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Chemical Approach to Signal Transduction by Inositol Triphosphate

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Abstract

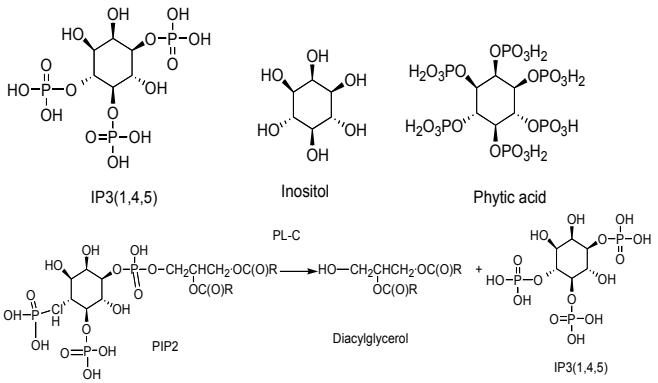
Berridge discovered that inositol 1,4,5-trisphophate (IP3) was generated at the cell surface in response to cell stimulation and functioned as a second messenger to release Ca^{2+} from internal stores. Ozaki et al. succeeded in the first total synthesis of optically active IP_3 by 13 steps. He supported the signal transduction studies by supplying necessary reagents such as IP_3, other IPx, phosphatidyl inositol, new synthetic methods and reagents. He discovered the regulators of Ca^{2+} release and consequent cellular processes.

Keywords: Signal transduction; Inositol trisphosphate; IP3Phosphatidyl inositol; Regulator of cellular process

Introduction

The fact that diacyl glycerol is second messenger was found by late Professor Yasutomi Nishizuka [1] and the fact that Inositol triphosphate (IP_3) is a second messenger was discovered by Michael Berridge who showed that it functioned to release Ca^{2+} from internal stores. This bifurcating signaling system is of fundamental importance in regulating a wide range of cellular process.

Signals (first messenger) like light, noise, taste, odor, hormone, neurotransmitter, drug attach to the plasma membrane where they are recognized by cell surface receptors. Upon binding of the ligand to the appropriate receptor, activation of G protein activates in turn phospholipase C. Active phospholipase C hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) giving rise to two products: 1,2-diacylglycerol and inositol 1,4,5-triphosphate (IP_3). IP_3 stimulates the release of Ca^{2+} from the intracellular stores in the endoplasmic reticulum through IP_3 receptor while regulating a wide range of cellular processes.



Why Plant Biosynthesize Inositol

The rice bran, wheat, corn contain much phytic acid (inositol hexaphosphate) as Ca salt. Plant make glucose by photo synthesis from carbon dioxide and water. Some of glucose is converted to inositol. Inositol is converted to phospholipids (PIP_2) and phytic acid. PIP_2 is converted to IP_3 and diacylglycerol. These two compounds are essential for signal transduction of plant. Plant makes phytic acid as storage of phosphorous. Phosphorous is an essential atom as fertilizer because ii is an essential atom to make nucleic acid, DNA. The seed store phosphorous atom as a store so that even when seed germinate at no phosphorous land [1].

Discovery of IP_3

Phospholipid was discovered by Bollow in 1961 [2] from bovine brain. The hypothesis of Michell [3] that the receptor controlled hydrolysis of phosphoinositides could be directly linked to cellular calcium mobilization. The observation by Berridge D-myo-inositol 1,4,5-trisphosphate (IP_3) act as a second messenger, a fundamental cell-signal transduction mechanism has been elucidated. IP_3 stimulates the release of Ca^{2+} from the intracellular stores in the endoplasmic reticulum through IP_3 receptor while regulating a wide range of cellular processes [4-25].

Synthetic Competition of Inositol P

The discovery of inositol phosphate in particular IP_3 led to the dramatic stimulation for the synthesis of inositol phosphates. Many persons challenged the synthesis of inositol phosphate, starting from inositol, glucurolactone, phytic acid, arenas, quinic acid and L-quebrachitol.

A symposium; Inositol phosphates and Derivatives. Synthesis, biochemistry, and therapeutic potential was held by the division of carbohydrate Chemistry at the 200th National meeting of the American Chemical Society, Washington DC, August 26-31.1990. ACS Symposium Series. 463 Edited by Allen B.Reitz was published.

The key problems in the synthesis of inositol phosphates are (1) synthesis and optical resolution of suitably protected inositol derivatives, (2) efficient phosphorylation of vicinal hydroxy groups.

In 1986, Ozaki et al succeeded in the first total synthesis of optically active myo-inositol tris (1,4,5) phosphate from myo-inositol by 13 steps [26]. At this report, phosphorylation yield of 2,3,6-tribenzyl myo-inositol by dianilidephophotyl chloride isolation yield was only 10%. Then we have studied phosphorylation reagents and discovered new phsphorylation method Then we could get IP_3 by best method in good

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yield as shown in Figure 1 [26,27].

This IP_3 is produced by this method at DOJINDO (Kumamoto, Japan) and is distributed all over the world by the name of synthetic IP_3.

The synthesis of $I(1,4,5)P_3$ are reported by many investigators Billington and Vacca (from myo-inositol orthoformate [28], Ballou, from myo-inisitol [29], Gigg [30], Ley from arenes using Pseudomonasoxidation [31], Falch from Quinic acid [32], Stepanov and Shvets [33], Prestwich prepared D-myo-(^{3}H)$I(1,4,5)P_3$, essential and most used reagent for the study of signal transduction [34,35] Phosphothioate analogur of IP_3 by Potter [36].

Different Source and Methods

IP_3 was obtained through 6 different sources:

- Starting from myo –inositol [26-32,35-38]
- Starting from L-quebrachitol (natural rubber industry by-product) [39-43]
- Siarting from arenes [33]
- Starting frm Quinic acid [34]
- Starting from D-glucuronolactone [42]
- Chemoenzymztic synthesis of D-myo-inositol 1,4,5—trisphosphate [43-49]

Methods to Get Optically Pure Compound by 5 Different Methods

› Separation of diastereomers

- L- mentoxy acetyl chloride gave best result, because desired product was crystal [26]

› Starting from optically pure natural product

- From D-glucuronolactone [42], From Quinic acid [34]
- From L-quebrachitol [39-43]

› Use of tartaric acid ester [50]

› Use of enzyme (like Phosphorylase). Enzyme aided synthesis of D-myo-inositol 1,4,5-trisphosphate [43-48]

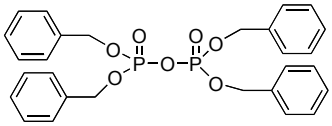
› Enzymic resolution of racemic 1,2:5,6-di-O-cyclohexylidene and 1,2:3,4-di-O-cyclohexylidene-myo-inositol [45]

› Enzymic resolution of sterically hindered myo-inositol derivatives [48]

› Enzyme aided regioselective acylation of nucleosides [49]

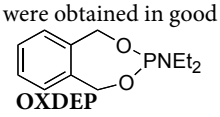
Phosphorylation Reagents [51]

- Tetrabenzyl pyrophosphate (TBPP) and n-BuLi [52].



TBPP +
n-BuLi

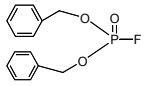
- New phosphorylating reagent called OXDEP (o-xylylene N,N-diethylphosphoamidite) [53,54]. By using this reagent, IP_3 and PIPx were obtained in good yield [27].



+ Tetrazol

OXDEP

- **DBPF** Dibenzyl phosphorofluororidate $(BnO)_2P(O)F$ [55]. This reagent was used for the synthesis of phosphofloridate analogues. Obtained phosphofloridates showed very interesting biological activity [56].



DBPF

- Step wise phosphorylation using PCl_3, BnOH, C_6H_5COOOH [57]
- Phosphorothioate synthesis based on the redox reaction of phosphite with tellurium (IV) chloride [58].

Discovery of Phosphonium Salt Methodology

This phosphonium salt methodology [59,60] provide a regioselective phospholylation. 1,2-Diol were phosphorylated regioselectively at C-1 with tribebzyl phosphite to give 1-dibenzyl phosphate 2-hyroxy free compound as shown in Figure 2. Other phosphory lating reagents do not have such selectivity. By using this free hydroxy group, we could get 2-acyl analog and IPx and PIPx. Three kind of combined reagents are possible.

Trialkyl phosphite and pyridinium bromide perbromide method [59]

$(RO)_3P$ + $PyHBr_3$,

1H-Tetrazol catalyzed the reaction of trialkyl phosphite [61]

$(PO)_3P$ + Tetrazole

Utilization of oxidizing character of $TeCl_4$ [62]

$(RO)_3P$ + $TeCl_4$

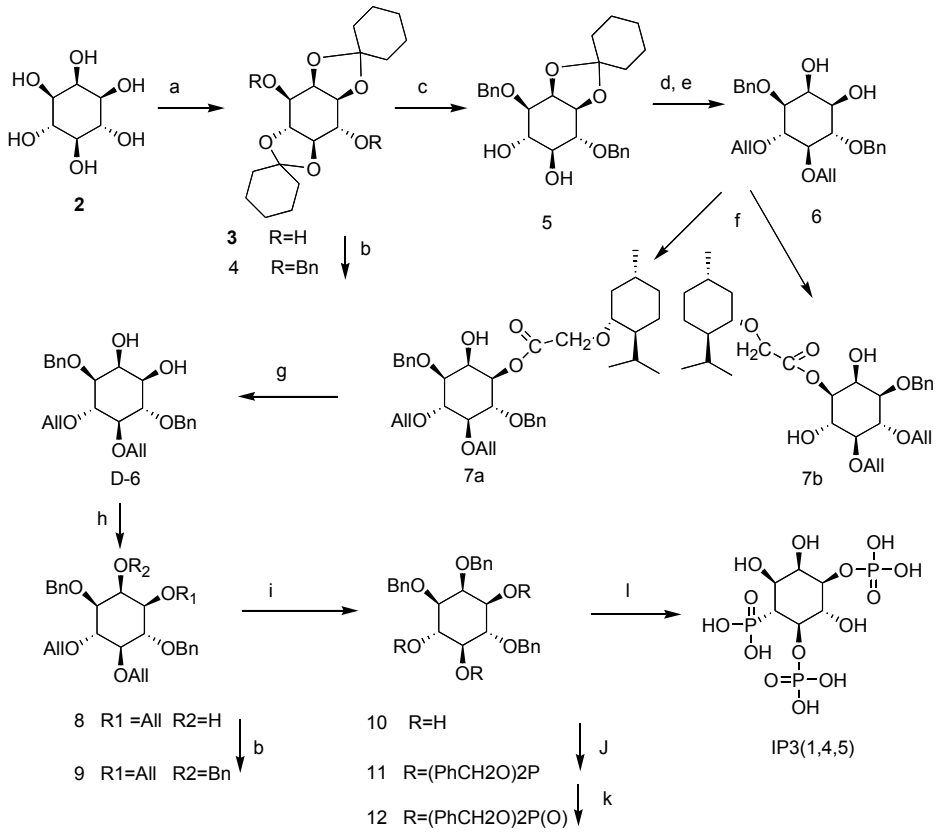
The reaction of an alcohol with a trialkylphophite in the presence of pyridinuum bromide per bromide proceed via the phosphonium salt $(RO)_3P^+Br$ to afford the triester R1-OP(O)$(OR)_2$, which can be converted to the phosphoric monoester by deprotection.

On the other hand, starting from dialkyl phosphoamidite $(R0)_2PNR$,'the corresponding triester product (R_1O-R_2O-P(O)OR") gave phosphoric mixed diesters.

The reactivity of phosphonium salt toward an alcohol seems to be between P^{III} and P^V, therefore we expected that the phosphonium salt methodology would provide a regioselective phosphorylation method. 1,2-Diol was phosphorylated regioselectively.

Applying the phosphonium salt approach to the synthesis of phosphoinositides, the use of glyceryl phosphite, which was derived by the reaction of the glycerol derivatives with dimethylphosphoramidite in the presence of tetrazol, gave the protected PI(4,5)P2.

We synthesized Phosphatidylinositol 3,4,5-trisphosphate [63,64], Unsaturated phosphatidyl inositol-3,4,5-trisphosphate [65], myo-inositol 1.2,5,6-tetrakisphosphate [66], 4-α-D-glucopyranosyl-myo-inositol, enzymic transglycosylation product. [67], 2,6-Di-O-(D-mannopyranosyl)phosphatidyl-D-myo-inositol [68], Phosphofluoridate analogs of myo-inositol 1,4,5-tris(phosphate) [56].



a:1-EtO-cyclohexane/TsOH, b:NaH/BnCl/DMF, c: (HOCH2)2/TsOH,.d: NaH/AllBr/DMF.

e :aq.AcOH, f: ll-MentAcCl/Py, g: aq.NaOH/MeOH, h: AllBr/NaOH, i: RhCl(PPh3)3/DABCO thenHCl/MeOH

j: (PhCH2O)2PN(i-Pr)2. k: mCPBA, l: H2/5% Pd-C

Figure 1: Synthesis of D—myo-inositol 1,4,5-trisphosphate

Finding of New Reaction, New Methods and New Reagents

Finding of new protection methods

- Protection by tetraisopropyldisiloxane-1,3-diyl group [69]
- Proximately assisted and chemoselectively cleavable protecting groups for alcohols, 2-[2-(arylmethyloxy)ethyl]benzoic esters [70].

Finding of new deprotection methods

- Deprotection of methyl group by AlCl3-NaI ,AlCl3-Bu4NI [71]
- Deprotection of benzyl and allyl group by AlCl3-dimethyl aniline [72]
- Deprotection p-methoxybenzyl by trimethylsilylchloride-tin(II) chloride—anisole [73].

Finding of diastereoselective addition methods

Diastereoselective addition of organometallics to α-keto esters [74].

Finding of diastereoselective reduction methods

Diastereoselective reduction of ketoester bearing chiro-inositol as chiral auxiliaries [75].

Finding of novel deacylation Methods

A Grignard reagent was used for deacylation without affecting the neighboring base-sensitive functional groups [76].

Finding of novel enatioselective acylation and deacylation Method

Enantioselective acylation and deacylation method using enzyme [38,77].

Finding of glycosidation method

Glycosidation based on phosphite chemistry [78,79]

Phosphorylation of inositol 1,4,5-trisphosphate analogs by 3-kinase and dephosphorylation of inositol 1,3,4,5-tetrakisphosphate analogs by 5-phosphatase [80].

Use of Inositol Derivatives as Chiral Auxialiaries

- Diastereoselective addition of organometallics to keto esters [74].
- Asymmetric synthesis of tetrahydrofurans by diastereoselective (3+2) cycloaddition of allylsilanes with ketoesters bearing optically active cyclitol as a chiral auxiliary [81].
- Preparation of optically active D 2-isooxazolines via addition

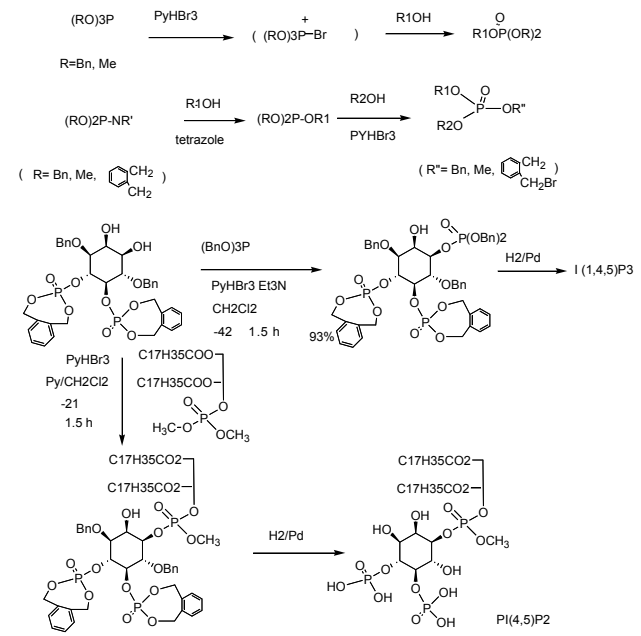


Figure 2: Phosphosphonium salt methodology for the synthesis of IPx nd PIPx.

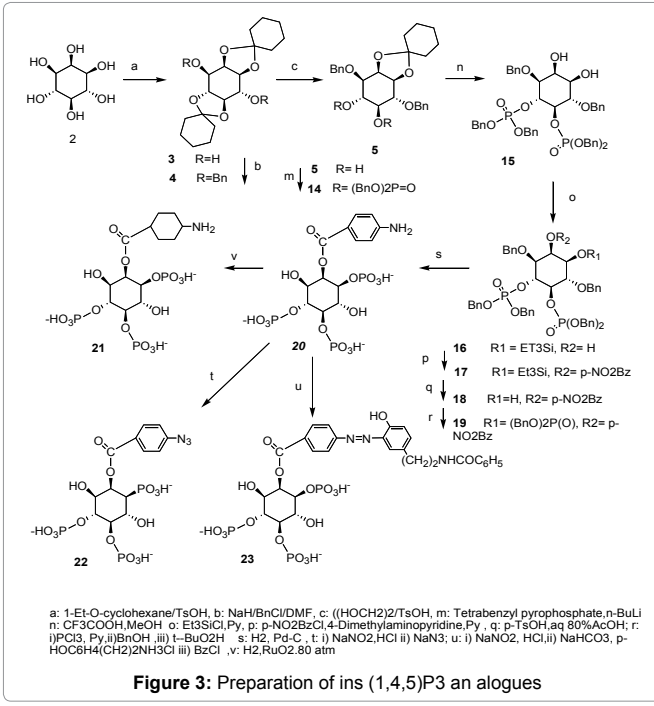


Figure 3: Preparation of ins (1,4,5)P3 an alogues

of nitril oxides to chiral acryloyoxy esters bearing cyclitols as auxiliaries [82].

- Asymmetric synthesis of functionalized tertially alcohols by the diastereoselective aldol reaction [83].

Preparation of IPx, IP_3 derivatives and IP_3 Analog, and Assessment of their Activities

Synthesized inositol poly phosphate [66,84-86]

Myo-inositol 1-phosphate [87,88], myo-inositol 1.3.4-trisphosphate [89], myo-inositol 1.4,6-trisphosphate [90], myo-inositol 1.3.4.5-tetrakisphosphate [91-93], myo-inositol 1.4,5,6-tetrakisphosphate [94], myo-inositol 2,4,5-trisphosphate [57], 1,2-cyclic-4,5-, 1,4,5- and 2,4,5-triphosphate [95], myo-inositol 1.2,5,6-tetrakisphosphate [65], 2,6-Di-O-(D- mannopyranosyl) phosphatidyl-D-myo-inositol [68], Phosphofluoridate analogs of myo-inositol 1,4,5-tris(phosphate) [55]. 4-a-D-glucopyranosyl-myo-inositol [50].

2-substituted IP_3 analogs

- These were synthesized as shown in Figure 3. These analogs were used for the preparation of affinity columns [96].
- Many IP_n and derivatives were prepared and their activities were measured by Prof. Hirata, Masato [96-113].
- Synthesis of IP_3 having biotinyl and azidobenzoyl groups [100].
- Synthesis of 2-substituted myo-inositol 1,3,4,5-tetrakis(phosphate) and 1,3,4,5,6-pentakis(phosphateanalogues [101].

Phosphofloridate analogues

Phosphofluoridate analogs of myo-inositol 1,4,5-tris(phosphate) were prepared as shown in Figure 4 [56].

The three phosphofluoridates thus prepared had potencies for inhibiting (^{3}H) $InsP_3$ binding to purified $InsP_3$ receptor that were less than for $InsP_3$. Two analogues 44 and 40 were found to inhibit the dephosphorylation of (^{1}H) Ins P_3 by the 5-phsphatase with potencies similar to that for $InsP_3$. Surprisingly, the inhibitory potency of 5-phosphofluoridate 44 toward 5-phosphosphatase was higher (about 20 fold) than those of $InsP_3$ and the another fluoridates 40 and 45.

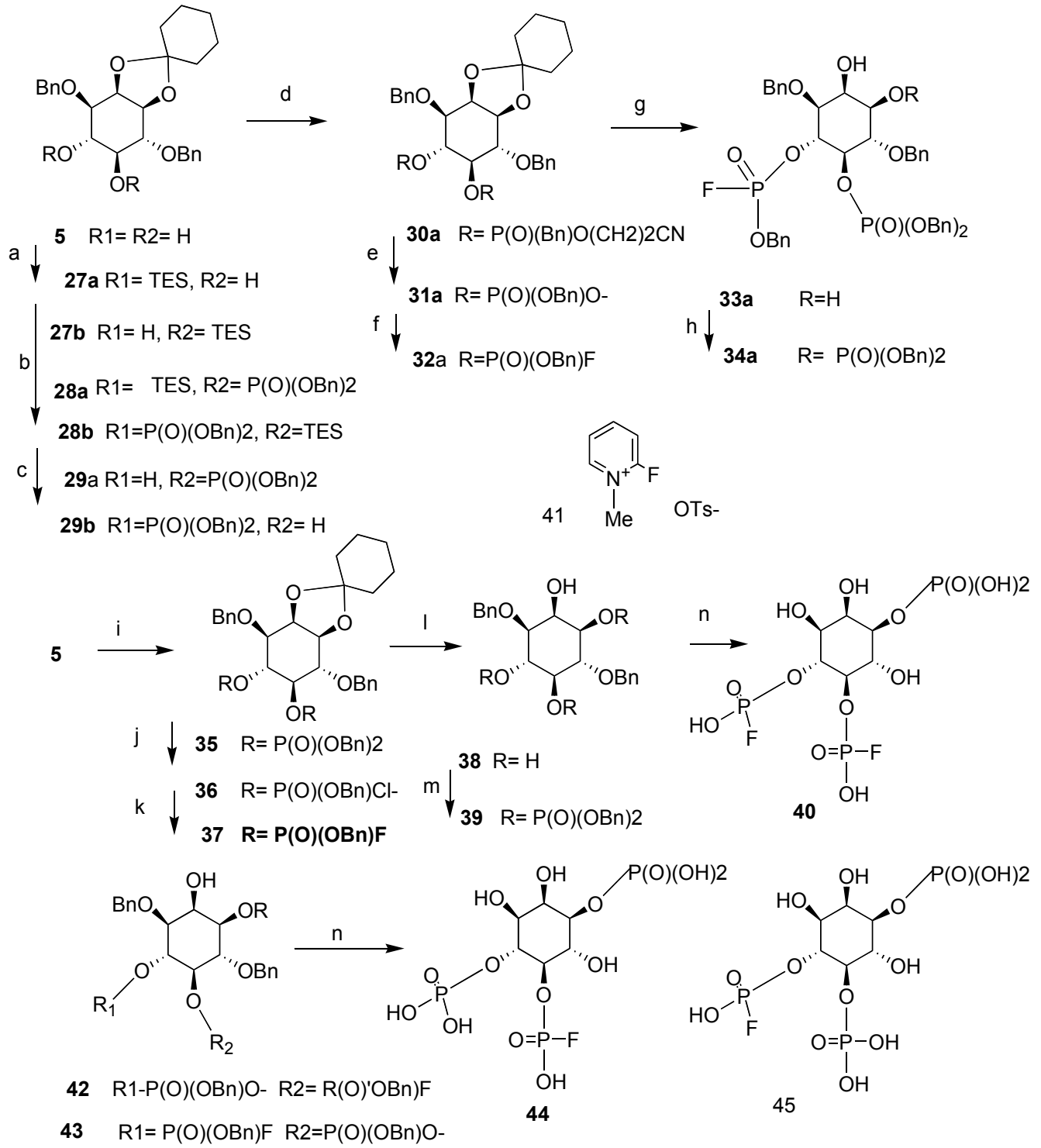
Preparation of Affinity Column

Inositol 1,4,5-trisphosphate affinity columns 24, 25 were prepared from 20, 21 as shown in Figure 5 to fish out IP_3-binding proteins [98,113,114].

Isolation and Characterization of Many IP_3-Binding Proteins

The following many proteins were isolated by affinity column and characterizations were carried out [103,111].

- IP_3 binding protein [102,103,113,115] co-work with Hirata Masato
- Phospholipase C-d1 [110,116] co-work with Hirata Masato.
- Porcine tracheal smooth muscle aldrase [109], collaboration with Carl Baron and Masato Hirata.
- 3-Kinase, 5-phosphatase [111,117] collaboration withVan Dijken
- Growth factor activating protein [112,118] collaboration with Moriya Shigeharu
- IP_3 3-kinase from porcine smooth muscle [119-121] co-work with Denborough.
- RAC-protein kinase (PKB/Akt [120] collaboration with Matsuzaki
- Expression and characterization of IP_3-binding domain of phosphatidyl inositol-specific phospholipase C [122] collaboration with Yagisawa, Hitoshi.
- IP_3 3-kinase from chicken erythrocytes [123] collaboration with George Myer.



a: Et3SiCl, Py b: (BnO)2PN i-Pr2 , Tetrazol then MCPBA. c: Bu4NF.3H2O, PhCO2H, THF,d: NC-(CH2)2O(BnO)PNiPr2,Tetrazole then MCPBA, e: Et3N MeCN,rt 2h, f.: :41, Et3N, g CF3COOH, h: (BnO)3P, PyHBr3,Et3N, H2 Pd-C ,AcOH-MeOH-H2O, i: (BnO)2PN iPr2,Tetrazole then MCPBA, j: PhSH,Et3N, k:: **41,** Et3N , l: CF3COOH, m: (BnO)3P,PyHBr3,Et3N n: H2, Pd-C

Figure 4: Synthesis of Phosphofluoridate analogues.

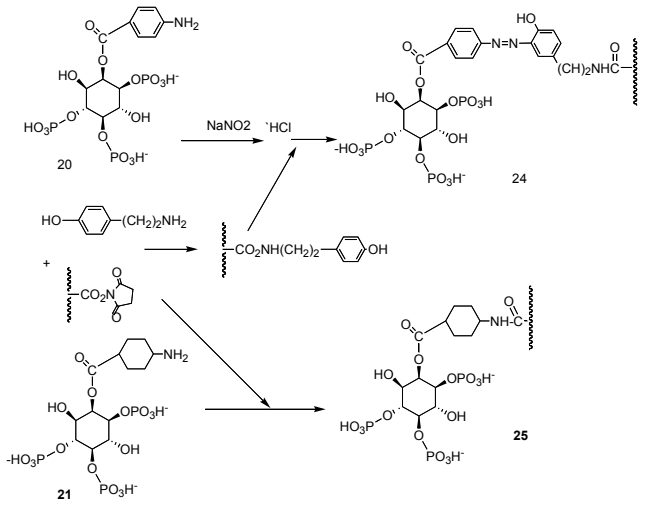


Figure 5: Preparation of IP3 affinity resin

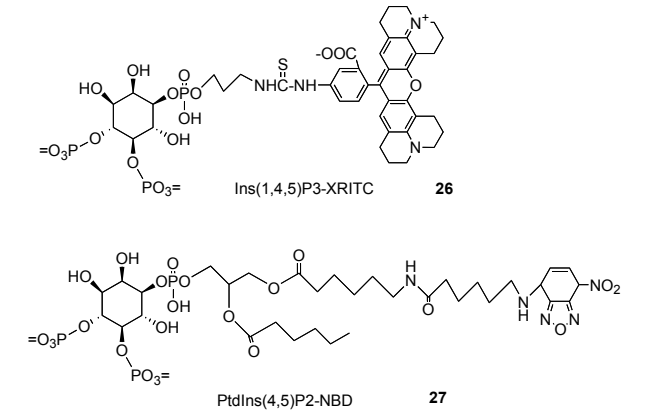


Figure 6: Fluorescent IP3 and PIP2

- Homogeneous Ca^{2+} Stores [124] collaboration with Inoue, Masumi
- Na+,K+- ATPase [125] collaboration with Lin, Hai
- Plasma membrane PtIns-4,5-P_2 [126] collaboration with Ronald Holz

Observation of Behaviors of IPx, PIPx and Ca^{2+} Flux in the cells

IP_3 and PIPx are charged compounds. Therefore they do not readily penetrate through cell membranes. But it becomes permeable following salt formation with amine and this is a new method to put IP_n or PIP_n into the cell [127-130].

Ozaki synthesized about 20 fluorescent IP_3, IP_4, PIP, PIP_2 containing fluorescent amines with green and red colors (Figure 6), and introduced these tagged molecules into cells. He then used fluorescent microscopy.

He observed how and how fast the IP_n or PIP_n entered into the cell and how moved and how changed, metabolized and also observed a calcium flux (time, location, concentration) in NIH 3T3 Fibloblasts, when complexes of carrier and Ptd Ins (4,5) or Inos (1,4,5) P_3 were added extra cellular. He took more than a thousand pictures and movies.

Detection of Ca^{2+} Flux

Fluoro-3 was used to measure intracellular calcium concentration. In case of IP_3 complex, Ca^{2+} maximum peak (2.5×10^{-7} M) was observed after 3.5 min. after addition of IP_3. In case of PIPx complex, Ca^{2+} maximum peak (4.2×10^{-7} M) was observed after 6.5 min.

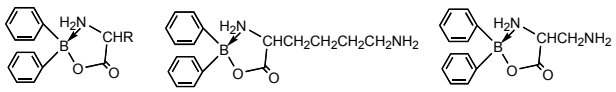
Discovery of DAB; Regulators of Ca^{2+} Release and Cellular Response

In 1997, we identified 2-aminoethyl diphenylborinate (2-APB) as being an IP_3 receptor inhibiter and regulate IP_3 induced calcium release [131,132]. This discovery rose a substantial interest and had a great impact as it gained more than 600 citations and more than 1000 studies on 2-APB have been published so far. This was supported by increasing sales of 2-APB by Sigma-Aldrich as membrane-permeable modulator of calcium release. We aimed at generate better modulator of calcium release than 2-APB.

We synthesizes several 2APB analogues and measured their inhibitory activities on Store Operated Calcium Entry (SOCE) and IP_3 Induced Calcium Release (IICR).

We found that bis boron compound DBP 161 and DBP 163 were 10 times more effective than 2-APB [133-138] We extended these studies and synthesized 493 analogues [139,140] increasing the number of borons, changing diphenyl to diaryl, monoaryl, mono-aliphatic dialiphatic compounds, substitution of aminoethyl to amino acid derivative as well as aminoethanol to aminoethylthiol and studied the structure/activities correlation.

We found that Diphenyl (amino acidonate O,N) borane DAB are best compounds



DAB 911 919

We found [139,140] that compounds DAB Diphenyl (aminoacidonate N,O)borane could regulate IP_3- induced Ca^{2+} release (IICR), Store-Operated Ca^{2+} entry (SOCE)) and could regulate cellular responses. We found that the adduct of amino acid (especially basic amino acid) and diphenyl borinic acid have strong inhibitory activity to SOCE. And some of them 919 Diphenyl (2,3-diaminopropionate O,N) borane, 911 Diphenyl (L- lysinate O,N) borane showed 10 times strong activity than 2-APB. 2APB is said to be a excellent lead compound for heat disease and Alzheimer`s diseases as Berridge predicts [141-147].

2APB analogues presented in this study could be proven to be excellent lead compounds for many human diseases including heart disease [143,144], Alzheimer`s [145-146] and Huntington disease [148,149].

We found that boron compounds also can inhibit transglutaminase (Ca^{2+}-dependent enzyme) [130]. There are many neurodegenerative disease, including Alzheimer`s disease, Huntington`s disease [136,149]. The boron compounds were found to be effective as inhibitor of acyl protein thioesterase [150].

We looked for more effective transglutaminase inhibitors. We synthesized 250 β- aminoethyl ketones and found that these compounds had strong transglutaminase inhibitory activities [151,152]. A typical compound is 5-bromo-2-thienyl-(N-t-butyl-N-benzyl)-aminoethyl ketone.

Acknowledgement

I would like to thank Dr. M. J. Berridge for valuable suggestions and advices.

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