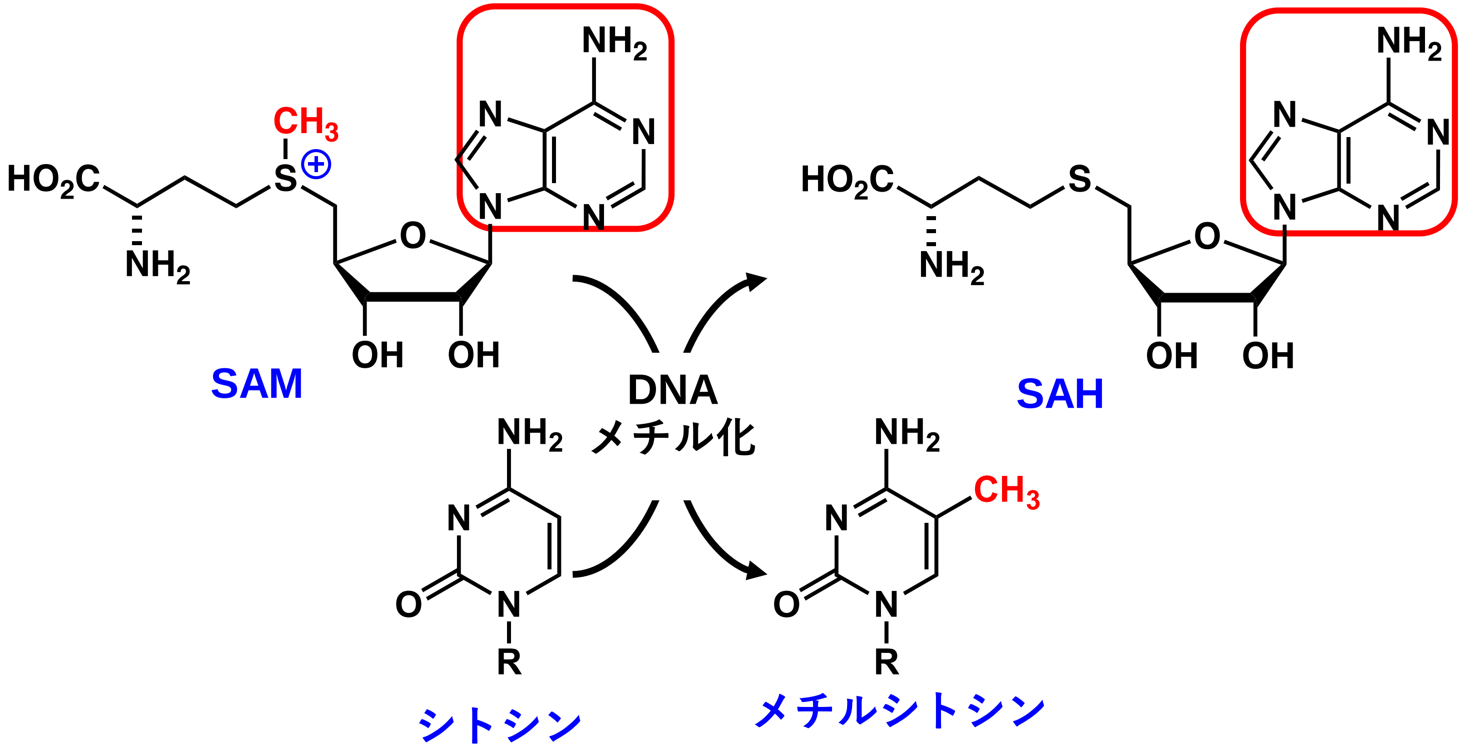
新技術説明会
New Technology Presentation Meetings!

エピジェネティックを司るSAMやSAHの新規誘導体の合成

静岡県立大学　薬学部
医薬品製造科学分野
教授　菅敏幸

令和2年10月27日

メチル基供与源：SAM (S-Adenosyl-L-methionine)



DNAのメチル化：DNAの塩基配列を伴わない制御

エピジェネティック制御
遺伝子発現、細胞表現形の変化

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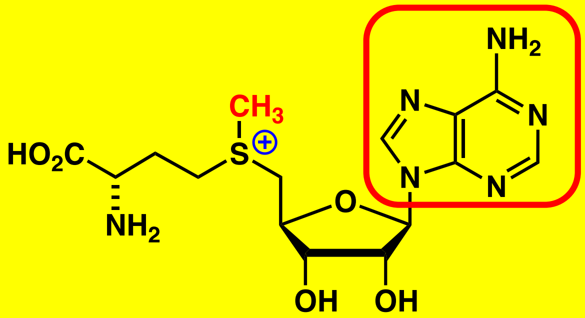
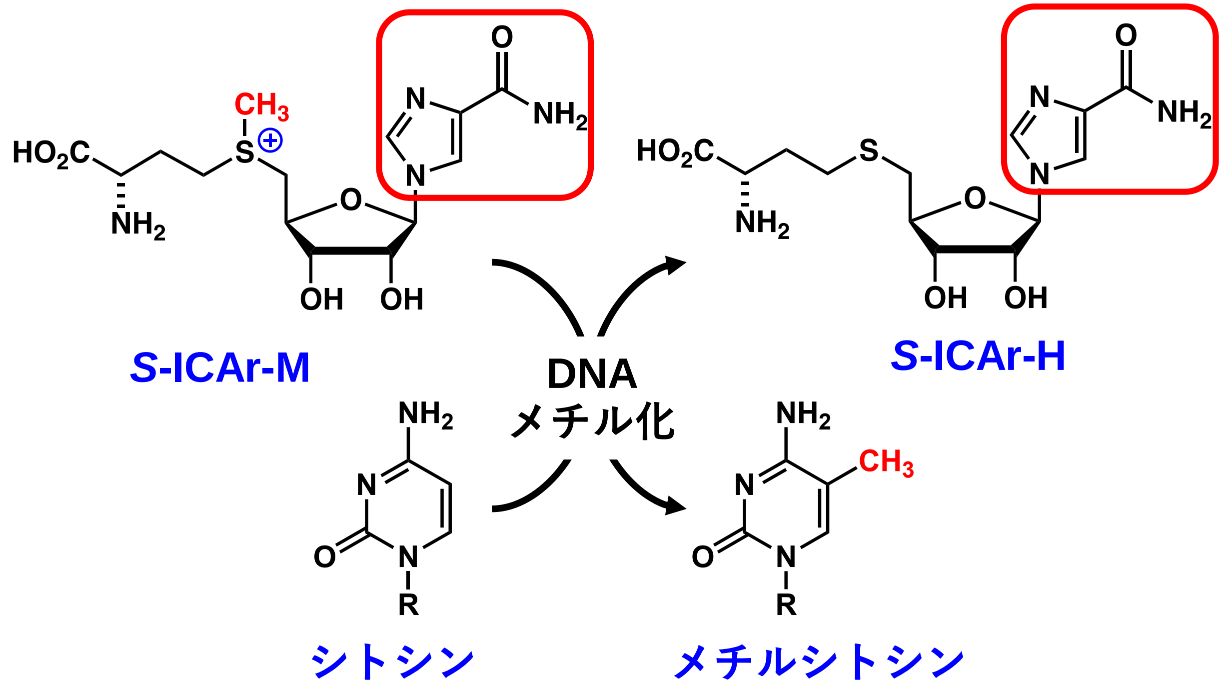
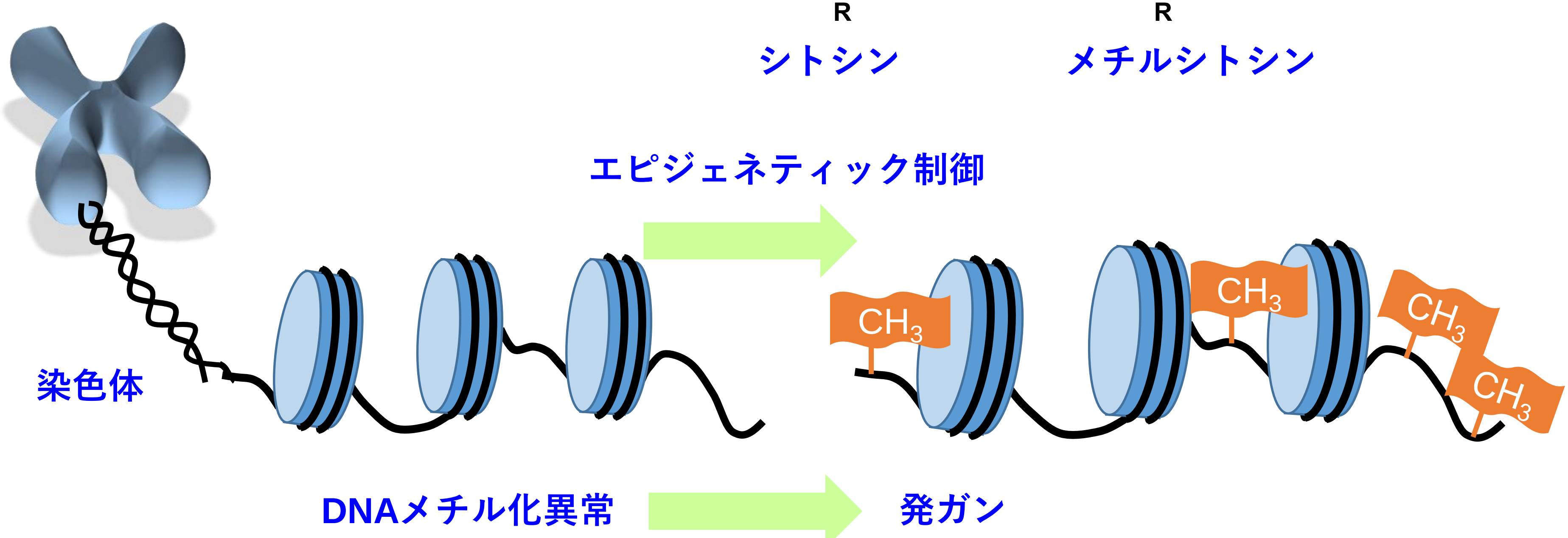


SAM (*S*-adenocy-L-lmethionine)

生体内の普遍的メチル供与体





新技術の特徴

- 新規SAH誘導体の両異性体を含む
  合成方法の確立

- 硫黄原子のメチル化による
  新規SAM誘導体の合成

想定される用途

- 医療中間体（がん治療薬、育毛剤等）のリード化合物など
- 生理活性物質のリード化合物など

食料危機を救うキノコ由来の天然物

・静岡大学河岸教授の宿舎の芝で，「フェアリーリング」を発見（2003年）

河岸教授の宿舎

静大キャンパス内宿舎

繁茂

コムラサキシメジ

この経験が契機となり研究開始（2004年）

“フェアリーリング（Fairy Rings）”とは？

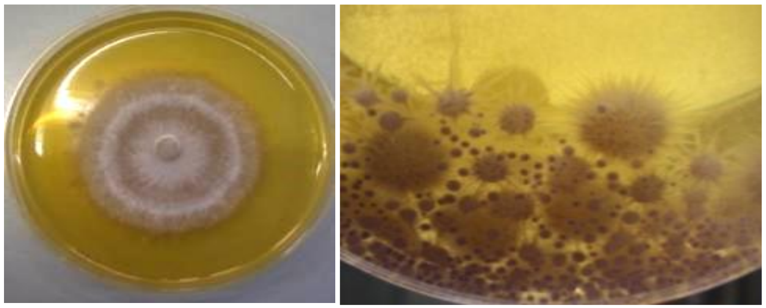
芝が繁茂し，時には枯死，後にキノコが発生

1884年Natureが1675年の最初の科学的記述を紹介
その妖精の正体（何故繁茂する？）は謎

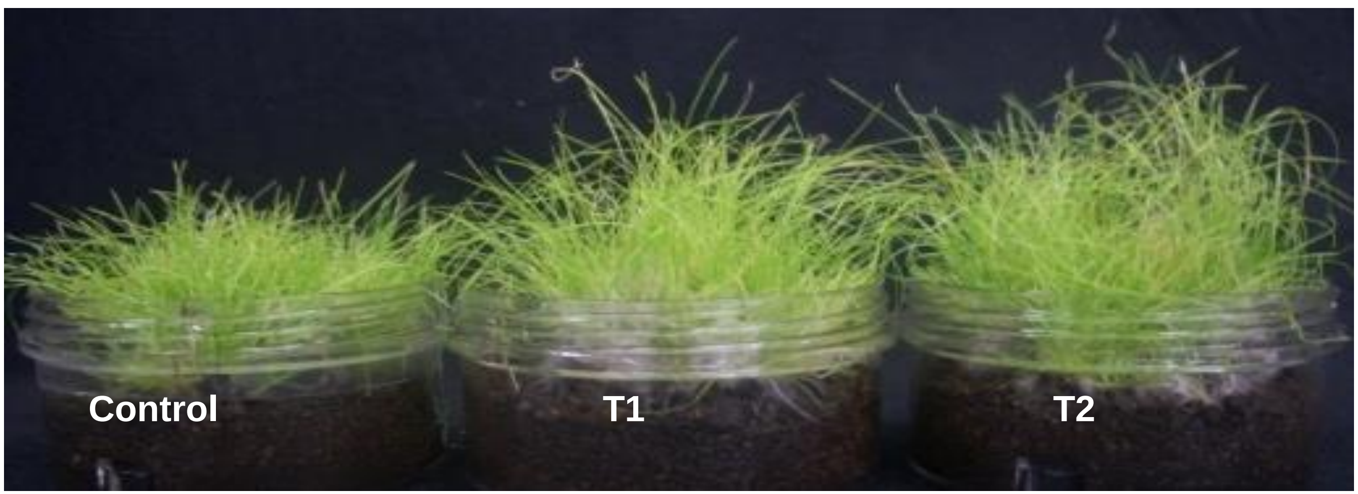
河岸教授の仮説
「キノコが特異的な植物成長調節物質を産生している」

培養したコムラサキシメジがシバの成長促進

コムラサキシメジの培養



液体培養した菌を、シバを植えたシャーレ中の土に植え、3週間培養した。



T1 （新鮮菌体0.5ｇを植菌）　T2 （新鮮菌体1.5ｇを植菌）

食料危機を救うキノコ由来の天然物

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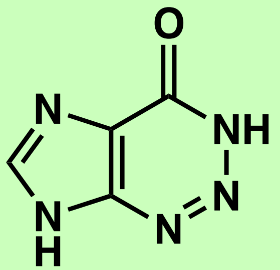
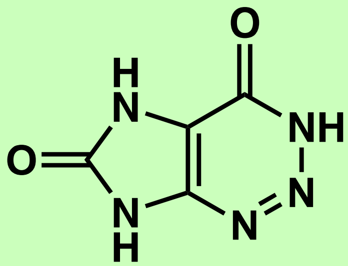
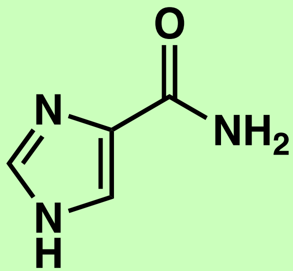


AHX
（2-azahypoxanthine）
コムラサキシメジから発見

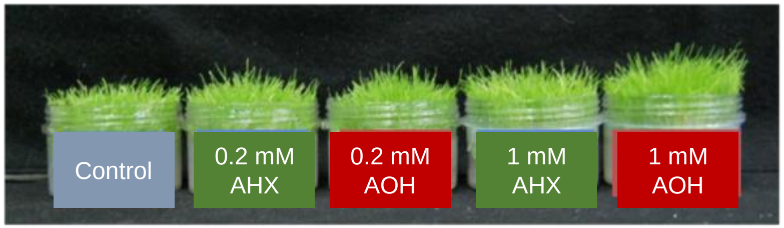


AOH
（2-aza-8-oxohypoxanthine）
AHX代謝産物，イネから発見

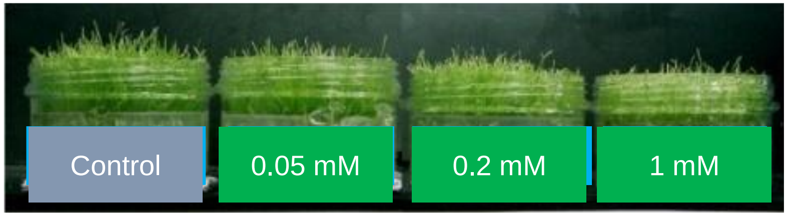


ICA
（imidazole-4-carboxamide）
コムラサキシメジから発見

３連続窒素原子を有する6員環の天然有機化合物は，**AHXとAOHが史上初**



AHXとAOHのシバに対する活性（成長促進）



ICAのシバに対する活性（成長抑制）

ChemBioChem, 11, 1373 (2010)
J. Agric. Food Chem., 58, 9956 (2010)
Angew. Chem. Int. Ed., 53, 1552 (2014)

RESEARCH NEWS & VIEWS

PLANT SCIENCE

Fairy chemicals

Those who cultivate manicured lawns curse 'fairy rings' of mushrooms (pictured) and the rapid grass growth associated with them. The compound that stimulates this growth, 2-azahypoxanthine (AHX), was isolated from a fungus in 2010, but Choi *et al.* now report in *Angewandte Chemie* that plants also produce it (J.-H. Choi *et al. Angew. Chem. Int. Edn* http://doi.org/f2phhs; 2014).

The authors treated several plants with AHX, and observed that it was metabolized to a compound called 2-aza-8-oxohypoxanthine (AOH). They went on to show that both AHX and AOH are produced by plants, and are present in rice at levels similar to those of plant hormones.

Choi *et al.* found that a member of the purine metabolic pathway is converted to AHX and AOH in rice, and they extracted crude enzymes that catalyse the reactions involved from rice and *Arabidopsis*, a model plant. They conclude that AHX and AOH are formed in a previously unknown metabolic pathway.

Intriguingly, AOH stimulates rice growth, albeit not as much as AHX. Frustrated haters of fairy rings could perhaps take heart from the thought that both compounds hold promise for horticulture. Andrew Mitchinson

Nature 505巻, 298頁（2014年1月16日発行）

３化合物を，表題に因んでフェアリー化合物（Fairy Chemicals：FCsと略称）と命名

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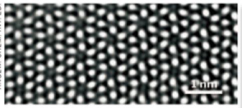
SCIENCE & TECHNOLOGY CONCENTRATES

ATOMIC INSIGHTS ON SHARK TEETH

Considering that neither brushing nor flossing is part of a shark's daily dental regimen, the animals get remarkably few cavities. To get an idea of what makes shark teeth so resistant to decay, researchers in Japan aimed a transmission electron microscope at the enamel on the creature's chompers. Normally the microscope's electron beam can damage biomineralized material. But by using low-dose imaging techniques, Yuichi Ikuhara and Zhongchang Wang of Tohoku University and colleagues were able to minimize such damage and directly image every individual atom in the enamel (*Angew. Chem. Int. Ed.* 2014, DOI: 10.1002/anie.201307689). The enamel is made of fluorapatite, $Ca_5(PO_4)_3F$, which appears to the researchers as hexagons of calcium, phosphorus, and oxygen atoms with fluorine atoms at their centers. Making calculations based on these images, they determined that fluorine is partially covalently bound to calcium in the enamel. This suggests that fluorine is critical to stabilizing the hexagonal frames. Loss of fluorine atoms would leave atom-sized holes and weaken the teeth.—BH

ANGEW. CHEM. INT. ED.



This TEM image of shark tooth enamel reveals hexagonal bright spots representing closely spaced calcium, phosphorus, and oxygen atomic columns. The spot at the center of each hexagon represents a fluorine atom.

NANOPORES FIND PHOSPHATES

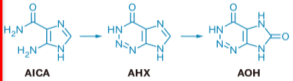
Strawlike proteins embedded into lipid membranes—known as nanopores—are already invaluable in genomics research. Scientists can sequence DNA by analyzing subtle differences in ionic current that occur as nucleotides thread through the nanopore and partially block ion flow. By applying nanopore technology to proteomics, a research team is now able to detect phosphorylation patterns on proteins that regulate protein activity (*Nat. Biotechnol.* 2014, DOI: 10.1038/nbt.2799). To coax a protein "camel" through the "eye" of a nanopore needle, Christian B. Rosen, David Rodriguez-Larrea, and Hagan Bayley of the University of Oxford added a short DNA sequence to the C-terminus of the protein thioredoxin. Their technique distinguished whether thioredoxin was phosphorylated in one of two positions, in both positions, or in neither position. The nanopores can determine populations of phosphorylation patterns in hundreds of individual copies of a protein, which is useful information in cancer diagnostic research, although the method currently detects phosphorylation only near the ends of proteins. Other teams have used motor proteins to feed an entire protein through a nanopore, a method Bayley's group hopes to adapt to overcome the detection limitation. The technology has been patented and licensed to Oxford Nanopore Technologies, a company Bayley founded.—CD

FAIRY RINGS SHARE MAGICAL CHEMISTRY

For centuries, people around the world have been mystified by the formation of circles or arcs of accelerated plant growth in woodlands and grassy fields. The rings sometimes erupt with mushrooms, adding to the intrigue. Myth and superstition led these geometric patterns of plant growth to be called fairy rings. In 2010, a research team led by Hirokazu Kawagishi of Shizuoka University, in Japan, discovered that the "fairy" is the plant-growth regulator 2-azahypoxanthine (AHX), one of several purine-based natural products made by fungi. The researchers determined how AHX is produced from 5-aminoimidazole-4-carboxamide (AICA)—a compound in the purine metabolic pathway in animals, plants, and microorganisms—and began figuring out the complete biosynthesis pathway of the compounds in hopes of finding a practical use of the plant hormones in agriculture. Kawagishi's team has now reported the discovery of an additional AHX metabolite, 2-aza-8-oxohypoxanthine (AOH), which is produced from AHX by the enzyme xanthine oxidase. And after detecting AHX and AOH in plants such as rice, the researchers have uncovered that the plants themselves actually biosynthesize the compounds (*Angew. Chem. Int. Ed.* 2014, DOI: 10.1002/anie.201308109). Kawagishi is now leading an effort to isolate key enzymes in the purine biosynthetic pathways as models for new agrochemicals or for engineering genetically modified plants.—SR

WIKIMEDIA COMMONS

A fruiting fairy ring on a suburban lawn is the result of a set of natural products that regulate plant growth, including AHX and AOH.



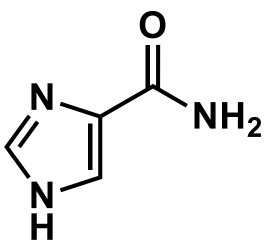
ENZYME CATALYSIS ILLUSTRATED

A tenet of enzyme catalysis is that the catalyst should bind the transition state more strongly than the ground state. Although the principle is widely applied, particularly with catalytic antibodies, chemists have lacked a simple, well-characterized model to illustrate this seminal system. Jay S. Siegel at China's Tianjin University, J. Fraser Stoddart of Northwestern University, and colleagues report in *Nature Chemistry* that they've designed a representative reaction that depicts a catalytic conformational change (2014, DOI: 10.1038/nchem.1842). The team studied the inversion of corannulene, a bowl-shaped hexacyclic aromatic hydrocarbon that has an energy barrier to inversion of 11.5 kcal/mol. That energy barrier can be lowered to about 7.9 kcal/mol by a catalyst that stabilizes the planar intermediate state. The catalyst, known as $ExBox^{4+}$, is a cyclic macromolecule made from two extended bipyridinium units that selectively bind planar polycyclic aromatics. When complexed inside $ExBox^{4+}$, the energy barrier for bowl-flipping lowers because of the catalyst's increased affinity for the flat transition state of corannulene. The corannulene bowl-to-bowl inversion process—like an umbrella flipping inside out—happens 10 times as fast with $ExBox^{4+}$ than without it. "The dependence of this example on shapes, rather than on the intricate mechanistic details of a more complicated organic reaction, gives it a visual simplicity that every chemist can understand," writes Boston College's Lawrence T. Scott in an accompanying perspective.—EKW

アメリカ化学会Chemical & Engineering News (VOLUME 92, NUMBER 4)　2014月1月27日発行

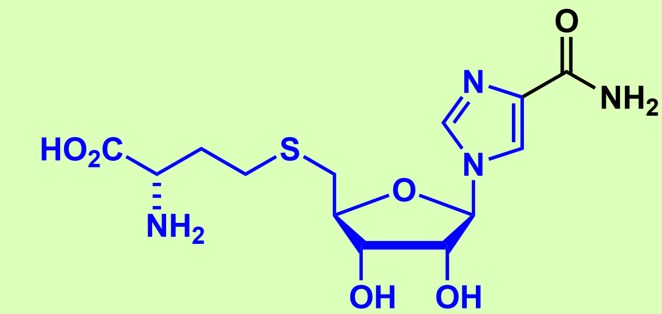
Mitchinson, A. *Nature* 2014, *505*, 298.　doi:10.1038/505298a

S-ICAr -H :フェアリー化合物の代謝物

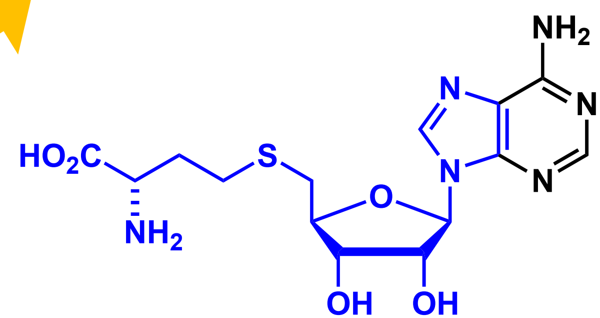


ICA

Increase crop yields



SIH
(*S*-ICA-ribosyl homocysteine)



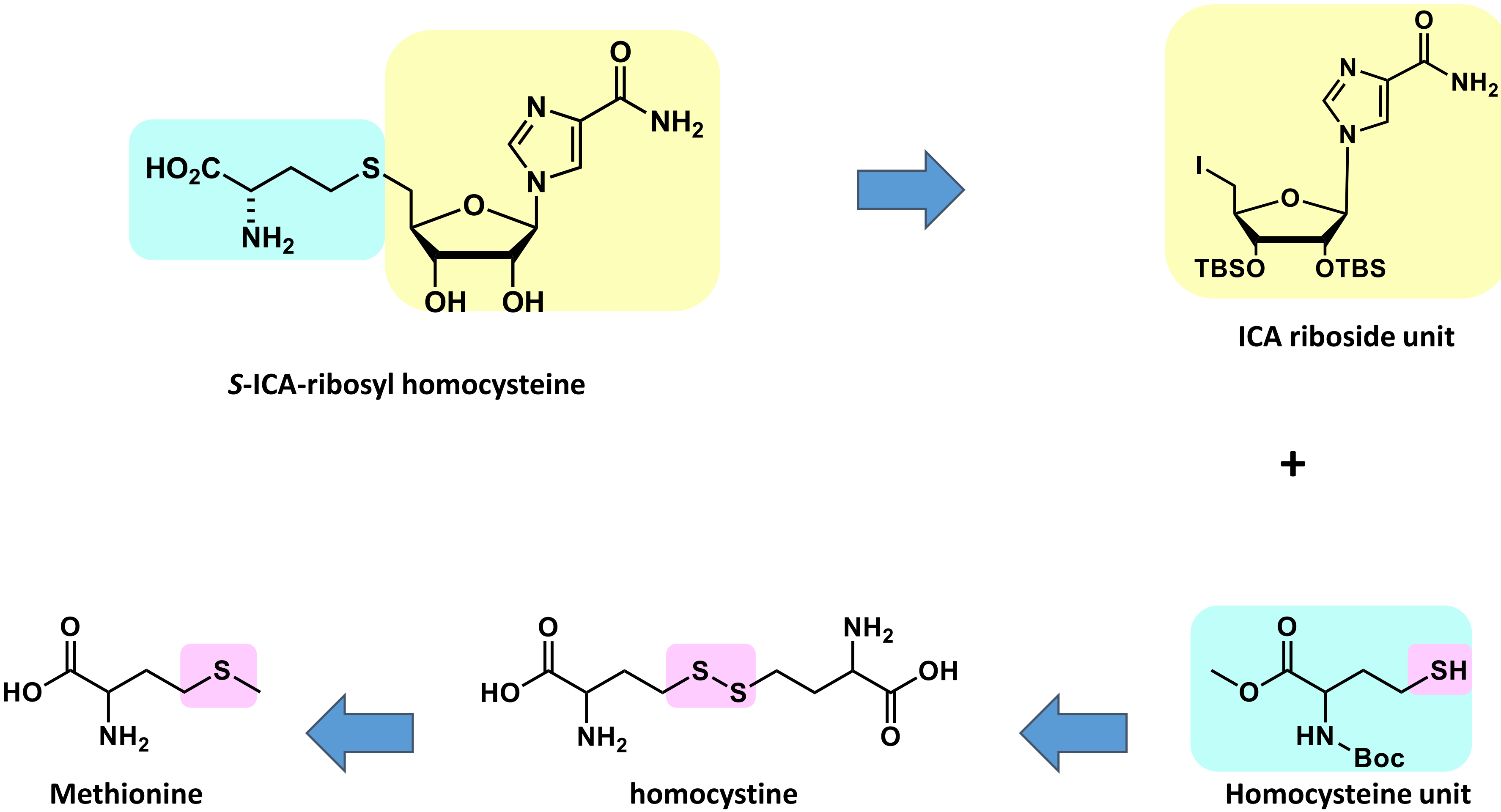
SAH
(*S*-Adenocyl homocysteine)

新規SAH誘導体のS-ICAr-H(S-ICAリボシルホモシステイン)の合成法

菅敏幸、稲井誠、大内仁志、河岸洋和、崔宰熏

特願2018－95270、２０１８年５月１７日出願、静岡県公立大学法人

S-ICAr-Hの合成戦略



L-Homocysteineユニットの合成

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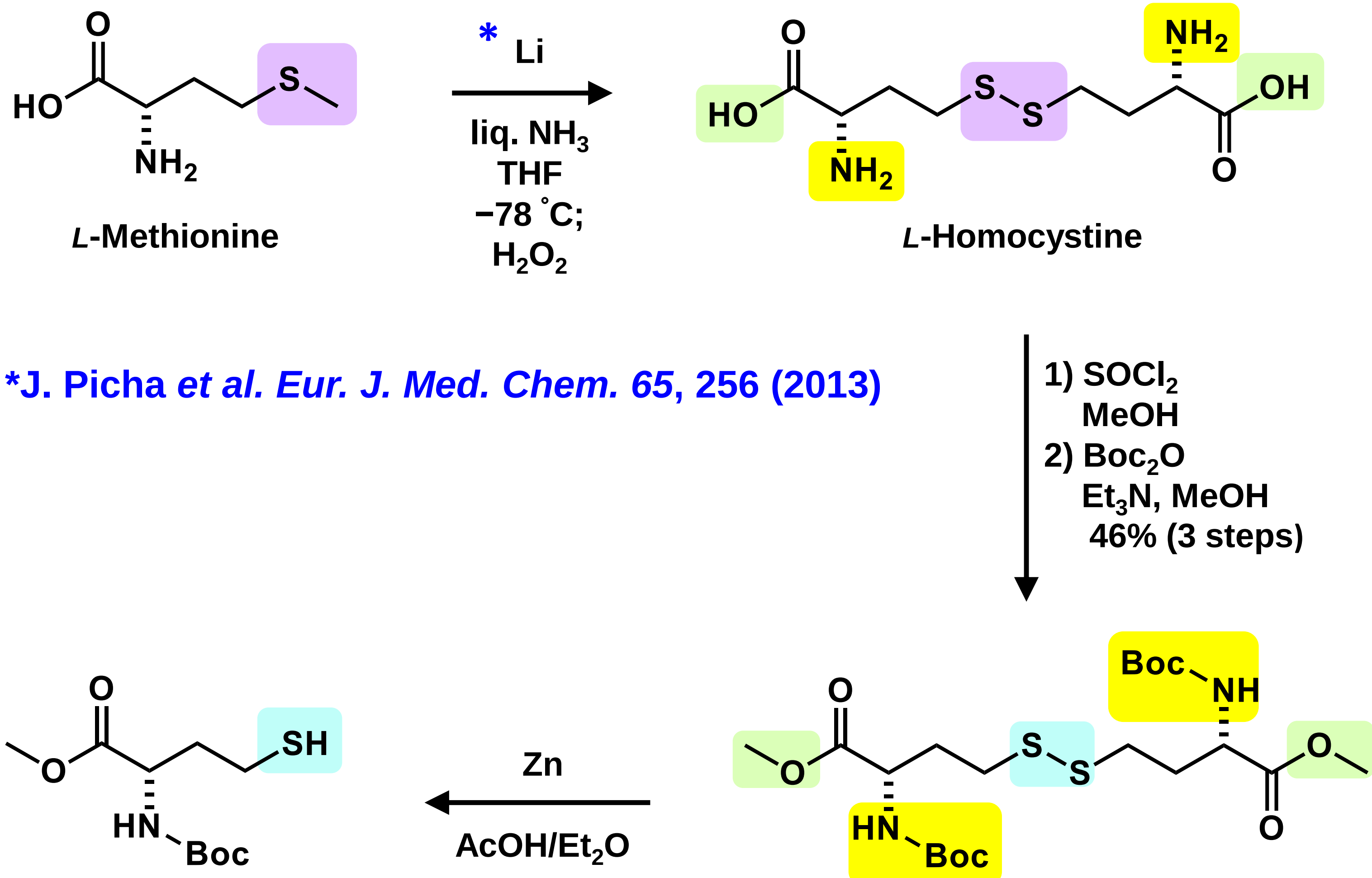
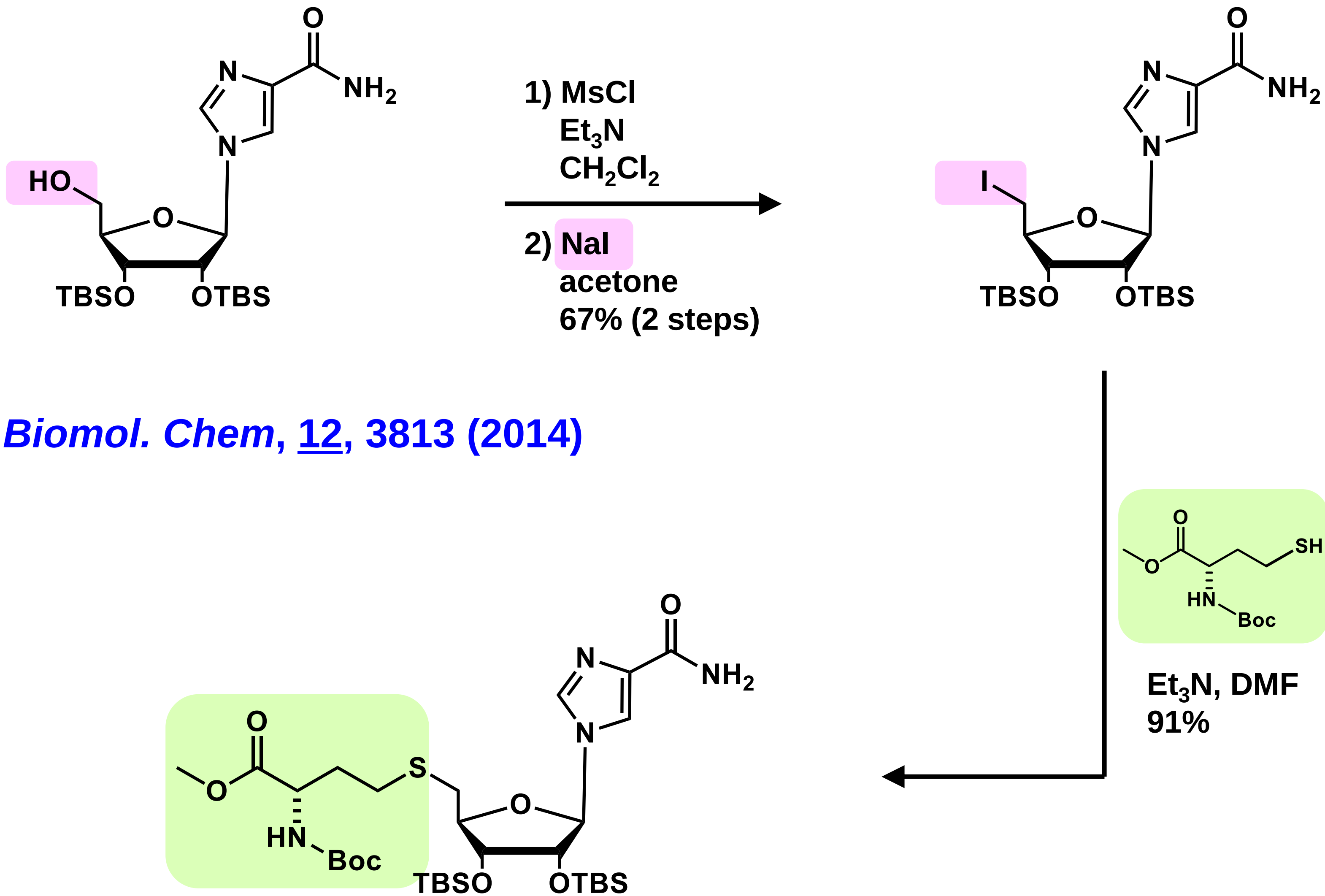


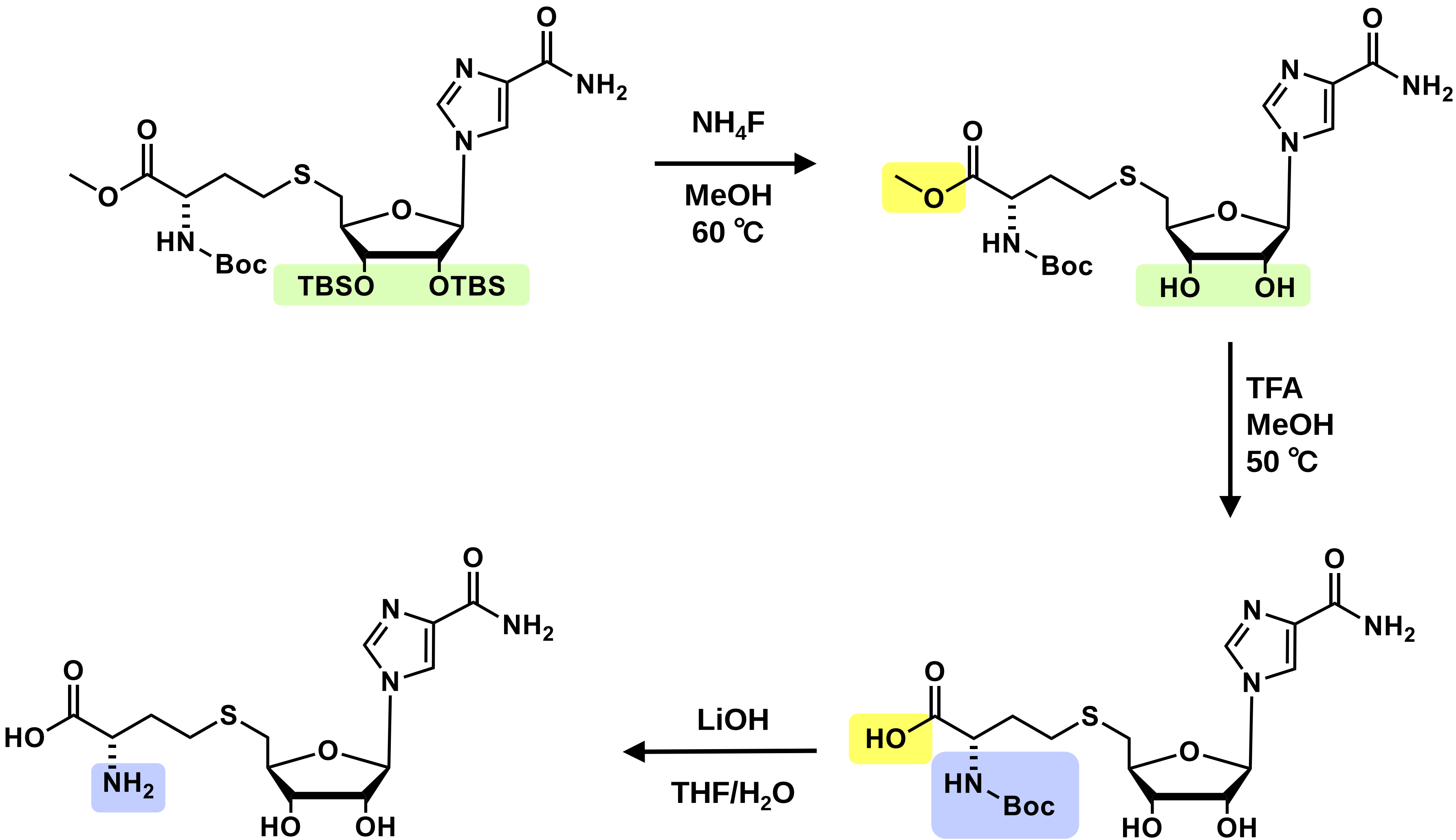
*J. Picha *et al. Eur. J. Med. Chem. 65*, 256 (2013)

S-ICArと L-homocysteineの連結



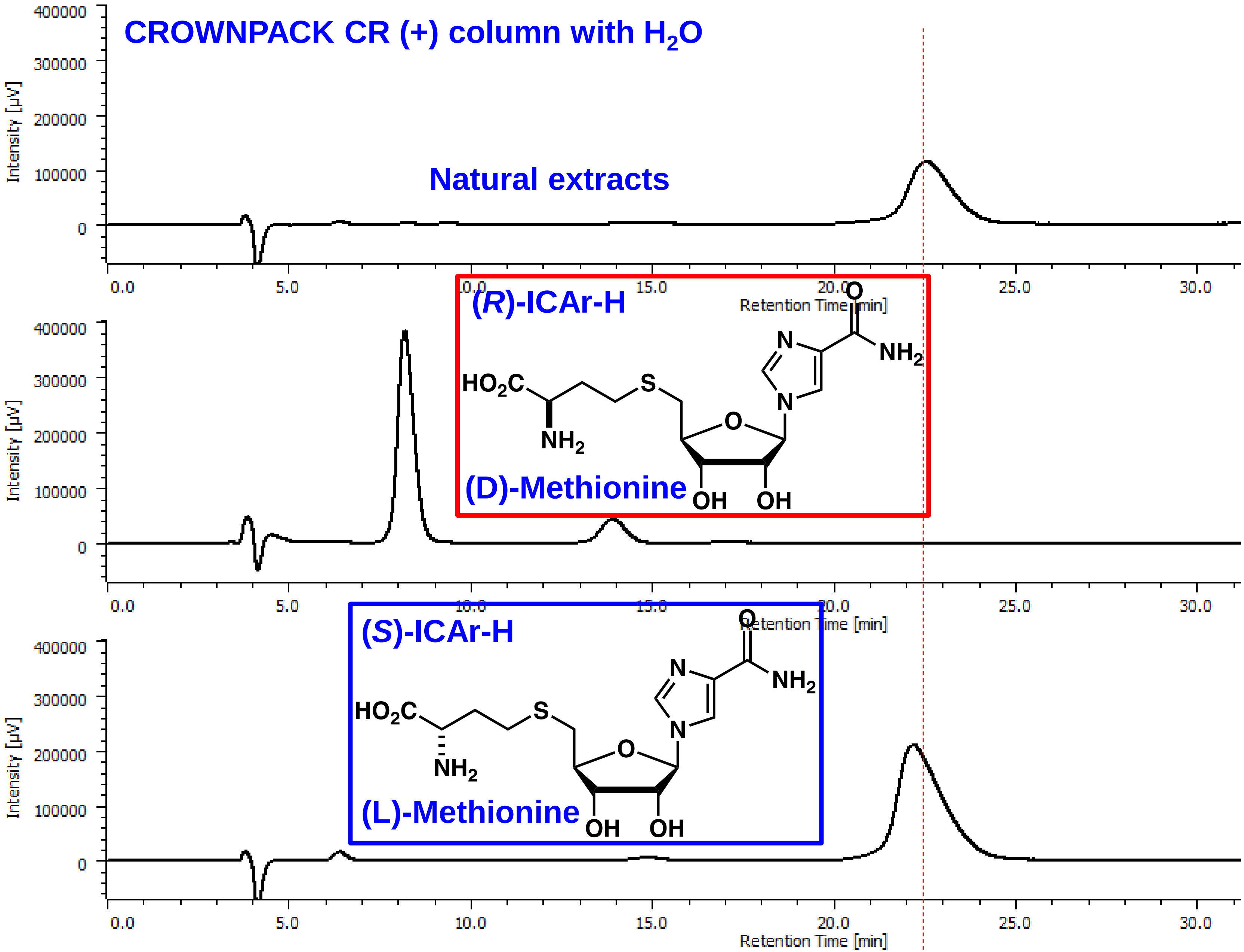
Org. Biomol. Chem, 12, 3813 (2014)

S-ICAr-Hの合成

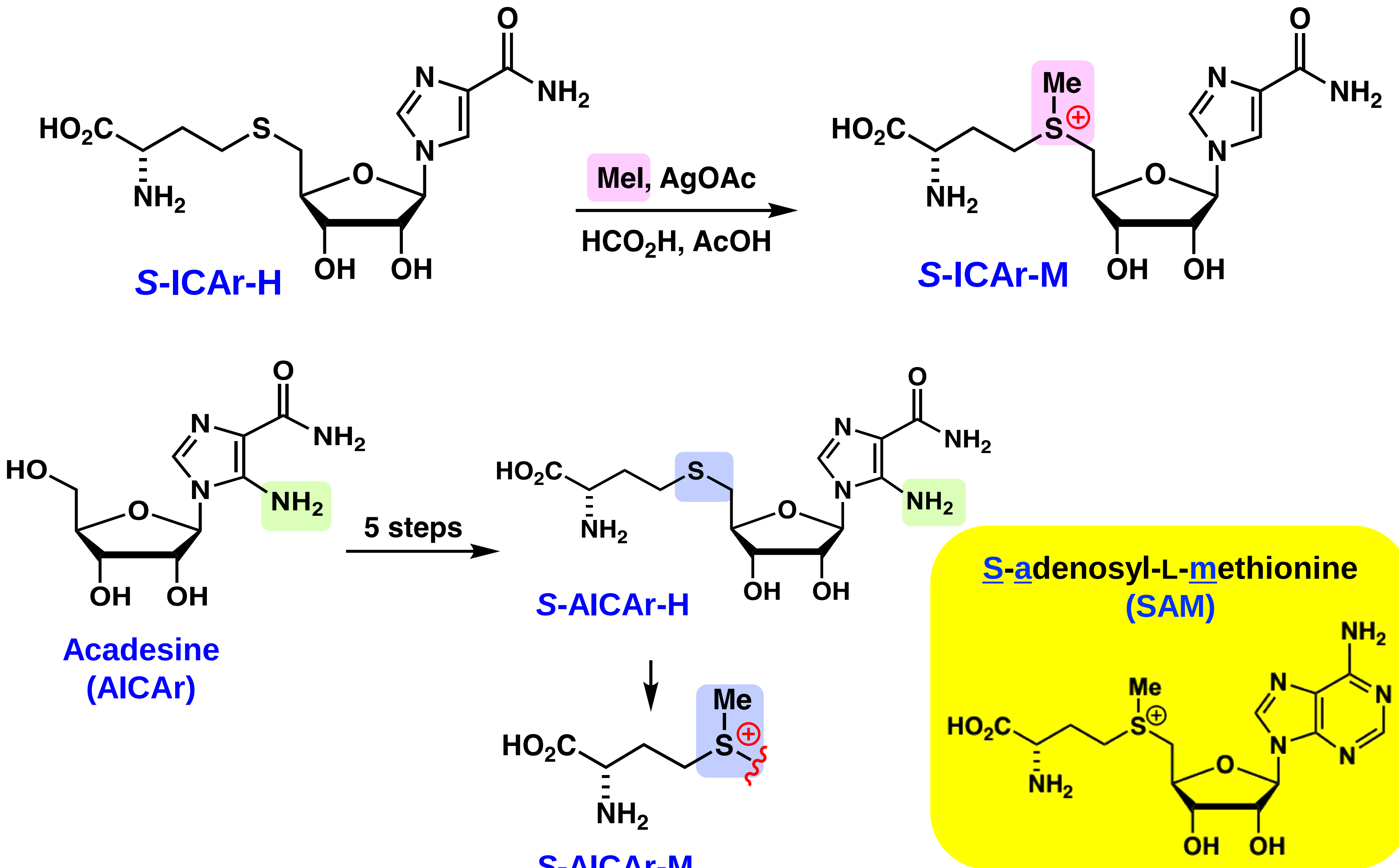


S-ICAr-H (L-homocysteine)

S-ICAr-Hの絶対配置の決定

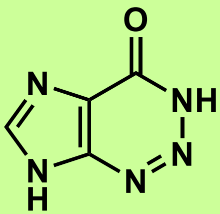


新規誘導体：*S*-ICAr-M, *S*-AICAr-H, *S*-AICAr-Mの合成

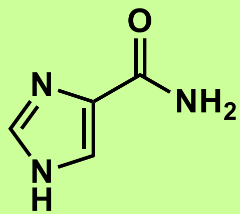


保有するFCs (Fairy Chemicals)

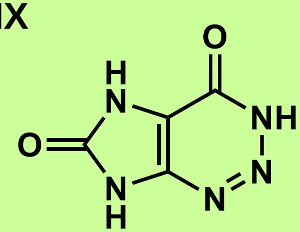
圃場実験の実現



AHX

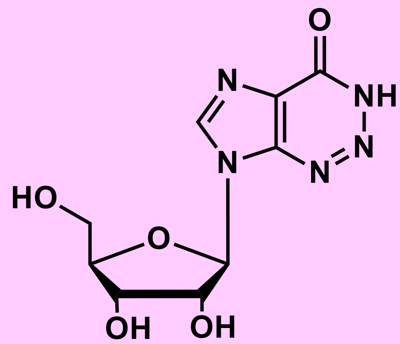


ICA

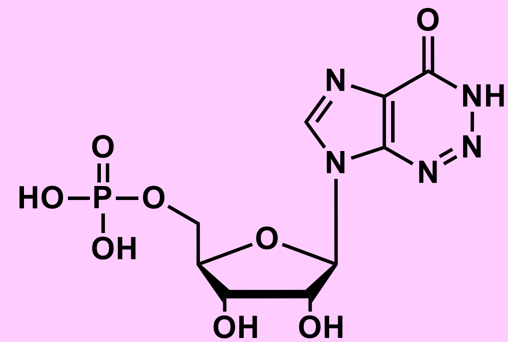


AOH

存在の確認

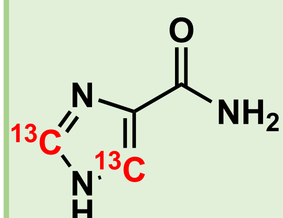


AHX-riboside

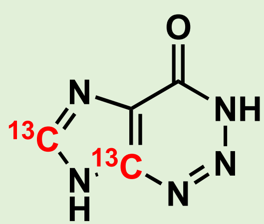


AHX-ribotide

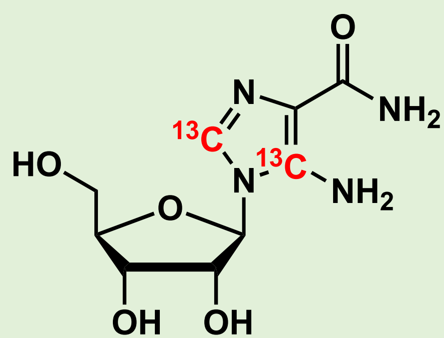
微量成分の検出法の確立



[2,5-$^{13}C_2$]-ICA

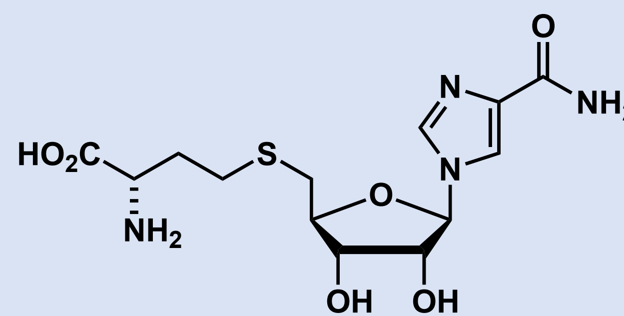


[4,8-$^{13}C_2$]-AHX



[2,5-$^{13}C_2$]-AICAr

代謝物合成（絶対配置確定）



S-ICA-ribosyl L-homocysteine

実用化にむけた課題

- 機能性、生理活性試験
- S-ICAr-Mのメチル化能力の証明
- S-ICAr-Hの酵素阻害能力の証明
- S-ICAr-MとS-ICAr-Hの生物活性

企業への要望

- 機能性、生理活性試験についての共同研究

分野：医薬品、肥料、化成品、化粧品など
広く求めています。

本技術に関する知的財産権

- 発明の名称　：新規SAH誘導体のS-ICAr-H (S-ICAリボシルホモシステイン)の合成法
- 出願番号　：特願2018－95270
- 出願人　：静岡県公立大学法人
- 発明者　：菅敏幸、稲井誠、大内仁志 河岸洋和、崔宰熏

お問い合わせ先

御連絡をお待ちしております。

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