

## Chemical Approach to Signal Transduction by Inositol Triphosphate

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### Abstract

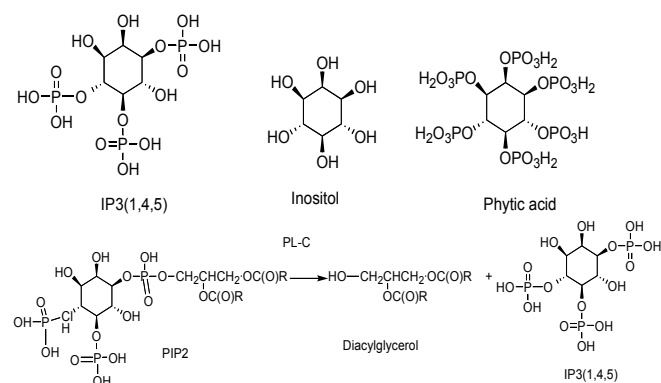
Berridge discovered that inositol 1,4,5-trisphosphate (IP<sub>3</sub>) was generated at the cell surface in response to cell stimulation and functioned as a second messenger to release Ca<sup>2+</sup> from internal stores. Ozaki et al. succeeded in the first total synthesis of optically active IP<sub>3</sub> by 13 steps. He supported the signal transduction studies by supplying necessary reagents such as IP<sub>3</sub>, other IP<sub>x</sub>, phosphatidylinositol, new synthetic methods and reagents. He discovered the regulators of Ca<sup>2+</sup> release and consequent cellular processes.

**Keywords:** Signal transduction; Inositol triphosphate; IP<sub>3</sub>Phosphatidylinositol; 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<sub>3</sub>) is a second messenger was discovered by Michael Berridge who showed that it functioned to release Ca<sup>2+</sup> 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<sub>2</sub>) giving rise to two products: 1,2-diacylglycerol and inositol 1,4,5-trisphosphate (IP<sub>3</sub>). IP<sub>3</sub> stimulates the release of Ca<sup>2+</sup> from the intracellular stores in the endoplasmic reticulum through IP<sub>3</sub> 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<sub>2</sub>) and phytic acid. PIP<sub>2</sub> is converted to IP<sub>3</sub> 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 it 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<sub>3</sub>

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<sub>3</sub>) act as a second messenger, a fundamental cell-signal transduction mechanism has been elucidated. IP<sub>3</sub> stimulates the release of Ca<sup>2+</sup> from the intracellular stores in the endoplasmic reticulum through IP<sub>3</sub> receptor while regulating a wide range of cellular processes [4-25].

### Synthetic Competition of Inositol P

The discovery of inositol phosphate in particular IP<sub>3</sub> led to the dramatic stimulation for the synthesis of inositol phosphates. Many persons challenged the synthesis of inositol phosphate, starting from inositol, glucorolactone, 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 200<sup>th</sup> 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 dianilidephosphotyl chloride isolation yield was only 10%. Then we have studied phosphorylation reagents and discovered new phosphorylation method Then we could get IP<sub>3</sub> by best method in good

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

This IP<sub>3</sub> is produced by this method at DOJINDO (Kumamoto, Japan) and is distributed all over the world by the name of synthetic IP<sub>3</sub>.

The synthesis of I(1,4,5)P<sub>3</sub> are reported by many investigators Billington and Vacca (from myo-inositol orthoformate [28], Ballou, from myo-inositol [29], Gigg [30], Ley from arenes using Pseudomonasoxidation [31], Falch from Quinic acid [32], Stepanov and Shvets [33], Prestwich prepared D-myo-(<sup>3</sup>H)I(1,4,5)P<sub>3</sub>, essential and most used reagent for the study of signal transduction [34,35] Phosphothioate analog of IP<sub>3</sub> by Potter [36].

### Different Source and Methods

IP<sub>3</sub> was obtained through 6 different sources:

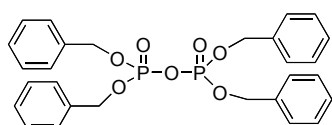
- Starting from myo -inositol [26-32,35-38]
- Starting from L-quebrachitol ( natural rubber industry by-product) [39-43]
- Starting from arenes [33]
- Starting from Quinic acid [34]
- Starting from D-glucuronolactone [42]
- Chemoenzymtic synthesis of D-myo-inositol 1,4,5—triphosphate [43-49]

### 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-triphosphate [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]

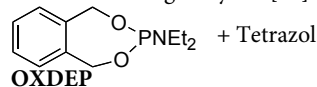
- Tetrabenzyl pyrophosphate (TBPP) and n-BuLi [52].



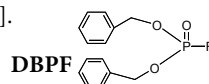
TBPP  
n-BuLi

- New phosphorylating reagent called OXDEP (o-xylylene N,N-diethylphosphoramidite) [53,54]. By using this reagent, IP<sub>3</sub> and PIPx

were obtained in good yield [27].



- **DBPF** Dibenzyl phosphorofluoridate (BnO)<sub>2</sub>P(O)F [55]. This reagent was used for the synthesis of phosphofluoridate analogues. Obtained phosphofluoridates showed very interesting biological activity [56].

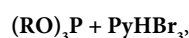


- Step wise phosphorylation using PCl<sub>3</sub>, BnOH, C<sub>6</sub>H<sub>5</sub>COOH [57]
- Phosphorothioate synthesis based on the redox reaction of phosphite with tellurium (IV) chloride [58].

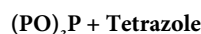
### Discovery of Phosphonium Salt Methodology

This phosphonium salt methodology [59,60] provide a regioselective phosphorylation. 1,2-Diol were phosphorylated regioselectively at C-1 with triethyl phosphite to give 1-dibenzyl phosphate 2-hydroxy free compound as shown in Figure 2. Other phosphorylating 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.

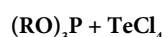
Trialkyl phosphite and pyridinium bromide perbromide method [59]



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



Utilization of oxidizing character of TeCl<sub>4</sub> [62]



The reaction of an alcohol with a trialkylphosphite in the presence of pyridinium bromide per bromide proceed via the phosphonium salt (RO)<sub>3</sub>P<sup>+</sup>Br<sup>-</sup> to afford the triester R<sub>1</sub>-OP(O)(OR)<sub>2</sub>, which can be converted to the phosphoric monoester by deprotection.

On the other hand, starting from dialkyl phosphoramidite (RO)<sub>2</sub>PNR, the corresponding triester product (R<sub>1</sub>O-R<sub>2</sub>O-P(O)OR<sup>3</sup>) gave phosphoric mixed diesters.

The reactivity of phosphonium salt toward an alcohol seems to be between P<sup>III</sup> and P<sup>V</sup>, 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)P<sub>2</sub>.

We synthesized Phosphatidylinositol 3,4,5-triphosphate [63,64], Unsaturated phosphatidyl inositol-3,4,5-triphosphate [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].

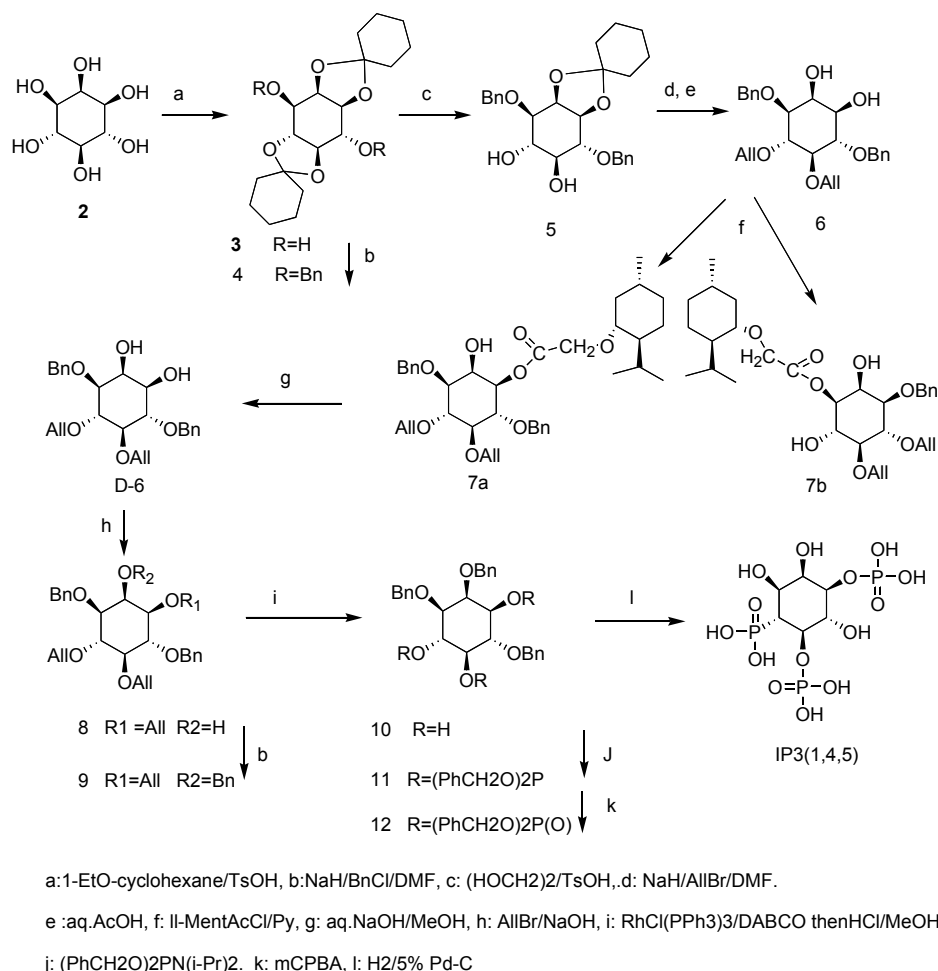


Figure 1: Synthesis of D—myo-inositol 1,4,5-trisphosphate

## Finding of New Reaction, New Methods and New Reagents

### Finding of new protection methods

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

### Finding of new deprotection methods

- Deprotection of methyl group by AlCl<sub>3</sub>-NaI, AlCl<sub>3</sub>-Bu<sub>4</sub>NI [71]
- Deprotection of benzyl and allyl group by AlCl<sub>3</sub>-dimethyl aniline [72]
- Deprotection p-methoxybenzyl by trimethylsilylchloride-tin(II) chloride—anisole [73].

### Finding of diastereoselective addition methods

Diastereoselective addition of organometallics to  $\alpha$ -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 enantioselective acylation and deacylation Method

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

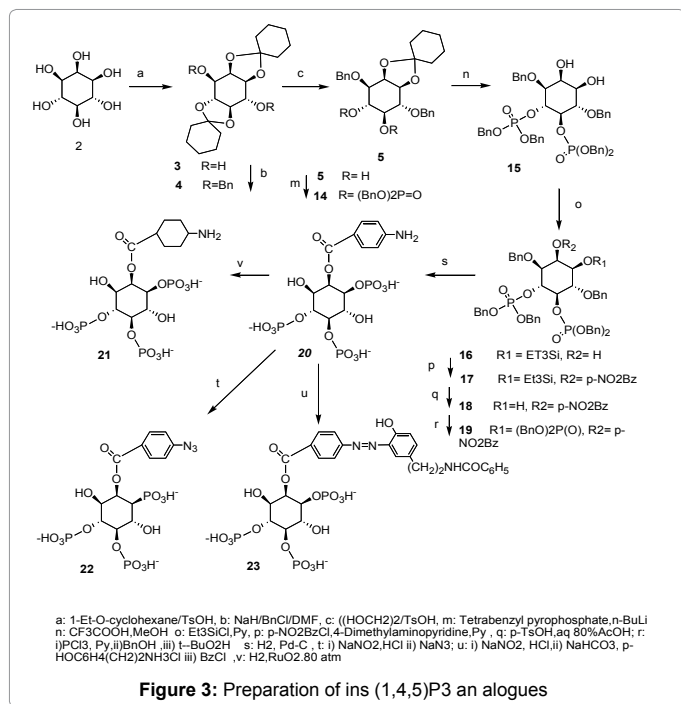
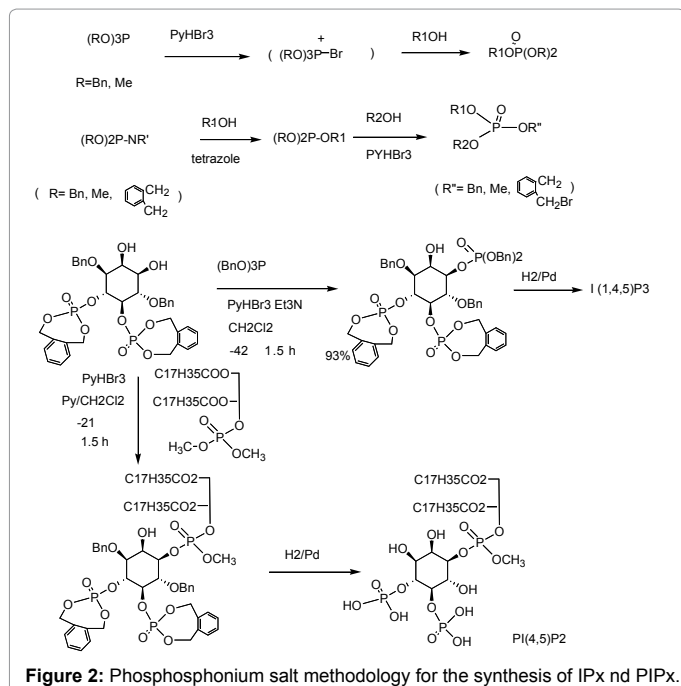
## Finding of glycosidation method

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 Auxiliaries

- 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



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

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

### Preparation of IP<sub>x</sub>, IP<sub>3</sub> derivatives and IP<sub>3</sub> 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<sub>3</sub> analogs

- These were synthesized as shown in Figure 3. These analogs were used for the preparation of affinity columns [96].
- Many IP<sub>n</sub> and derivatives were prepared and their activities were measured by Prof. Hirata, Masato [96-113].
- Synthesis of IP<sub>3</sub> 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(phosphate) analogues [101].

#### Phosphofluoridate 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 (<sup>3</sup>H) InsP<sub>3</sub> binding to purified InsP<sub>3</sub> receptor that were less than for InsP<sub>3</sub>. Two analogues 44 and 40 were found to inhibit the dephosphorylation of (<sup>3</sup>H) InsP<sub>3</sub> by the 5-phosphatase with potencies similar to that for InsP<sub>3</sub>. Surprisingly, the inhibitory potency of 5-phosphofluoridate 44 toward 5-phosphatase was higher (about 20 fold) than those of InsP<sub>3</sub> and the another fluoridates 40 and 45.

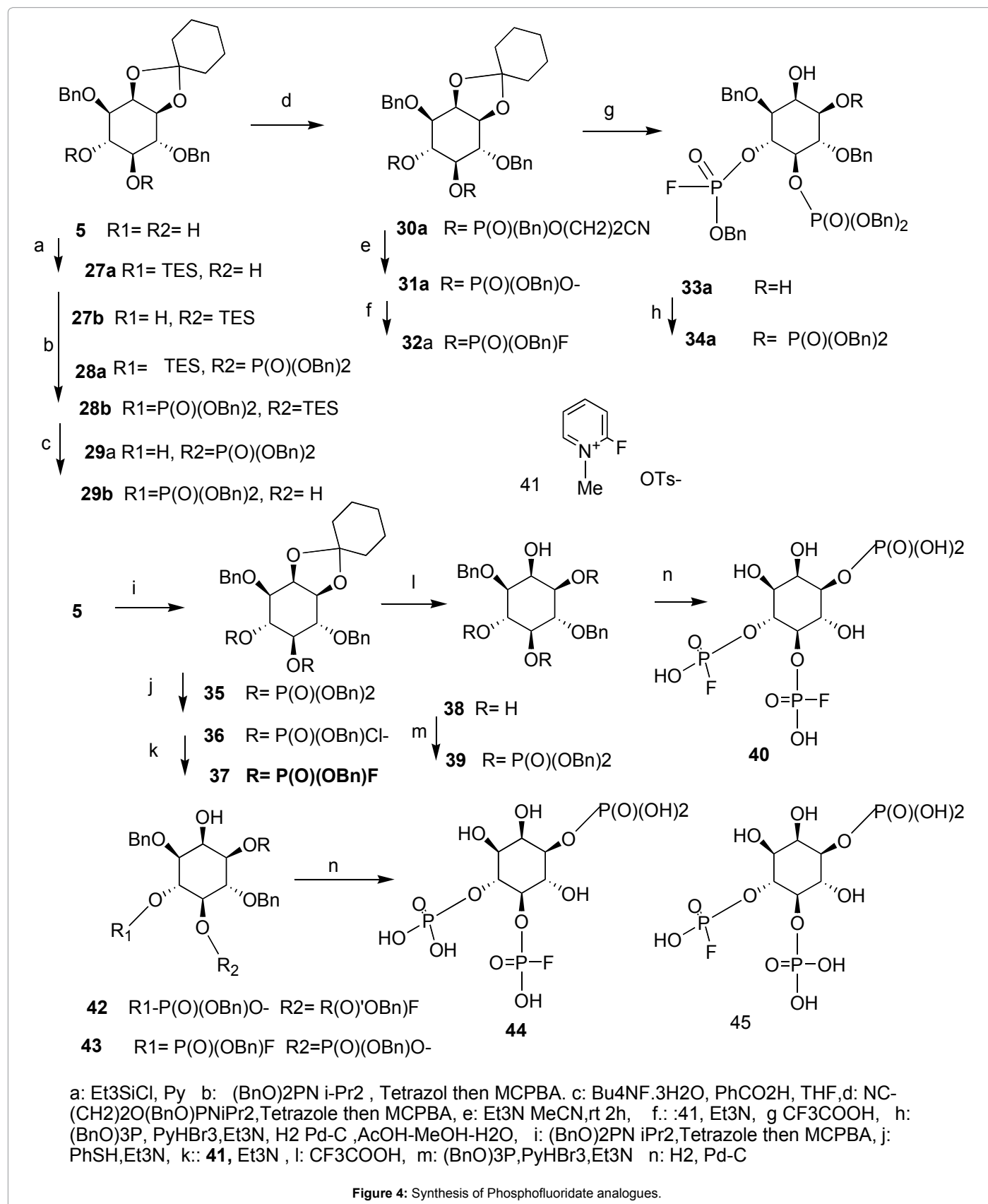
#### Preparation of Affinity Column

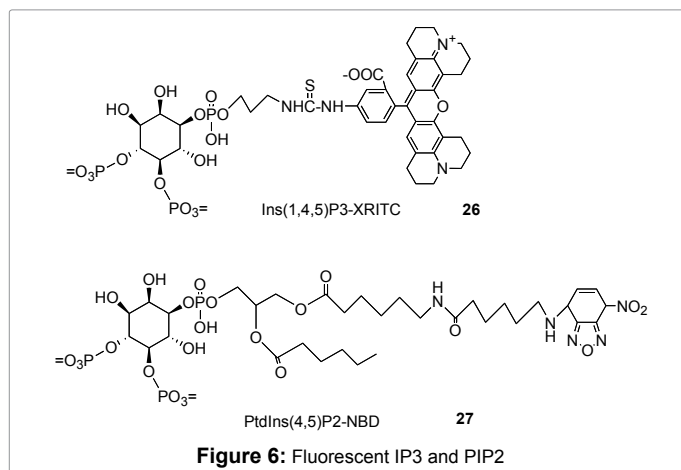
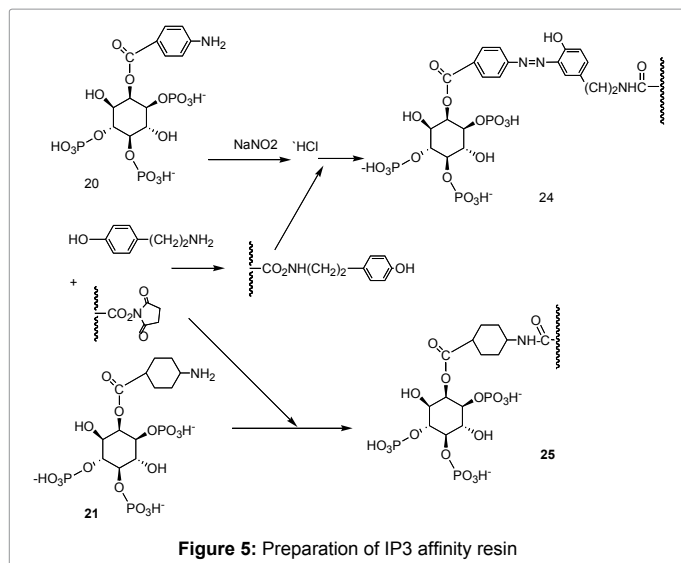
Inositol 1,4,5-trisphosphate affinity columns 24, 25 were prepared from 20, 21 as shown in Figure 5 to fish out IP<sub>3</sub>-binding proteins [98,113,114].

#### Isolation and Characterization of Many IP<sub>3</sub>-Binding Proteins

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

- IP<sub>3</sub> 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 aldase [109], collaboration with Carl Baron and Masato Hirata.
- 3-Kinase, 5-phosphatase [111,117] collaboration with Van Dijken
- Growth factor activating protein [112,118] collaboration with Moriya Shigeharu
- IP<sub>3</sub> 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<sub>3</sub>-binding domain of phosphatidyl inositol-specific phospholipase C [122] collaboration with Yagisawa, Hitoshi.
- IP<sub>3</sub> 3-kinase from chicken erythrocytes [123] collaboration with George Myer.





- Homogeneous Ca<sup>2+</sup> Stores [124] collaboration with Inoue, Masumi
- Na<sup>+</sup>,K<sup>+</sup>-ATPase [125] collaboration with Lin, Hai
- Plasma membrane PtdIns-4,5-P<sub>2</sub> [126] collaboration with Ronald Holz

### Observation of Behaviors of IP<sub>x</sub>, PIP<sub>x</sub> and Ca<sup>2+</sup> Flux in the cells

IP<sub>3</sub> and PIP<sub>x</sub> 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<sub>n</sub> or PIP<sub>n</sub> into the cell [127-130].

Ozaki synthesized about 20 fluorescent IP<sub>3</sub>, IP<sub>4</sub>, PIP, PIP<sub>2</sub> 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<sub>n</sub> or PIP<sub>n</sub> entered into the cell and how moved and how changed, metabolized and also observed a calcium flux (time, location, concentration) in NIH 3T3 Fibroblasts, when complexes of carrier and Ptd Ins (4,5) or Inos (1,4,5) P<sub>3</sub> were added extra cellular. He took more than a thousand pictures and movies.

### Detection of Ca<sup>2+</sup> Flux

Fluoro-3 was used to measure intracellular calcium concentration. In case of IP<sub>3</sub> complex, Ca<sup>2+</sup> maximum peak (2.5×10<sup>-7</sup>M) was observed after 3.5 min. after addition of IP<sub>3</sub>. In case of PIP<sub>x</sub> complex, Ca<sup>2+</sup> maximum peak (4.2×10<sup>-7</sup>M) was observed after 6.5 min.

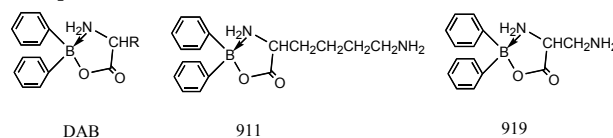
### Discovery of DAB; Regulators of Ca<sup>2+</sup> Release and Cellular Response

In 1997, we identified 2-aminoethyl diphenylborinate (2-APB) as being an IP<sub>3</sub> receptor inhibitor and regulate IP<sub>3</sub> 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<sub>3</sub> 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



We found [139,140] that compounds DAB Diphenyl (amino acidonate N,O)borane could regulate IP<sub>3</sub>- induced Ca<sup>2+</sup> release (IICR), Store-Operated Ca<sup>2+</sup> 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<sup>2+</sup>-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

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