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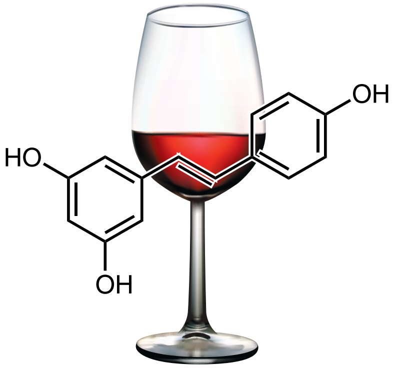


Resveratrol

CONTENTS

Elements in Pharmaceutical Drugs

Kentaro Sato

If you were asked to list chemical elements in the order of abundance in human body, could you answer it right away? In terms of the number of atoms, the most physiologically abundant element is hydrogen, followed by oxygen, carbon, nitrogen, phosphorus, and sulfur. Minerals like calcium and other minutely present elements such as iron and copper play essential roles, but they constitute only about 1 percent altogether. Clearly, the sextet of C, H, O, N, S, and P owns an important place in physiology.

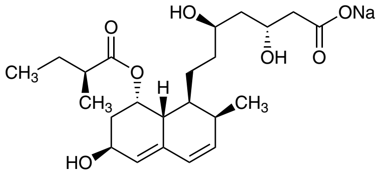
Most pharmaceutical drugs that we take are also made up of these six elements. Drug molecules enter human systems and produce medicinal effects, so it is natural that their compositions resemble to that of human body. However, there are always interesting exceptions in which you can find unusual elements. The previous article focused on anticancer drugs, so this time let us look at other drug types featuring metallic elements.

Group I Elements

A survey of drug compositions would find many examples containing sodium and potassium. However, most of these drugs are the salts of sodium or potassium, meaning that the metals are used as “counterions” to simply increase the solubility of the parent acidic drug. For example, a famous hyperlipidemia drug pravastatin is isolated as a lactone from its natural source, but is hydrolyzed into the sodium salt of carboxylic acid in order to increase the solubility.

A well-known example in which an alkali metal itself has a medicinal property is lithium. Salts of lithium such as lithium carbonate play an essential role in the treatment of bipolar disorder, a mental illness that typically involves alternating states of mania and depression.

The effect of lithium was discovered by sheer serendipity. Around the late 1940’s, an Australian psychiatrist John Cade decided to inject urea to lab animals based on his hypothesis that the dysfunction of the urea metabolism was causing bipolar disorder. Since free urea was poorly soluble in water, he used it in lithium salt form,



Pravastatin Sodium

which led to the observation of a dramatic therapeutic effect. Cade carefully investigated into the results, and concluded that it was not the urea but the lithium ion from the salt that was responsible. The effect of lithium was eventually proven in human clinical trials and lithium became an important medicine in psychiatric therapy.

Despite the widespread use of lithium around the world since the discovery, its mechanism of action is still unknown. One theory suggests that lithium helps regulating the internal clock system, while another theory states that it affects the interneuron signal transmission process. The actual mechanism is probably a combination of multiple functions. Nevertheless, this kind of drug is perhaps most unlikely to come out from today's systematic drug discovery approach.

Group II Elements

Beryllium, the lightest element among the Group II elements, has no medicinal application because of its low natural abundance and high toxicity. In contrast, magnesium (a row below beryllium in the periodic table) is known to be less toxic. Magnesium oxide is an ingredient of stomach medicines as acid neutralizer and also used as a safe laxative. In addition, the deficiency of magnesium has been reported to be linked with the risks of diabetes and depression. Though not always recognized, magnesium is surely an important element for our body.

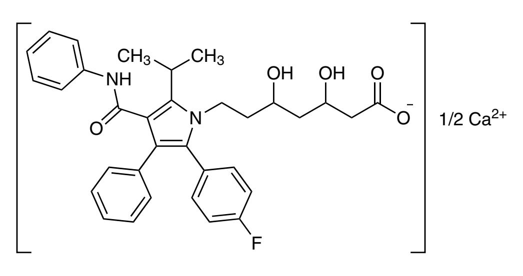
Calcium is not only an important constituent of bones, but also an essential player in intercellular signal transduction. Calcium deficiency causes a serious medical condition known as hypocalcemia and there are many supplementary medications for it. In other applications, calcium can be found as the counterion of a number of drugs including the biggest blockbuster of all time, Lipitor®, which is technically called the calcium salt of atorvastatin.

Strontium (atomic number 38) shows very similar chemical properties to calcium. Therefore, when people are exposed to radioactive strontium by a nuclear experiment or a nuclear plant accident, it can cause long-term damages by accumulating in the bones.

Interestingly, there is actually a drug that makes use of this troublesome property of strontium. Strontium-89 is a radioactive isotope that emits a beta ray with the half-life of 50.5 days, and it can be used as a medicine that alleviates the severe pains associated with metastatic bone cancer. It is strange that a radioactive isotope of strontium has both cancer-inducing and pain-relieving properties, but this is an example of the complex relationships between human body and radioactivity, and between human body and drugs.

Barium is below strontium in the periodic table and is well-known as the radiocontrast agent used in X-ray imaging of the digestive system. Despite the unpopularity because of its unpleasant taste and stressful aftercare, there are good reasons why it is used.

The X-ray radiocontrast agent is barium sulfate, which is insoluble in water thus not absorbed by the digestive system and non-toxic. And because barium is a large element with atomic number 56 it effectively scatters X-ray, providing the visualization of the stomach and the intestines in white color after drinking the chalky liquid. Because it is also inexpensive, barium will likely continue to be used for years to come. However, its user-friendliness has been improved in recent years by reducing the dose and improving the taste. The experience of undergoing a medical examination is therefore getting less painful.



Atorvastatin Calcium

Transition Metal Elements

As mentioned in the beginning, the six elements C, H, O, N, S, and P constitute the core of human body. But supporting life requires contributions from not just these six elements but also various metal elements. The biologically essential metal elements include chromium, manganese, cobalt, nickel, copper, and molybdenum, some of which might be unexpected.

Many transition metal elements are toxic, however, when overdosed. Therefore, there are only a few examples of them being used for pharmaceutical purposes. For instance, certain mercury compounds were once used widely as antiseptics but are no longer used today because of the toxicity concerns.

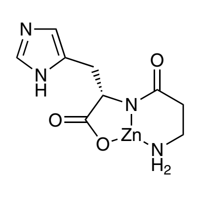
Like the proverb “fight poison with poison,” there are heavy metal based drugs that can protect us against the toxicity of another heavy metal. An example is zinc acetate used as the treatment of Wilson’s disease, which involves the accumulation of inorganic coppers in the body. Zinc acetate is thought to hinder the absorption of copper in the digestive system.

Zinc is also utilized in stomach medicines. A zinc complex called polaprezinc functions to repair gastric mucosal injury. Additionally, ointments containing zinc oxide has been used traditionally as a safe medicine to treat various skin problems. Zinc is probably the most frequently used transition metal element in pharmaceutical drugs.

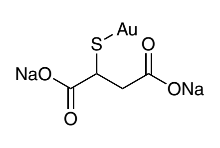
Gold complexes such as sodium aurothiomalate and auranofin are great examples of pharmaceutically used organometallic complexes. In auranofin, the thiosugar and the phosphine bind to the gold atom, making the molecule look like a catalyst of chemical reaction. These complexes are used as a medication of rheumatoid arthritis and the mechanism of action is considered to involve accumulation in the joint fluids, preventing collagen decomposition, and binding and neutralizing inflammation causing substances.

Recently, lanthanum carbonate has been approved as the drug for hyperphosphatemia. In the patients suffering from kidney disease, the serum concentration of phosphate ions becomes abnormally high due to inefficient removal of the ions. The phosphates react with the calciums in the serum and causes serious conditions such as muscle weakness and calcification of organ tissues and blood vessels. Because most foods contain phosphates, an effective way to remove them becomes necessary.

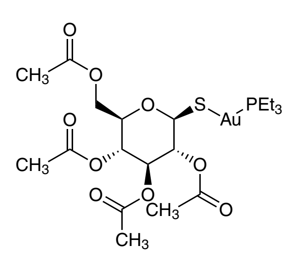
When a patient takes lanthanum carbonate after meals, the lanthanum ions bind strongly to the phosphate ions, alleviating aforementioned symptoms. In the past, patients



Polaprezinc



Sodium Aurothiomalate



Auranofin

used to have to avoid having tasty foods that are also high in phosphates. Lanthanum is a relatively anonymous element to general public, but let us hope it becomes a savior for thousands of patients.

Another transition metal element with a promising medicinal potential would be vanadium. Vanadium is used as an additive in steel industry and is categorized as one of the rare metals. It has so far been considered an unrelated element to human health even though certain types of mushroom and sea skirt are known to selectively ingest vanadium, which implies some sort of biological functions.

Recent studies are showing that vanadium may be effective in treating diabetes. It has been reported that the daily administration of 150mg of vanadyl sulfate ($VOSO_4$) to diabetic patients resulted in lowered blood sugar levels. It is quite interesting that a simple metal salt shows a similar medicinal effect to that of peptidic insulin composed of 51 amino acids. If the absorption could be further improved (by organometallic complexation, for example) and the toxicity problem could be solved, practical use would become realistic. Since peptidic insulin can be taken only by injection, the development of an orally administered antidiabetic drug would be significant.

As you have seen, there are surprisingly large numbers of metal-containing pharmaceutical drugs. These compounds have been generally overlooked by medicinal scientists because of the preconceived impression about toxicity. However, it seems there are more drug seeds waiting to be discovered and there should be ways to explore. With unbiased research, this field could become pharmaceutical gold mine.

Introduction of the author :

Kentaro Sato

[Brief career history] He was born in Ibaraki, Japan, in 1970. 1995 M. Sc. Graduate School of Science and Engineering, Tokyo Institute of Technology. 1995-2007 Researcher in a pharmaceutical company. 2007-Present Freelance science writer. 2009-2012 Project assinstant professor of the graduate school of Science, the University of Tokyo.
[Specialty] Organic chemistry
[Website] The Museum of Organic Chemistry <http://www.org-chem.org/yuuki/MOC.html>

Visit to a Science Club

Science Club at Rikkyo Ikebukuro Junior & Senior High School (Part 1)

Introduction

In this journal, we would like to introduce science club activities by junior and senior high school students, who are striving hard for a dream to become a future scientist. On this occasion we visited a science club at Rikkyo Ikebukuro Junior & Senior High School on January 22, 2013, just after the National Center Test for University admissions was held. They have achieved excellent results in competitions such as the International Chemistry Olympiad and Japan Science & Engineering Challenge. Education at Rikkyo School emphasizes a focus on the pursuit of truth and cooperation, and aims to nurture independence of students. We were invited to their laboratory after a greeting with a teacher/club advisor Mr. Goto and a teacher/assistant advisor Mr. Tsushima at the entrance, and saw students there performing experiments on their own.

Science Club of Rikkyo Ikebukuro Junior & Senior High School

In academic year 2012, 22 students (10 junior high and 12 senior high) belong to the club. Activities are taking place four times a week for two hours each. An interesting feature of the club is that students form a team with those having the same theme, appoint a team leader and make experiment plans on their own. Teachers are pretty busy supporting students' entire activities, giving strict safety guidance on their experiment plans and preparing facilities, equipment and chemicals at their requests. "I would like students to experience a self-motivated study like the one in university laboratories" says Mr. Goto, a teacher/advisor. One of the other great appeals is that the school is attached to a university so that, as necessary, students may use facilities of nearby Rikkyo University, College of Science.

Mr. Goto and science club members (TCI reagents are thankfully used).

Experiment by each team (A big feature is that students are respectively working through a team experiment). Mr. Tsushima is directly instructing an experiment.

Student Voices

Mr. Arima, a former captain, and Mr. Soejima, a back-to-back gold medal winner of the International Chemistry Olympiad, commented on their motivation behind starting chemistry.

Mr. Arima: I was greatly attracted to the experiments by the science club that I saw at R.I.F. (Rikkyo Ikebukuro High School Festival).

Mr. Soejima: I have been very interested in creating new compounds with my own hands.

Both seemed to have been fascinated with chemical experiments.

From left, Teacher/Advisor Mr. Goto, Mr. Soejima, Mr. Arima, New captain Mr. Okada, Teacher/Advisor Mr. Tsushima.

Research presentation and competition entry

Daily study results are submitted for the Japan Student Science Award. In regard to the International Chemistry Olympiad and Chemistry Grand Prix aimed at high school students, all club members from a first grade of junior high school participate in the competitions whether they submit their results or not. “A sense of unity is established among team members by participating in contests together” says Mr. Goto. Not to mention that they have achieved brilliant results in every competition. At the end of school year, a club newsletter summarizing their activity results is published (B5-sized 135 pages in 2011). Aside from research presentations, many other attempts are made to attract the interest of students such as a tour of domestic frontier research facilities and factories during a summer camp.

Award winning results of 2012:

Japan Science & Engineering Challenge (JSEC 2012)

Honor award (Mr. Soejima): Crystal growth control of MOF-5 with coordination modulation

This is a study that examines crystal growth control of MOF-5 by adding benzoic acid after synthesizing MOF-5, metal organic framework (porous coordination polymer), from terephthalic acid and zinc.
Reference: http://www.asahi.com/shimbun/jsec/2012/jsec2012/12fin_finalist.html

Honorable mention award (Mr. Takahashi): Consideration of phthalocyanine synthesis by Wyler's method

This is a study that performs the Wyler's method for phthalocyanine synthesis under aqueous conditions at room temperature.

Japan Student Science Award - Tokyo round (High school category)

Grand Award (Mr. Arima): Alteration of complex based on differences of cation

This is a study that examines a change of solution color and crystal structure of potassium trioxalatoferrate (III) through alteration of coexisting cation.

Incentive Award (Mr. Ohira): Depolymerization of PET resin

This is a study that performs to reproduce the depolymerization of PET resin in a high school laboratory.

Japan Student Science Award - Tokyo round (Junior high school category)

Grand Award (Mr. Koike): Creation of a fine copper mirror

This is a study that researches conditions to create a fine copper mirror by varying amounts of silver nitrate water solution, tin(II) chloride water solution, and Fehling's solution A and B.

Incentive Award (Mr. Tsujimoto): Staining of vinylon

This is a study that examines a staining method of vinylon with BTB and litmus solution.

Competition results of 2012:

International Chemistry Olympiad 2012: Gold medal (Mr. Soejima)
High School Chemistry Grand Prix 2012: Grand prix (Mr. Soejima), Gold medal (Mr. Takahashi)
Japan Biology Olympiad 2012: Gold medal (Mr. Soejima)
Physics Challenge 2012: Bronze medal (Mr. Takahashi)

As you can see, the science club of Rikkyo Ikebukuro Junior & Senior High School has been very active and received a great number of brilliant prizes. In the next issue we are going to give you a detailed report on research activities of each student.

Science "Summer" Seminar

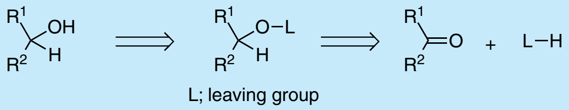
Carbonyl Olefination (3)

Takeshi Takeda

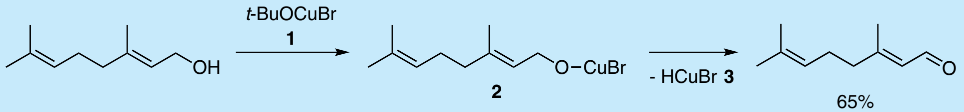
Department of Applied Chemistry, Tokyo University of Agriculture and Technology

1. Designing of Synthetic Organic Reactions

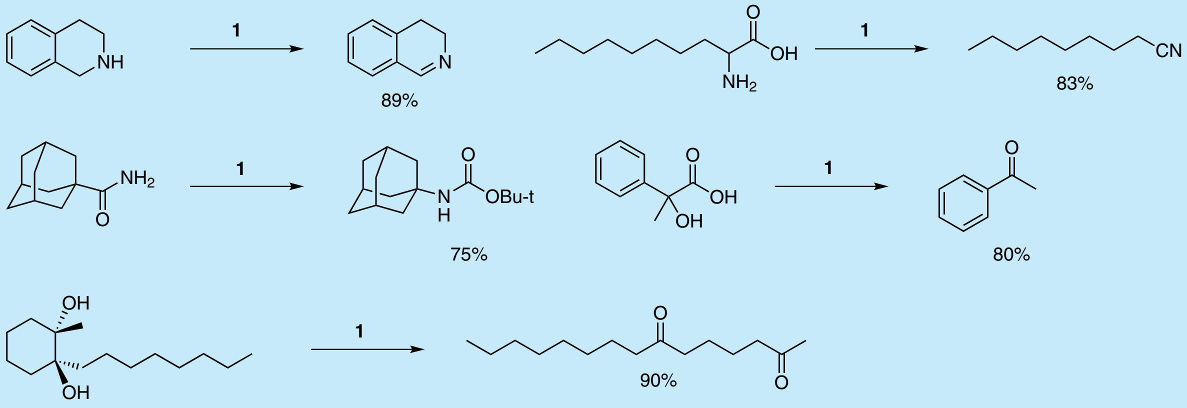
In the two preceding issues, some problems encountered in carbonyl olefination were discussed. At the end of this series, an approach to developing new synthetic reactions is described in connection with the reaction mechanism of carbonyl olefination. For good understanding of organic reactions and creating new synthetic methods, it is important to focus on the most basic principle of each reaction mechanism. For example, most oxidation of alcohols can be regarded as elimination of a leaving group on oxygen and α-proton as shown in Scheme 1. Indeed, the treatment of geraniol with bromocopper(II) *tert*-butoxide (**1**) produces geranial (Scheme 2).1) The oxidation is assumed to proceed via the formation of copper(II) alkoxide **2** and following elimination of copper hydride **3**. Based on this simple idea, oxidations of amines,2) α-amino acids,3) amides,4) α-hydroxy acids,3) and *trans*-cyclic diols5) have been achieved (Scheme 3). The copper(II)-promoted transformation of hydrazones into *gem*-dichlorides and the preparation of dithioortho esters by the copper(II)-promoted reaction of lithium alkoxides with tributyl[bis(phenylthio)methyl]stannane described in the previous issue have also been developed as parts of this study.



Scheme 1



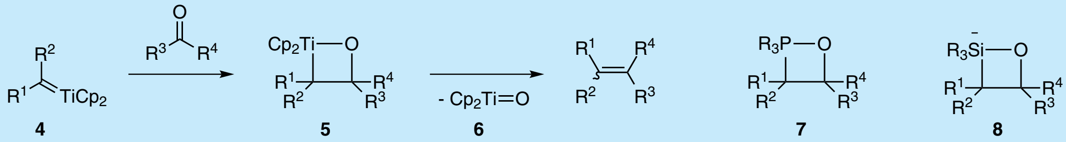
Scheme 2



Scheme 3

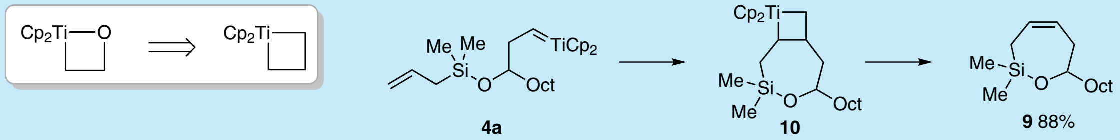
2. Oxatitanacyclobutane

The intermediates of carbonyl olefination using titanium-carbene complexes **4** are suggested to be oxatitanacyclobutanes **5** and the following elimination of titanocene oxide **6** affords olefins (Scheme 4). Simply stated, the Wittig and Peterson reactions also proceed via the formation of similar oxaheterocycles **7**, **8** and subsequent deoxygenation process. Thus, it is likely that new carbonyl olefination is realized by designing novel oxametallacyclobutanes which contain a highly oxophilic element. Such an approach would enable us to overcome some difficulties in carbonyl olefination described in the foregoing two issues.

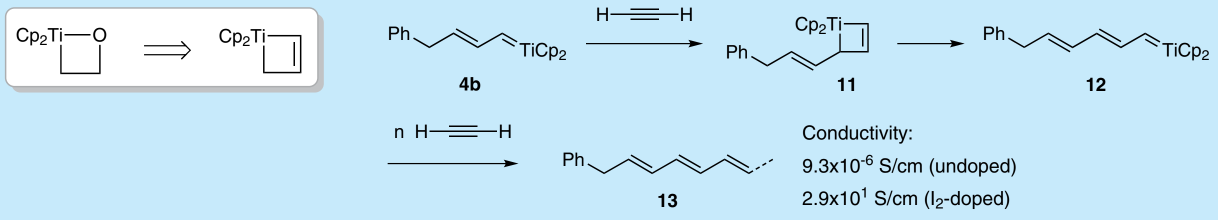


Scheme 4

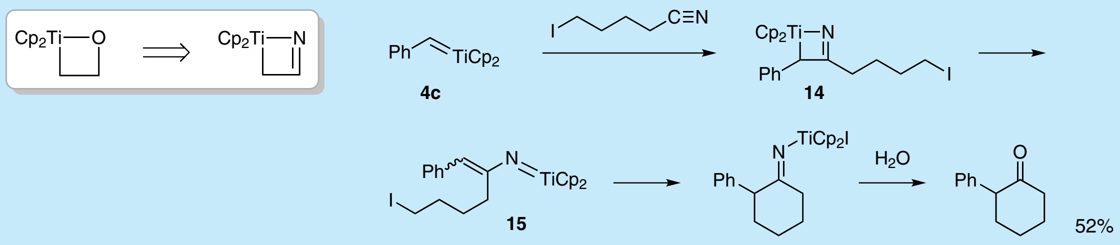
Designing new reactive intermediates is a powerful tool to create synthetic organic reactions, and indeed, various four-membered titanacycles which are analogous to the titanacycles **5** are the intermediates of a variety of molecular transformations. A typical example is illustrated in Scheme 5. The titanium carbene complex bearing an allylsilane moiety **4a** generated from the corresponding unsaturated thioacetal results in the formation of unsaturated oxasilacycle **9** through the formation of titanacyclobutane **10** and extrusion of methylidenetitanocene.[7] The metathesis-type degradation of titanacyclobutene **11**, generated by the reaction of the carbene complex **4b** with acetylene, in contrast, produces the new carbene complex **12** with two-carbon homologation, and hence the carbene complexes generated from thioacetals act as initiators for the polymerization of acetylene. Under appropriate reaction conditions, such polymerization produces a conductive polyacetylene film **13** (Scheme 6).[8] The carbene complex **4c** also reacts with the δ-iodonitrile to form the azatitanacyclobutene **14**. Its ring opening produces the titanium vinylimido complex **15** which affords the cyclohexanone after intramolecular alkylation and hydrolysis (Scheme 7).[9]



Scheme 5

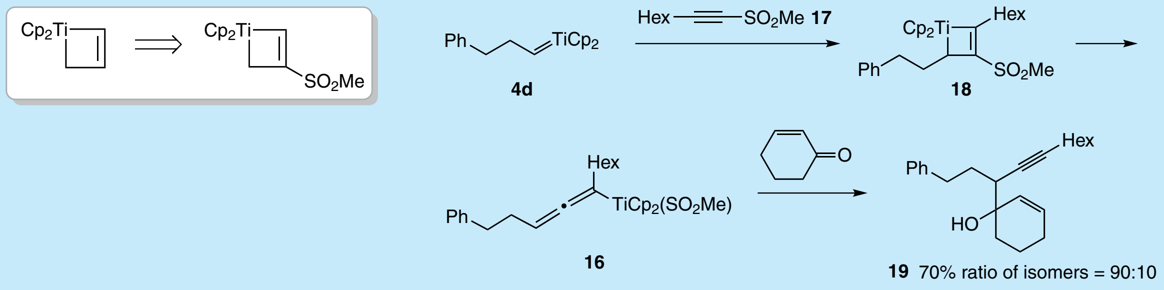


Scheme 6



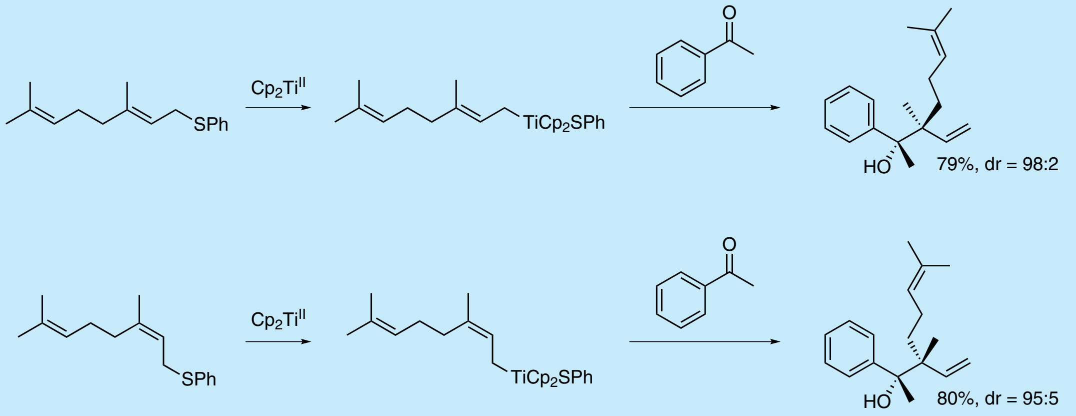
Scheme 7

A new stereoselective carbon-carbon bond formation has been realized through the further modification of titanacyclobutene intermediates. The allenyltitanocene **16** is formed by the reaction of carbene complex **4d** with the alkynyl sulfone **17** followed by the β-elimination of a methylsulfonyl group from the resulting titanacyclobutene **18**. The organotitanium species **16** reacts with 2-cyclohexene to afford *tert*-homopropargyl alcohol **19** with high diastereoselectivity (Scheme 8).10)



Scheme 8

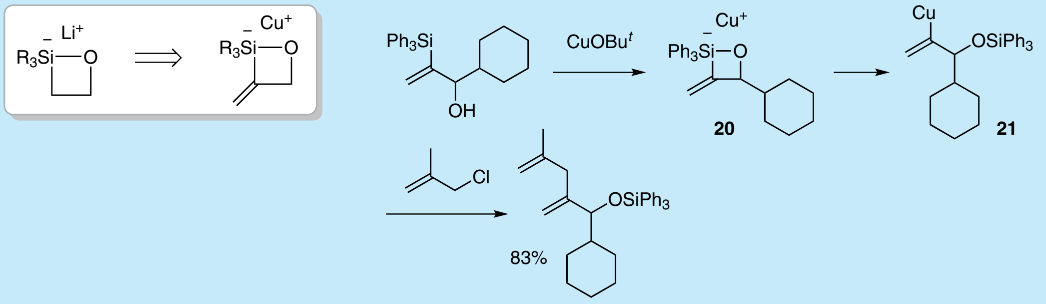
In general, the reaction of allylmetals with ketones is less diastereoselective than their reaction with aldehydes. On the basis of the high diastereoselectivity observed in the reaction of allenyltitanocene **16** with 2-cyclohexenone, the highly stereoselective11) or stereospecific12) allylations of various ketones have also been established (Scheme 9).



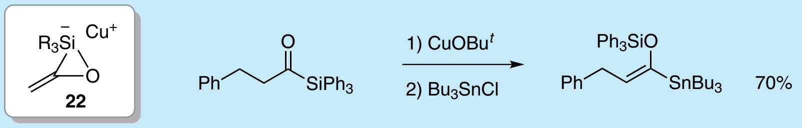
Scheme 9

3. Oxasilacycles

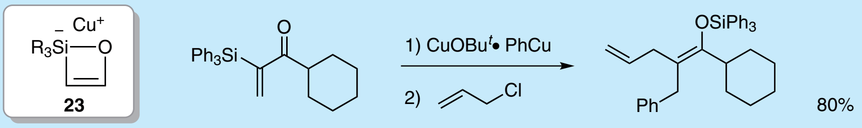
A slight modification of the four-membered silicates **8** brings a new cross-coupling reaction of alkenylsilanes. The cyclic silicate **20** with a copper(I) counterion undergoes the transmetallation between silicon and copper to form alkenylcopper species **21** (Scheme 10).13) The organocopper compound thus formed is reactive toward organic halides, and thus the similar processes are promising as new methods for the stereoselective formation of highly substituted olefins. The three-membered homologues **22** (Scheme 11),14) the unsaturated analogues **23** (Scheme 12),15) and their five-membered homologues **24** (Scheme 13),16) **25** (Scheme 14)17) are assumed to be the intermediates of the reactions which produce silyl enol ethers and highly substituted olefins with extremely high stereoselectivity.



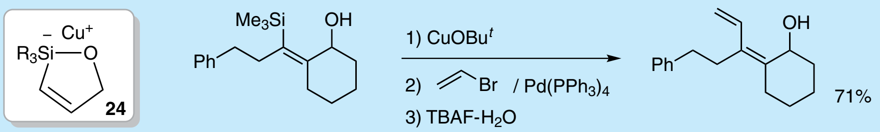
Scheme 10



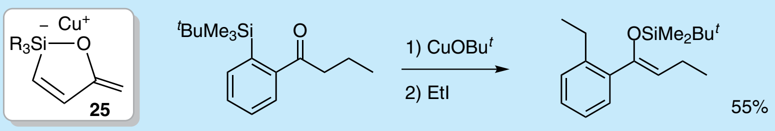
Scheme 11



Scheme 12



Scheme 13



Scheme 14

4. Concluding Remarks

As described above, the designing of various oxametallacycles opens the possibility to create new molecular transformations. Our carbonyl olefination utilizing titanium carbene complexes has been developed based on the unanticipated finding that alkenylcyclopropanes are produced by the reaction of β,γ-unsaturated thioacetals with titanocene(II)-1-butene complex.[18] This finding further enabled us to develop a variety of synthetic reactions through the process of designing new reaction intermediates. Such "designing reaction intermediate approach" to create new synthetic methods might be somewhat unique to our group and, of course, each researcher in this field has his/her own way of doing research. It is my hope that our "way of doing research" described in this serial can be of some help for you to do your research work.

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Takeshi Takeda obtained his Ph.D. (1977) in chemistry from Tokyo Institute of Technology. He joined the University of Tokyo as an Assistant Professor in 1977. After a half year of postdoctoral work at University of California, Los Angeles, he moved to Tokyo University of Agriculture and Technology as an Associate Professor in 1981. He was appointed to a Professor-ship in 1994.
He received an Incentive Award in Synthetic Organic Chemistry, Japan (1987) and a Chemical Society of Japan Award for Creative Work (2003).
His current research interests include organic chemistry, organometallic chemistry, and organic synthesis.

Science "Special" Seminar

Can Resveratrol be the Multidrug in Longevity Society?

Yoko Fujiwara

Graduate School of Humanities and Sciences, Ochanomizu University

Polyphenol is general term for botanical constituent has phenolic hydroxyl in molecule, including catechin, chlorogenic acid, or flavonoids such as daizein and quercetin. The polyphenol in foods is not essential nutrients, which used as energy or body structural component, but it has many physiological functions and started to use in supplement. Especially, the most attractive polyphenol is resveratrol, found from red wine, recently.

Physiological active substance in red wine polyphenol

Resveratrol (3,4',5-trihydroxy-*trans*-stilbene) is botanical antibacterial agent called phytoalexin, produced for protecting from fungus or bacteria, and structured three hydroxyl on stilbene skeleton (Fig.1). Resveratrol is rich in grape and peanuts skin. Also, it is well known polyphenol rich in red wine may explain French paradox, the French consume high fat diet much more than other Europeans but relatively low mortality by ischemic cardiac disease. Initially, resveratrol has emphasized by preventing arteriosclerosis, pathogenesis of ischemic cardiac disease, from its powerful antioxidant effect via inhibit blood low density lipoprotein (LDL) oxidation and reduce the form cell formation macrophage uptake LDL and suppress deposition to vascular wall.1) Also, resveratrol is well known for estrogenic activity, antiinflamation, and antitumor action.

On the other hand, longevity phenomenon is well known while yeast was energy restriction, silent information regulator 2 (sir2) is activated and increasing division frequency.2) Resveratrol is the one has the effect that activating sir2 without energy restriction to yeast,3) as well as C. elegans and drosophila, therefore, resveratrol has been attracted for longevity. Eventually, in 2006, resveratrol had reported extend life span on high fat diet.4) At this stage, extending life span effect is different in mammalian from the yeast. It improves various symptoms of lifestyle-related disease under the condition of high fat diet, improve impaired glucose tolerance by obesity, improve exercise function and its rising energy expenditure by mitochondrial hyperactivity, moreover, ward off dementia by improving brain function. In this longevity society, resveratrol expected as preventing/treating various diseases.
The mechanism for extending lifespan of resveratrol is thought to mediated by SIRT1, human homolog of sir2, researching for resveratrol-related substance and drug development targeting for SIRT1 activation. There are amount of modified resveratrol complex have synthesized and some of them are over thousands times effective than resveratrol.5) In 2012, clinical research of SIRT1 activator was reported, and pharmaceutical products from resveratrol would be developed in the near future.

The structure of resveratrol and its bioactivities

Resveratrol has two genometrical isomers that are *trans* and *cis* forms in binding between A and B rings in the nature. *Trans*-resveratrol has strong bioactivity and the 4-hydroxy group is essential for antioxidation like radical scavenging ability. Conversely, strong radical scavenging ability might impinge for biological reaction. Resveratrol has been reported as genotoxicity like sister chromatid exchanges (SCE), and even thousandth of mitomycin, SCE inducer, concentration, resveratrol inhibit cell proliferation on concentration dependency.6) Genotoxicity disappeared when 3-hydroxy group has removed. Interestingly, both of diethylstilbestrol (DES), endocrine disrupting chemical, and

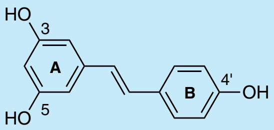

Fig.1 Structure of resveratrol

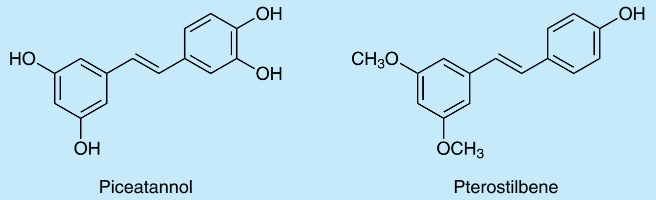

Fig.2 Structure of resveratrol analogues

4-hydroxy tamoxifen, activates metabolite of drug for cancer treatment called tamoxifen, have 4-hydroxy group as well as resveratrol. However, all of bioactivities of resveratrol could not be explained by antioxidation of 4-hydroxy group. Even 4-hydroxy group has removed, bioactivities are still remained in some cases. Therefore, the relationship of these structure and bioactivity will beneficial information for drug development from resveratrol analogues.

Resveratrol analogues in the nature

Piceatannol (3,4,3',5'-tetrahydroxy-*trans*-stilbene), has four hydroxy group, or pterostilbene (3,5-dimetoxy-4'-hydroxy-*trans*-stilbene), 3-hydroxy and 5-hydroxy is substitute for metoxy, are resveratrol inductor with bioacitivity in the nature (Fig. 2). Resveratrol can be found in grape, peanuts and berries like blueberry or bilberry. In the berries, *trans*-resveratrol, piceatannol, and pterostilbene are contained and those concentration could be changed depend on the race, growing condition or climate. Piceatannol has bioactivity like resveratrol but its mechanism is not the same. In consequence of substituting hydroxyl for methoxy in pterostilbene, it remains intracellulary and bioavailability is higher than resveratrol and expecting other physiological function other than resveratrol.

Due to the usage for the ingredient is limited to extract from natural plant for the supplement in the health food, those derivative concentration in the ingredient might determine the efficacy and price of the supplement. Root of Japanese knotweed, Kojokon, contains *trans*-resveratrol and its glycoside still more than grapes and does not contain *cis*-, therefore, it is used as the ingredient of resveratrol in overseas, recently. Unfortunately, in Japan, root of Japanese knotweed has been used as herbal medicine “polygonum cuspidatum root” and it cannot be used as a supplement under the pharmaceutical affairs law.

The advantages of polyphenol…

Polyphenol such as resveratrol is not essential nutrient as mentioned at the beginning. Mechanism to digest and absorb the nutrient into the body for human and animals is quite different with those for polyphenol. Most of the polyphenol is metabolized by drug-metabolizing system, thus, even that is efficacy to the body, it is metabolized quickly. Several polyphenol that effective for the body is found from foods which regularly intake everyday, such as catechin in tea, coffee polyphenol, resveratrol in wine, and isoflavone in miso soup. Considerations for polyphenol intake as supplement are amount and timing, as well as safety.

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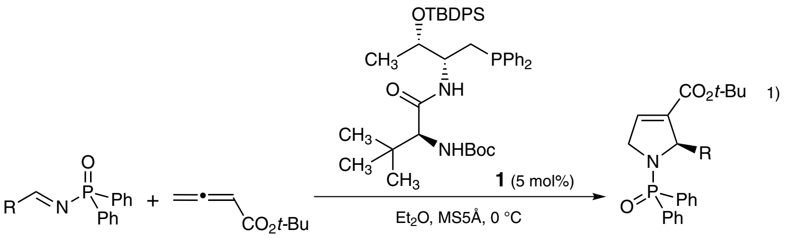
Yoko Fujiwara received her Ph.D. from Ochanomizu University in 1993. Later, she worked as a research fellow of Japan Foundation for Aging and Health, Baker Medical Research Institute and then, Japan Health Sciences Foundation. In 1997, she joined Ochanomizu University as a lecturer. She was appointed to a Professor-ship in 2010.
In 1997, she received an Incentive Award in Japan Society of Nutrition and Food Science.
Her research interests are nutritional chemistry and lipid nutrition.

A Novel Dipeptide-Based Chiral Phosphine Organocatalyst for Asymmetric Cyclization

T2937 *O*-TBDPS-D-Thr-*N*-Boc-L-*tert*-Leu-Diphenylphosphine (1) 100mg



Entry	R	Time (h)	Y. (%)	*ee* (%)
1	$CH_3CH_2CH_2$-	0.5	92	96
2	$PhCH_2CH_2$-	0.5	81	95
3	PhCH=CH-	0.5	81	96
4	Ph	1	82	95
5	4-OMeC_6H_4-	1	94	98
6	2-naphthyl-	1	86	96

The dipeptide-based chiral phosphine (**1**), which was developed by Lu *et al.*, is an efficient and versatile organocatalyst for the [3+2] and [4+2] asymmetric cyclizations of allenoates with unsaturated compounds.1-3) For example, the [3+2] cyclization of allenoates with alkyl or arylimines proceeds in the presence of 5 mol% of **1**, affording the reaction products in good yields and high enantioselectivities.1) Notably, **1** is stable in the air at room temperature.

Typical Procedure (entry 1: R = $CH_3CH_2CH_2$-) :
To a dried round bottom flask is added *N*-butylidene-*P*,*P*-diphenylphosphinic amide (27.1 mg, 0.1 mmol), *O*-TBDPS-D-Thr-*N*-Boc-L-*tert*-Leu-diphenylphosphine (3.6 mg, 0.005 mmol) and MS5Å (60 mg) under N_2, followed by the addition of anhydrous Et_2O (1 mL). The reaction mixture is cooled to 0 °C, *tert*-butyl 2,3-butadienoate (22 µL, 0.15 mmol) is then added, and the mixture is stirred at 0 °C for 30 min. The reaction mixture is then filtered (to remove MS5Å) and concentrated under reduced pressure. The residue is purified by column chromatography on silica gel (eluent: hexane/EtOAc = 10:1 to 2:1) to afford the cycloaddition product (37.9 mg, 92% yield, 96% *ee*) as a colorless oil.

References

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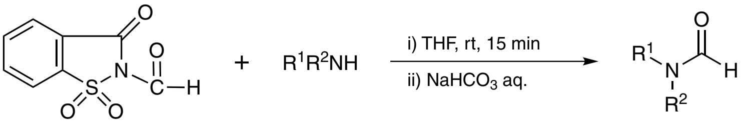
X. Han, F. Zhong, Y. Wang, Y. Lu, *Angew. Chem. Int. Ed.* **2012**, *51*, 767.
2) Enantioselective [3+2] cyclization of allenoates with acrylates or maleimides
a) X. Han, Y. Wang, F. Zhong, Y. Lu, *J. Am. Chem. Soc.* **2011**, *133*, 1726. b) Q. Zhao, X. Han, Y. Wei, M. Shi, Y. Lu, *Chem. Commun.* **2012**, *48*, 970.
3) Enantioselective [4+2] annulations of allenoates with activated alkenes
F. Zhong, X. Han, Y. Wang, Y. Lu, *Chem. Sci.* **2012**, *3*, 1231.

Novel Powerful *N*-Formylating Reagent

F0854 *N*-Formylsaccharin (1) 5g

N-Formylsaccharin (**1**), which was developed by Cossy *et al.*, is a novel powerful formylating reagent. Several methods or reagents for the *N*-formylation of amines, for example, the method using formic acid in the presence of an activating reagent such as DCC, or paraformaldehyde, have been reported. However, these methods are often lacking generality, or need heating reaction conditions. The use of **1** makes it possible to formylate amines under mild conditions. In particular, the selective *N*-formylation proceeds in the case of using amino alcohols as substrates.

N-Formylation of Primary and Secondary Amines



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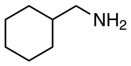
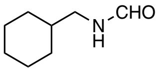
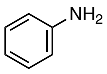
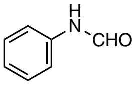
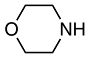
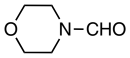
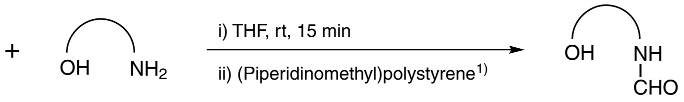
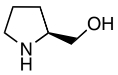
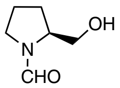
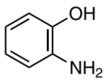
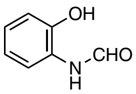
Amine	Product	Y. (%)
		quant.
		81
		75

Selective *N*-Formylation of Amino Alcohols

1



Amine	Product	Y. (%)
		55
		90

1) Due to the water solubility of *N*-formylamino alcohols, the polymer-supported base is used in order to trap the acidic byproducts.

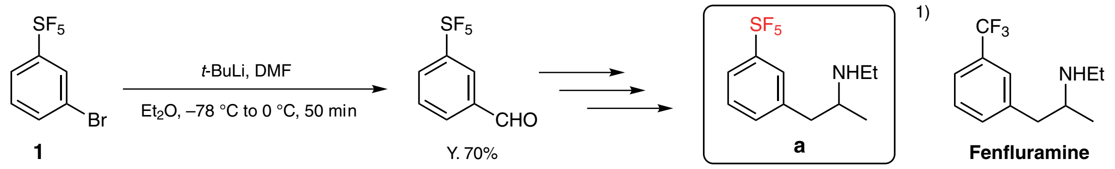
Reference

1) *N*-Formylsaccharin: A new formylating agent
T. Cochet, V. Bellosta, A. Greiner, D. Roche, J. Cossy, *Synlett* **2011**, 1920.

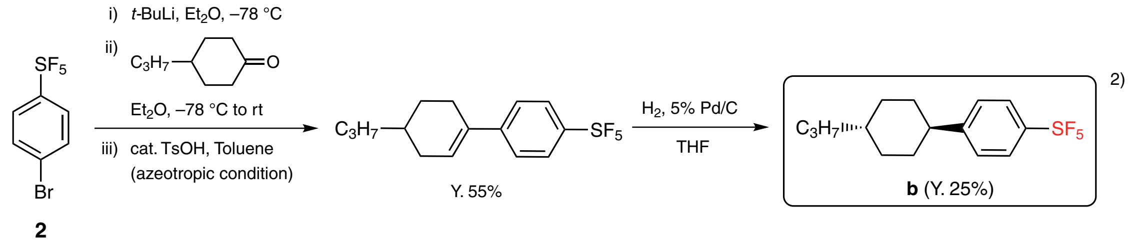
Pentafluorosulfanyl Compounds

B3866	**3-Bromophenylsulfur Pentafluoride (1)**	**1g**
B3867	**4-Bromophenylsulfur Pentafluoride (2)**	**1g**
A2042	**3-Aminophenylsulfur Pentafluoride (3)**	**5g**
A2043	**4-Aminophenylsulfur Pentafluoride (4)**	**5g**
C2583	**4-Chlorophenylsulfur Pentafluoride (5)**	**1g**
F0823	**2-Fluorophenylsulfur Pentafluoride (6)**	**1g**
F0824	**4-Fluorophenylsulfur Pentafluoride (7)**	**1g**
I0694	**3-Iodophenylsulfur Pentafluoride (8)**	**1g**
I0695	**4-Iodophenylsulfur Pentafluoride (9)**	**1g, 5g**
N0742	**3-Nitrophenylsulfur Pentafluoride (10)**	**1g**
N0743	**4-Nitrophenylsulfur Pentafluoride (11)**	**1g, 5g**
P1969	**Phenylsulfur Pentafluoride (12)**	**1g**
T2829	***p*-Tolylsulfur Pentafluoride (13)**	**1g**

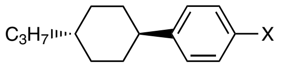
Compounds containing the pentafluorosulfanyl group (–SF_5) possess high electron-withdrawing property and strong lipophilic character. These compounds have been attracting attention as potent building blocks in the fields of pharmaceuticals, agrochemicals and functional materials. For example, it has been reported that compound **a** prepared from 3-bromophenylsulfur pentafluoride (**1**) is a SF_5 analog of fenfluramine, which is known as an anorectic agent, significantly enhances the affinity for the 5-HT_{2b}, 5-HT_{2c} and 5-HT_6 receptors than fenfluramine.1)



In addition, it also has been reported that the liquid crystal using compound **b**, which is prepared from 4-bromophenylsulfur pentafluoride (**1**), has significantly improved dielectric anisotropy (Δε), compared with other fluorinated analogs such as –F and –CF_3.2)



Dielectric anisotropy Δε of **b** is improved than other related fluorinated liquid crystals



b Δε = 12.0
X = F Δε = 4.3
X = CF_3 Δε = 8.6

References

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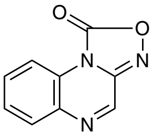
J. T. Welch, D. S. Lim, *Bioorg. Med. Chem.* **2007**, *15*, 6659.
2) Liquid crystals based on hypervalent sulfur fluorides: pentafluorosulfuranyl as polar terminal group
P. Kirsch, M. Bremer, M. Heckmeier, K. Tarumi, *Angew. Chem. Int. Ed.* **1999**, *38*, 1989.

Guanylate Cyclase Inhibitor

O0400 1*H*-[1,2,4]Oxadiazolo[4,3-*a*]quinoxalin-1-one (= ODQ) (1) 25mg



1

Guanylate cyclase is an enzyme that catalyzes the formation of guanosine 3',5'-monophosphate (cGMP) from guanosine triphosphate (GTP) and soluble guanylate cyclase (sGC) is the receptor for nitric oxide (NO).[1)]

1*H*-[1,2,4]Oxadiazolo[4,3-*a*]quinoxalin-1-one (ODQ, **1**) is a selective and irreversible inhibitor of sGC[2,3)] and its inhibition of the enzyme is NO-competitive.[4)] ODQ decreased the minimum alveolar anesthesia concentration for isoflurane anesthesia in rats but did not affect their arterial blood pressure or heart rate.[5)]

References

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A. Friebe, D. Koesling, *Circ. Res.* **2003**, *93*, 96.
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J. Garthwaite, E. Southam, C. L. Boulton, E. B. Nielsen, K. Schmidt, B. Mayer, *Mol. Pharmacol.* **1995**, *48*, 184.
3) Novel guanylyl cyclase inhibitor, ODQ reveals role of nitric oxide, but not of cyclic GMP in endothelin-1 secretion
F. Brunner, H. Stessel, W. R. Kukovetz, *FEBS Lett.* **1995**, *376*, 262.
4) Characterization of 1*H*-[1,2,4]oxadiazolo[4,3-*a*]quinoxalin-1-one as a heme-site inhibitor of nitric oxide-sensitive guanylyl cyclase
A. Schrammel, S. Behrends, K. Schmidt, D. Koesling, B. Mayer, *Mol. Pharmacol.* **1996**, *50*, 1.
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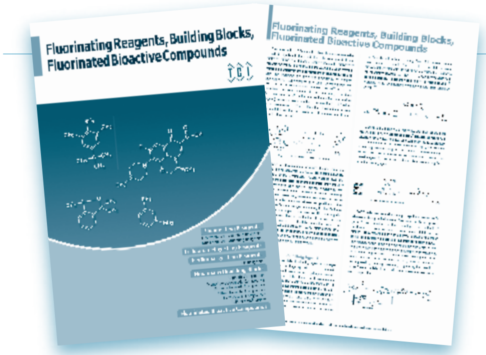
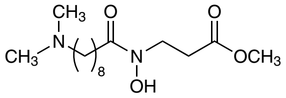
S. Cechova, T. N. Pajewski, *Anesth. Analg.* **2004**, *99*, 752.



Jumonji Domain-containing Histone Demethylase (JHDM) Inhibitor

D4078 *N*-(9-Dimethylamino-1-oxononyl)-*N*-hydroxy-β-alanine Methyl Ester (= NCDM-32b) (**1**)

5mg



NCDM-32b (**1**)

compound	IC$_{50}$ (μM)[a]			
	JMJD2C	JMJD2A	PHD1	PHD2
NOG	500	250	2.1	5.6
PCA (TCI code: P0553)	9.4	4.2	1.5	6.1
NCDM-32	1.0	3.0	>100	>100

[a] Values are means of at least two experiments.

Jumonji domain-containing histone demethylase (JHDM) is an enzyme catalyzing the demethylation of the methylated lysine residue in histone, which regulates the expression of *Mdm2* oncogene and *p53* anti-oncogene. NCDM-32b (**1**), developed by Suzuki, Miyata *et al.*, forms NCDM-32 losing a methyl group of the ester moiety by hydrolytic degradation, and shows an inhibitory activity against JMJD2C, a kind of JHDM. NCDM-32 inhibits the growth of HCT116 colon cancer cells with a combination of LSD1 inhibitor.

Reference

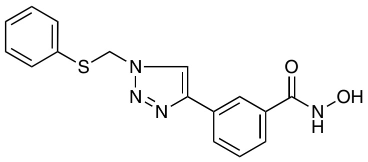
S. Hamada, T. Suzuki, K. Mino, K. Koseki, F. Oehme, I. Flamme, H. Ozasa, Y. Itoh, D. Ogasawara, H. Komaarashi, A. Kato, H. Tsumoto, H. Nakagawa, M. Hasegawa, R. Sasaki, T. Mizukami, N. Miyata, *J. Med. Chem.* **2010**, *53*, 5629.

Related Compounds

P0553	2,4-Pyridinedicarboxylic Acid Hydrate (= PCA)	5g,	25g
A2411	NCL-1•HCl		5mg
D4015	Daminozide	5g,	25g
A2501	Acetyldinaline	10mg,	50mg
D4188	4-(Dimethylamino)-*N*-[7-(hydroxyamino)-7-oxoheptyl]benzamide (= M 344)	20mg,	100mg
S0892	Splitomicin	200mg,	1g
T2477	Trichostatin A		10mg
S0519	Sodium Butyrate	25g,	100g
P0823	Valproic Acid	25mL,	500mL
S0894	Valproic Acid Sodium Salt	25g,	100g

Histon Deacetylase 8 (HDAC8) Selective Inhibitor

H1340 *N*-Hydroxy-3-[1-(phenylthio)methyl-1*H*-1,2,3-triazol-4-yl]benzamide (= NCC-149) (1) 5mg



NCC-149 (**1**)

compound	IC$_{50}$ (μM)^a					
	HDACs (nuclear extract)	class I			class IIa	class IIb
		HDAC1	HDAC2	HDAC8	HDAC4	HDAC6
vorinostat (TCI code: H1388)	0.17	0.27	0.78	1.5	>10	0.21
NCC-149 (TCI code: H1340)	54	38	>100	0.070	44	2.4

[a] Values are means of at least three experiments.

NCC-149 (**1**), developed by Suzuki, Miyata *et al.*, selectively inhibits histon deacetylase 8 (HDAC8). Histon deacetylase (HDAC) regulates gene expression, such as the tumor-suppressor gene, by catalyzing the deacetylation reaction of the acetylated lysine residue in histon. HDAC8, an isoform of histon deacetylase, has been reported to be implicated in T-cell lymphomas and neuroblastoma tumorigenesis. It is expected that NCC-149 will be used as an epigenetics research tool and an anticancer agent because of its selective inhibitory activity of HDAC8 and tumor cell growth.

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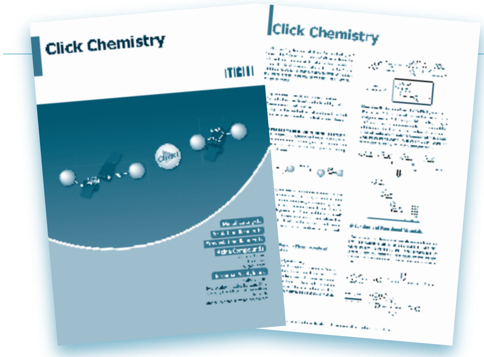
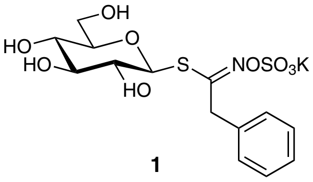
Related Compound

H1388	Vorinostat (= SAHA)	200mg



Glucosinolate

G0397 Glucotropaeolin Potassium Salt (1) 10mg



1

Glucosinolates are sulfur-containing phytochemicals present in the families Brassicaceae (cabbage, broccoli, mustard, *etc.*), Capparaceae (capers), *etc.* There are three major types of glucosinolates, aliphatic, aromatic, and indolic. These types are synthesized from different amino acid precursors: alanine, isoleucine, leucine, methionine, and valine for aliphatic glucosinolates, phenylalanine and tyrosine for aromatic glucosinolates, and tryptophan for indolic glucosinolates.1)

Glucosinolates are hydrolyzed by the endogenous enzyme, myrosinase, to yield isothiocyanates, thiocyanates, nitriles, and elementary sulphur.2) Benzyl isothiocyanate is a product of the enzymatic hydrolysis of glucotropaeolin2,3) and is one of the most intensively studied isothiocyanates as an anti-cancer agent.4-10) The compound shown above is glucotropaeolin potassium salt (**1**).

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