoid (CBD) under standard basic conditions. Removal of the t-butyl ester protecting group under acidic conditions generates the desired product.



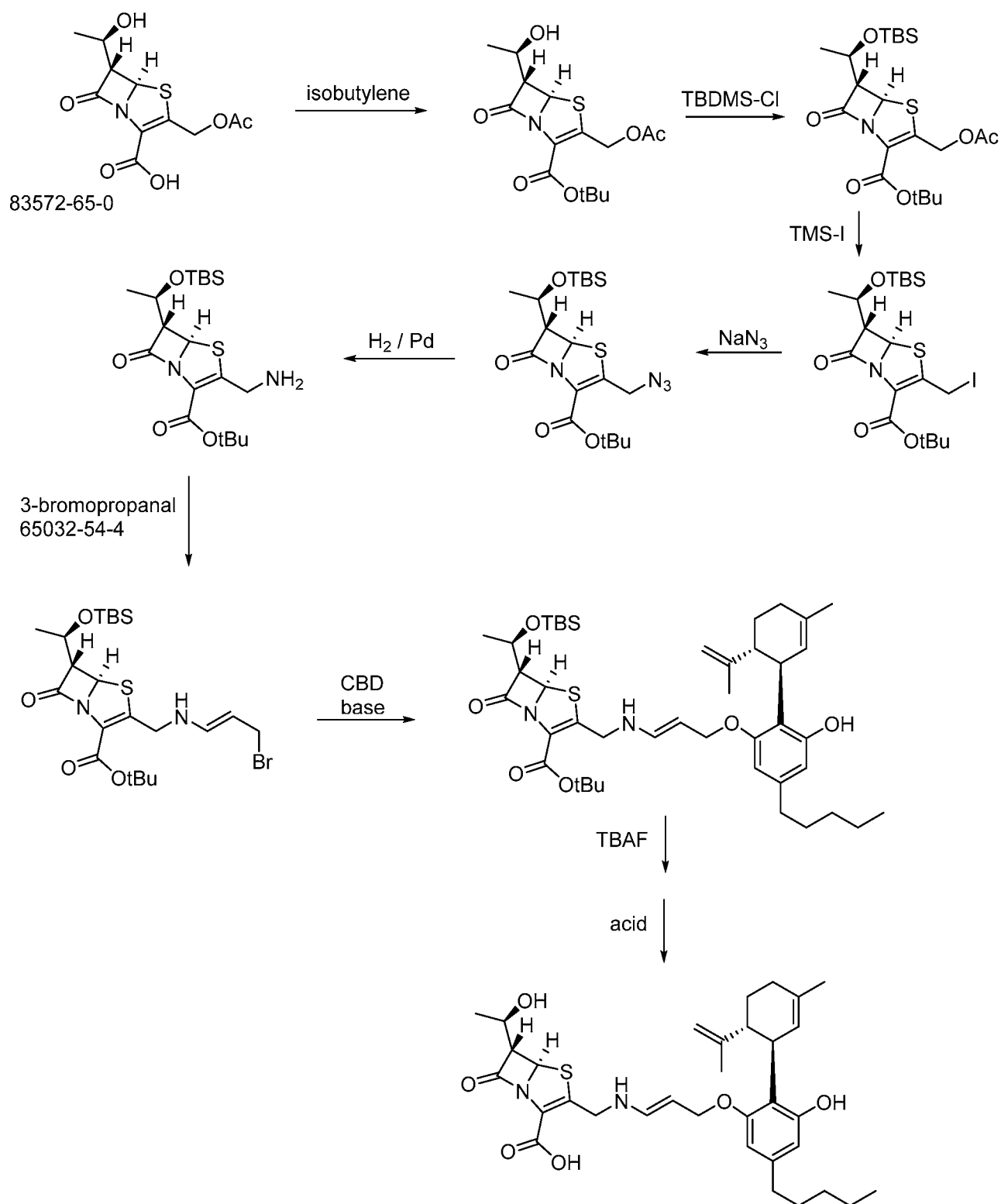
Carbacephem Conjugate Molecules

[104] Carbacephem propenylamine linked conjugate molecules are synthesized according to the following Scheme. The starting material [177472-75-2] is protected as the t-butyl ester under standard isobutylene conditions and then is acylated with a side chain of choice. The acetate group is then converted to the iodide with TMS-I as has been reported for similar molecules (WO 96/04247). The iodide is then converted to the azide which is then reduced to the amine, both steps under standard conditions. Condensation of the amine with a 3-halopropanal (3-bromo, 65032-54-4) produces the bromopropenyl intermediate which is then used to alkylate the cannabinoid (CBD) under standard basic conditions. Removal of the t-butyl ester protecting group under acidic conditions generates the desired product.



Penem Conjugate Molecules

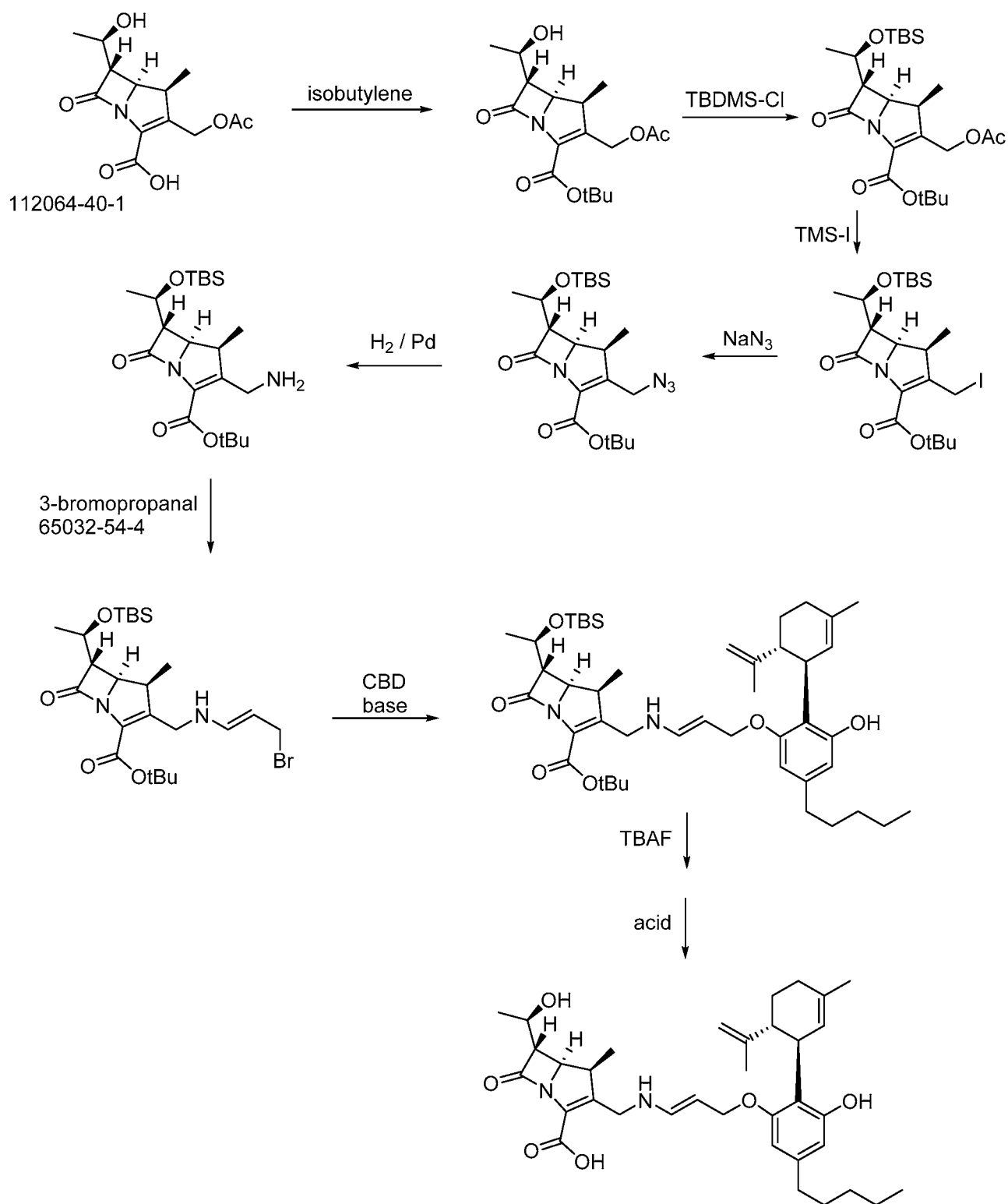
[105] Penem propenylamine linked conjugate molecules are synthesized according to the following Scheme. The starting material [83572-65-0] is protected as the t-butyl ester under standard isobutylene conditions and then the secondary alcohol is protected as the TBDMS ether. The acetate group is then converted to the iodide with TMS-I as has been reported for similar molecules (WO 96/04247). The iodide is then converted to the azide which is then reduced to the amine, both steps under standard conditions. Condensation of the amine with a 3-halopropanal (3-bromo, 65032-54-4) produces the bromopropenyl intermediate which is then used to alkylate the cannabinoid (CBD) under standard basic conditions. Removal of the TBDMS ether and t-butyl ester protecting groups under standard conditions gives the desired product.



Carbapenem Conjugate Molecules

[106] Carbapenem propenylamine linked conjugate molecules are synthesized according to the following Scheme. The starting material [112064-40-1] is protected as the t-butyl ester under standard isobutylene conditions and then the secondary alcohol is protected as the TBDMS ether. The acetate group is then converted to the iodide with TMS-I as has been reported for similar

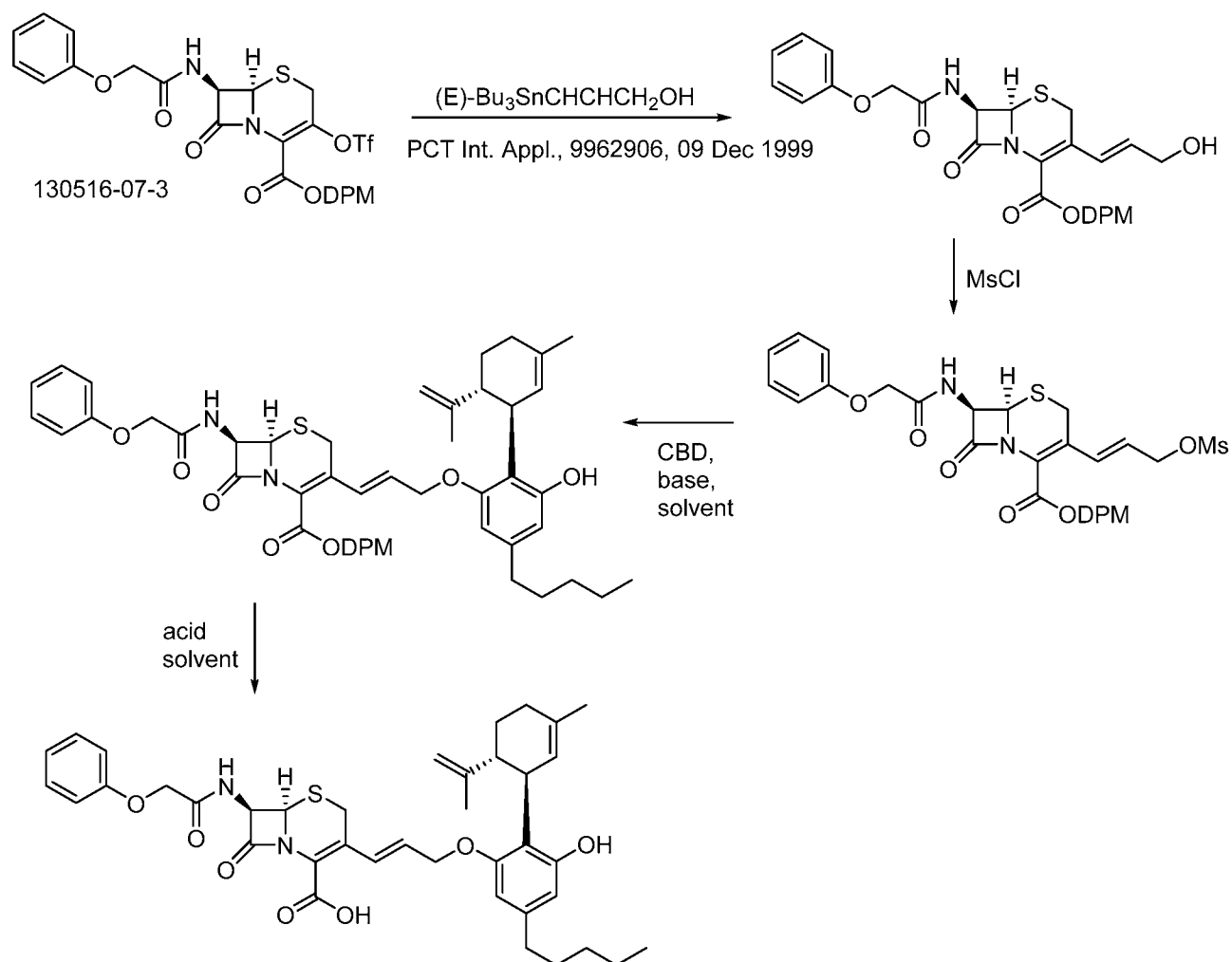
molecules (WO 96/04247). The iodide is then converted to the azide which is then reduced to the amine, both steps under standard conditions. Condensation of the amine with a 3-halopropanal (3-bromo, 65032-54-4) produces the bromopropenyl intermediate which is then used to alkylate the cannabinoid (CBD) under standard basic conditions. Removal of the TBDMS ether and t-butyl ester protecting groups under standard conditions gives the desired product.



Example 7. Alkene-linked conjugate molecules

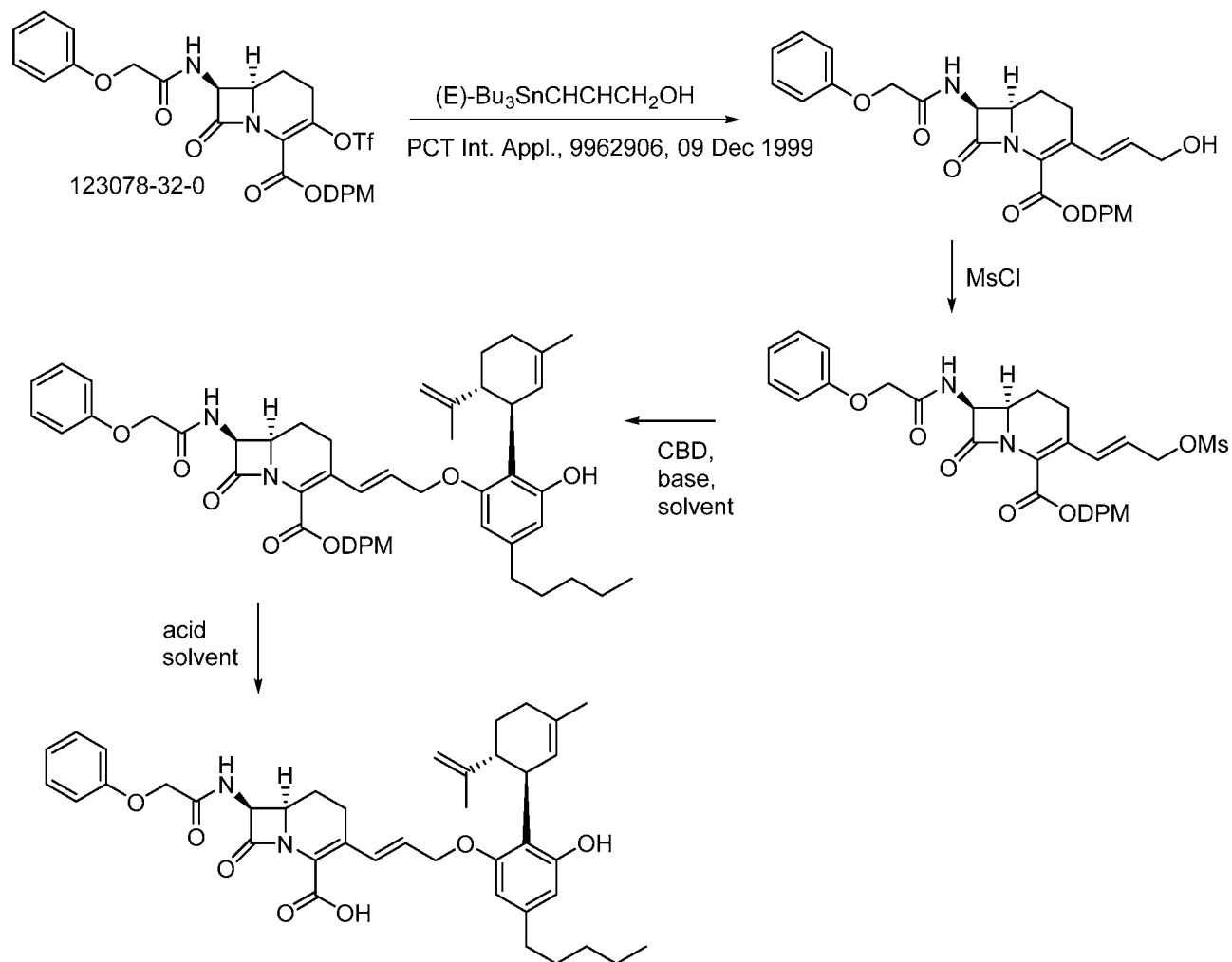
Cephem Conjugate Molecules

[107] Cephem alkene linked conjugate molecules are synthesized according to the following Scheme. The starting material [130516-07-3] has been reported previously (Journal of Organic Chemistry (1993), 58(8), 2296-2301). It is reacted with the organostannane under conditions described for related molecules (WO 99/62906) to give the allylic alcohol intermediate. The alcohol is then activated as the mesylate and reacted with the cannabinoid (CBD) under basic conditions to produce the alkene linked intermediate. Removal of the DPM protecting group under standard conditions gives the desired product.



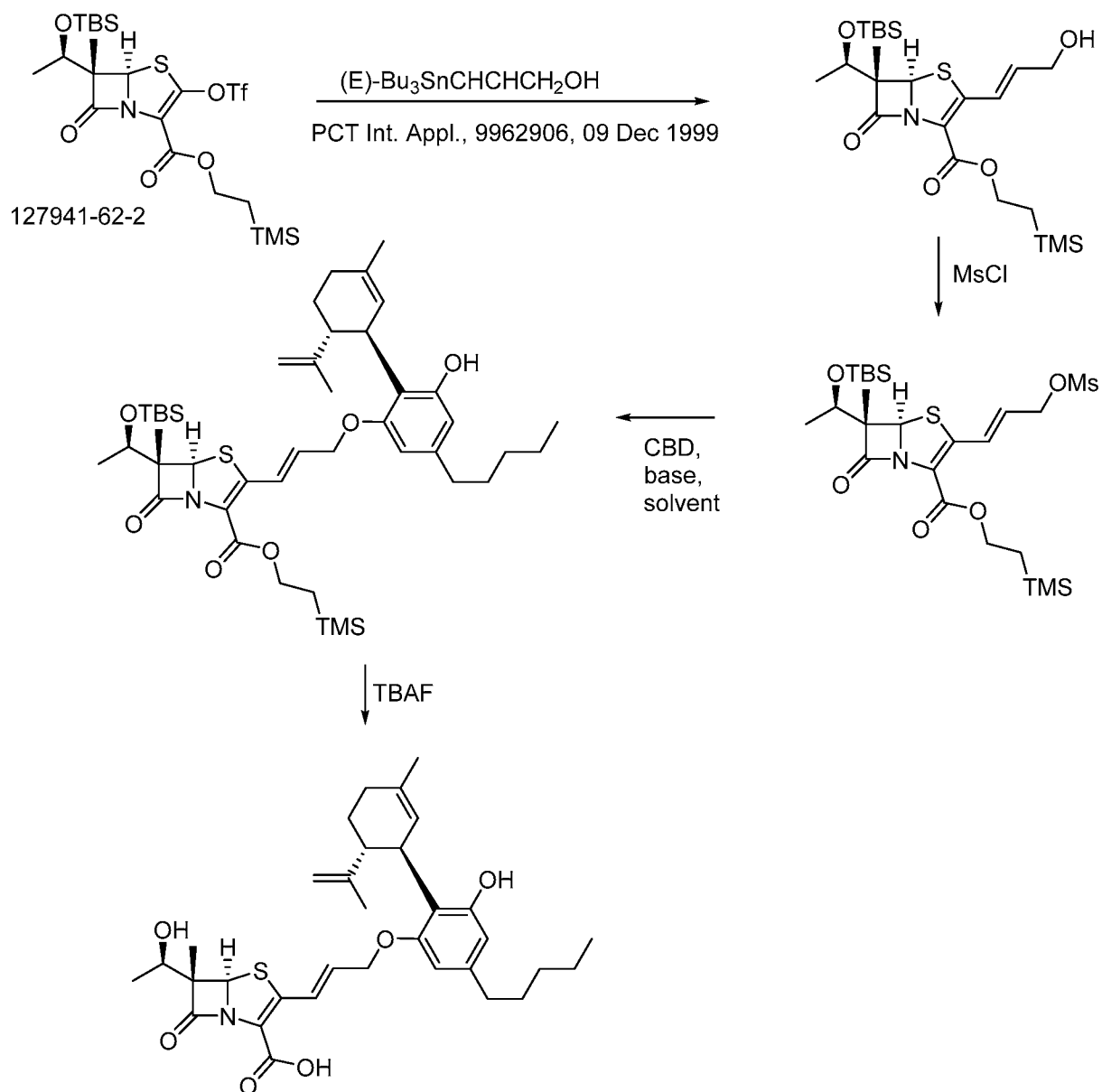
Carbacephem Conjugate Molecules

[108] Carbacephem alkene linked conjugate molecules are synthesized according to the following Scheme. The starting material [123078-32-0] has been reported previously (Journal of Organic Chemistry, 54(24), 5828-30; 1989). It is reacted with the organostannane under conditions described for related molecules (WO 99/62906) to give the allylic alcohol intermediate. The alcohol is then activated as the mesylate and reacted with the cannabinoid (CBD) under basic conditions to produce the alkene linked intermediate. Removal of the DPM protecting group under standard conditions gives the desired product.

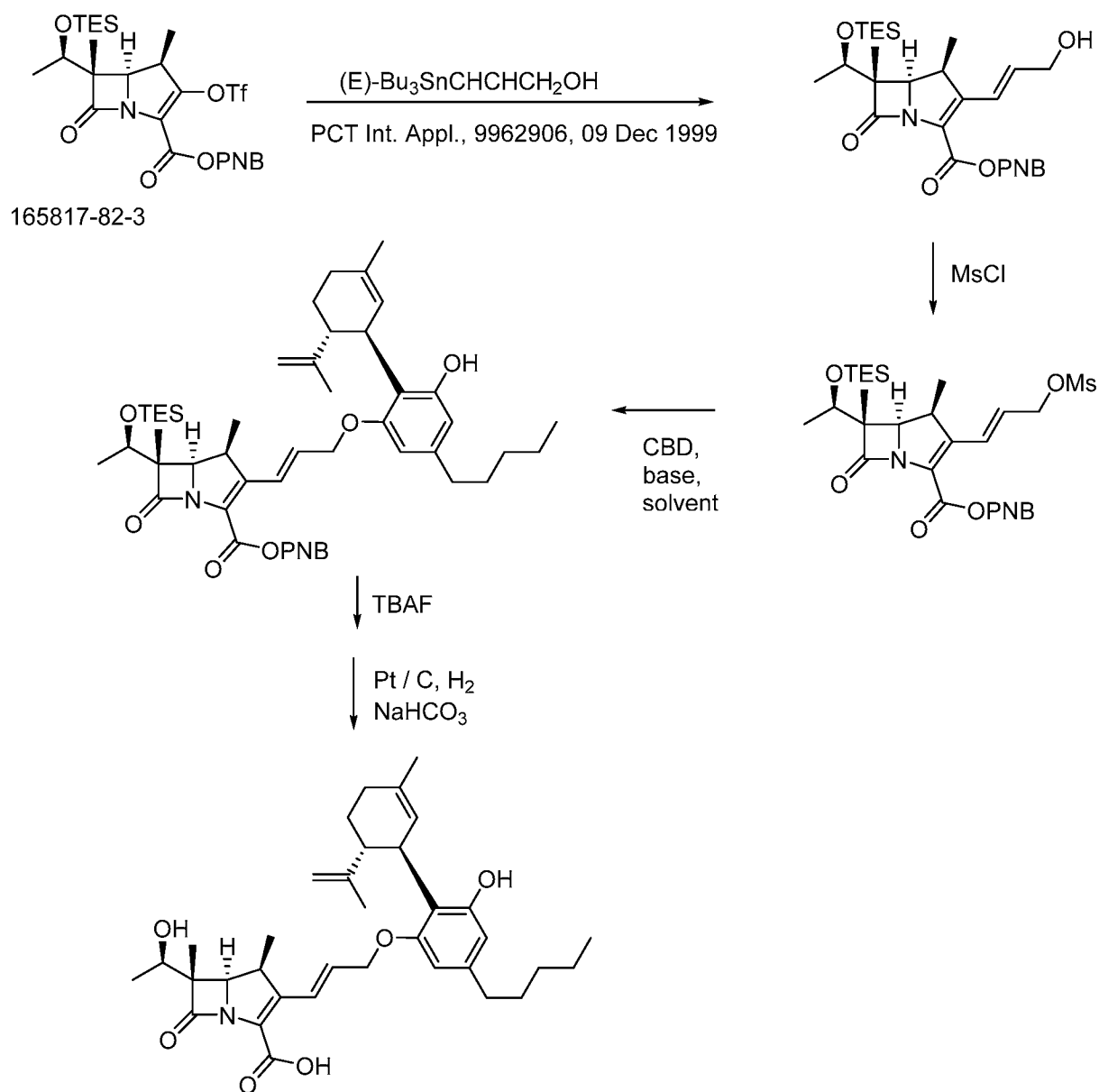


Penem Conjugate Molecules

[109] Penem alkene linked conjugate molecules are synthesized according to the following Scheme. The starting material [127941-62-2] has been previously reported (U.S. patent 4,895,940). It is converted to the allylic alcohol intermediate as previously described for similar molecules (WO 99/62906). The alcohol is then activated as the mesylate and reacted with the cannabinoid (CBD) under basic conditions to produce the alkene linked intermediate. Removal of the TBDMS ether and trimethylsilyl ethyl ester protecting groups is achieved under standard conditions of excess TBAF to give the desired product.



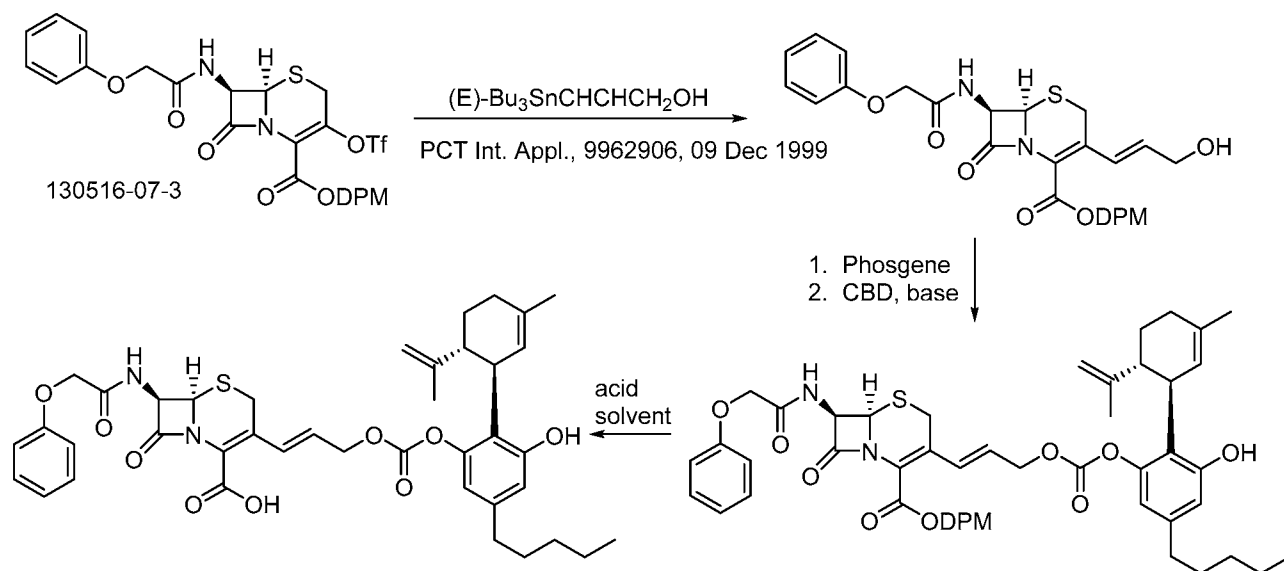
[110] Carbapenem alkene linked conjugate molecules are synthesized according to the following Scheme. The starting material [165817-82-3] along with its conversion to the allylic alcohol intermediate has been described previously (WO 99/62906). The alcohol is then activated as the mesylate and reacted with the cannabinoid (CBD) under basic conditions to produce the alkene linked intermediate. Removal of the TES ether and PNB ester groups under standard conditions produces the desired product.



Example 8. Propenyl carbonate-linked conjugate molecules

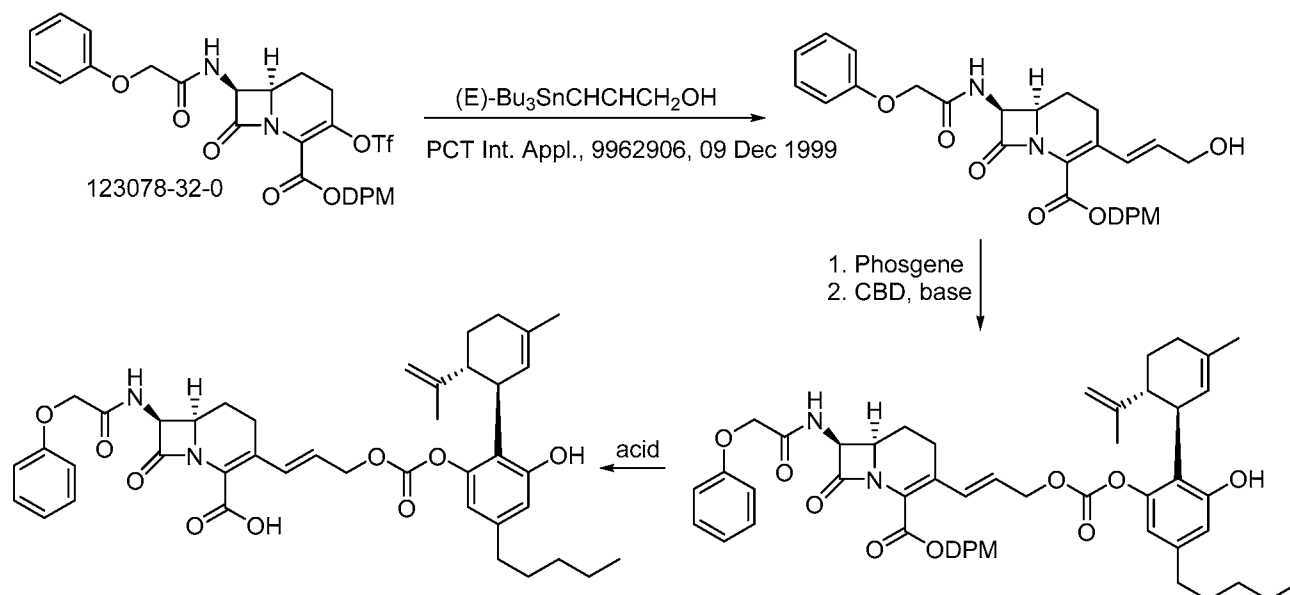
Cephem Conjugate Molecules

[111] Cephem propenyl carbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material [130516-07-3] has been reported previously (Journal of Organic Chemistry (1993), 58(8), 2296-2301). It is converted to the allylic alcohol intermediate as previously described for similar molecules (WO 99/62906). This alcohol is reacted with phosgene and the resulting intermediate reacted with the cannabinoid (CBD) under basic conditions to form the carbonate group. Removal of the DPM ester protecting group under standard acidic conditions produces the desired product.



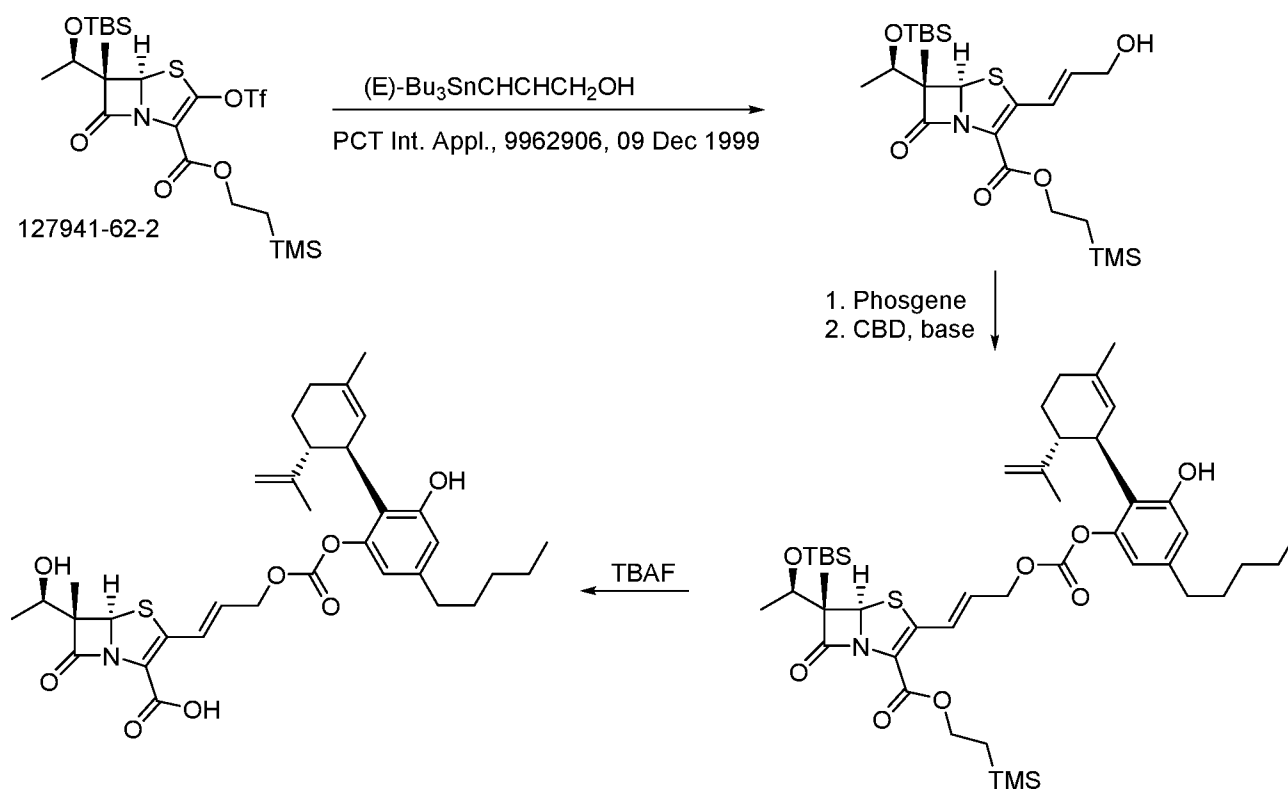
Carbacephem Conjugate Molecules

[112] Carbacephem propenyl carbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material [123078-32-0] has been reported previously (Journal of Organic Chemistry (1993), 58(8), 2296-2301). It is converted to the allylic alcohol intermediate as previously described for similar molecules (WO 99/62906). This alcohol is reacted with phosgene and the resulting intermediate reacted with the cannabinoid (CBD) under basic conditions to form the carbonate group. Removal of the DPM ester protecting group under standard acidic conditions produces the desired product.



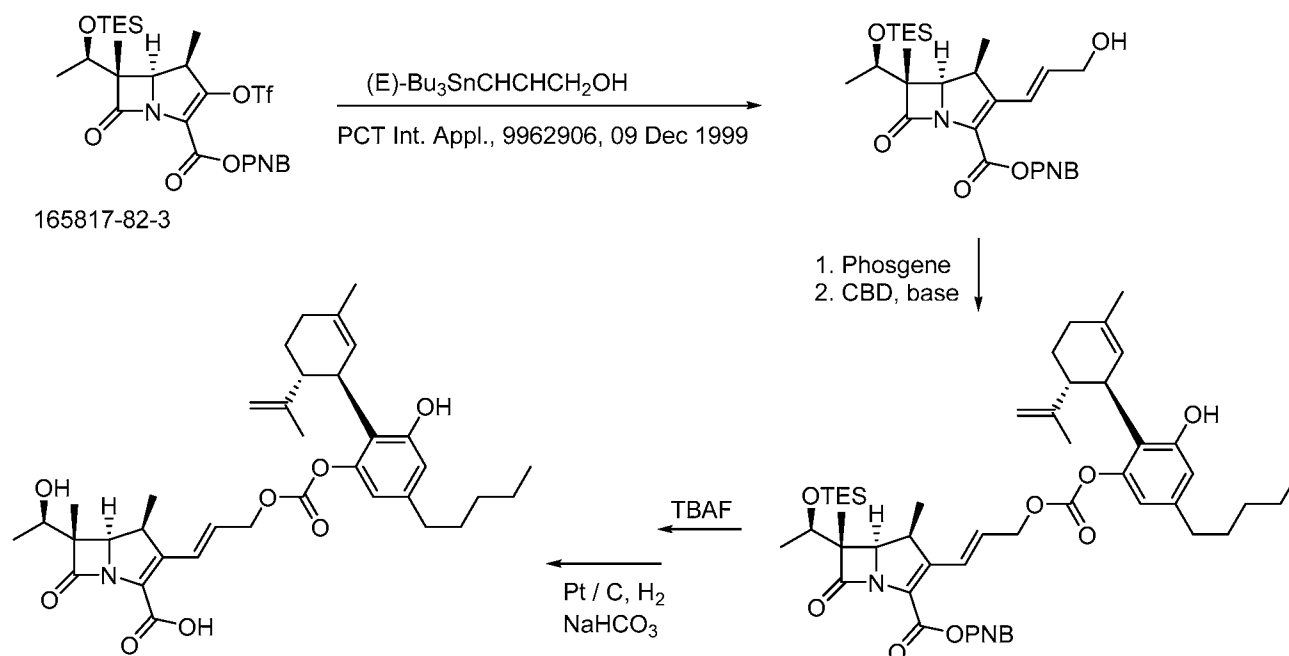
Penem Conjugate Molecules

[113] Penem propenyl carbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material [127941-62-2] has been previously reported (U.S. patent 4,895,940). It is converted to the allylic alcohol intermediate as previously described for similar molecules (WO 99/62906). The alcohol is then reacted with phosgene and the resulting intermediate reacted with the cannabinoid (CBD) under basic conditions to form the carbonate group. Removal of the TBDMS ether and trimethylsilylethyl ester protecting groups is achieved under standard conditions of excess TBAF to give the desired product.



Carbapenem Conjugate Molecules

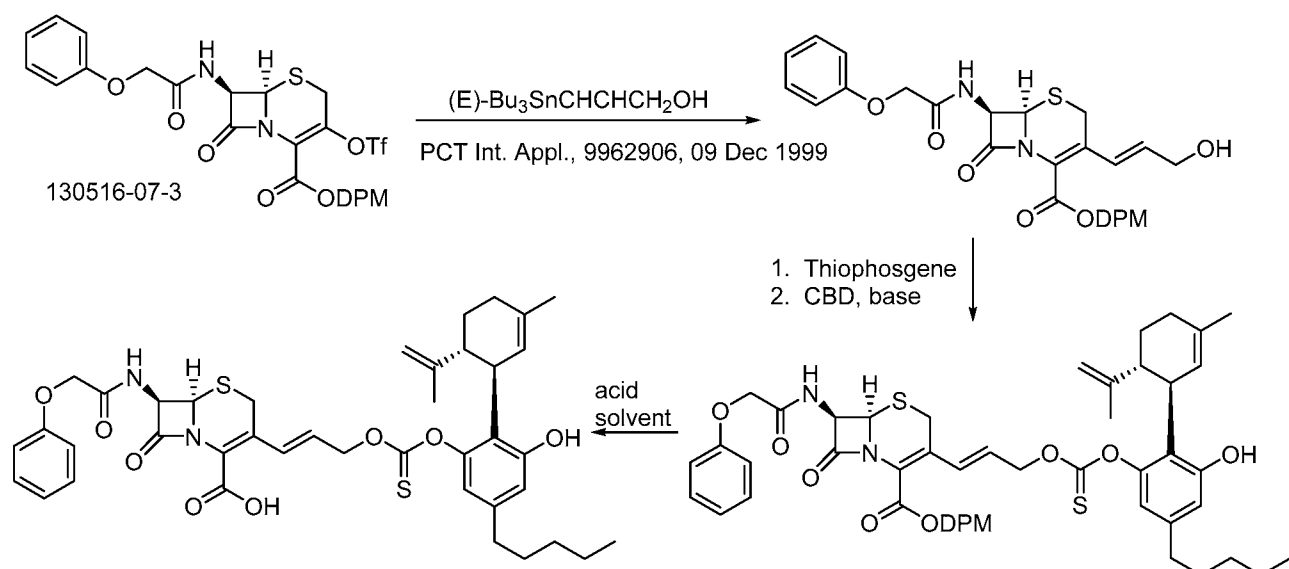
[114] Carbapenem propenyl carbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material [165817-82-3] along with its conversion to the allylic alcohol intermediate has been described previously (WO 99/62906). The alcohol is then reacted with phosgene and the resulting intermediate reacted with the cannabinoid (CBD) under basic conditions to form the carbonate group. Removal of the TES ether and PNB ester groups under standard conditions produces the desired product.



Example 9. Propenyl thiocarbonate-linked conjugate molecules

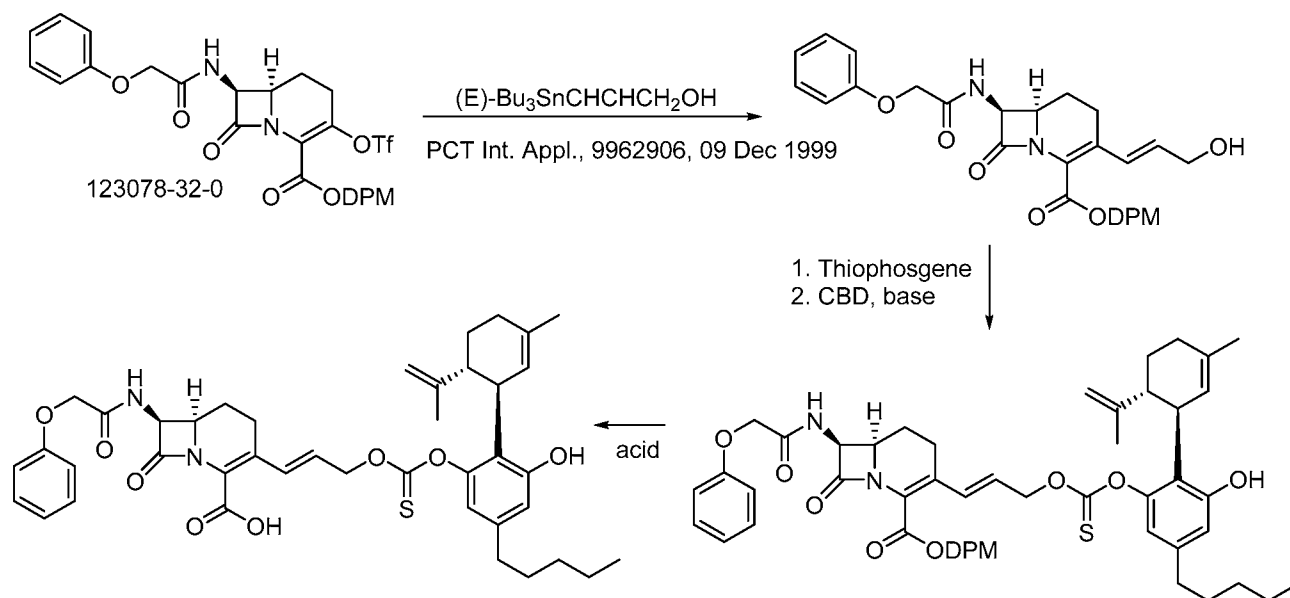
Cephem Conjugate Molecules

[115] Cephem propenyl thiocarbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material [130516-07-3] has been reported previously (Journal of Organic Chemistry (1993), 58(8), 2296-2301). It is converted to the allylic alcohol intermediate as previously described for similar molecules (WO 99/62906). This alcohol is reacted with thiophosgene and the resulting intermediate reacted with the cannabinoid (CBD) under basic conditions to form the thiocarbonate group. Removal of the DPM ester protecting group under standard acidic conditions produces the desired product.



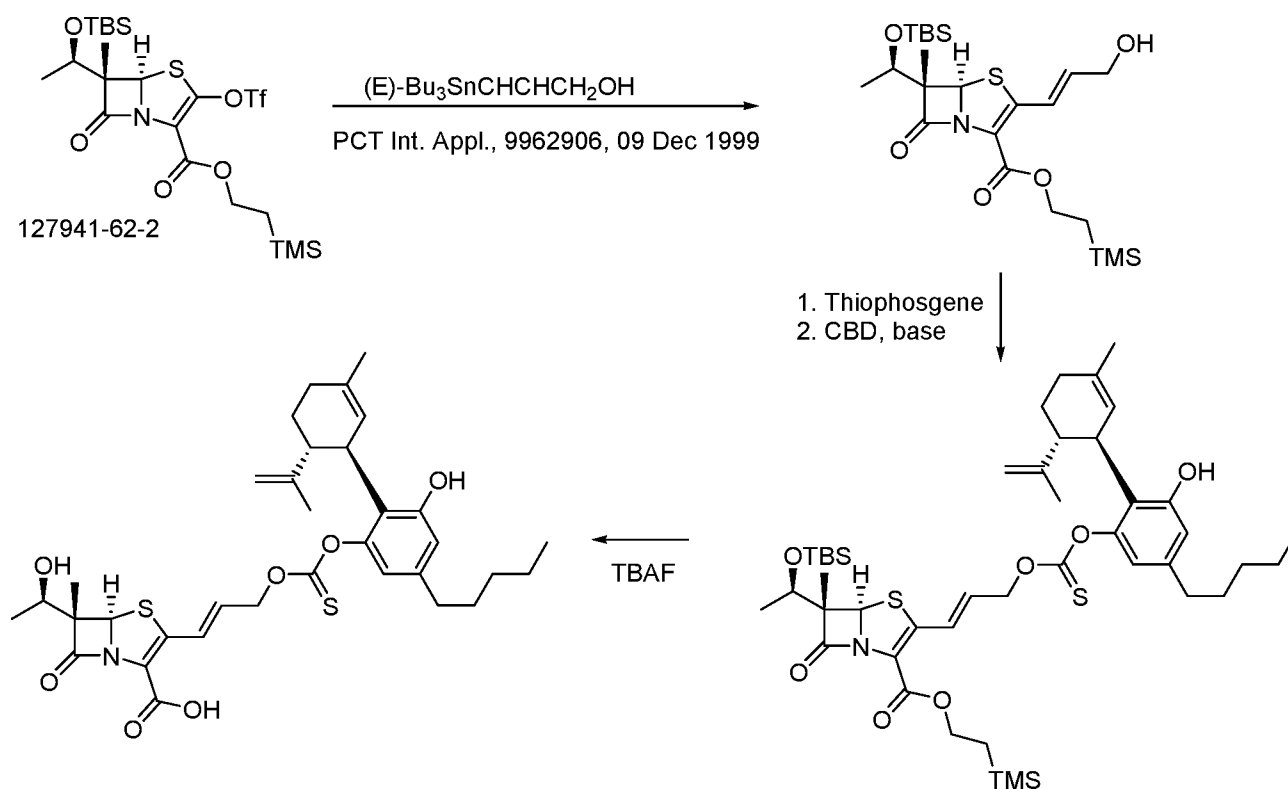
Carbacephem Conjugate Molecules

[116] Carbacephem propenyl thiocarbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material [12078-32-0] has been reported previously (Journal of Organic Chemistry (1993), 58(8), 2296-2301). It is converted to the allylic alcohol intermediate as previously described for similar molecules (WO 99/62906). This alcohol is reacted with thiophosgene and the resulting intermediate reacted with the cannabinoid (CBD) under basic conditions to form the thiocarbonate group. Removal of the DPM ester protecting group under standard acidic conditions produces the desired product.



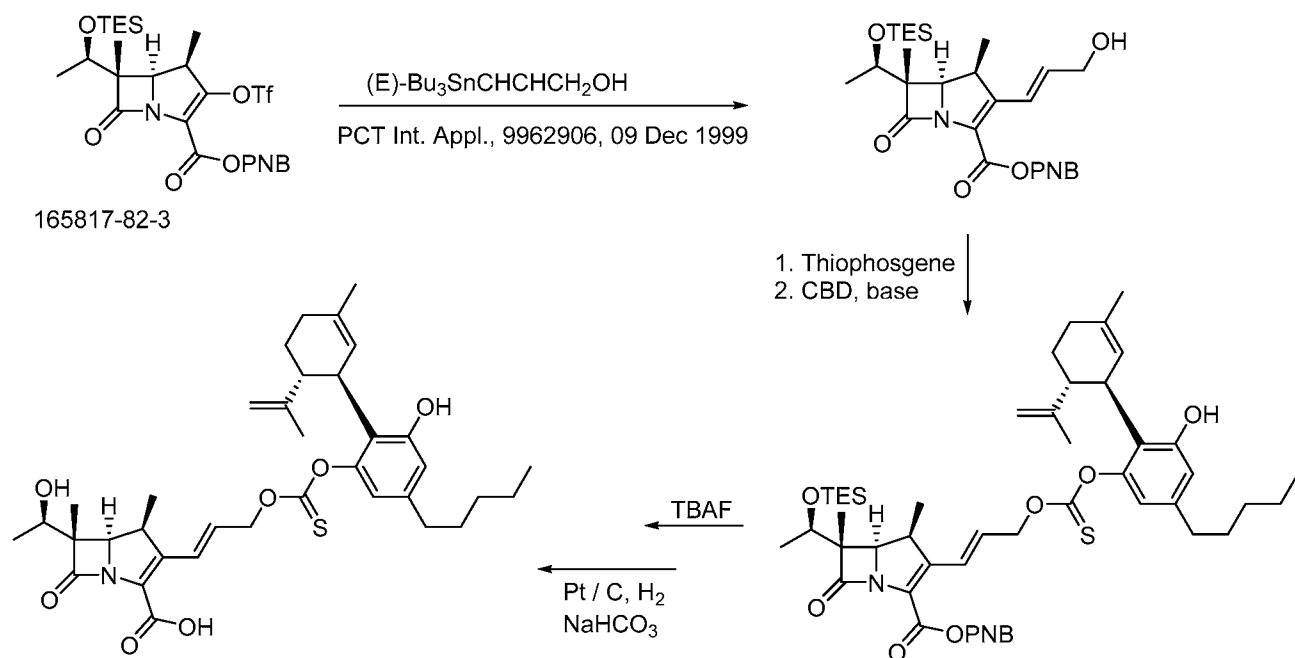
Penem Conjugate Molecules

[117] Penem propenyl thiocarbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material [127941-62-2] has been previously reported (U.S. patent 4,895,940). It is converted to the allylic alcohol intermediate as previously described for similar molecules (WO 99/62906). The alcohol is then reacted with thiophosgene and the resulting intermediate reacted with the cannabinoid (CBD) under basic conditions to form the thiocarbonate group. Removal of the TBDMS ether and trimethylsilylethyl ester protecting groups is achieved under standard conditions of excess TBAF to give the desired product.



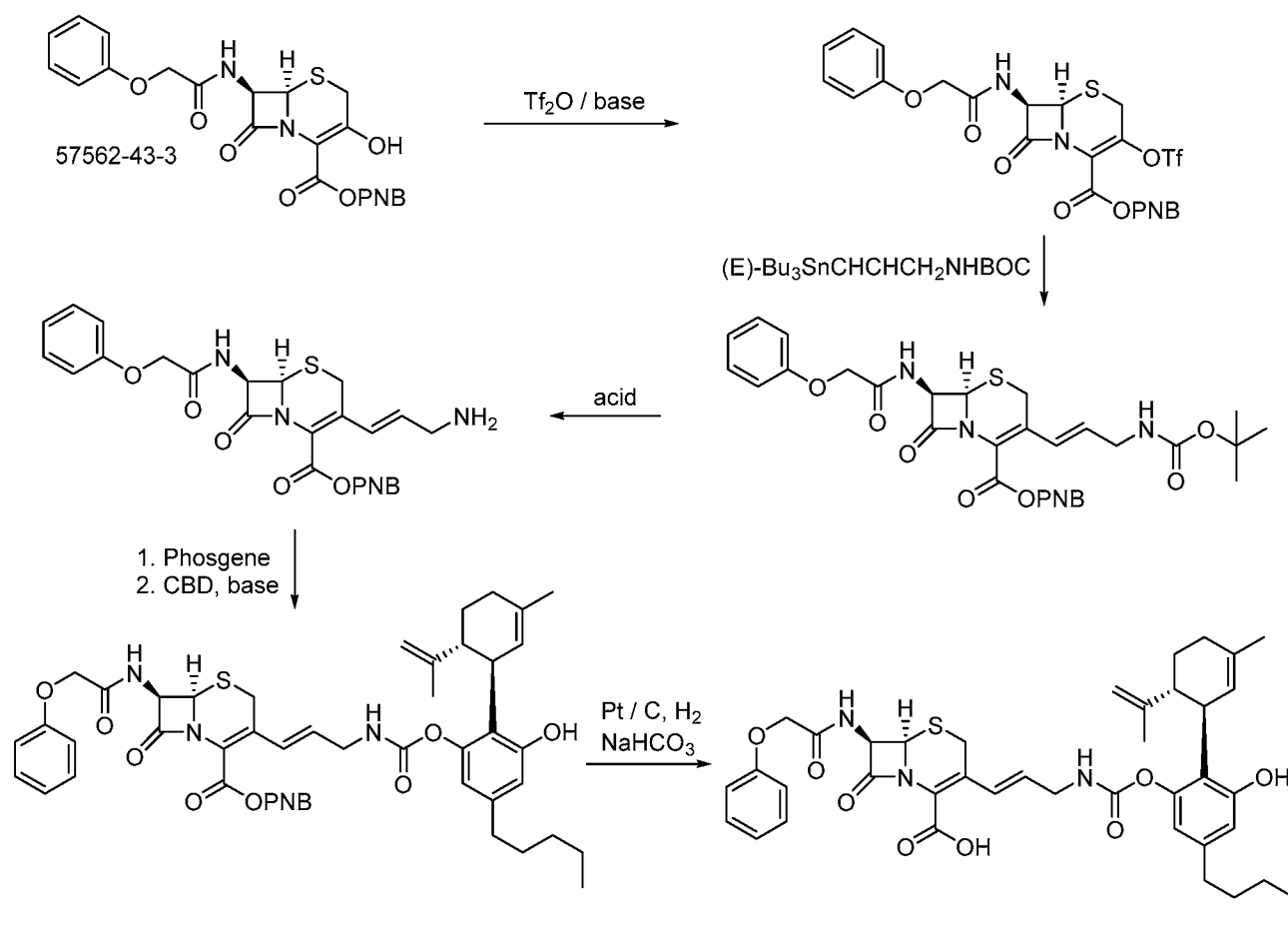
Carbapenem Conjugate Molecules

[118] Carbapenem propenyl thiocarbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material [165817-82-3] along with its conversion to the allylic alcohol intermediate has been described previously (WO 99/62906). The alcohol is then reacted with thiophosgene and the resulting intermediate reacted with the cannabinoid (CBD) under basic conditions to form the thiocarbonate group. Removal of the TES ether and PNB ester groups under standard conditions produces the desired product.



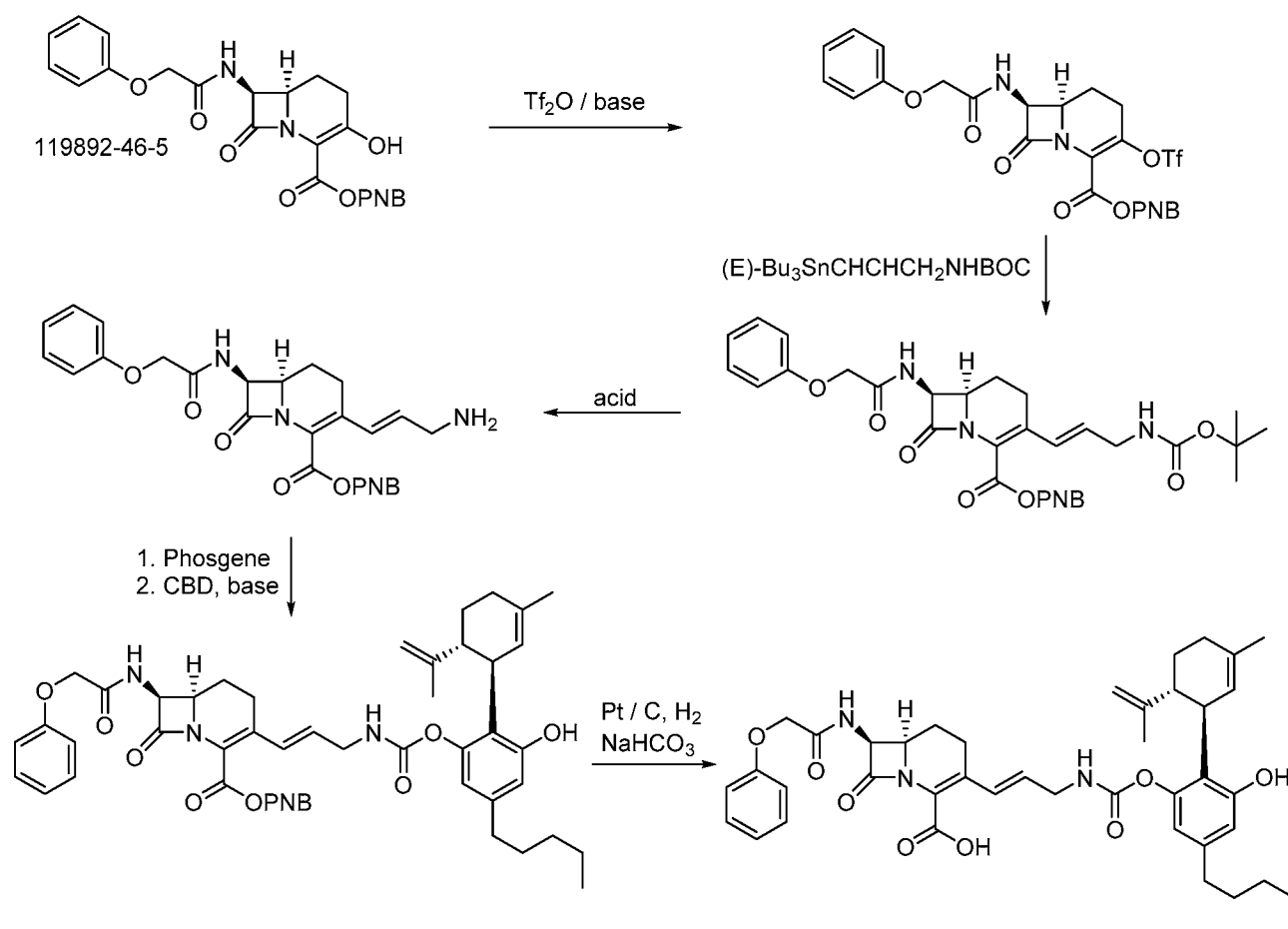
Example 10. Propenyl carbamate-linked conjugate molecules**Cephem Conjugate Molecules**

[119] Cephem propenyl carbamate linked conjugate molecules are synthesized according to the following Scheme. The starting material [57562-43-3] has been reported (CN 103588788 A 20140219). It is converted under standard conditions to the enol triflate, which is reacted with the BOC-protected aminoorganostannane [139111-44-7] (use in similar cephem triflate: Bioorganic & Medicinal Chemistry Letters (2010), 20(15), 4635-4638) followed by BOC removal under standard conditions to give the propenyl amine intermediate. This amine is reacted with phosgene and the resulting intermediate reacted with the cannabinoid (CBD) under basic conditions to form the carbamate group. Removal of the PNB ester group under standard conditions produces the desired product.



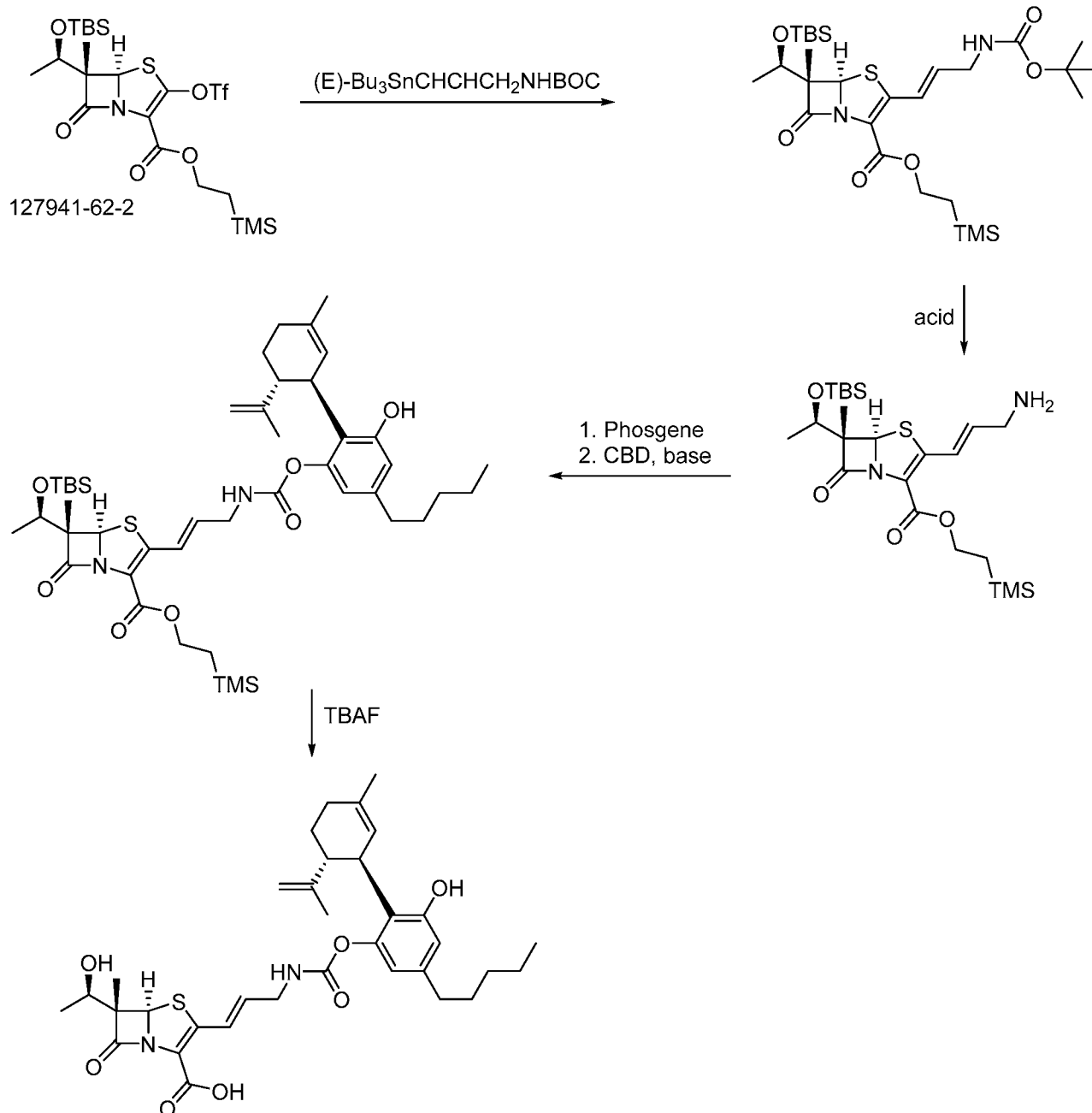
Carbacephem Conjugate Molecules

[120] Carbacephem propenyl carbamate linked conjugate molecules are synthesized according to the following Scheme. The starting material [119892-46-5] (WO 2010/030810, and references cited therein) is converted under standard conditions to the enol triflate, which is reacted with the BOC-protected aminoorganostannane [139111-44-7] (use in similar cephem triflate: Bioorganic & Medicinal Chemistry Letters (2010), 20(15), 4635-4638) followed by BOC removal under standard conditions to give the propenyl amine intermediate. This amine is reacted with phosgene and the resulting intermediate reacted with the cannabinoid (CBD) under basic conditions to form the carbamate group. Removal of the PNB ester group under standard conditions produces the desired product.



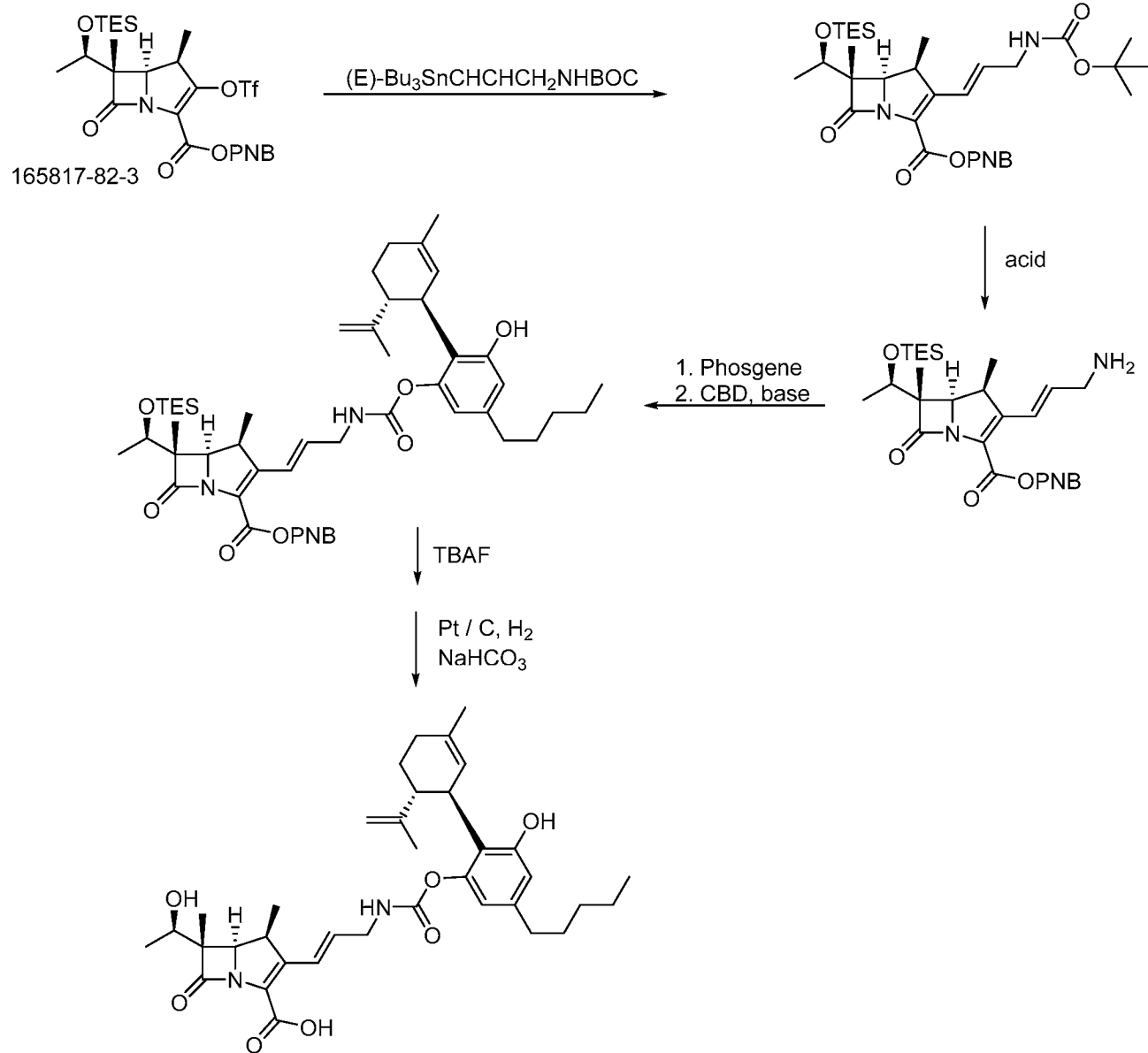
Penem Conjugate Molecules

[121] Penem propenyl carbamate linked conjugate molecules are synthesized according to the following Scheme. The starting material [127941-62-2] has been previously reported (U.S. patent 4,895,940). Reaction with the BOC-protected aminoorganostannane [139111-44-7] (use in similar cephem triflate: Bioorganic & Medicinal Chemistry Letters (2010), 20(15), 4635-4638) followed by BOC removal under standard conditions gives the propenyl amine intermediate. This amine is reacted with phosgene and the resulting intermediate reacted with the cannabinoid (CBD) under basic conditions to form the carbamate group. Removal of the TES ether and trimethylsilylethyl ester groups under standard conditions produces the desired product.



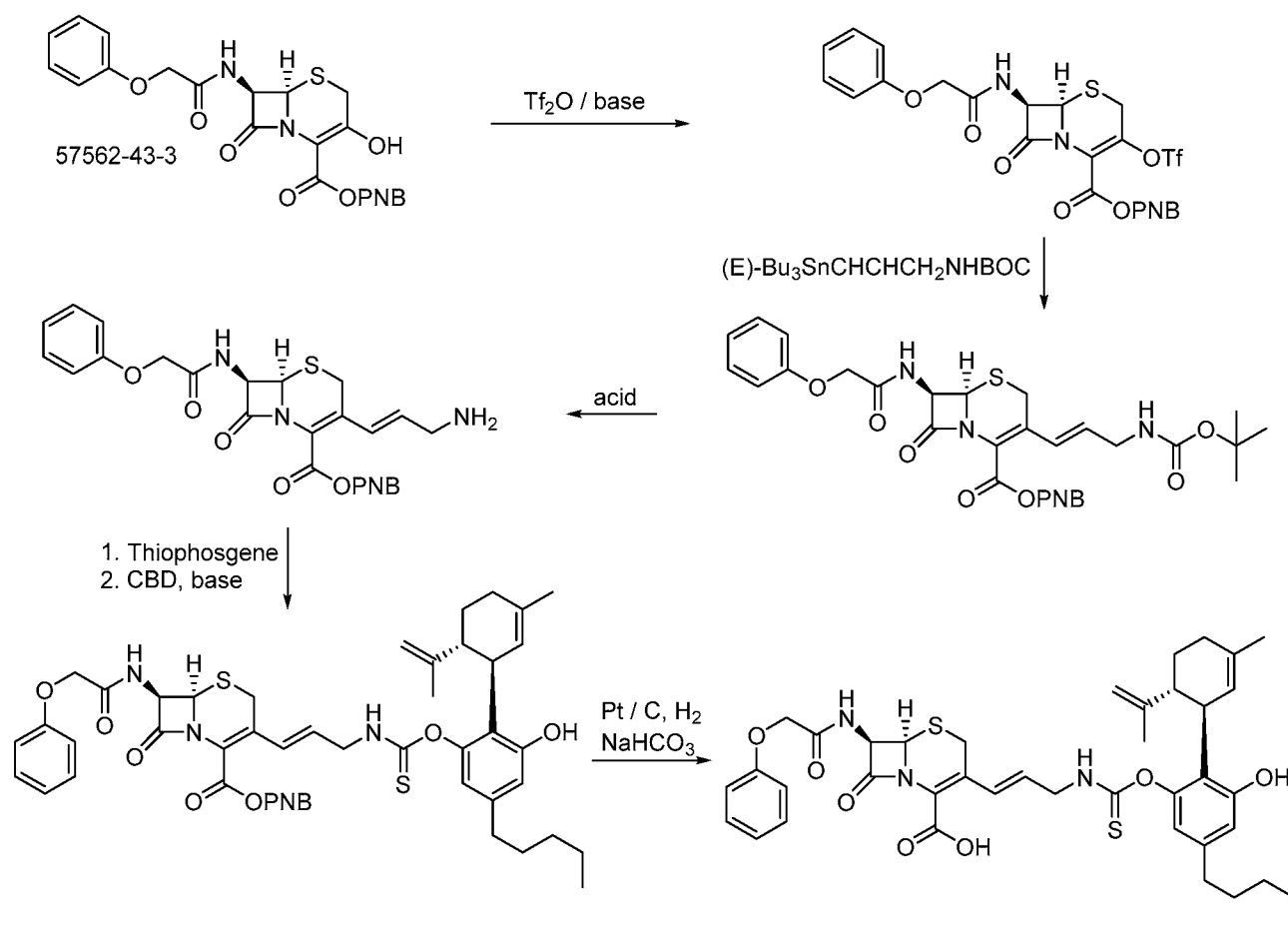
Carbapenem Conjugate Molecules

[122] Carbapenem propenyl carbamate linked conjugate molecules are synthesized according to the following Scheme. The starting material [165817-82-3] has been described previously (WO 99/62906). Reaction with the BOC-protected aminoorganostannane [139111-44-7] (use in similar cephem triflate: *Bioorganic & Medicinal Chemistry Letters* (2010), 20(15), 4635-4638) followed by BOC removal under standard conditions gives the propenyl amine intermediate. This amine is reacted with phosgene and the resulting intermediate reacted with the cannabinoid (CBD) under basic conditions to form the carbamate group. Removal of the TES ether and PNB ester groups under standard conditions produces the desired product.



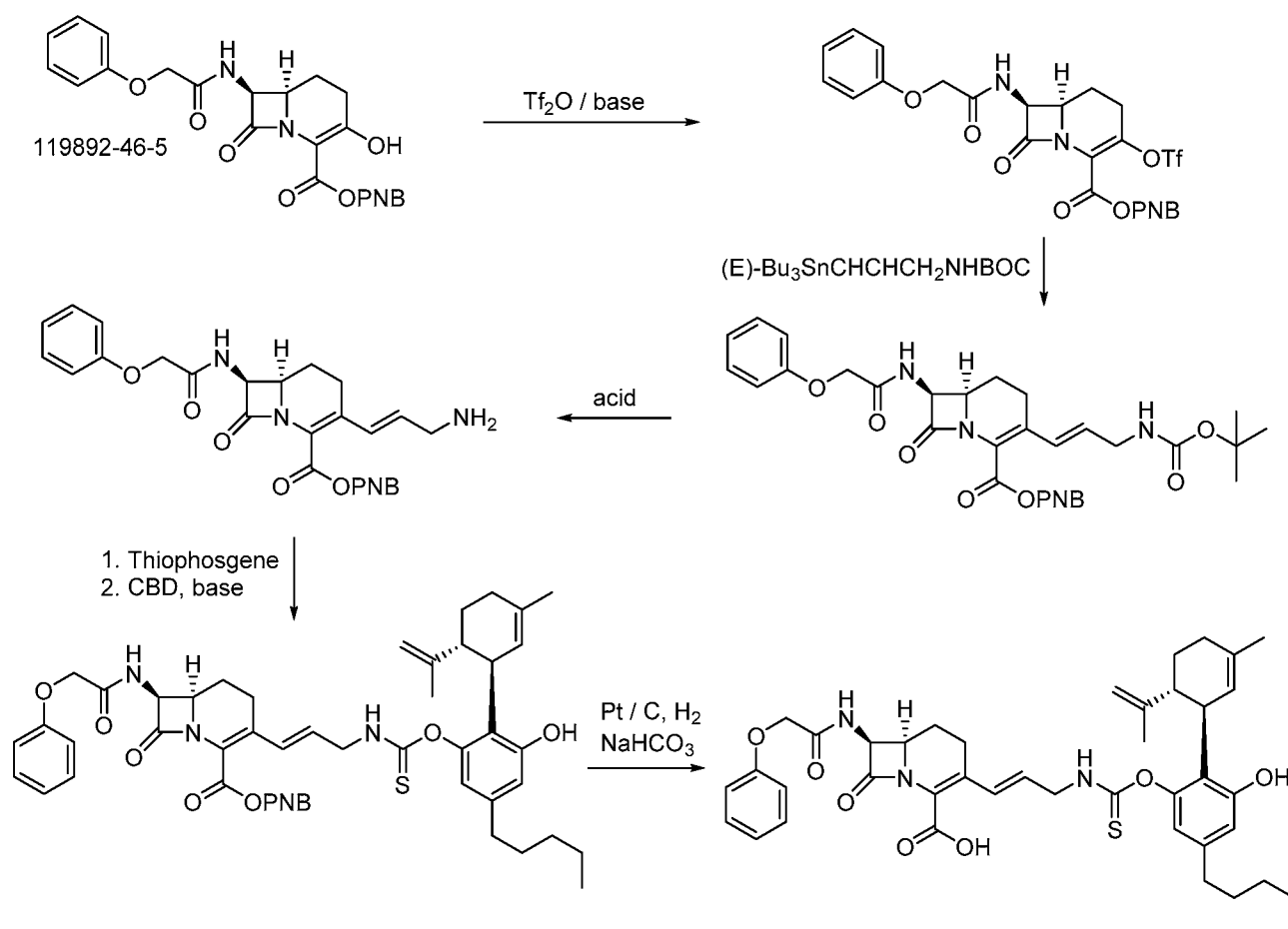
Example 11. Propenyl thiocarbamate-linked conjugate molecules**Cephem Conjugate Molecules**

[123] Cephem propenyl thiocarbamate linked conjugate molecules are synthesized according to the following Scheme. The starting material [57562-43-3] has been reported (CN 103588788 A 20140219). It is converted under standard conditions to the enol triflate, which is reacted with the BOC-protected aminoorganostannane [139111-44-7] (use in similar cephem triflate: Bioorganic & Medicinal Chemistry Letters (2010), 20(15), 4635-4638) followed by BOC removal under standard conditions to give the propenyl amine intermediate. This amine is reacted with thiophosgene and the resulting intermediate reacted with the cannabinoid (CBD) under basic conditions to form the thiocarbamate group. Removal of the PNB ester group under standard conditions produces the desired product.



Carbacephem Conjugate Molecules

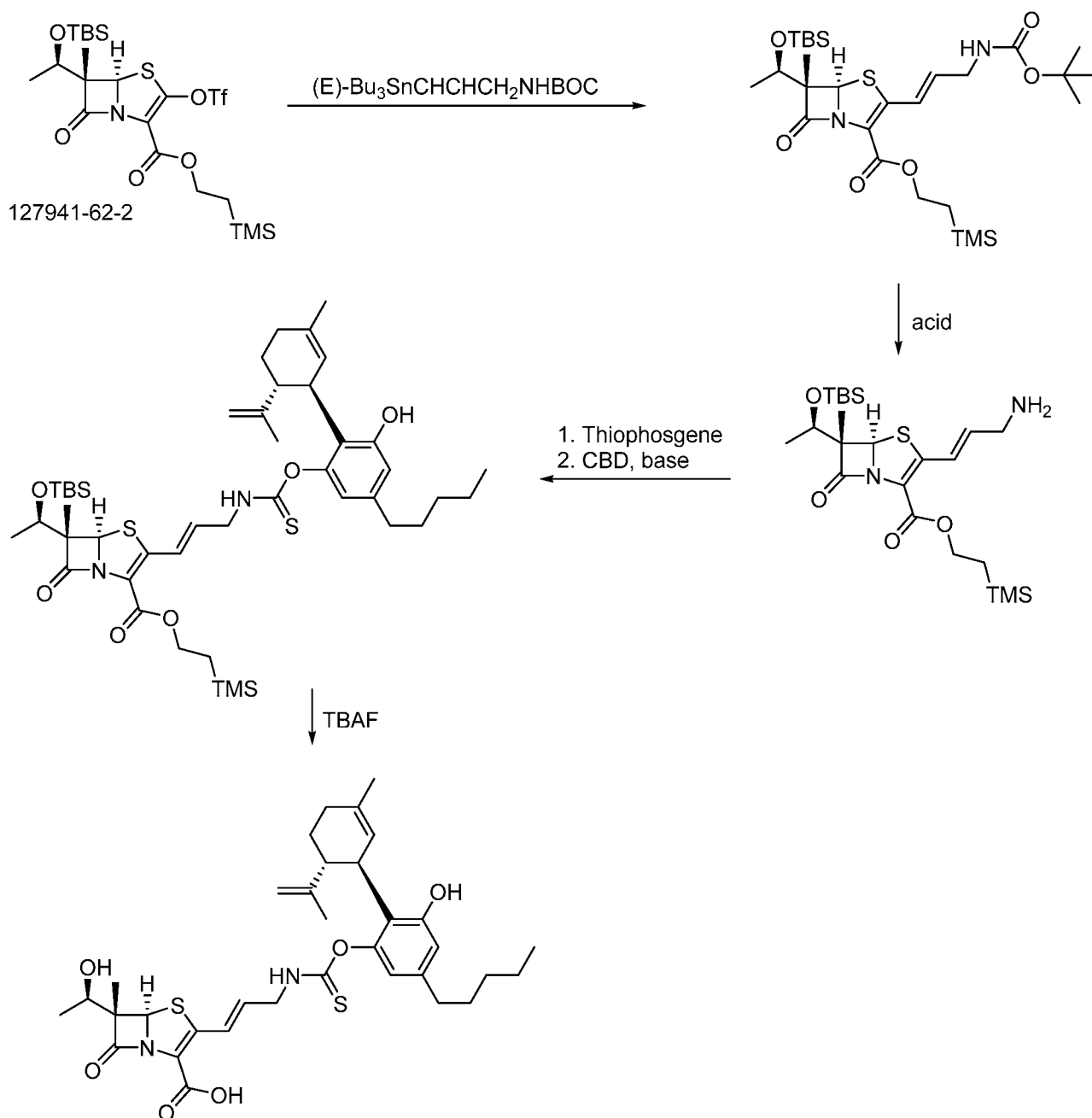
[124] Carbacephem propenyl thiocarbamate linked conjugate molecules are synthesized according to the following Scheme. The starting material [119892-46-5] (WO 2010/030810, and references cited therein) is converted under standard conditions to the enol triflate, which is reacted with the BOC-protected aminoorganostannane [139111-44-7] (use in similar cephem triflate: Bioorganic & Medicinal Chemistry Letters (2010), 20(15), 4635-4638) followed by BOC removal under standard conditions to give the propenyl amine intermediate. This amine is reacted with thiophosgene and the resulting intermediate reacted with the cannabinoid (CBD) under basic conditions to form the thiocarbamate group. Removal of the PNB ester group under standard conditions produces the desired product.



Penem Conjugate Molecules

[125] Penem propenyl thiocarbamate linked conjugate molecules are synthesized according to the following Scheme. The starting material [127941-62-2] has been previously reported (U.S. patent 4,895,940). Reaction with the BOC-protected aminoorganostannane [139111-44-7] (use in similar cephem triflate: Bioorganic & Medicinal Chemistry Letters (2010), 20(15), 4635-

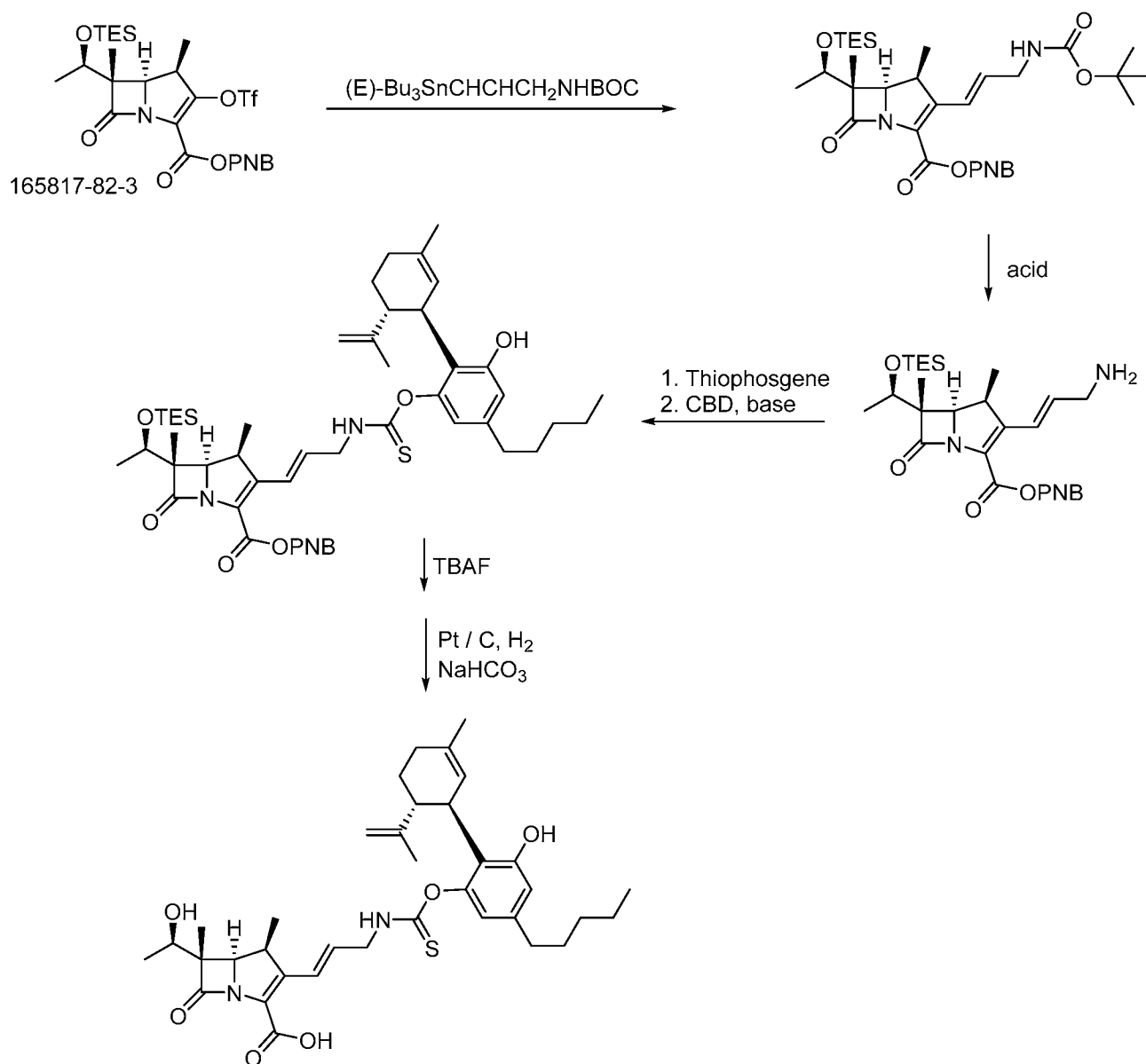
4638) followed by BOC removal under standard conditions gives the propenyl amine intermediate. This amine is reacted with thiophosgene and the resulting intermediate reacted with the cannabinoid (CBD) under basic conditions to form the thiocarbamate group. Removal of the TES ether and trimethylsilylethyl ester groups under standard conditions produces the desired product.



Carbapenem Conjugate Molecules

[126] Carbapenem propenyl thiocarbamate linked conjugate molecules are synthesized according to the following Scheme. The starting material [165817-82-3] has been described previously (WO 99/62906). Reaction with the BOC-protected aminoorganostannane [139111-

44-7] (use in similar cephem triflate: Bioorganic & Medicinal Chemistry Letters (2010), 20(15), 4635-4638) followed by BOC removal under standard conditions gives the propenyl amine intermediate. This amine is reacted with thiophosgene and the resulting intermediate reacted with the cannabinoid (CBD) under basic conditions to form the thiocarbamate group. Removal of the TES ether and PNB ester groups under standard conditions produces the desired product.

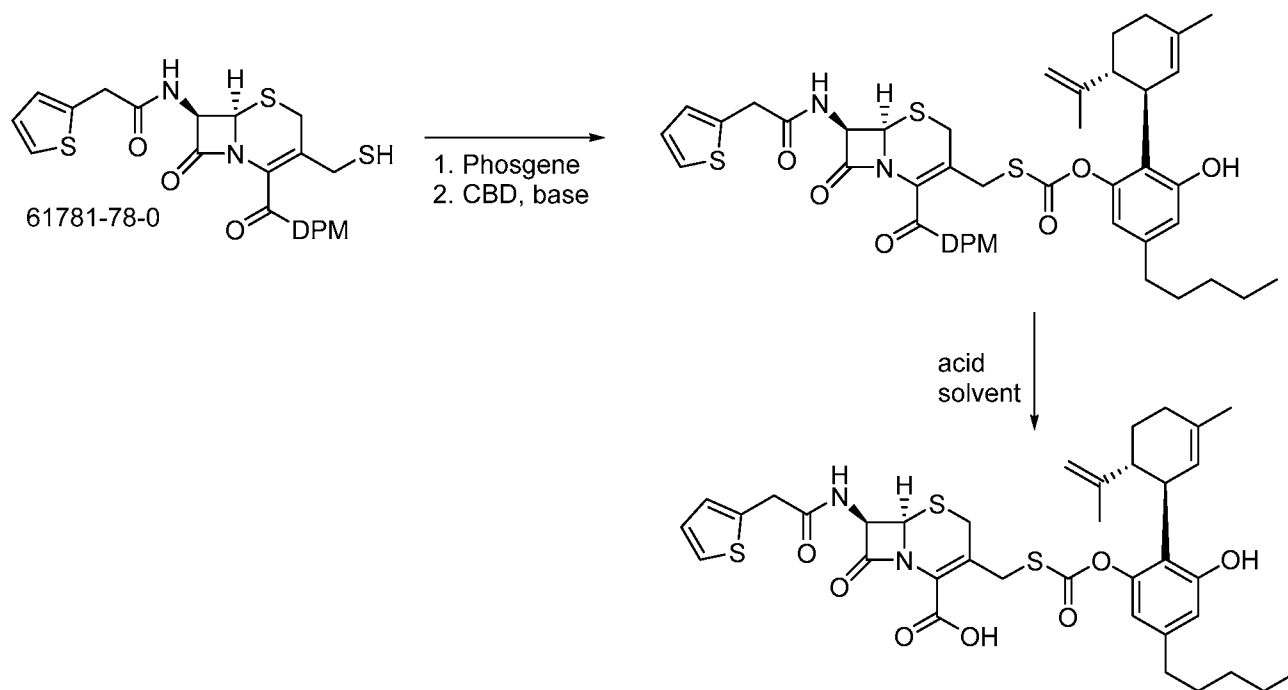


Example 12. S-alkyl thiocarbonate-linked conjugate molecules

Cephem Conjugate Molecules

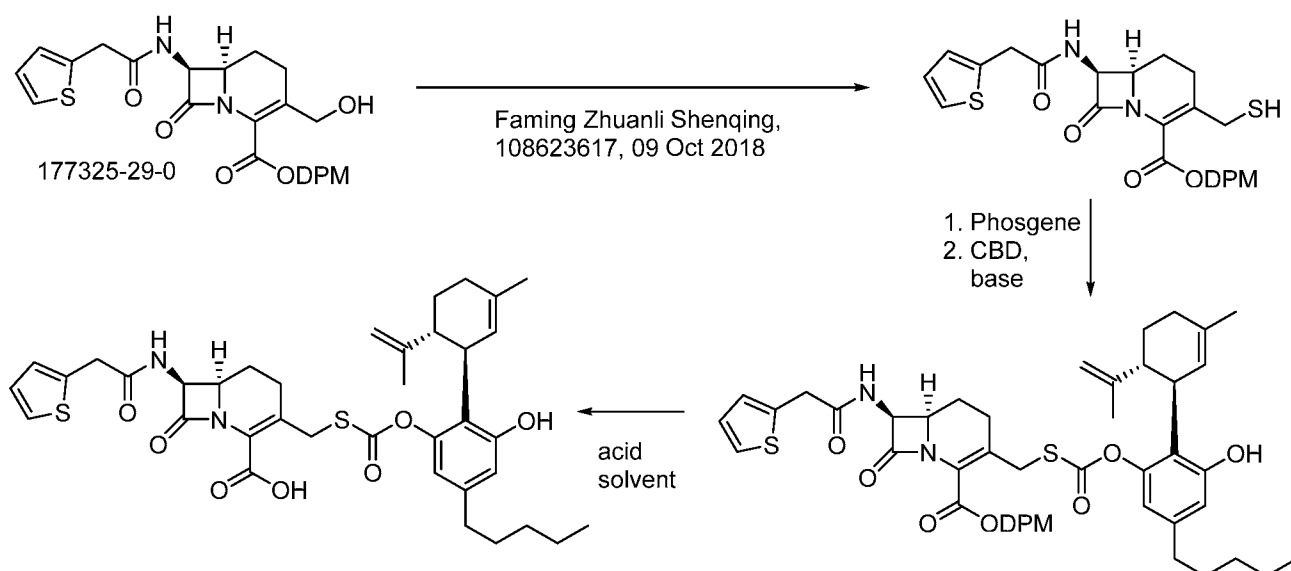
[127] Cephem S-alkyl thiocarbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material [61781-78-0] has been described previously (U.S. (1976), US 3979384 A 19760907). Reaction with phosgene and the cannabinoid (CBD) under

standard basic conditions to form the S-alkyl thiocarbonate linked intermediate. Removal of the diphenylmethyl ester protecting group gives the desired product.



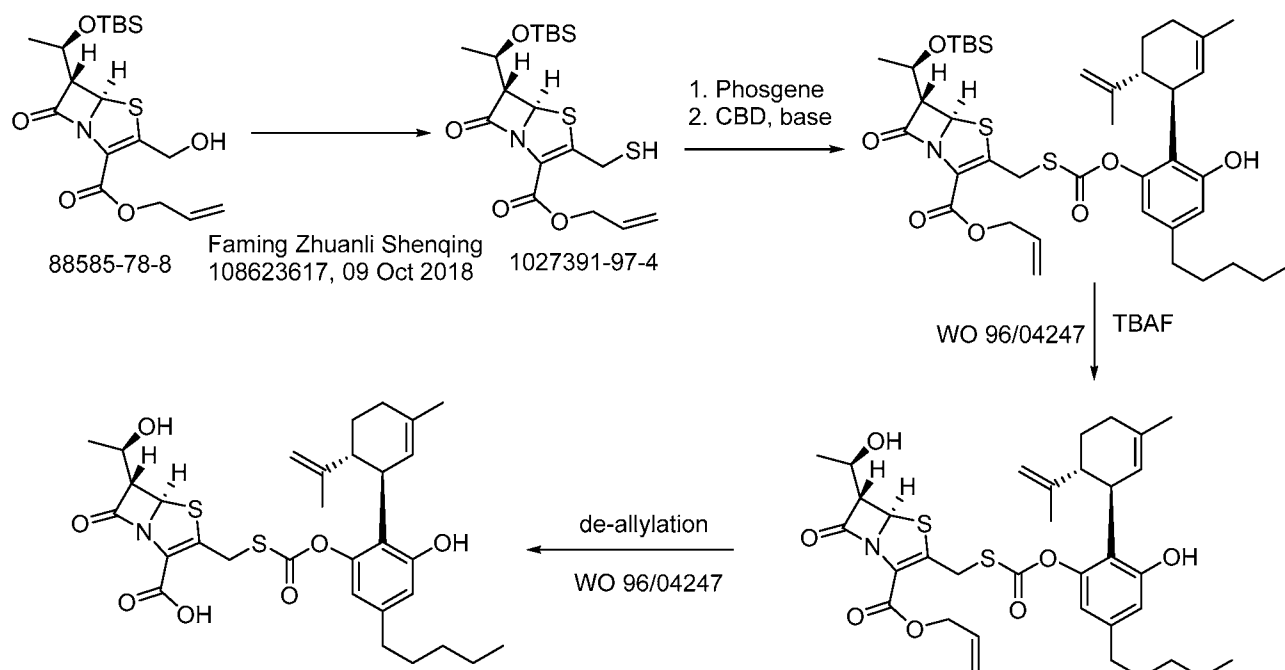
Carbacephem Conjugate Molecules

[128] Carbacephem S-alkyl thiocarbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material [177325-29-0] is converted to the thiol intermediate using previously described (Faming Zhuanli Shenqing, 108623617, 09 Oct 2018) conditions for a related system. The thiol intermediate is reacted with phosgene and the cannabinoid (CBD) under standard basic conditions to form the S-alkyl thiocarbonate linked intermediate. Removal of the diphenylmethyl ester protecting group gives the desired product.



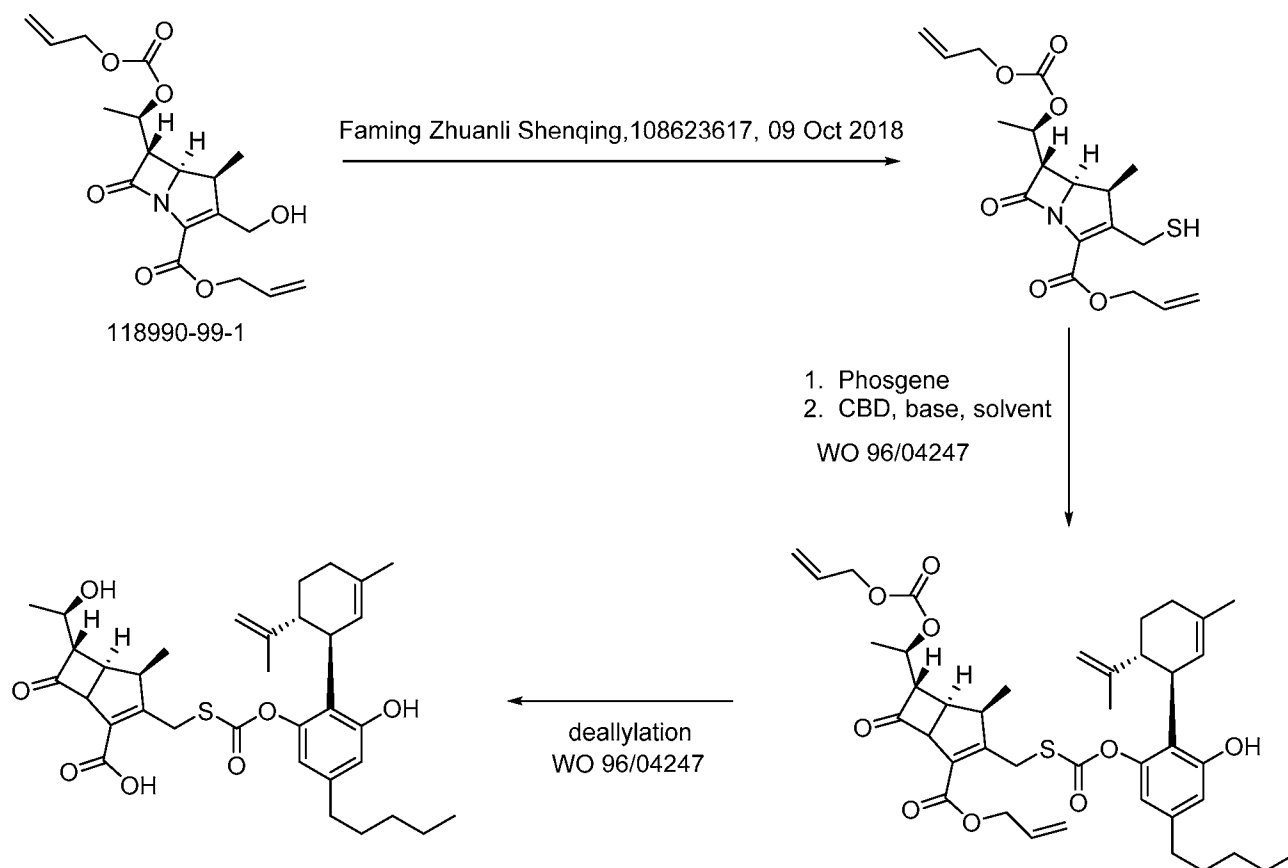
Penem Conjugate Molecules

[129] Penem S-alkyl thiocarbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material [88585-78-8] is converted to the thiol intermediate using previously described (Faming Zhuanli Shenqing, 108623617, 09 Oct 2018) conditions for a related system. The thiol intermediate is reacted with phosgene and the cannabinoid (CBD) under standard basic conditions to form the S-alkyl thiocarbonate linked intermediate. Removal of the silyl ether and allyl ester protecting groups gives the desired product.



Carbapenem Conjugate Molecules

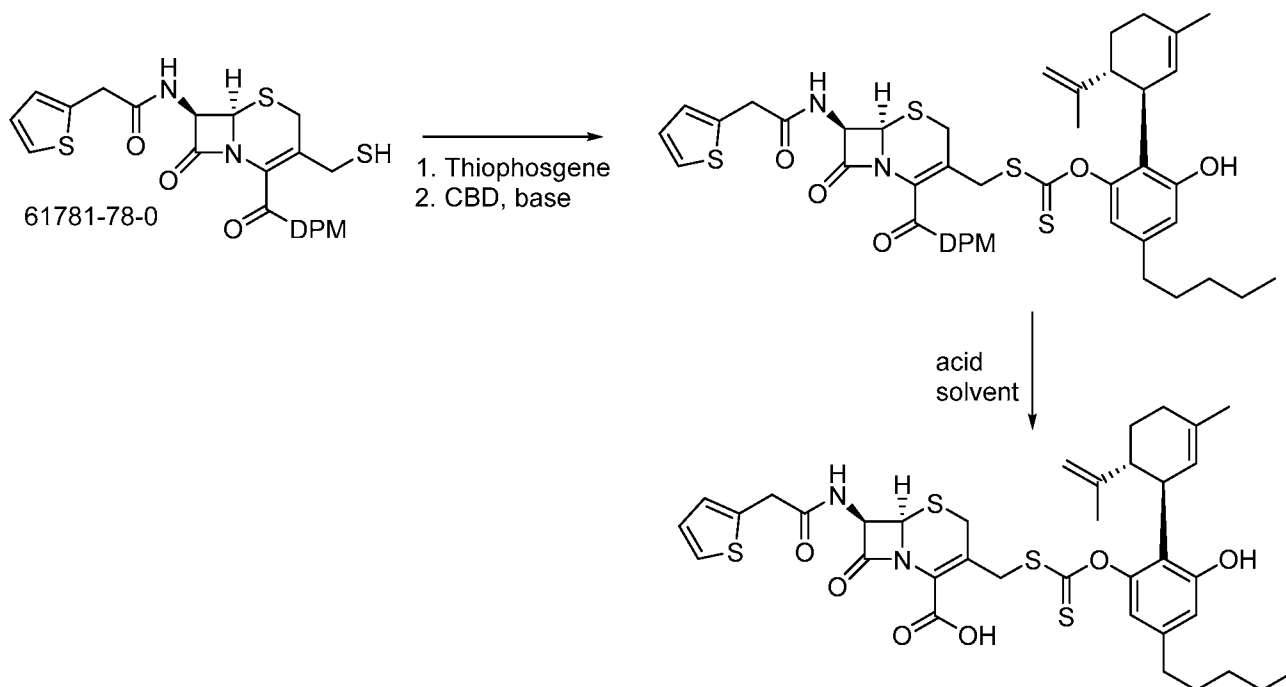
[130] Carbapenem S-alkyl thiocarbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material [118990-99-1] is converted to the thiol intermediate using previously described (Faming Zhuanli Shenqing, 108623617, 09 Oct 2018) conditions for a related system. The thiol intermediate is reacted with phosgene and the cannabinoid (CBD) under standard basic conditions to form the S-alkyl thiocarbonate linked intermediate. Removal of the allyl protecting groups gives the desired product.



Example 13. Xanthate-linked conjugate molecules

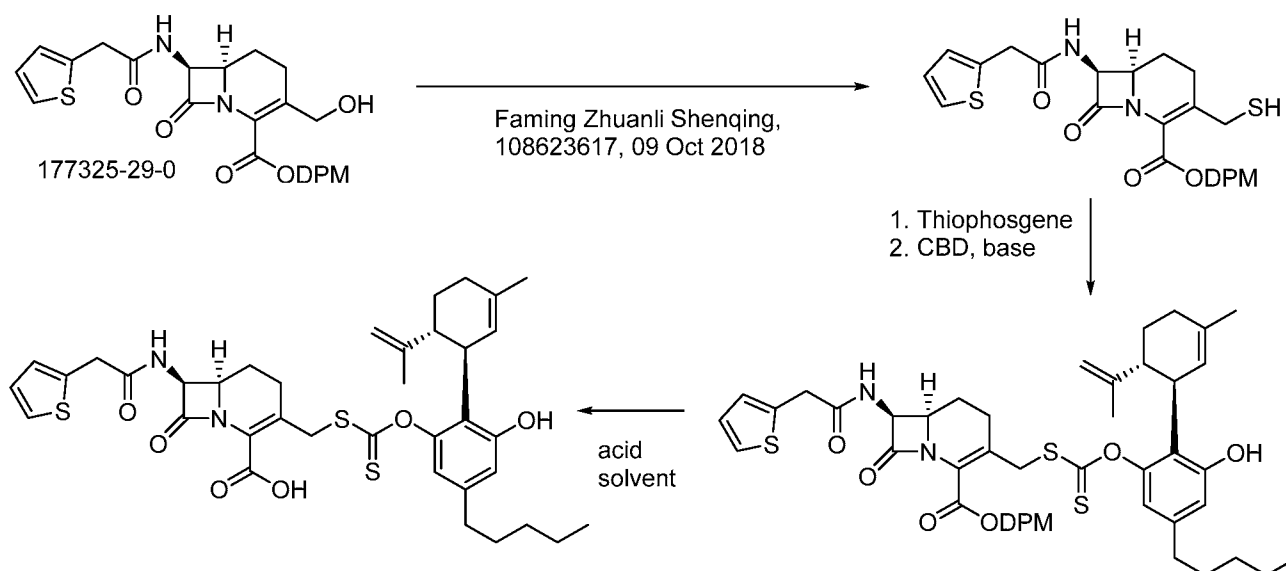
Cephem Conjugate Molecules

[131] Cephem xanthate linked conjugate molecules are synthesized according to the following Scheme. The starting material [61781-78-0] has been described previously (U.S. (1976), US 3979384 A 19760907). Reaction with thiophosgene and the cannabinoid (CBD) under standard basic conditions to form the xanthate linked intermediate. Removal of the diphenylmethyl ester protecting group gives the desired product.



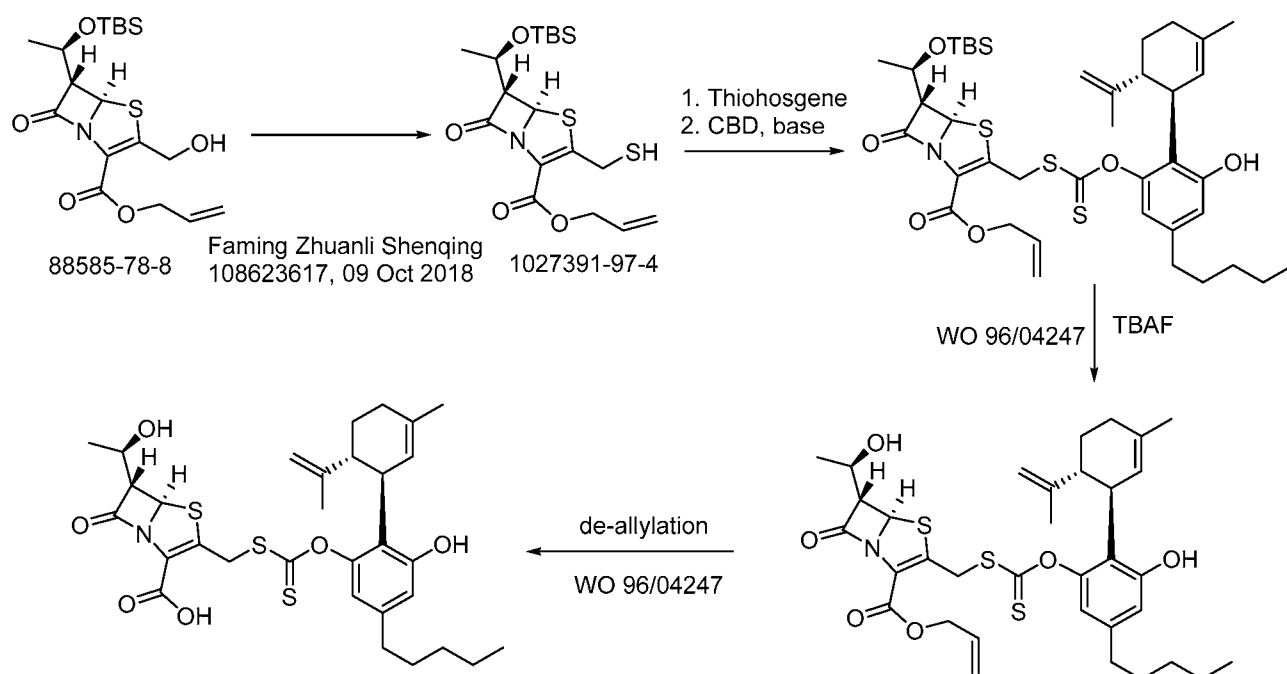
Carbacephem Conjugate Molecules

[132] Carbacephem xanthate linked conjugate molecules are synthesized according to the following Scheme. The starting material [177325-29-0] is converted to the thiol intermediate using previously described (Faming Zhuanli Shenqing, 108623617, 09 Oct 2018) conditions for a related system. The thiol intermediate is reacted with thiophosgene and the cannabinoid (CBD) under standard basic conditions to form the xanthate linked intermediate. Removal of the diphenylmethyl ester protecting group gives the desired product.



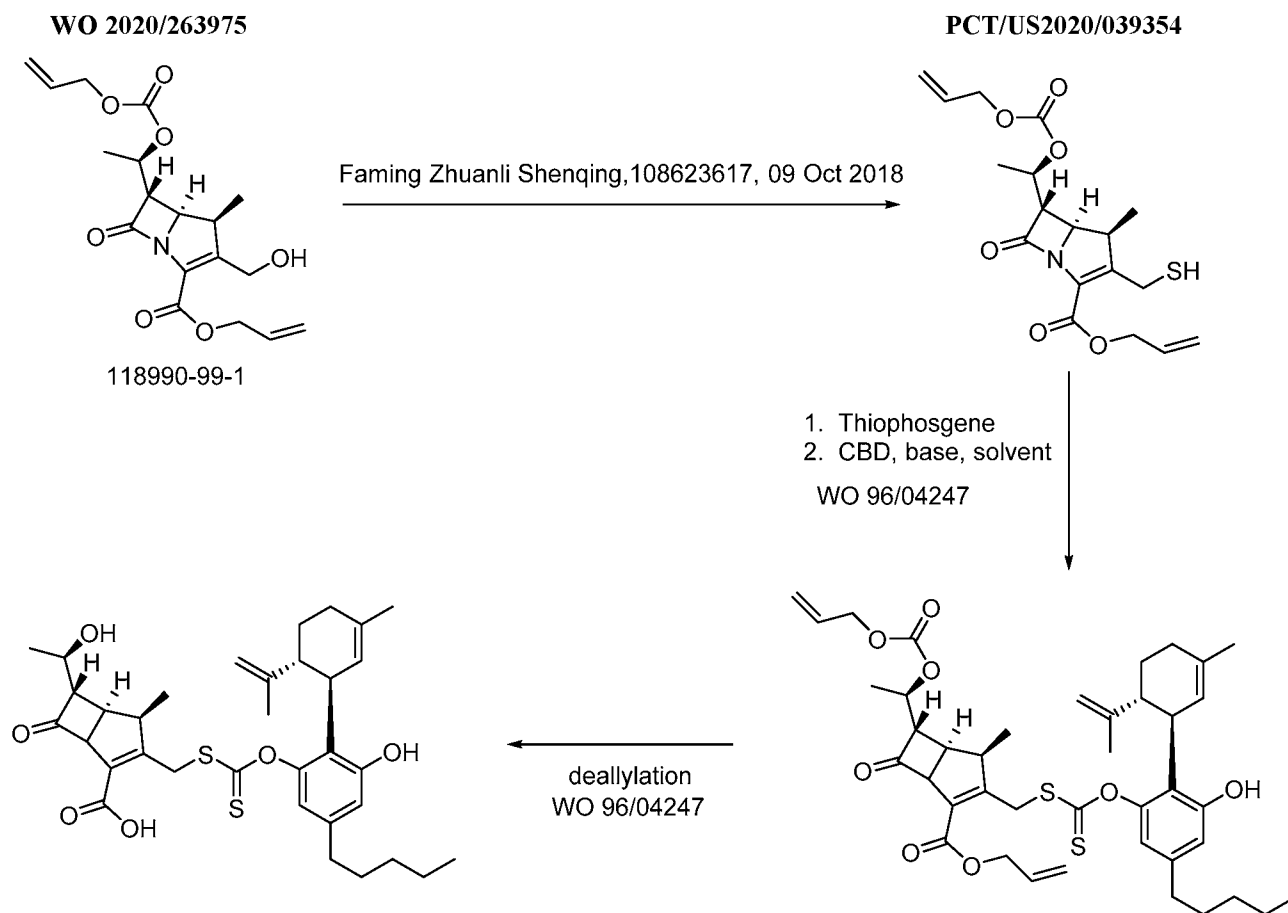
Penem Conjugate Molecules

[133] Penem xanthate linked conjugate molecules are synthesized according to the following Scheme. The starting material [88585-78-8] is converted to the thiol intermediate using previously described (Faming Zhuanli Shenqing, 108623617, 09 Oct 2018) conditions for a related system. The thiol intermediate is reacted with thiophosgene and the cannabinoid (CBD) under standard basic conditions to form the xanthate linked intermediate. Removal of the silyl ether and allyl ester protecting groups gives the desired product.



Carbapenem Conjugate Molecules

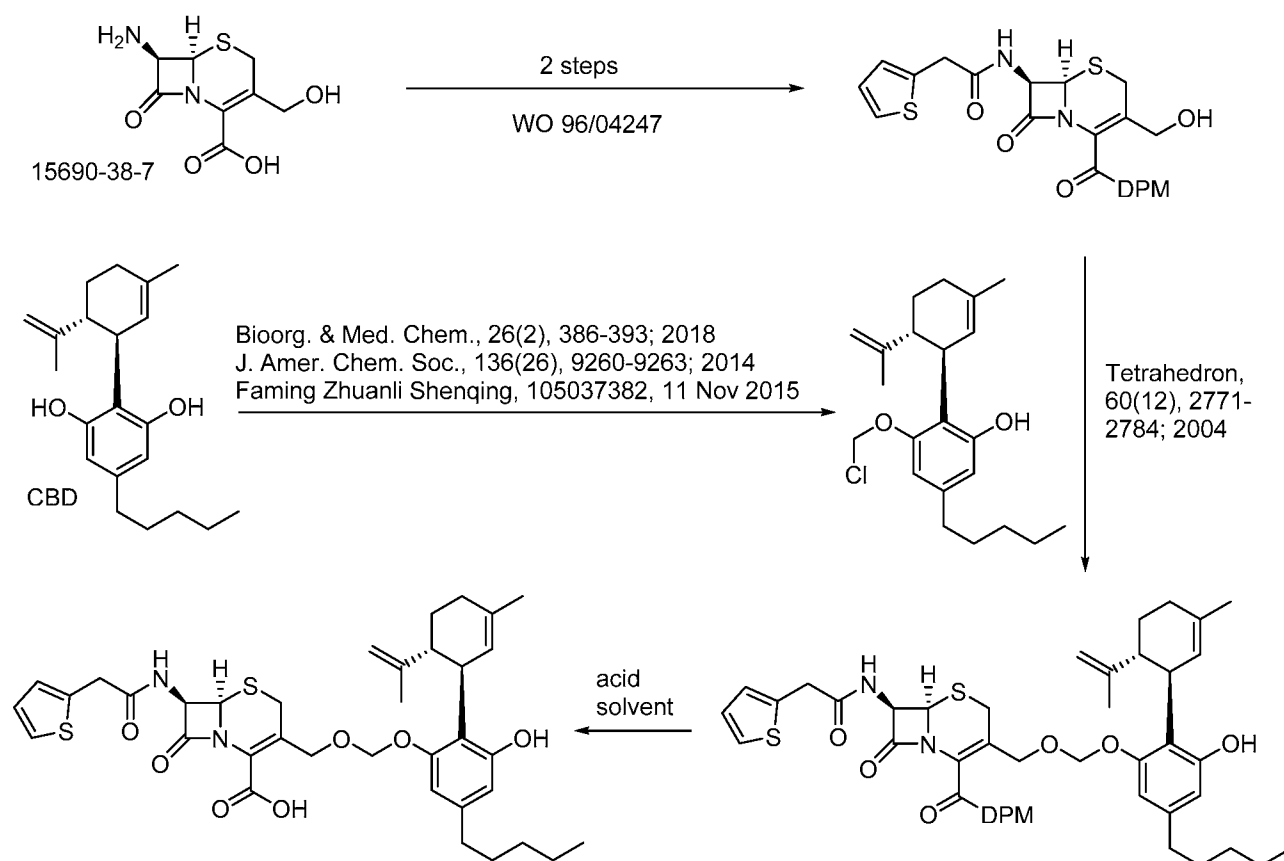
[134] Carbapenem xanthate linked conjugate molecules are synthesized according to the following Scheme. The starting material [118990-99-1] is converted to the thiol intermediate using previously described (Faming Zhuanli Shenqing, 108623617, 09 Oct 2018) conditions for a related system. The thiol intermediate is reacted with thiophosgene and the cannabinoid (CBD) under standard basic conditions to form the xanthate linked intermediate. Removal of the allyl protecting groups gives the desired product.



Example 14. Acetal-linked conjugate molecules

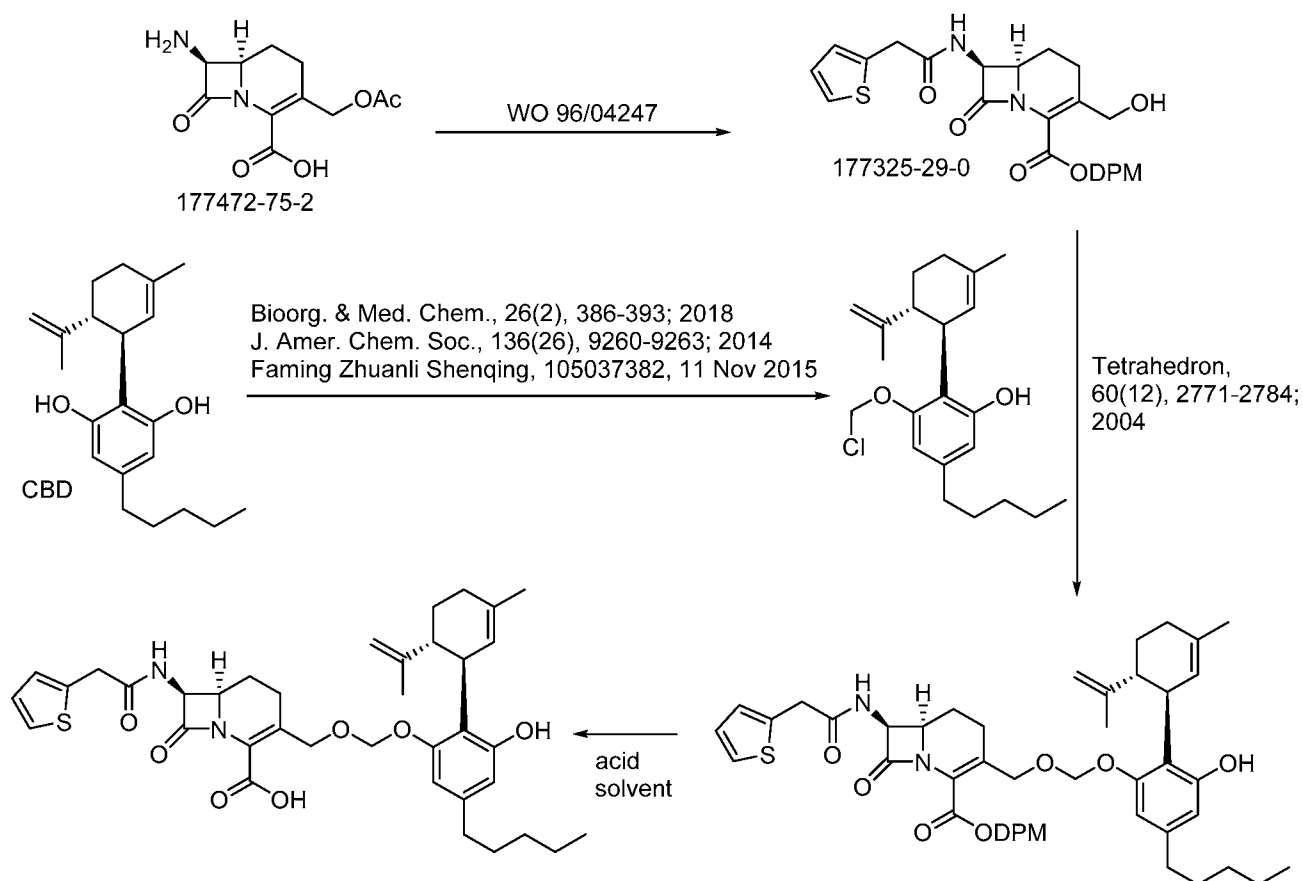
Cephem Conjugate Molecules

[135] Cephem acetal linked conjugate molecules are synthesized according to the following Scheme. The starting material [15690-38-7] is converted to a hydroxymethyl intermediate containing a side chain and protecting ester of choice as described in the literature (WO 96/04247). A cannabinoid (CBD) is converted to the O-chloromethyl intermediate via reported conditions (Bioorg. & Med. Chem., 26(2), 386-393; 2018; J. Amer. Chem. Soc., 136(26), 9260-9263; 2014; Faming Zhuanli Shenqing, 105037382, 11 Nov 2015). The hydroxymethyl and O-chloromethyl intermediates are reacted under previously reported conditions (Tetrahedron, 60(12), 2771-2784; 2004) to generate the acetal link. Removal of the diphenylmethyl ester protecting group gives the product.



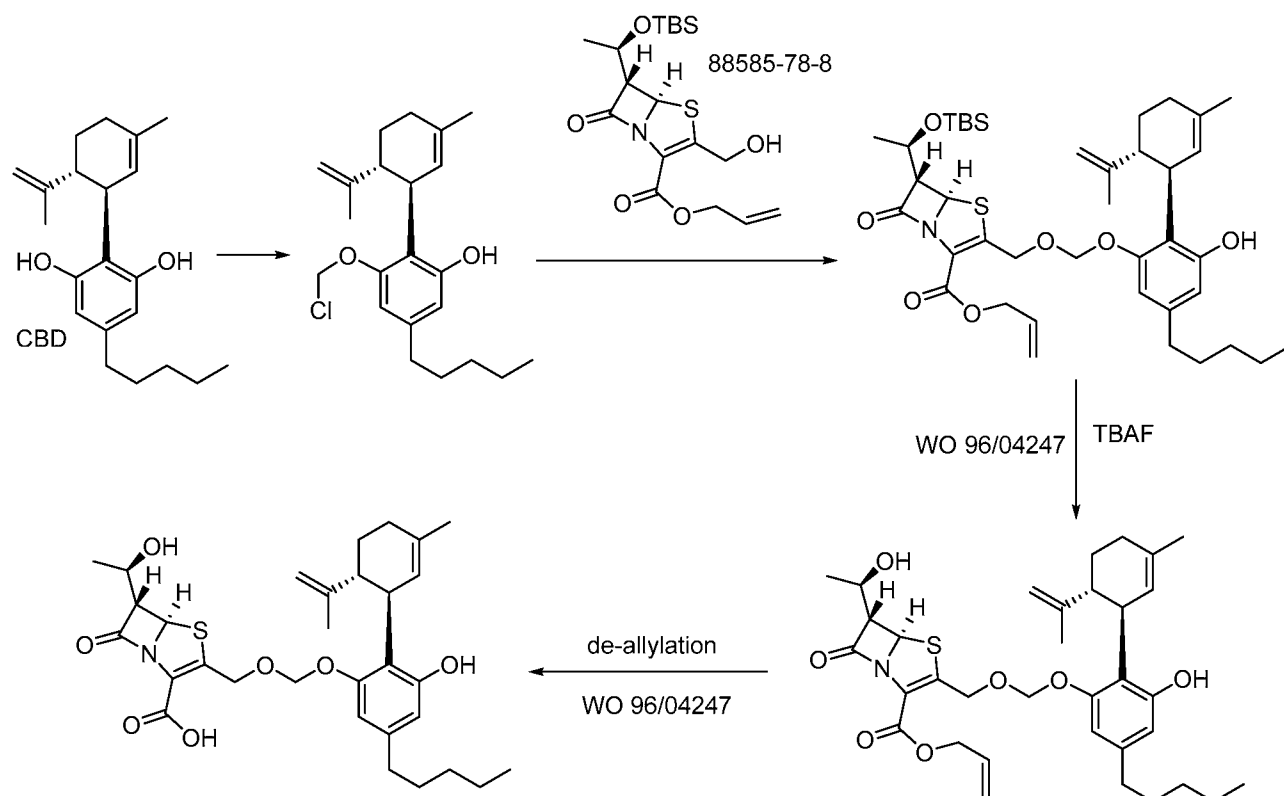
Carbacephem Conjugate Molecules

[136] Carbacephem acetal linked conjugate molecules are synthesized according to the following Scheme. The starting material [177472-75-2] is converted to a hydroxymethyl intermediate containing a side chain and protecting ester of choice as described in the literature (WO 96/04247). A cannabinoid (CBD) is converted to the O-chloromethyl intermediate via reported conditions (Bioorg. & Med. Chem., 26(2), 386-393; 2018; J. Amer. Chem. Soc., 136(26), 9260-9263; 2014; Faming Zhuanli Shenqing, 105037382, 11 Nov 2015). The hydroxymethyl and O-chloromethyl intermediates are reacted under previously reported conditions (Tetrahedron, 60(12), 2771-2784; 2004) to generate the acetal link. Removal of the diphenylmethyl ester protecting group gives the product.



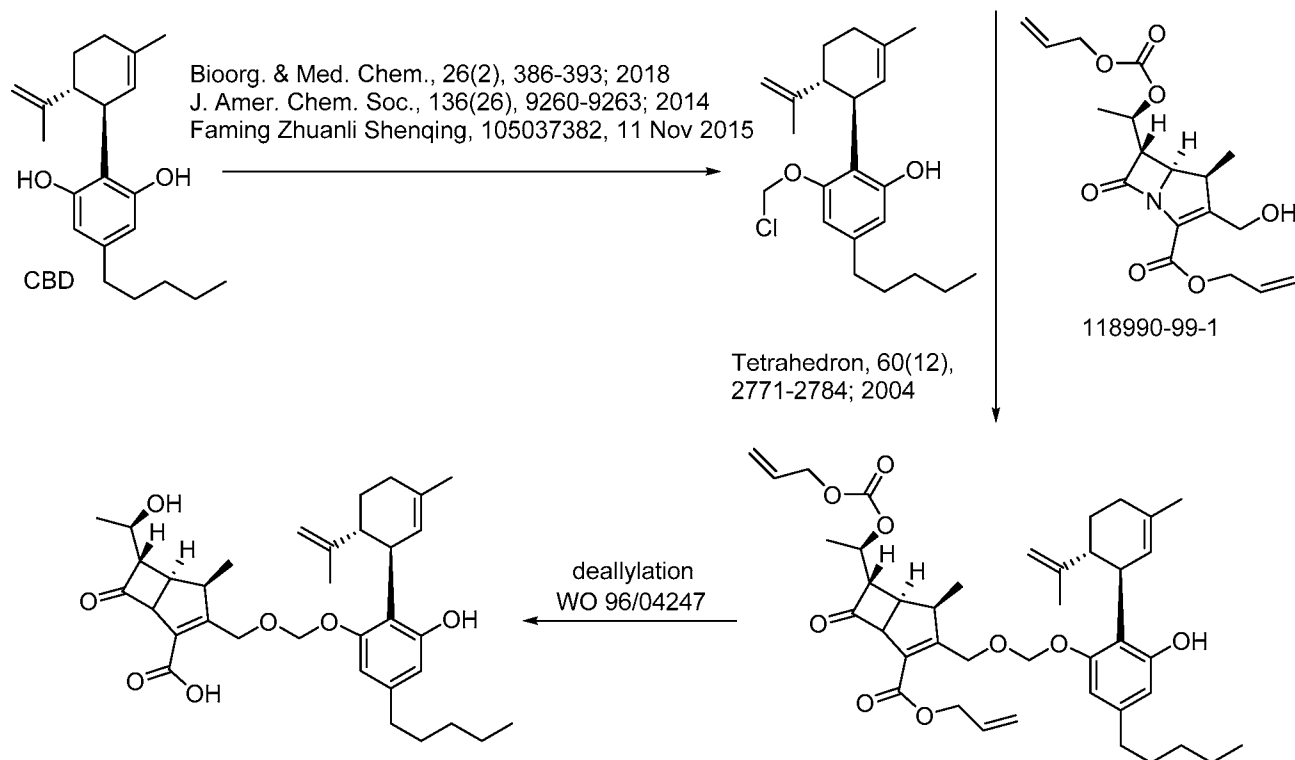
Penem Conjugate Molecules

[137] Penem acetal linked conjugate molecules are synthesized according to the following Scheme. A cannabinoid (CBD) is converted to its O-chloromethyl intermediate via reported conditions (Bioorg. & Med. Chem., 26(2), 386-393; 2018; J. Amer. Chem. Soc., 136(26), 9260-9263; 2014; Faming Zhuanli Shenqing, 105037382, 11 Nov 2015). This intermediate is reacted with a hydroxymethyl penem [88585-78-8] under reported conditions (Tetrahedron, 60(12), 2771-2784; 2004) to form the acetal link. Removal of the silyl ether and allyl ester protecting groups under standard conditions gives the product.



Carbapenem Conjugate Molecules

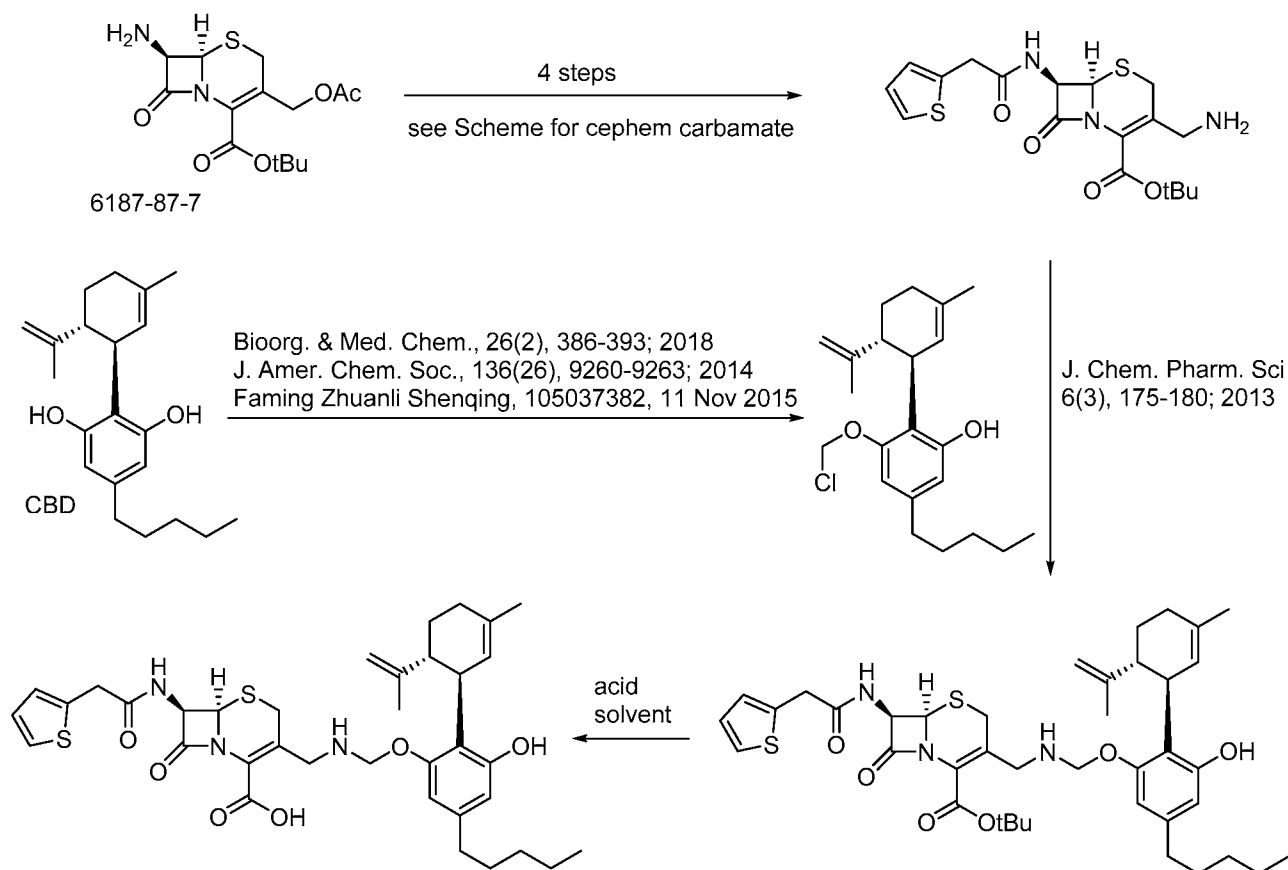
[138] Carbapenem acetal linked conjugate molecules are synthesized according to the following Scheme. A cannabinoid (CBD) is converted to its O-chloromethyl intermediate via reported conditions (Bioorg. & Med. Chem., 26(2), 386-393; 2018; J. Amer. Chem. Soc., 136(26), 9260-9263; 2014; Faming Zhuanli Shenqing, 105037382, 11 Nov 2015). This intermediate is reacted with a hydroxymethyl carbapenem [118990-99-1] under reported conditions (Tetrahedron, 60(12), 2771-2784; 2004) to form the acetal link. Removal of the allyl protecting groups under standard conditions gives the product.



Example 15. Amino-linked conjugate molecules

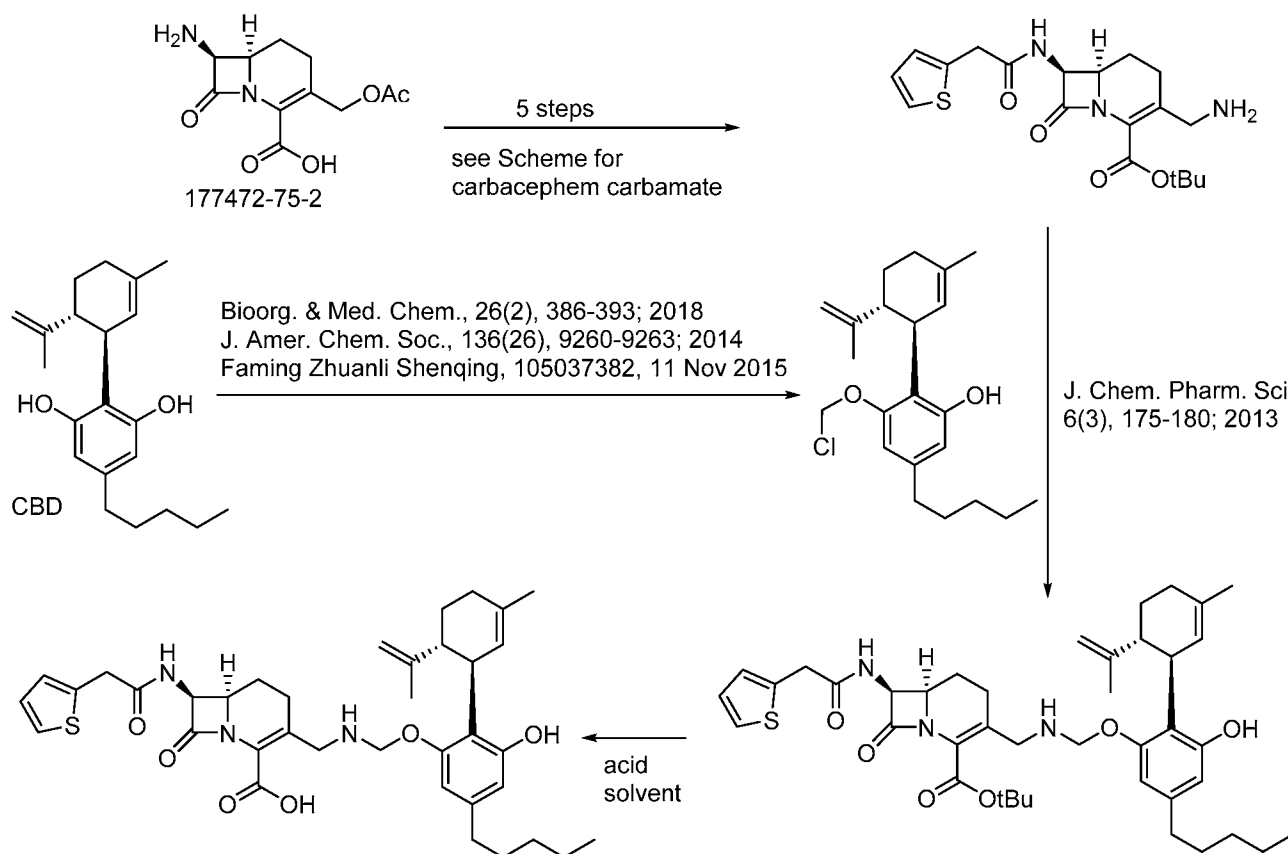
Cephem Conjugate Molecules

[139] Cephem amino-linked conjugate molecules are synthesized according to the following Scheme. The aminomethyl cephem intermediate is synthesized according to the scheme shown above for cephem carbamate-linked conjugate molecules. A cannabinoid (CBD) is converted to its O-chloromethyl intermediate via reported conditions (Bioorg. & Med. Chem., 26(2), 386-393; 2018; J. Amer. Chem. Soc., 136(26), 9260-9263; 2014; Faming Zhuanli Shenqing, 105037382, 11 Nov 2015). This intermediate is reacted (for conditions and related examples, see Journal of Chemical and Pharmaceutical Sciences, 6(3), 175-180; 2013) with the aminomethyl cephem to give the amino-linked intermediate. Removal of the t-butyl ester protecting group gives the product.



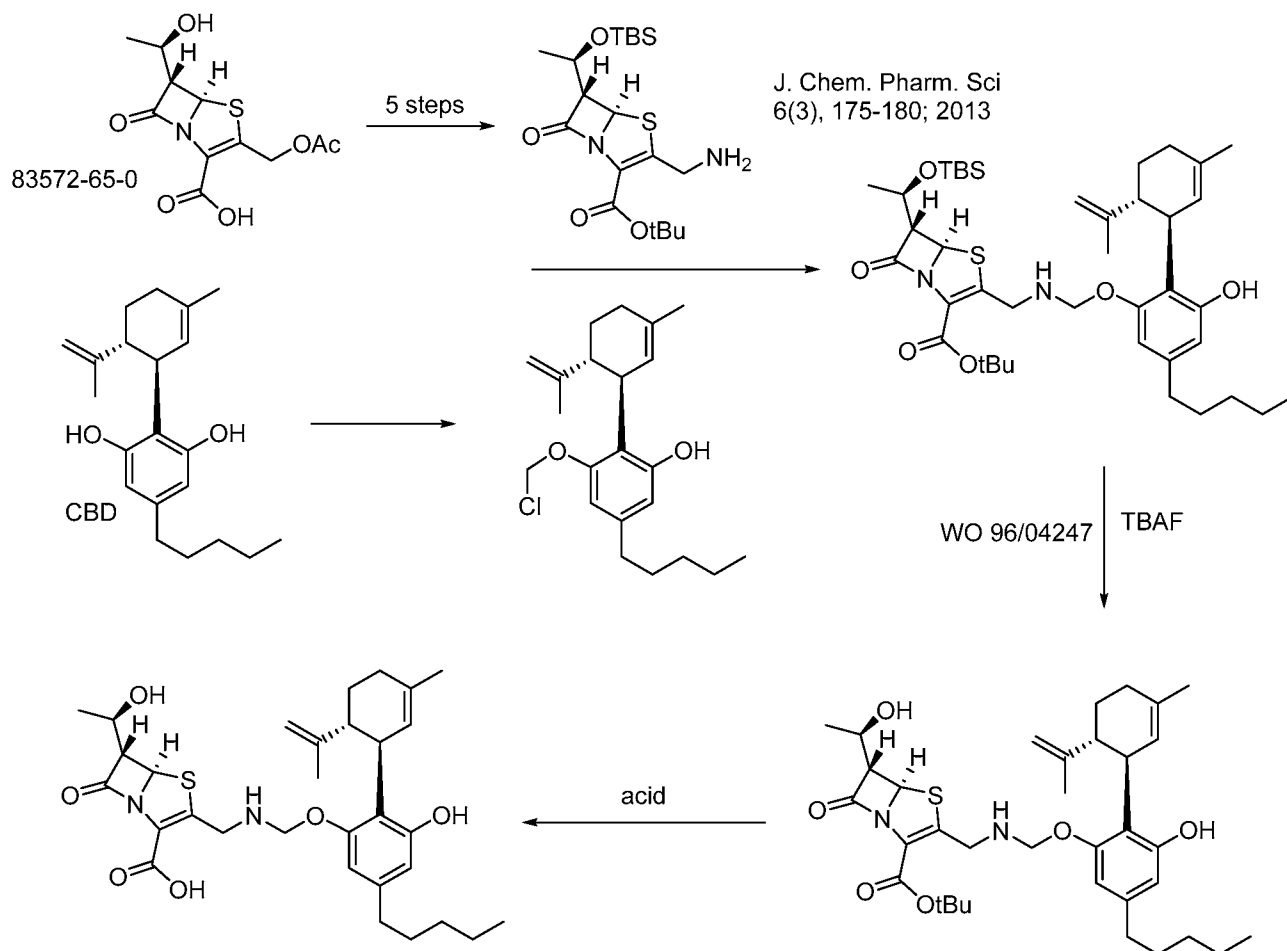
Carbacephem Conjugate Molecules

[140] Carbacephem aminal linked conjugate molecules are synthesized according to the following Scheme. The aminomethyl carbacephem intermediate is synthesized according to the scheme shown above for carbacephem carbamate linked conjugate molecules. A cannabinoid (CBD) is converted to its O-chloromethyl intermediate via reported conditions (Bioorg. & Med. Chem., 26(2), 386-393; 2018; J. Amer. Chem. Soc., 136(26), 9260-9263; 2014; Faming Zhuanli Shenqing, 105037382, 11 Nov 2015). This intermediate is reacted (for conditions and related examples, see Journal of Chemical and Pharmaceutical Sciences, 6(3), 175-180; 2013) with the aminomethyl carbacephem to give the aminal linked intermediate. Removal of the t-butyl ester protecting group gives the product.



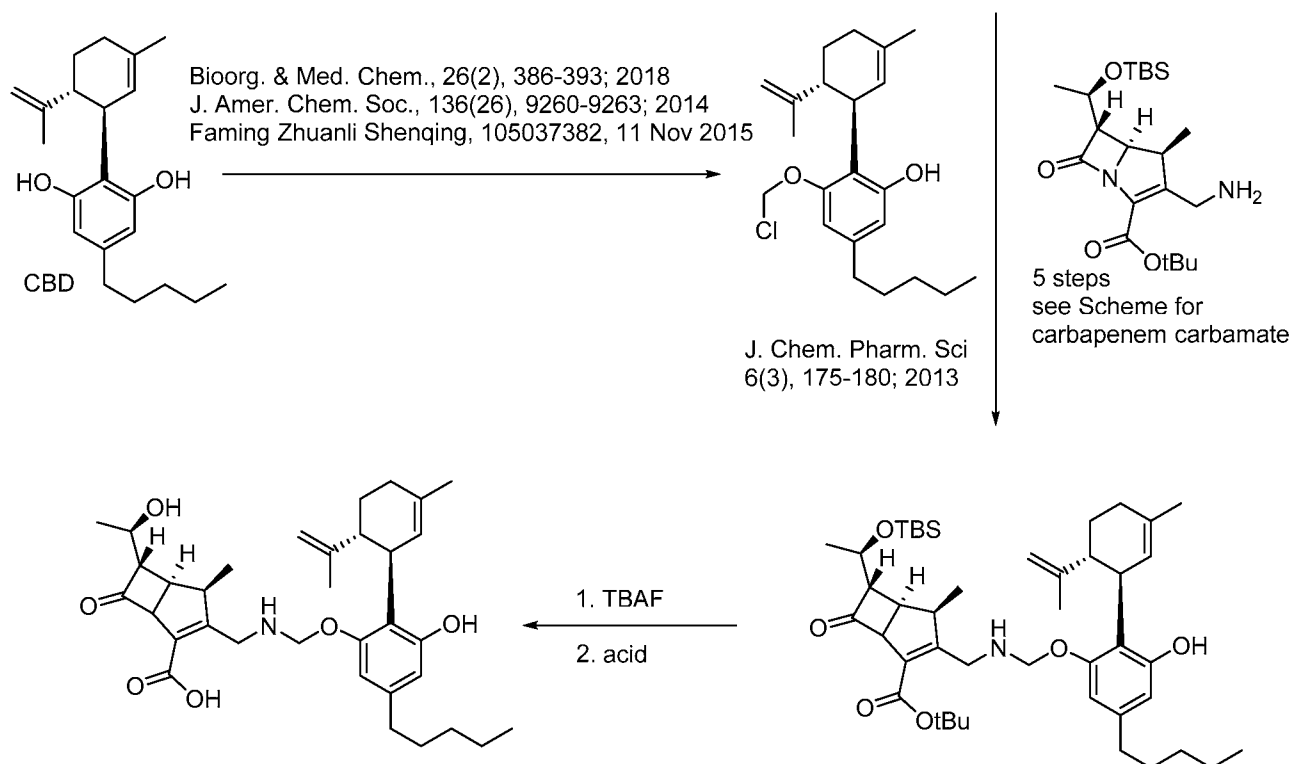
Penem Conjugate Molecules

[141] Penem amination linked conjugate molecules are synthesized according to the following Scheme. The aminomethyl penem intermediate is synthesized in 5 steps according to the scheme shown above for penem carbamate linked conjugate molecules. A cannabinoid (CBD) is converted to its O-chloromethyl intermediate via reported conditions (Bioorg. & Med. Chem., 26(2), 386-393; 2018; J. Amer. Chem. Soc., 136(26), 9260-9263; 2014; Faming Zhuanli Shenqing, 105037382, 11 Nov 2015). This intermediate is reacted (for conditions and related examples, see Journal of Chemical and Pharmaceutical Sciences, 6(3), 175-180; 2013) with the aminomethyl penem to give the amination linked intermediate. Removal of the t-butyl ester protecting group gives the product.



Carbapenem Conjugate Molecules

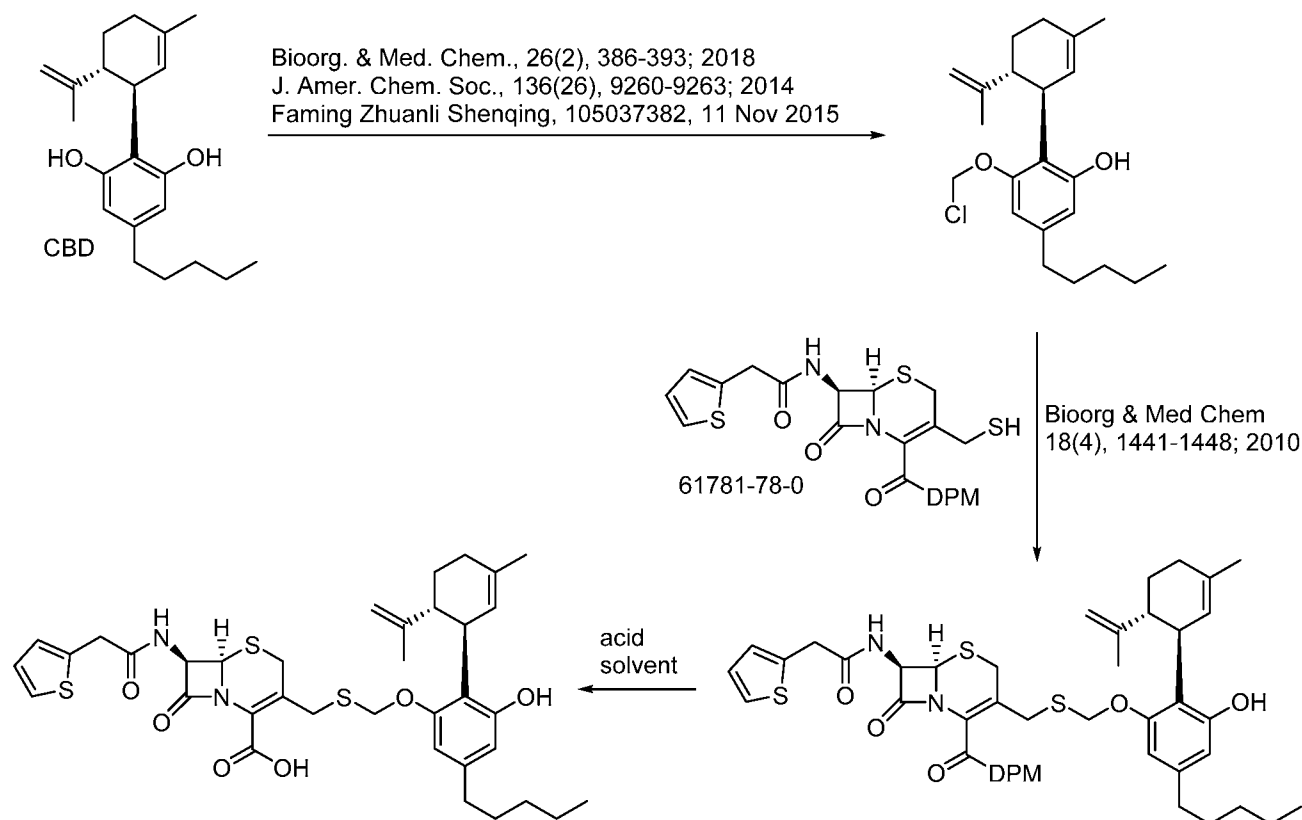
[142] Carbapenem amination linked conjugate molecules are synthesized according to the following Scheme. The aminomethyl carbapenem intermediate is synthesized in 5 steps according to the scheme shown above for carbapenem carbamate linked conjugate molecules. A cannabinoid (CBD) is converted to its O-chloromethyl intermediate via reported conditions (Bioorg. & Med. Chem., 26(2), 386-393; 2018; J. Amer. Chem. Soc., 136(26), 9260-9263; 2014; Faming Zhuanli Shenqing, 105037382, 11 Nov 2015). This intermediate is reacted (for conditions and related examples, see Journal of Chemical and Pharmaceutical Sciences, 6(3), 175-180; 2013) with the aminomethyl carbapenem to give the amination linked intermediate. Removal of the silyl ether and t-butyl ester protecting groups gives the product.



Example 16. Thioacetal-linked conjugate molecules

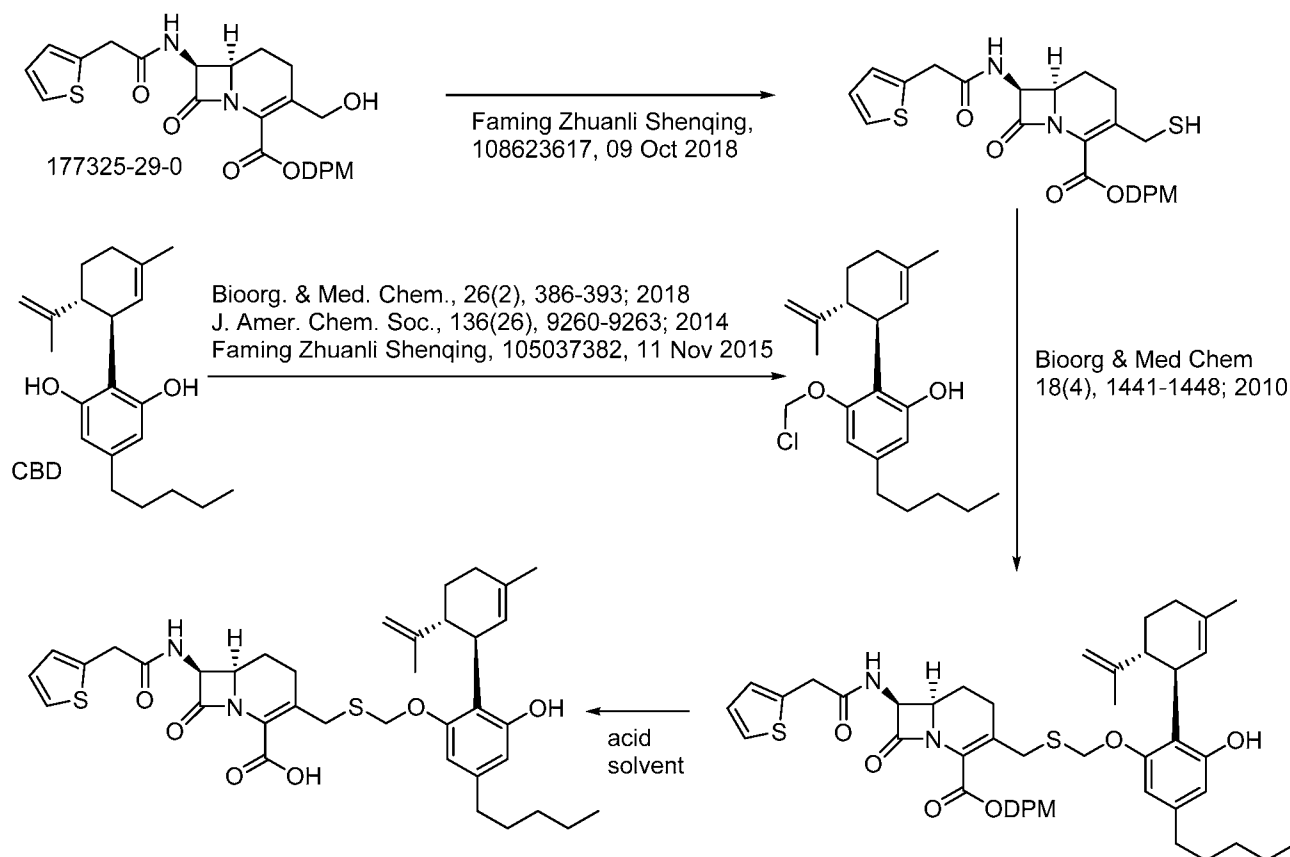
Cepem Conjugate Molecules

[143] Cepem thioacetal linked conjugate molecules are synthesized according to the following Scheme. A cannabinoid (CBD) is converted to its O-chloromethyl intermediate via reported conditions (Bioorg. & Med. Chem., 26(2), 386-393; 2018; J. Amer. Chem. Soc., 136(26), 9260-9263; 2014; Faming Zhuanli Shenqing, 105037382, 11 Nov 2015). This intermediate is reacted (for conditions and related examples, see Bioorganic & Medicinal Chemistry, 18(4), 1441-1448; 2010) with the thiomethyl cepem [61781-78-0] to give the thioacetal linked intermediate. Removal of the diphenylmethyl ester protecting group gives the product.



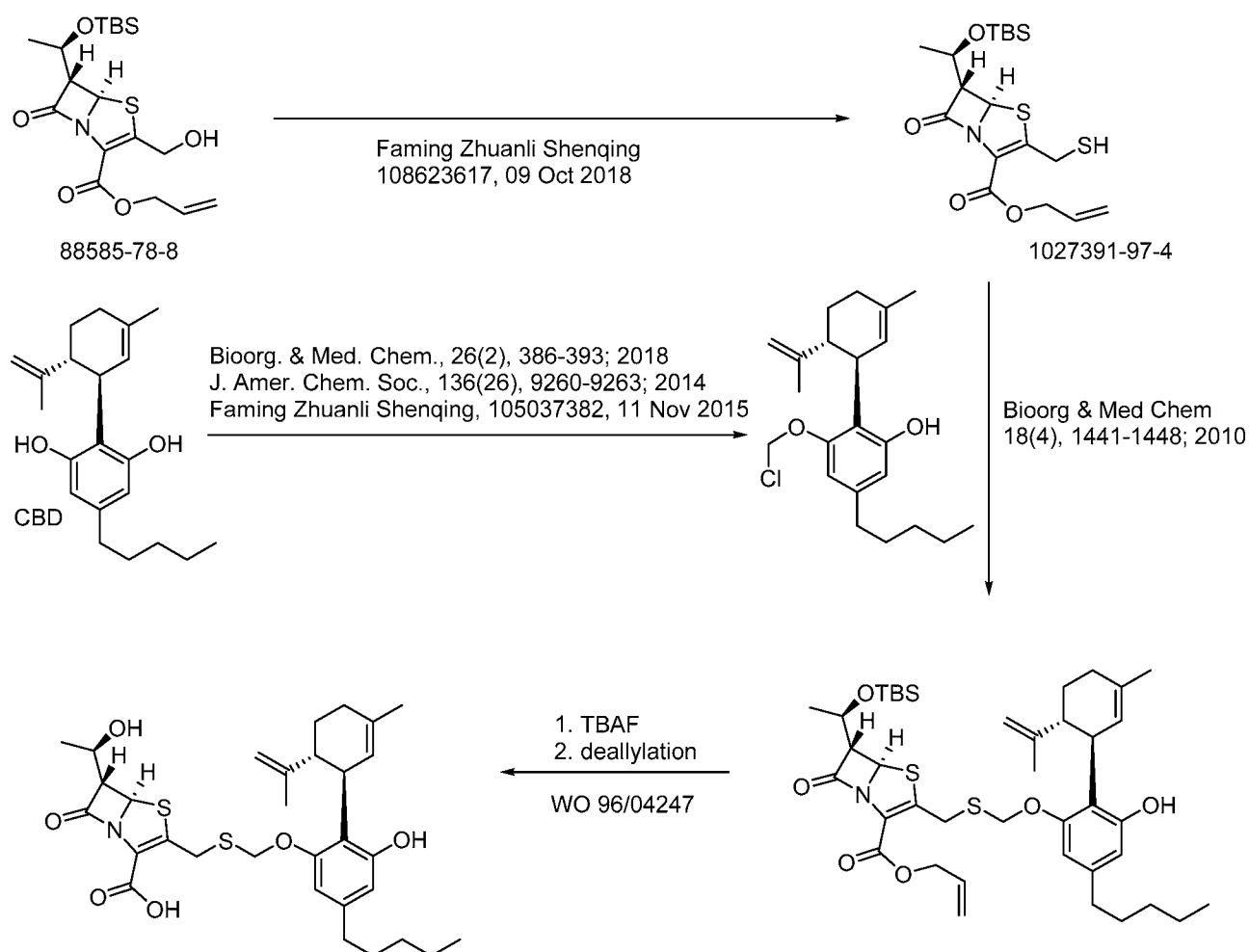
Carbacephem Conjugate Molecules

[144] Carbacephem thioacetal linked conjugate molecules are synthesized according to the following Scheme. The starting material [177325-29-0] is converted to the thiol intermediate using previously described (Faming Zhuanli Shenqing, 108623617, 09 Oct 2018) conditions for a related system. A cannabinoid (CBD) is converted to its O-chloromethyl intermediate via reported conditions (Bioorg. & Med. Chem., 26(2), 386-393; 2018; J. Amer. Chem. Soc., 136(26), 9260-9263; 2014; Faming Zhuanli Shenqing, 105037382, 11 Nov 2015). This intermediate is reacted (for conditions and related examples, see Bioorganic & Medicinal Chemistry, 18(4), 1441-1448; 2010) with the thiol carbacephem intermediate to give the thioacetal linked intermediate. Removal of the diphenylmethyl ester protecting group gives the product.



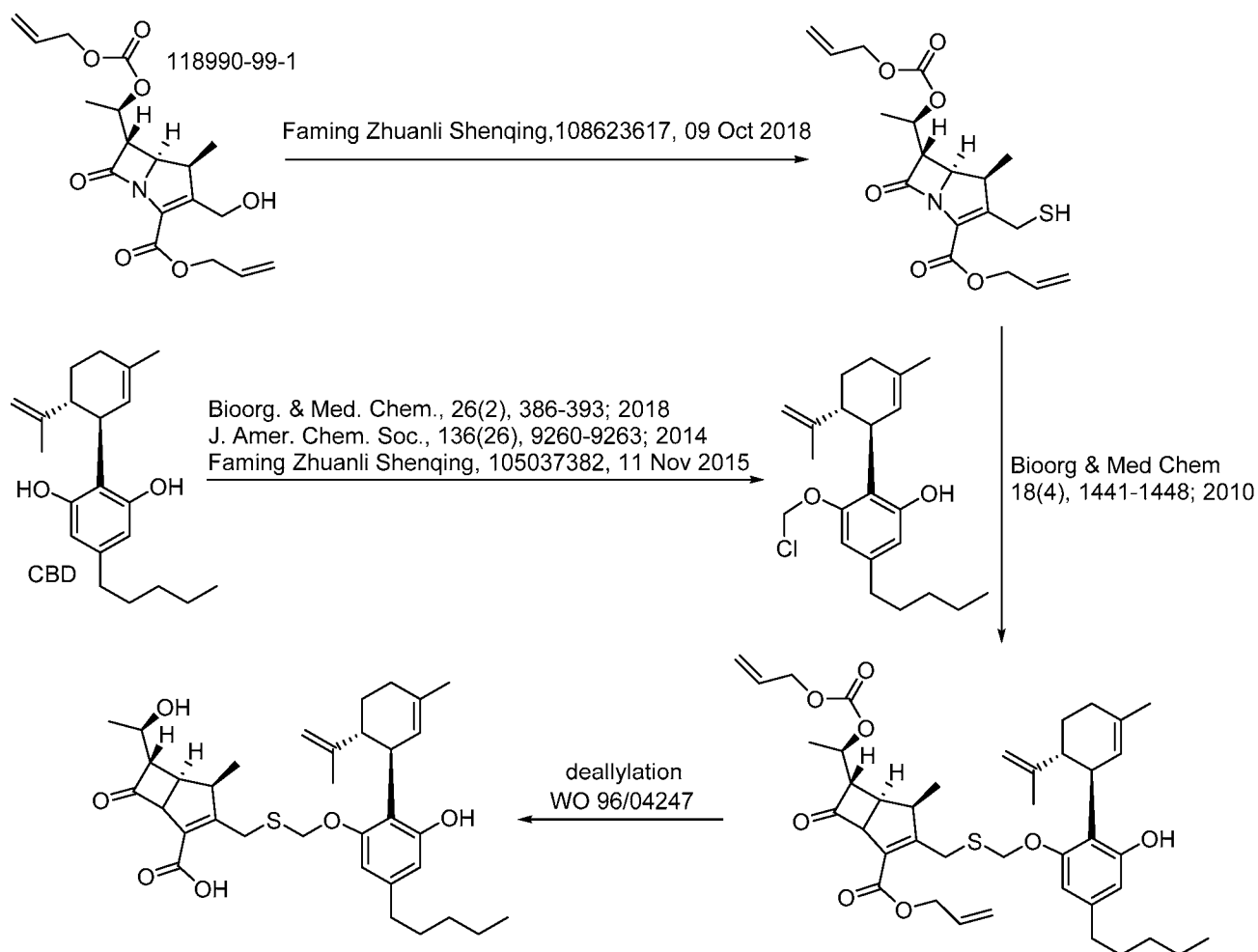
Penem Conjugate Molecules

[145] Penem thioacetal linked conjugate molecules are synthesized according to the following Scheme. The starting material [88585-78-8] is converted to the thiol intermediate [1027391-97-4] using previously described (Faming Zhuanli Shenqing, 108623617, 09 Oct 2018) conditions for a related system. A cannabinoid (CBD) is converted to its O-chloromethyl intermediate via reported conditions (Bioorg. & Med. Chem., 26(2), 386-393; 2018; J. Amer. Chem. Soc., 136(26), 9260-9263; 2014; Faming Zhuanli Shenqing, 105037382, 11 Nov 2015). This intermediate is reacted (for conditions and related examples, see Bioorganic & Medicinal Chemistry, 18(4), 1441-1448; 2010) with the thiol penem intermediate to give the thioacetal linked intermediate. Removal of the silyl ether and allyl ester protecting groups gives the product.



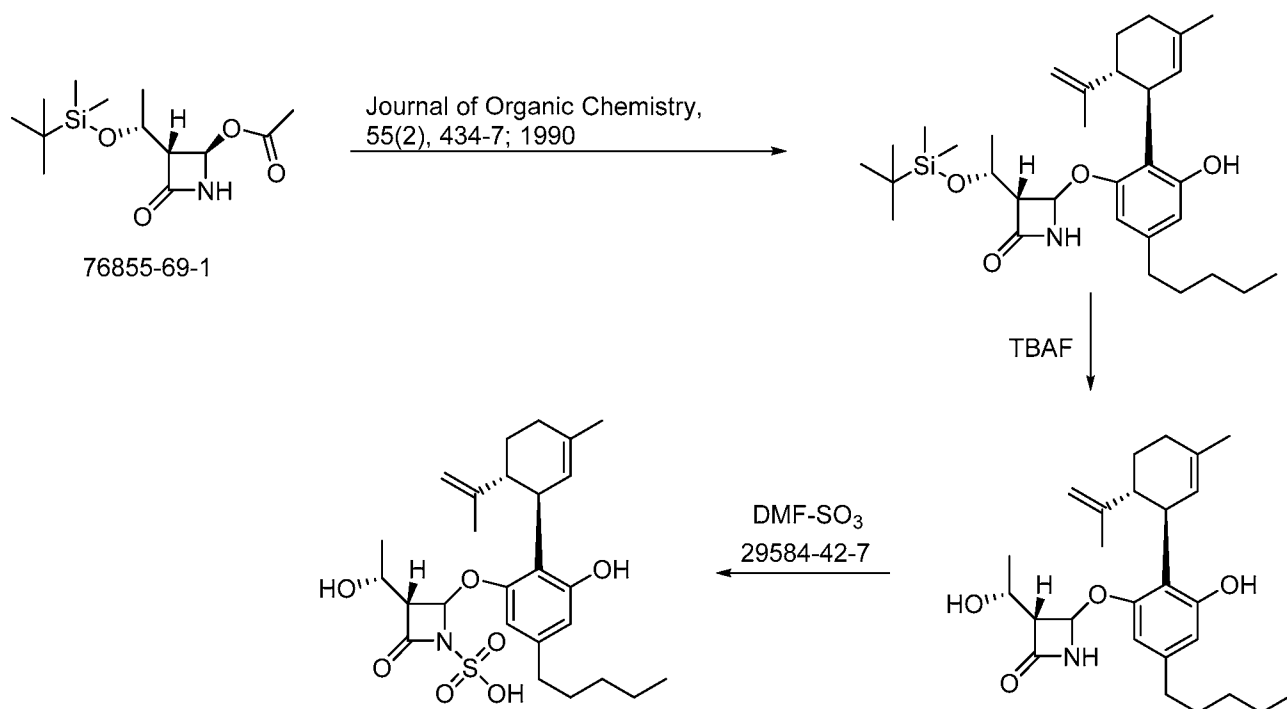
Carbapenem Conjugate Molecules

[146] Carbapenem thioacetal linked conjugate molecules are synthesized according to the following Scheme. The starting material [118990-99-1] is converted to the thiol intermediate using previously described (Faming Zhuanli Shenqing, 108623617, 09 Oct 2018) conditions for a related system. A cannabinoid (CBD) is converted to its O-chloromethyl intermediate via reported conditions (Bioorg. & Med. Chem., 26(2), 386-393; 2018; J. Amer. Chem. Soc., 136(26), 9260-9263; 2014; Faming Zhuanli Shenqing, 105037382, 11 Nov 2015). This intermediate is reacted (for conditions and related examples, see Bioorganic & Medicinal Chemistry, 18(4), 1441-1448; 2010) with the thiol carbapenem intermediate to give the thioacetal linked intermediate. Removal of the allyl protecting groups gives the product.



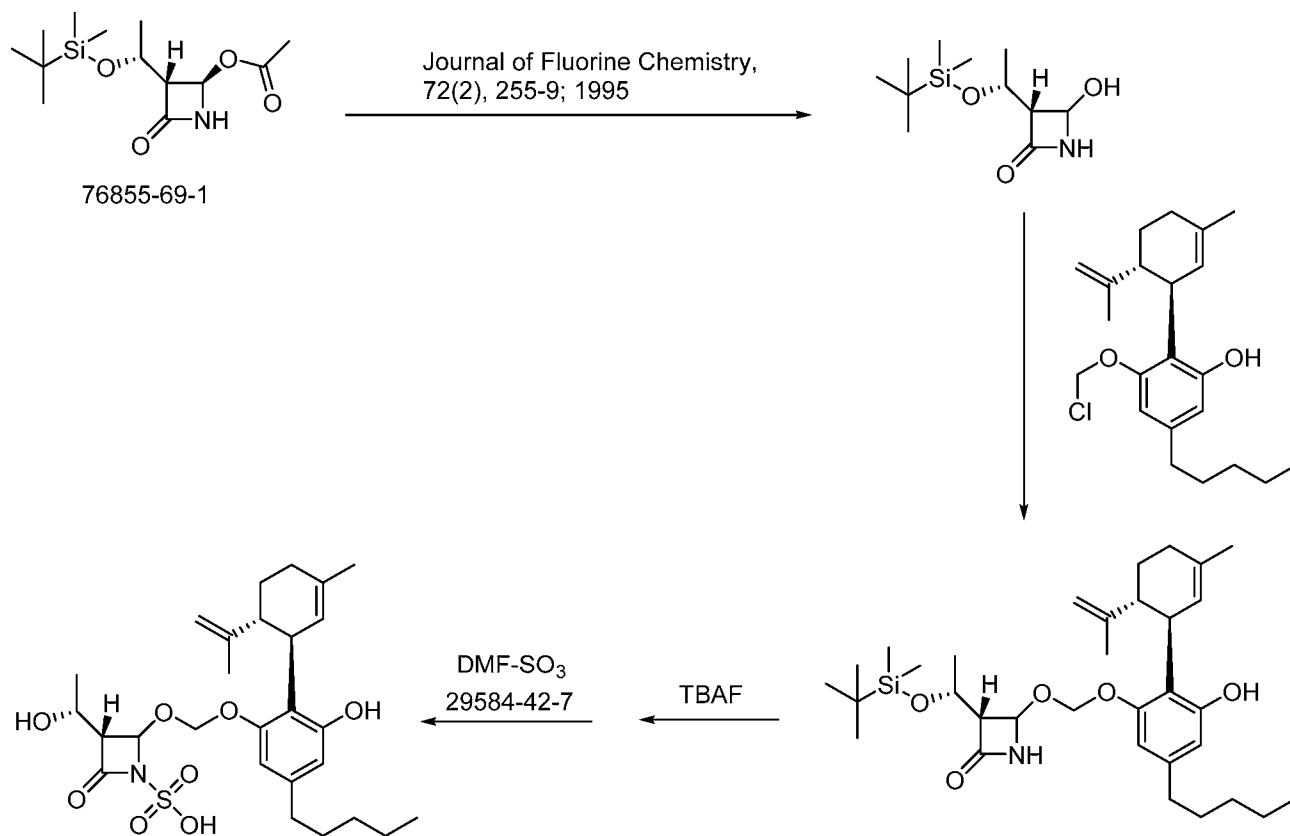
Example 17. Monobactam ether-linked conjugate molecules

[147] Monobactam ether linked conjugate molecules are synthesized according to the following Scheme. The starting material [76855-69-1] is reacted under reported conditions (Journal of Organic Chemistry, 55(2), 434-7; 1990) for phenolic compounds to form the ether link. Removal of the silyl ether protecting group under standard conditions followed by sulfonation using established conditions gives the product.



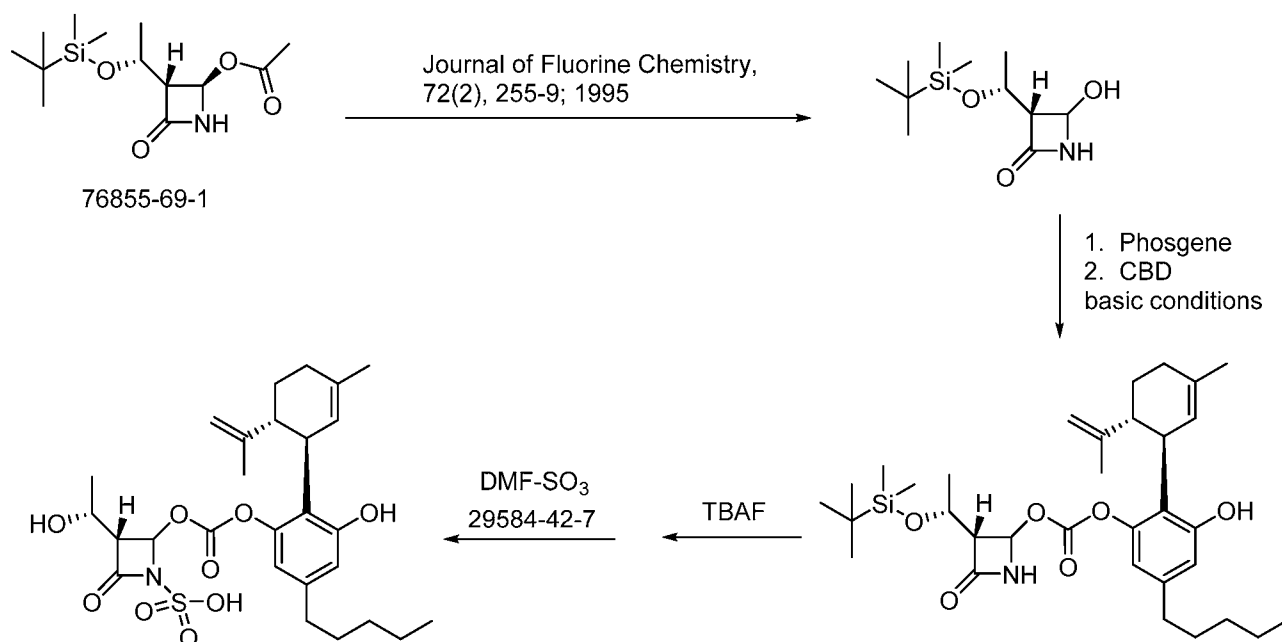
Example 18. Monobactam acetal-linked conjugate molecules

[148] Monobactam acetal linked conjugate molecules are synthesized according to the following Scheme. The starting material [76855-69-1] is deacetylated under reported conditions (*Journal of Fluorine Chemistry*, 72(2), 255-9; 1995) to give the 2-hydroxy intermediate. This hydroxy group is then alkylated with the O-chloromethyl cannabinoid which is prepared as described in the cephem acetal example in this Application to form the acetal link. Removal of the silyl ether protecting group followed by sulfonation using established conditions gives the product.



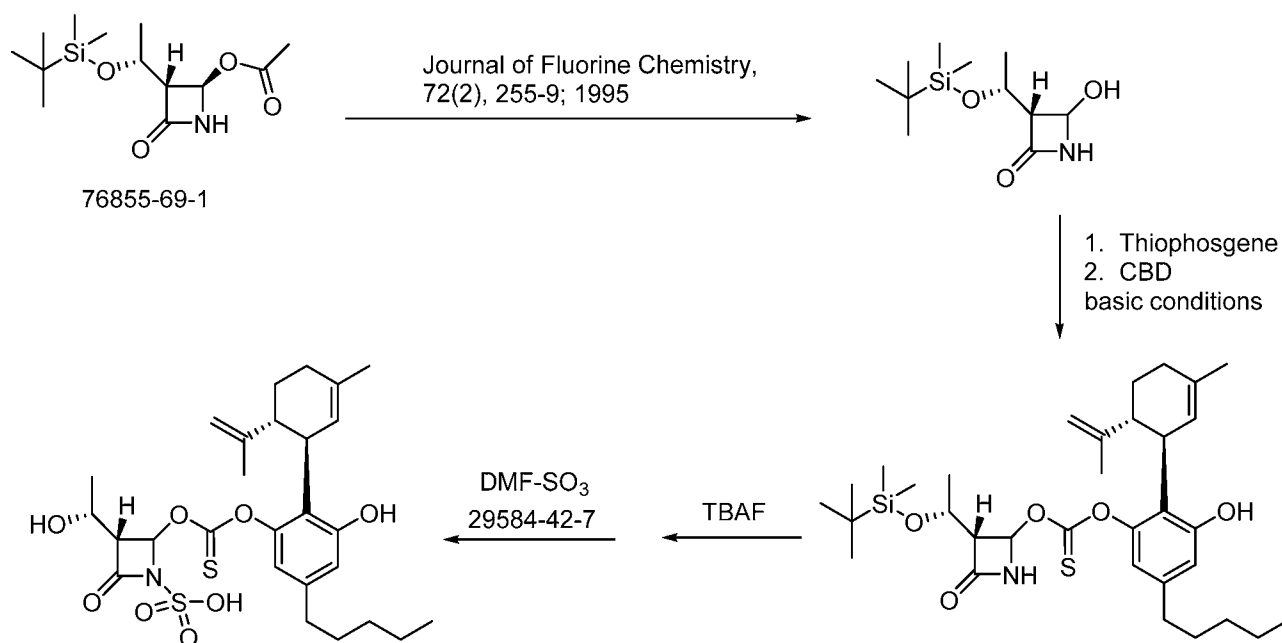
Example 19. Monobactam carbonate-linked conjugate molecules

[149] Monobactam carbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material [76855-69-1] is deacetylated under reported conditions (*Journal of Fluorine Chemistry*, 72(2), 255-9; 1995) to give the 2-hydroxy intermediate. This hydroxy group is then reacted with phosgene and a cannabinoid (CBD) under standard basic conditions to form the carbonate link. Removal of the silyl ether protecting group followed by sulfonation using established conditions gives the product.



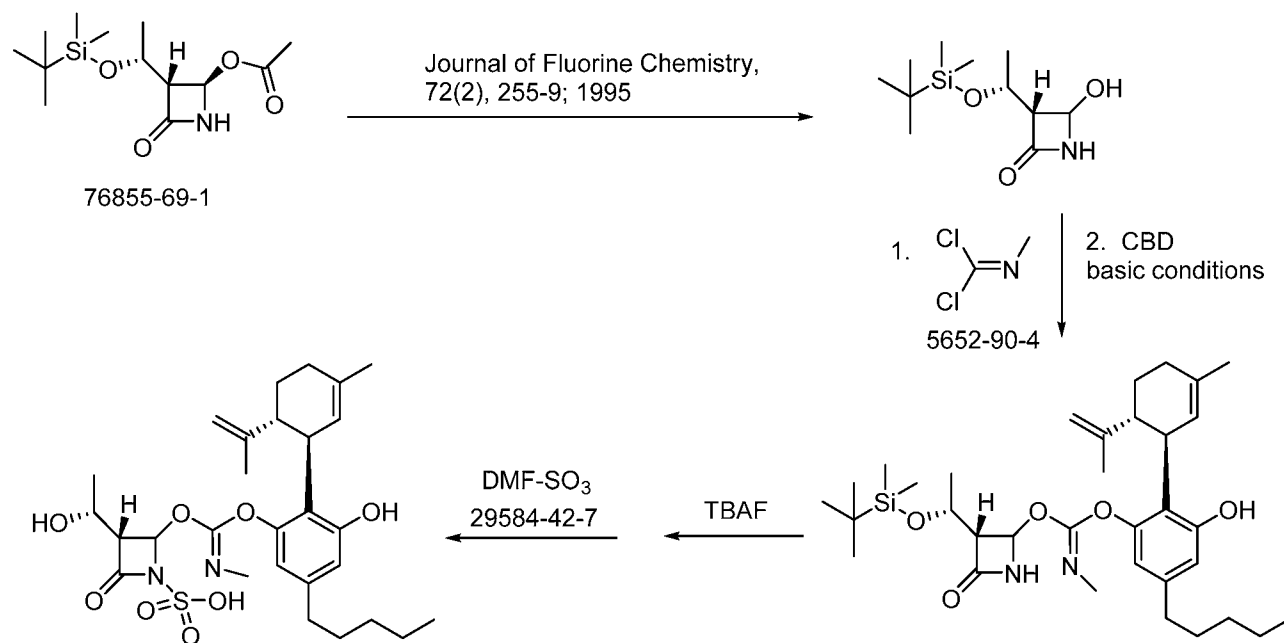
Example 20. Monobactam thiocarbonate-linked conjugate molecules

[150] Monobactam thiocarbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material [76855-69-1] is deacetylated under reported conditions (*Journal of Fluorine Chemistry*, 72(2), 255-9; 1995) to give the 2-hydroxy intermediate. This hydroxy group is then reacted with thiophosgene and a cannabinoid (CBD) under standard basic conditions to form the carbonate link. Removal of the silyl ether protecting group followed by sulfonation using established conditions gives the product.



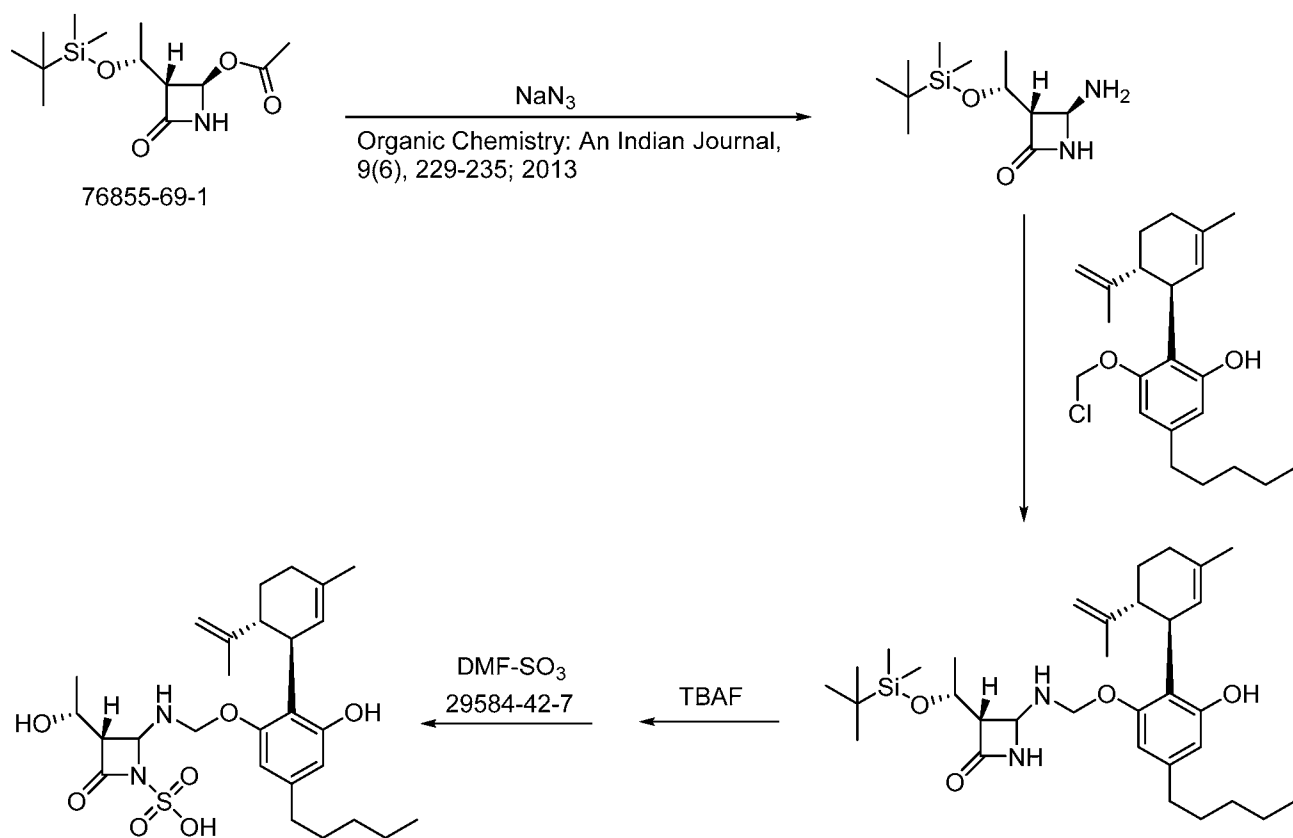
Example 21. Monobactam imidate-linked conjugate molecules

[151] Monobactam imidate linked conjugate molecules are synthesized according to the following Scheme. The starting material [76855-69-1] is deacetylated under reported conditions (Journal of Fluorine Chemistry, 72(2), 255-9; 1995) to give the 2-hydroxy intermediate. This hydroxy group is then reacted with methyl imidocarbonyl chloride [5652-90-4] and a cannabinoid (CBD) under reported conditions (Tetrahedron Letters, 23(35), 3539-42; 1982) to form the imidate link. Removal of the silyl ether protecting group followed by sulfonation using established conditions gives the product.



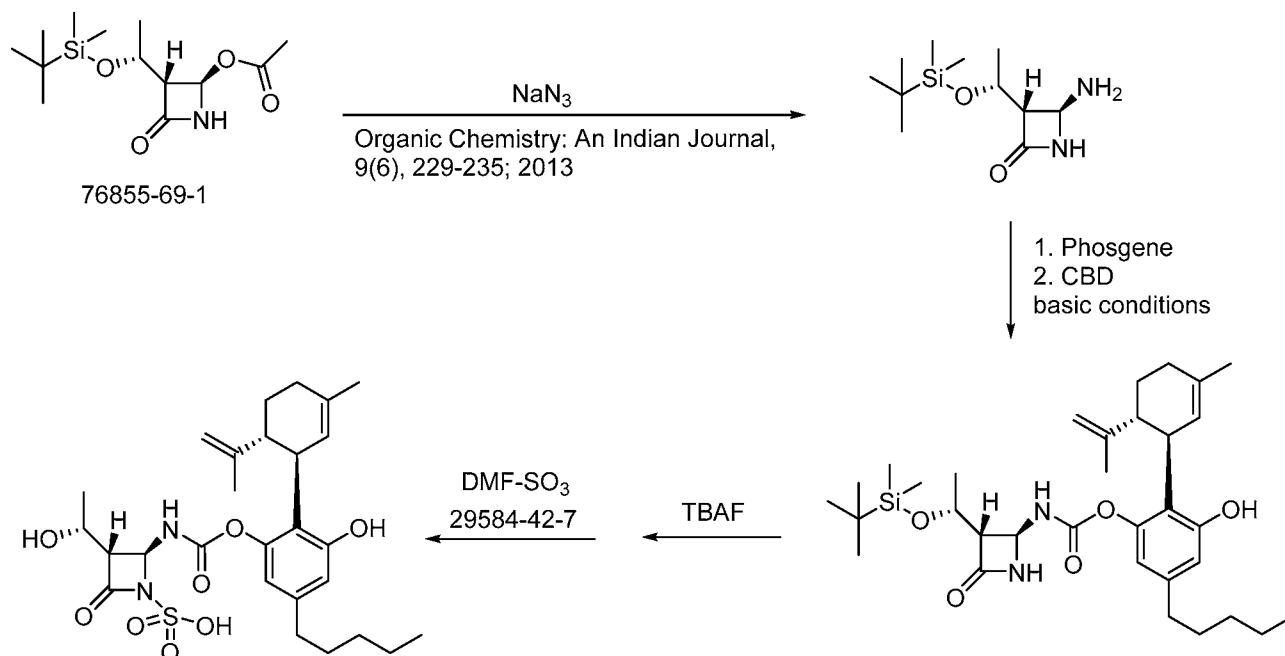
Example 22. Monobactam amination-linked conjugate molecules

[152] Monobactam amination linked conjugate molecules are synthesized according to the following Scheme. The starting material [76855-69-1] is converted to the corresponding amine under reported conditions (Organic Chemistry: An Indian Journal, 9(6), 229-235; 2013) to give the 2-amino intermediate. This amino group is then alkylated with the O-chloromethyl cannabinoid which is prepared as described in the cephem acetal example in this Application to form the acetal link. Removal of the silyl ether protecting group followed by sulfonation using established conditions gives the product.



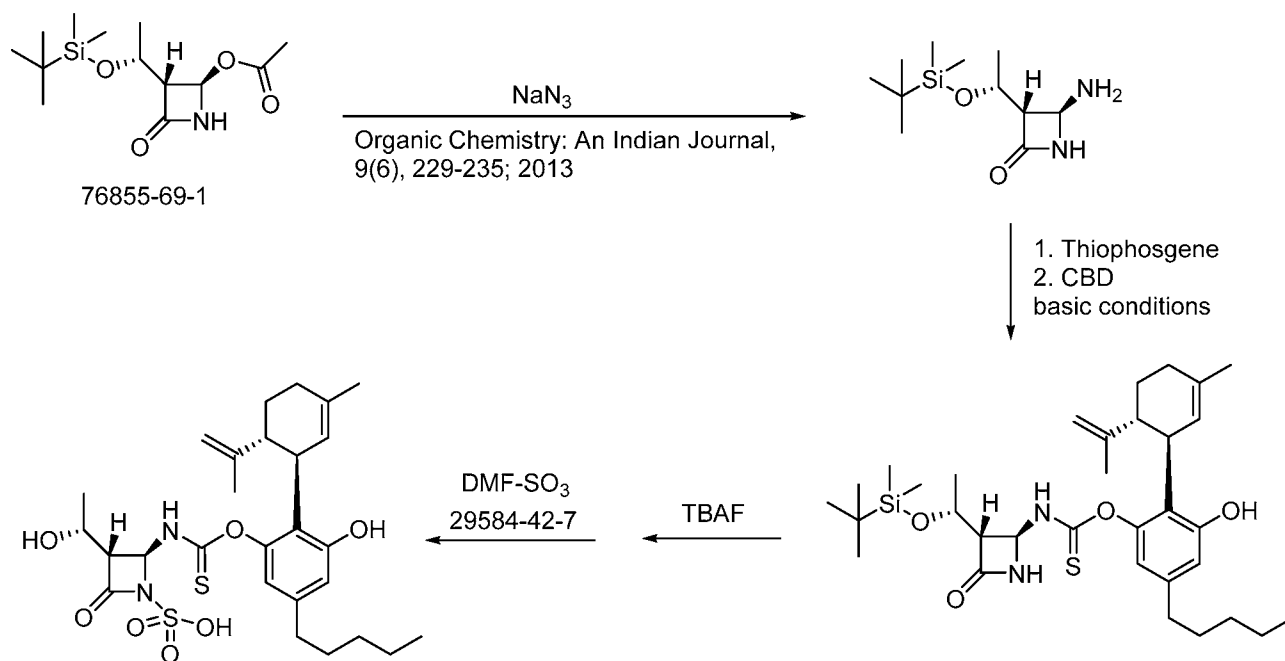
Example 23. Monobactam carbamate-linked conjugate molecules

[153] Monobactam carbamate linked conjugate molecules are synthesized according to the following Scheme. The starting material [76855-69-1] is converted to the corresponding amine under reported conditions (Organic Chemistry: An Indian Journal, 9(6), 229-235; 2013) to give the 2-amino intermediate. This amino group is then reacted with phosgene and a cannabinoid (CBD) under standard basic conditions to form the carbamate link. Removal of the silyl ether protecting group followed by sulfonation using established conditions gives the product.



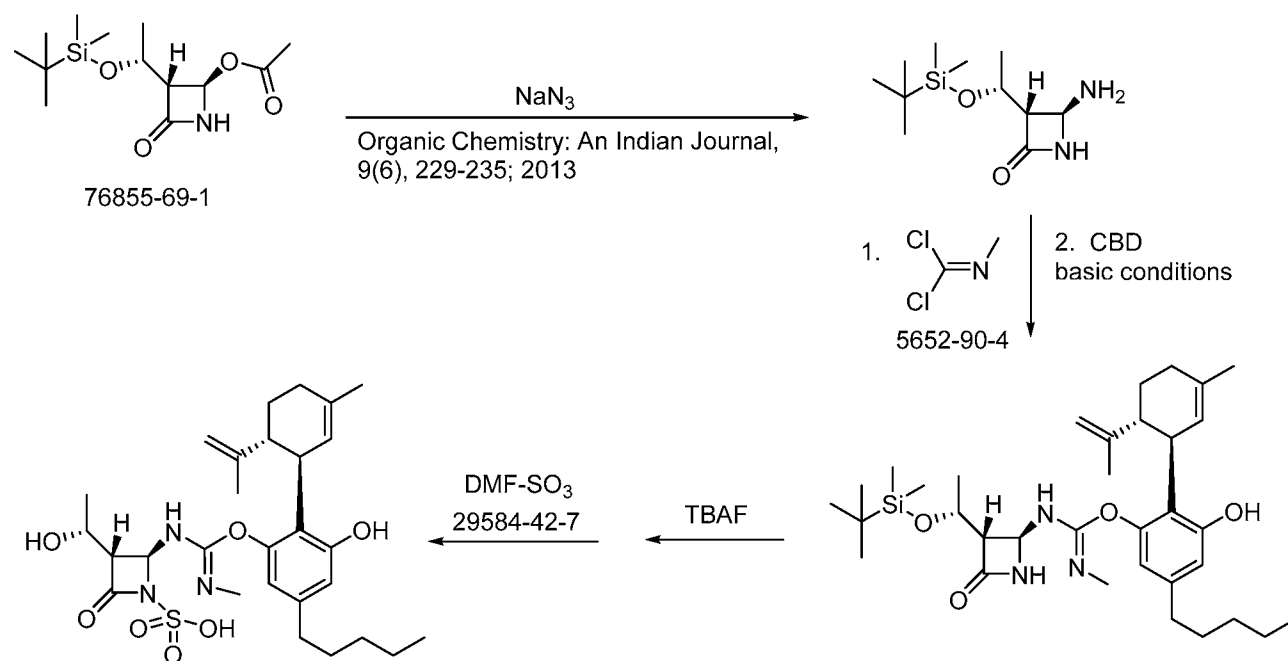
Example 24. Monobactam thiocarbamate-linked conjugate molecules

[154] Monobactam thiocarbamate linked conjugate molecules are synthesized according to the following Scheme. The starting material [76855-69-1] is converted to the corresponding amine under reported conditions (Organic Chemistry: An Indian Journal, 9(6), 229-235; 2013) to give the 2-amino intermediate. This amino group is then reacted with thiophosgene and a cannabinoid (CBD) under standard basic conditions to form the thiocarbamate link. Removal of the silyl ether protecting group followed by sulfonation using established conditions gives the product.

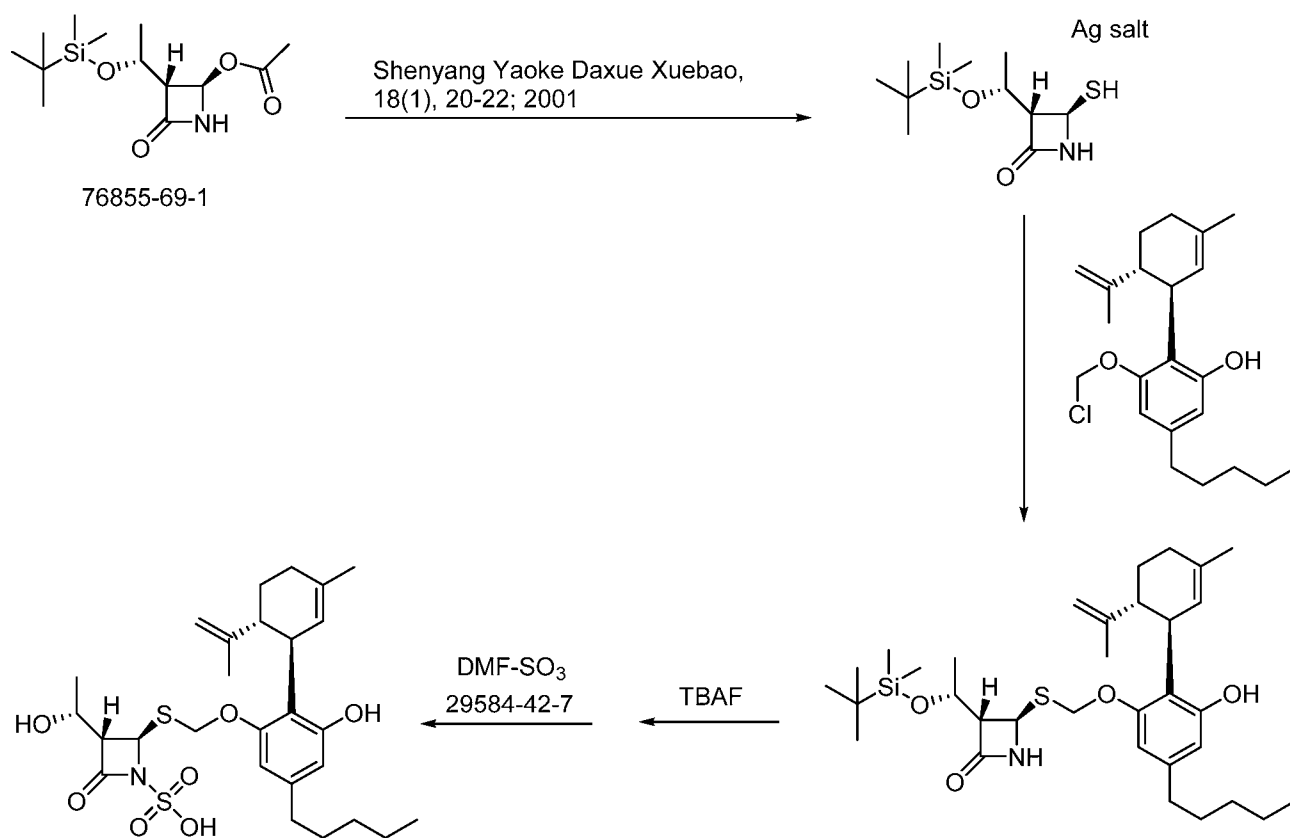


Example 25. Monobactam isourea-linked conjugate molecules

[155] Monobactam isourea linked conjugate molecules are synthesized according to the following Scheme. The starting material [76855-69-1] is converted to the corresponding amine under reported conditions (Organic Chemistry: An Indian Journal, 9(6), 229-235; 2013) to give the 4-amino intermediate. This amino group is then reacted with methyl imidocarbonyl chloride [5652-90-4] and a cannabinoid (CBD) under reported conditions (Tetrahedron Letters, 23(35), 3539-42; 1982) to form the isourea link. Removal of the silyl ether protecting group followed by sulfonation using established conditions gives the product.

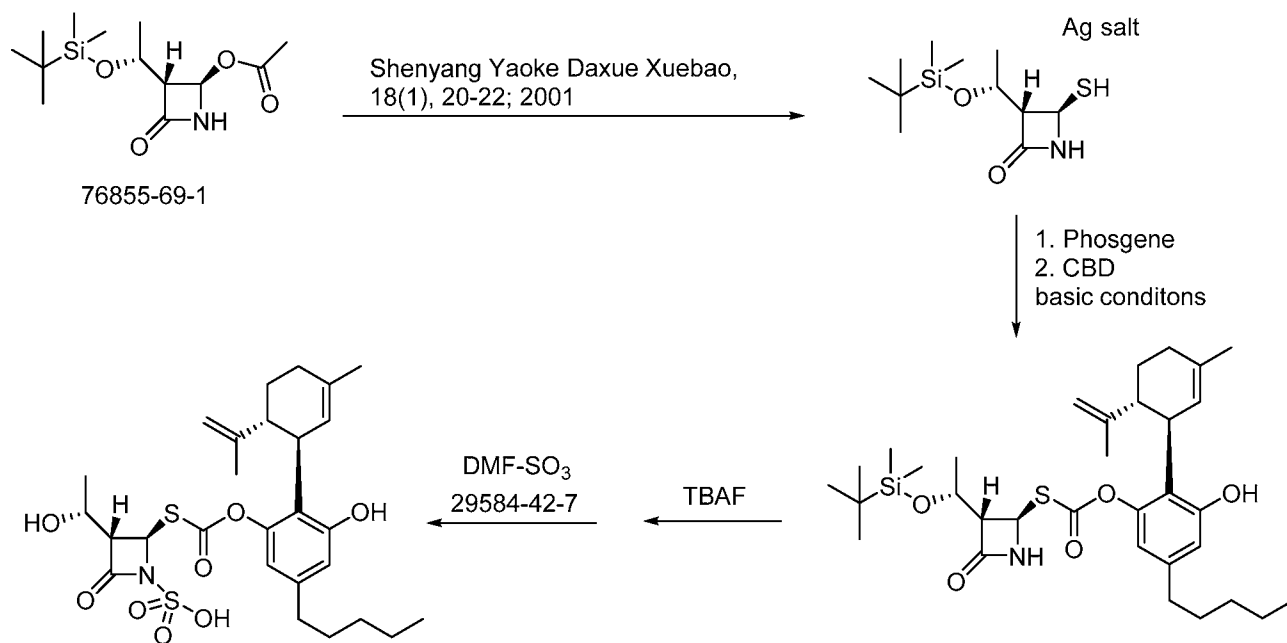
**Example 26. Monobactam thioacetal-linked conjugate molecules**

[156] Monobactam thioacetal linked conjugate molecules are synthesized according to the following Scheme. The starting material [76855-69-1] is converted to the thiol silver salt using reported conditions (Shenyang Yaoke Daxue Xuebao, 18(1), 20-22; 2001) to give the 2-SH intermediate. This thiol group is then alkylated with the O-chloromethyl cannabinoid which is prepared as described in the cephem acetal example in this Application to form the thioacetal link. Removal of the silyl ether protecting group followed by sulfonation using established conditions gives the product.



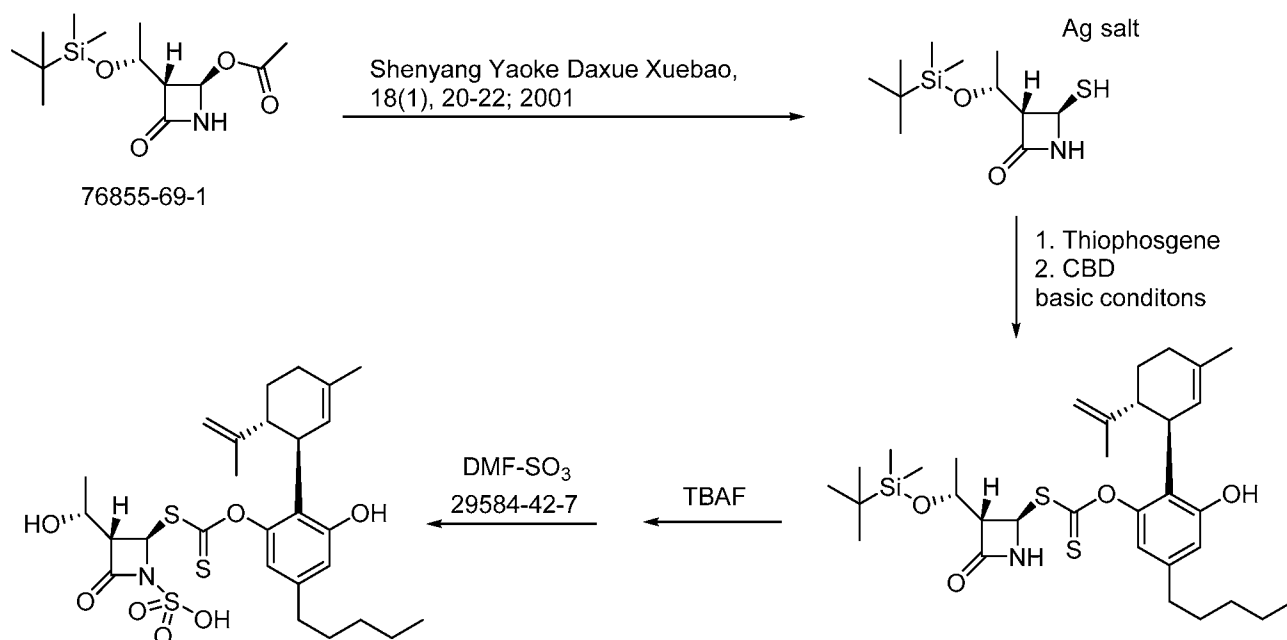
Example 27. Monobactam S-alkyl thiocarbonate-linked conjugate molecules

[157] Monobactam S-alkyl thiocarbonate linked conjugate molecules are synthesized according to the following Scheme. The starting material [76855-69-1] is converted to the thiol silver salt using reported conditions (*Shenyang Yaoke Daxue Xuebao*, 18(1), 20-22; 2001) to give the 2-SH intermediate. This thiol group is then reacted with phosgene and a cannabinoid (CBD) under standard basic conditions to form the S-alkyl thiocarbonate link. Removal of the silyl ether protecting group followed by sulfonation using established conditions gives the product.



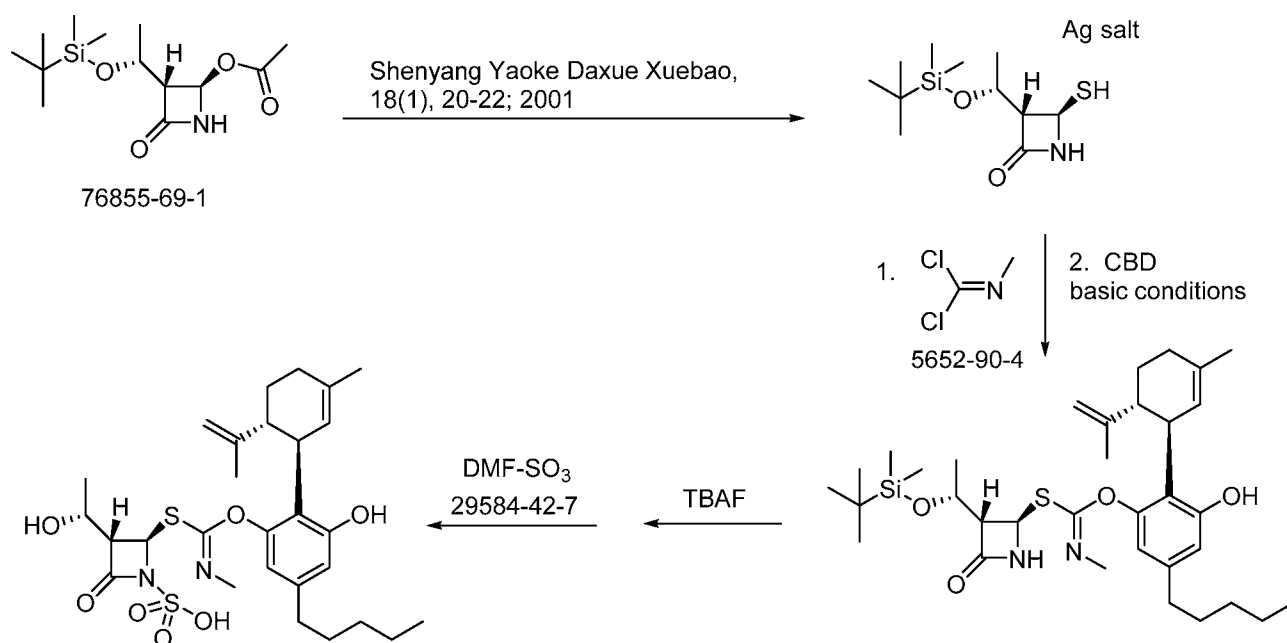
Example 28. Monobactam xanthate-linked conjugate molecules

[158] Monobactam xanthate linked conjugate molecules are synthesized according to the following Scheme. The starting material [76855-69-1] is converted to the thiol silver salt using reported conditions (Shenyang Yaoke Daxue Xuebao, 18(1), 20-22; 2001) to give the 2-SH intermediate. This thiol group is then reacted with thiophosgene and a cannabinoid (CBD) under standard basic conditions to form the xanthate link. Removal of the silyl ether protecting group followed by sulfonation using established conditions gives the product.

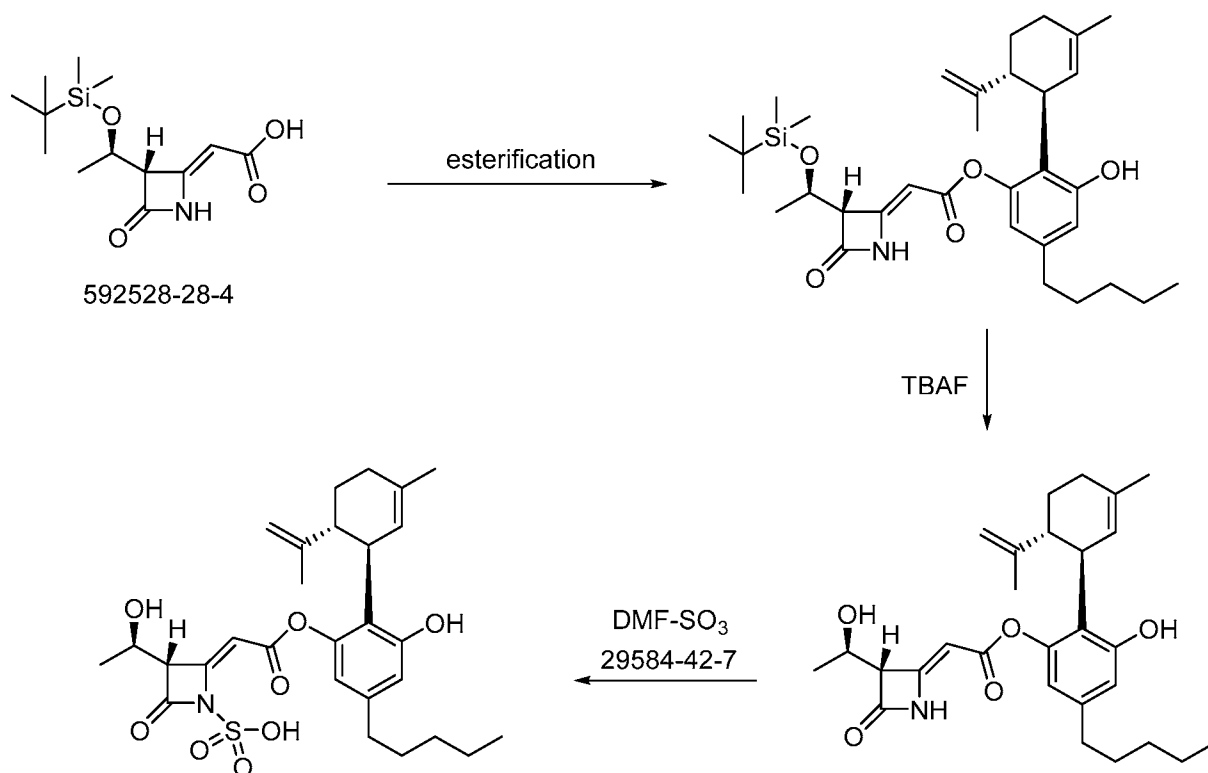


Example 29. Monobactam thioimide-linked conjugate molecules

[159] Monobactam thioimide linked conjugate molecules are synthesized according to the following Scheme. The starting material [76855-69-1] is converted to the thiol silver salt using reported conditions (Shenyang Yaoke Daxue Xuebao, 18(1), 20-22; 2001) to give the 2-SH intermediate. This thiol group is then reacted with methyl imidocarbonyl chloride [5652-90-4] and a cannabinoid (CBD) under reported conditions (Tetrahedron Letters, 23(35), 3539-42; 1982) to form the thioimide link. Removal of the silyl ether protecting group followed by sulfonation using established conditions gives the product.

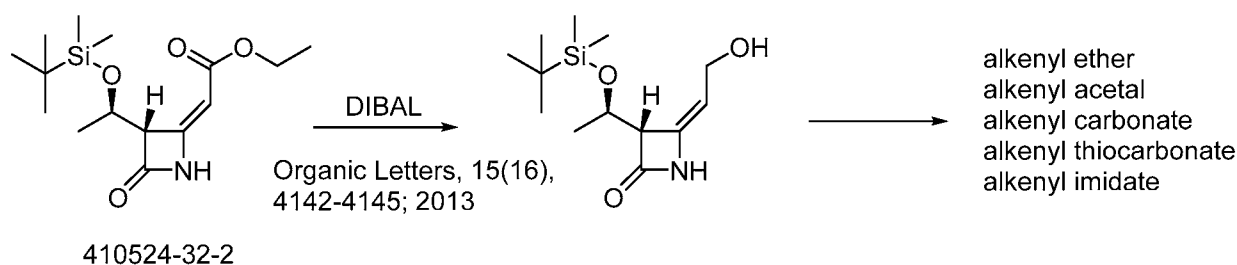
**Example 30. Monobactam alkenyl ester-linked conjugate molecules**

[160] Monobactam alkenyl ester linked conjugate molecules are synthesized according to the following Scheme. The starting material [592528-28-4] is esterified with a cannabinoid (CBD) under standard conditions. Removal of the silyl ether protecting group followed by sulfonation using established conditions gives the product.



Example 31. Monobactam alkenyl ether-, alkenyl acetal-, alkenyl carbonate-, alkenyl thiocarbonate-, and alkenyl imidate-linked conjugate molecules

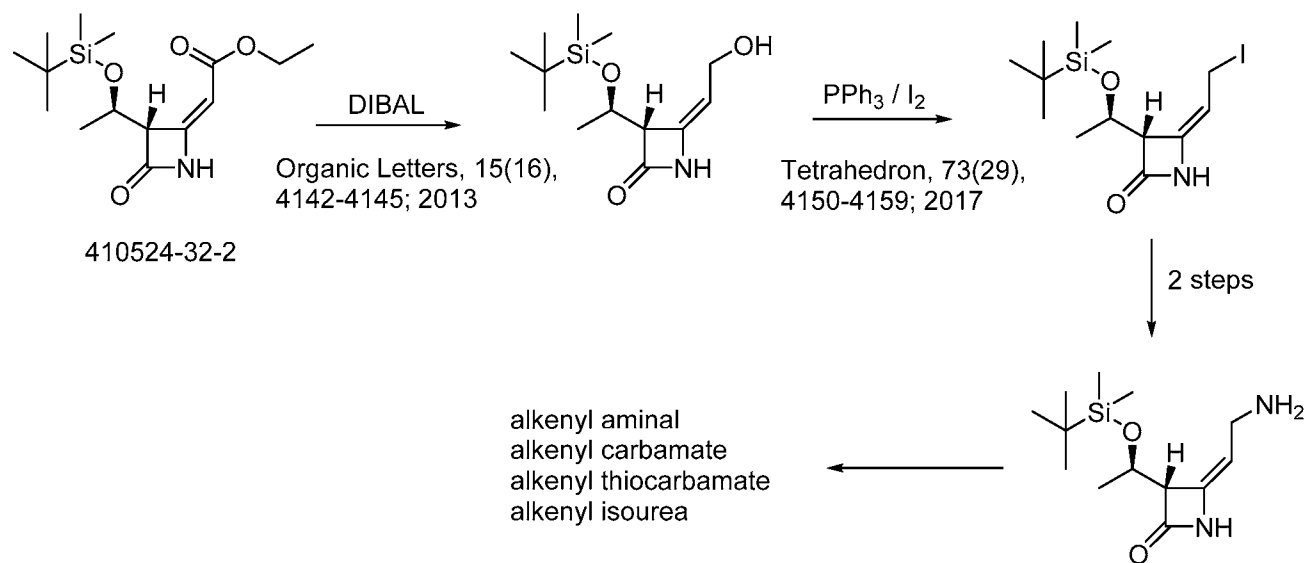
[161] Monobactam alkenyl ether, alkenyl acetal, alkenyl carbonate, alkenyl thiocarbonate, and alkenyl imidate linked conjugate molecules are synthesized as shown in the Scheme below. The starting material [410524-32-2] is reduced to the alcohol intermediate using previously reported conditions (Organic Letters, 15(16), 4142-4145; 2013). This alcohol is reacted and connected to a cannabinoid by any of the aforementioned links, using the previously described chemistry and conditions associated with the non-alkenyl variant.



Example 32. Monobactam alkenyl aminal-, alkenyl carbamate-, alkenyl thiocarbamate-, and alkenyl isourea-linked conjugate molecules

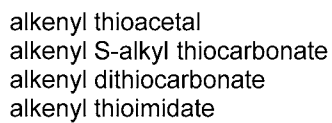
[162] Monobactam alkenyl aminal, alkenyl carbamate, alkenyl thiocarbamate, and alkenyl isourea linked conjugate molecules are synthesized as shown in the Scheme below. The starting material [410524-32-2] is reduced to the alcohol intermediate. This alcohol is then converted to

the iodide using known (Tetrahedron, 73(29), 4150-4159; 2017) conditions. The iodide intermediate is converted to the primary amine using the two step azide addition / reduction protocol described above for synthesis of propenylamine cephem conjugate molecules. This amine is then reacted and connected to a cannabinoid by any of the aforementioned links, using the previously described chemistry and conditions associated with the non-alkenyl variant.



Example 33. Monobactam alkenyl thioacetal-, alkenyl S-alkyl thiocarbonate-, alkenyl dithiocarbonate-, and alkenyl thioimide-linked conjugate molecules

[163] Monobactam alkenyl thioacetal, alkenyl S-alkyl thiocarbonate, alkenyl dithiocarbonate, and alkenyl thioimide linked conjugate molecules are synthesized as shown in the Scheme below. The starting material [410524-32-2] is reduced to the alcohol intermediate using previously reported conditions (Organic Letters, 15(16), 4142-4145; 2013). This alcohol is reacted with Lawesson's reagent under reported conditions (Journal of the American Chemical Society, 130(15), 5052-5053; 2008) to give the corresponding thiol intermediate. This thiol is then reacted and connected to a cannabinoid by any of the aforementioned links, using the previously described chemistry and conditions associated with the non-alkenyl variant.



CLAIMS

1. A conjugate molecule, or a pharmaceutically acceptable salt thereof, comprising a first β -lactam antibiotic component, a first linker, and a cannabinoid component, wherein the first linker is covalently attached to a first hydroxy group of the cannabinoid component, wherein:

(a) the first β -lactam antibiotic component is selected from the group consisting of a first cephem component, a first carbacephem component, a first penem component, and a first carbapenem component covalently attached at its 3 position to the first linker; or

(b) the first β -lactam antibiotic component is a first monobactam component covalently attached at its 2 position to the first linker.

2. The conjugate molecule of claim 1, or the pharmaceutically acceptable salt thereof, wherein the cannabinoid component further comprises a second hydroxy group.

3. The conjugate molecule of claim 2, or the pharmaceutically acceptable salt thereof, further comprising a second β -lactam antibiotic component covalently attached to a second linker, wherein the second linker is covalently attached to the second hydroxy group of the cannabinoid component.

4. The conjugate molecule of any of claims 1-3, or the pharmaceutically acceptable salt thereof, wherein the first β -lactam antibiotic component is a first cephem component.

5. The conjugate molecule of any of claims 1-4, or the pharmaceutically acceptable salt thereof, wherein the first cephem component is provided by a cephem selected from the group consisting of cefazolin, cephalexin, cefadroxil, cefapirin, cefazedone, cefazaflur, cefradine, cefroxadine, ceftezole, cefaloglycin, cephacetrile, cefalonium, cefaloridine, cefalotin, cefatrizine, cefaclor, cefotetan, cephamycin, cefoxitin, cefprozil, cefuorixime, cefuroxime axetil, cefamandole, cefminox, cefonicid, ceforanide, cefotiam, cefbuperazone, cefuzonam, cefmetazole, cefixime, ceftriaxone, ceftazidime, cefoperazone, cefdinir, cefcapene, cefdaloxime, ceftizoxime, cefminoxime, cefotaxime, cefpiramide, cefpodoxime, ceftibuten, cefditoren, cefetamet, cefodizime, cefpimizole, cefsulodin, cefteram ceftiolene, flomoxef, latamoxef, cefepime, cefozopran, cefpirome, cefquinome, ceftaroline fosamil, ceftolozane, ceftobiprole, ceftiofur, cefquinome, and cefovecin.

12. The conjugate molecule of claim 8 or claim 11, or the pharmaceutically acceptable salt thereof, wherein the first carbacephem is loracarbef.

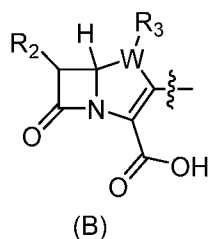
13. The conjugate molecule of any of claims 1-3, or the pharmaceutically acceptable salt thereof, wherein the first β -lactam antibiotic component is a first penem component.

14. The conjugate molecule of claim 14, or the pharmaceutically acceptable salt thereof, wherein the first penem component is provided by a penem selected from the group consisting of faropenem and ritipenem.

15. The conjugate molecule of any of claims 1-3, or the pharmaceutically acceptable salt thereof, wherein the first β -lactam antibiotic component is a first carbapenem component.

16. The conjugate molecule of claim 15, or the pharmaceutically acceptable salt thereof, wherein the first carbapenem component is provided by a carbapenem selected from the group consisting of ertapenem, doripenem, imipenem, meropenem, biapenem, and panipenem.

17. The conjugate molecule of any of claims 1-3, or the pharmaceutically acceptable salt thereof, wherein the first β -lactam antibiotic component falls within structural Formula (B):



wherein W is S or C; and R₂ is a side chain of a first penem or a side chain of a first carbapenem;

and when W is C, R₃ is H, -CH₃, or phenyl, wherein the phenyl is optionally substituted with 1, 2, 3, or 4 groups independently selected from the group consisting of halide, trifluoromethyl, C1-C6 linear or branched alkyl optionally substituted with up to nine fluorine atoms, and C1-C6 linear or branched heteroalkyl containing 1, 2, or 3 atoms independently selected from O, N, and S and optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms.

18. The conjugate molecule of claim 17, or the pharmaceutically acceptable salt thereof, wherein R₂ is the side chain of the first penem.

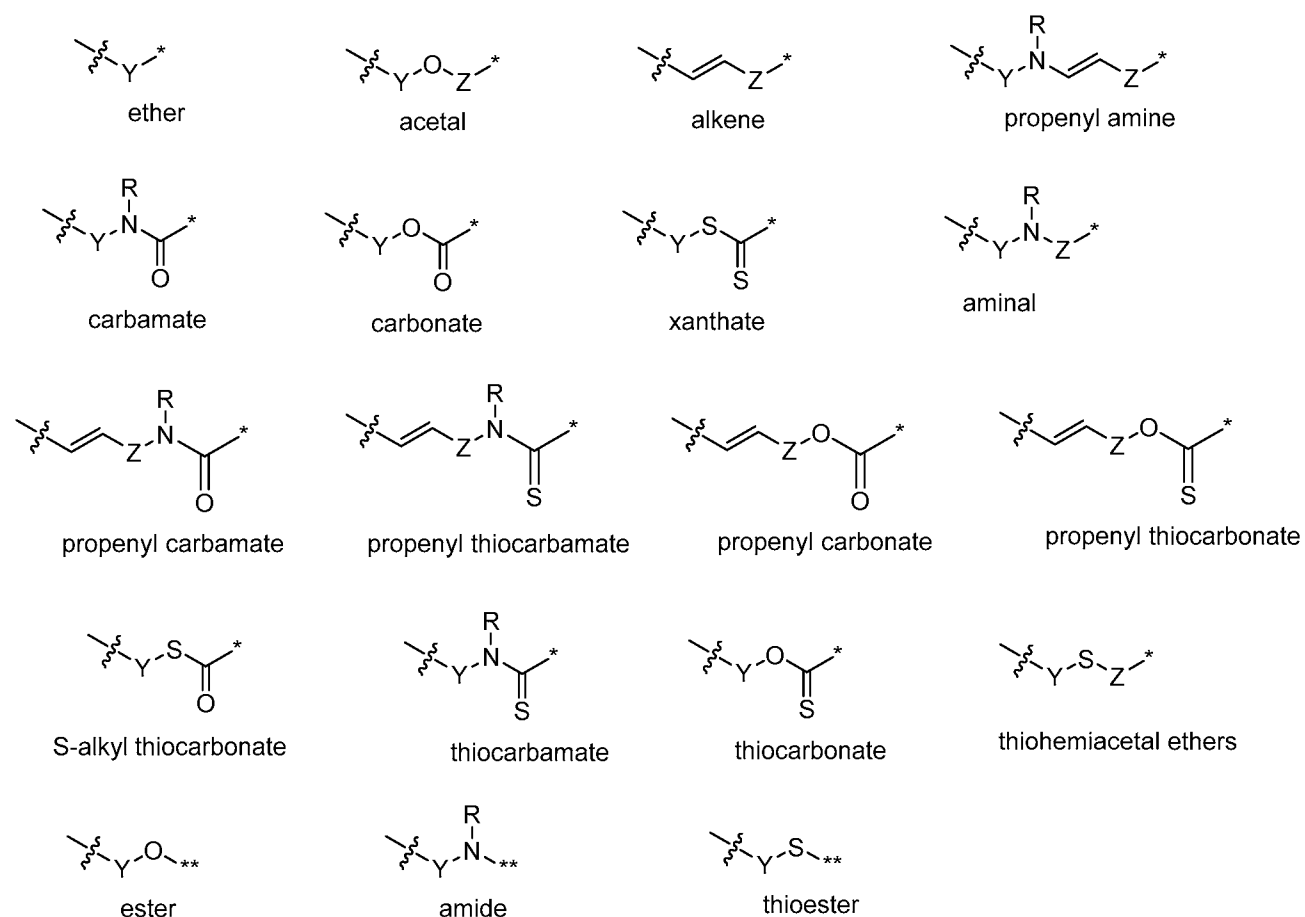
19. The conjugate molecule of claim 18, or the pharmaceutically acceptable salt thereof, wherein the first penem is selected from the group consisting of faropenem and ritipenem.

20. The conjugate molecule of claim 17, or the pharmaceutically acceptable salt thereof, wherein R₂ is the side chain of the first carbapenem.

21. The conjugate molecule of claim 20, or the pharmaceutically acceptable salt thereof, wherein the first carbapenem is selected from the group consisting of ertapenem, doripenem, imipenem, meropenem, biapenem, and panipenem.

22. The conjugate molecule of claim 17 or claim 20, or the pharmaceutically acceptable salt thereof, wherein R₃ is β-methyl.

23. The conjugate molecule of any of claims 1-22, or the pharmaceutically acceptable salt thereof, wherein the first linker is selected from the group consisting of Group AB linkers:



wherein * indicates a site of covalent attachment to the oxygen atom from the OH of a cannabinoid component, ** in cases such as ester, amide, and thioester indicates the site of covalent attachment to the carbon atom of a carbonyl component of a carboxylic acid - bearing cannabinoid component, and  marks a bond by which the linker is covalently attached to the β -lactam antibiotic component, and wherein

Y is absent or is $-\text{CH}_2$, $-\text{CHCH}_3$, or $-\text{CH}$ -phenyl;

Z is CR_1R_2 ; and

R, R_1 and R_2 independently are selected from the group consisting of:

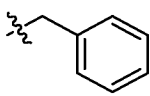
- (a) H;
- (b) C1-C8 linear or branched alkyl, optionally substituted with
 - (1) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 - (2) 1, 2, or 3 substituents independently selected from the Group One Substituents;
- (c) C1-C8 linear or branched heteroalkyl containing 1, 2, or 3 heteroatoms independently selected from O, N, and S and optionally substituted with
 - (1) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 - (2) 1, 2, or 3 substituents independently selected from the Group One Substituents;
- (d) phenyl, optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of:
 - (1) C1-C6 linear or branched alkyl, optionally substituted with
 - (i) 1, 2, 3, 4, 5, or 6 fluorine atoms; and/or
 - (ii) 1 or 2 substituents independently selected from the Group Two Substituents; and
 - (2) C1-C6 linear or branched heteroalkyl containing 1 or 2 heteroatoms independently selected from O, N, and S and optionally substituted with
 - (i) 1, 2, 3, 4, 5, or 6 fluorine atoms; and/or
 - (ii) 1 or 2 substituents independently selected from the Group One Substituents;
- (e) a 6- to 10-membered aromatic, optionally substituted with 1, 2, 3, or 4 substituents independently selected from the group consisting of:
 - (1) phenyl;
 - (2) halide;
 - (3) cyano;
 - (4) C1-C6 linear or branched alkyl, optionally substituted with

(i) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 (ii) 1, 2, or 3 substituents independently selected from the Group Two Substituents, and
 (5) C1-C6 linear or branched heteroalkyl containing 1, 2, or 3 atoms independently selected from O, N, and S and optionally substituted with

(i) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 (ii) 1, 2, or 3 substituents independently selected from the Group Two Substituents;

(f) 5- to 10-membered heteroaromatic comprising 1, 2, 3, 4, 5, or 6 heteroatoms independently selected from O, N, and S and optionally substituted with 1, 2, 3, or 4 substituents independently selected from

(1) phenyl;
 (2) halide;
 (3) cyano;
 (4) trifluoromethyl;
 (5) C1-C6 linear or branched alkyl optionally substituted with
 (i) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 (ii) 1, 2, or 3 substituents independently selected from the Group Two Substituents; and
 (6) C1-C6 linear or branched heteroalkyl containing 1, 2, or 3 atoms independently selected from O, N, and S and optionally substituted with
 (i) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 (ii) 1, 2, or 3 substituents independently selected from the Group Two Substituents;

(g) , optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of:

(1) C1-C6 linear or branched alkyl, optionally substituted with
 (i) 1, 2, 3, 4, 5, or 6 fluorine atoms; and/or
 (ii) 1, 2, or 3 substituents independently selected from the Group Two Substituents;

(h) 3- to 9-membered cycloheteroalkyl having 1, 2, or 3 heteroatoms independently selected from O, N, and S and optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of:

(1) C1-C6 linear or branched alkyl, optionally substituted with
 (i) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 (ii) 1, 2, or 3 substituents independently selected from the Group Two Substituents,

(2) C1-C6 linear or branched heteroalkyl, optionally substituted with

- (i) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms and/or
- (ii) 1, 2, or 3 substituents independently selected from the Group Two Substituents,

(3) phenyl, optionally substituted with 1, 2, or 3 substituents independently selected from the Group Two Substituents, and

(4) 5- to 10-membered heteroaromatic, optionally substituted with 1, 2, or 3 substituents independently selected from the Group Two Substituents; and

(i) C3-C6 cycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from:

(1) C1-C6 linear or branched alkyl, optionally substituted with

- (i) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
- (ii) 1, 2, or 3 substituents independently selected from the Group Two Substituents,

(2) C1-C6 linear or branched heteroalkyl, optionally substituted with

- (i) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
- (ii) 1, 2, or 3 substituents independently selected from the Group Two Substituents,

(3) phenyl, optionally substituted with 1, 2, or 3 substituents independently selected from Group Two Substituents; and

(4) 5- to 10-membered heteroaromatic, optionally substituted with 1, 2, or 3 substituents independently selected from the Group Two Substituents;

OR

R₁ and R₂, together with the atom to which they are attached, form a 3- to 9-membered cycloheteroalkyl having 1, 2, 3, or 4 heteroatoms independently selected from O, S, and N, wherein the cycloheteroalkyl optionally is substituted with 1, 2, or 3 substituents independently selected from, C1-C6 linear or branched alkyl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms, C1-C6 linear or branched heteroalkyl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms, phenyl optionally substituted with 1, 2, or 3 substituents independently selected from Group Two Substituents, or 5- to 10-membered heteroaromatic optionally substituted with 1, 2, or 3 independently selected from Group Two Substituents,

Group One Substituents is a group of substituents consisting of:

(a) -OH;

- (b) $-\text{NH}_2$;
- (c) $=\text{O}$;
- (d) $=\text{S}$;
- (e) $=\text{NR}_7$, where R_7 is H or is C1-C3 linear or branched alkyl or C1-C3 linear or branched heteroalkyl comprising an O, N, or S atom;
- (f) $-\text{C}(\text{O})\text{OR}_4$, wherein R_4 is H or C1-C3 linear or branched alkyl;
- (g) $-\text{C}(\text{O})\text{NR}_5\text{R}_6$, wherein R_5 and R_6 independently are H or C1-C6 linear or branched alkyl;
- (h) halide;
- (i) C1-C6 linear or branched alkoxy;
- (j) C1-C6 linear or branched alkylamino;
- (k) C1-C6 linear or branched dialkylamino;
- (l) 6- to 10-membered aromatic, optionally substituted with 1, 2, 3, or 4 substituents independently selected from
 - (i) phenyl;
 - (ii) halide;
 - (iii) cyano;
 - (iv) C1-C6 linear or branched alkyl, optionally substituted with
 - (1) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 - (2) 1, 2, or 3 substituents independently selected from the Group Two Substituents; and
 - (v) C1-C6 linear or branched heteroalkyl containing 1, 2, or 3 atoms independently selected from O, N, and S and optionally substituted with
 - (1) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 - (2) 1, 2, or 3 substituents independently selected from the Group Two Substituents;
- (m) 5- to 10-membered heteroaromatic, optionally substituted with 1, 2, 3, or 4 substituents independently selected from
 - (i) phenyl;
 - (ii) halide;
 - (iii) cyano;
 - (iv) C1-C6 linear or branched alkyl, optionally substituted with
 - (1) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 - (2) 1, 2, or 3 substituents independently selected from the Group Two Substituents; and
 - (v) C1-C6 linear or branched heteroalkyl containing 1, 2, or 3 atoms independently selected from O, N, and S and optionally substituted with
 - (1) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or

- (2) 1, 2, or 3 substituents independently selected from the Group Two Substituents;
- (n) 3- to 9-membered cycloheteroalkyl having 1, 2, or 3 heteroatoms independently selected from O, N, and S, optionally substituted with 1, 2, 3, or 4 substituents independently selected from
- (i) phenyl;
 - (ii) halide;
 - (iii) cyano;
 - (iv) C1-C6 linear or branched alkyl, optionally substituted with
 - (1) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 - (2) 1, 2, or 3 substituents independently selected from the Group Two Substituents; and
 - (v) C1-C6 linear or branched heteroalkyl containing 1, 2, or 3 atoms independently selected from O, N, and S and optionally substituted with
 - (1) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 - (2) 1, 2, or 3 substituents independently selected from the Group Two Substituents; and
- (o) C3-C6 cycloalkyl, optionally substituted with 1, 2, 3, or 4 substituents independently selected from
- (i) phenyl;
 - (ii) halide;
 - (iii) cyano;
 - (iv) C1-C6 linear or branched alkyl, optionally substituted with
 - (1) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 - (2) 1, 2, or 3 substituents independently selected from the Group Two Substituents; and
 - (v) C1-C6 linear or branched heteroalkyl containing 1, 2, or 3 atoms independently selected from O, N, and S and optionally substituted with
 - (1) 1, 2, 3, 4, 5, 6, 7, 8, or 9 fluorine atoms; and/or
 - (2) 1, 2, or 3 substituents independently selected from the Group Two Substituents;

Group Two Substituents is a group of substituents consisting of:

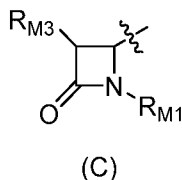
- (a) -OH;
- (b) -NH₂;
- (c) =O;
- (d) =S;

- (e) =NR₇, where R₇ is H or is C1-C3 linear or branched alkyl or C1-C3 linear or branched heteroalkyl comprising an O, N, or S atom;
- (f) -C(O)OR₄, wherein R₄ is H or C1-C3 linear or branched alkyl;
- (g) -C(O)NR₅R₆, wherein R₅ and R₆ independently are H or C1-C6 linear or branched alkyl;
- (h) halide;
- (i) cyano;
- (j) trifluoromethyl;
- (k) C1-C6 linear or branched alkoxy;
- (l) C1-C6 linear or branched alkylamino;
- (m) C1-C6 linear or branched dialkylamino;
- (n) 6- to 10-membered aromatic; and
- (o) 5- to 10-membered heteroaromatic comprising 1, 2, 3, 4, 5, or 6 heteroatoms independently selected from O, N, and S.

24. The conjugate molecule of any of claims 1-3, or the pharmaceutically acceptable salt thereof, wherein the first β -lactam antibiotic component is a first monobactam component.

25. The conjugate molecule of claim 1 or claim 24, or the pharmaceutically acceptable salt thereof, wherein the first monobactam component is provided by a monobactam selected from the group consisting of aztreonam, tigemonam, carumonam, and nocardicin.

26. The conjugate molecule of any of claims 1-3, or the pharmaceutically acceptable salt thereof, wherein the first β -lactam antibiotic component falls within structural Formula (C):

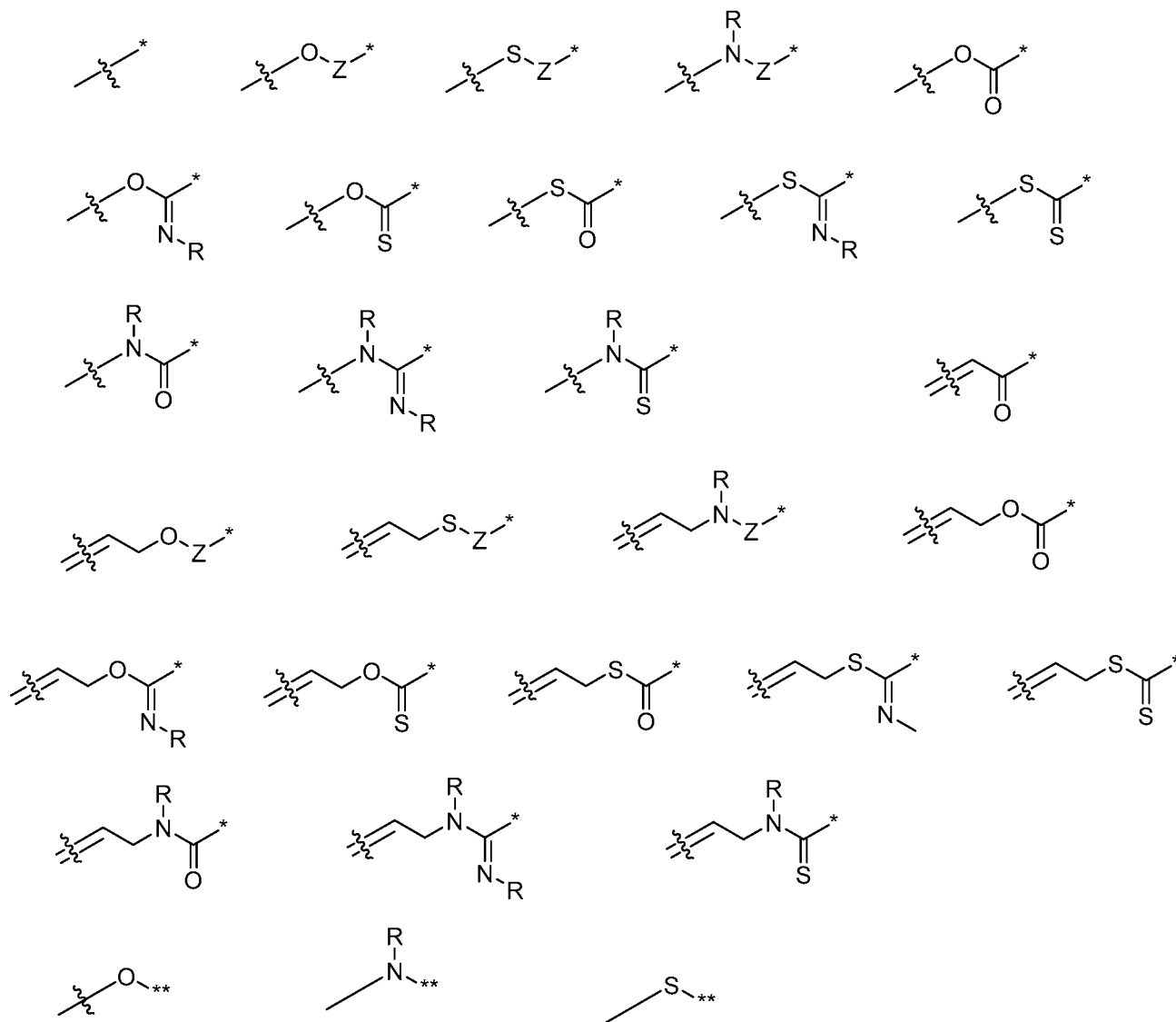


wherein R_{M3} is a first position 3 monobactam substituent, and R_{M1} is a first position 1 monobactam substituent.

27. The conjugate molecule of claim 26, or the pharmaceutically acceptable salt thereof, wherein the first position 3 monobactam substituent is provided by a monobactam selected from the group consisting of aztreonam, tigemonam, carumonam, and nocardicin.

28. The conjugate molecule of claim 26 or claim 27, or the pharmaceutically acceptable salt thereof, wherein the first position 1 monobactam substituent is provided by a monobactam selected from the group consisting of aztreonam, tigemonam, carumonam, and nocardicin.

29. The conjugate molecule of any of claims 1-3 and 24-28, or the pharmaceutically acceptable salt thereof, wherein the first linker is selected from the group consisting of Group C linkers:



in which $*$, $**$, Z , and R are as defined in claim 23.

30. The conjugate molecule of any of claims 2-29, or the pharmaceutically acceptable salt thereof, wherein the second β -lactam antibiotic component is a second cephem component.

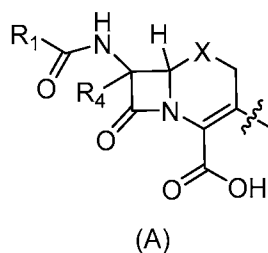
31. The conjugate molecule of claim 30, or the pharmaceutically acceptable salt thereof, wherein the second cephem component is provided by a cephem selected from the group

consisting of cefazolin, cephalixin, cefadroxil, cefapirin, cefazedone, cefazaflur, cefradine, cefroxadine, ceftezole, cefaloglycin, cephradine, cefalonium, cefaloridine, cefalotin, cefatrizine, cefaclor, cefotetan, cephamycin, cefoxitin, cefprozil, cefuorixime, cefuroxime axetil, cefamandole, cefminox, cefonicid, ceforanide, cefotiam, cefbuperazone, cefuzonam, cefmetazole, cefixime, ceftriaxone, ceftazidime, cefoperazone, cefdinir, cefcapene, cefdaloxime, ceftizoxime, cefminoxime, cefotaxime, cefpiramide, cefpodoxime, ceftibuten, cefditoren, cefetamet, cefodizime, cefpimizole, cefsulodin, cefteteram ceftiolene, flomoxef, latamoxef, cefepime, ceftazopran, cefpirome, ceftquinome, ceftaroline fosamil, ceftolozane, ceftobiprole, ceftiofur, ceftquinome, and ceftovecin.

32. The conjugate molecule of any of claims 2-29, or the pharmaceutically acceptable salt thereof, wherein the second β -lactam antibiotic component is a second carbacephem component.

33. The conjugate molecule of claim 32, or the pharmaceutically acceptable salt thereof, wherein the second carbacephem component is provided by loracarbef.

34. The conjugate molecule of any of claims 2-29, or the pharmaceutically acceptable salt thereof, wherein the second β -lactam antibiotic component falls within structural Formula (A):



wherein X is S, C, or O; R₁ is a side chain of a second cephem or a side chain of a second carbacephem; and R₄ is H or -OCH₃.

35. The conjugate molecule of claim 34, or the pharmaceutically acceptable salt thereof, wherein R₁ is the side chain of the second cephem.

36. The conjugate molecule of claim 34 or claim 35, or the pharmaceutically acceptable salt thereof, wherein the second cephem is selected from the group consisting of cefazolin, cephalixin, cefadroxil, cefapirin, cefazedone, cefazaflur, cefradine, cefroxadine, ceftezole, cefaloglycin, cephradine, cefalonium, cefaloridine, cefalotin, cefatrizine, cefaclor, cefotetan,

cephamycin, cefoxitin, cefprozil, cefuorixime, cefuroxime axetil, cefamandole, cefminox, cefonicid, ceforanide, cefotiam, cefbuperazone, cefuzonam, cefmetazole, cefixime, ceftriaxone, ceftazidime, cefoperazone, cefdinir, cefcapene, cefdaloxime, ceftizoxime, cefminoxime, cefotaxime, cefpiramide, cefpodoxime, ceftibuten, cefditoren, cefetamet, cefodizime, cefpimizole, cefsulodin, ceftaram ceftiolene, flomoxef, latamoxef, cefepime, cefozopran, cefpirome, cefquinome, ceftaroline fosamil, ceftolozane, ceftobiprole, ceftiofur, cefquinome, and cefovecin.

37. The conjugate molecule of claim 34, or the pharmaceutically acceptable salt thereof, wherein R₁ is the side chain of the second carbacephem.

38. The conjugate molecule of claim 34 or claim 37, or the pharmaceutically acceptable salt thereof, wherein the second carbacephem is loracarbef.

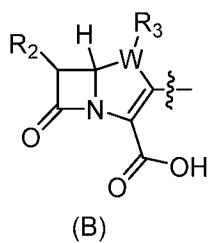
39. The conjugate molecule of any of claims 2-29, or the pharmaceutically acceptable salt thereof, wherein the second β -lactam antibiotic component is a second penem component.

40. The conjugate molecule of claim 39, or the pharmaceutically acceptable salt thereof, wherein the second penem component is provided by a penem selected from the group consisting of faropenem and ritipenem.

41. The conjugate molecule of any of claims 2-29, or the pharmaceutically acceptable salt thereof, wherein the second β -lactam antibiotic component is a second carbapenem component.

42. The conjugate molecule of claim 41, or the pharmaceutically acceptable salt thereof, wherein the second carbapenem component is provided by a carbapenem selected from the group consisting of ertapenem, doripenem, imipenem, meropenem, biapenem, and panipenem.

43. The conjugate molecule of any of claims 2-29, or the pharmaceutically acceptable salt thereof, wherein the second β -lactam antibiotic component falls within structural Formula (B):



wherein W is S or C; and R₂ is a side chain of a second penem or a side chain of a second carbapenem;

and when W is C, R₃ is H, CH₃, or phenyl, wherein the phenyl is optionally substituted with 1-4 groups selected from the group consisting of halide, trifluoromethyl, C1-C6 linear or branched alkyl optionally substituted with up to nine fluorine atoms, and C1-C6 linear or branched heteroalkyl containing 1 to 3 atoms independently selected from O, N, and S and optionally substituted with up to 9 fluorine atoms.

44. The conjugate molecule of claim 43, or the pharmaceutically acceptable salt thereof, wherein R₂ is the side chain of the second penem.

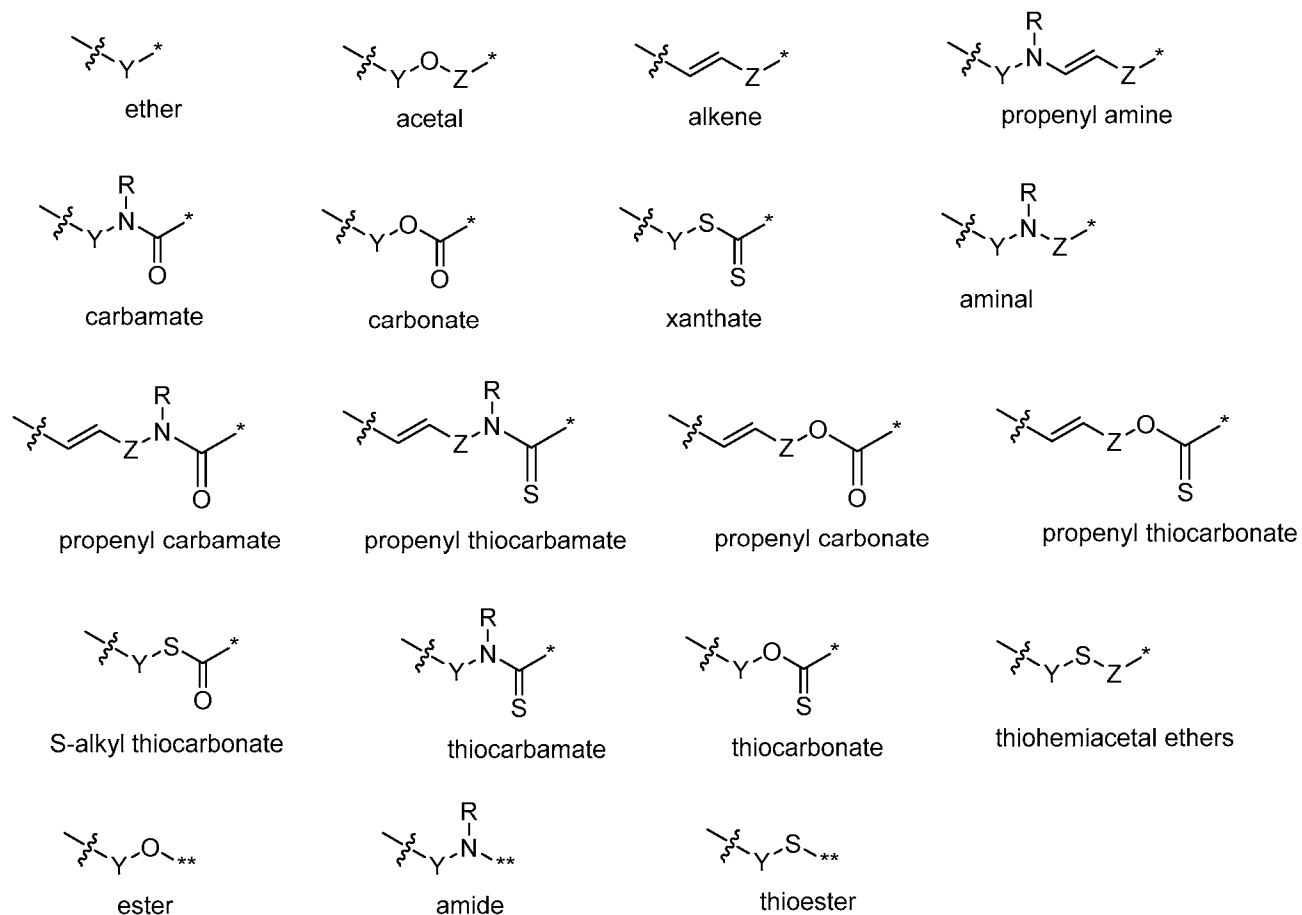
45. The conjugate molecule of claim 44, or the pharmaceutically acceptable salt thereof, wherein the second penem is selected from the group consisting of faropenem and ritipenem.

46. The conjugate molecule of claim 43, or the pharmaceutically acceptable salt thereof, wherein R₂ is the side chain of the second carbapenem.

47. The conjugate molecule of claim 46, or the pharmaceutically acceptable salt thereof, wherein the second carbapenem is selected from the group consisting of ertapenem, doripenem, imipenem, meropenem, biapenem, and panipenem.

48. The conjugate molecule of claim 43 or claim 46, or the pharmaceutically acceptable salt thereof, wherein R₃ is β -methyl.

49. The conjugate molecule of any of claims 2-3 and 30-48, or the pharmaceutically acceptable salt thereof, wherein the second linker is selected from the group consisting of Group AB linkers:

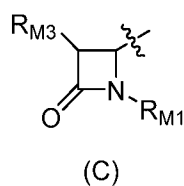


wherein *, **, , Y, Z, R, R₁, and R₂ are as defined in claim 23.

50. The conjugate molecule of any of claims 2-29, or the pharmaceutically acceptable salt thereof, wherein the second β -lactam antibiotic component is a second monobactam component.

51. The conjugate molecule of claim 50, or the pharmaceutically acceptable salt thereof, wherein the second monobactam component is provided by a monobactam selected from the group consisting of aztreonam, tigemonam, carumonam, and nocardicin.

52. The conjugate molecule of any of claims 2-29, or the pharmaceutically acceptable salt thereof, wherein the second β -lactam antibiotic component falls within structural Formula (C):

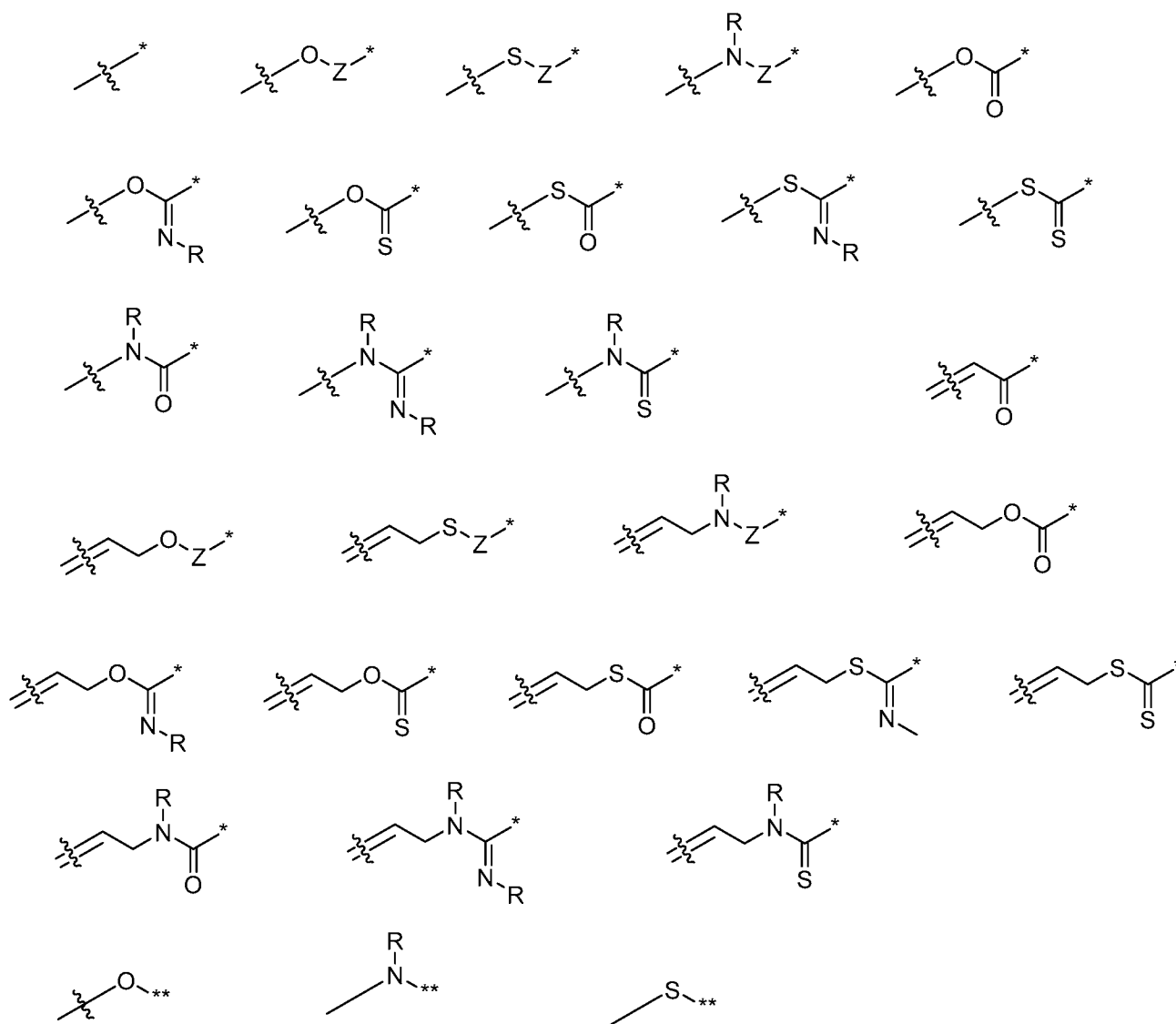


wherein R_{M3} is a second position 3 monobactam substituent, and R_{M1} is a second position 1 monobactam substituent.

53. The conjugate molecule of claim 52, or the pharmaceutically acceptable salt thereof, wherein the second position 3 monobactam substituent is provided by a monobactam selected from the group consisting of aztreonam, tigemonam, carumonam, and nocardicin.

54. The conjugate molecule of claim 52 or claim 53, or the pharmaceutically acceptable salt thereof, wherein the second position 1 monobactam substituent is provided by a monobactam selected from the group consisting of aztreonam, tigemonam, carumonam, and nocardicin.

55. The conjugate molecule of any of claims 2-29 and 50-54, or the pharmaceutically acceptable salt thereof, wherein the second linker is selected from the group consisting of Group C linkers:



wherein *, **, $\sim$, Z, and R are as defined in claim 23.

56. The conjugate molecule of any of claims 1-55, or the pharmaceutically acceptable salt thereof, wherein the cannabinoid component is provided by a cannabinoid selected from the group consisting of a cannabigerol, a cannabichromene, a cannabidiol, a tetrahydrocannabinol, a cannabicyclol, a cannabielsoin, a cannabinol, a cannabinodiol, a cannabitriol, a dehydrocannabifuran, a cannabifuran, a cannabichromanone, and a cannabiripsol, or an active metabolite thereof.

57. The conjugate molecule of claim 56, or the pharmaceutically acceptable salt thereof, wherein the cannabinoid component is a cannabidiol component.

58. The conjugate molecule of any of claims 1-57, wherein the first hydroxy group is an aromatic hydroxy group.

59. The conjugate molecule of any of claims 2-58, wherein the second hydroxy group is an aromatic hydroxy group.

60. A pharmaceutical composition comprising a conjugate molecule of any of claims 1-59, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle.

61. The pharmaceutical composition of claim 60, which comprises a racemic mixture of conjugate molecules.

62. The pharmaceutical composition of claim 60, which comprises a single enantiomer of the conjugate molecule.

63. The pharmaceutical composition of claim 60, which comprises a mixture of diastereomers of the conjugate molecule.

64. The pharmaceutical composition of claim 60, which comprises a mixture of double bond isomers of the conjugate molecule.

65. The pharmaceutical composition of claim 60, which comprises a Z-double bond isomer of the conjugate molecule.

66. The pharmaceutical composition of claim 60, which comprises a E-double bond isomer of the conjugate molecule.

67. The pharmaceutical composition of claim 60, which comprises an isotopic variant of the conjugate molecule.

68. A method of treating a bacterial infection, comprising administering to a patient in need thereof a conjugate molecule of any of claims 1-59 or a pharmaceutically acceptable salt thereof.

69. The method of claim 65, wherein the patient has cystic fibrosis and wherein at least the first β -lactam antibiotic component is a first monobactam component.

70. A method of treating inflammation, comprising administering to a patient in need thereof a conjugate molecule of any of claims 1-59 or a pharmaceutically acceptable salt thereof.

71. The method of claim 70, wherein the inflammation is associated with a disorder selected from the group consisting of type I diabetes, cancer, Alzheimer's disease, cachexia, muscle-wasting diseases, allergies, rheumatoid arthritis, scleroderma, rheumatic fever, inflammatory bowel disease, myasthenia gravis, multiple sclerosis, Guillain-Barre syndrome, conjunctiva of the eye, systemic lupus erythematosus, encephalitis, Adult Respiratory Distress Syndrome, psoriasis, emphysema, and muscular dystrophy.

72. The method of any of claims 68-71, further comprising co-administering to the patient a β -lactamase inhibitor.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 20/39354

A. CLASSIFICATION OF SUBJECT MATTER
 IPC - C07D 311/00; C07D 311/22; C07D 501/36 (2020.01)
 CPC - C07D 311/22; A61P 31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
 See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,285,941 A (Machida et al.) 25 August 1981 (25.08.1981); col 1, ln 10-15	1-4, 6, 8-9, 11, 13-21, 24, 26-27
A	US 6,627,625 B1 (Koppel) 30 September 2003 (30.09.2003) col 16, ln 35-45	1-4, 6, 8-9, 11, 13-21, 24, 26-27
A	US 2013/0281424 A1 (UNIVERSITY OF NOTRE DAME DULAC) 24 October 2013 (24.10.2013); abstract, para [0063]	1-4, 6, 8-9, 11, 13-21, 24, 26-27
A	US 2014/0302121 A1 (Bevier) 09 October 2014 (09.10.2014); entire document	1-4, 6, 8-9, 11, 13-21, 24, 26-27
A	US 9,345,691 B2 (STEM CELL MEDICINE LTD.) 24 May 2016 (24.05.2016); entire document	1-4, 6, 8-9, 11, 13-21, 24, 26-27

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
 "D" document cited by the applicant in the international application
 "E" earlier application or patent but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

10 September 2020

Date of mailing of the international search report

06 OCT 2020

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 20/39354

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 5, 7, 10, 12, 22-23, 25, 28-72
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.