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Design and synthesis of an inositol phosphate analog based on computational docking studies

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ABSTRACT

A virtual library of 54 inositol analog mimics of In(1,4,5)P_3 has been docked, scored, and ranked within the binding site of human inositol 1,4,5-trisphosphate 3-kinase A (IP_3-3KA). Chemical synthesis of the best scoring structure that also met distance criteria for 3′-OH to -P in phosphate has been attempted along with the synthesis of (1*S*,2*R*,3*S*,4*S*)-3-fluoro-2,4-dihydroxycyclohexanecarboxylic acid as an inositol analog, useful for non-invasive visualization and quantitation of IP_3-3KA enzymatic activity.

1. Introduction

Inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3 or IP_3] **2** is one of many inositol phosphates, which occurs in mammalian cells.[1] As a secondary messenger, Ins(1,4,5)P_3 is responsible for triggering the release of Ca^{2+} from intracellular stores in the endoplasmic reticulum after four of the molecules bind to the IP_3-R receptor (inositol trisphosphate receptor) and causes concomitant activation.[2] Ins(1,4,5)P_3 has a short half-life within the cells and is either metabolized by a kinase to form Ins(1,3,4,5)P_4 or metabolized by a phosphatase to form Ins(1,4)P_2.[2] The kinase, 1,4,5-trisphosphate 3-kinase (IP_3-3K) is responsible for the specific addition of a phosphate to the 3′-OH of Ins(1,4,5)P_3.[3] Three mammalian isoforms of IP_3-3K that have been isolated (designated A, B, and C) each have a catalytic domain composed of N (amine terminal), C (acid terminal), and IP (inositol phosphate) lobes. The crystal structure of human isoform A (IP_3-3KA) shows that the majority of direct interactions with Ins(1,4,5)P_3 is through the IP lobe, and only two (Lys264 and Lys419) come from C lobe. The Lys264 residue interacts with the 3′-OH group, that is phosphorylated and likely assists with the transfer of the phosphate from ATP.[4]

The IP_3-3K isoforms are highly expressed in immune and nervous systems, suggesting the enzymes might have the potential to be used as drug targets in those areas; however, isoform selectivity might be an issue.[5,6] In oncology, inositol 1,4,5-trisphosphate 3-kinase A (IP_3-3KA) was first shown to be down-regulated in oral squamous cell carcinoma, suggesting that IP_3-3KA may be used as a potential prognostic marker.[7] More recently, it has been suggested as a potential therapeutic target due to its functional role for the motility of malignant transformed cells.[8] This suggests that analogs of Ins(1,4,5)P_3 have the potential to be developed into novel therapeutic or diagnostic agents for multiple disorders.

Binding and competition studies have been reported for Ins(1,4,5)P_3 analogs with replacement of the phosphate groups with phosphorothioate or at the 2′-OH position with an ester group.[9,10] Prior to this, Safrany et al. explored analogs with fluorine in the 2′-position and found them to be weaker substrates for IP_3-3K.[11] More recently, Poinas et al. studied the interaction of the catalytic domain of IP_3-3KA with several inositol phosphate analogs and found that removal of the 2′-OH was tolerated and would still allow for substrate activity.[12]

We describe the design and synthesis of an Ins(1,4,5)P_3 analog with substantial differences to known substrate analogs. In

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our structure, we maintain the important 3′-OH position, all three phosphate groups have been either removed entirely or replaced with isosteres, and fluorine occupies the 2′-position (Fig. 1).

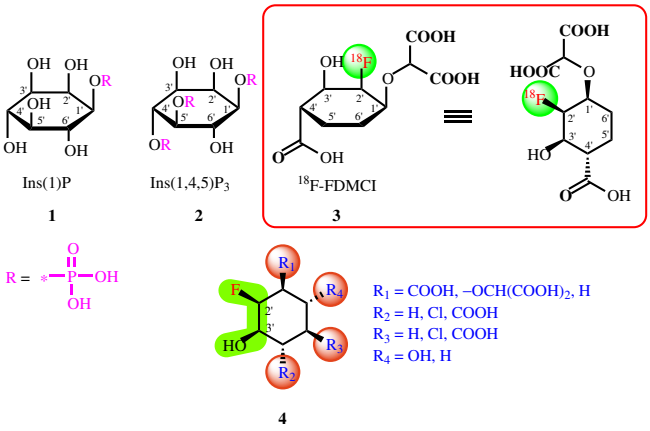


Fig. 1. Representation of inositol mono- and tri-phosphates, and radiolabeled ^{19}F inositol mimetic analog along the core of 2-fluoro-3-hydroxy inositol analog **4** for virtual library of substrates.[13]

2. Results and discussion

In our current study, the core structure of D-*myo*-inositol-1-phosphate [Ins(1)P] **1** was subjected to molecular modeling in an effort to elicit a cell-permeable analog, which could be radiofluorinated with ^{18}F (compound **3**, Fig. 1). Thus **3** has the unique features of a phosphate group mimetic (carboxylic acid) at 4′-position, while the 5′ and 6′-positions lack the hydroxyl groups[13] to prevent possible phosphorylation at these positions. This lead compound was named ^{18}F-FDMCI. The paradigm for imaging IP_3-3K activity with ^{18}F-FDMCI as its substrate is that ^{18}F-FDMCI should be transported into the cell by inositol transporter and be selectively phosphorylated on the 3′-hydroxyl by IP_3-3K to ^{18}F-FDMCI-3′-phosphate. ^{18}F-FDMCI-3′-phosphate is not a substrate for the inositol transporter, and being very polar, cannot cross the cell membrane, and thus will be trapped inside the cell.[12]

In order to identify a suitable mimic of inositol 1,4,5,-trisphosphate **2** [Ins(1,4,5)P_3] to be radiolabeled and used as an imageable substrate, we first pursued the search for suitable isosteres of the phosphate group, in hopes that the phosphates may be eliminated (at least partially) from the substrate. A search of commercially available compounds similar to Ins(1,4,5)P_3 led mostly to five- to nine-membered ring systems substituted with carboxylate groups. The ability of the carboxylate groups to mimic the phosphate groups was confirmed through GRID calculations with both phosphate and carboxylate probes, which showed overlapping contours. Therefore, it would be expected that these groups would have similar interactions with the receptor. However, the phosphate groups in **2** [Ins(1,4,5)P_3] extend out further from the ring when compared with similarly attached carboxylate groups on the same core, so a simple one-to-one replacement of the phosphates with carboxylates might not adequately span the distance between charged regions in the binding site. To address this limitation, the extended group malonic acid was considered as one of the variations on a central cyclohexane ring **4**. A virtual library was created from the combination of elements shown in Fig. 1, with fluorine in position C2′ and hydroxyl in position C3′ on the ring **4**.

This small focused library of 54 compounds was docked, scored, and ranked within the binding site of human inositol 1,4,5-trisphosphate 3-kinase.[14] The score would normally play a major role in the evaluation of the compounds as inhibitors; however, we are designing a substrate not an inhibitor. Thus the score would not be expected to have a complete correlation with the percentage of phosphorylation, since the molecule may still interact nicely with the binding site from an energy standpoint yet to fail to present a necessary group in the proper orientation for enzymatic activity. In this particular case, it is important to present the 3′-OH or equivalent group for phosphorylation. This led to the decision to utilize the distance from 3′-OH to phosphorus as the primary metric and score as a secondary metric. In the enumeration of the virtual library, more than one OH on the ring is possible, so a post-docking analysis was done in order to identify the 3′-OH in each compound and record the distance for all 540 configurations. When considering the score in combination with compounds matching the distance criteria, the number of compounds meeting these criteria was reduced considerably. Top four compounds are shown in Fig. 2 and the top first candidate **3** (DM103-104_B1_S5_S1_S3_S3) was selected for chemical synthesis. The best docked configuration compound is shown in Fig. 3.

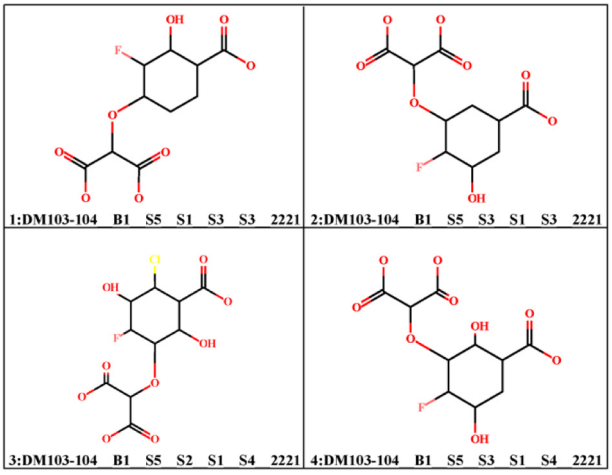


Fig. 2. Top compounds matching distance and scoring data.

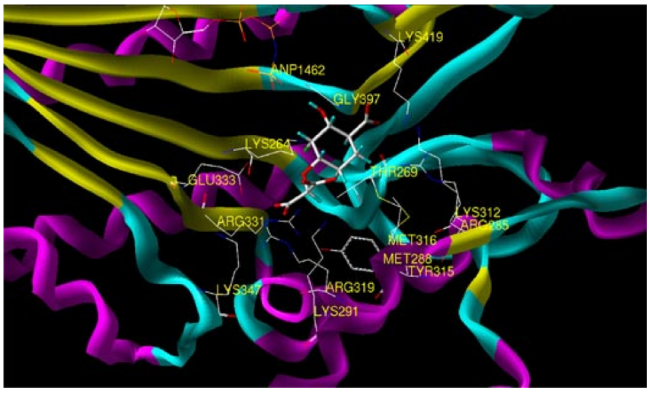
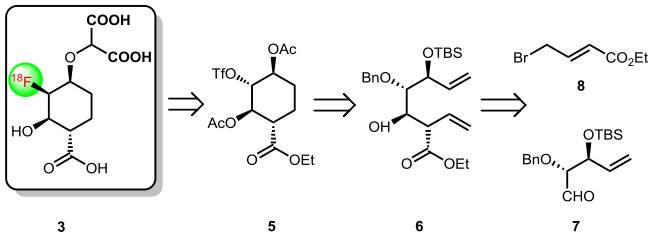


Fig. 3. Best scoring structure that also met distance criteria for 3′-OH to -P in phosphate: shown docked into crystal structure of human inositol 1,4,5-trisphosphate 3-kinase.

The critical part in the synthesis of inositol derivative cyclohexanecarboxylic acid **3** is the establishment of the correct stereochemistry at C1, C2, C3, and C4 positions (Scheme 1). From the synthesis point of view the core structure of **3** resembles (+)-cyclophellitol, a potent β-glucosidase inhibitor.[15] The protective group of the C2-hydroxy position has to be orthogonal to the rest of the protecting groups to allow fluorination at C3 position in



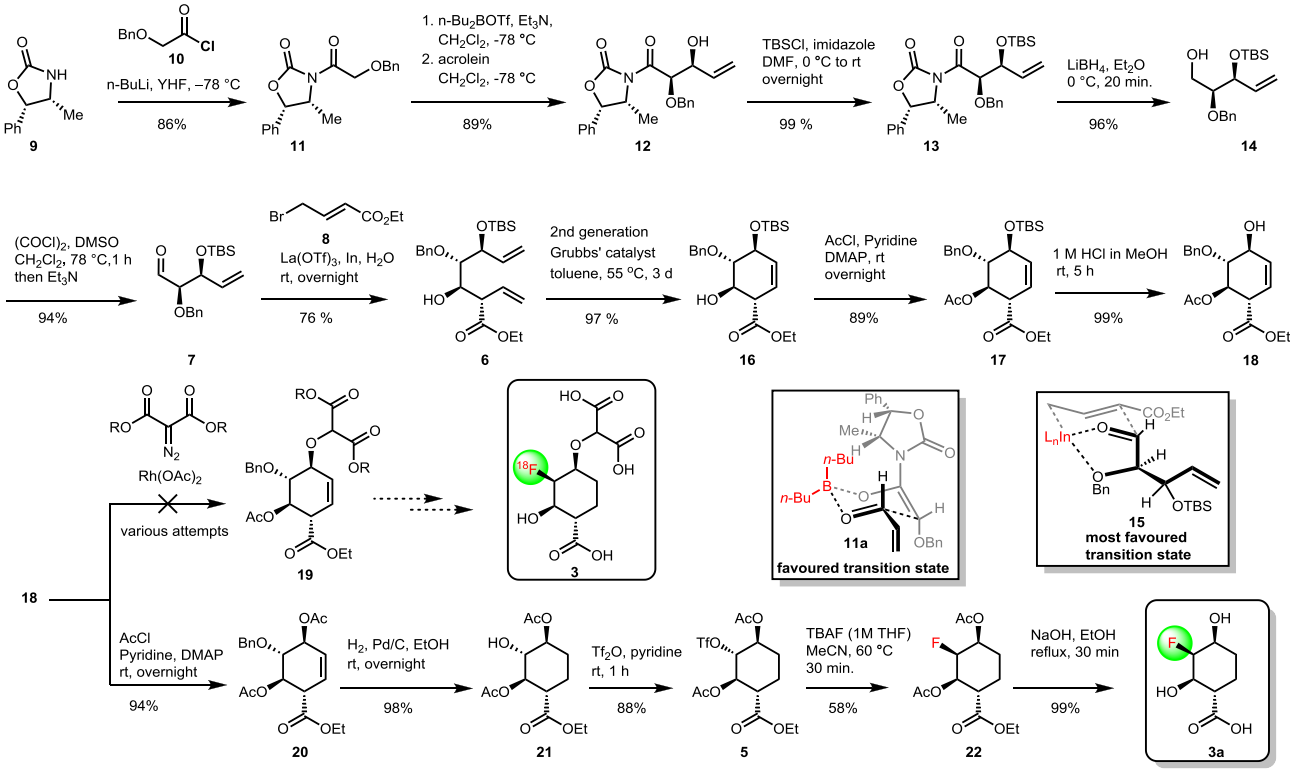
Scheme 1. Retrosynthetic analysis for compound **3**.

the final stage of the synthesis. We envisioned that compound **3** can be generated from the corresponding cyclohexane **5**, which can be prepared from the ring closing metathesis from the diene **6**. The diene **6** can be prepared from the γ,δ-unsaturated aldehyde **7** via an indium promoted reaction with a substituted allylic halide **8** (Scheme 1).

To establish the relative and absolute stereochemistry of the first initial fragment aldehyde **7**, the Evan's chiral auxiliary-directed aldol reaction was chosen (Scheme 2). The known oxazolidinones **9** was deprotonated with *n*-butyllithium and then coupled with commercially available benzyloxyacetyl chloride **10** to generate the imide **11**.[16] The condensation of the imide **11** with acrolein under standard conditions resulted *syn*-β-hydroxyl imide **12**[17] as a single diastereomer with high yield. The *syn* selectivity can be attributed to the favorable transition state (**11a**) where the dialkylborane favors the *Z*-enolate in which the alkyl group of the aldehyde derivative adopts a pseudoequatorial position (Scheme 2). Conversion of the free hydroxyl group into *tert*-butyldimethylsilyl (TBS) ether **13** was accomplished with TBSCl and imidazole in DMF. Removal of the chiral auxiliary using $LiBH_4$ in ether at 0 °C afforded the corresponding primary alcohol **14**, which was then converted into the corresponding aldehyde **7** under Swern oxidation conditions.

After having the aldehyde **7** in hand, we adopted the Loh's indium-mediated allylation reaction conditions that were modified by Madsen and co-workers.[15,18] Coupling of ethyl 4-bromocrotonate **8** with the α-benzyloxy aldehyde **7** in the presence of lanthanum triflate and indium power in water provided a single diastereomer of the coupled product **6** in 76% yield (Scheme 2). The *syn* stereochemical outcome of **6** can be explained by invoking a chelated intermediate **15** where the allylindium coordinates to the aldehyde carbonyl and α-benzyloxy group affording the *syn* product.[19] Having established the required stereocenters as well as the appropriate two terminal olefins, we are now in position to employ the key ring closing metathesis. Thus, treatment of **6** with the Grubb's second generation catalyst provided the highly substituted cyclohexene **16** in near quantitative yield. The newly formed hydroxyl group in **16** was protected with acetyl chloride, and then removal of the TBS group to give **17** was achieved in 1 M HCl in MeOH solution. Our computational docking experiments suggested that the top best scoring structure should have malonic acid on C3′ hydroxyl group, which would be an ideal candidate for initial PET imaging studies. Unfortunately all our efforts to alkylate the hydroxyl group with the carbenoid derived from diazomalonic acid ester to give **19** were ineffective. Since the alkylation with malonic acid became difficult we decided to acetylate the alcohol functionality to proceed further to synthesize an alternate analog **3a**, which is also a potential PET imaging agent. Treatment of the free hydroxyl group of **18** with acetyl chloride gave the corresponding diacetylated cyclohexene **20** in 94% yield.

Hydrogenation of the olefin and deprotection of the benzyl group were achieved simultaneously with a catalytic amount of palladium on carbon to afford **21**. Treatment of **21** with triflic anhydride in pyridine provided the triflate **5**, which was upon treatment with 1 M solution of TBAF in THF at 60 °C for 30 min gave the fluorine-substituted compound **22** in 58% yield with inversion in stereochemistry.[20] Deacetylation of **22** in boiling ethanol



Scheme 2. Synthesis of (1*S*,2*R*,3*R*,4*S*)-3-fluoro-2,4-dihydroxycyclohexane carboxylic acid **3a** using Evan's chiral auxiliary and RCM as key steps.

in presence of NaOH for 30 min provided the (1*S*,2*R*,3*R*,4*S*)-3-fluoro-2,4-dihydroxycyclohexane carboxylic acid **3a** in 99% yield (Scheme 2).

We compared the results of additional docking of compounds **3** and **3a** in Surflex-Dock (Figs. 4 and 5). We found that the highest ranked structure for compound **3** that met the distance criteria to phosphate had a score of 8.98 and a distance of 4.6 Å. The docking configuration differed from Dock in that it flipped the orientation of the malonic acid and carboxylic acid groups on the molecule. For comparison, Rank 1 had a higher score of 9.41, but a much longer distance of 9.1 Å. The highest ranked configuration for compound **3a** had a score of 6.08 and distance of 3.9 Å.

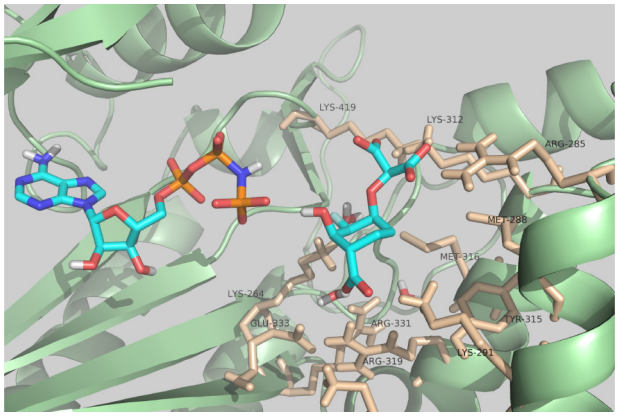


Fig. 4. Proposed docking of compound **3** (Rank 3) from Surflex-Dock. Image generated using PyMol 1.5.0.5.[22]

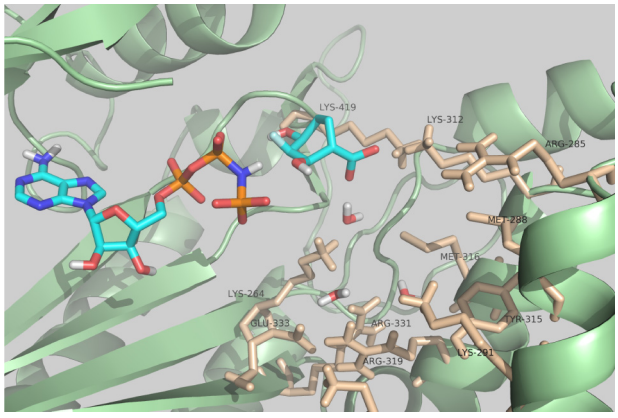


Fig. 5. Proposed docking of compound **3a** (Rank 1) from Surflex-Dock. Image generated using PyMol 1.5.0.5.[22]

In summary, we created a small virtual library of 54 compounds, which were docked in the binding site of human inositol 1,4,5-trisphosphate 3-kinase. The top scoring structures were selected based on both docking score and the ability to meet distance criteria for 3′-OH to -P in phosphate of the ATP analog. Based on computational docking experiments we have attempted the synthesis of the top best inositol analog as well as the synthesis of (1*S*,2*R*,3*R*,4*S*)-3-fluoro-2,4-dihydroxycyclohexane carboxylic acid **3a**, which we sought as a potential PET imaging probe for non-invasive visualization and quantitation of IP_3-3K activity. We are currently in the process of efficacy studies of the non-radioactive **3a** using corresponding precursor molecules and performing in vitro time-dependent accumulation and washout studies in different glioma cell lines, which will be reported in due course along with the synthesis of ^{18}F radiolabeled **3a**.

3. Experimental section

3.1. General

All reagents and solvents were obtained from Sigma–Aldrich (Milwaukee, WI) or Fisher Scientific (Pittsburg, PA) and used without further purification. Analytical HPLC was performed on a Varian Prostar system, with a Varian Microsorb-MW C18 column (250×4.6 mm; 5 μ) using the following solvent system *A*=0.1% TFA in water and *B*=0.1% TFA in acetonitrile. Varian Prepstar preparative system equipped with a Prep Microsorb-MW C18 column (250×41.4 mm; 6 μ; 60 Å) was used for preparative HPLC with the same solvent systems. Mass spectra (ion spray, a variation of electrospray) were acquired on an Applied Biosystems Q-trap 2000 LC–MS–MS. UV was measured on Perkin–Elmer Lambda 25 UV/vis spectrometer. IR was measured on Perkin–Elmer Spectra One FT-IR spectrometer. Optical rotations were measured at 20 °C on a Perkin–Elmer model 341 polarimeter. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Biospin spectrometer with a B-ACS 60 auto sampler (600.13 MHz for ^1H NMR, 564.57 MHz for ^{19}F NMR, and 150.92 MHz for ^{13}C NMR). Chemical shifts (δ) are determined relative to $CDCl_3$ referenced to 7.26 ppm for ^1H NMR and 77.16 ppm for ^{13}C NMR, and CF_3COOH as an external standard for ^{19}F NMR. Proton–proton coupling constants (*J*) were given in Hertz and spectral splitting patterns are designated as singlet (s), doublet (d), triplet (t), quadruplet (q), multiplet or overlapped (m), and broad resonance (br). Flash column chromatography was performed using Merck silica gel 60 (mesh size 230–400 ASTM) or using an Isco (Lincoln, NE) combiFlash Companion or SQ16x FC system with RediSep columns (normal phase silica gel, mesh size 230–400 ASTM) and Fisher Optima TM grade solvents. Thin-layer chromatography (TLC) was performed on E. Merck (Darmstadt, Germany) silica gel F-254 aluminum-backed plates with visualization under UV (254 nm) and by staining with potassium permanganate or ceric ammonium molybdate.

*3.1.1. (4R,5S)-3-(2-(Benzyloxy) acetyl)-4-methyl-5-phenyloxazolidin-2-one (**11**).* *n*-Butyllithium (199 mmol, 1.6 M in hexane) was added dropwise to a solution of oxazolidinone **9**[21] (32 g, 38 mmol) in anhydrous THF (80 mL) under nitrogen at −78 °C. After the mixture was stirred at −78 °C for 30 min, benzyloxyacetic chloride **10** (35 mL, 220 mmol) was slowly added and the resultant light yellow solution was maintained at −78 °C for an additional 30 min, then allowed to warm to 0 °C in about 1 h. Then, satd aqueous ammonium chloride solution (100 mL) was added, and the volatiles were removed under reduced pressure. The residue was diluted with dichloromethane (200 mL) then, washed with water (100 mL), satd aqueous sodium bicarbonate solution (2×100 mL), brine solution, and dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residual viscous red oil was recrystallized from toluene as a white crystalline *N*-(acetoacety1) derivative **11** (50.5 g, 86% yield): R_f=0.7 (50% EtOAc in hexane); $[\alpha]_D^{23}$ +31.6° (*c* 1.04, $CHCl_3$); IR ν_{max} 2981.37, 2861.1, 1775.31, 1716.25, 1348.19, 1125.29 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 0.79 (d, *J*=6.6 Hz, 3H, CH_3), 4.59 (s, 2H), 4.67 (s, 2H), 4.83 (q, *J*=7.3, 6.6 Hz, 1H, $CHCH_3$), 5.90 (d, *J*=7.6 Hz, 1H, −O*CH*Ph), 7.2–7.5 (m, 10H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 4.4, 53.4, 69.3, 72.2, 79.2, 125.9, 127.6, 127.7, 128.2, 128.4, 128.4, 133.8, 137.9, 152.8, 169.6. HRMS ($C_{19}H_{19}NO_4 + Na^+$) calcd 348.1206, found 348.1176 $[M+Na]^+$.

*3.1.2. (4R,5S)-3-((2R,3S)-2-(Benzyloxy)-3-hydroxypent-4-enoyl)-4-methyl-5-phenyloxazolidin-2-one (**12**).* To a solution of imide **11** (20 g, 61.53 mmol) in DCM (60 mL) at −40 °C was added di-*n*-

butylboryl trifluoromethanesulfonate (67 mmol, 1 M in DCM), followed by triethylamine (11 mL, 75 mmol). The solution was stirred at −40 to −30 °C for 1 h and then cooled to −78 °C. Freshly distilled acrolein was added dropwise and the mixture was stirred at −78 °C for 1.5 h, and then warmed to 0 °C for 30 min. The reaction was quenched at 0 °C by dropwise addition of pH 7 phosphate buffer (1.2 mmol per oxazolidinone), methanol (4 mL/mmol of oxazolidinone), and 30% H_2O_2, stirred for 1 h at 0 °C. The aqueous layer was extracted with DCM (3×60 mL), and the combined organic solution was washed with satd sodium bicarbonate solution (2×50 mL), satd sodium chloride (50 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue obtained was purified by flash column chromatography over silica gel (hexanes/EtOAc, 3:1) to give **12** (20.9 g, 89% yield) as a colorless oil. R_f=0.5 (50% EtOAc in hexane); $[\alpha]_D^{23}$ +50.9 (*c* 1.02, $CHCl_3$); IR ν_{max} 3547.85, 2992.28, 2877.41, 1787.71, 1711.91, 1354.37, 1115.37 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.85 (d, *J*=6.5 Hz, 3H), 2.81 (d, *J*=7.2 Hz, 1H), 4.47 (s, 1H), 4.57 (d, *J*=11.5 Hz, 1H), 4.67 (d, *J*=11.5 Hz, 1H), 4.73 (t, *J*=6.3 Hz, 1H), 5.28 (m, 2H), 5.38 (d, *J*=17.2 Hz, 1H), 5.67 (d, *J*=7.1 Hz, 1H), 5.99 (m, 1H), 7.2–7.5 (m, 10H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 55.4, 73.5, 73.8, 79.8, 80.0, 117.2, 125.7, 128.3, 128.5, 128.5, 128.8, 129.0, 132.0, 136.6, 137.0, 153.1, 170.2. HRMS ($C_{22}H_{23}NO_5$+Na) calcd 404.1468, found 404.1471 $[M+Na]^+$.

*3.1.3. (4R,5S)-3-((2R,3S)-2-(Benzyloxy)-3-(tert-butyldimethylsilyloxy) pent-4-enoyl)-4-methyl-5-phenyloxazolidin-2-one (**13**).* To a solution of the alcohol **12** (1 g, 2.62 mmol) and imidazole (463 mg, 6.8 mmol) in DMF (4 mL) was added TBSCl (529 mg, 3.4 mmol) at 0 °C. After stirring at room temperature for 48 h, the reaction mixture was diluted with ethyl acetate and washed with water, satd $NaHCO_3$, brine, and dried over $MgSO_4$, filtered, and concentrated to give the oil, which was purified by flash column chromatography over silica gel (5:1 hexanes/EtOAc) to obtain 1.3 g of **13** (yield 99%). R_f=0.55 (silica, 50% EtOAc in hexane); $[\alpha]_D^{23}$ +5 (*c* 1.0, $CHCl_3$); IR ν_{max} 3547.85, 2992.28, 2877.41, 1787.71, 1711.91, 1354.37, 1115.37 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.08 (s, 3H), 0.77 (d, *J*=6.5 Hz, 3H), 0.89 (s, 9H), 4.11 (q, *J*=7.0 Hz, 1H), 4.46 (t, *J*=6.1 Hz, 1H), 4.60 (t, *J*=6.7 Hz, 1H), 4.63 (d, *J*=11.88 Hz, 1H), 4.68 (d, *J*=11.88 Hz, 1H), 5.19 (d, *J*=10.44 Hz, 1H), 5.26 (d, *J*=16.0 Hz, 1H), 5.45 (d, *J*=5.8 Hz, 1H), 5.53 (d, *J*=5.8 Hz, 1H), 5.28 (m, 2H), 5.96 (m, 1H), 7.25 (d, *J*=8.3 Hz, 3H), 7.31 (t, *J*=7.3 Hz, 2H), 7.37 (d, *J*=6.6 Hz, 3H), 7.41 (t, *J*=7.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 4.7, 14.5, 18.4, 26.0, 55.4, 73.6, 75.4, 79.3, 80.1, 117.0, 125.7, 128.0, 128.4, 128.5, 128.8, 128.9, 133.2, 136.9, 137.7, 152.8, 170.7. HRMS ($C_{28}H_{37}NO_5Si$) calcd 496.2514, found 496.2501 $[M+H]^+$.

*3.1.4. (2S,3S)-2-(Benzyloxy)-3-(tert-butyldimethylsilyloxy) pent-4-en-1-ol (**14**).* To a solution of auxiliary imide **13** (750 mg, 1.5 mmol) and anhydrous MeOH (91 μL, 2.25 mmol) in ether (16 mL) was added $LiBH_4$ (2.25 mmol, 2 M in THF) at 0 °C. The reaction was stirred for an hour then the mixture was quenched with Rochelle salt and stirred for an additional 1.5 h. The mixture was diluted with water and the aqueous layer was extracted with ether (4×40 mL) and the combined organic extracts were washed with satd aqueous $NaHCO_3$, brine, and dried over $MgSO_4$, filtered, and concentrated. The crude was purified by flash column chromatography over silica gel (hexanes/EtOAc, 3:1) to get **14** as colorless oil (470 mg, 96% yield). R_f=0.7 (silica, 50% EtOAc in hexane); $[\alpha]_D^{23}$ +5.2 (*c* 1.0, $CHCl_3$); IR ν_{max} 3460.67, 2955.23, 2929.51, 2857.45, 1254.29, 1059.44, 1027.54 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ −0.01 (s, 3H), 0.00 (s, 3H), 0.85 (s, 9H), 2.09 (s, 1H), 3.47 (q, *J*=5.2 Hz, 1H), 3.53 (dd, *J*=6.3 Hz, 1H), 3.67 (dd, *J*=6.3 Hz, 1H), 4.30 (t, *J*=5.3 Hz, 1H), 4.59 (d, *J*=11.88 Hz, 1H), 4.67 (d, *J*=11.88 Hz, 1H), 5.14 (d, *J*=10.56 Hz, 1H), 5.26 (d, *J*=17.2 Hz, 1H), 5.91 (m, 1H), 7.25 (m, 1H), 7.30 (d, *J*=4.4 Hz, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.0, −4.7, 18.1, 25.8, 61.7, 73.0, 83.6, 81.7, 115.9, 127.8, 128.5, 136.8, 138.4. HRMS ($C_{18}H_{30}O_3Si$) calcd 323.2037, found 323.2021 $[M+H]^+$.

*3.1.5. (2R,3S)-2-(Benzyloxy)-3-(tert-butyldimethylsilyloxy)pent-4-enal (**7**).* To a solution of oxalyl chloride (216 μL, 2.5 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added DMSO (293 μL, 3.75 mmol) dropwise and stirred for 20 min. Then, the alcohol **14** (400 mg, 1.25 mmol) dissolved in CH_2Cl_2 (2 mL) was added slowly. After 30 min, Et_3N (1 mL, 7.5 mmol) was added and stirred for 30 min. The reaction mixture was warmed to room temperature within 1 h and was quenched with satd NH_4Cl solution, the aqueous solution was extracted with CH_2Cl_2 and the combined organic solution was dried over $MgSO_4$, filtered, and concentrated. The residue obtained was purified by flash column chromatography over silica gel (hexane/EtOAc, 5:1) to give **7** as clear oil (373 mg, 94% yield). R_f=0.5 (silica, 17% EtOAc in hexane); $[\alpha]_D^{23}$ −6.3 (*c* 1.0, $CHCl_3$); IR ν_{max} 2954.80, 2929.79, 2857.48, 1733.56, 1252.90, 1086.74 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ −0.004 (s, 3H), 0.00 (s, 3H), 0.88 (s, 9H), 3.74 (d, *J*=5.5 Hz, 1H), 4.43 (t, *J*=5.3 Hz, 1H), 4.53 (d, *J*=12.0 Hz, 1H), 4.71 (t, *J*=12.0 Hz, 1H), 5.17 (d, *J*=10.56 Hz, 1H), 5.26 (d, *J*=17.2 Hz, 1H), 5.94 (m, 1H), 7.27 (m, 1H), 7.31 (d, *J*=4.4 Hz, 4H), 9.64 (d, *J*=2.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.1, −4.6, 18.1, 25.7, 72.9, 73.7, 85.7, 116.6, 128.0, 128.0, 128.5, 136.9, 137.3, 202.4. HRMS ($C_{18}H_{28}O_3Si$) calcd 321.1880, found 321.1869 $[M+H]^+$.

*3.1.6. (2S,3R,4S,5S)-Ethyl 4-(benzyloxy)-5-(tert-butyldimethylsilyloxy)-3-hydroxy-2-vinylhept-6-enoate (**6**).* To a solution of the aldehyde **7** (4.1 g, 12.8 mmol) in H_2O (55 mL) was added ethyl 4-bromocrotonate **8** (7.4 mL, 40.9 mmol), $La(OTf)_3$ (15.75 g, 26.9 mmol), and indium (60 mesh, 3.4 g, 29.4 mmol). After being stirred for 48 h at room temperature, the mixture was filtered through Celite, which was rinsed with Et_2O. The filtrate was concentrated and purified by FC (EtOAc/hexane, 1:5) to afford compound **6** as a colorless oil[8] (4.22 g, 76%). R_f=0.4 (silica, 17% EtOAc in hexane); $[\alpha]_D^{23}$ −49.3 (*c* 1.1, $CHCl_3$); IR ν_{max} 3525.04, 2956.27, 2930.08, 2857.79, 1735.35, 1639.14, 1251.21, 1079.01 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ −0.007 (s, 3H), 0.0 (s, 3H), 0.86 (s, 9H), 1.20 (t, *J*=7.1 Hz, 3H), 2.55 (d, *J*=9.4 Hz, 1H), 3.18 (t, *J*=9.4 Hz, 1H), 3.36 (d, *J*=6.7 Hz, 1H), 4.00 (t, *J*=9.3 Hz, 1H), 4.10 (m, 2H), 4.34 (t, *J*=6.5 Hz, 1H), 4.34 (t, *J*=6.5 Hz, 1H), 4.56 (d, *J*=11.6 Hz, 1H), 4.88 (d, *J*=11.6 Hz, 1H), 4.95 (d, *J*=17.2 Hz, 1H), 5.10 (d, *J*=10.3 Hz, 1H), 5.16 (d, *J*=10.4 Hz, 1H), 5.27 (d, *J*=17.2 Hz, 1H), 5.65 (m, 1H), 5.93 (m, 1H), 7.25 (m, 1H), 7.32 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ −4.8, −4.5, 14.1, 18.1, 25.8, 55.5, 60.7, 71.0, 73.8, 74.0, 79.7, 116.5, 119.6, 127.8, 128.4, 133.2, 137.9, 138.2, 172.4. HRMS ($C_{24}H_{38}O_5Si$) calcd 435.2561, found 435.2543 $[M+H]^+$.

*3.1.7. (1S,4S,5S,6R)-Ethyl 5-(benzyloxy)-4-(tert-butyldimethylsilyloxy)-6-hydroxycyclohex-2-enecarboxylate (**16**).* To a solution of the diene **6** (910 mg, 2.1 mmol) in toluene (50 mL) was added Grubb's second generation catalyst (180 mg, 0.21 mmol), and the mixture was stirred at 60 °C in the dark for 4 days. The mixture was evaporated to dryness and purified by flash column chromatography (EtOAc/hexane, 1:3) to give compound **16** (826 mg, 97%) as a colorless oil. R_f=0.4 (silica, 25% EtOAc in hexane); $[\alpha]_D^{23}$ +69.9 (*c* 1.0, $CHCl_3$); IR ν_{max} 3527.96, 2951.03, 2927.93, 2855.59, 1719.70, 1652.02, 1181.33, 1079.01, 1042.00 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.0 (s, 6H), 0.80 (s, 9H), 1.14 (t, *J*=7.1 Hz, 3H), 2.82 (s, 1H), 3.12 (dd, *J*=8.2, 2.6 Hz, 1H), 3.38 (dd, *J*=7.2 Hz, 1H), 4.05 (m, 3H), 4.21 (dd, *J*=7.0, 2.7 Hz, 1H), 4.60 (d, *J*=11.5 Hz, 1H), 4.80 (d, *J*=11.6 Hz, 1H), 5.50 (s, 2H), 7.16 (m, 1H), 7.23 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ −4.6, −4.5, 14.1, 18.0, 25.8, 50.0, 61.2, 70.1, 72.2, 74.9, 83.6, 122.9, 127.7, 128.5. 131.5, 138.4, 171.9. HRMS ($C_{22}H_{34}O_5Si$) calcd 407.2248, found 407.2217 $[M+H]^+$.

*3.1.8. (1S,4S,5S,6R)-Ethyl 6-acetoxy-5-(benzyloxy)-4-(tert-butyldimethylsilyloxy)cyclohex-2-enecarboxylate (**17**).* To a solution of the

alcohol **16** (550 mg, 1.35 mmol) and pyridine (1 mL, 13.5 mmol) in DCM (20 mL) was added acetyl chloride (265 μL, 3.4 mmol) at 0 °C. The reaction was stirred at room temperature for 18 h. The mixture was evaporated to dryness and purified by flash column chromatography (EtOAc/hexane, 1:5) to give compound **17** (540 mg, 89%) as a white solid. R_f=0.25 (silica, 25% EtOAc in hexane); $[\alpha]_D^{23}$ +74.0 (*c* 1.0, $CHCl_3$); IR ν_{max} 2957.56, 2930.05, 2856.48, 1748.77, 1726.46, 1348.82, 1234.30 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ −0.02 (s, 3H), 0.0 (s, 3H), 0.81 (s, 9H), 1.14 (t, *J*=7.1 Hz, 3H), 1.18 (s, 3H), 3.24 (m, 1H), 3.51 (d, *J*=7.4 Hz, 1H), 4.04 (m, 2H), 4.32 (m, 1H), 4.58 (d, *J*=11.5 Hz, 1H), 4.72 (d, *J*=11.6 Hz, 1H), 5.36 (t, *J*=7.1 Hz, 2H), 5.51 (d, *J*=10.2, 1H), 5.56 (d, *J*=10.2, 1H), 7.20 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ −4.6, −4.6, 14.0, 18.0, 20.9, 25.8, 48.6, 61.4, 70.8, 72.5, 75.1, 82.4, 122.3, 127.4, 128.3, 132.0, 138.5, 169.8, 170.9. HRMS ($C_{24}H_{36}O_6Si$) calcd 449.2354, found 449.2371 $[M+H]^+$.

*3.1.9. (1S,4S,5R,6R)-Ethyl 6-acetoxy-5-(benzyloxy)-4-hydroxycyclohex-2-enecarboxylate (**18**).* To a solution of **17** (200 mg, 0.45 mmol) in EtOH (10 mL) was added concentrated HCl (220 μL), after stirring at room temperature for 18 h, the reaction mixture was concentrated to give compound **18** (149 mg, 99%) as a colorless oil. R_f=0.1 (silica, 25% EtOAc in hexane); $[\alpha]_D^{23}$ +77.6 (*c* 1.0, $CHCl_3$); IR ν_{max} 3357.00, 3033.02, 2977.88, 298.83, 1732.57, 1457.75, 1370.04, 1228.54 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.24 (t, *J*=7.1 Hz, 3H), 2.01 (s, 3H), 2.68 (s, 1H), 3.35 (m, 1H), 3.60 (t, *J*=7.8 Hz, 1H), 4.13 (m, 2H), 4.34 (m, 1H), 4.73 (d, *J*=11.5 Hz, 1H), 4.78 (d, *J*=11.6 Hz, 1H), 5.51 (t, *J*=7.1 Hz, 2H), 5.64 (d, *J*=10.2, 1H), 5.74 (d, *J*=10.2, 1H), 7.32 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 21.0, 48.7, 61.5, 71.0, 75.0, 82.3, 123.4, 127.7, 127.9, 128.7, 130.3, 138.1, 169.8, 170.7. HRMS ($C_{18}H_{22}O_6$) calcd 335.1489, found 335.1461 $[M+H]^+$.

*3.1.10. (1R,2R,3S,6S)-2-(Benzyloxy)-6-(ethoxycarbonyl)cyclohex-4-ene-1,3-diyl diacetate (**20**).* Acylation procedure was similar to compound **17** to give **20** as colorless oil. $[\alpha]_D^{23}$ +88.5 (*c* 1.0, $CHCl_3$); IR ν_{max} 3031.60, 2983.47, 2936.80, 1733.03, 1370.07, 1228.54 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.23 (t, *J*=7.1 Hz, 3H), 1.99 (s, 3H), 2.02 (s, 3H), 3.36 (m, 1H), 3.82 (t, *J*=7.8 Hz, 1H), 4.12 (m, 2H), 4.69 (m, 2H), 5.50 (m, 1H), 5.55 (t, *J*=7.1 Hz, 2H), 5.69 (d, *J*=10.2, 1H), 5.77 (d, *J*=10.2, 1H), 7.30 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.0, 20.9, 21.0, 47.7, 61.5, 70.4, 72.6, 74.2, 78.5, 125.1126.8, 127.5, 127.7, 128.3, 138.0, 169.6, 17.0.1, 170.2. HRMS ($C_{20}H_{24}O_7$) calcd 377.1595, found 377.1561 $[M+H]^+$.

*3.1.11. (1S,2R,3R,4S)-4-(Ethoxycarbonyl)-2-hydroxycyclohexane-1,3-diyl diacetate (**21**).* Compound **20** (170 mg, 0.45 mmol) was mixed with wet 10% Pd−C in MeOH (20 mL) under balloon-H_2 for 18 h and filtered through Celite. The filtrate was evaporated to dryness and purified by flash column chromatography (EtOAc/hexane, 1:1) to give **21** (127 mg, 98%) as a white solid. R_f=0.5 (silica, 50% EtOAc in hexane); $[\alpha]_D^{23}$ +12.3 (*c* 1.0, $CHCl_3$); IR ν_{max} 3490.74, 2958.98, 1724.03, 1229.03, 1026.93 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.20 (t, *J*=7.1 Hz, 3H), 1.37 (q, *J*=13.0 Hz, 1H), 1.61 (q, *J*=13.5 Hz, 1H), 1.96 (d, *J*=13.98 Hz, 1H), 2.03 (s, 3H), 2.0 (s, 3H), 2.51 (t, *J*=11.94 Hz, 1H), 2.67 (b, 1H), 3.49 (t, 1H), 4.08 (m, 2H), 4.76 (t, 1H), 5.09 (t, *J*=9.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.1, 20.9, 21.2, 24.0, 28.4, 47.1, 61.1, 74.5, 74.6, 170.9, 170.9, 171.7. HRMS ($C_{13}H_{20}O_7$) calcd 289.1282, found 289.1261 $[M+H]^+$.

*3.1.12. (1S,2R,3R,4S)-4-(Ethoxycarbonyl)-2-(trifluoromethyltnqh_0009;sulfonyloxy)cyclohexane-1,3-diyl diacetate (**5**).* To a solution of **21** (100 mg, 0.35 mmol) in DCM (25 mL) was added triflate anhydride (100 μL, 0.575 mmol), the reaction mixture was stirred at room temperature for 60 min. The solvent was evaporated to dryness and the compound was purified by flash column chromatography (EtOAc/hexane, 1:1) to give **5** (128 mg, 88%) as a white solid. R_f=0.5 (silica, 25% EtOAc in hexane); IR ν_{max} 2953.10, 1753.95, 1731.99, 1410.48, 1183.83 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.24 (t, *J*=7.1 Hz, 3H), 1.47 (q, *J*=14.4 Hz, 1H), 1.73 (q, *J*=13.5 Hz, 1H), 2.03 (d, *J*=13.98 Hz, 1H), 2.07 (s, 3H), 2.09 (s, 3H), 2.29 (d, *J*=10, 3.2 Hz, 1H), 2.60 (td, *J*=14.2, 3.7 Hz, 1H), 4.11 (m, 2H), 4.83 (t, *J*=9.8 Hz, 1H), 4.98 (td, *J*=9.5, 4.98 Hz, 1H), 5.38 (t, *J*=10.32 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.1, 20.6, 20.8, 23.5, 28.5, 47.5, 61.7, 70.5, 71.0, 86.8, 115.2, 117.3, 119.4, 121.5 (q, CF_3 coupling, *J*=315 Hz), 169.2, 169.8, 170.4. HRMS ($C_{14}H_{19}F_3O_9S + NH_4^+$) calcd 438.1040, found 438.1072 $[M+NH_4]^+$.

*3.1.13. (1S,2R,3S,4S)-4-(Ethoxycarbonyl)-2-fluorocyclohexane-1,3-diyl diacetate (**22**).* To a solution of **5** (30 mg, 0.072 mmol) in acetonitrile (15 mL) was added TBAF (216 μL of 1 M solution in THF, 0.216 mmol), the reaction mixture was stirred at room temperature for 15 min and then heated at 50 °C for 30 min. The reaction mixture was evaporated to dryness and purified by flash column chromatography (EtOAc/hexane, 1:1) to give **22** (12 mg, 58%) as a white solid. R_f=0.2 (silica, 25% EtOAc in hexane); ^1H NMR (600 MHz, $CDCl_3$) δ 1.17 (t, *J*=7.1 Hz, 3H), 1.49 (qd, *J*=13.2, 3.9 Hz, 1H), 1.75 (qd, *J*=13.5, 3.2 Hz, 1H), 1.85 (m, 1H), 2.0 (s, 3H), 2.03 (s, 3H), 2.82 (td, *J*=11.94, 4.1 Hz, 1H), 4.07 (m, 2H), 4.75 (ddd, *J*=28.18, 5.12, 1.72 Hz, 1H), 4.88 (d, *J*=54.13 Hz, 1H), 4.99 (ddd, *J*=27.45, 11.71, 1.73 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.1, 20.7, 20.9, 23.8 (J_{C4-F1}=2.25 Hz), 24.0, 41.9 (J_{C4-F1}=2.25 Hz), 61.0, 70.4 (J_{C3-F1}=17.82 Hz), 71.5 (J_{C3-F1}=17.82 Hz), 89.0 (J_{C1-F1}=184.76 Hz), 169.7, 169.9, 172.2; ^{19}F NMR (564.57 MHz, $CDCl_3$) −215.18. HRMS ($C_{13}H_{19}FO_6$) calcd 291.1258, found 291.1271 $[M+H]^+$.

*3.1.14. (1S,2R,3S,4S)-3-Fluoro-2,4-dihydroxycyclohexanecarboxylic acid (**3**).* To a solution of **17** (10 mg, 0.034 mmol) in EtOH (3 mL) was added NaOH (100 μL of 1 M solution in water 0.1 mmol), the reaction mixture was refluxed for 30 min. The reaction mixture was evaporated to dryness and purified by Prep HPLC (10% CH_3CN in water). The correct fractions indicated by Mass Spec were collected to give **3** (6 mg, 99% yield). R_f=0.4 (silica, 25% acetonitrile in water); ^1H NMR (600 MHz, D_2O) δ 1.02 (t, *J*=7.5 Hz, 1H), 1.19 (q, *J*=13.2 Hz, 1H), 1.45 (q, *J*=13.5, 1H), 1.65 (d, 1H), 2.25 (t, *J*=10.60 Hz, 1H), 3.49 (q, *J*=7.1 Hz, 1H), 4.62 (m, 2H), 4.68 (d, *J*=54.07 Hz, 1H); ^{13}C NMR (150 MHz, D_2O) δ 24.4, 26.4, 47.2, 68.9 (J_{C3-F1}=17.92 Hz), 70.8 (J_{C3-F1}=17.82 Hz), 94.5 (J_{C1-F1}=175.86 Hz), 182.3; ^{19}F NMR (564.57 MHz, $CDCl_3$) −217.29. HRMS ($C_7H_{11}FO_4$) calcd 177.0569, found 177.0543 $[M-H]^-$.

4. Modeling

4.1. Initial design work

Modeling calculations for initial design work were conducted on a four-processor MIPS R16000 Silicon Graphics Tezro running Sybyl 7.1 or Sybyl 7.2 (Tripos, Inc, St. Louis, MO). The program Grid[23] (Molecular Discovery) was used to calculate the preference of various probes in the vicinity of the binding site. For searching of the structural databases, the Unity and Concord modules in Sybyl were used. Compound libraries used for searching were received in the SDF file format from the several vendors and converted to a 3D database using Unity. Sybyl programming language (SPL) scripts[24] were utilized as part of the ligand conversion and docking analysis.

The crystal structure of human inositol 1,4,5-trisphosphate 3-kinase was obtained from the RCSB PDB website (www.pdb.org) as entry 1w2c.[4,25] Chain B, waters, and all non-protein atoms except for ANP and Mn were removed from the structure. The protein preparation tool was utilized to add caps to the N- and C-terminus. AMBER parameters and associated charges were applied to the structure after adding hydrogens. The D-*myo*-inositol-1,4,5-triphosphate ligand was prepared by adding hydrogens and assigning Gasteiger−Hückel charges. The combinatorial library was constructed with CombiLibMaker Module of Sybyl; however, it was necessary to manually correct the stereochemistry for some attachment points. A total of 54 compounds (3×3×3×2) were

generated in 2D SLN format. Those structures were then converted to 3D, ionized, and converted to a single multi-mol2 formatted file using an SPL script. For all the virtual compounds we utilized a −1 (negative 1) charge for all the carboxylate groups as would be expected for this functional group at a pH of 7.

Docking was completed with the Dock 5.2.0 from UCSF.[26] The DMS program distributed with Dock was utilized to generate the surface and spheres were generated within 10 Å of the ligand with SPHGEN utility.[27] A box with default boundary was created around the spheres using the SHOWBOX utility and scoring function potential grids were pre-calculated using the GRID utility in Dock. Docking was completed with defaults, except that 10 configurations were requested for each structure. Post processing of the docking structures and energies was done with an SPL script (see Supplementary data) that identified the 3-OH position and determined configurations having a distance of less than 4.6 Å to the phosphorus atom.

4.2. Additional docking

Additional docking calculations were conducted on a 2-eight core (16-core) 3.0 Ghz AMD Opteron system running RHEL 6.x. Structural preparation, minimization, and visualization of the docking results were completed in the Sybyl-X 2.0 suite from Tripos.[28] Docking calculations were completed with Surflex-Dock v2.601.12048.[29] This structure 1w2c was read into Sybyl and Chain B was removed. The two sulfate groups in the structure and all waters except 2035, 2036, and 2070 were also removed. Bonds to the Mn were removed and the Mn was changed to Mg, since Mn is not a valid atom type for the MMF94 force field as implemented in Sybyl. A basic protein preparation was done to repair sidechains and charge the termini. Hydrogens were added to the entire structure and corrected on the phosphate groups. Lone pair atom types added during the hydrogen addition stage were also removed. A staged minimization was used to optimize the structure and this consisted of 250 steps each for hydrogens only, waters, hydrogens+sidechains, hydrogens+sidechains+backbone except Cα, ligands, and all atoms. The Powell minimize method was utilized with initial Simplex optimization. The MMFF94 force field was selected and a non-bonded cutoff of 12 Å was applied. A distance dependent dielectric of 2.0 was used to further screen the electrostatic interactions. The Surflex-Dock protomol was defined based on the crystal ligand. Docking of compounds **3** and **3a** was completed with 'pgeomx' modes.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.11.092.

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