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(54) METHOD FOR SYNTHESIS OF CIGUATOXIN CTX1B AND COMPOUND USEFUL FOR THE SYNTHESIS OF CIGUATOXIN CTX1B

(57) Disclosed is a method for total synthesis of CTX1B, which is developed for the synthesis of a ciguatoxin analogue such as CTX3C and enables the more efficient application of an established reaction to the total synthesis of CTC1B. More specifically, disclosed is a method for total synthesis of CTX1B comprising; an O.S-acetal formation for synthesizing a novel compound (3); a radical cyclization reaction for constructing a 9-membered ring formation reaction including a novel compound (6) through a novel compound (8) and yielding a compound (D); and a deprotection for yielding CTX1B. Also disclosed are novel compounds (1) to (8) which are particularly useful for synthesis of CTX1B and can be used for the synthesis of a ciguatoxin analogue.

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to the establishment of a method for total synthesis of ciguatoxin CTX1B which is a homolog of ciguatoxin, further, relates to a provision of compounds useful to make possible an effective method for preparation of said total synthesis.

BACKGROUND OF THE INVENTION

[0002] Food-poisoning, ciguatera caused by poisoning of originally non-toxic fishes, widely occurs in coral reef islands region of subtropical and tropical regions, and more than 50,000 people suffer annually from ciguatera. Although the mortality is not so high, symptoms such as abnormal sensation, diarrhea, lassitude, arthralgia or itching last for several months under some circumstances. Ciguatoxins (CTX), which are isolated and the structure of which is decided as a main originated poison of ciguatera, are macromolecules characterized by fused 13 ether rings and their molecular length is approximately 3 nm, further more than 20 kinds of homolog are existing. Ciguatoxins are produced from dinoflagellate *Gambierdiscus toxicus* and accumulate in fishes by means of food chain. Since approximately 400 kinds of toxic fishes are normal from the view points of appearance, taste and odor, it is not safe to exploit fish sources of southern sea region. Therefore, the development of detective method of ciguatoxins by means of easy and high sensitive immunological measuring method of ciguatoxins is strongly expected.

[0003] Ciguatoxins bind specifically to voltage-sensitive Na^+ channels (VSSC) of excitable membranes, activate it and generate toxicity, however, the activation mechanism of ciguatoxins at structural level is not made clear yet. Ciguatoxins exist in nature is very small and cultural production by the dinoflagellate is very slow, detail biological research and the preparation of anti-CTX antibody using natural product is virtually impossible. Under said circumstances, the quantitative supply of natural ciguatoxins by practical chemical synthesis is strongly desired.

[0004] Inventors of the present invention already proposed a total synthesis of CTX3C, which is one of main homolog of ciguatoxin (non patent document 1, Proc. Natl. Acad. Sci. U.S.A. 101, 1203-12018 (2004)). Further, the inventors developed a Sandwich immunoassay that can detect CTX3C easily (non patent document 2, J. Am. Chem. Soc. 125, 7608-7612 (2003)) and are now investigating to apply it to identification of a ciguatera fish. However, since CTX3C is mainly contained in a herbivorous fish, preparation of an antibody originated to other homolog is necessary for detection of ciguatoxin from a carnivorous fish.

[0005] CTX1B is the most typical ciguatoxin contained mainly in a carnivorous fish and has more complicated structure than CTX3C, and is known as the most historically important ciguatoxin whose structure is firstly decided in 1989. At the decision of structure, 0.3 mg of CTX3B isolated from 4000 kg of poisonous moray is used. However, since it was actually impossible to obtain practical amount of sample from nature, development of total synthesis of CTX1B is awaited for the actual use of CTX1B as a standard sample.

[0006] Generally, in total synthesis, if partial structure is different, development of a new synthesis route becomes necessary. However, for the purpose to synthesis many ciguatoxin homologs existing in nature in a unified fashion, the inventors have developed convergent total synthesis, which is characterized to be remarkably simple and more reliable compared with competitive methods. By said method, supply of over than several mg of CTX3C became possible up to this time. According to said concept, since there is possibility that carnivorous fishes accumulate ciguatoxin by higher concentration than herbivorous fishes because carnivorous fishes are locating at upper position of food chain than herbivorous fishes and is more dangerous as a ciguatera poisoned fish, the inventors of the present invention considered to develop a new effective total synthesis of CTX1B for the purpose of investigation of CTX1B.

[0007] At the development of a new effective total synthesis, the inventors of the present invention considered to utilize the reaction sequence which were already developed for synthesis of CTX3C. Namely, the inventors considered to apply the coupling of ABCDE ring segments with HIJKLM ring segments and subsequent construction of FG ring to CTX1B. However, since 7-members ring E-structure, and a side chain existing in A ring segments of CTX1B are structurally different from CTX3C, direct application of methodology used in CTX3C was impossible. Therefore, the inventors planned to develop a higher yielding process from a view point of effective preparation of the aimed compound.

(1) At the formation of 7-members ring of compound D at radical ring forming reaction, preparation process of CTX3C can not be used. Therefore, the inventors designed compound 5 that has pentafluoroacrylate instead of conventionally used methylacrylate and yield of ring forming reaction is remarkably improved.

(2) At deprotection of naphthylmethyl (NAP) group, side chain of A ring segment is very unstable to acid and compound E acetal intermediate is formed at conventional acid hydrolysis of acetal. Therefore, various investigations for condition are carried out and it is understood that acetal can be removed by condition of 1N hydrochloric acid/methanol, and the total synthesis of CTX1B can be carried out for the first time. Further, at above mentioned

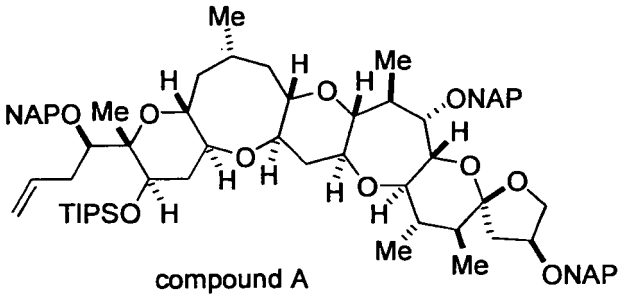
development, the inventors considered to utilize HIJKLM ring segments compound A, which was already reported in a paper (non-patent document 3, J. Org. Chem. 69, 2797-2804 (2004)), and compound C (non-patent document 4, J. Org. Lett., 6, 751-754 (2004)) as one of intermediates, according to the thinking that O,S-acetal compound 3, which is the most important intermediate, can be synthesized by coupling reaction developed by the inventors that permits neutral condition.

SUBJECT OF THE INVENTION

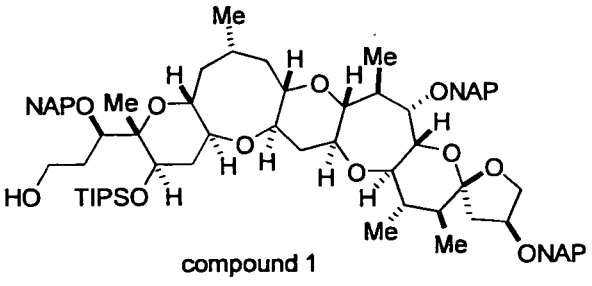
[0008] The subject of the present invention is to provide an effective method for total synthesis of CTX1B by high yield. Aiming to accomplish said subject, the inventors of the present invention considered that the designing of an intermediate that can apply an established reaction to be considered rational in synthesis of ciguatoxin analogous compound is important. That is, the subject of this invention is to provide an useful compound that can be used for an effective method for total synthesis of CTX1B, further to link to an improvement of synthesis of ciguatoxin analogous compound. From said points of view, the inventors of the present invention continued investigation and adopted O,S-acetal forming reaction that synthesizes compound 3. and 9-rings forming reaction from compound 6 to 8, further, developed a radical ring-forming reaction to obtain afore mentioned compound D and a deprotection reaction to obtain CTX1B newly, and by synthesizing all new compounds to link the intermediate to aimed compound, and can accomplish afore mentioned subject.

DISCLOSURE OF THE INVENTION

[0009] The first one of the present invention is a method for synthesizing the aimed compound of CTX1B including following 10 processes. First process is comprised of oxidizing double bond in compound A by using osmium tetra oxide to change to a diol derivative of compound A, and after transforming the diol to an aldehyde by oxidation cleavage by using sodium periodate, reducing the aldehyde to alcohol using sodium borohydride to obtain compound 1 (process 1).

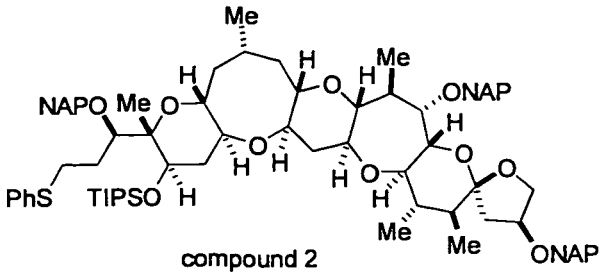


compound A



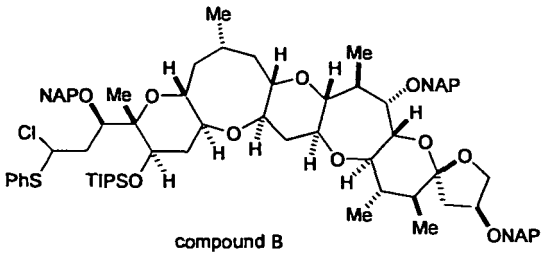
compound 1

Second process is transforming the alcohol of compound 1 to compound 2 using diphenyldisulfide·tributylphosphine (process 2).



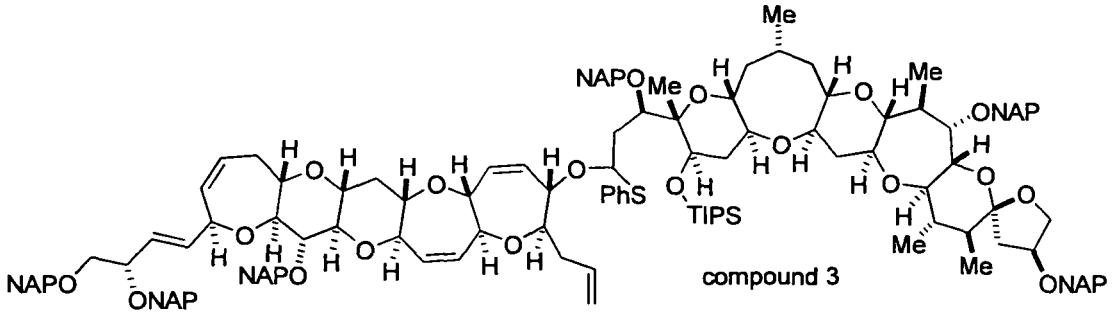
compound 2

Third process comprises of transforming the compound 2 to α-chrolosulphide to synthesize the compound B, and synthesizing compound 3 by joining the ABCDE ring segments compound C (Refer to the non-patent document 4, J. Org. Lett., 6, 751-754 (2004)) and the compound B as O,S-acetal using silver triflate (AgOTf) (process 3), under the presence of DTBMP (dimethylsulfooxide).



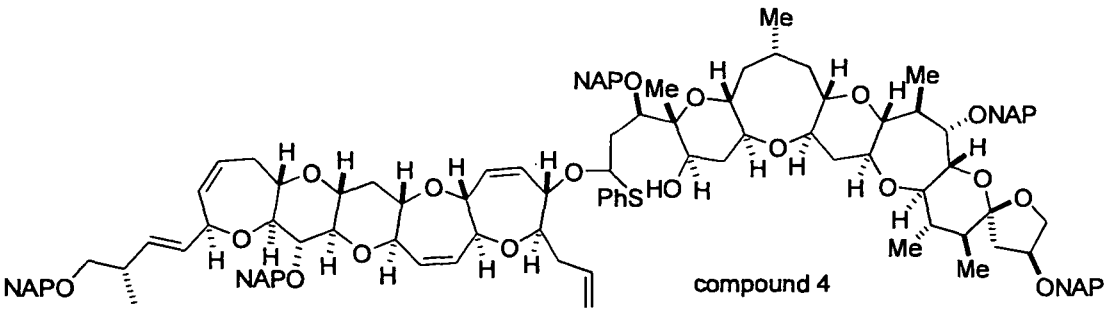
compound B

(process 3).



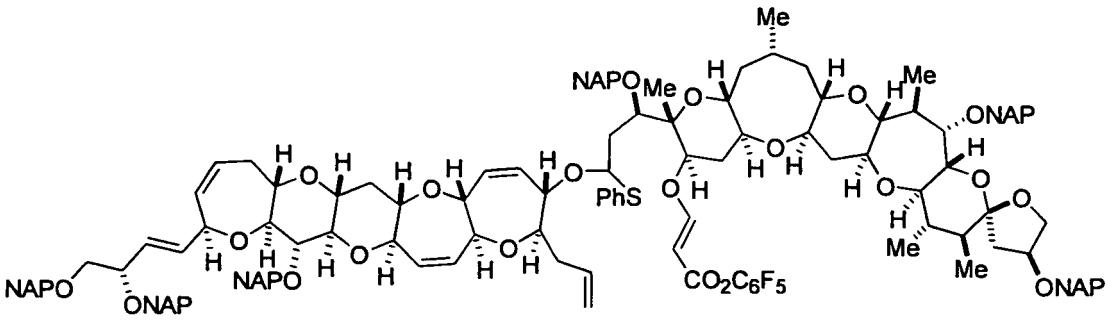
compound 3

Forth process is forming the compound 4 by removing TIPS (triisopropylsilyl) group from the compound 3 using TBAF (tetrabutylammonium fluoride) (process 4).



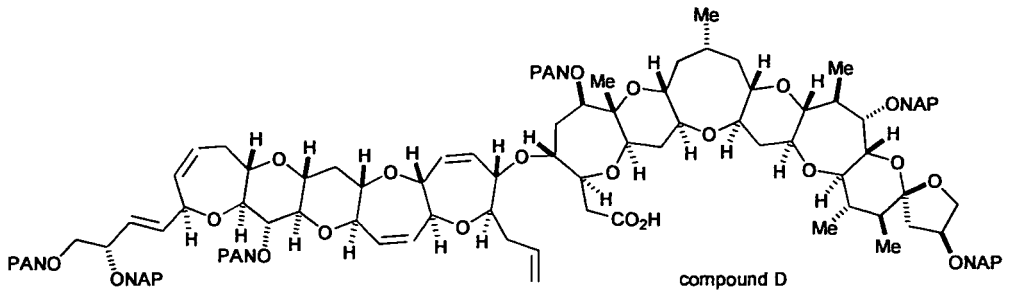
compound 4

Fifth process is forming the compound 5 by joining pentafluorophenylpropiolate to alcohol of above mentioned compound 4 (process 5).



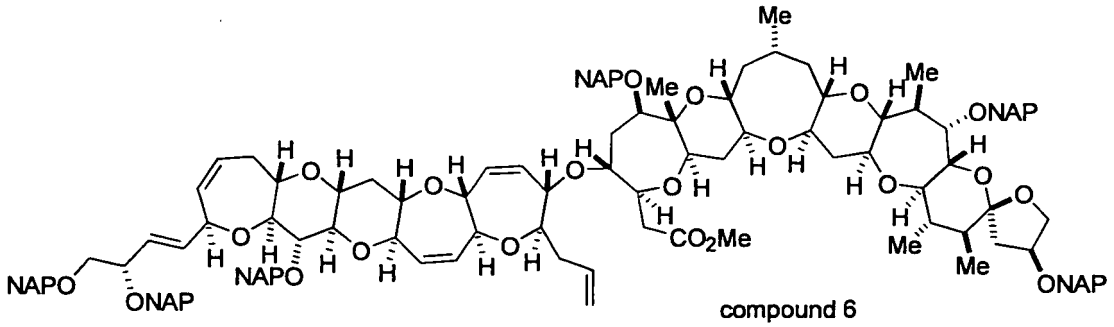
compound 5

Sixth process comprises of transforming the compound 5 to carboxylic acid compound D by forming G ring part by carrying out radical cyclizing reaction on said compound 5 treating by AIBN (α , α'-azobis(isobutyronitrile)) and tributyltin hydride, and



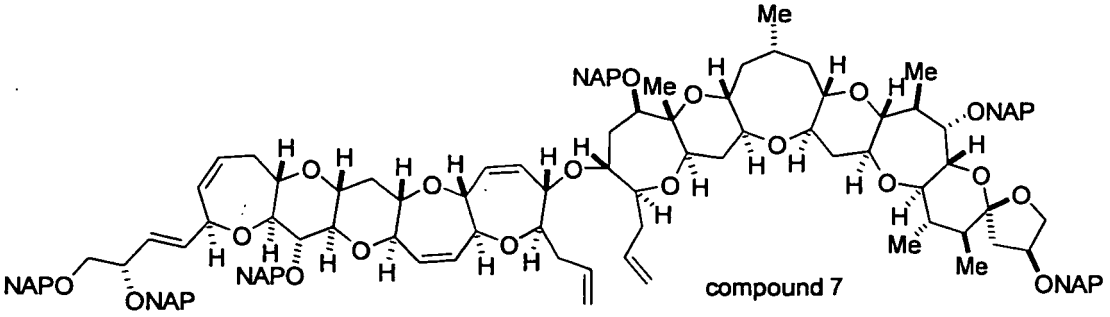
compound D

transforming to methyl ester by acting trimethylsilyldiazomethane and to form compound 6 (process 6).



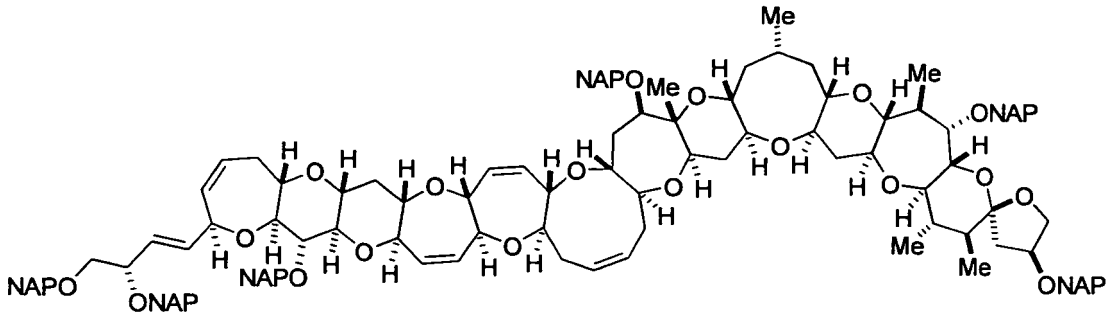
compound 6

Seventh process is forming compound 7 by reducing methyl ester of above mentioned compound 6 by using diisobutylaluminum hydrate under lower temperature condition, then transforms to olefin by Wittig reaction (process 7).



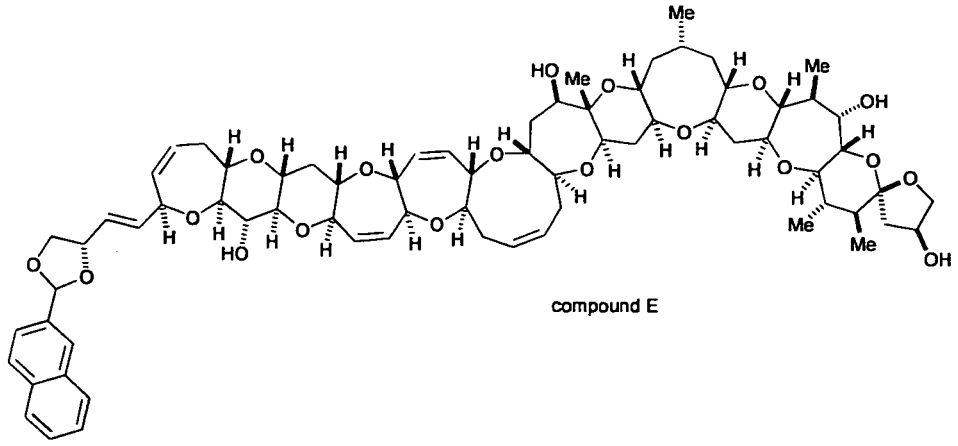
compound 7

Eighth process is forming compound 8 by forming F ring part by carrying out ring closure methathesis reaction acting Grubbs catalyst to above mentioned compound 7 (process 8).



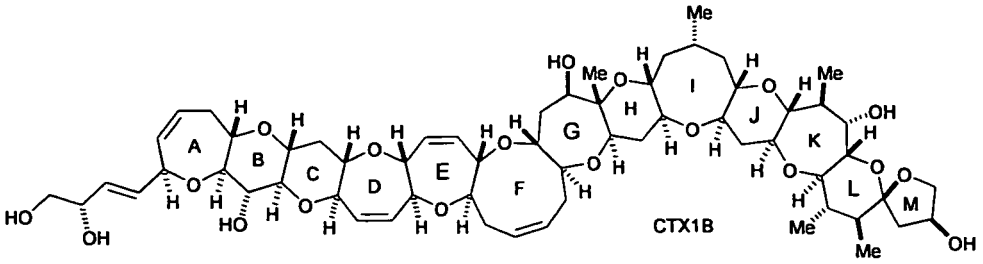
compound 8

Ninth process is synthesizing compound E, 1,2-diol of A ring side chain of which is protected by naphthylacetal, by oxidizing 6 NAP (2-naphthylmethyl) groups using DDQ (2,3-dichloro-5,6-dicyano-1,4 -benzoquinone) and removing 5 NAP groups (process 9).



compound E

Tenth process is obtaining aimed compound CTX1B by acid treatment of above mentioned compound E (process 10).



[0010] The second one of the present invention is a novel compound represented by compound 1, which is useful for the method to prepare CTX1B. The third one of the present invention is a novel compound represented by compound 2, which is useful for the method to prepare CTX1B. The fourth one of the present invention is a novel compound represented by compound 3, which is useful for the method to prepare CTX1B. The fifth one of the present invention is a novel compound represented by compound 4, which is useful for the method to prepare CTX1B. The sixth one of the present invention is a novel compound represented by compound 5, which is useful for the method to prepare CTX1B. The seventh one of the present invention is a novel compound represented by compound 6, which is useful for the method to prepare CTX1B. The eighth one of the present invention is a novel compound represented by compound 7, which is useful for the method to prepare CTX1B. And the ninth one of the present invention is a novel compound represented by compound 8, which is useful for the method to prepare CTX1B.

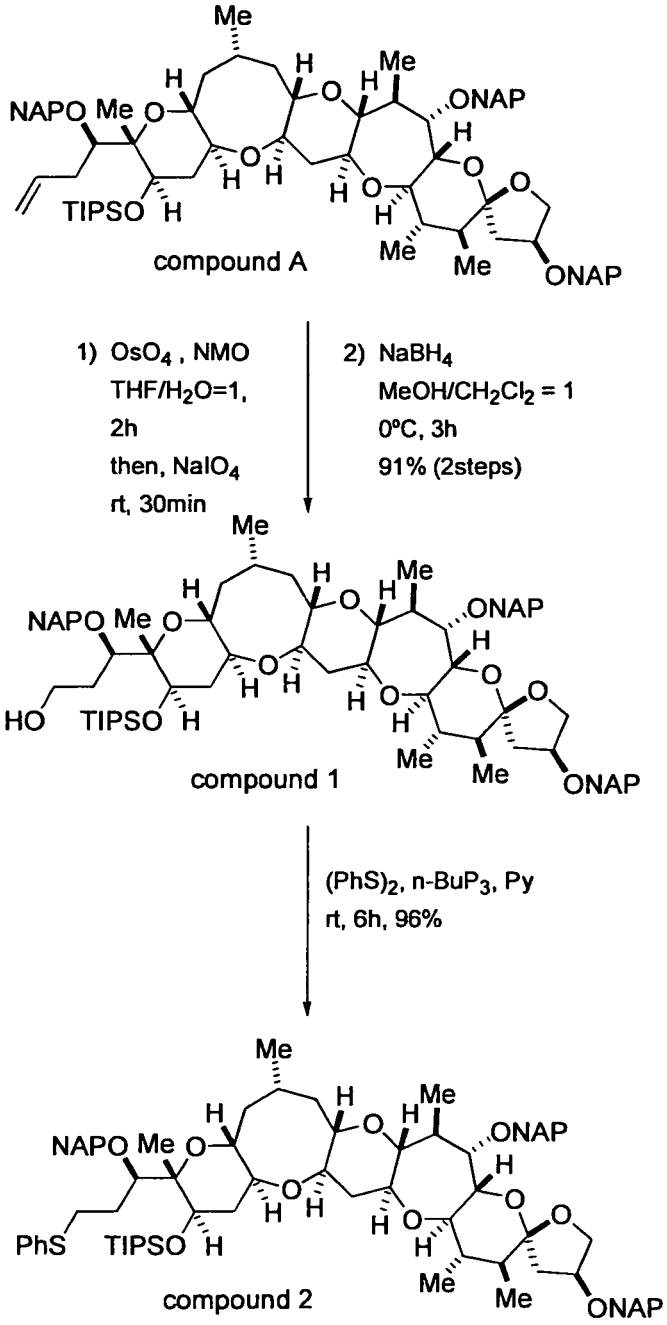
EFFECT OF THE INVENTION

[0011] The offering of an effective total synthesis of CTX1B of the present invention is important from the view point that practical amount of said compound to ensure a progress in the research of biological science or a development for detection of Ciguatera poisoned fish can be supplied, and has an effect that can be practically used as a standard specimen of Ciguatera food-poisoning happened in all over the world.

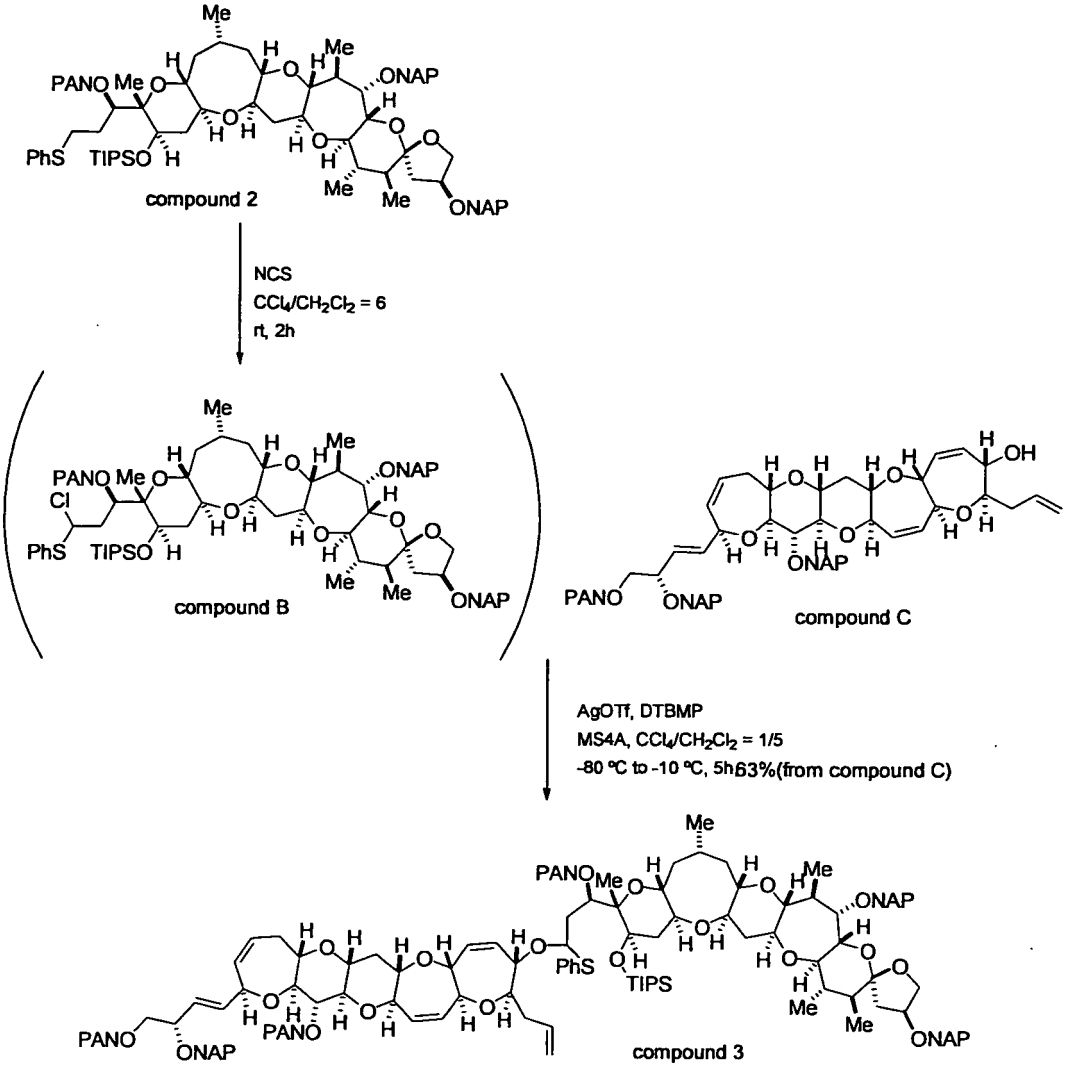
PREFFERED EMBODIMENT OF THE INVENTION

[0012] The present invention will be illustrated more in detail.
A. Since HIJKLM ring segments compound A (J. Org. Chem. 69, 2797-2804 (2004)), which was reported in afore mentioned non-patent document 3, has a structure corresponding to half of CTX1B, said compound A is used as an intermediate for synthesis of CTX1B. By reaction condition mentioned in following reaction formula, double bond of compound A is oxidized by osmium tetra oxide and transformed to diol, then transformed to aldehyde by oxidation cleavage by sodium periodate (at room temperature), after that, reduced to alcohol using sodium borohydride and obtain compound 1 (yield of these two processes is 91%).

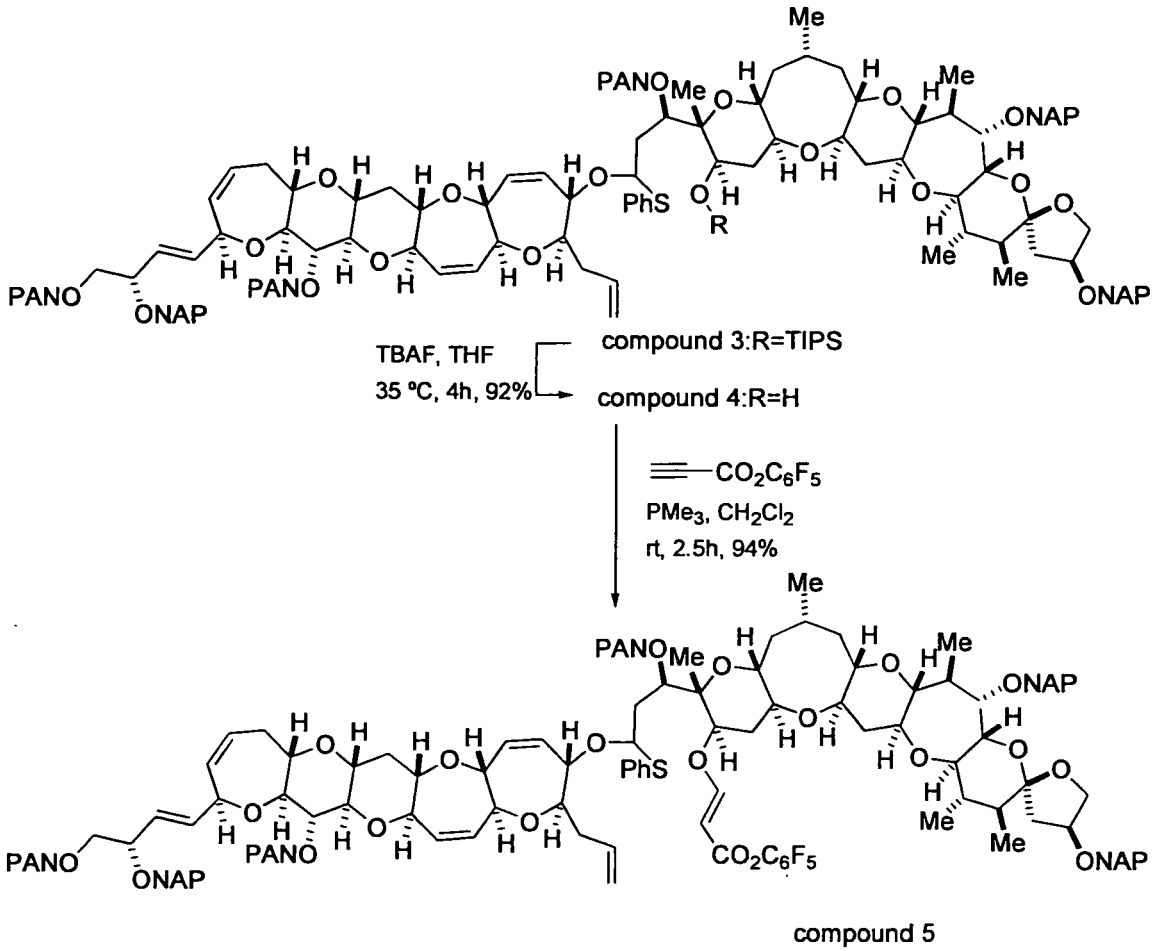
[0013] Alcohol of compound 1 is transformed to compound 2 using diphenyldisulfide·tributylphosphine (at room temperature, yield is 96%).



[0014] Compound 2 is transformed to α -chrolosulphide in 6:1 mixed solvent of carbon tetrachloride and dichloromethane using NSC and compound B is synthesized. Then, ABCDE ring segments compound C, which is already reported in paper (afore mentioned non-patent document 4, J. Org. Lett., 6, 751-754 (2004)), and compound B are joined as O, S-acetal using silver triflate (AgOTf) in 1:5 mixed solvent of carbon tetrachloride and dichloromethane under the presence of DTBMP and compound 3 is obtained (yield to compound C is 63%).

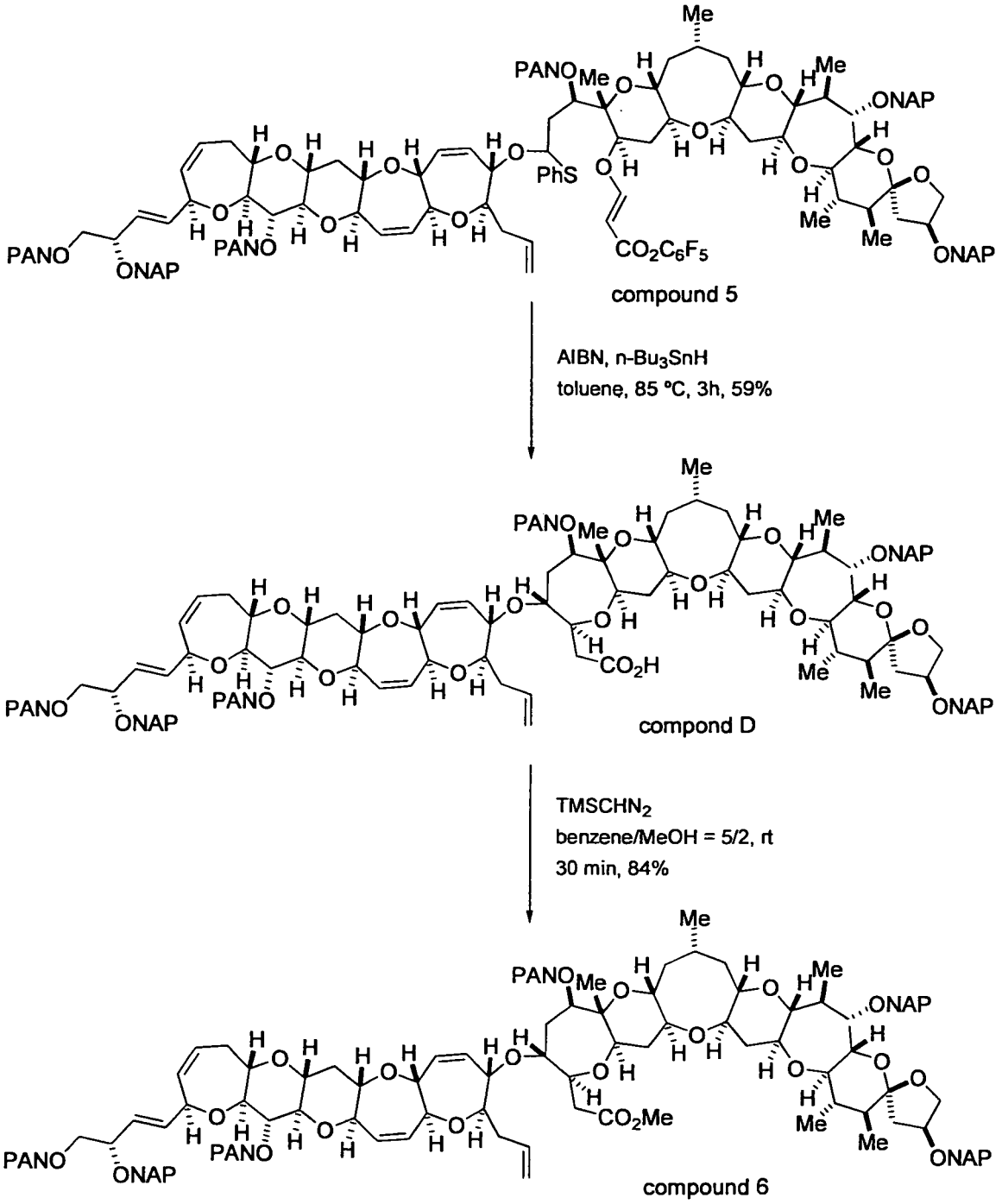


[0015] TIPS group of compound 3 is removed by TBAF and compound 4 is formed (yield is 92%). Pentafluorophenylpropiolateacrylate is introduced into alcohol of compound 4 using pentafluorophenylpropiolate and trimethylphosphine and compound 5 is formed (yield is 94%).

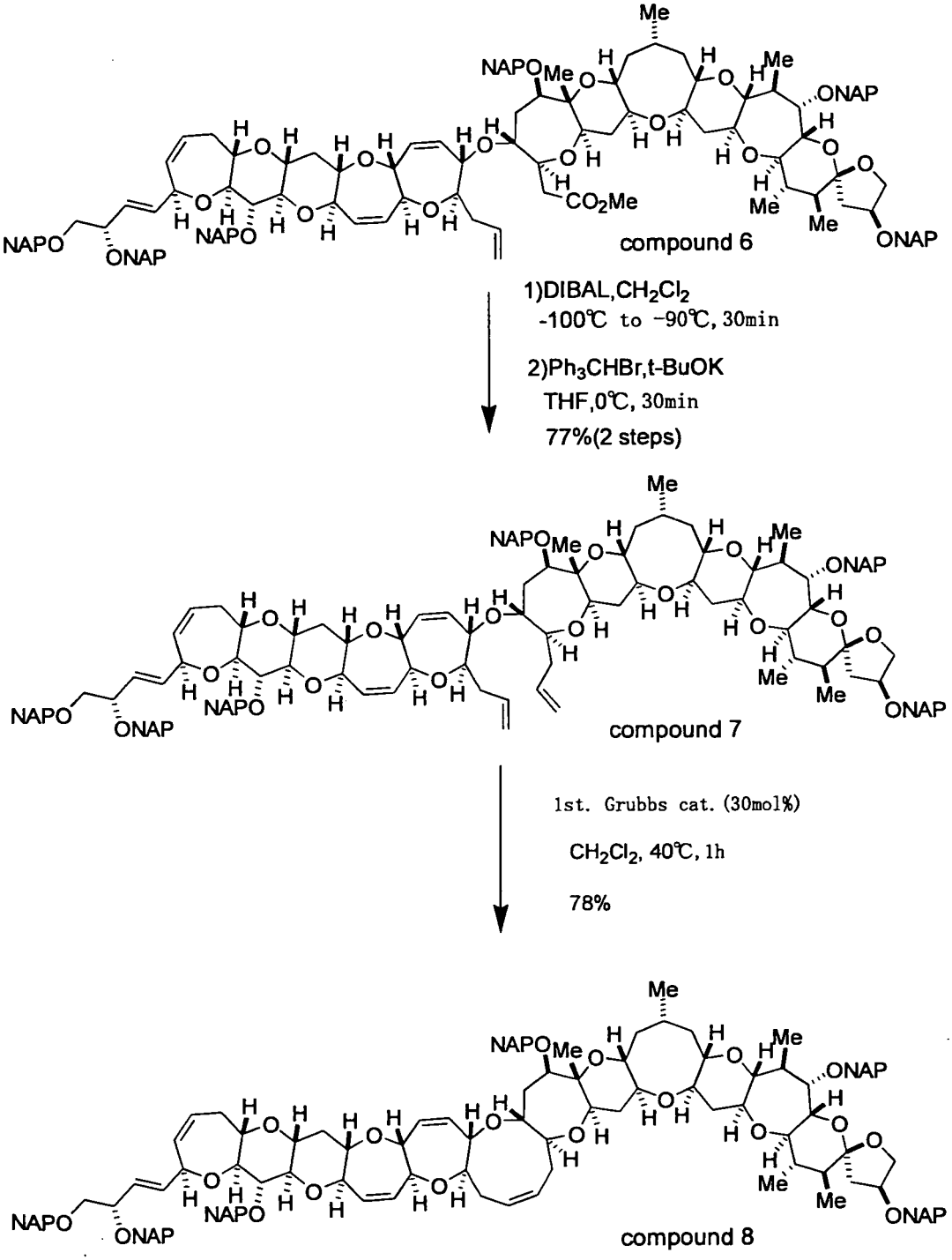


compound 5

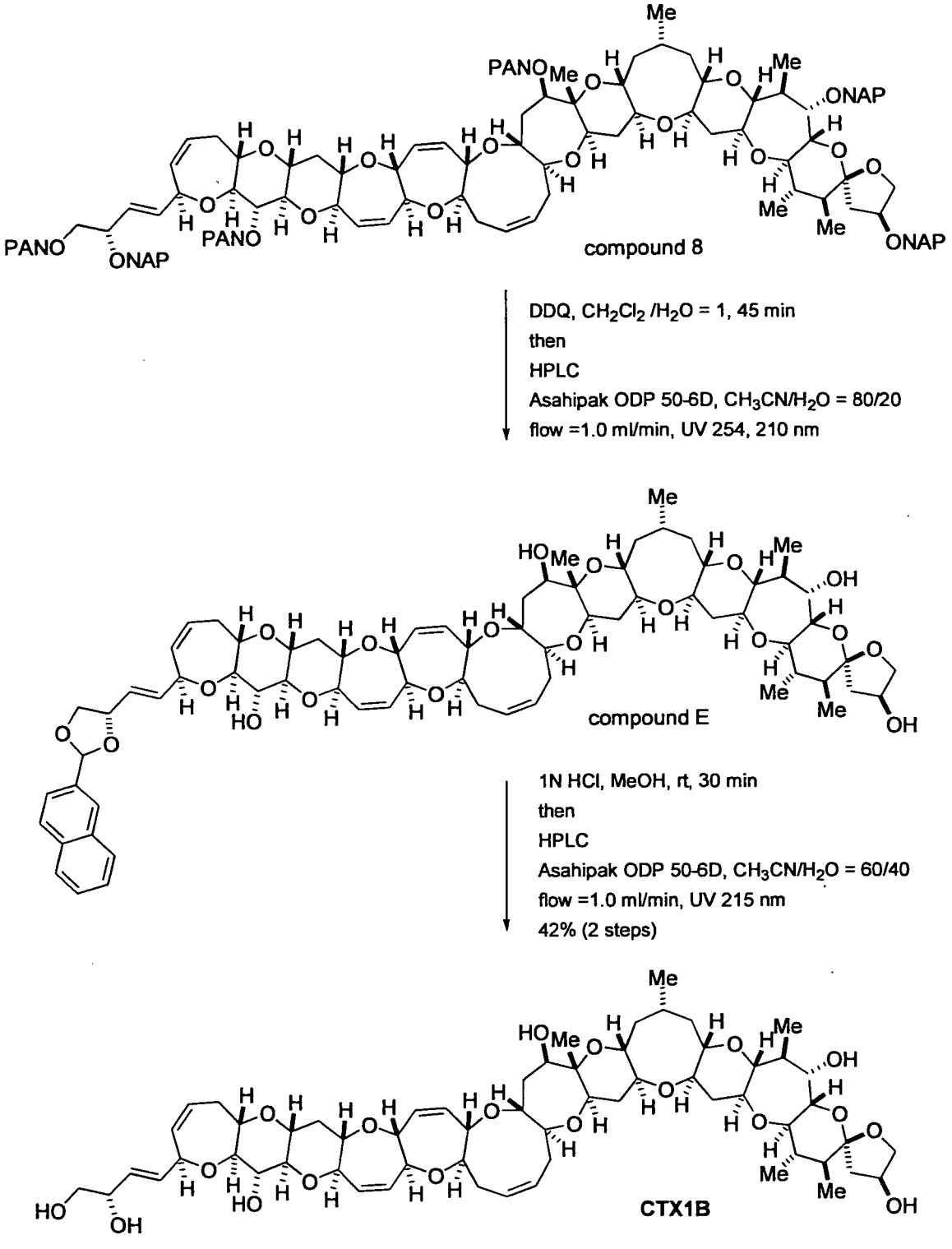
[0016] Radical cyclizing reaction is carried out on compound 5 by treating with AIBN and tributyltin hydride in toluene at 85°C and G ring part is formed, thus carboxylic acid compound D is obtained. In mixed solvent of benzene and methanol, trimethylsilyldiazomethane is acted to compound D so as to transform to methyl ester, and compound 6 is formed.



[0017] Methyl ester of compound 6 is reduced to aldehyde by diisobutylalminum hydride under low temperature condition, then transformed to olefin by Wittig reaction and compound 7 is formed. Grubbs catalyst is acted to compound 7 and F ring part is formed by carrying out ring closure methathesis reaction, and compound 8 is obtained.



[0018] Six NAP groups of compound 8 are oxidized using DDQ and 5 NAP groups is removed, thus compound E characterized that 1,2-diol of A ring side chain is protected by naphthylacetal is formed. Finally, compound E is treated by 1N hydrochloric acid in methanol solvent and total synthesis of CTX1B, which is aimed compound, is accomplished.



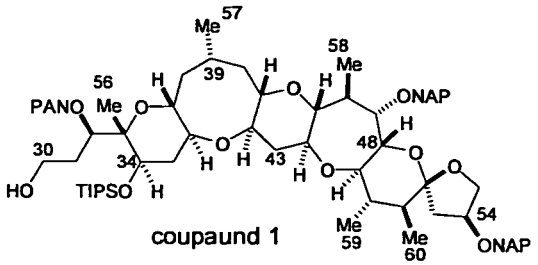
EXAMPLES

[0019] More concrete synthesis will be shown as Examples, however, these Examples are shown to understand the present invention more easily and not intending the scope of the present invention.

Example 1

Synthesis of compound 1

[0020]



coupaund 1

[0021] HIJKLM ring segments compound A (151mg, 129 μ mol) is dissolved in mixed solvent (0.1M) of THF (0.86mL)-water(0.43mL), then osmium tetra oxide (19mM, t-BuOH solution, 710 μ L, 13.4 μ mol) and NMO (50% aqueous solution, 94 μ L L, 402 μ mol) are added and stirred vigorously for 2 hours. To this solution, phosphoric acid buffer solution (pH =7.0, 3.0mL, 0.04M) and sodium periodate (120mg, 536 μ mol) are added gradually and stirred at room temperature for 3 hours. Reaction is stopped by adding saturated $Na_2S_2O_3$ aqueous solution to this solution and diluted by ethyl acetate and saturated $NaHCO_3$ aqueous solution. Water phase is extracted by ethyl acetate for 3 times, and combined organic layer is washed by saturated brine, then is dried by Na_2SO_4. Solvent is concentrated and crude aldehyde is used to the next reaction without refining.

CH_2Cl_2 (5.0mL, 0.25M) solution of aldehyde is cooled to 0°C, and sodium borohydride (25mg, 670 μ mol) is added and stirred for 30 minutes. Reaction is stopped by adding saturated NH_4Cl aqueous solution into this solution and diluted by ethyl acetate. Water phase is extracted by ethyl acetate for 3 times, and combined organic layer is washed by saturated brine, then is dried by Na_2SO_4. Solvent is concentrated and refined by a flash column, then alcohol of compound 1 (138mg, 1.17 μ mol) is obtained. Total yield of this 2 processes is 91%. Features of compound 1 are shown in Table 1.

(Table 1)

$[\alpha]_D^{23}$ -10.3 (c 0.41, $CHCl_3$); IR (film) ν 2926, 2865, 1723, 1463, 1090 cm^{-1}

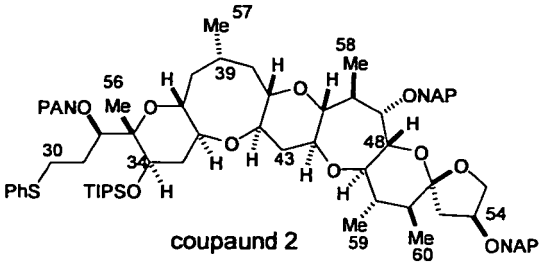
^1H NMR (500 MHz, $CDCl_3$) δ 7.83-7.41 (21H, m, NAPx3), 4.81 (1H, d, *J* = 12.0 Hz, NAP), 4.79 (1H, d, *J* = 12.0 Hz, NAP), 4.73 (1H, d, *J* = 12.0 Hz, NAP), 4.66 (1H, d, *J* = 12.0 Hz, NAP), 4.61 (1H, d, *J* = 12.0 Hz, NAP), 4.58 (1H, d, *J* = 12.0 Hz, NAP), 4.31 (1H, dd, *J* = 11.5, 5.0 Hz, H34), 4.26 (1H, m, H54), 3.97 (1H, dd, *J* = 9.5, 1.5 Hz, H55), 3.88-3.80 (4H, m, H30, H32, H44, H55), 3.64 (1H, m, H30), 3.61 (1H, d, *J* = 9.5 Hz, H48), 3.43-3.41 (2H, m, H47, H49), 3.39 (1H, ddd, *J* = 9.5, 3.5, 3.5 Hz, H37), 3.15 (1H, ddd, *J* = 11.5, 9.5, 5.0 Hz, H36), 3.10 (1H, ddd, *J* = 11.5, 9.5, 5.0 Hz, H42), 2.98 (1H, ddd, *J* = 9.5, 2.5, 2.5 Hz, H41), 2.84 (1H, dd, *J* = 9.0, 4.0 Hz, H45), 2.25-2.14 (6H, m, H31, H35, H43, H46, H53, H53), 1.95 (1H, m, H31), 1.89-1.77 (3H, m, H38, H39, H40), 1.73 (1H, ddd, *J* = 11.5, 11.5, 11.5 Hz, H35), 1.67-1.53 (4H, m, H38, H40, H50, H51), 1.39 (1H, ddd, *J* = 11.5, 11.5, 11.5 Hz, H43), 1.18 (3H, S, Me56), 1.09 (3H, d, *J* = 7.5 Hz, Me58), 1.07-1.02 (30H, m, TIPS, Me57, Me59, Me60)

^{13}C NMR (125 MHz, $CDCl_3$ δ136.7, 136.3, 135.6, 133.26, 133.24, 133.1, 132.9, 132.8, 128.1, 127.9, 127.86, 127.83, 127.74, 127.72, 127.69, 127.65, 126.2, 126.14, 126.12, 126.0, 125.9, 125.8, 125.68, 125.65, 108.9, 86.7, 84.6, 82.9, 80.8, 80.0, 79.6, 78.5, 77.8, 74.1, 73.7, 72.1, 71.9, 71.8, 71.4, 71.1, 68.0, 58.7, 42.5, 41.6, 40.4, 40.0, 38.4, 38.2, 31.5, 29.9, 27.5, 22.6, 19.9, 18.4, 18.3, 18.19, 18.14, 15.9, 14.1, 14.0, 13.5, 13.4, 13.0, 12.9

MALDI-TOF MS, calcd. for $C_{74}H_{96}NaO_{10}Si$ 1199.6620 ($M+Na^+$), found for 1199.6620

Synthesis of compound 2

[0022]



Into pyridine (1.2mL, 0.1M) solution of compound 1 (138mg, 117 μ mol), PhSSP (153mg, 702 μ mol) and n-PBu_3 (175 μ L, 702 μ mol) are added and stirred at room temperature for 6 hours. Reaction is stopped by adding saturated NH_4Cl aqueous solution into this solution and diluted by ethyl acetate. Water phase is extracted by ethyl acetate for 3 times, and combined organic layer is washed by saturated brine, then is dried by Na_2SO_4. Solvent is concentrated and refined by a flash column, then thiophenylether of compound 2 (143 mg, 113 μ mol , 96%) is obtained. Features of compound 2 are shown in Table 2.

(Table 2)

$[\alpha]_D^{25}$ -3.3 (c 0.47, $CHCl_3$); IR (film) ν 2927, 2858, 1708, 1464, 1093, 1030cm^{-1}

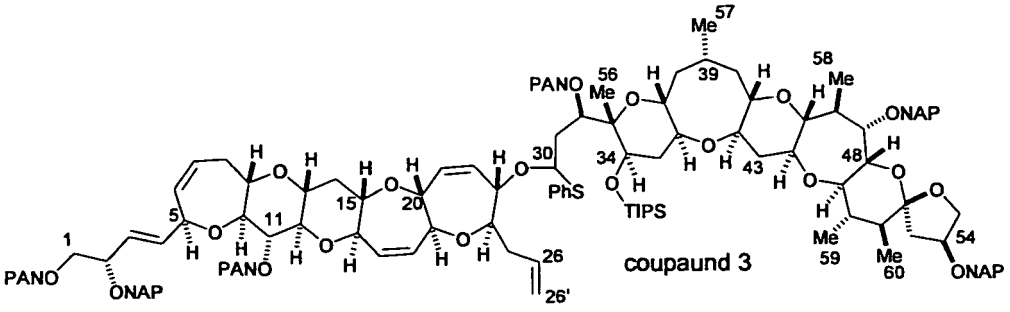
^1H NMR (500 MHz, $CDCl_3$) δ 7.83-7.11 (26H, m, NAPx3, PhS), 4.81 (1H, d, *J* = 12.0 Hz, NAP), 4.81 (1H, d, *J* = 12.5 Hz, NAP), 4.76 (1H, d, *J* = 12.5 Hz, NAP), 4.75 (1H, d, *J* = 12.0 Hz, NAP), 4.62 (1H, d, *J* = 12.0 Hz, NAP), 4.59 (1H, d, *J* = 12.0 Hz, NAP), 4.27 (1H, m, H54), 4.21 (1H, dd, *J* = 12.0, 5.0 Hz, H34), 3.98 (1H, d, *J* = 9.5 Hz, H55), 3.86 (1H, ddd, *J* = 12.0, 9.0, 5.0 Hz, H44), 3.83 (1H, dd, *J* = 9.5, 5.5 Hz, H55), 3.77 (1H, dd, *J* = 7.5, 3.5 Hz, H32), 3.62 (1H, d, *J* = 9.5 Hz, H48), 3.64 (1H, m, H30), 3.44 (1H, d, *J* = 3.5 Hz, H47), 3.43 (1H, dd, *J* = 9.5, 9.5 Hz, H49), 3.30 (1H, ddd, *J* = 10.0, 10.0, 3.0 Hz, H37), 3.17 (1H, ddd, *J* = 13.5, 9.0, 4.5 Hz, H30), 3.11 (1H, ddd, *J* = 12.0, 10.0, 5.0 Hz, H42), 3.09 (1H, ddd, *J* =12.0, 10.0, 5.0 Hz, H36), 3.00 (1H, ddd, *J* = 10.0, 10.0, 2.5 Hz, H41), 2.93 (1H, ddd, *J* = 13.5, 8.5, 7.5 Hz, H30), 2.86 (1H, dd, *J* = 9.0, 4.5 Hz, H45), 2.20 (1H, ddd, *J* = 12.0, 5.0, 5.0 Hz, H43), 2.18 (1H, m, H46), 2.16 (1H, m, H53), 2.15 (1H, m, H53), 2.13 (1H, ddd, *J* = 12.0, 5.0, 5.0 Hz, H35), 2.10 (1H, m, H31), 2.00 (1H, m, H31), 1.86 (1H, m, H40), 1.82 (1H, m, H39), 1.79 (1H, m, H36), 1.72 (1H, ddd, *J* = 12.0, 12.0, 12.0 Hz, H35), 1.61 (1H, m, H50), 1.59 (1H, m, H51), 1.56 (1H, m, H36), 1.54 (1H, m, H40), 1.39 (1H, ddd, *J* = 12.0, 12.0, 12.0 Hz, H43), 1.12 (3H, S, Me56), 1.09 (3H, d, *J* = 7.5 Hz, Me58), 1.07 (3H, d, *J* = 7.0 Hz, Me57), 1.06 (3H, d, *J* = 7.0 Hz, Me59), 1.04 (21H, m, TIPS), 1.02 (3H, m, Me60)

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 136.74, 136.17, 135.6, 133.25, 133.23, 133.1, 132.9, 132.8, 132.7, 128.7, 128.6, 128.1, 127.85, 127.83, 127.73, 127.71, 127.68, 127.63, 126.2, 126.1, 126.0, 125.98, 125.92, 125.8, 125.7, 125.68, 125.64, 125.61, 125.5, 108.9, 86.6, 84.5, 82.9, 80.9, 80.8, 80.1, 78.5, 77.8, 74.2, 73.4, 72.1, 71.8, 71.4, 71.1, 68.5, 60.4, 42.4, 41.5, 40.5, 40.0, 38.4, 38.3, 30.3, 29.6, 28.1, 27.5, 21.0, 19.9, 18.46, 18.43, 18.38, 18.34, 18.2, 18.1, 15.9, 14.17, 14.11, 13.8, 13.5, 13.4, 13.0

MALDI-TOF MS, calcd. for $C_{76}H_{102}NaO_{10}SSi$ 1291.6704 ($M+Na^+$), found for 1291.6624

Synthesis of compound 3

[0023]



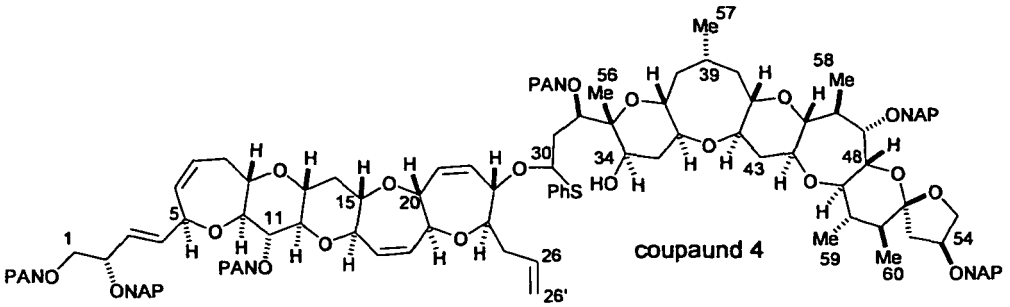
[0024] N-chlorosuccinimide (2.67mg, 20 μ mol) is dissolved in CH_2Cl_2 (50 μ L) and added into CCl_4 (280 μ L, 0.07M) solution of compound 2 (24.6mg, 19.4 μ mol) solution, stirred at room temperature for 2 hours and compound B is formed. This solution is dropped slowly into -80°C cooled CH_2Cl_2 solution of compound C (11.2mg, 12.1mol), silver triflate (7.5mg, 32.3 μ mol), DTBMP (13.3mg, 64.5 μ mol) and activated MS4A (40mg), stirred for 2 hours and elevated the temperature to -10°C. This reacted solution is filtrated by 0°C cooled open column and concentrated. After that, refined by a flash column and compound 3, O,S-acetal (16.6mg, 7.57 μ mol, 63%) is obtained. Features of compound 3 are shown in Table 3.

(Table 3)

$[\alpha]_D^{23}$ 4.5 (c 1.00, CH_2Cl_2); IR (film) ν 2927, 2865, 1775, 1716, 1459, 1344, 1291, 1090, 816 cm^{-1};
^1H NMR (500 MHz, C_6D_6) δ 8.02-6.92 (47H, m, NAPx6, PhS), 6.11 (1H, ddd, *J* = 13.0, 2.5, 2.5 Hz, H22), 5.98 (1H, dd, *J* = 15.0, 2.5 Hz, H4), 5.93 (1H, dd, *J* = 15.0, 2.5 Hz, H3), 5.84 (1H, dddd, *J* = 17.0, 10.0, 5.5, 5.5 Hz, H26), 5.79 (1H, d, *J* = 11.5 Hz, H17), 5.78 (1H, d, *J* = 11.5 Hz, H18), 5.70 (1H, ddd, *J* = 11.5, 3.0, 3.0 Hz, H6), 5.61 (1H, ddd, *J* = 13.0, 2.5, 2.5 Hz, H21), 5.53 (1H, m, H7), 5.33 (1H, dd, *J* = 10.0, 3.0, 3.0 Hz, H30), 5.24 (2H, s, NAP), 5.21 (1H, d, *J* = 12.5 Hz, NAP), 5.14 (1H, d, *J* = 12.5 Hz, NAP), 5.06 (1H, dd, *J* = 17.0, 2.0 Hz, H26'), 4.98 (1H, dd, *J* = 10.0, 2.0 Hz, H26'), 4.86 (1H, d, *J* = 12.5 Hz, NAP), 4.82 (1H, d, *J* = 12.5 Hz, NAP), 4.81 (1H, d, *J* = 12.0 Hz, NAP), 4.62 (1H, d, *J* = 12.0 Hz, NAP), 4.54 (1H, m, H5), 4.51 (2H, s, NAP), 4.47 (1H, dd, *J* = 12.0, 5.0 Hz, H34), 4.38 (1H, dd, *J* = 10.0, 3.0 Hz, H32), 4.32 (2H, s, NAP), 4.23 (1H, m, H23), 4.20 (1H, m, H2), 4.18 (1H, m, H19), 4.15 (1H, m, H44), 4.08 (1H, m, H54), 4.04 (1H, d, *J* = 10.0 Hz, H55), 3.96 (1H, d, *J* = 9.5 Hz, H48), 3.91 (1H, m, H20), 3.78 (1H, dd, *J* = 10.0, 5.0 Hz, H55), 3.75 (1H, dd, *J* = 10.0, 2.0 Hz, H1), 3.73 (1H, dd, *J* = 9.5, 9.5 Hz, H49), 3.71 (1H, d, *J* = 8.0 Hz, H16), 3.67 (1H, dd, *J* = 9.0, 9.0 Hz, H11), 3.65 (1H, m, H24), 3.62 (1H, d, *J* = 3.0 Hz, H47), 3.56 (1H, dd, *J* = 9.0, 9.0 Hz, H10), 3.52 (1H, dd, *J* = 10.0, 4.5 Hz, H1), 3.32 (1H, m, H37), 3.30 (1H, ddd, *J* = 9.0, 9.0, 5.5 Hz, H9), 3.19 (1H, dd, *J* = 9.0, 9.0 Hz, H12), 3.11 (1H, m, H15), 3.10 (1H, m, H41), 3.03 (1H, dd, *J* = 9.5, 5.0 Hz, H45), 3.02 (1H, m, H36), 2.99 (1H, m, H42), 2.93 (1H, ddd, *J* = 11.5, 9.0, 4.5 Hz, H13), 2.85 (1H, m, H31), 2.59 (1H, ddd, *J* = 16.0, 9.0, 4.5 Hz, H8), 2.53 (1H, m, H25), 2.51 (1H, m, H31), 2.49 (1H, m, H46), 2.47 (1H, m, H43), 2.33 (1H, m, H8), 2.31 (1H, m, H35), 2.29 (1H, m, H14), 2.23 (1H, m, H53), 2.21 (1H, m, H53), 2.20 (1H, m,H25), 2.03 (1H, m, H40), 1.97 (1H, m, H50), 1.95 (1H, m, H35), 1.92 (1H, m, H38), 1.83 (1H, m, H39), 1.77 (1H, ddd, *J* = 12.0, 12.0, 12.0 Hz, H43), 1.67 (1H, ddd, *J* = 1.5, 11.5, 11.5 Hz, H14), 1.63 (1H, m, H40), 1.59 (1H, m, H38), 1.54 (1H, m, H51), 1.13 (3H, m, Me58), 1.13 (21H, m, TIPS), 1.12 (3H, m, Me56), 1.11 (3H, d, *J* = 6.5 Hz, Me59), 1.08 (3H, d, *J* = 7.0 Hz, Me60), 0.98 (3H, d, *J* = 7.0 Hz, Me57);
^{13}C NMR (125 MHz, C_6D_6) δ 176.5, 137.6, 137.5, 137.3, 136.9, 136.7, 136.43, 136.41, 135.1, 134.4, 134.2, 134.05, 133.99, 133.97, 133.95, 133.92, 133.57, 133.54, 133.52, 133.4, 133.3, 131.4, 131.1, 129.2, 129.1, 128.48, 128.45, 128.41, 128.35, 128.19, 128.16, 128.13, 128.12, 128.0, 127.7, 126.9, 126.67, 126.65, 126.57, 126.55, 126.46, 126.44, 126.34, 126.29, 126.23, 126.20, 126.15, 126.12, 126.05, 126.02, 126.00, 125.98, 125.92, 125.86, 125.79, 117.4, 109.5, 89.9, 87.3, 85.6, 84.6, 83.5, 83.1, 82.2, 81.8, 81.5, 80.8, 80.5, 79.9, 79.3, 79.2, 79.1, 78.6, 78.2, 76.8, 75.3, 74.7, 74.3, 73.9, 73.5, 73.1, 72.9, 72.8, 71.7, 71.3, 71.1, 68.9, 68.1, 60.1, 43.2, 42.2, 41.5, 40.9, 39.2, 39.1, 38.2, 37.6, 34.9, 34.7, 31.7, 30.2, 29.2, 28.1, 20.2, 18.73, 18.69, 16.3, 14.4, 13.9, 13.6, 11.2
MALDI-TOF MS, calcd. for $C_{139}H_{158}NaO_{19}SSi$ 2214.0780 ($M+Na^+$), found for 2213.9349

Synthesis of compound 4

[0025]



coupaund 4

TBAF (1.0M THF solution, 23 μ L, 23 μ mol) is added to THF (300 μ L, 0.02M) solution of compound 3 (12.6mg, 5.74

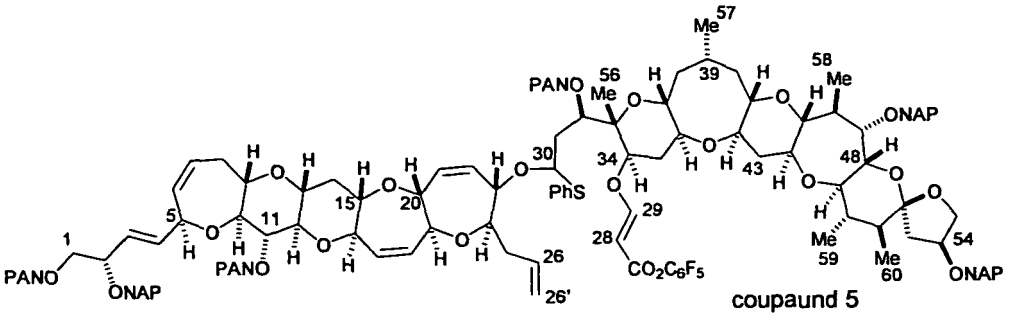
μ mol) and stirred at 35°C for 4 hours. After this solution is concentrated, refined using a flush column and alcohol of compound 4 (10.78mg, 5.30 μ mol, 92%) is obtained. Features of compound 4 are shown in Table 4.

(Table 4)

$[\alpha]_D^{23}$ 10.2 (c 1.00, CH_2Cl_2); IR (film) ν 3221, 2926, 1775, 1715, 1456, 1347, 1177, 1088, 817 cm^{-1};
^1H NMR (500 MHz, C_6D_6) δ 7.99-6.98 (47H, m, NAPx6, PhS), 6.14 (1H, ddd, *J* = 13.0, 3.0, 3.0 Hz, H22), 5.99 (1H, dd, *J* = 16.0, 1.5 Hz, H4), 5.96 (1H, dd, *J* = 16.0, 1.5 Hz, H3), 5.86 (1H, d, *J* = 12.5 Hz, H17), 5.84 (1H, d, *J* = 12.5 Hz, H18), 5.78 (1H, dddd, *J* = 17.0, 10.5, 6.5, 6.5 Hz, H26), 5.71 (1H, ddd, *J* = 13.0, 3.0, 3.0 Hz, H21), 5.69 (1H, ddd, *J* = 11.5, 3.0, 3.0 Hz, H6), 5.52 (1H, dddd, *J* = 11.5, 7.0, 4.0, 3.5 Hz, H7), 5.23 (2H, s, NAP), 5.20 (1H, dd, *J* = 7.0, 6.5 Hz, H30), 5.01 (1H, dd, *J* = 17.0, 2.5 Hz, H26'), 4.98 (1H, dd, *J* = 10.0, 2.5 Hz, H26'), 4.88 (1H, d, *J* = 12.5 Hz, NAP), 4.85 (1H, d, *J* = 12.5 Hz, NAP), 4.82 (1H, d, *J* = 12.0 Hz, NAP), 4.70 (1H, d, *J* = 12.0 Hz, NAP), 4.65 (1H, d, *J* = 12.0 Hz, NAP), 4.62 (1H, d, *J* = 12.0 Hz, NAP), 4.53 (1H, m, H5), 4.52 (1H, d, *J* = 12.0 Hz, NAP), 4.49 (1H, d, *J* = 12.0 Hz, NAP), 4.40 (1H, ddd, *J* = 8.0, 3.0, 3.0 Hz, H23), 4.34 (2H, s, NAP), 4.28 (1H, dd, *J* = 9.0, 3.0 Hz, H19), 4.21 (1H, m, H44), 4.19 (1H, m, H2), 4.09 (1H, m, H54), 4.07 (1H, d, *J* = 9.5Hz, H55), 4.01 (1H, m, H20), 3.96 (1H, d, *J* = 8.5 Hz, H48), 3.96 (1H, m, H32), 3.95 (1H, m, H34), 3.83 (1H, d, *J* = 8.0 Hz, H16), 3.82 (1H, dd, *J* = 8.5, 8.5 Hz, H49), 3.81 (1H, dd, *J* = 9.5, 4.5 Hz, H55), 3.70 (1H, dd, *J* = 9.0, 9.0 Hz, H11), 3.69 (1H, dd, *J* = 10.5, 3.0 Hz, H1), 3.66 (1H, d, *J* = 3.0 Hz, H47), 3.61 (1H, ddd, *J* = 8.0, 4.0, 4.0 Hz, H24), 3.53 (1H, dd, *J* = 10.5, 4.5 Hz, H1), 3.51 (1H, dd, *J* = 9.0, 9.0 Hz, H10), 3.30 (1H, m, H9), 3.28 (1H, m, H37), 3.16 (1H, dd, *J* = 9.0, 9.0 Hz, H12), 3.13 (1H, m, H15), 3.07 (1H, dd, *J* = 9.5, 4.5 Hz, H45), 3.05 (1H, m, H41), 2.92 (1H, ddd, *J* = 11.5, 9.0, 4.0 Hz, H13), 2.88 (1H, m, H42), 2.71 (1H, m, H31), 2.70 (1H, m, H36), 2.59 (1H, ddd, *J* = 15.5, 8.0, 4.0 Hz, H8), 2.56 (1H, m, H46), 2.49 (1H, m, H25), 2.46 (1H, m, H31), 2.41 (1H, ddd, *J* = 13.0, 5.0, 5.0 Hz, H43), 2.32 (1H, ddd, *J* = 11.5, 4.0, 4.0 Hz, H14), 2.29 (1H, m, H8), 2.24 (1H, m, H53), 2.23 (1H, m, H53), 2.20 (1H, m, H25), 2.16 (1H, m, H35), 2.05 (1H, m, H50), 2.02 (1H, m, H40), 1.78 (1H, m, H39), 1.76 (1H, m, H35), 1.72 (1H, ddd, *J* = 12.5, 12.5, 12.5 Hz, H43), 1.70 (1H, ddd, *J* = 1.5, 11.5, 11.5 Hz, H14), 1.60 (1H, m, H38), 1.56 (1H, m, H51), 1.52 (1H, m, H40), 1.32 (3H, s, Me56), 1.27 (3H, d, *J* = 6.5 Hz, Me59), 1.18 (1H, m, H38), 1.17 (3H, d, *J* = 7.5 Hz, Me60), 1.16 (3H, d, *J* = 6.5 Hz, Me58), 0.93 (3H, d, *J* = 7.5 Hz, Me57)
^{13}C NMR (125 MHz, C_6D_6) δ 176.4, 137.6, 137.3, 136.9, 136.7, 136.4, 135.4, 135.0, 134.4, 134.00, 133.99, 133.97, 133.95, 133.94, 133.8, 133.7, 133.58, 133.55, 133.52, 132.8, 132.6, 131.0, 129.3, 129.1, 128.8, 128.47, 128.42, 128.35, 128.2, 128.0, 127.7, 127.5, 126.88, 126.85, 126.67, 126.65, 126.59, 126.56, 126.52, 126.49, 126.47, 126.45, 126.38, 126.33, 126.29, 126.23, 126.14, 126.08, 126.00, 125.93, 125.89, 117.4, 109.6, 89.8 87.34, 87.27, 85.57, 85.52, 84.4, 83.8, 83.59, 83.54, 83.49, 83.1, 82.2, 81.8, 81.5, 80.9, 80.04, 79.99, 79.2, 78.6, 77.5, 76.8, 75.4, 74.9, 73.9, 73.6, 73.5, 72.9, 71.7, 71.3, 71.1, 67.5, 46.7, 46.2, 43.3, 42.3, 41.3, 40.8, 39.2, 38.5, 37.8, 37.6, 37.3, 34.9, 32.0, 30.2, 28.6, 27.9, 23.0, 20.2, 16.3, 14.4;
MALDI-TOF MS, calcd. for $C_{130}H_{138}NaO_{19}S$ 2057.9451 ($M+Na^+$), found for 2057.5975

Synthesis of Compound 5

[0026]



coupaund 5

[0027] Into CH_2Cl_2 (300 μ L, 0.02M) solution of compound 4 (6.7mg, 3.29 μ mol) and pentaphenylpropiorate (3.1mg, 13.2 μ mol), PMe3 (1.0M THF solution, 6.6 μ L, 6.6 μ mol) is added and stirred at room temperature for 30 minutes. Further, same process to add same equivalent of pentaphenylpropiorate and PMe3 and to stir at room temperature for 30 minutes is repeated for 4 times. After this solution is concentrated, refined using a flush column and acrylate of

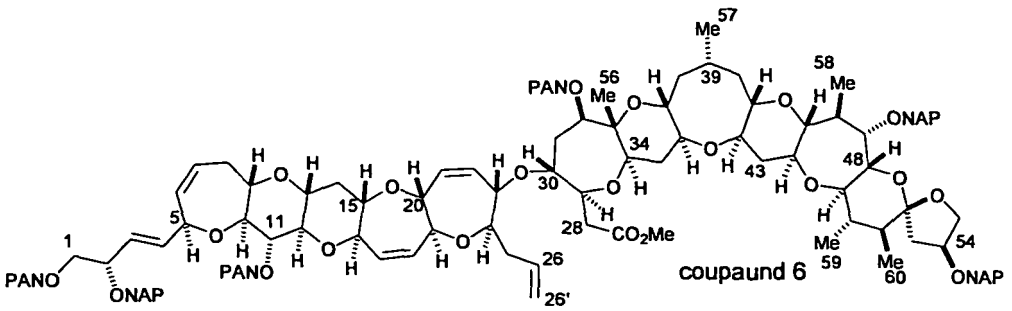
compound 5 (7.0mg, 3.08 μ mol, 94%) is obtained. Features of compound 5 are shown in Table 5.

(Table 5)

$[\alpha]_D^{24}$-6.7 (*c* 1.00, CH_2Cl_2); IR (film) ν 3055, 2925, 1750, 1637, 1520, 1457, 1088, 817 cm^{-1};
^1H NMR (500 MHz, C_6D_6) δ 7.99-7.00 (47H, m, NAPx6, PhS), 7.69 (1H, d, *J* = 12.0 Hz, H29), 6.14 (1H, ddd, *J* = 12.5, 2.5, 2.5 Hz, H22), 5.99 (1H, dd, *J* = 16.0, 2.5 Hz, H4), 5.96 (1H, dd, *J* = 16.0, 2.5 Hz, H3), 5.88 (1H, dddd, *J* = 17.0, 10.5, 7.0, 7.0 Hz, H26), 5.84 (1H, d, *J* = 13.0 Hz, H17), 5.82 (1H, d, *J* = 13.0 Hz, H18), 5.69 (1H, ddd, *J* = 12.5, 2.5, 2.5 Hz, H21), 5.67 (1H, ddd, *J* = 13.0, 2.0, 2.0 Hz, H6), 5.58 (1H, d, *J* = 12.0 Hz, H28), 5.53 (1H, m, H7), 5.26 (1H, dd, *J* = 10.0, 4.5 Hz, H30), 5.24 (2H, s, NAP), 5.10 (1H, dd, *J* = 17.0, 2.0 Hz, H26'), 4.98 (1H, dd, *J* = 10.5, 2.0 Hz, H26'), 5.00 (1H, d, *J* = 11.5 Hz, NAP), 4.92 (1H, d, *J* = 11.5 Hz, NAP), 4.85 (2H, s, NAP), 4.81 (1H, d, *J* = 12.0 Hz, NAP), 4.62 (1H, d, *J* = 12.0 Hz, NAP), 4.53 (1H, m, H5), 4.51 (2H, s, NAP), 4.33 (2H, s, NAP), 4.30 (1H, m, H23), 4.23 (1H, m, H44), 4.21 (1H, m, H2), 4.18 (1H, m, H19), 4.09 (1H, m, H54), 4.06 (1H, m, H34), 3.99 (1H, d, *J* = 9.0 Hz, H48), 3.98 (1H, m, H20), 3.97 (1H, m, H32), 3.96 (1H, m, H55), 3.81 (1H, dd, *J* = 9.0, 9.0 Hz, H49), 3.80 (1H, dd, *J* = 9.5, 4.5 Hz, H55), 3.77 (1H, d, *J* = 10.0 Hz, H16), 3.71 (1H, dd, *J* = 9.0, 9.0 Hz, H11), 3.68 (1H, dd, *J* = 10.0, 7.0 Hz, H1), 3.66 (1H, d, *J* = 3.5 Hz, H47), 3.61 (1H, m, H24), 3.56 (1H, dd, *J* = 9.0, 9.0 Hz, H10), 3.52 (1H, dd, *J* = 10.0, 4.0 Hz, H1), 3.31 (1H, ddd, *J* = 9.0, 9.0, 4.5 Hz, H9), 3.21 (1H, m, H37), 3.20 (1H, dd, *J* = 9.0, 9.0 Hz, H12), 3.12 (1H, ddd, *J* = 11.5, 10.0, 5.0 Hz, H15), 3.06 (1H, dd, *J* = 9.5, 5.0 Hz, H45), 3.03 (1H, m, H41), 2.92 (1H, ddd, *J* = 11.5, 9.0, 5.0 Hz, H13), 2.89 (1H, m, H42), 2.73 (1H, m, H36), 2.62 (1H, m, H8), 2.60 (1H, m, H31), 2.57 (1H, m, H46), 2.54 (1H, m, H25), 2.40 (1H, m, H31), 2.35 (1H, m, H8), 2.32 (1H, m, H43), 2.29 (1H, m, H14), 2.27 (1H, m, H25), 2.23 (1H, m, H53), 2.22 (1H, m, H53), 2.03 (1H, m, H50), 2.00 (1H, m, H40), 1.86 (1H, m, H35), 1.76 (1H, m, H38), 1.72 (1H, m, H39), 1.68 (1H, ddd, *J* = 11.5, 11.5, 11.5 Hz, H43), 1.68 (1H, ddd, *J* = 1.5, 11.5, 11.5 Hz, H14), 1.59 (1H, m, H35), 1.56 (1H, m, H40), 1.54 (1H, m, H51), 1.36 (1H, m, H38), 1.25 (3H, d, *J* = 6.0 Hz, Me59), 1.16 (3H, d, *J* = 7.5 Hz, Me58), 1.14 (3H, d, *J* = 7.0 Hz, Me60), 1.02 (3H, s, Me56), 0.91 (3H, d, *J* = 7.5 Hz, Me57);
^{13}C NMR (125 MHz, C_6D_6) δ 165.21, 163.52, 142.9, 142.8, 141.6, 140.9, 140.4, 139.2, 139.1, 137.9, 137.6, 137.1, 136.9, 136.7, 136.5, 136.4, 135.4, 135.0, 134.4, 134.00, 133.99, 133.97, 133.95, 133.93, 133.91, 133.58, 133.56, 133.52, 133.47, 133.37, 131.6, 130.9, 129.4, 129.3, 129.1, 128.7, 128.6, 128.5, 128.42, 128.38, 128.37, 128.35, 128.14, 128.12, 128.0, 126.9, 126.8, 126.65, 126.64, 126.60, 126.58, 126.55, 126.52, 126.48, 126.46, 126.39, 126.37, 126.29, 126.27, 126.23, 126.22, 126.15, 126.10, 125.99, 125.92, 125.88, 125.75, 125.70, 117.6, 109.5, 95.7, 89.0 87.4, 87.3, 85.5, 84.6, 83.7, 83.5, 83.4, 82.4, 82.3, 81.8, 81.7, 81.5, 80.8, 79.34, 79.30, 79.2, 79.1, 78.6, 78.0, 76.8, 75.4, 74.8, 74.4, 73.9, 73.8, 73.6, 73.5, 72.9, 72.8, 71.8, 71.3, 71.1, 46.57, 46.0, 43.3, 42.2, 41.2, 40.9, 39.2, 38.2, 37.6, 36.5, 34.9, 34.7, 30.5, 30.2, 28.4, 27.9, 20.2, 16.3, 14.0, 13.7;
MALDI-TOF MS, calcd. for $C_{139}H_{139}F_5NaO_{21}S$ 2293.9347 ($M+Na^+$), found for 2293.9377

Synthesis of Compound 6

[0028]



coupaund 6

[0029] Degassed toluene (4.3mL, 0.001M) solution of compound 5 (6.7mg, 3.29 μ mol), AIBN (7.1mg, 43 μ mol) and n-Bu_3SnH (58 μ L, 215 μ mol) is heated to 85°C and stirred for 3 hours. After this solution is cooled down, refined directly using a flush column and carboxylic acid of compound D (5.0mg, 2.50 μ mol, 59%) is obtained. Compound D is not refined more and used to the next reaction.

[0030] $TMSCHN_2$ (2.0M hexane solution, 13 μ L, 25mol) is added into mixed solution (0.01M) of benzene (0.86mL) -methanol (0.43mL) of carboxylic acid (5.0mg, 2.50 μ mol) of compound D and stirred for 30minutes, This solution is diluted by benzene and water, and reaction is stopped by dropping acetic acid. Ethyl acetate and saturated $NaHCO_3$

aqueous solution, and water phase is extracted by ethyl acetate for 3 times. Organic layer is washed by saturated brine and dried by Na_2SO_4. Solvent is concentrated, refined by a flush column and methyl ester (4.2mg, 2.09 μ mol, 84%) of compound 6 is obtained. Features of compound 6 are shown in Table 6.

(Table 6)

$[\alpha]_D^{25}$ 10.6 (c 0.50, CH_2Cl_2); IR (film) ν 2924, 2854, 1738, 1456, 1334, 1270, 1089, 817 cm^{-1};

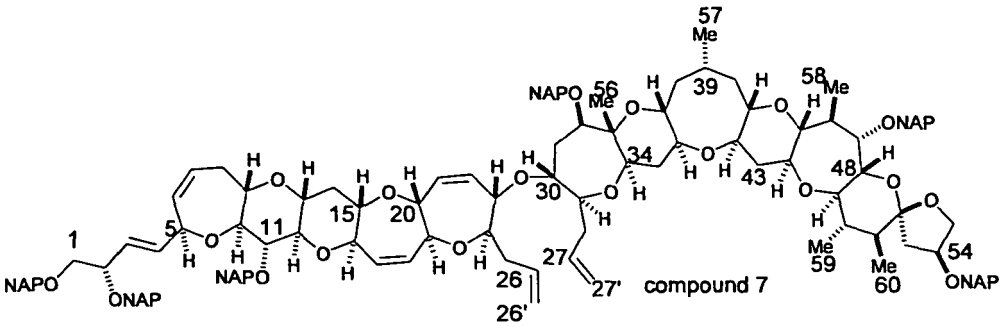
^1H NMR (500 MHz, C_6D_6) δ 7.99-7.01 (42H, m, NAPx6), 6.00 (1H, dd, *J* = 16.0, 2.0 Hz, H4), 5.96 (1H, dd, *J* = 16.0, 2.0 Hz, H3), 5.95 (1H, dddd, *J* = 17.0, 10.5, 7.0, 7.0 Hz, H26), 5.86 (1H, d, *J* = 13.0 Hz, H17), 5.84 (1H, d, *J* = 13.0 Hz, H18), 5.69 (1H, ddd, *J* = 11.0, 3.0, 3.0 Hz, H6), 5.53 (1H, d, *J* = 11.0 Hz, H21), 5.52 (1H, m, H7), 5.51 (1H, d, *J* = 11.0 Hz, H22), 5.23 (2H, s, NAP), 5.23 (1H, d, *J* = 12.5 Hz, NAP), 5.17 (1H, dd, *J* = 17.0, 3.0 Hz, H26'), 5.07 (1H, dd, *J* = 10.5, 3.0 Hz, H26'), 5.01 (1H, d, *J* = 12.5 Hz, NAP), 4.87 (1H, d, *J* = 12.5 Hz, NAP), 4.84 (1H, d, *J* = 12.5 Hz, NAP), 4.81 (1H, d, *J* = 12.0 Hz, NAP), 4.62 (1H, d, *J* = 12.0 Hz, NAP), 4.54 (1H, m, H5), 4.51 (2H, s, NAP), 5.42 (1H, dd, *J* = 7.0, 7.0 Hz, H29), 4.33 (2H, s, NAP), 4.27 (1H, d, *J* = 9.0 Hz, H19), 4.19 (1H, m, H44), 4.17 (1H, m, H2), 4.09 (1H, m, H54), 4.06 (1H, d, *J* = 10.5 Hz, H30), 3.99 (1H, d, *J* = 9.5 Hz, H23), 3.98 (1H, m, H55), 3.96 (1H, d, *J* = 9.0 Hz, H20), 3.83 (1H, d, *J* = 10.0 Hz, H16), 3.81 (1H, m, H55), 3.80 (1H, m, H32), 3.69 (1H, dd, *J* = 9.0, 3.5 Hz, H1), 3.68 (1H, dd, *J* = 9.0, 9.0 Hz, H11), 3.68 (1H, d, *J* = 9.0 Hz, H48), 3.65 (1H, d, *J* = 3.0 Hz, H47), 3.63 (1H, m, H34), 3.60 (1H, m, H24), 3.53 (1H, dd, *J* = 9.0, 3.5 Hz, H1), 3.52 (1H, dd, *J* = 9.0, 9.0 Hz, H49), 3.49 (1H, m, H37), 3.43 (1H, dd, *J* = 9.0, 9.0 Hz, H10), 3.31 (3H, s, MeO), 3.30 (1H, m, H9), 3.15 (1H, ddd, *J* = 11.5, 10.0, 4.5 Hz, H15), 3.10 (1H, m, H41), 3.09 (1H, dd, *J* = 9.0, 9.0 Hz, H12), 3.06 (1H, dd, *J* = 9.5, 4.5 Hz, H45), 2.98 (1H, m, H36), 2.94 (1H, m, H42), 2.92 (1H, m, H13), 2.58 (1H, m, H8), 2.57 (1H, m, H25), 2.55 (1H, m, H46), 2.44 (1H, dd, *J* = 11.0, 7.0 Hz, H28), 2.40 (1H, m, H14), 2.38 (1H, m, H25), 2.36 (1H, m, H43), 2.34 (1H, m, H8), 2.24 (1H, m, H53), 2.23 (1H, m, H53), 2.14 (1H, dd, *J* =11.0, 7.0 Hz, H28), 2.11 (1H, m, H35), 2.08 (1H, m, H50), 2.07 (1H, m, H31), 2.03 (1H, m, H38), 2.01 (1H, m, H40), 1.89 (1H, m, H31), 1.86 (1H, m, H35), 1.85 (1H, m, H39), 1.72 (1H, ddd, *J* = 11.5, 11.5, 11.5 Hz, H43), 1.70 (1H, ddd, *J* = 1.5, 11.5, 11.5 Hz, H14), 1.65 (1H, m, H40), 1.59 (1H, m, H38), 1.57 (1H, m, H51), 1.29 (3H, s, Me56), 1.26 (3H, d, *J* = 6.0 Hz, Me59), 1.15 (3H, d, *J* = 6.5 Hz, Me58), 1.10 (3H, d, *J* = 8.0 Hz, Me60), 0.96 (3H, d, *J* = 7.0 Hz, Me57);

^{13}C NMR (125 MHz, C_6D_6) δ 170.80, 137.9, 137.7, 137.3, 136.9, 136.7, 136.5, 135.3, 135.2, 134.4, 134.3, 134.2, 134.04, 133.99, 133.96, 133.94, 133.61, 133.59, 133.55, 133.53, 131.4, 130.0, 129.3, 129.2, 128.6, 128.46, 128.42, 128.38, 128.35, 128.30, 128.16, 128.14, 128.0, 126.9, 126.8, 126.66, 126.63, 126.58, 126.55, 126.47, 126.44, 126.35, 126.29, 126.22, 126.13, 126.06, 125.99, 125.94, 125.88, 125.7, 117.4, 109.5, 87.4, 87.1, 85.6, 84.2, 83.8, 83.4, 82.4, 82.2, 81.74, 81.66, 81.2, 80.9, 80.26, 80.22, 80.1, 79.4, 79.22, 79.18, 78.6, 78.5, 76.8, 75.3, 74.9, 74.1, 73.9, 73.6, 73.5, 72.9, 72.8, 71.7, 71.3, 71.1, 47.2, 46.3, 43.3, 42.3, 41.4, 40.7, 39.9, 39.2, 38.5, 37.6, 36.1, 34.9, 32.6, 32.4, 32.0, 28.2, 27.1, 23.1, 20.2, 17.3, 16.4, 14.0, 13.8, 9.7;

MALDI-TOF MS, calcd. for $C_{128}H_{138}NaO_{21}$ 2033.9628 ($M+Na^+$), found for 2033.9634

Synthesis of compound 7

[0031]



compound 7

[0032] DIBAL solution (0.9M hexane solution, 17 μ L, 15.1 μ mol) is dropped slowly to compound 6 (3.2mg, 1.51 μ mol), which is cooled down to -100°C, stirred for 30 minutes and elevate the temperature to -90°C. Reaction is stopped by adding Ethyl acetate and saturated NH_4Cl aqueous solution and diluted by ethyl acetate. Water layer is extracted by ethyl acetate for 3 times and combined organic layer is washed by saturated brine and dried by Na_2SO_4. Solvent is

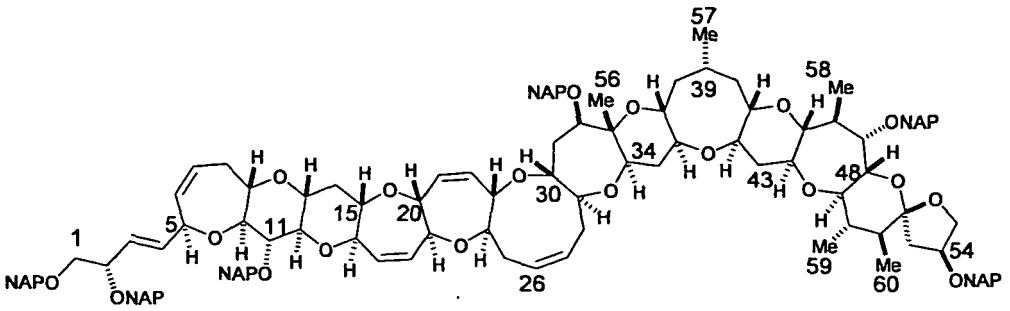
concentrated and crude aldehyde is obtained. This aldehyde is not refined and used in next reaction.
THF (1.0mL, 0.001M) of triphenylphosphonium bromide (54mg, 151 μ mol) is treated with t-BuOK (8.4mg, 75 μ mol) at 0°C, and mixture is stirred at 0°C for 20 minutes. THF solution (0.5mL) of aldehyde is introduced and is stirred at 0°C for 30 minutes. Reaction is stopped by adding saturated NH_4Cl aqueous solution and water solution is extracted by ethyl acetate. Organic layer is washed with saturated brine, then dried by Na_2SO_4. Solvent is concentrated and refined by a flush column and hexaene(2.3mg, 1.16 μ mol, total of two process is 77%) of compound 7 is obtained. Features of compound 7 are shown in Table 7.

(Table 7)

$[\alpha]_D^{27}$ 2.2 (c 0.50, CH_2Cl_2); IR (film) ν 2924, 1727, 1514, 1438, 1262, 1175, 1089, 818 cm^{-1};
^1H NMR (500 MHz, C_6D_6) δ 7.99-7.01 (42H, m, NAPx6), 5.99 (1H,m, H4), 5.97 (1H, m, H3), 5.92 (1H, dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, H26), 5.88 (1H, dddd, *J* = 17.0, 10.5, 7.0, 7.0 Hz, H27), 5.86 (1H, d, *J* = 12.0 Hz, H17), 5.84 (1H, d, *J* = 12.0 Hz, H18), 5.70 (1H, ddd, *J* = 11.5, 3.0, 3.0 Hz, H6), 5.53 (1H, m, H7), 5.51 (1H, d, *J* = 13.0 Hz, H21), 5.46 (1H, d, *J* = 13.0 Hz, H22), 5.24 (2H, s, NAP), 5.20 (1H, d, *J* = 12.0 Hz, NAP), 5.13 (1H, dd, *J* = 17.0, 2.5 Hz, H26'), 5.06 (1H, dd, *J* = 10.0, 2.5Hz, H26'), 5.05 (1H, dd, *J* = 10.5, 2.0 Hz, H27'), 5.04 (1H, d, *J* = 12.0 Hz, NAP), 5.01 (1H, dd, *J* = 17.0, 2.5 Hz, H27'), 4.86 (1H, d, *J* = 12.5 Hz, NAP), 4.83 (1H, d, *J* = 12.5 Hz, NAP), 4.81 (1H, d, *J* = 12.5 Hz, NAP), 4.62 (1H, d, *J* = 12.5 Hz, NAP), 4.54 (1H, m, H5), 4.51 (2H, s, NAP), 4.33 (2H, s, NAP), 4.20 (1H, m, H2), 4.18 (1H, d, *J* = 9.0 Hz, H19), 4.17 (1H, m, H44), 4.10 (1H, m, H30), 4.08 (1H, m, H54), 4.06 (1H, m, H55), 3.99 (1H, d, *J* = 9.5 Hz, H48), 3.94 (1H, d, *J* = 9.0 Hz, H20), 3.89 (1H, dd, *J* = 7.0, 7.0 Hz, H29), 3.83 (1H, d, *J* = 9.5 Hz, H16), 3.81 (1H, m, H55), 3.80 (1H, dd, *J* = 9.5, 9.5 Hz, H49), 3.77 (1H, d, *J* = 9.0 Hz, H23), 3.70 (1H, dd, *J* = 9.0, 3.5 Hz, H11) 3.69 (1H, dd, *J* = 10.5, 4.0 Hz, H1), 3.66 (1H, d, *J* = 3.5 Hz, H47), 3.57 (1H, dd, *J* = 8.5, 4.5 Hz, H34), 3.54 (1H, m, H24), 3.52 (1H, dd, *J* =10.5, 4.0 Hz, H1), 3.52 (1H, m, H32), 3.51 (1H, m, H37), 3.48 (1H, dd, *J* = 9.0, 9.0 Hz, H10), 3.29 (1H, ddd, *J* = 9.0, 9.0, 4.0 Hz, H9), 3.16 (1H, ddd, *J* = 11.5, 9.5, 4.5 Hz, H15), 3.14 (1H, dd, *J* = 9.0, 9.0 Hz, H12), 3.11 (1H, m, H41), 3.06 (1H, dd, *J* = 8.5, 4.5 Hz, H45), 2.98 (1H, m, H36), 2.96 (1H, m, H42), 2.93 (1H, m, H13), 2.58 (1H, ddd, *J* = 16.0, 9.0, 4.5 Hz, H8), 2.55 (1H, m, H46), 2.53 (1H, m, H25), 2.41 (1H, ddd, *J* = 11.5, 4.5, 4.5 Hz, H43), 2.35 (1H, ddd, *J* = 11.5, 4.5, 4.5 Hz, H14), 2.29 (1H, m, H8), 2.27 (1H, m, H25), 2.24 (1H, m, H53), 2.23 (1H, m, H53), 2.22 (1H, m, H28), 2.14 (1H, m, H31), 2.13 (1H, m, H35), 2.07 (1H, m, H38), 2.06 (1H, m, H40), 2.04 (1H, m, H50), 2.02 (1H, m, H28), 1.96 (1H, m, H31), 1.93 (1H, m, H35), 1.90 (1H, m, H39), 1.73 (1H, ddd, *J* = 11.5, 11.5, 11.5 Hz, H43), 1.71 (1H, ddd, *J* = 1.5, 11.5, 11.5 Hz, H14), 1.65 (1H, m, H40), 1.59 (1H, m, H38), 1.56 (1H, m, H51), 1.27 (3H, d, *J* = 7.0 Hz, Me59), 1.25 (3H, s, Me56), 1.23 (3H, d, *J* = 7.5 Hz, Me60), 1.22 (3H, d, *J* = 6.5 Hz, Me58), 0.96 (3H, d, *J* = 6.0 Hz, Me57);
^{13}C NMR (125 MHz, C_6D_6) δ 137.6, 137.3, 136.9, 136.7, 136.5, 135.4, 135.2, 135.0, 134.4, 134.2, 134.1, 134.04, 134.01, 133.99, 133.98, 133.96, 133.95, 133.92, 133.59, 133.55,133.53,133.31, 131.5, 131.1, 130.8, 130.4, 129.3, 129.2, 128.47, 128.42, 128.35, 128.2, 126.9, 126.66, 126.65, 126.58, 126.56, 126.54, 126.48, 126.45, 126.34, 126.29, 126.24, 126.23, 126.21, 126.13, 126.07, 126.00, 125.94, 125.88, 125.7, 124.93, 124.88, 117.4, 109.5, 87.4, 87.2, 85.6, 84.5, 83.8, 83.50, 83.46, 82.8, 82.2, 81.8, 81.2, 80.83, 80.77, 80.4, 79.4, 79.22, 79.18, 78.6, 76.8, 75.4, 74.9, 74.0, 73.9, 73.6, 73.51, 73.46, 72.84, 72.81, 72.5, 71.83, 71.75, 71.3, 71.1, 63.3, 62.4, 46.4, 43.3, 42.3, 41.4, 40.7, 40.3, 39.2, 38.5, 37.6, 36.3, 34.9, 34.4, 32.0, 27.7, 27.3, 25.4, 24.2, 22.0, 20.2, 16.4, 14.2, 14.0, 9.8;
MALDI-TOF MS, calcd. for $C_{128}H_{138}NaO_{19}$ 2001.9730 ($M+Na^+$), found for 2001.9711

Synthesis of compound 8

[0033]



compound 8

[0034] $(PCy_3)_2Cl_2Ru$ =CHPh (Grubbs catalyst, 0.2mg, 0.24 μ mol) is added to CH_2Cl_2(1.0mL, 0.7nM) solution of frozen and de-aired compound 7 (1.3mg, 0.66 μ mol) and stirred at 40°C for 4 hours. To this solution, Et_3N (0.1mL) is introduced and reaction is stopped, then concentrated and refined by a flush column, thus pentaene (1.0mg, 0.51 μ mol, 78%) of compound 8 is obtained. Features of compound 8 are shown in Table 8.

(Table 8)

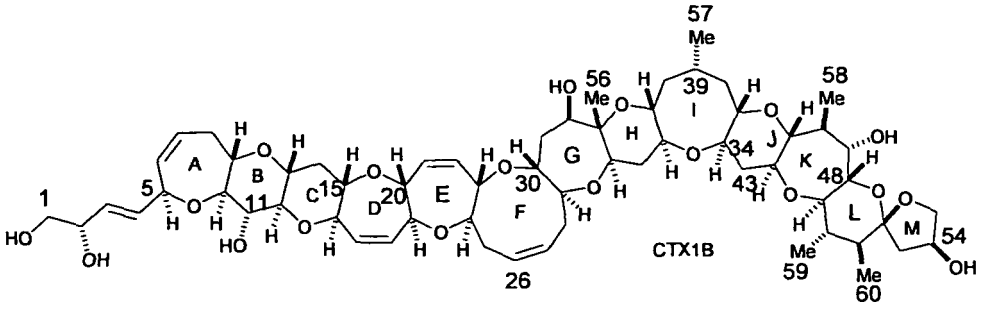
$[\alpha]_D^{25}$-6.2 (c 0.10, CH_2Cl_2); IR (film) ν 2924, 2854, 1736, 1457, 1268, 1092 cm^{-1};

^1H NMR (500 MHz, C_6D_6) δ 8.00-7.00 (42H, m, NAPx6), 5.99 (1H, dd, *J* = 15.5, 3.5 Hz, H4), 5.95 (1H, dd, *J* = 15.5, 3.5 Hz, H3), 5.89 (1H, d, *J* = 13.0 Hz, H18), 5.88 (1H, m, H26), 5.88 (1H, m, H27), 5.86 (1H, m H21), 5.78 (1H, d, *J* = 13.0 Hz, H17), 5.69 (1H, ddd, *J* = 11.0, 3.0, 3.0 Hz, H6), 5.57 (1H, m, H22), 5.53 (1H, m, H7), 5.26 (2H, s, NAP), 4.99 (1H, d, *J* = 12.5 Hz, NAP), 4.88 (1H, d, *J* = 12.5 Hz, NAP), 4.84 (1H, d, *J* = 12.5 Hz, NAP), 4.83 (1H, d, *J* = 12.5 Hz, NAP), 4.81 (1H, d, *J* = 12.5 Hz, NAP), 4.61 (1H, d, *J* = 12.5 Hz, NAP), 4.55 (1H, m, H5), 4.50 (2H, s, NAP), 4.34 (2H, s, NAP), 4.26 (1H, m, H44), 4.19 (1H, m, H2), 4.10 (1H, m, H54), 4.07 (1H, d, *J* = 9.5 Hz, H48), 4.01 (1H, d, *J* = 10.0 Hz, H55), 4.00 (1H, d, *J* = 9.0 Hz, H20), 3.98 (1H, m, H23), 3.92 (1H, m, H19), 3.84 (1H, d, *J* = 9.0 Hz, H16), 3.83 (1H, dd, *J* = 9.5, 9.5 Hz, H49), 3.81 (1H, dd, *J* = 10.0, 5.0 Hz, H55), 3.74 (1H, dd, *J* = 9.0, 3.5 Hz, H11), 3.72 (1H, dd, *J* = 6.5, 6.5 Hz, H30), 3.67 (1H, dd, *J* = 10.0, 7.0 Hz, H1), 3.67 (1H, d, *J* = 3.5 Hz, H47), 3.59 (1H, dd, *J* = 9.0, 9.0 Hz, H10), 3.53 (1H, m, H32), 3.52 (1H, dd, *J* =10.0, 4.0 Hz, H1), 3.51 (1H, m, H29), 3.49 (1H, m, H24), 3.46 (1H, m, H37), 3.33 (1H, ddd, *J* = 9.0, 9.0, 4.0 Hz, H9), 3.27 (1H, dd, *J* = 9.0, 9.0 Hz, H12), 3.17 (1H, ddd, *J* = 11.5, 9.0, 4.0 Hz, H15), 3.13 (1H, m, H41), 3.10 (1H, dd, *J* = 9.0, 4.5 Hz, H45), 3.05 (1H, m, H42), 3.03 (1H, m, H34), 2.96 (1H, m, H13), 2.94 (1H, m, H36), 2.87 (1H, m, H25), 2.86 (1H, m, H28), 2.61 (1H, ddd, *J* = 16.0, 8.0, 4.0 Hz, H8), 2.58 (1H, m, H25), 2.58 (1H, m, H28), 2.56 (1H, m, H46), 2.48 (1H, ddd, *J* = 12.0, 5.0, 5.0 Hz, H43), 2.39 (1H, m, H31), 2.34 (1H, m, H14), 2.33 (1H, m, H8), 2.24 (1H, m, H53), 2.23 (1H, m, H53), 2.21 (1H, m, H31), 2.14 (1H, m, H50), 2.09 (1H, m, H40), 2.06 (1H, m, H35), 2.02 (1H, m, H38), 1.87 (1H, m, H39), 1.86 (1H, m, H35), 1.79 (1H, ddd, *J* = 12.0, 12.0, 12.0 Hz, H43), 1.72 (1H, ddd, *J* = 11.5, 11.5, 11.5 Hz, H14), 1.66 (1H, m, H40), 1.60 (1H, m, H38), 1.56 (1H, m, H51), 1.36 (3H, s, Me56), 1.29 (3H, d, *J* = 6.5 Hz, Me59), 1.17 (3H, d, *J* = 7.5 Hz, Me58), 1.16 (3H, d, *J* = 7.0 Hz, Me60), 0.98 (3H, d, *J* = 7.5 Hz, Me57);

MALDI-TOF MS, calcd. for $C_{126}H_{134}NaO_{19}$ 1973.9421 ($M+Na^+$), found for 1973.9417

Synthesis of aimed compound CTX1B.

[0035]



[0036] DDQ (1.6mg, 6.9 μ mol) is added to CH_2Cl_2 (100 μ L)-water(100 μ L) solution of compound 8 (450 μ g, 0.23 μ mol) and stirred at room temperature for 45 minutes. Na_2S_2O3 aqueous solution is added and reaction is stopped, and diluted by ethyl acetate and saturated $NaHCO_3$ aqueous solution. Water phase is extracted by ethyl acetate for 5 times and combined organic layer is washed by saturated brine, then solvent is concentrated. Obtained mixture is refined by HPLC and compound E is obtained. Hydrochloric acid (1N. 50 μ L) is added to methanol (200 μ L) solution of compound E is added and stirred at room temperature for 30 minutes. Saturated $NaHCO_3$ aqueous solution is added to this solution and reaction is stopped, then concentrated. This mixture is diluted by water and ethyl acetate for 5 times, and combined organic layer is concentrated. Crude CTX1B is refined by HPLC and CTX1B (108 μ mg, 0.097 μ mol, 42%) is obtained. Features of synthesized CTX1B are shown in Table 9.

(Table 9)

^{1}H NMR (500 MHz, C_6D_5N) δ 7.30 (1H, d, *J* = 4.0 Hz, OH11), 6.75 (1H, d, *J* = 3.5 Hz, OH47), 6.63 (1H, d, *J* = 4.0 Hz, OH2), 6.52 (1H, d, *J* = 4.0 Hz, OH54), 6.39 (1H, t, *J* = 5.0 Hz, OH1), 6.38 (1H, dd, *J* = 15..0, 3.0 Hz, H4), 6.35 (1H, dd, *J* = 15.0, 3.0 Hz, H3), 6.03 (1H, d, *J* = 13.0 Hz" H22), 5.97 (1H, m, H26), 5.97 (1H, m, H27), 5.91 (1H, ddd, *J* = 11.5, 3.0, 3.0 Hz, H6), 5.89 (1H, d, *J* = 12.5 Hz, H18), 5.53 (1H, dddd, *J* = 11.5, 8.0, 3.0, 3.0 Hz, H7), 5.74 (1H, d, *J* = 12.5 Hz, H17), 5.67 (1H, m H21), 5.26 (1H, m, OH54), 4.86 (1H, m, H5), 4.86 (1H, m, H54), 4.69 (1H, m, H2), 4.48 (1H, ddd, *J* = 12.0, 10.0, 5.0 Hz, H44), 4.22 (1H, dd, *J* = 3.5, 3.5 Hz, H47), 4.21 (1H, m, H20), 4.19 (1H, m, H55), 4.17 (1H, m, H55), 4.16 (1H, m, H32), 4.10 (1H, ddd, *J* = 9.0, 9.0, 4.0 Hz, H11), 4.07 (1H, d, *J* = 10.0 Hz, H48), 4.05 (1H, m, H19), 4.03 (1H, m, H23), 4.02 (1H, d, *J* = 10.0 Hz, H16), 4.00 (1H, ddd, *J* = 10.0, 5.0, 5.0 Hz, H1), 3.98 (1H, dd, *J* =10.0, 5.0, 5.0 Hz, H1), 3.97 (1H, dd, *J* = 10.0, 10.0 Hz, H49), 3.78 (1H, m, H29), 3.76 (1H, dd, *J* = 9.0, 9.0 Hz, H10), 3.61 (1H, m, H24), 3.57 (1H, m, H30), 3.54 (1H, m, H15), 3.50 (1H, m, H37), 3.49 (1H, ddd, *J* = 9.0, 9.0, 4.0 Hz, H9), 3.44 (1H, dd, *J* = 9.0, 9.0 Hz, H12), 3.35 (1H, ddd, *J* = 12.0, 9.0, 4.5 Hz, H13), 3.34 (1H, m, H36), 3.34 (1H, m, H42), 3.32 (1H, dd, *J* = 12.0, 4.5 Hz, H34), 3.22 (1H, ddd, *J* = 10.0, 10.0, 3.0 Hz, H41), 3.21 (1H, dd, *J* = 10.0, 5.0 Hz, H45), 2.94 (1H, m, H25), 2.94 (1H, m, H28), 2.73 (1H, ddd, *J* = 16.0, 8.0, 4.0 Hz, H8), 2.60 (1H, m, H31), 2.59 (1H, m, H43), 2.59 (1H, m, H46), 2.57 (1H, m, H31), 2.56 (1H, m, H14), 2.53 (1H, m, H8), 2.40 (1H, dd, *J* = 9.0, 6.5 Hz, H53), 2.36 (1H, m, H28), 2.34 (1H, dd, *J* = 9.0, 3.5 Hz, H53), 2.26 (1H, ddd, *J* = 12.0, 4.5, 4.5 Hz, H35), 2.20 (1H, m, H25), 2.04 (1H, m, H40), 2.00 (1H, m, H50), 1.92 (1H, ddd, *J* = 12.0, 12.0, 12.0 Hz, H35), 1.90 (1H, m, H39), 1.85 (1H, ddd, *J* = 12.0, 12.0, 12.0 Hz, H14), 1.83 (1H, m, H38), 1.78 (1H, ddd, *J* = 12.0, 12.0, 12.0 Hz, H43), 1.73 (1H, m, H40), 1.67 (1H, m, H51), 1.54 (1H, m, H38), 1.38 (3H, s, Me56), 1.32 (3H, d, *J* = 7.0 Hz, Me59), 1.31 (3H, d, *J* = 6.0 Hz, Me58), 1.23 (3H, d, *J* = 6.5 Hz, Me60), 0.93 (3H, d, *J* = 7.0 Hz, Me57);
MALDI-TOF MS, calcd. for $C_{60}H_{86}O_{19}$ 1133.5661 ($M+Na^+$), found for 1133.5583

[0037] Illustration of shortened marks in this application

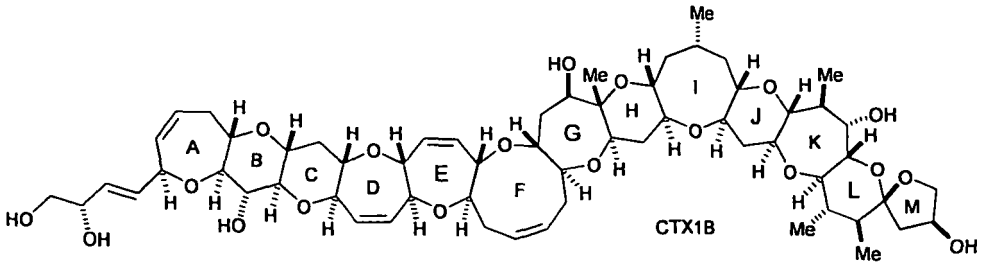
AIBN	α, α'-azobis(isobutyronitrile)
Cy	cyclohexyl
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminumhydride
DMSO	dimethylsulfooxide
DTBMP	2,6-di-butyl-4-methylpyridine
Grubbs catalyst	benzylidene-bis(tricyclohexylphosphine)dichlororuthenium
HPLC	high performance liquid chromatography
Me	Methanol
NaHMDS	sodium bis(trimethylsilyl)amide
NAP	2-naphthylmethyl
Ph	phenyl
TBAF	tetrabutylammonium fluoride
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TMS	trimethylsilyl
TIPS	triisopropylsilyl

INDUSTRIAL APPLICABILITY

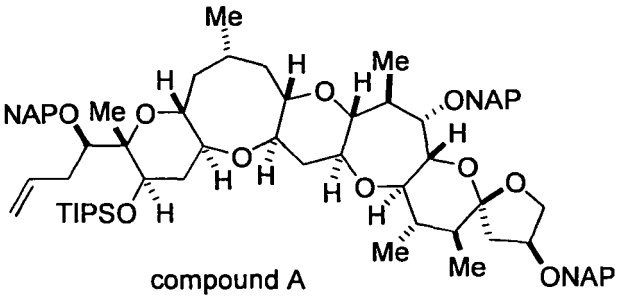
[0038] The present invention makes possible to provide necessary amount of said compound for progressing bio-science research or development of method for detection of ciguatera poisoned fish, and is useful for industrial use applicable as a standard sample for ciguatera food-poisoning happened in all over the world.

Claims

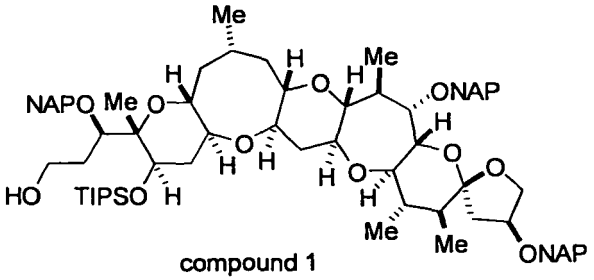
1. A method for preparation of CTX1B including following 10 processes,



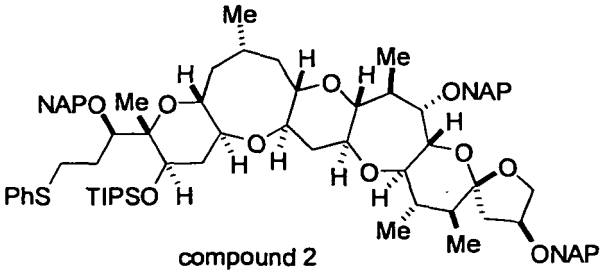
a double bond of compound A



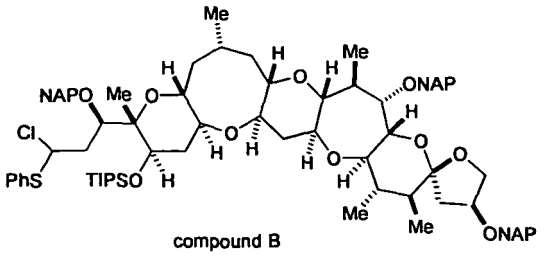
is oxidized by osmium tetra oxide and changed to diol derivative of compound A, transformed the diol to aldehyde by oxidation cleavage by sodium periodate, then reduced the aldehyde to alcohol using sodium borohydride and obtain compound 1 (process 1),



alcohol of compound 1 is transformed to compound 2 using diphenyldisulfide·tributylphosphine (process 2),

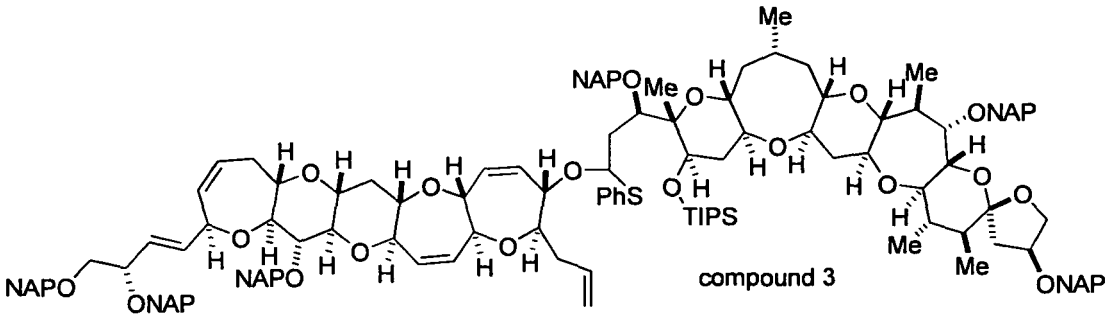


said compound 2 is transformed to α-chrolosulphide and synthesize compound B,



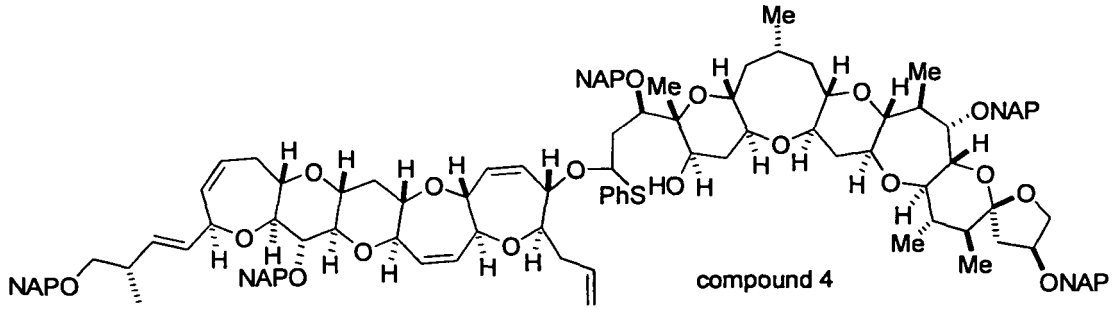
compound B

under the presence of DTBMP said compound B is joined to the ABCDE ring segments compound C as O,S-acetal using silver triflate and compound 3 is formed (process 3),



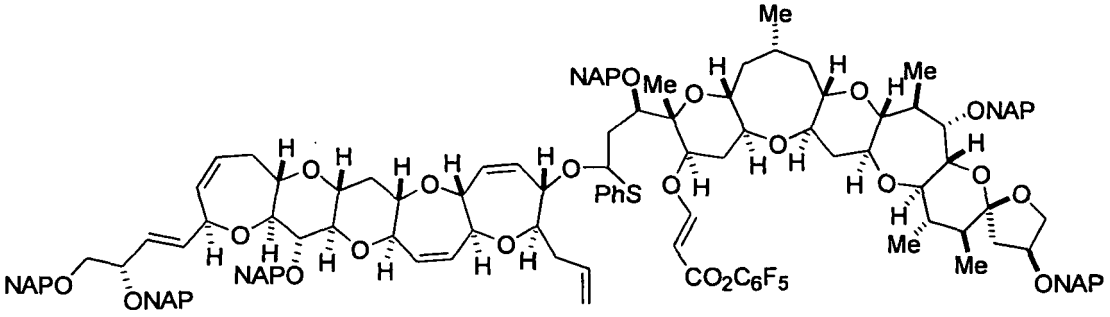
compound 3

TIPS group of said compound 4 is removed using TBAS and form compound 4 (process 4),



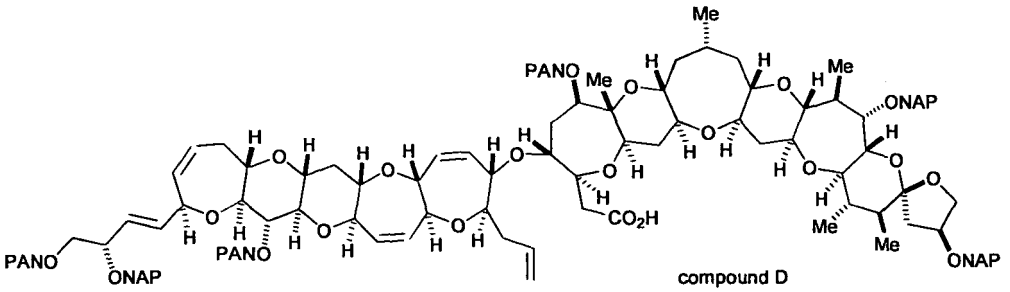
compound 4

pentafluorophenylpropiolate is joined to alcohol of said compound 4 using trimethylphosphine and compound 5 is formed (process 5),



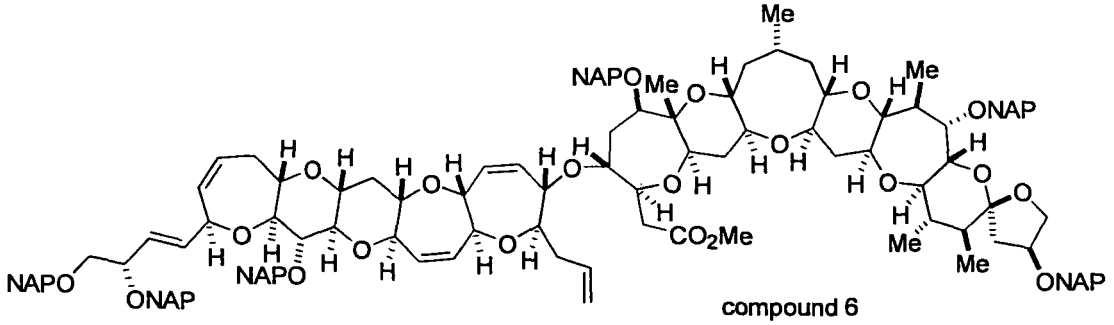
compound 5

carry out radical cyclizing reaction on said compound 5 by treating with AIBN and tintributyl hydride and form G ring part, so that compound 5 transforms to carboxylic acid compound D, then



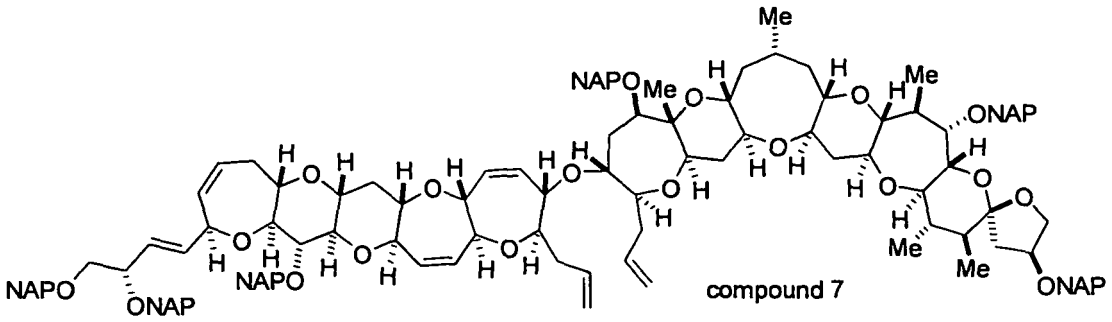
compound D

transforms to methyl ester by acting trimethylsilyldiazomethane and forms compound 6 (process 6),



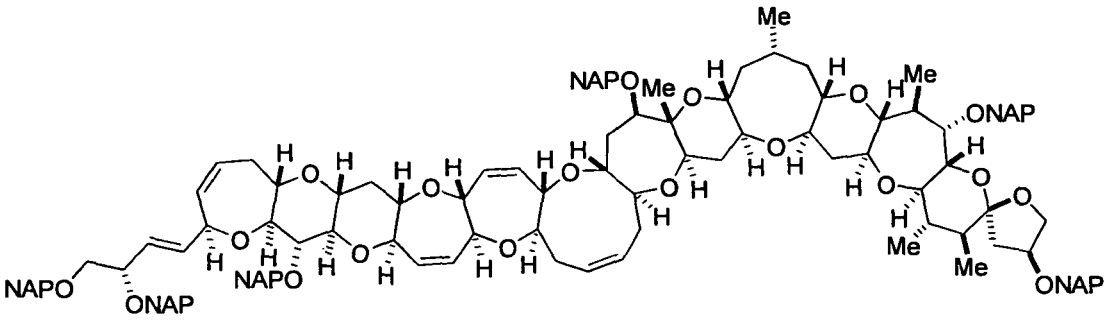
compound 6

forms compound 7 (process 7) by reducing methyl ester of said compound 6 by diisobutylaluminum hydrate under lower temperature condition, then transforms to olefin by Wittig reaction,



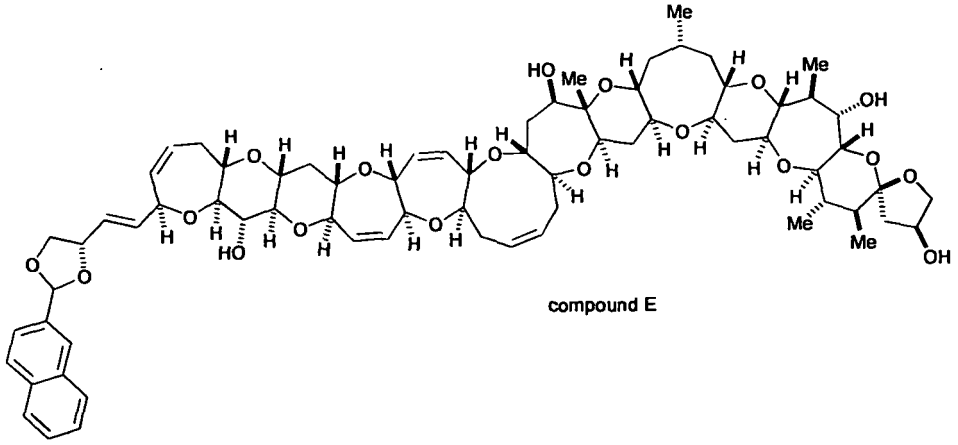
compound 7

forms compound 8 (process 8) by forming F ring part by carrying out ring closure methathesis reaction acting Grubbs catalyst to said compound 7,



compound 8

synthesizes compound E, 1,2-diol of A ring side chain of which is protected by naphthylacetal, by oxidizing 6 NAP groups using DDQ and removing 5 NAP groups (process 9), then



compound E

carries out acid treatment on said compound E (process 10),
wherein, in compounds A, B, D, E, CTX1B and compounds 1-8, NAP is 2-naphthylmethyl group, Me is methyl group, TIPS is triisopropylsilyl group, Ph is phenyl group, further, shortened mark DTBMP is 2,6-di-butyl-4-methylpyridine, TBAF is tetrabutylammonium fluoride, AIBN is α, α'-azobis(isobutyronitrile), DDQ is 2,3-dichloro-5,6-dicyano -1,4-benzoquinone.

2. A novel compound represented by compound 1 to be used for preparation of CTX1B of claim 1.

3. A novel compound represented by compound 2 to be used for preparation of CTX1B of claim 1.

4. A novel compound represented by compound 3 to be used for preparation of CTX1B of claim 1.

5. A novel compound represented by compound 4 to be used for preparation of CTX1B of claim 1.

6. A novel compound represented by compound 5 to be used for preparation of CTX1B of claim 1.

7. A novel compound represented by compound 6 to be used for preparation of CTX1B of claim 1.

8. A novel compound represented by compound 7 to be used for preparation of CTX1B of claim 1.

9. A novel compound represented by compound 8 to be used for preparation of CTX1B of claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2007/050545

A. CLASSIFICATION OF SUBJECT MATTER
C07D493/22(2006.01)i, *C07D519/00*(2006.01)i, *C07F7/18*(2006.01)i, *C07B61/00*(2006.01)n

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)
C07D493/22, C07D519/00, C07F7/18, C07B61/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Jitsuyo Shinan Koho 1922-1996 Jitsuyo Shinan Toroku Koho 1996-2007
Kokai Jitsuyo Shinan Koho 1971-2007 Toroku Jitsuyo Shinan Koho 1994-2007

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
BIOSIS(STN), CAplus(STN), CASREACT(STN), EMBASE(STN), MEDLINE(STN), REGISTRY(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	TATAMI, A. et al, A concise route to the right wing of ciguatoxin, Tetrahedron Letters, 2003, 44, p.5229-5233	2-5 1,6-9
X A	KOBAYASHI, S. et al, Synthesis of the fully functionalized ABCDE ring moiety of ciguatoxin, Org Lett, 2004, Vol.6, No.5, p.751-754	2-5 1,6-9
X A	INOUE, M. et al, First- and second-generation total synthesis of ciguatoxin CTX3C, Proc Natl Acad Sci U S A, 2004, Vol.101, No.33, p.12013-12018	2-5 1,6-9
P,X	INOUE, M. et al, Total synthesis of ciguatoxin and 51-hydroxyCTX3C, J Am Chem Soc, 2006, Vol.128, No.29, p.9352-9354	1-9

☐ 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
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"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	Date of mailing of the international search report
22 March, 2007 (22.03.07)	03 April, 2007 (03.04.07)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (April 2005)

REFERENCES CITED IN THE DESCRIPTION

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Non-patent literature cited in the description

- *Proc. Natl. Acad. Sci. U.S.A.,* 2004, vol. 101, 1203-12018 **[0004]**
- *J. Am. Chem. Soc.,* 2003, vol. 125, 7608-7612 **[0004]**
- *J. Org. Chem.,* 2004, vol. 69, 2797-2804 **[0007] [0012]**
- *J. Org. Lett.,* 2004, vol. 6, 751-754 **[0007] [0009] [0014]**