TOTAL SYNTHESIS OF 7-Epi-FR 66979 AND 7-Epi-FR 900482

By

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Written under the direction of
Professor Leslie Jimenez
And approved by

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New Brunswick, New Jersey
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ABSTRACT OF THE DISSERTATION

TOTAL SYNTHESIS OF 7-Epi-FR 66979 AND 7-Epi-FR 900482

By WEIDONG PAN

Dissertation Director:

Professor Leslie Jimenez

The completion of the total synthesis of 7-Epi-FR 66979 and 7-Epi-FR 900482 is presented in this thesis. The natural product FR 66979 and FR 900482 were isolated by the Fujisawa Pharmaceutical Corporation from Streptomyces sandaensis. They are antibiotics with potent antitumor activity.

The first stage of the total synthesis is to make indole ester. For the preparation of the precursor of the indole ester, the commercial available starting material 3-hydroxymethylphenol was converted to benzyl aldehyde by using the reagents paraformaldehyde and lewis catalyst SnCl$_4$ after the selective protection of hydroxymethyl group. After the phenol had been protected, this benzyl aldehyde precursor was transformed to indole ester by the Hemetsberger-Knittel reaction in 61% yield.

The second stage of the total synthesis is to make fully functionalized pyrroloindole. The indole ester was reduced by DIBAL and then was oxidized to indole aldehyde. The vinylsulfonium salt reacted with this indole aldehyde to form the
tetracyclic oxirane, then subsequently treated by sodium azide in acetone-water to afford pyrroloindole in 74% yield.

The third stage of the total synthesis is to synthesize the core ring system. The fully functionalized pyrroloindole was successfully oxidized by two equivalents of dimethyldioxirane (DMDO) in acetone/water to give ring expanded hydroxylamine hemiketal ring system in 57% yield.

The final stage of the total synthesis is to complete the total synthesis. One of the challenging steps is to prepare the hydroxymethyl group on this core structure. With many studies, the hydrosilylation-oxidation was found to be a good method to make the hydroxymethyl group on this complex molecule. After converting the hydroxymethyl group to urethane and deprotection, 7-Epi-FR 66979 was successfully obtained. With a one step oxidation of 7-Epi-FR 66979, 7-Epi-FR 900482 was prepared. This total synthesis is the shortest and most efficient so far. Epi-FR 66979 is synthesized in 20 steps while epi-FR 900482 required 21 steps.

The attempt of making the beta configuration of the hydroxymethyl group on the 7-position for FR 66979 and FR 900482 is also described in this thesis. The efforts included intramolecular hydrosilylation-oxidation, less hindered intermolecular hydrosilylation-oxidation, catalytic hydroboration-oxidation and Danishefsky’s methods of the epoxidation and opening. Both less hindered intermolecular hydrosilylation-oxidation and Danishefsky’s methods provided intermediate with beta configuration of hydroxymethyl, but the final product was not obtained. A less hindered intermolecular hydrosilylation-oxidation method will provide the best chance to get the natural product when additional more intermediates are prepared in the future.
In the first place, I wish to express my profound gratitude to my thesis advisor Professor. Leslie Jimenez for her supervision, advice, suggestion, encouragement and support through this research. I also want to thank all people in Professor Leslie Jimenez’s group. They give me lot of help from the beginning of research to the end. Many colleagues at the Schering-Plough Research Institute gave me help in my research. I would like to thank Dr. Stephane Bogen for his help, encouragement and discussion. I would also like to thank to Dr. Ronald Doll for his support and encouragement for my part time research. Many thanks in particular to Dr. Jun Qin for his greatly helpful suggestions and discussion. I also benefited from the discussion with colleagues Dr. Xianhai Huang, Dr. Xin Dai, Dr. Guoqin Li, and Dr. Youlong Yu. I would like to thank them. I gratefully thank for Dr. T.M Chan and Dr. Alexei Buevich at the NMR group of structure chemistry at the Schering-Plough Research Institute for analyzing the structure of important intermediates and final target compound of my research.

I gratefully acknowledge the Schering-Plough Research Institute for education assistance program. Without the support in tuition, facilities and chemicals from Schering-Plough, I could not complete the Ph. D thesis.

My deepest gratitude goes to my wife Li Tan and daughter Emily Pan for their unflagging love and support through the time of my research. This dissertation is simply impossible without them.
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<tr>
<td>Ac₂O</td>
<td>acetic anhydride</td>
</tr>
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<td>acetic acid</td>
</tr>
<tr>
<td>Alloc</td>
<td>(allyloxy)carbonyl</td>
</tr>
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</tr>
<tr>
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<td>isopropanol</td>
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<td>J</td>
<td>coupling constant in hertz</td>
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<td>KHDMS</td>
<td>potassium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>L</td>
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<td>liquid chromatography-mass spectrometry</td>
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<tr>
<td>MOM</td>
<td>methoxymethyl ether</td>
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mp melting point
MPM methoxybenzyl
MS mass spectrum
Ms methylsulfonyl
MTO methyltrioxorhenium
$m/z$ mass to charge ratio
N normal
NaBH₃CN sodium cyanoborohydride
NMO 4-methylmorpholine N-oxide
NOE nuclear Overhauser effect
NOESY nuclear overhauser effect spectroscopy
OsO₄ Osmium tetroxide
Pd(OAc)₂ palladium(II) acetate
Pf $N$-9-phenylfluoren-9-yl
PMB $para$-methoxybenzyl
Ph phenyl
Ph₃CBF₄ trityl fluoroborate
Ph₃P triphenylphosphine
(Ph₃P)₄Pd tetra(triphenylphosphine)palladium
PhSH thiophenol
$i$-Pr isopropyl
PSL pseudomonas stutzeri lipase
Pt(DVDS) platinum, bis[1,3-bis( 2-ethenyl)-1,1,3,3-
tetramethyldisiloxane]-

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<tr>
<td>q</td>
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<tr>
<td>RCM</td>
<td>ring-closing metathesis</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBS or TBDMS</td>
<td>tert-butyldimethylsilyl</td>
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<tr>
<td>TBDPS</td>
<td>tert-butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBHP</td>
<td>tert-butyl hydroperoxide</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>Tf₂O</td>
<td>trifluoromethanesulfonic (triflic) anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
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<tr>
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<td>thin layer chromatography</td>
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<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Triton B</td>
<td>benzyl(trimethyl)azanium hydroxide</td>
</tr>
<tr>
<td>Troc</td>
<td>2,2,2-trichloroethoxycarbonyl</td>
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<tr>
<td>Ts or p-Ts</td>
<td>tosyl, para-toluenesulfonyl</td>
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Total Synthesis of 7-Epi-FR 66979 and 7-Epi-FR 900482
I. Introduction

1. Isolation and Biological Properties

In 1987 and 1989, a new class of aziridine natural products FR 900482 and FR 66979 (Figure 1) similar to the mitomycins in their mechanism of action, were isolated by the Fujisawa Pharmaceutical Corporation from *Streptomyces sandaensis*. The structures of FR 900482 and FR 66979, were a mixture of two stereoisomers A and B, in equilibrium due to their unique hydroxylamine hemiketal functionality.

![Figure 1. Structure of FR 66979 and FR 900482](image)

They also reported that FR 900482 and FR 66979 are antibiotics with potent antitumor activity and are at least as active as mitomycin C (Figure 2) and have less toxicity. The studies found that the FR 900482 and FR 66979 are effective against leukemia P388, melanoma B16, lymphoma EL4, mammary carcinoma FM3A, leukemia...
L1210 and baby hamster kidney (BHK-21) cells at low concentration. In the further development of more potent and less toxic agents, FK 973\textsuperscript{4} and FK 317\textsuperscript{5} (Figure 2), semisynthetic derivatives from FR 900482, were found to be potent antitumor candidates.

![Figure 2. Structures of Mitomycin C, FK 973 and FK 317](image)

The mode\textsuperscript{6} of antitumor action of FR 900482 and FR 66979 shown in Scheme 1 involves a DNA-cross coupling reaction induced by cytosolic reduction. Thus, FR 900482 and FR 66979 are activated by bioreduction and aromatization to form 4, which undergoes DNA-cross coupling. The cross-linking disrupts translation and then prevents rapid cellular division related to cancer.
2. Structural Features and Synthetic Challenges

The unique structures and antitumor bioactivities of FR 900482 and FR 66979 have made them interesting targets for total synthesis. FR 900482 and FR 66979 exist as a mixture of stereoisomers, which interconvert through the hydroxylamine ketone (Scheme 2). They have four contiguous stereogenic centers at C7, C8, C9 and C10. From current total syntheses, there are two common approaches to the core of the natural products, which are nitroso or amine oxide cyclization to give hemiketal core and the oxidation of pyrroloindole intermediate to form the aminooxyhemiketal derivative. Because FR 900482 and FR 66979 can be made by one simple chemical transformation, the total synthesis of either one can be treated as a formal total synthesis of the other.
Scheme 2. Equilibrium of FR 900482 and FR 66979
II. Various Strategies for the Total Syntheses of FR 900482 and FR 66979

In 1992, Fukuyama reported the first total synthesis of FR900482\(^7\). After that, Danishefsky in 1995 finished another racemic total synthesis\(^8\). In 1997, first enantioselective total synthesis was reported by Terashima\(^10\). Following that, Williams\(^11\), Fukuyama\(^12\), and Ciufolini\(^13\) also reported enantioselective total syntheses in 2002. Martin\(^14\) and Paleo\(^15\) reported formal total synthesis in 2000 and 2003. In 2008, Trost\(^16\) reported total synthesis of epi 7-Epi-(+)-FR900482.

1. The Fukuyama First Total Synthesis and Enantioselective Total Synthesis

In 1992, the first total synthesis of FR 900482 was reported by Fukuyama\(^7\) (Scheme 3). They started with N-benzylamine 7 to form butenolide 8 after 10 steps transformation. The reactive butenolide 8 was protected by thiophenol. The hydroxyl group was removed by acetylation and reduction with triethylsilane. The azido lactone was further reduced with zinc to provide amine lactone 9. The critical transformation of lactone 9 to 8-membered amine 10 was achieved by the reduction of the lactone with DIBAL, then followed by reductive amination with sodium cyanoborohydride in 83% yield. After converting 10 to 11 in 12 steps, the key pentacyclic compound 12 was obtained in 98% yield by hydrazinolysis of the acetate, deprotection of TBS ether with n-Bu\(_4\)NF, and protection of the diol as an acetonide. The final target was obtained with
additional 11 steps. In conclusion, FR 900482 was synthesized in 41 steps in overall 0.011% yield.

Scheme 3. Fukuyama first total synthesis

In 2002, Fukuyama developed enantioselective total synthesis which began with a Sonagashira coupling of chiral acetylene $\text{13}$ and aryl triflate $\text{14}$ to afford $\text{15}$ in 83% yield (Scheme 4). Regioselective formation of the ketone $\text{16}$ was achieved by conjugate addition of second amines to triple bond and hydration. After compound $\text{16}$ was converted to epoxide $\text{17}$ by 6 steps, TBS ether was selectively deprotected, the
resulting alcohol was oxidized to aldehyde, then the aryl nitro was hydrogenated over Pt/C (5%) to realize the intramolecular reductive hydroxylamination to form the N-hydroxybenzazocine 18. With 3 steps, 18 was converted to ketone 19. The key construction of the hydroxymethyl group and tetra cyclic core ring system was realized by one pot reaction in 77% yield, which 19 was treated with paraformaldehyde and catalytic amount LiOH in aqueous THF, followed by the addition of 1N HCl. The final target was obtained by additional 14 steps transformation in overall 13% yield. The total synthesis was finished in 33 steps in overall 0.7% yield.
Schem 4. Fukuyama enantioselective total synthesis

2. Danishefsky Cycloaddition Approaches Racemic Total Synthesis

Danishefsky’s synthesis featured a Diels-Alder reaction as a key step to prepare the core of natural product (Scheme 5). Diels-Alder reaction between 21 and 22 provided 23 in 80% yield, which was converted to 24 after additional 8 steps reaction.
Compound 24 underwent Heck arylation to provide tetracycle core 25 in 93% yield. The construction of the hydroxymethyl group was more difficulty than they expected. In their early study\(^9\), a long route was developed to complete this task. Then, the compound 26 was obtained by Osmylation, epoxidation and SmI\(_2\) reduction. Finally, they finished the total synthesis in 31 steps.

**Scheme 5. Danishefsky total synthesis**

3. Terashima Total Synthesis-Aldol Cycloaddition

In 1997, Terashima’s enantioselective total synthesis (Scheme 6)\(^{10}\) started with L-diethyl tartrate to prepare optically active aliphatic compound 28 in 15 steps. They
made aromatic compound 27 in 15 steps starting from 5-hydroxyisophthalic acid. Then, the coupling reaction of enantiomerically pure compound 28 with aromatic compound 27 was conducted by treating with sodium hydride in THF to provide compound 29 in a quantitative yield. Dialdehyde 30 was prepared in 6 steps from 29. The diol 31 was obtained in 48% yield from 30 after intramolecular aldol coupling and reduction. The S configuration of the hydroxymethyl group in compound 31 was converted to R configuration of hydroxymethyl group in compound 32 was achieved by protection, oxidation, deprotection and epimerization with DBU in THF. Compound 32 was converted to the final natural product in additional 15 steps. Overall, this total synthesis was 57 steps with a 0.032% overall yield.
Scheme 6. Terashima total synthesis

4. Ring Closing Metathesis: Martin Formal Total Synthesis
In 1995, Grubbs reported ring-closing metathesis to construct the eight membered tetrahydrobenzazocine intermediate of FR 900482\textsuperscript{17}. This was utilized by Martin to complete the formal total synthesis\textsuperscript{14} (Scheme 7). The racemic diol compound 35 was prepared from 34 in 6 steps. Desymmetrization of the racemic diol 35 by using PSL and vinyl acetate yielded the S configuration hydroxy acetate 36 in 74% yield and 94% ee. The absolute configuration at C (7) of compound 37 for FR 900482 was obtained by a series of hydroxyl protecting group interchanges. The N-allylamine 38 was prepared in additional 4 steps from 37. A tandem Swern oxidation, Grignard addition from compound 38 provided the RCM precursor 39. Subsequent ring closing metathesis of 39 provided benzazocine 40, which was converted to 41 of Fukuyama’s synthesis in additional 8 steps transformation.
Scheme 7. Martin formal total synthesis

5. Williams Enantioselective Total Synthesis

In 2002, Williams’s synthesis\(^{11}\) featured DMDO oxidation as key step to convert 46 to 47 (Scheme 8). Optically active aziridine 43 coupled with trisubstituted
nitrobenzene 42, followed by 6 additional steps to give eight-membered-ring amine 45. Ketone 46 was obtained from 45 in 6 steps. A simultaneous oxidative deprotection of eight-membered-ring aminoketone 46 by DMDO formed the core structure of hydroxylamine hemiketal 47. The synthesis was completed in 33 steps with overall 0.34% yield.

Scheme 8. Williams total synthesis

6. Homo-Brook Fragmentation: Ciufolini Total Synthesis

In 2002, Ciufolini\textsuperscript{13} (Scheme 9) reported the total synthesis by using the homo-Brook triggered fragmentation. $S_E'$ addition of 49 to aldehyde 48, which was prepared
from Martin’s intermediate 2-(2-nitroaryl)-propanediol in 4 steps\textsuperscript{14}, provided alcohol 50. The intramolecular 1,3-dipolar cyclization between azide and double bond in 49, followed by photolysis afforded 51 in 62% yield. The aziridine 51 underwent a base induced homo-Brook fragmentation to provide 52 in 49% yield. The remaining synthesis is an extension of work performed by Fukuyam, which were N-oxidation and N-acetylation, epoxidation, cyclization, formation of aziridine, and deprotection. Finally, regioselective ammonolysis and concomitantly deprotected the acetyl groups to complete FR 66979. Overall, this total synthesis was completed in 28 steps in 0.23% yield.
7. Paleo Formal Total Synthesis

In 2003, Paleo reported another formal total synthesis (Scheme 10). Amino alcohol 55 was prepared by regioselective ring opening of enantio pure epoxide 54 with 53, while 53 was prepared from 3,5-dinitrop-toluic acid in 3 steps and 54 was prepared from L-methionine methyl ester hydrochloride. Aziridine compound 56 was obtained in 4 steps from 55. Deprotonation of 56 with KHMDS in THF followed by intramolecular condensation with aziridino methyl ester provided the eight membered
ring 57. Hydroxymethylation of 57 was achieved by the formation of enone, epoxidation and reduction. A series of steps similar to Fukuyama finished the synthesis of 60 (+) FK-973.

Scheme 10. Paleo formal total synthesis

8. Trost Total Synthesis of epi-(+)-FR 900482
In 2008, Trost reported the total synthesis 7-Epi (+)-FR 900482 (Scheme 11). Reductive amination between the aziridine 62 and aniline 61 afforded 63. Deprotection and activation provided 5-membered ring 64. Heck reaction of 64 afforded tetracyclic intermediate 65. Inspired by the pioneering works of Dmitrientko and Ziegler, they applied the Polonovski reaction, followed by an oxidative ring expansion to afford hydroxylamine hemiketal 66. In five additional steps, 66 was converted to epi-(+)-FR900482. Overall, this total synthesis was completed in 25 steps in 1.24% yield.

Scheme 11. Trost epi total synthesis
III. Retrosynthetic Plan

In 2003, our lab reported a new approach to make hydroxylamine hemiketal from pyrroloindole substrate\textsuperscript{22}. Because the FR 900482 and FR 66979 generate mitoses in vivo as the active DNA cross-linking agent, it will provide rapid access to the core structure if they could interconvert. Several groups worked on the oxidation of the pyrroloindole core\textsuperscript{20(b), 21(b), 23}. Our lab successfully established that oxidation of pyrroloindole 67 by aqueous dimethyldioxirane afforded tricyclic core 68 in a 59% yield (Scheme 12)\textsuperscript{21}.

![Scheme 12. DMDO oxidation](image)

Based on our success to access the core structure, we planned our total synthesis as outlined in Scheme 13. The target compound FR 900482 and FR 66979 could obtained from the intermediate 69 by several steps including aziridine formation, hydroxyl methylation, deprotection and oxidation. Compound 69 is accessible from functionalized pyrrolo[1,2-a]indole 70 by DMDO oxidation. Indole 71 can be
converted to pyrrolo[1,2-a]indoles 70 by reaction with diisopropylvinylsulfonium triflate, followed by the addition of sodium azide. Ethyl azidoacetate 73 reacts with benzaldehyde 72 to give an indole ester, which is reduced to indole aldehyde 71. Functionalized benzaldehyde 72 is readily available from commercially available 3-hydroxymethylphenol 74.

Scheme 13. Retrosynthetic plan
IV. Synthesis of Functionalized Indole-2-Carboxylate

The first stage for this total synthesis is to make the important intermediate indole ester 79 (Scheme 14). There are several methods to synthesize functionalized indole. The Hemetsberger-Knittel reaction had been recognized as one of the most important methods for the synthesis of indole-2-carboxylate\textsuperscript{24}. Initially we started with commercial available material 3-hydroxymethylphenol 74. In our early study, compound 74 was treated with chloroform and aqueous sodium hydroxide to prepare ortho phenol aldehyde. This reaction gave low yield and undesired regional by-product. A more efficient way to make aldehyde 76 was to selectively protect hydroxyl methyl group, then react with paraformaldehyde in the presence of a Lewis acid catalyst\textsuperscript{25}. The two steps gave a 76% yield. Cleaving the acetate by potassium carbonate and protecting phenol with a benzyl in one pot provided 77 in 98% yield. To streamline the synthesis, the hydroxymethyl group is protected by the Bom group, which was accomplished with DIPEA, benzyl chloromethyl ether with n-Bu\textsubscript{4}NI as catalyst to give 78 in an 83% yield. With 78 in hand, indole 79 was prepared by base-mediated aldol reaction of aryl aldehyde 78 with ethyl azidoacetate, then subsequent thermal cyclization.
Scheme 14. Synthesis of Indole-2-Carboxylate
V. Synthesis of Pyrroloindole

Scheme 15. Synthesis of pyrroloindole

The next challenge was to make the ring expansion intermediate 70 (Scheme 15). In order to make tricyclic ring intermediate 81, indole aldehyde 71 should be prepared. It was easily prepared from indole-2-carboxylate 79 by reduction with DIBAL, followed by oxidation with MnO$_2$ in an overall 81% yield. The synthesis of tricyclic compound 81 was developed in our lab in 1999$^{26}$ (Scheme 16). The diisopropylvinylsulfonium salt reacted with indole-2-carboxaldehyde 71 to form the tetracyclic oxirane 86, then subsequently treatment with sodium azide in acetone-water
afforded 81 in a 74% yield. This conversion gave a racemic product 81 because an achiral vinylsulfonium salt was used.

 Scheme 16. The formation of pyrroloindole

After the tricyclic product 81 was formed, it was converted into mesylate 82 (Scheme 15). The compound 82 was treated with preformed mixture of phosphorus oxychloride and dimethylformamide, followed by water to give 83 in 98% yield. Aldehyde 83 was then reduced by sodium cyanoborohydride in methanol to provide 70 in a 61% yield. It was found that low yield is due to poor solubility of 83 in methanol. After switching the solvent to a mixture of CH$_3$OH/DMF, the yield was improved to almost quantitative yield.
VI Synthesis of Core Ring System

Methodology developed earlier in our lab\textsuperscript{22}, was applied to the core ring system 92, which was successfully prepared by dimethyldioxirane (DMDO) oxidation in 57\% yield (Scheme 17). For this reaction, the first step is presumably to form an epoxide on indole double bond, which has an equilibration with zwitterionic intermediate 88. Then, water attack the zwitterionic intermediate 88 to form diol 89. A second equivalent of DMDO oxidized the diol 89 to form the intermediate 91 which eventually lead to the formation of hydroxylamine hemiketal ring system 92. Hemiketal 92 was a mixture of two diastereomers which was indicated by TLC. The mixture of diastereomers of 92 was not isolated during the study of the next several steps.
Scheme 17. Synthesis of core ring system

Because the hydroxyl hemiketal is not stable, it was necessary to protect this hydroxyl group (Scheme 18). One easy way to do that was protection by acetate group. The compound 92 was treated with acetic anhydride, Et$_3$N and DMAP in dichloromethane to give intermediate 93 in 70% yield. The tertiary alcohol didn’t react with acetic anhydride, so this condition has a good selectivity. The next step is dehydration of the tertial alcohol of intermediate 93. The first study on dehydration of compound 93 was tried by Burgess’ reagent. This reaction didn’t give the desired product, even heated to 55°C and 80°C. The best condition for the dehydration of 93 was found by using thionyl chloride with pyridine in THF$^{27}$. This reaction was conducted at -60°C to -10°C for 1 hour to give product 94 in an 81% yield.
Scheme 18. Protection and dehydration
VII. The Challenge of Making Hydroxymethyl Group

Once the double bond has been formed in the core system, the next key step is to convert this double bond into hydroxymethyl group. As reported by Danishefsky et al., it was more difficult than expected to complete this task. Because Danishefsky’s method required three steps to make hydroxymethyl group alternative methods should be developed to shorten the syntheses.

The hydroboration oxidation was tried first on compound 94 (Scheme 19). Borane in THF and BBr₂.Me₂S were tried and followed by standard oxidation with H₂O₂ in aqueous Na₂CO₃. The desired product was not obtained, instead TLC showed decomposed baseline by-product. Another reagent BHCl₂.dioxane, which reported by Brown in 2001 as a superior reagent for the selective hydroboration of terminal alkenes, was also tried. However, this superior reagent still didn’t work on the substrate 94.

Scheme 19. Hydroboration and oxidation (1)
The failure of the reaction may due to the labile group of azido and mesylate. Based on the results, the azido and mesylate group should be converted to aziridine before the hydroboration oxidation. Compound 94 in THF/water was treated with triphenylphosphine and DIPEA for seventeen hours at room temperature to give intermediate 96 in 41% yield (Scheme 20). The aziridine group of 96 is also necessary to be protected by benzyl chloroformate before the hydroboration oxidation. If it is not protected, it will face a selective protection with generated hydroxyl group. This is not a convenient choice. Compound 96 in dichloromethane/water was treated with benzyl chloroformate and sodium bicarbonate to give product 87 in moderate yield. The hydroboration was conducted by two different reagents BH₃·THF and BH₃·Me₂S in THF at room temperature on substrate 97 (Scheme 20). Both conditions didn’t give the desired product. It might be due to bulky protecting group, which blocked the approach of borane reagents.

Scheme 20. Hydroboration and oxidation (2)
Followed the results of hydroboration of fully protected intermediate 97, the next study of hydroboration oxidation should be on the unprotected hemiketal aziridine intermediate. Dehydration of compound 92 by thionyl chloride in THF and pyridine provided compound 99 in 42% yield (Scheme 21). Compound 99 was treated with triphenylphosphine and DIPEA in THF/water to give unprotected hemiketal aziridine 100 in 51% yield. The hydroboration and oxidation were conducted on the unprotected hydroxyl hemiketal aziridine 100. MS and TLC indicated the product generated, but HNMR showed the product was tertiary alcohol, no desired product was detected. The results indicated that hydroboration oxidation does work on this unprotected hemiketal aziridine 100, but did not provide the desired product 102, instead the the tertiary alcohol 101 was obtained.
Scheme 21. Hydroboration and oxidation (3)

The reason to give Markonikov product may be due to the chelation of borane to two oxygen of hydroxyl hemiketal (Scheme 22). Once the borane chelate with two oxygen, it will deliver hydrogen to terminal position and borane attach on 7 position to keep the chelation with two oxygen. After the oxidation, compound 101 was obtained. The reagents of hydroboration used in this reaction were not only BH$_3$.THF and BH$_3$.Me$_2$S, but also 9-BBN, and catecholborane. The 9-BBN and catecholborane did not give any product, which means the bulky reagents can not approach the double bond even with no protecting group on the hydroxyl group.
Scheme 22. The chelation in hydroboration
VIII. Hydrosilylation – Oxidation a Successful Way to Make Hydroxymethyl Group

Another alternative way to make the hydroxymethyl group from a double bond can be done by hydrosilylation-oxidation. Since Tamao developed this new methodology for the one-pot anti-Markonikov hydration of olefins to primary alcohols by platinum catalyzed hydrosilylation and then oxidation of resulting alkylsilane, this strategy has been recognized as a powerful method for the synthesis of various alcohols, ketones and hydroxyl ketones from simple available materials in recent years. In 2004, Jens Beckmann reported that the $\text{H}_2\text{PtCl}_6$ catalyzed hydrosilylation of the terpenes (+)-a-fenchene, (-)-2-methylene bornane, (+)-camphene and (-)-3-methylene fenchane by using $\text{HSiMe}_2\text{Cl}$ or $\text{HSiMeCl}_2$ proceeded with high regioselectivity and in some cases, with high diastereoselectivity. KF-assisted oxidation of the hydrosilylation products gave predominately endo-terpene alcohol. This method was tried on substrate 104 (Scheme 22). The compound 104 was treated with catalytic $\text{H}_2\text{PtCl}_6$ and 10 equivalent $\text{HSiMe}_2\text{Cl}$ in dichloromethane at room temperature, but unfortunately this condition didn’t work on this substrate.
Scheme 23. \( \text{H}_2\text{PtCl}_6 \) catalyzed hydrosilylation

In the early 2002, another potent Adams’ catalyst PtO\( _2 \) had been reported on hydrosilylation\(^{31} \). Charles Mioskowsk reported that although Speier’s catalyst (\( \text{H}_2\text{PtCl}_6\cdot6\text{H}_2\text{O} \)) was one of the most efficient, but if the substrates containing aminated functions Speier’s catalyst gave only moderate yields and low reproducibility probably as a result of poisoning of the catalyst by the amino function. From their results, PtO\( _2 \) catalyst proved to be a highly potent hydrosilylation catalyst compatible with a large range of functionalities including amino functions.

The precursor 108 of hydrosilylation was obtained from TMS protected hemiketal 106 (Scheme 24). The protection group had been switched to TMS on hemiketal was because of the much better yield for next step of forming aziridine. Once the aziridine 107 was obtained, it was treated with benzyl chloroformate to provide fully protected substrate 108 in 86% yield.
Compound 108 was treated with silane reagents and Adams’ catalyst PtO$_2$ in THF at 55°C for 24 hours (Scheme 25). These silane reagents included Cl$_3$SiH, ClMe$_2$SiH, Ph$_2$SiH, (EtO)$_2$MeSiH and ClPh$_2$SiH. Only the dimethylphenylsilane was found working on this substrate. This condition gave the silane compound 109 in 52% yield, but also gave double bond saturated by-product 110 in 48% yield. Once the silane compound 109 was treated with TBAF in THF and followed by potassium fluoride, potassium bicarbonate and hydrogen peroxide to give a diol with Cbz cleaved crude product. The crude product was treated with pyridine and one equivalent benzyl chloroformate in dichloromethane at 0°C to provide the desired diol 111 in 69% yield in two steps. Thus, the hydrosilylation-oxidation was successfully applied in the total synthesis of FR 900482 and FR 66979.
Scheme 25. Hydrosilylation with Adams’ catalyst PtO₂

The mechanism of catalysis of hydrosilylation as proposed by Chalk and Harrod is shown below (Scheme 26). The reaction includes oxidative addition, alkene insertion, and reductive elimination.

Scheme 26. Hypothesis of mechanism of hydrosilylation
IX. The Completion of 7-Epi-FR 66979 and 7-Epi-FR 900482

Since the ring expansion gave two diastereomers, the two diastereomers were able to get separation in compound 106 (Scheme 24). Each diastereomer was carried through the next several steps including the hydrosilylation-oxidation reaction to give minor diastereomer 111-1 and major diastereomer 111-2. Finally, the racemic diastereomer 111-1 and 111-2 were carried out for next two steps (Scheme 27). 111-1 or 111-2 was treated with trichloroacetyl isocyanate, followed by methanol and silica gel worked up to provide the urethane 112-1 and 112-2 in 87% yield. The strategy of global cleavage was tried by hydrogenation under the condition of hydrogen gas, 10% Pd/C in EtOAc. This condition only cleave benzyl and carboxybenzyl group. It does not like the description from Terashima, which they claimed 89% yield of cleavage by hydrogenation with 10% Pd/C in EtOAc. The other conditions of catalytic hydrogenation were tried by using 10% Pd/C, 20% Pd(OH)₂ and Pd black in MeOH or EtOH, from several hours to 24 hours. For these conditions, only benzyl and carboxybenzyl were cleaved in first several hours. After over 10 hours the Bom group was cleaved, but the product was decomposed at same time due to N-O bond connected to hemiketal was reduced. Fortunately, the catalytic transfer hydrogenolysis conducted by using 10% formic acid in methyl alcohol in the presence of a catalytic amount of palladium black at room temperature for 2.5 hours complete the global deprotection in a 83% yield. The structure of deprotection product was confirmed by HNMR and C¹³-NMR and compared with the structure of FR 66979 published on the Journal of
Antibiotics. The regret is that both of diastereomers give 7-Epi-FR66979. The major isomer 7-Epi-FR66979 was conducted under Swern oxidation condition to give 7-Epi-FR900482-2 in 60% yield. Unfortunately the minor 7-Epi-FR900482-1 was not available because there is no enough amount of the minor 7-Epi-FR66979-1 for oxidation.

Scheme 27. The Completion of 7-Epi-FR 66979 and 7-Epi-FR 900482
The structure of 7-Epi-FR 900482-2 was determined by 2-D NMR. Proton and carbon resonances of 7-Epi-FR 900482-2 were assigned by using COSY, NOESY, HSQC and HMBC experiments. The structure of 7-Epi-FR 900482-2 was established based on HMBC correlations. Relative stereochemistry of the C$_7$ and C$_9$, C$_{10}$ carbon centers was determined by strong NOE’s between the H$_7$ and H$_9$ protons (Scheme 28).

Scheme 28. The structure of 7-Epi-FR 900482-2

Proton NMR spectra of 7-Epi-FR 900482-2 were very close to those of previously published for minor isomer of 7-Epi (+)-FR900482 by Trost$^{16}$ (Table 1). Compared with major isomer of 7-Epi (+)-FR 900482 of Trost by HNMR and C$^{13}$ NMR, there are big difference with 7-Epi-FR 900482-2. Although Trost didn’t publish C$^{13}$ NMR of minor, it can be concluded that 7-Epi-FR 900482-2 is racemic minor 7-Epi (+)-FR 900482.
Table 1. Proton NMR Spectra of 7-Epi-FR 900482-2 and Minor Isomer of 7-Epi (+)-FR900482 of Trost

<table>
<thead>
<tr>
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<th>7-Epi-FR 900482-2</th>
<th>7-Epi (+)-FR 900482 (minor isomer of Trost)</th>
<th>Δδ(1H), (ppm)</th>
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</thead>
<tbody>
<tr>
<td>δ(1H), (ppm); J(H,H), (Hz)</td>
<td>δ(1H), (ppm); J(H,H), (Hz)</td>
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<td>9.66 (s, 1H)</td>
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<td>4.51 (dd, J=5.6, 11.5, 1H)</td>
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<td>4.24 (dd, J=2.9, 11.5, 1H)</td>
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<tr>
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<tr>
<td>3.42 (dd, J=2.9, 5.6, 1H)</td>
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<tr>
<td>2.33 (m, 2H)</td>
<td>2.23 (m, 2H)</td>
<td>0.1</td>
<td></td>
</tr>
</tbody>
</table>

The assigned structure of 7-Epi-FR 900482-2 was also supported by the experiments of two diastereomers 113 and 114 (Scheme 29). The yield from 114 for hydrosilylation is two times higher than from 113, which means that trans diastereomer 113 is too bulky to react with silane because both face are hindered. The cis diastereomer 114 is less hindered on bottom face and the silane can easily approach from there.

The possible reason for giving epimer can also be explained by the Scheme 29. The aziridine group with Cbz on trans isomer 113 blocked the top face. The top face is more hindered than bottom face, so the complex of silane will go bottom phase to approach the double bond. It will give cis silane compound with aziridine by syn addition. When the substrate is cis isomer 114, the bridge oxygen and TMS on
hydroxyl group blocked the top face, as the same reason, it will give cis silane compound with aziridine. As a final result, the generated hydroxyl methyl group is at same side with aziridine after oxidation.

Interestingly our 7-Epi-FR 66979 and 7-Epi-FR 900482 only showed one diastereomer from NMR analysis. The tautomerization in hydroxyl hemiketal is not fast than we imaged. One experiment was to put compound \( \text{116} \) in EtOAc solvent after TMS group on compound \( \text{115} \) was cleaved by TBAF (Scheme 30). In one to three hours, the TLC only showed one spot of one diastereomer. The TLC showed two spots of two diastereomers after 18 hours, but still the major spot is diastereomer \( \text{116} \), the minor spot is diasteromer \( \text{117} \). The TLC showed that diastereomer \( \text{116} \) didn’t change if there is no solvent after 18 hours. Due to the slow tautomerization of hydroxyl hemiketal, it is reasonable that the small amount of final product only show one diastereomer in NMR.
Scheme 30. Tautomerization in hydroxyl hemiketal
X. The Efforts on Approaching Natural Product of FR 66979 and FR 900482

1. Intramolecular hydrosilylation

Because the intramolecular hydrosilylation of allyl and homoallyl alcohols and subsequent oxidative cleavage of the organosilicon intermediates has been found to be widely applicable to the region- and stereo-controlled synthesis of a wide variety of 1,3-diols\(^{35}\), it could be a good conversion of cis hydroxyl hemiketal 118 and cis hydroxyl aziridine 120 to desired diol of natural product after oxidation since it will undergo syn addition from top face (Scheme 31).

![Scheme 31. The strategy of intramolecular hydrosilylation](image)
There is various catalyst were utilized in intramolecular hydrosilylation. In 2000, Robertson published the intramolecular hydrosilylation of diisopropylsilane derivative by using Wilkinson’s catalyst Rh(PPh₃)₃Cl in quantitative yield\(^\text{36}\). Both the hemiketal azido 118 and hemiketal aziridine 120 were tried by using Rh(PPh₃)₃Cl catalyzed intramolecular hydrosilylation after the diisopropylsilane 122 and 124 were made (Scheme 32). Unfortunately, this condition didn’t work on the two substrates. Since the catalyst PtO₂, H₂PtCl₆ and Pt(DVDS) have been used in intermolecular and intramolecular hydrosilylation\(^\text{32,37}\), they were applied to the substrate 124 by heating in THF for 17 hours. These conditions still didn’t give cyclic product 125. Not only diisopropylsilane compounds were tested, but also dimethylsilane and diphenylsilane compounds were tested with same condition. No one substrate gives cyclic silane compound.

Scheme 32. Rh(PPh₃)₃Cl catalyzed intramolecular hydrosilylation
Besides the catalytic intramolecular hydrosilylation, there is also radical intramolecular hydrosilylation reported by Roberts to give very good yield and selectivity. The substrate 126 was added into dioxane and followed by catalytic amount of di-tertbutyl hyponitrite and triphenylsilanethiol in two portions (Scheme 33). The mixture were heated at 60°C for three hours, HNMR indicated that the double bond didn’t change after work-up. Even this reaction was heated to reflux for overnight, HNMR still didn’t show the product.

![Scheme 33. Radical intramolecular hydrosilylation](image)

2. Less hindered intermolecular hydrosilylation

The intermolecular hydrosilylation oxidation from fully protected intermediates provided 7-Epi-FR 66979 and 7-Epi-FR 900482. For cis diastereomer 118, its top face is convex face and bottom face is concave face. In theory, the convex face is less hinder than concave face. If there is no protecting group on hydroxyl group of cis diastereomer 118, Ph₂MeSiH may access from top face to form beta configuration hydroxymethyl group after oxidation which is natural product required. The substrate 118 in THF was treated with PhMe₂SiH and catalytic amount PtO₂ at 50°C for 24 hours,
no product was detected, but starting material disappeared after work-up (Scheme 34). The experiment demonstrated that the mesylate and azido group were not stable at this condition. Hydrosilylation didn’t work on this substrate.

Scheme 34. Less hindered intermolecular hydrosilylation (1)

With the same idea, the unprotected hemiketal aziridine intermediate 120 was tried the hydrosilylation-oxidation (Scheme 35). The initial study had been tried in small scale. It did give two diastereomers. However, the yield is very low. The yield for desired product is only about 2%. LC-MS showed the double bond saturated by-product was major product. It is not clear why the chemoselectivity favored reduction of double bond. The efforts of changing chemoselectivity have been made by modifying the conditions of the reaction. The first try is to change the reaction temperature. The reaction didn’t work at 25°C, 35°C and 40°C. The lowest temperature to make the reaction working is 45°C, but at this temperature it didn’t improve yield and change chemoselectivity. At higher temperature 65°C, the reaction also favored the double bond saturated selectivity.

The second try is to change the amount of starting material dimethylphenylsilane. The condition of two equivalents, and six equivalents of
dimethyphenylsilane were used in the reaction. The results showed the more starting material, the faster reaction. Six equivalents of dimethylphenylsilane made the reaction completion in 24 hours. Two equivalent of dimethylphenylsilane made the reaction completion in 48 hours. The ratio of product and by-product didn’t change.

Scheme 35. Less hindered intermolecular hydrosilylation (2)

The third try is to change the silane reagent. In the beginning of the study of the hydrosilylation various silane reagents had been screened. Only the dimethylphenylsilane worked on our substrate. However, one of silane reagent didn’t try which is dimethylpyridylsilane. It has similar structure with dimethylphenylsilane and was reported by Yoshida\textsuperscript{39} to be used on hydrosilylation of alkenes and alkynes in high yield in the presence of a catalytical amount of RhCl(PPh\textsubscript{3})\textsubscript{3}. Because the 2-PyMe\textsubscript{2}SiH was more reactive than 3-PyMe\textsubscript{2}SiH and 4-PyMe\textsubscript{2}SiH in the rhodium-catalyzed reaction, 2-PyMe\textsubscript{2}SiH had been chosen to do the hydrosilylation of substrate.
131 (Scheme 36). Both the catalyst RhCl(PPh₃)₃ and PtO₂ were tested in the hydrosilylation at 45°C and 55°C, but neither product nor double bond saturated by-product were detected from the reaction.

Scheme 36. Less hindered intermolecular hydrosilylation (3)

3. Catalytic hydroboration-oxidation

In the early study of hydroboration, many borane reagents were used under normal conditions. No catalytic hydroboration was used in our studies. In the 90s, Evans and Fu reported Rhodium (I) catalyzed hydroboration by using catecholborane. For styrene, they reported that the selectivity favored Markovnikov product. In 1993, Doyle reported that catalyst dirhodium (II) tetraacetate gave the different selectivity of styrene in catalyzed hydroboration. Considered the selectivity, catalyst dirhodium (II) tetraacetate was our choice for the catalytic hydroboration. Compound 131 was treated with dirhodium (II) tetraacetate and catecholborane at room temperature (Scheme 37). TLC and LC-MS monitored the reaction, but indicated no reaction with this condition.
Another choice to make β hydroxyl methyl group on this specific substrate is to try the method of Danishefsky. In 1997, Weinreb reported high yield to install hydroxymethyl group on styrene terminal double bond for (-)-pancracine and (-)-coccinnine total synthesis by DMDO epoxidation and FeCl₃ opening. Our key hemiketal intermediate come from ring expansion of DMDO oxidation. When the functional group on the core intermediates had been transferred to protected intermediate 134, DMDO oxidation may directly give epoxide on double bond. Because there is no protecting group on hydroxyl hemiketal, it may favor to form β epoxide configuration. The desired β hydroxyl methyl group may be obtained after it is opened by FeCl₃ or SmI₂. The compound 134 was treated with DMDO at -20°C and monitored by TLC and MS (Scheme 38). The MS indicated the molecular weight of epoxide product 135 in 20 minutes, but TLC showed that the major spot was the decomposed base line product. After one hour, the reaction mixture was concentrated to remove solvent and purified by preparative thin-layer chromatography plate, but no product 135 was obtained.
To consider the compound stability for epoxidation and opening, it’s better to protect the hydroxyl group of hemiketal. The protecting group better be small, easily form and deprotectable. The acetate is a good candidate. The compound 134 was treated with acetic anhydride, Et₃N and catalytic DMAP in dichloromethane for 48 hours to provide compound 137 in 100% yield (Scheme 39).

With the fully protected compound 137 in hand, various epoxidation conditions had been explored (Scheme 40). DMDO was still unsuccessful to the protected 137. m-CPBA was tested on this substrate, but it didn’t give desired product. Seung Bum Park reported that m-CPBA epoxidation of styrene provided desired product in high yield in the presence of DTBMP (Di-tert-butyl-4-methylpyridine) as a proton sponge.\(^3\)
The compound 137 was treated with m-CPBA, DTBMP in dichloromethane for 5 hour, LC-MS indicated no desired product. Sharpless reported another efficient method for epoxidation of olefins including styrene in high yield by using aqueous $\text{H}_2\text{O}_2$ and catalytic MTO (methyltrioxorhenium)/pyridine\(^{44}\). Shortly afterward Herrmann reported pyrazole as a superior additive to pyridine because pyrazole is not affected under the reaction conditions while pyridine is oxidized to pyridine N-oxide during epoxidation\(^{45}\). Based on these information, Compound 137 was treated with aqueous $\text{H}_2\text{O}_2$, catalytic MTO/pyrazole in dichloromethane. No product was detected by MS, even after 3 days. In the formal total synthesis of (+)-FR 900482 by Paleo, they reported the epoxidation of enone by $\text{H}_2\text{O}_2$ with TBAF or TBHP (tert-butyl hydroperoxide) with Triton B\(^{15}\). Both conditions had been tried on compound 137, but neither one work.

Since no conditions found for direct epoxidation of substrate 137, the two steps condition of Danishefsky\(^8\) will be the choice. Osmylation of compound 137 provided a 4:3:2 mixture of diols 139 in 91% yield, which treated with diisopropyl azodicarboxylate and triphenylphosphine to gave a 7:1 mixture of compound 138 in 77% yield. Because the opening of epoxide of two diastereomer will give same
stereochemistry of hydroxyl compound by SmI$_2$ according Danishefsky’s report$^8$, the mixture of 138 and mixture of 139 were not isolated.

Scheme 41. Danishefsky’s condition for epoxidation

Compound 138 was treated with SmI$_2$, N,N-dimethylethanolamine in THF at -78°C. The LC-MS indicated that the epoxide was opened, but the acetate group had been cleaved (Scheme 42). Unprotected hemiketal epoxide 141 was then studied under same condition. Mass spectra indicated that the epoxide was opened, but hemiketal was reduced.
Since single electronic reduction could not provide the desired product, the compound 138 was conducted under the condition of the lewis acid mediated epoxide opening (Scheme 43). Unfortunately, lewis acid FeCl$_3$ or BF$_3$.etherate failed to open the epoxide. For similar substrate of 138, Danishefsky reported that the lewis acid FeCl$_3$ mediated epoxide opening didn’t work if the protecting group on hemiketal is MOM$^8$. They said it may be due to the consequence of labile ether functions at C$_5$ and C$_8$. It may be the similar reason for the failure of 138 with the labile C$_5$ ether and C$_8$ acetate functions.
Scheme 43. Lewis acid mediated epoxide opening

With these results, the MOM group on hemiketal is essential for this substrate. The compound 134 was treated with methyl chloromethyl ether and DIPEA in dichloromethane at room temperature to provide MOM protected intermediate 144 in 71% yield (Scheme 44). The mixture of diastereomer (3:1) diol 145 was obtained by osmylation of compound 144 in 85% yield. Diol 145 was then converted to epoxide mixture of diastereomer (3:1) 146 through routine transformations.
The epoxide intermediate 146 was treated with samarium diiodide and N,N-dimethylethanolamine in THF at -78°C to provide two mixture of diastereomer hydroxymethyl intermediate 147 (major) and 148 (minor) in 60% yield (Scheme 45). This reaction should be handled carefully since it will generate the elimination product 144 if the reagent SmI$_2$ was added too fast. From the previous study we know that 146 was a mixture of two diastereomers which major diastereomer was cis configuration hemiketal with aziridine and minor diastereomer was trans configuration hemiketal with aziridine. From Danishefsky’s SmI$_2$ epoxide opening reaction we know that hydroxymethyl group was trans configuration with hemiketal. Based on these informations, the structure of 147 and 148 could be assumed as drawn in Scheme 45.
Scheme 45. Epoxide opening by reduction of SmI$_2$

With successful installation of hydroxymethyl group at C$_7$ stereogenic center, our next goal was to form urethane on hydroxymethyl group. The final product FR 66979 may be obtained after deprotection if the urethane was successfully installed. Compound 147 was treated with large excess of trichloroacetyl isocyanate in dichloromethane. This reaction gave low yield after overnight reaction. Compound 148 didn’t work at the same condition, even after heating the reaction for overnight. The alternative route was to form phenyl carbonate, followed by the addition of NH$_3$ in isopropanol (Scheme 46). Quantitative yield was obtained when 147 was reacted with phenyl chloroformate, pyridine in dichloromethane. The yield of urethane was about 10% even after a long reaction period, detected by LC-MS. Compound 148 had no reactivity for the formation of phenyl carbonate, even with harsh condition. The results supported the assumed structures that 147 was cis configuration of hydroxymethyl group with MOM protected hemiketal and 148 was trans configuration of hydroxymethyl group with MOM protected hemiketal. Because in 148 the trans-aziridine blocked the bottom face and the top face has the MOM group, this prevented the reaction of 148 with trichloroacetyl isocyanate and phenyl chloroformate. Although
the phenyl carbonate trans 149 was easily prepared, urethane 150 was generated in low yield due to the large groups at the C₅, C₇ and C₈ positions. To avoid this problem, deprotection of MOM should be the next step after the formation of phenyl carbonate.

![Scheme 46. Formation of phenyl carbonate and urethane](image)

By using the deprotection condition of Danishefsky, phenyl carbonate 149 was treated with two equivalents of Ph₃CBF₄, and one equivalent of di-tert-butylpyridine at room temperature and monitored by LC-MS (Scheme 47). The reaction didn’t occur in two hours. After additional one equivalent of Ph₃CBF₄ was added and stirred for one hour, LC-MS indicated 152 and 153 were generated. 0.1mg of 152 and 0.2mg of 153
were obtained from 0.5mg of starting material 149 after work-up and purification. Their structures cannot be confirmed by HNMR with this low scale reaction.

Scheme 47. Deprotection of MOM by Ph$_3$CBF$_4$

Tays$^{46}$ reported the deprotection of MOM with high yield by 1.0M BCl$_3$ in dichloromethane at -40°C. This condition was applied to 148 (Scheme 48). 0.7mg of cis 148 was treated with BCl$_3$ in dichloromethane at -40°C to -10°C for one hour LC-MS indicated 154 was generated with 70% yield. Not only did this condition cleave the MOM group, but it also cleaved BOM and benzyl groups.

Scheme 48. Deprotection of MOM by BCl$_3$ (1)
The trans phenyl carbonate 149 was reacted in a similar way (Scheme 49). Unfortunately the reaction didn’t provide desired product even with longer reaction time and room temperature, but only cleaved the BOM group. This may be due to that the phenyl carbonate was a large group which made steric hinder near the MOM group.

![Scheme 49. Deprotection of MOM by BCl₃ (2)](image)

Finally the trans phenyl carbonate 155 was cleaved by stronger lewis acid BBr₃ at -40°C to -10°C in two hours. MS indicated that the MOM, benzyl, and benzyl carbamate groups were cleaved at same time (Scheme 50). But the LC-MS also showed many by-product peaks. Due to low scale reaction, the product was not isolated after work-up. The crude product was treated with 2M NH₃ in iPrOH to give final product FR 66979 which was indicated by MS. The crude HNMR also showed the peaks of product. The pure product had not been obtained after the purification by preparative thin-layer chromatography plate, so the final product had not been confirmed by NMR.
Scheme 50. Deprotection of MOM by BBr$_3$

5. Second time to work out the hydrosilylation oxidation

Although the methodology of making the hydroxylmethyl group by epoxidation and opening worked on Danishefsky’s intermediate 25 and our intermediate 134, Danishefsky’s synthesis required 10 steps to get final product after installed the hydroxylmethyl group. By using this methodology in our total synthesis had trouble cleaving the protecting group. We felt it is still worth developing the conditions for the hydrosilylation oxidation in our substrate. Further study on the hydrosilylation oxidation of the less hindered substrate was conducted on the substrate 134 (Scheme 51). It was found that if the concentration was low, 3.2µM/mL, the reaction of hydrosilylation with 10% PtO$_2$ provided an acceptable yield of product (54%) and the double bond saturated by-product was dramatically decreased. After oxidation, the reaction gave two diastereomers. The HNMR of each diastereomer was different with the same intermediate of two diastereomers of epi-FR66979. Because the structure of 158 has four diastereomers and two diastereomers from fully protected intermediate already gave two epimers, the remaining should give natural product. The finalization of the total synthesis with this intermediate was not finished since we didn’t get enough
of this intermediate. It is the great hope for the future if we prepare more the precursor 134 of hydrosilylation the natural product will be obtained with short steps from this unique method of hydrosilylation and oxidation.

Scheme 51. Hydrosilylation and oxidation in very dilute solution
XI. Conclusions

This total synthesis started from 3-hydroxymethylphenol in six steps by Hemetsberger-Knittel indole synthesis to make Methyl 4-(benzyloxy)-6-((benzyloxymethoxy)methyl)-1H-indole-2-carboxylate 69 in overall 34.7% yield. In additional six steps, the indole 69 was converted to racemic tricyclic pyrroloindole 60 in overall 49% yield which involved the method to make pyrroloindole by using vinylsulphonium salt developed early in our lab.

The DMDO ring expansion oxidation was successfully applied in the total synthesis. The pyrroloindole 60 was oxidized to hemiketal core 82 by DMDO in 57% yield. The installation of hydroxymethyl group is a challenge. Hydroboration only worked on unprotected hydroxyhemiketal, but gave the wrong regional isomer. Intermolecular hydrosilylation-oxidation successfully afforded the hydroxymethyl compound 100 in 35% yield. After the conversion of two diastereomers 101 and 103 to urethane 102 and 104, the global deprotection by catalytic transfer hydrogenation gave epi-FR66979 in 83% Yield. The Swern oxidation of epi-FR66979 provided epi-FR900482 in 60% yield. Overall the total synthesis was completed in 21 steps to provide epi-FR66979 in 1.06% yield and in 22 steps to provide epi-FR900482 in 0.64% yield.

The effort to install the beta hydroxymethyl group involved intramolecular hydrosilylation-oxidation, but it was not successful. Further efforts involved the epoxidation and opening by samarium diiodide reduction. The hydroxymethyl group had been successfully installed. Final product was not obtained due to the deprotection
issues. Another effort to work out hydrosilylation oxidation on less hindered hydroxylamine hemiketal intermediate was successful. Hydrosilylation oxidation with unprotected hydroxyl hemiketal substrate 134 in very dilute solution provide modest of yield of desired product. It will provide natural product with few steps if more intermediate 134 is prepared in the future.
XII. Experiment

General: All melting points were determined by MEL-TEMP® Laboratory Devices, USA melting point apparatus. Nuclear magnetic resonance (NMR) spectra were acquired using a Bruker Avance 500 Digital NMR (500 MHz) spectrometer and Varian 600 MHz spectrometers. NMR chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane (TMS) or relative to the residual proton signal of CHCl₃ (7.24 ppm) or the carbon signal of ¹³CDCl₃ (77.0 ppm). The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), and doublet of doublets (dd). Infrared (IR) spectral measurements were carried out with a Thermo Nicolet/Avatar 360 FT IR spectrometer. Low resolution mass (MS) spectra are taken with Waters Micromass ZQ MM1mass spectrometer, and high resolution mass (HRMS) spectra were obtained on a Thermo Electron High Resolution Orbitrap mass spectrometer.

All reactions involving air or moisture sensitive reagents were conducted under nitrogen atmosphere with dry solvents. Unless otherwise noted, reagents were obtained from commercially available sources and use without further purification. The anhydrous solvents tetrahydrofuran (THF), methylene chloride (CH₂Cl₂), toluene, dimethylsulfoxide (DMSO), N,N-dimethylformamide (DMF) were obtained from Aldrich and Acros and used as received.
Reaction monitored by thin-layer chromatography (TLC) using ANALTECH TLC Plates (Scored 10 x 20 cm, 250 microns). Flash column chromatography was performed on Biotage Flash Horizon purification system and Analogix IntelliFlash 310 purification system by using 8g ~ 300g silica gel pre-packed columns. Preparative thin-layer chromatography purifications were carried out on ANALTECH Pre. TLC Plates (20 x 20 cm, 1000 microns).

3-Hydroxybenzyl acetate (75). To 3-hydroxymethylbenzyl alcohol (74) (29.00g, 0.24mmol) in ethyl acetate/hexanes (320mL/640mL) was added 250.00g of Al₂O₃. The resulting mixture was heated at reflux for two days which TLC indicated about half of starting material reacted. Continued to reflux the reaction for another two days, which TLC showed the reaction almost completed. The reaction mixture was cooled to room temperature, filtered to remove Al₂O₃. The filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (Ethyl acetate/hexane 2:3) to give 75 (36.00g, Yield 91%) as a white solid. mp 48-49°C. IR: 3400.0, 2918.8, 1713.1, 1455.9, 1261.4, 750.2 cm⁻¹; HNMR (500 MHz, CDCl₃) δ 7.24 (t, J=7.88 Hz, 1H), 6.92 (d, J=7.57 Hz, 1H), 6.84 (s, 1H), 6.79 (d, J=8.20 Hz, 1H), 5.06 (s, 2H), 4.88 (s, 1H), 2.11 (s, 3 H); ¹³C NMR (125 MHz,
4-Formyl-3-hydroxybenzyl acetate (76). To a solution of 3-hydroxybenzyl acetate (75) (15.60g, 93.87mmol) in toluene (500mL) was added SnCl₄ (1.2mL, 10.3mmol) and tri-n-octylamine (16.4mL, 37.5mmol) at room temperature. The resulting mixture was stirred at room temperature for 20min, then paraformaldehyde (8.45g, 0.28mol) was added and the mixture was heated at 95°C for 16 hours. The reaction mixture was cooled to room temperature, poured into ice water, then acidified to PH=1 with 1N HCl. Extracted with EtOAc. The separated organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/CH₂Cl₂ 1:24) to give 76(15.1g, Yield 83%) as a white solid. mp 42~43°C. IR: 3401.2, 2921.0, 1745.5, 1663.2, 1222.8, 1046.4, 804.7, 748.6 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ 11.06 (s, 1H), 9.88 (s, 1H), 7.55 (d, J=8.51 Hz, 1H), 6.97 (d, J=6.6 Hz, 1H), 6.96 (s, 1H), 5.12 (s, 2H), 2.15 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) 196.5, 162.2, 146.3, 134.4, 120.5, 119.0, 116.5, 65.5, 21.3; HRMS calcd for C₁₀H₁₁O₄(M+H) 195.0657, found 195.0666
2-(Benzyloxy)-4-(hydroxymethyl)benzaldehyde (77). K$_2$CO$_3$ (46.97g, 0.25mol) was added into a solution of MeOH (300mL) and CHCl$_3$ (600mL) and heated at reflux for 20 minutes, followed by 4-formyl-3-hydroxybenzyl acetate (76) (11.0g, 56.6mmol). Benzyl bromide (6.9mL, 57.7mmol) was added after 5min and the reaction mixture was heated at reflux for 24 hours. The solution was poured into an ice water and extracted with ether (2x500mL). The combined organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Ethyl acetate/hexane 3:7) to give 77 (13.10g, Yield 98%) as a pale yellow oil. IR: 3582.7, 3406.2, 2918.2, 1678.4, 1426.8, 1256.2, 1156.6, 810 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 10.51 (s, 1H), 7.83 (d, J=7.88 Hz, 1H), 7.46-7.34 (m, 5H), 7.13 (s, 1H), 6.99 (d, J=7.88, 1H), 5.20 (s, 2H), 4.75 (s, 2 H); $^{13}$C NMR (125 MHz, CDCl$_3$) 189.9, 161.8, 150.1, 136.4, 129.2, 129.1, 128.7, 127.8, 124.7, 119.2, 111.1, 70.9, 65.1; HRMS calcd for C$_{13}$H$_{15}$O$_3$ (M+H) 243.0994, found 243.0998
2-(Benzyloxy)-4-((benzyloxymethoxy)methyl)benzaldehyde (78). To 2-(Benzyloxy)-4-(hydroxymethyl)benzaldehyde (77) (15.20g, 62.74mmol) in methylene chloride (600mL) was added n-Bu₄NI, (2.32g, 6.27mmol), DIPEA (43.7mL, 251mmol), followed by benzyl chloromethyl ether (26.2mL, 188mmol) at 0°C. The resulting mixture was stirred at room temperature for 17 hours. The originally pale yellow reaction mixture was turned to orange solution. It was washed with saturated sodium bicarbonate and brine. The separated organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Ethyl acetate/hexane 1:4) to give 78 (18.81g, Yield 83%) as a pale yellow oil. IR: 3484.3, 3031.8, 2881.1, 1682.5, 1429.0, 1257.7, 1049.2, 812.5, 736.6 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ 10.52 (s, 1H), 7.84 (d, J=7.88 Hz, 1H), 7.46-7.28 (m, 10H), 7.08 (s, 1H), 6.00 (d, J=7.88, 1H), 5.18 (s, 2H), 4.86 (s, 2 H), 4.68 (s, 2H), 4.65 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) 189.8, 161.6, 147.2, 138.0, 136.4, 129.7, 129.1, 129.1, 129.0, 128.9, 128.7, 128.3, 128.3, 128.2, 127.9, 127.8, 124.8, 120.2, 112.0, 94.7, 70.9, 70.2, 69.3; HRMS calcd for C₂₃H₂₃O₄ (M+H) 363.1588, found 363.1585
Methyl 4-(benzyl oxy)-6-((benzyl oxymethoxy)methyl)-1H-indole-2-carboxylate (79). To a solution of 2-(Benzyloxy)-4-((benzyl oxymethoxy)methyl) benzaldehyde (78) (16.20g, 44.70mmol) and ethyl azidoacetate (31.99g, 223mmol) in anhydrous methanol (250mL) was added sodium methoxide in methanol (50mL, 268mmol) dropwise at -30°C ~ -40°C. The reaction was warmed up to 3°C and stirred at this temperature for 18 hours which TLC indicated the reaction completed. Ice water and saturated ammonium chloride solution were added and the mixture was extracted with ether. The organic layer was washed with brine. It was dried over anhydrous MgSO₄. Dry xylene (30mL) was added into the solution and concentrated under reduced pressure to give a clear oil. The oil was quickly added over refluxing anhydrous xylene. The resulting solution was heated to 142°C for 3hrs under N₂. TLC showed the reaction completed. The xylenes were removed in the rotary evaporator. The residue was crystallized by CH₂Cl₂/Hexane (1/2). The filtrate was purified by flash column chromatography (EtOAc/CH₂Cl₂ 1:19) to give 79 (11.76g, Yield 61%) as a pale yellow solid. mp 114.2~114.5°C. IR: 3327.6, 2913.5, 1689.4, 1438.8, 1275.4, 1133.7, 814.1, 745.1, 697.8 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ 8.90 (s, 1H), 7.49 (d, J=6.94 Hz, 2H), 7.41 (d, J=7.25 Hz, 2H), 7.39-7.28 (m, 6H), 7.26 (s, 1H), 6.02 (s, 1H), 6.60 (s, 1H), 5.19 (s, 2H), 4.86 (s, 2 H),
4.72 (s, 2H), 4.66 (s, 2H), 3.93 (s, 3H); $^{13}$C NMR (125 MHz, CDCl3) 162.7, 154.2, 138.5, 138.3, 137.4, 137.2, 129.0, 128.9, 128.4, 128.2, 127.8, 126.6, 119.3, 107.2, 104.9, 101.8, 94.3, 70.5, 70.3, 70.0, 52.4; HRMS calcd for C$_{26}$H$_{26}$NO$_5$ (M+H) 432.1811, found 432.1799.

(4-(Benzyloxy)-6-((benzyloxymethoxy)methyl)-1H-indol-2-yl)methanol (80). To a solution of Methyl 4-(benzyl oxy)-6-((benzyloxymethoxy)methyl)-1H-indole-2-carboxylate (79) (6.99g, 16.2mmol) in anhydrous methylene chloride (330mL) was added slowly DIBAL (48.6mL, 48.6mmol) at -78°C. After 3 hours reacted at -78°C, the mixture was quenched by addition of 100mL 1N HCl at same temperature. The solid was filtered. The filtrate was extracted with methylene chloride and washed with saturated sodium bicarbonate solution and brine. The organic layer was dried by anhydrous MgSO$_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Ethyl acetate/hexane 3:2) to give 80 (6.25g, yield 95%) as a pale yellow solid. mp 82.8-83.1°C. IR: 3422.0, 3030.5, 2878.6, 1621.6, 1453.3, 1264.4, 1164.5, 820.6, 736.5, 697.6 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.41 (s, 1H), 7.54 (d, J=7.57 Hz, 1H), 7.47-7.33 (m, 8H), 7.01 (s, 1H), 6.66 (s, 1H), 6.60 (s, 1H), 5.25 (s, 2H), 4.89 (s, 2H), 4.82 (s, 2H), 4.76 (s, 2H), 4.72 (s, 2H); $^{13}$C NMR (125
4-(Benzyloxy)-6-((benzyloxymethoxy)methyl)-1H-indol-2-carbaldehyde (71). To a solution of (4-(Benzyloxy)-6-((benzyloxymethoxy)methyl)-1H-indol-2-yl)methanol (80) (10.66g, 26.4mmol) in anhydrous methylene chloride (250mL) was added slowly MnO₂ (35.7g, 0.40mol) at room temperature. The reaction was heated at reflux for 40 minutes. TLC indicated the reaction completed. Filtered it through celite and washed by hot CH₂Cl₂ (200mL). The filtrate was concentrated to dryness to give 71 (9.0g, yield 85%) as a pale yellow solid. mp 117.5-117.8 °C. IR: 3293.1, 2937.57, 2880.4, 1658.6, 1572.8, 1270.4, 1147.8, 808.6, 755.5, 694.2 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ 9.80 (s, 1H), 9.34 (s, 1H), 7.53 (d, J=6.94 Hz, 2H), 7.47-7.42 (m, 3H), 7.36-7.32 (m, 1H), 7.07 (s, 1H), 6.63 (s, 1H), 5.23 (s, 2H), 4.90 (s, 2H), 4.76 (s, 2H), 4.70 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) 182.0, 154.8, 139.8, 139.5, 138.2, 137.1, 135.6, 129.0, 128.9, 128.5, 128.3, 128.2, 127.9, 119.5, 113.4, 105.0, 101.7, 94.4, 70.4, 70.4, 70.1; HRMS calcd for C₂₅H₂₆NO₄ (M+H) 404.18618, found 404.18478.
1-azido-8-(benzyloxy)-6-((benzyloxymethoxy)methyl)-2,3-dihydro-1H-
pyrrolo[1,2-a]indol-2-ol (81). To a solution of 4-(Benzyloxy)-6-
((benzyloxymethoxy)methyl)-1H-indol-2-carbaldehyde (71) (9.0g, 22.4mmol) in THF
(300mL) was added NaH under N₂ at 0°C. After 20min, diisopropylvinylsulfonium
triflate (13.4g, 44.8mmol) in 20mL THF was added slowly. Then the reaction mixture
was stirred at room temperature for 14 hours. NaN₃ in 108mL of acetone/H₂O (1/1) was
added and stirred for another 20 hours. H₂O (300mL) was added and the aqueous
solution was extracted with CH₂Cl₂ (2x200mL). The combined organic layer was dried
over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product
was purified by flash column chromatography (EtOAc/CH₂Cl₂ 2:23) to give 81 (7.84g,
Yield 74%) as a pale yellow solid. mp 95.4-95.7°C. IR: 3407.5, 2880.4, 2095.8,
1568.67, 1446.1, 1245.9, 1045.6, 739.2, 698.3 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ
7.55-7.50 (m, 2H), 7.46 -7.31(m, 8H), 6.93 (s, 1H), 6.71 (s, 1H), 6.65 (s, 1H), 5.24 (s,
2H), 4.81 (s, 2 H), 4.81 (d, J=2.52 Hz, 1H), 4.76 (s, 2H), 4.69 (s, 2H), 4.37 – 4.30(m,
1H), 3.95-3.89 (m, 1H), 2.50 (d, J=4.73 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) 153.2,
138.3 137.7, 136.4, 134.7, 133.5, 128.9, 128.4, 128.3, 128.2, 127.8, 123.0, 103.8, 102.2,
1-azido-8-(benzyloxy)-6-((benzyloxymethoxy)methyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-2-yl methanesulfonate (82). To a solution of 1-azido-8-(benzyloxy)-6-((benzyloxymethoxy)methyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-2-ol (81) (7.84g, 16.7mmol) in CH$_2$Cl$_2$ (190mL) was added Et$_3$N (9.3mL, 66.6mmol) and MsCl (2.6mL, 33.4mmol) dropwise at 0°C. The reaction was stirred at 0°C for 2 hours which TLC indicated the reaction completed. Diluted it with ether and washed it with water. Aqueous layer was extracted with ether (2x200mL). Combined organic layer was dried over anhydrous MgSO$_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Ethyl acetate/hexane 2:3) to give 82 (9.15g, Yield 99.9%) as a pale yellow solid. mp 87.9-88.2 °C. IR: 3435.0, 2872.2, 2099.9, 1621.8, 1572.8, 1442.0, 1364.4, 1241.8, 1168.2, 1045.6, 739.2, 694.2 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.52-7.27 (m, 10H), 6.92 (s, 1H), 6.73 (s, 1H), 6.64 (s, 1H), 5.52-5.47 (m, 1H), 5.21(s, 2H), 5.16 (d, J=2.20Hz, 1H), 4.86 (s, 2H), 4.73 (s, 2H), 4.66 (s, 2H), 4.53 (dd, J=5.13Hz, J=12.45Hz, 1H), 4.27 (dd, J=2.20Hz, J=12.45Hz, 1H), 3.11 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) 162.4, 157.0, 147.1, 139.3,
1-azido-8-(benzyloxy)-6-((benzyloxymethoxy)methyl)-9-formyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-2-yl methanesulfonate (83). Phosphorus oxychloride (12.5mL, 133.6mmol) was added dropwise into anhydrous DMF (81mL) at 0°C under N₂. After the mixture was stirred for 45 minutes, 1-azido-8-(benzyloxy)-6-((benzyloxymethoxy)methyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-2-yl methanesulfonate (82) (9.16g, 16.7mmol) in anhydrous THF (420mL) was added slowly at 0°C. The solution was stirred at room temperature for 20 hours. Then water (95mL) was added and stirred for 4 hours at room temperature. The aqueous layer was extracted with CH₂Cl₂ (3x200mL). The combined organic layer was dried over anhydrous MgSO₄. Filtered and concentrated to dryness. Purified it by flash column chromatography (Ethyl acetate/hexane 1:1) to give 83 (9.44 g, Yield 98%) as a yellow solid. mp 98.5-98.7°C. IR: 2928.7, 2114.9, 1656.7, 1541.6, 1366.4, 1172.8, 1048.2, 743.3, 694.2 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ 10.48 (s, 1H), 7.52-7.32 (m, 10H), 7.01 (s, 1H), 6.87 (s, 1H), 5.62 (s, 1H), 5.19 (s, 2H), 5.51 (d, J=4.4Hz, 1H), 5.27 (s,
2H), 4.90 (s, 2H), 4.78 (s, 2 H), 4.70 (s, 2H), 4.53 (dd, J=4.73Hz, J=12.93Hz, 1H),
4.40 (d, J=12.93Hz), 3.14 (s, 3H). $^{13}$C NMR (125 MHz, CDCl3) 187.9, 154.3, 141.5,
136.8, 136.0, 134.3, 129.2, 128.9, 128.7, 128.3, 128.2, 128.0, 113.8, 104.8, 104.0, 94.5,
84.7, 70.9, 70.2, 70.1, 62.9, 50.7, 39.2; HRMS calcd for C$_{29}$H$_{29}$N$_4$O$_7$S (M+H) 577.1757,
found 577.1746.

![Chemical Structure](image)

1-azido-8-(benzyloxy)-6-((benzyloxymethoxy)methyl)-9-methyl-2,3-dihydro-
1H-pyrrolo[1,2-a]indol-2-yl methanesulfonate (70). 1-azido-8-(benzyloxy)-6-
((benzyloxymethoxy)methyl)-9-formyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-2-yl
methanesulfonate (83) (9.63g, 16.7mmol) in 300mL of MeOH and 70mL of DMF was
added NaBH$_3$CN (4.21g, 66.8mmol) at 0°C. At the same time, 2.0N HCl in ether was
added dropwise with indicator of Methyl-orange (a few crystals) to keep solution was
acidic condition. The reaction mixture was stirred at room temperature for 3 hours,
TLC indicated the reaction completed. The mixture was concentrated under reduced
pressure. The residue was diluted with water and extracted with CH$_2$Cl$_2$ (2x200mL).
Organic layer was dried over anhydrous MgSO$_4$ and filtered, concentrated down.
Purified it by flash column chromatography (Ethyl acetate/hexane 2:3) to give 70 (9.30
g, Yield 99%) as a white solid mp 95.3-95.5 °C. IR: 2929.8, 2103.2, 1565.2, 1364.7,
1176.1, 1044.3, 738.1, 697.6 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) 7.57-7.34 (m, 10H), 6.90 (s, 1H), 6.64 (s, 1H), 5.56-5.52 (m, 1H), 5.23(s, 2H), 5.21(s, 1H), 4.91 (s, 2H), 4.78 (s, 2H), 4.73 (s, 2H), 4.53 (dd, J=5.04Hz, J=11.98Hz, 1H), 4.28 (dd, J=1.89Hz, J=11.98Hz, 1H), 3.15 (s, 3H), 2.61 (s, 3H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) 155.1, 138.4, 137.7, 134.8, 134.3, 132.2, 128.9, 128.9, 128.7, 128.3, 128.1, 127.7, 108.5, 103.4, 101.7, 94.2, 85.3, 70.6, 70.4, 70.0, 62.3, 49.4, 39.1. HRMS calcd for C\(_{29}\)H\(_{31}\)N\(_4\)O\(_6\)S (M+H) 563.1939, found 563.1964.

\[
\text{1-azido-8-(benzyloxy)-6-(benzyloxymethoxymethyl)-9-hydroxy-9a-}
\text{trimethylsilyloxy-4,9a-epoxy-9-methyl-2,3-dihydro-2-(methanesulfonyloxy)-1H-}
\text{pyrrolo[1,2-a]-indole (156). To a solution of 1-azido-8-(benzyloxy)-6-}
\text{((benzyloxymethoxy)methyl)-9-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-2-yl}
\text{methanesulfonate (70) (150mg, 0.27mmol) in acetone (2mL) was added DMO}(\text{(16mL, 0.80mmol) and water (0.2mL) at 0°C. The reaction mixture was stirred at 0°C for 3 hours, which TLC showed the reaction almost completed. The mixture was concentrated under reduced pressure and diluted it with EtOAc. Washed with brine. Dried it over anhydrous Na\(_2\)SO\(_4\). Filtered and concentrated to dryness to give 141mg of crude product.}
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To above crude product in anhydrous CH$_2$Cl$_2$ (2mL) was added Et$_3$N (0.11mL, 0.81mmol), TMSCl (0.069mL, 0.41mmol) and DMAP (3.2mg, 0.027mmol). The mixture was stirred at 0°C for 3 hours. The mixture was diluted with EtOAc and washed with saturated aqueous NaHCO$_3$, and brine. It was dried over anhydrous Na$_2$SO$_4$, then filtered and concentrated down. Purified it by flash column chromatography (Ethyl acetate/hexane 2:3) to give **156** (74 mg, Yield 40%) as a pale yellow oil. IR: 2913.5, 2114.4, 1427.9, 1358.9, 1253.6, 1177.3, 1053.8, 745.1 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$7.51-7.32 (m, 10H), 6.87 and 6.75 (s, 1H), 6.61 and 6.43 (s, 1H), 5.14 (s, 2H), 4.89 and 4.86(s, 2H), 4.79-4.72 (m, 1H), 4.68 and 4.66 (s, 2H), 4.61 and 4.60 (s, 2H), 4.49(dd, J=8.19Hz, J=13.56Hz, 0.6H), 4.45 (d, J= 10.7Hz, 0.4H), 4.33 (s, 0.6H), 3.86 (d, J= 10.4Hz, 0.4H), 3.76-3.78 (m, 0.4H), 3.51-3.46 (m, 0.6H), 3.11 and 3.04 (s, 3H), 1.64 and 1.60 (s, 3H), 0.322 and 0.20(s, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$) 157.6, 148.2, 140.2, 138.1, 135.7, 129.4, 129.2, 129.1, 128.9, 128.7, 128.4, 128.3, 128.2, 118.3, 111.0, 107.1, 107.0, 100.8, 94.7, 94.6, 76.4, 74.0, 71.5, 70.2, 69.3, 61.3, 60.1, 38.7, 30.1, 24.1, 22.4, 2.4, 2.2. HRMS calcd for C$_{32}$H$_{41}$N$_4$O$_9$SS$_5$(M+H) found 685.2358 w/error 0.0492ppm.
1-azido-8-(benzyloxy)-6-(benzyloxymethoxymethyl)-9-methylene-9a-trimethylsilyloxy-4,9a-epoxy-9-methyl-2,3-dihydro-2-(methanesulfonyloxy)-1H-pyrrolo[1,2-a]-indole (106). To a solution of 1-azido-8-(benzyloxy)-6-(benzyloxymethoxymethyl)-9-hydroxy-9a-trimethylsilyloxy-4,9a-epoxy-9-methyl-2,3-dihydro-2-(methanesulfonyloxy)-1H-pyrrolo[1,2-a]-indole (156) (300mg, 0.43mmol) in THF (3mL) was added DIPEA (0.28mL, 1.72mmol), followed by SOCl₂ (0.064mL, 0.88mmol) in THF (1mL) at -60°C. The mixture was stirred at -60°C ~ -10°C for 1 hour. Mass spectrum indicated the reaction completed. The reaction was quenched by the addition of saturated aqueous NaHCO₃. The reaction mixture was diluted with EtOAc and washed with water, 1N aqueous HCl and brine. It was dried over anhydrous Na₂SO₄. Filtered and concentrated to dryness. Purified it by flash column chromatography (Ethyl acetate/hexane 2:3) to give racemic 106-1 (149mg) and racemic 106-2 (80mg, Yield 80%) as a yellow oil. IR: 3031.7, 2937.3, 2115.3, 1608.4, 1567.4, 1343.6, 1051.1, 879.9, 738.5, 698.5 cm⁻¹. $^1$H NMR (500 MHz, CDCl₃) 106-1: δ 7.50-7.31 (m, 10H), 6.87 (s, 1H), 6.86 (s, 1H), 6.62 (s, 1H), 5.81 (s, 1H), 5.22-5.12 (m, 2H), 4.73 (s, 1H), 4.86s (s, 2H), 4.67 (s, 2H), 4.61(s, 2H), 4.26-4.17 (m, 1H), 3.86 (d, J=10.4Hz, 1H), 3.79-3.66 (m, 1H), 3.04 (s, 3H), 0.20 (s, 9H). $^{13}$C NMR (125 MHz, CDCl₃) 106-1: 159.6, 158.4, 145.7, 139.7, 136.5, 134.1, 129.1, 128.9, 128.7, 128.4, 128.3, 127.4, 120.6, 113.2, 109.0, 101.9, 94.6, 73.5, 71.4, 70.4, 70.1, 69.2, 65.8, 59.7, 38.7, 2.2.

HRMS calcd for C₃₂H₃₉N₄O₈SSi(M+H) found 667.22579 w/error 1.83ppm.

$^1$H NMR (500 MHz, CDCl₃) 106-2: δ 7.49 (s, 1H), 7.54-7.33 (m, 8H), 7.08 (s, 1H), 6.81 (s, 1H), 6.73 (s, 1H), 5.77 (s, 1H), 5.19 (s, 2H), 4.83 (s, 2H), 4.77-4.75 (m,
1H), 4.66 (s, 2H), 4.58 (s, 2H), 4.03 (d, J=3.15Hz, 1H), 3.89 and 3.87 (d, J=3.47Hz, 1H), 3.46 and 3.43 (s, 1H), 2.42 (s, 3H), 0.22 (s, 9H). $^{13}$C NMR (125 MHz, CDCl3) **106-2**: 158.1, 148.0, 139.6, 139.1, 138.1, 136.7, 129.1, 128.9, 128.7, 128.5, 128.3, 128.2, 128.0, 118.0, 114.1, 113.1, 108.9, 98.7, 94.4, 74.6, 71.2, 70.4, 70.1, 69.2, 64.3, 62.5, 52.6, 45.3, 38.4, 30.3, 29.4, 2.1.

HRMS calcd for C$_{32}$H$_{39}$N$_4$O$_8$SS$_i$(M+H) found 667.2270 w/error 1.7984ppm.

**Racemic 107-1 and Racemic 107-2.** To a solution of compound **106-1 or 106-2** (130mg, 0.20mmol) in THF/water (2.0mL/0.2mL) was added DIPEA (0.089mL, 0.54mmol) and PPh$_3$ (82mg, 0.31mmol). The reaction mixture was stirred at room temperature for 24 hours. The mixture was diluted with dichloromethane and washed with brine. The organic layer was dried over anhydrous Na$_2$SO$_4$, then filtered and concentrated down. It was purified by flash column chromatography (Ethyl acetate/hexane 3:2) to give **107**. (84mg, Yield 70%) as a yellow oil. IR: 2917.1, 1725.8, 1438.8, 1275.4, 1111.9, 1050.2, 752.3 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) **107-1**: 8.74-7.27 (m, 10H), 6.65 (s, 1H), 6.48 (s, 1H), 6.43 (s, 1H), 5.72 (s, 1H), 5.11 (s, 2H), 4.81 (s, 2H), 4.63(s, 2H), 4.57 (s, 2H), 3.91 (d, J= 13.9Hz, 1H), 3.71-3.55 (m, 2H), 2.75 (d, J=6.6Hz, 1H), 2.37 (d, J=5.86Hz, 1H), 0.23 (s, 9H). $^{13}$C NMR (125 MHz, CDCl3) **107-1**: 158.4, 138.4, 138.2, 137.0, 133.1, 132.6, 132.5, 132.4, 129.0, 128.9, 128.6, 128.3,
115.4, 115.2, 113.0, 111.2, 106.5, 94.3, 74.1, 71.1, 69.9, 69.4, 65.3, 62.5, 52.9, 40.0, 30.3, 30.1, 27.1, 2.5.

HRMS calcd for C$_{31}$H$_{37}$N$_2$O$_5$S$_i$ (M+H) found 545.24717 w/error -1.30ppm.

$^1$H NMR (500 MHz, CDCl$_3$) **107-2**: 87.50-7.28 (m, 10H), 6.74 (s, 1H), 6.54 (s, 1H), 6.49 (s, 1H), 5.83 (s, 1H), 5.18-5.08 (m, 2H), 4.83 (s, 2H), 4.64 (s, 2H), 4.59 (s, 2H), 3.79 (d, J=14.64Hz, 1H), 3.62-3.53 (m, 1H), 2.22 (s, 2H), 0.18 (s, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$) **107-2**: 158.7, 139.1, 136.7, 129.1, 129.0, 128.9, 128.6, 128.3, 128.2, 115.4, 112.4, 107.1, 94.5, 71.3, 70.1, 69.4, 55.2, 2.3.

HRMS calcd for C$_{31}$H$_{37}$N$_2$O$_5$Si (M+H) found 545.2466 w/error 0.0835ppm.

**Racemic 108-1 and Racemic 108-2.** To a solution of compound **107-1** or **107-2** (30mg, 0.055mmol) in dichloromethane (1.0mL) at 0°C was added benzyl chloroformate (9.4mL, 0.066mmol) slowly. The mixture was stirred at 0°C for 1hrs, MS showed the reaction almost completed. The mixture was diluted with ethyl acetate and washed with saturated aqueous NH$_4$Cl and brine. The organic layer was dried over anhydrous Na$_2$SO$_4$, then filtered and concentrated down. It was purified by flash column chromatography (Ethyl acetate/hexane 3:7) to give **108**. (32mg, Yield 86%). IR: 2952.9, 1728.0, 1572.8, 1433.9, 1276.4, 1167.1, 1052.6, 845.0, 698.1 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) **108-1**: 87.44-7.19 (m, 15H), 6.64 (s, 1H), 6.54 (s, 1H), 6.41 (s, 1H),
5.77 (s, 1H), 5.09 (s, 2H), 5.09-5.01 (m, 2H), 4.81 (s, 2H), 4.62 (s, 2H), 4.55 (s, 2H), 3.86 (d, J=1.56Hz, 1H), 3.73 (d, J=14.85, 1H), 3.19 (d, J=6.25Hz, 1H), 2.81 (dd, J=2.34Hz, J=7.03Hz, 1H), 0.20 (s, 9H). $^{13}$C NMR (125 MHz, CDCl3) **108-1**: 138.6, 138.3, 137.1, 131.0, 130.5, 130.3, 130.1, 130.0, 129.0, 128.9, 128.5, 128.4, 128.2, 127.9, 114.0, 113.7, 111.6, 107.2, 94.4, 71.2, 70.2, 69.6, 68.2, 52.2, 45.8, 33.6, 2.4.

HRMS calcd for C$_{39}$H$_{43}$N$_2$O$_7$S$_i$(M+H) found 679.28395 w/error -0.88ppm.

$^1$H NMR (500 MHz, CDCl$_3$) **108-2**: δ7.50-7.29 (m, 15H), 6.71 (s, 1H), 6.47 (s, 1H), 6.46 (s, 1H), 5.91 (s, 1H), 5.25-5.03 (m, 4H), 4.83 (s, 2H), 4.70 (s, 1H), 4.63 (s, 2H), 4.57 (s, 2H), 3.83 (d, J=14.64Hz, 1H), 3.56 (dd, J=6.59Hz, J=15.38Hz, 1H), 2.84-2.78 (m, 1H), 2.71 (d, J=6.59Hz, 1H), 0.17 (s, 9H). $^{13}$C NMR (125 MHz, CDCl3) **108-2**: 162.7, 158.5, 147.3, 139.2, 137.5, 136.7, 136.2, 132.6, 132.5, 129.1, 129.0, 128.9, 128.7, 128.6, 128.3, 128.2, 127.4, 115.6, 107.0, 94.5, 93.1, 71.3, 70.2, 70.1, 69.4, 68.5, 54.4, 40.1, 35.6, 2.4.

HRMS calcd for C$_{39}$H$_{43}$N$_2$O$_7$S$_i$(M+H) found 679.2829 w/error -0.5091mmu.

**Racemic 111-1 and Racemic 111-2.** To a solution of compound **108-1** or **108-2** (30mg, 0.044mmol) in THF (0.4mL) at room temperature was added dimethylphenylsilane (0.014mL, 0.088mmol) and PtO$_2$ (0.20mg, 0.0009mmol). The
mixture was heated at 55°C for 24 hours, MS showed the reaction almost completed. It was filtered and concentrated to dryness to give a crude product.

To above crude product in anhydrous THF (1.2mL) was added TBAF (0.13mL, 0.13mmol). The mixture was stirred at room temperature for 1 hours, then KF (5.1mg, 0.088mmol) and KHCO3 (13mg, 0.13mmol) were added, followed by MeOH (1.2mL), and H2O2 (0.091mL, 0.88mmol). The mixture was stirred at 58°C for 2hrs. After cooled down, the mixture was diluted with EtOAc (5mL) and washed with water and brine. The organic layer was dried over anhydrous Na2SO4, then filtered and concentrated to dryness to give 13mg of a diol with Cbz cleaved crude product.

To above crude product in anhydrous 1mL of DCM was added pyridine (0.011mL, 0.13mmol) at 0°C, followed by benzyl chloroformate (7.5mg, 0.044mmol) in 0.5 mL of DCM dropwise. MS showed the reaction completed after 30min. It was concentrated down and purified by preparative thin-layer chromatography plate(Ethyl acetate/hexane 1:1) to give 111 (9.6mg, Yield 35%). 1H NMR (500 MHz, CDCl3) 111-1: δ7.49-7.31 (m, 15H), 6.69 (s, 1H), 6.46 (s, 1H), 5.19 (s, 2H), 5.18-5.08 (m, 2H), 4.85 (s, 2H), 4.68 (s, 1H), 4.65 (s, 2H), 4.59 (s, 2H), 4.08-4.01 (m, 1H), 3.99-3.91 (m, 1H), 3.85 (dd, J=2.21Hz, 15.13Hz, 1H), 3.57 (dd, J=6.62Hz, 15.13Hz, 1H), 3.48 (dd, J=2.52Hz, J=8.20Hz, 1H), 3.00-2.92 (m, 1H), 2.88-2.82 (m, 1H), 2.78 and 2.77 (s, 1H).

13C NMR (125 MHz, CDCl3) 111-1: 162.4, 157.0, 147.1, 139.3, 138.1, 136.9, 135.5, 129.1, 128.9, 128.8, 128.7, 128.5, 128.2, 128.0, 127.5, 113.4, 111.3, 106.4, 94.6, 93.2, 70.5, 70.1, 69.7, 69.4, 62.9, 54.0, 41.9, 40.3, 36.6, 30.1.

HRMS calcd for C36H37N2O8 (M+H) found 625.25499 w/error -2.86 ppm
$^1$H NMR (500 MHz, CDCl$_3$) **111-2**: δ 7.46-7.27 (m, 15H), 6.66 (s, 1H), 6.43 (s, 1H), 5.16 (s, 2H), 5.17-5.06 (m, 2H), 4.82 (s, 2H), 4.73 (s, 1H), 4.62 (s, 2H), 4.56 (s, 2H), 4.06-3.99 (m, 1H), 3.96-3.89 (m, 1H), 3.81 (dd, J=2.20Hz, 14.65Hz, 1H), 3.54 (dd, J=5.86Hz, 14.65Hz, 1H), 3.46 (dd, J=2.93Hz, J=8.06Hz, 1H), 3.01-2.94 (m, 1H), 2.85-2.79 (m, 1H), 2.76 and 2.74 (s, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) **111-2**: 162.4, 157.0, 147.1, 139.3, 138.1, 136.9, 135.5, 129.2, 129.1, 128.9, 128.8, 128.5, 128.2, 127.5, 113.4, 111.3, 106.4, 94.6, 93.2, 70.5, 70.1, 69.7, 69.4, 62.9, 54.0, 41.9, 40.3, 36.5.

HRMS calcd for C$_{36}$H$_{37}$N$_2$O$_8$ (M+H) found 625.2534 w/error -1.7372 ppm

**Racemic 112-1 and 112-2.** To a solution of compound **111-1** or **111-2** (5.6mg, 0.009mmol) in CH$_2$Cl$_2$ (0.5mL) was added trichloroacetyl isocyanate (0.0021mL, 0.018mmol). The mixture was stirred at 0°C for 10 minutes. The reaction was quenched by MeOH (5 drops) and concentrated down. The residue was dissolved in methanol (2mL) and treated with silica gel (70mg). After 5 hours of stirring, the mixture was filtered and washed with ethyl acetate. It was concentrated down and purified by preparative thin-layer chromatography plate (MeOH/ CH$_2$Cl$_2$ 1:9) to give **112** (5.2mg, Yield 87%). $^1$H NMR (500 MHz, CDCl$_3$) **112-1**: δ 7.47-7.31 (m, 15H), 7.01 (s, 1H), 6.71 (s, 1H), 6.49 (s, 1H), 5.17 (s, 2H), 5.15-5.03 (m, 2H), 4.87 (s, 2H), 4.67 (s, 2H),
4.61 (s, 2H), 4.60-4.54 (m, 1H), 3.84 (d, J=16.71Hz, 1H), 3.77 (t, J=6.31Hz, 1H), 3.57 (dd, J=6.31Hz, J=14.82Hz, 1H), 3.41 (d, J=4.73Hz, 1H), 2.82-2.77 (m, 1H), 2.71 and 2.70 (s, 1H), 2.30 (s, 1H), 1.91-1.86 (m, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) 112-1: 162.5, 157.6, 157.0, 147.6, 139.5, 138.1, 136.8, 135.7, 129.1, 128.9, 129.0, 128.9, 128.8, 128.6, 128.2, 127.8, 125.9, 111.4, 106.2, 94.7, 91.7, 70.7, 70.1, 69.7, 69.2, 68.4, 62.9, 54.4, 40.1, 39.8, 35.9, 34.6, 30.7, 30.1, 26.0.

$^1$H NMR (500 MHz, CDCl$_3$) 112-2: δ 7.45-7.29 (m, 15H), 6.68 (s, 1H), 6.46 (s, 1H), 5.14 (s, 2H), 5.12-5.00 (m, 2H), 4.85 (s, 2H), 4.64 (s, 2H), 4.58 (s, 2H), 4.57-4.50 (m, 1H), 3.82 (d, J=13.18Hz, 1H), 3.75 (t, J=6.59Hz, 1H), 3.55 (dd, J=6.59Hz, J=15.38Hz, 1H), 3.39 (d, J=2.93Hz, 1H), 2.79-2.73 (m, 1H), 2.69 and 2.67 (s, 1H), 2.27 (s, 1H), 1.88-1.82 (m, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) 112-2: 161.8, 157.2, 146.7, 146.0, 141.1, 138.0, 136.1, 135.6, 129.3, 129.0, 128.9, 128.7, 128.3, 128.2, 127.9, 111.4, 108.8, 106.5, 95.7, 94.8, 71.0, 70.2, 69.5, 69.2, 66.6, 54.6, 36.8, 35.4, 33.1. HRMS calcd for C$_{36}$H$_{37}$N$_2$O$_8$ (M+H) found w/error -1.7372 ppm

Racemic 7-Epi-FR66979-1 and 7-Epi-FR66979-2. To a solution of compound 112-1 or 112-2 (5.2mg, 0.0078mmol) in 10% formic acid/MeOH (0.5mL) was added Pd black (1.0mg). The mixture was stirred at RT for 2.5 hours. MS and TLC indicated
the reaction completed. Filtered and concentrated down. Purified it by preparative thin-layer chromatography plate (MeOH/CH₂Cl₂ 1:4) to give **7-Epi-FR66979** (2.1 mg, Yield 83%). ¹H NMR (500 MHz, D₂O) **7-Epi-FR66979-1**: δ 6.59 (s, 1H), 6.38 (s, 1H), 4.46 (dd, J=5.68Hz, J=11.35Hz, 1H), 4.43 (s, 2H), 4.23 (dd, J=2.84Hz, J=11.35Hz, 1H), 3.50 (s, 2H), 3.37 (s, 1H), 3.23 (s, 1H), 2.35 (s, 1H). ¹³C NMR (125 MHz, CDCl₃) **7-Epi-FR66979-1**: 147.4, 142.1, 112.9, 110.0, 109.6, 63.6, 63.0, 55.3, 39.5, 28.7. MS (ESI) m/z 324 ([M + H]⁺).

¹H NMR (500 MHz, D₂O) **7-Epi-FR66979-2**: 6.61 (s, 1H), 6.40 (s, 1H), 4.46 (dd, J=5.68Hz, J=11.35Hz, 1H), 4.43 (s, 2H), 4.26 (dd, J=2.84Hz, J=11.35Hz, 1H), 3.60-3.57 (br s, 2H), 3.41-3.38 (m, 1H), 2.63-2.56 (m, 2H). ¹³C NMR (125 MHz, D₂O) **7-Epi-FR66979-2**: 159.7, 155.9, 146.4, 142.3, 112.2, 110.0, 109.8, 63.5, 62.7, 54.1, 39.5, 33.5, 29.9. MS (ESI) m/z 324 ([M + H]⁺).

**Racemic 7-Epi-FR900482-2.** DMSO (3uL) in anhydrous CH₂Cl₂ (0.1mL) was added dropwise to a stirred solution of oxalyl chloride (1.7uL) in anhydrous CH₂Cl₂ (0.1mL) at -78°C. After 2min, a solution of **7-Epi-FR66979-2** (2.5mg, 0.0077mmol) in 0.2mL of DCM/DMSO (1:1) was added dropwise and stirring was continued for 20min. After the addition of Et₃N (13uL, 0.092mmol, 12eq.), the mixture was gradually
warmed up to room temperature and further stirred for 20min. The reaction mixture was
concentrated down. Purified it by preparative thin-layer chromatography plate(MeOH/
CH₂Cl₂ 1:4) to give 7-Epi-FR900482-2 (1.5mg, yield 60%) as a white solid. ¹H NMR
(600 MHz, D₂O) δ 9.66 (s, 1H), 7.03 (s, 1H), 6.92 (s, 1H), 4.51 (dd, J=5.6Hz, J=11.5Hz,
1H), 4.24 (dd, J=2.9Hz, J=11.5Hz, 1H), (s, 2H), 3.51-3.54 (m, 2H), 3.42 (dd, J=2.9Hz,
J=5.6Hz, 1H), 2.33 (bs, 2H). ¹³C NMR (150 MHz, D₂O) 195.5, 159.5, 156.3, 147.3,
136.5, 120.6, 113.5, 110.5, 92.8, 62.2, 55.1, 39.9, 32.0, 28.2.
HRMS m/z found 322.1030 ([M + H]⁺) with error -1.228ppm

**Compound 137.** To compound 108 (79mg, 0.116mmol) in 5mL of THF was
added TBAF (0.17mL, 0.17mmol) at 0°C. The mixture was stirred at room temperature
for 1 hour. LC-MS showed the reaction completed. The reaction mixture was diluted
with EtOAc and washed with aqueous saturated NH₄Cl and brine. Organic layer was
dried over anhydrous MgSO₄. Filtered and concentrated to dryness to give 79mg of
crude product (89% purity)

To above crude product in 1mL of dichloromethane was added Et₃N (0.15mL,
1.06mmol) then followed by acetic anhydride (0.060mL, 0.63mmol) and DMAP
(5.0mg, 0.041mmol) at room temperature. The reaction mixture was stirred at room
temperature for 48 hours, LC-MS showed the reaction completed. The mixture was
diluted with EtOAc and washed with aqueous 0.5M HCl and brine. The organic layer
was dried over anhydrous Na$_2$SO$_4$. Filtered and concentrated down. Purified by column
with 7~40% EtOAc in hexane to give compound 137 (68.1mg, yield 100%) as a light
yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.50-7.32 (m, 14H), 7.28-7.24 (m, 1H), 6.79
and 6.71 (s, 1H), 6.66 and 6.63 (s, 1H), 6.54 and 6.48 (s, 1H), 5.73 and 5.57 (s, 1H),
5.25-5.08 (m, 3H), 4.88 and 4.87 (s, 2H), 4.69 and 4.68 (s, 2H), 4.63 and 4.62 (s, 2H),
4.18 (q, J=7.25Hz, 1H), 4.04 (t, J=14.82Hz, 1H), 3.81 (d, J=14.82Hz, 0.3H), 3.64 (dd,
J=6.31Hz, J=14.82Hz, 0.7H), 3.50 (d, J=6.62Hz, 0.3H), 3.22 (d, J=6.62Hz, 0.7H), 3.00
(d, J=6.62Hz, 0.3H), 2.96 (t, J=6.31Hz, 0.7H), 2.25 and 2.17 (s, 3H). $^{13}$C NMR (125
MHz, CDCl$_3$) 167.7, 163.3, 162.2, 158.7, 148.3, 147.0, 142.8, 139.8, 137.0, 136.6,
135.8, 133.5, 129.1, 129.0, 128.9, 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1,
117.3, 115.4, 113.1, 112.1, 111.9, 111.4, 107.5, 107.2, 96.7, 95.4, 94.6, 94.5, 71.4, 71.3,
70.1, 69.5, 69.4, 69.2, 68.4, 54.8, 53.9, 51.6, 43.7, 43.6, 38.6, 35.2, 34.2, 22.2, 14.6.

![Chemical structure diagram]

**Compound 139.** To compound 137 (48mg, 0.074mmol) in 2mL of THF,
0.6mL of acetone, and 0.6mL of water was added 4-methylmorpholine N-oxide (45mg,
0.37mmol) and OsO$_4$ (92µL, 0.015mmol) at room temperature. The mixture was stirred
at room temperature for 48 hour. LC-MS showed the reaction completed. The reaction quenched by the addition of aqueous Na$_2$S$_2$O$_3$ and extracted with EtOAc (2x10mL). The combined organic layer was washed with water and brine. Organic layer was dried over anhydrous MgSO$_4$. Filtered and concentrated down. It was purified by preparative thin-layer chromatography plate (EtOAc/hexane 4:1) to give 139 (46mg, Yield 91%) as a yellow oil. IR: , $^1$H NMR (500 MHz, CDCl$_3$) $\delta$7.53-7.34 (m, 15H), 6.78 and 6.70 and 6.64 (s, 1H), 6.51 and 6.44 (s, 1H), 5.28-5.23 (m, 1H), 5.21-5.16 (m, 1.5H), 5.15-5.10 (m, 1.5H), 5.03 (t, J=11.98Hz, 1H), 4.90 and 4.88 (s, 1H), 4.87 and 4.84 and 4.83 (s, 1H), 4.81 and 4.79 and 4.78 and 4.75 (s, 1H), 4.69 and 4.68 (s, 2H), 4.63 and 4.61 and 4.60 (s, 2H), 4.18 (q, J=7.25Hz, 2H), 3.91-3.85 (m, 1H), 3.56 (d, J=6.62Hz, 0.3H), 3.43 (s, 0.5H), 3.39 (d, J=6.62Hz, 0.3H), 3.07 and 3.08 (s, 0.4H), 3.04 (t, J=5.99Hz, 0.5H), 2.98 (t, J=6.31Hz, 0.5H), 2.91 (dd, J=2.21Hz, J=6.62Hz, 0.5H), 2.03 and 1.99 and 1.92 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) 158.0, 148.5, 141.3, 140.4, 138.1, 136.5, 136.3, 135.8, 135.7, 129.4, 129.2, 129.0, 128.9, 128.8, 128.7, 128.3, 128.2, 128.1, 112.0, 112.0, 111.8, 111.2, 106.8, 106.2, 94.9, 94.8, 94.7, 94.6, 94.4, 92.3, 73.0, 71.9, 71.8, 71.5, 71.3, 70.2, 69.4, 69.3, 69.2, 66.9, 65.6, 65.2, 60.8, 54.6, 52.4, 51.3, 42.1, 37.6, 37.0, 36.3, 36.1, 33.4, 21.5, 21.4, 21.2, 14.6.
**Compound 138.** To compound 139 (42mg, 0.062mmol) in 3mL of dichloromethane was added triphenylphosphine (32mg, 0.12mmol) and DIAD (27µL, 0.015mmol) at room temperature under a N\textsubscript{2} atmosphere. The reaction vessel was sealed and stirred in the dark at room temperature for 61 hours. LC-MS showed the reaction almost completed. The reaction mixture was concentrated to remove solvent. The residue was purified by preparative thin-layer chromatography plate (EtOAc/hexane 1:1) to give 138 (32mg, Yield 77%) as a yellow oil. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.57-7.34 (m, 15H), 6.73 and 6.70 and 6.67 (s,1H), 6.60 and 6.56 and 6.46 (s, 1H), 5.17-5.05 (m, 3H), 4.89 and 4.87 (s, 2H), 4.75 and 4.73 (s, 1H), 4.70 and 4.68 (s, 2H), 4.65 and 4.64 (s, 1H), 4.62 (s, 1H), 3.91 (d, J=6.31Hz, 0.5H), 3.88 (d, J=6.62Hz, 0.5H), 3.75-3.73 (m, 0.5H), 3.70 (d, J=5.68Hz, 0.5H), 3.18-3.12 (m, 1H), 2.71 (t, J=5.99Hz, 0.5H), 2.04 and 2.03 and 1.97 (s, 3H). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) 170.9, 162.7, 159.0, 148.5, 141.3, 140.2, 138.1, 136.3, 135.8, 135.7, 129.4, 129.2, 129.0, 128.9, 128.8, 128.7, 128.3, 128.2, 128.1, 112.0, 111.8, 107.0, 106.9, 106.1, 94.9, 94.8, 94.6, 94.4, 92.3, 73.0, 71.9, 71.8, 71.5, 71.3, 70.2, 70.1, 69.4, 69.3, 69.2, 69.1, 65.6, 65.2, 60.8, 54.6, 52.4, 51.3, 42.1, 37.6, 37.0, 36.3, 36.1, 33.4, 21.5, 21.4, 14.6.
Compound 144. To compound 108 (37mg, 0.054mmol) in 2mL of THF was added TBAF (0.081mL, 0.081mmol) at 0°C. The mixture was stirred at room temperature for 1 hour. LC-MS showed the reaction completed. The reaction mixture was diluted with EtOAc and washed with aqueous saturated NH₄Cl and brine. Organic layer was dried over anhydrous MgSO₄. Filtered and concentrated to dryness to give 41mg of crude product (87% purity)

To above crude product in 1mL of dichloromethane was added DIPEA (0.072mL, 0.43mmol) then followed by methyl chloromethyl ether (0.060mL, 0.63mmol) at room temperature. The reaction mixture was stirred at room temperature for 7 days, LC-MS showed the reaction completed. The mixture was poured into brine and extracted with CH₂Cl₂ x 2. The organic layer was dried over anhydrous Na₂SO₄. Filtered and concentrated down. Purified by column with 10~40% EtOAc in hexane to give compound 144 (25mg, yield 70%) as a light yellow oil.

$^1$H NMR (500 MHz, CDCl₃) δ 7.47-7.27 (m, 15H), 6.73 and 6.72 (s, 1H), 6.68 and 6.65 (s, 1H), 6.49 and 6.47 (s, 1H), 6.02 and 5.92 (s, 1H), 5.21-5.08 (m, 4H), 5.05 and 5.04 (s, 1H), 4.83 (s, 2H), 4.64 (s, 2H), 4.58 and 4.57 (s, 2H), 4.12 (q, J=7.03Hz, 0.5H), 3.96-3.89 (m, 1H), 3.56 (d, J=5.47Hz, 0.5H), 3.53 (d, J=6.25Hz, 0.5H), 3.51 (s, 0.5H), 3.47 (s, 2H), 2.86-2.76 (m, 2H), 2.05 (s, 1H). $^{13}$C NMR (125 MHz, CDCl₃) 161.9, 158.4, 146.8, 139.0, 136.1, 135.5, 135.1, 134.4, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 127.8, 127.6, 116.3, 111.9, 106.7, 94.4, 94.1, 92.0, 70.9, 69.7, 68.9, 68.5, 56.6, 53.2, 38.4, 34.3, 20.4, 14.2.
**Compound 145.** To compound 144 (20mg, 0.031mmol) in 1mL of THF, 0.3mL of acetone, and 0.3mL of water was added 4-methylmorpholine N-oxide (37mg, 0.31mmol) and OsO₄ (79µL, 0.012mmol) at room temperature. The mixture was stirred at room temperature for 48 hour. LC-MS showed the reaction completed. The reaction quenched by the addition of aqueous Na₂S₂O₃ and extracted with EtOAc (2x10mL). The combined organic layer was washed with water and brine. Organic layer was dried over anhydrous MgSO₄. Filtered and concentrated down. It was purified by preparative thin-layer chromatography plate (EtOAc/hexane 4:1) to give 145 (18mg, Yield 85%) as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ7.52-7.27 (m, 15H), 6.75 and 6.72 (s, 1H), 6.51 and 6.44 (s, 1H), 5.36 and 5.34 (s, 1H), 5.25 and 5.23 (s, 1H), 5.21-5.18 (s,1H), 5.14 (s, 2H), 5.09 and 5.06 (s, 1H), 4.89 and 4.83 (s, 2H), 4.63 and 4.62 (s, 2H), 4.58 and 4.56 (s, 2H), 4.41 (dd, J=5.47Hz, J=12.50Hz, 1H), 4.18 (t, J=9.38Hz, 1H), 4.11 (d, J=7.04Hz, 1H), 3.86(d, J=2.35Hz, 0.5H), 3.82 (d, J=1.56Hz, 0.5H), 3.63 (d, J=6.25Hz, 0.5H), 3.59 (d, J=6.25Hz, 0.5H), 3.43 and 3.41 (s, 3H), 3.37 (d, J=6.25Hz, 1H), 3.33 (s, 1H), 2.85 (t, J=7.04Hz, 1H), 2.20 (dd, J=5.47Hz, J=9.38Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) 161.9, 158.0, 149.6, 149.3, 148.8, 148.3, 141.89, 140.3, 137.6, 135.8, 135.2, 128.8, 128.6, 128.5, 128.2, 127.9, 127.8, 115.6, 112.7,
107.8, 95.0, 94.2, 92.2, 72.3, 71.8, 69.7, 68.9, 68.8, 68.7, 63.8, 60.4, 56.7, 53.9, 34.9, 31.2, 21.1, 14.2.

**Compound 146.** To compound **145** (18mg, 0.026mmol) in 1mL of dichloromethane was added triphenylphosphine (10mg, 0.039mmol) and DIAD (8µL, 0.040mmol) at room temperature under a N₂ atmosphere. The reaction vessel was sealed and stirred in the dark at room temperature for 61 hours. LC-MS showed the reaction almost completed. The reaction mixture was concentrated to remove solvent. The residue was purified by preparative thin-layer chromatography plate (EtOAc/hexane 1:1) to give **146** (8mg, Yield 75%) as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ7.55-7.29 (m, 15H), 6.71 and 6.68 (s, 1H), 6.54 and 6.51 and 6.44 (s, 1H), 5.47 (d, J=5.68Hz, 0.5H), 5.26-5.23 (m, 1H), 5.21-5.20 (s, 2H), 5.15 and 5.14 (s, 0.5H), 5.14 (d, J=2.21Hz, 0.3H), 5.07-5.04 (m, 0.7H), 5.03-4.98 (m, 0.5H), 4.86 and 4.84 (s, 2H), 4.67 and 4.65 (s, 1H), 4.63 (d, J=2.52Hz, 1H), 4.60 and 4.57 (s, 2H), 4.42-4.36 (m, 0.7H), 4.35-4.30 (m, 0.5H), 4.15 (q, J=6.94Hz, 0.3H), 3.84 (d, J=2.52Hz, 0.3H), 3.83 (d, J=2.52Hz, 0.3H), 3.75 (d, J=6.94Hz, 0.5H), 3.73 (d, J=6.62Hz, 0.2H), 3.70 (d, J=6.31Hz, 0.3H), 3.57 and 3.48 and 3.45 (s, 3H), 3.17-3.11 (m, 0.7H), 2.91-2.86 (m, 0.8H), 2.77 (d, J=6.62Hz, 0.2H), 2.07 (s, 0.3H). ¹³C NMR (125 MHz, CDCl3) 162.2,
Compound 147 and 148. To compound 146 (4mg, 0.006mmol) in 0.5mL of THF at -78°C was added N,N-dimethylethanolamine (9µL, 0.09mmol), then followed by SmI₂ (0.12mL, 0.012mmol) dropwise under a N₂ atmosphere. The reaction mixture was stirred at -78°C for 30 minutes. LC-MS indicated that product generated, but also had dehydration by-product. The reaction was quenched by aqueous 1M HCl and extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous MgSO₄. Filtered and concentrated down. The residue was purified by preparative thin-layer chromatography plate (EtOAc/hexane 1:1) to give 147 (1.4mg) and 148 (1mg) (total Yield 60%) as a yellow film. 147: ¹H NMR (500 MHz, CDCl₃) δ7.54-7.29 (m, 15H), 6.78 and 6.67 (s, 1H), 6.54 and 6.45 (s, 1H), 5.28-5.20 (m, 2H), 5.13-5.06 (m, 2H), 5.05-4.98 (m, 2H), 4.90 (d, J=7.57Hz, 1H), 4.86 (s, 2H), 4.66 (s, 2H), 4.59 (s, 2H), 4.21 (dd, J=5.36Hz, J=12.61Hz, 1H), 4.18-4.13 (m, 1H), 3.91 (dd, J=2.52Hz, J=14.82Hz, 1H), 3.83 and 3.80 (s, 1H), 3.55 (d, J=6.31Hz, 1H), 3.53 (s, 3H),
3.46-3.39 (m, 2H), 2.82 (dd, J=2.21Hz, J=6.94Hz, 1H). $^{13}$C NMR (125 MHz, CDCl3)
157.2, 137.3, 129.4, 129.3, 129.2, 129.1, 94.5, 91.8, 71.5, 70.0, 69.7, 68.9, 62.3, 56.7,
52.2, 47.9, 42.0, 34.6, 33.3, 30.1.

**148**: $^1$H NMR (500 MHz, CDCl3) δ 7.45-7.21 (m, 15H), 6.62 (s, 1H), 6.53 (s,
1H), 5.07-4.99 (m, 2H), 4.96 (d, J=3.91Hz, 2H), 4.75 (s, 2H), 4.62 (d, J=10.16Hz, 1H),
4.56 (s, 3H), 4.52 (s, 4H), 3.89 (d, J=10.94Hz, 1H), 3.67 (s, 2H), 3.30-3.23 (m, 1H),
3.21 (s, 3H), 2.56 (d, J=14.07Hz, 1H). $^{13}$C NMR (125 MHz, CDCl3) 154.8, 152.6,
148.4, 131.2, 129.0, 128.9, 128.8, 128.4, 128.3, 128.2, 127.9, 127.7, 127.4, 97.2, 95.8,
94.5, 73.3, 72.2, 70.9, 70.6, 70.1, 69.4, 67.8, 67.5, 56.3, 55.8, 55.6, 51.1, 39.3, 38.1,
37.9, 30.1.

**Compound 149.** To compound 147 (1mg, 0.0015mmol) in 0.1mL of
dichloromethane at -78°C was added pyridine (0.5µL, 0.006mmol) , then followed by
phenyl chloroformate (0.38µL, 0.003mmol) under a N$_2$ atmosphere. The reaction
mixture was stirred at room temperature for three hours. LC-MS indicated that the
reaction completed. The reaction mixture was diluted by EtOAc, then washed with
aqueous 1M HCl and brine. The organic layer was dried over anhydrous MgSO$_4$.
Filtered and concentrated to dryness to give 149 (1.2mg, Yield 100%) as a yellow film.

**147**: $^1$H NMR (500 MHz, CDCl3) δ 7.41-7.06 (m, 20H), 6.48 (s, 1H), 6.33 (s, 1H), 5.25
(d, J=7.03Hz, 1H), 4.99-4.97 (m, 3H), 4.95 (s, 1H), 4.77 (d, J=7.03Hz, 2H), 4.74 (s, 2H), 4.55 (s, 2H), 4.47 (s, 2H), 4.05 (q, J=7.82Hz, 1H), 3.85 (d, J=2.35Hz, 0.5H), 3.80 (d, J=5.47Hz, 0.5H), 3.78 (s, 1H), 3.63 (d, J=6.25Hz, 1H), 3.49 (s, 3H), 2.78 (dd, J=1.56Hz, J=6.25Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) 152.5, 151.4, 143.3, 136.9, 136.6, 130.0, 129.8, 129.1, 129.0, 128.9, 128.8, 128.7, 128.3, 128.2, 127.8, 126.7, 121.5, 121.3, 96.4, 94.4, 92.0, 74.8, 70.9, 70.0, 69.6, 69.2, 68.9, 66.3, 66.2, 62.0, 61.9, 46.6, 30.1.

**Racemic 158-1 and Racemic 158-2.** To a solution of compound 134 (5mg, 0.0082mmol) in toluene (2.1mL) at room temperature was added dimethylphenylsilane (7.7mg, 0.049mmol) and PtO$_2$ (0.36mg, 0.0016mmol). The mixture was heated at 55°C for 24 hours, MS showed the reaction almost completed. It was filtered and concentrated to dryness to give a crude product.

To above crude product in anhydrous THF (0.2mL) was added TBAF (0.013mL, 0.013mmol). The mixture was stirred at room temperature for 1 hours, then KF (1.5mg, 0.026mmol) and KHCO$_3$ (6.5mg, 0.065mmol) were added, followed by MeOH (0.1mL), and H$_2$O$_2$ (0.010mL, 0.086mmol). The mixture was stirred at 58°C for 2hrs. After cooled down, the mixture was diluted with EtOAc (2mL) and washed with water
and brine. The organic layer was dried over anhydrous Na₂SO₄, then filtered and concentrated to dryness to give 4mg of a diol with Cbz cleaved crude product.

To above crude product in anhydrous 1mL of DCM was added pyridine (1mg, 0.013mmol) at 0°C, followed by benzyl chloroformate (0.7mg, 0.0043mmol) in 0.1 mL of DCM dropwise. MS showed the reaction completed after 30min. It was concentrated down and purified by preparative thin-layer chromatography plate(Ethyl acetate/hexane 1:1) to give 158-1 (0.5mg) and 158-2 (1.1mg) overall yield of 32%. ¹H NMR (500 MHz, CDCl₃) 158-1: δ 7.68-7.22 (m, 15H), 6.54 (s, 1H), 6.31 (s, 1H), 5.02 (s, 2H), 4.76 (s, 2H), 4.57 (s, 2H), 4.50 (s, 2H), 4.18-4.10 (m, 1H), 4.08-4.02 (m, 1H), 3.88-3.82 (m, 1H), 3.77-3.71 (m, 1H), 3.63-3.57 (m, 1H), 3.24-3.14 (m, 1H), 2.81-2.76 (m, 1H), 2.57-2.52 (m, 1H). MS (ESI) m/z 625 ([M + H]⁺).

¹H NMR (500 MHz, CDCl₃) 158-2: δ 7.39-7.20 (m, 15H), 6.65 (s, 1H), 6.36 (s, 1H), 5.11 (s, 2H), 5.08-4.98 (m, 2H), 4.77 (s, 2H), 4.56 (s, 2H), 4.50 (s, 2H), 4.42 (s, 1H), 3.85-3.68 (m, 2H), 3.63 (s, 1H), 3.54 (d, J=6.25Hz, 1H), 3.51 (d, J=6.25Hz, 1H), 2.94-2.91 (m, 1H), 2.78 and 2.76(s, 1H). ¹³C NMR (125 MHz, CDCl₃). MS (ESI) m/z 625 ([M + H]⁺).
XIII Reference

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# M. Spectra

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δ (H)  9.0  7.6  4.2  3.4  2.3  2.0  1.8

δ (C)  6.0  5.6  5.3  4.7  3.9  3.7  3.5
7-Epi-FR 900482-2 $^{13}$C NMR
Compound 158-1 HNMR
Compound 158-2 HNMR
Curriculum Vitae

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EDUCATION

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PUBLICATIONS, PATENTS and PRESENTATIONS

• Toward the Back-Up of Boceprevir (SCH 503034): Discovery of New Extended P4-Capped Ketoamide Inhibitors of Hepatitis C Virus NS3 Serine Protease with Improved Potency and Pharmacokinetic Profiles. Bogen, Stephane L.; Pan, Weidong; Ruan, Sumei; Nair, Latha G.; Arasappan, Ashok; Bennett, Frank; Chen, Kevin X.; Jao, Edwin; Venkatraman, Srikanth; Vibulbhan, Bancha; Liu, Rong; Cheng, Kuo-Chi; Guo, Zhuyan; Tong, Xiao; Saksera, Anil K.; Girijavallabhan, Viiyoor; Njoroge, F. George. J. Med. Chem. 2009, 52(12), 3679-3688.
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