アカデミックプログラム［B講演］ | 16. 天然物化学・ケミカルバイオロジー：口頭B講演

2025年3月27日(木) 13:00 ~ 15:10 [A]A305(第3学舎 1号館 [3階] A305)

[[A]A305-2pm] 16. 天然物化学・ケミカルバイオロジー

座長：安藤 吉勇、若森 晋之介

日本語
13:00 ~ 13:20
[[A]A305-2pm-01]
イリジマシド類の全合成

○諏訪 朝也[1]、梅原 厚志[1]、佐々木 誠[1] (1. 東北大院生命)

日本語
13:20 ~ 13:40
[[A]A305-2pm-02]
Portimineの合成研究

○佐藤 大亮[1]、梅原 厚志[1]、佐々木 誠[1] (1. 東北大院生命)

英語
13:40 ~ 14:00
[[A]A305-2pm-03]
巨大ウイルスから発見した新しいタイプのテルペン合成酵素

○朴 治彦[1]、三橋 隆章[2]、堤 雄翔[1]、藤田 誠[1,2,3] (1. 東大院工、2. 分子研、3. 東大国際高等研究所東京カレッジ)

14:00 ~ 14:10
休憩

英語
14:10 ~ 14:30
[[A]A305-2pm-04]
イソダフロンガミンHの全合成

○岩本 青空[1]、平良 侑己[1]、仲野 暦[1]、佐々木 啓二[1]、小林 将一朗[1]、川北 玲史[1]、武井 孝也[1]、徳山 絢子[1]、友池 真斗[1]、中村 陽登[1]、千田 憲孝[1]、岡村 俊孝[1]、佐藤 隆章[1] (1. 慶應義塾大学)

英語
14:30 ~ 14:50
[[A]A305-2pm-05]
Manginoid Dの全合成

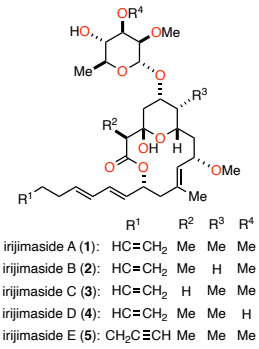
○加藤 光輝[1]、勝田 亮[1]、石神 健[1]、若森 晋之介[1] (1. 東農大生命)

英語
14:50 ~ 15:10
[[A]A305-2pm-06]
Development of Aldehyde-Forming Nef Reaction Initiated by Singlet Oxygen under Mild Conditions

○Ira Novita Sari[1], Bobo Yan[1], Tatsuya Morozumi[2], Yuichi Kamiya[1,3], Taiki Umezawa[1,3] (1. Graduate School of Environmental Science, Hokkaido University, 2. Faculty of Science, Hokkaido University, 3. Faculty of Environmental Earth Science, Hokkaido University)

イリジマシド類の全合成

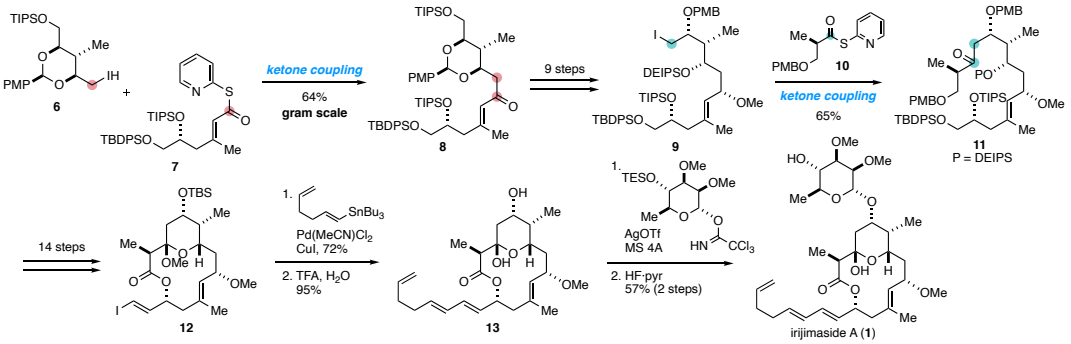
（東北大院生命）○諏訪 朝也・梅原 厚志・佐々木 誠
Total Synthesis of irijimasides (*Graduate School of Life Sciences, Tohoku University*)
○Tomoya Suwa, Atsushi Umehara, Makoto Sasaki



Irijimasides (**1**–**5**) are 14-membered macrolide glycosides isolated from marine cyanobacterium collected in Okinawa. These compounds inhibit osteoclast formation in mouse macrophage cells; therefore, they attracted attention for a drug lead compound for the treatment of osteoporosis. We initiated our research to establish an efficient synthetic method for irijimasides. Fragments **6** and **7** were linked using ketone coupling to afford ketone **8**. After conversion of **8** to iodide **9** in nine steps, the second ketone coupling of **9** and fragment **10** provided ketone **11**. Ketone **11** was converted to lactone **12** in a 14-step sequence, and subsequent introduction of a side chain and hydrolysis of the methyl acetal provided aglycone **13**. Finally, glycosylation and removal of the TES group accomplished the first total synthesis of irijimaside A (**1**). We also achieved total synthesis of irijimasides C–E (**3**–**5**) using the same strategy.

Keywords : Total Synthesis; Macrolide; Ketone Coupling

イリジマシド A–E（**1**–**5**）は、沖縄県沖で採取された海洋シアノバクテリアから単離・構造決定された 14 員環マクロリド配糖体である [1]。本天然物はマウス由来マクロファージ様細胞に対して破骨細胞の分化を阻害することから、新規骨粗鬆症治療薬のリード化合物として期待される。我々は、イリジマシド類の効率的な合成法の確立を目指して研究に着手した。ケトンカップリング [2] によってフラグメント **6** および **7** を連結してケトン **8** を得た。さらに 9 工程の変換により **8** をヨウ化アルキル **9** へ導き、続くフラグメント **10** とのケトンカップリング [2] によってケトン **11** を合成した。ケトン **11** は 14 工程の変換でラクトン **12** へ誘導した後に、側鎖の導入とメチルアセタールの加水分解を行ってアグリコン **13** へ変換した。最後に、グリコシル化と糖上の TES 基の除去を行うことでイリジマシド A（**1**）の全合成を達成した [3]。また、同様の合成手法を用いてイリジマシド C–E（**3**–**5**）の全合成にも成功した。



1) A. Yamano et al., *J. Nat. Prod.* **2020**, *83*, 1585. 2) A. Umehara, Y. Kishi, *Chem. Lett.* **2019**, *48*, 947. 3) T. Suwa et al., *Org. Lett.* **2024**, *26*, 4377.

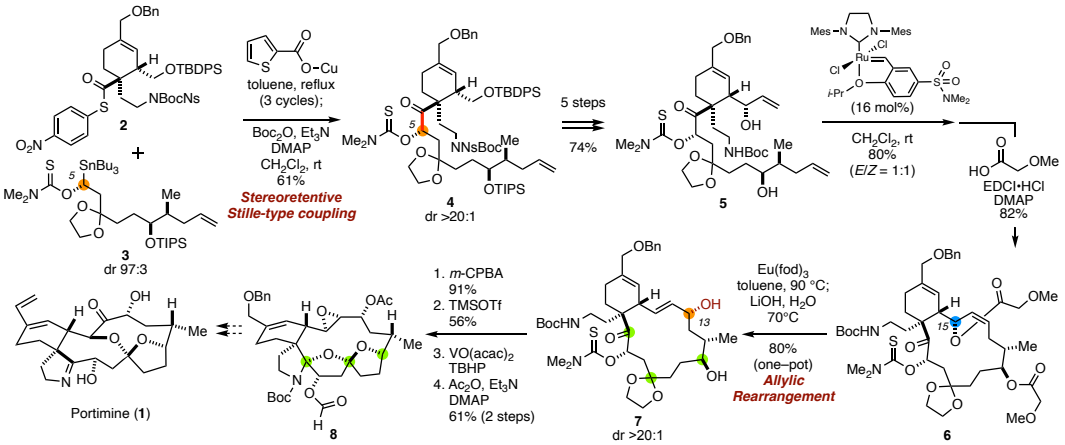
Portimine の合成研究

（東北大院生命科学）○佐藤 大亮・梅原 厚志・佐々木 誠
Synthetic Studies on Portimine (*Graduate School of Life Science, Tohoku University*)
○Daisuke Sato, Atsushi Umehara, Makoto Sasaki

Potimine (**1**) is a cyclic imine natural product isolated by Selwood in 2013. It induces apoptosis in various cancer cells at low concentrations, but shows low acute toxicity against mice. Only one total synthesis was reported by Baran in 2023. We succeeded in linking fragments **2** and **3** by a stereoretentive Stille-type coupling reaction. After construction of a 14-membered carbocycle by a ring-closing olefin metathesis, $Eu(fod)_3$-catalyzed rearrangement of allylic methoxyacetate **6** provided allylic alcohol **7** with the desired configuration at C13. Conversion of thiocarbamate to formate, followed by treatment with TMSOTf, resulted in the formation of a continuous framework of acetal and aminal. Finally, stereoselective epoxidation using $VO(acac)_2$/TBHP and acetylation provided epoxy acetate **8**. Construction of transannular acetal skeleton is currently under investigation.

Keywords : Total synthesis, cyclic imine natural products, apoptosis

Potimine（**1**）は、2013 年 Selwood らにより単離・構造決定された環状イミン天然物である [1]。マウスに対する毒性が低い一方、種々のがん細胞に対して低濃度でアポトーシスを誘導する。全合成は 2023 年に Baran らによって報告された一例のみである [2]。本研究では、立体保持の Stille 型カップリング [3] によってフラグメント **2** および **3** を収率 61%で連結することに成功した。閉環オレフィンメタセシスにより 14 員環骨格を構築し、メトキシアセテート **6** に対して $Eu(fod)_3$ を用いたアリル転位 [4] を行って C13 位に望みの立体配置を有するアルコール **7** を得た。**7** のチオカルバマートをホルメートに変換し、TMSOTf を作用させると、連続したアセタールとアミナール骨格が構築された。続く立体選択的エポキシ化とアセチル化を行い、エステル **8** とした。現在、架橋アセタール骨格の構築を検討中である。



1) A. I. Selwood et. al., *Tetrahedron Lett.* **2013**, *54*, 4705. 2) J. Tang et. al., *Nature* **2023**, *622*, 507.
3) H. Li et al., *Org. Lett.* **2011**, *13*, 3682. 4) B. Shull et. al., *J. Am. Chem. Soc*. **1996**, *118*, 11690.

巨大ウイルスから発見した新しいタイプのテルペン合成酵素

（東大院工 [1]・分子研 [2]・東大国際高等研 [3]）○朴 治彦 [1]・三橋 隆章 [2]・堤 雄翔 [1]・藤田 誠 [1,2,3]

New type of terpene synthases found from giant viruses ([1]*Graduate School of Engineering, The University of Tokyo*, [2]*Institute for Molecular Science*, [3]*Institutes for Advanced Study, The University of Tokyo*) ○Chieon Park,[1] Takaaki Mitsuhashi,[2] Sora Tsutsumi, [1] Makoto Fujita[1,2,3]

Terpenoids are one of the most structurally diverse families of natural products, with over 80,000 compounds reported to date. In this study, we identified a novel terpene synthase from giant viruses. This enzyme exhibits no sequence homology to any known terpene synthases and would possess a unique structure. However, our experiment suggested that it can catalyze the formation of cyclized terpenoid using polyprenyl diphosphate as a substrate. The structure of the enzyme product was analyzed using the crystalline sponge method[1)], and further NMR analysis confirmed it to be a new compound. These findings suggest that giant viruses serve as valuable reservoirs for the discovery of both novel enzymes and natural products.

Keywords：Giant Virus, Natural Products, Terpenoids, Terpene Synthase, Crystalline Sponge Method

テルペノイドは自然界における主要な天然物群の一つであり、これまでに 80,000 種類以上が報告されている。本研究では、巨大ウイルスから新規のテルペン合成酵素を発見した。本酵素は、既知のテルペン合成酵素と相同性を持たず、独自の構造を有していると推定されるが、ポリプレニル二リン酸を基質としてテルペノイドの基本骨格を形成できることが実験的に示唆された。本酵素の酵素産物については、結晶スポンジ法 [1)]および NMR を用いて構造解析を行い、新規化合物であることを確認した。本研究から、巨大ウイルスが新規酵素と新規天然物の探索源として有用であることが示唆される。

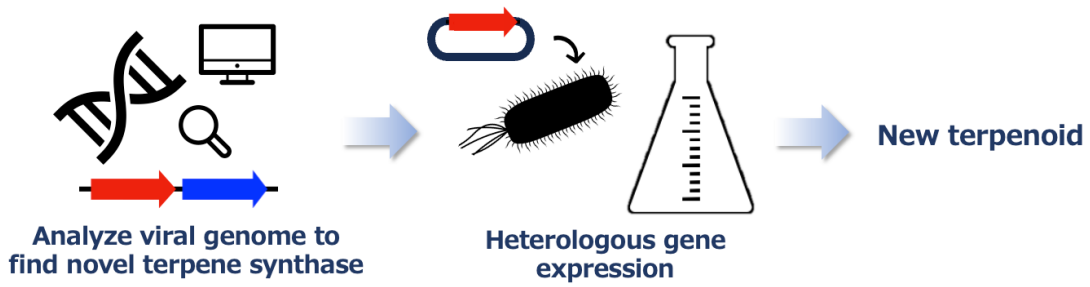


Fig 1. The scheme of this research

1) Y. Inokuma, S. Yoshioka, J. Ariyoshi, T. Arai, Y. Hitora, K. Takada, S. Matsunaga, K. Rissanen, M. Fujita, *Nature* **2013**, 495, 461–466.

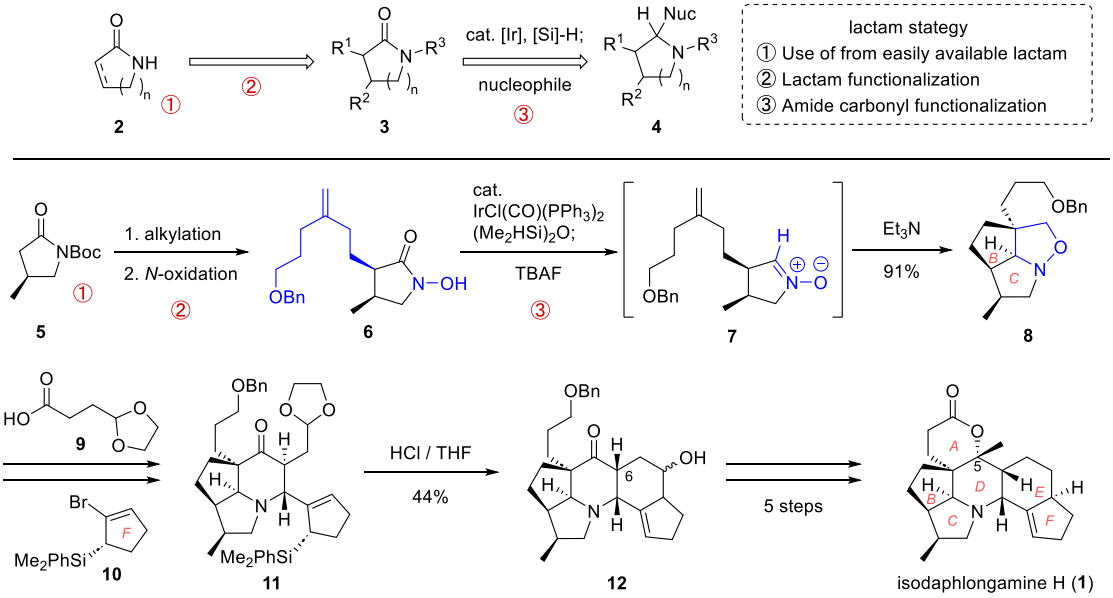
Total Synthesis of Isodaphlongamine H

([1]*Keio University*) ○Sora Iwamoto[1], Yuki Taira[1], Reki Nakano[1], Keiji Sasaki[1], Shoichiro Kobayashi[1], Reiji Kawakita[1], Koya Takei[1], Ayako Tokuyama[1], Manato Tomoike[1], Haruto Nakamura[1], Noritaka Chida[1], Toshitaka Okamura[1], Takaaki Sato[1]

Keywords: isodaphlongamine H; daphniphyllum alkaloids; nitrone; [3+2] cycloaddition

Isodaphlongamine H (**1**) is an unnatural 5-*epi* isomer of daphlongamine H,[1)] but is known to show the comparable cytotoxicity against several human cell lines. Structurally, it features a hexacyclic skelton containing eight stereocenters. In this study, we report the total synthesis of isodaphlongamine H (**1**) based on a lactam strategy to give highly substituted cyclic amines, which involves i) use of easily available lactam **2** as a starting material, ii) lactam functionalization, and iii) amide carbonyl functionalization.

Our synthesis commenced with alkylation and *N*-oxidation of easily available chiral lactam **5** to provide *N*-hydroxylactam **6**.[2)] As a key amide carbonyl functionalization, treatment of **6** with the Vaska complex and tetramethyldisiloxane, followed by addition of TBAF generated cyclic nitrone **7**.[3)] The resulting nitrone **7** was then heated in a one-pot process to promote an intramolecular [3+2] cycloaddition, affording isoxazolidine **8** in 91% yield. After isoxazolidine **8** was transformed to tetracyclic intermediate **11**, intramolecular Hosomi-Sakurai allylation furnished pentacyclic compound **12**, associated with epimerization at C6. The total synthesis of isodaphlongamine H (**1**) was accomplished in 5 steps from **12**.



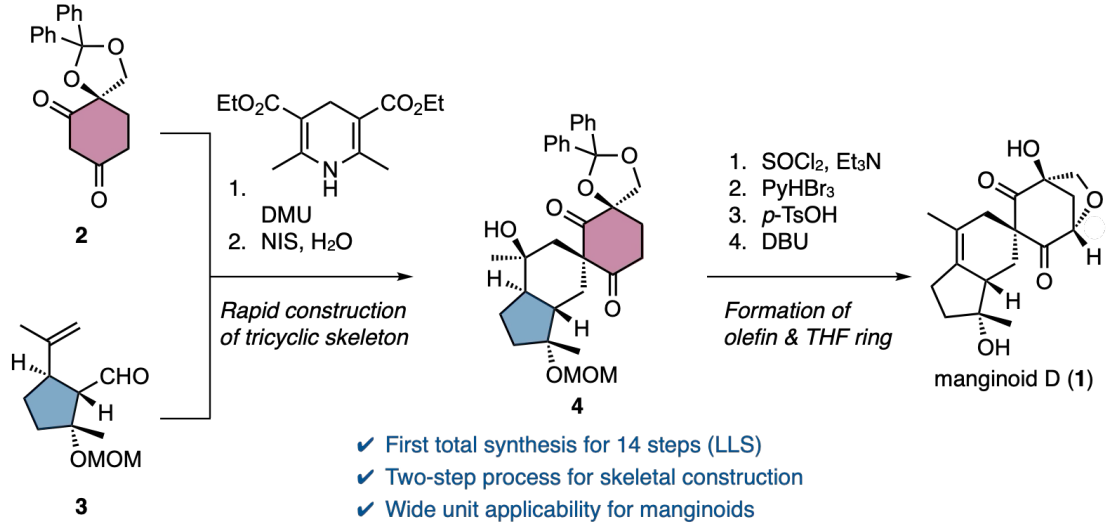
1) X.-J. Hao, *et al. Helv. Chim. Acta.* **2009**, *92*, 653. 2) N. Chida, T. Sato, *et al. Bull. Chem. Soc. Jpn.* **2023**, *96*, 529. 3) T. Sato, N. Chida, *et al. J. Am. Chem. Soc.* **2016**, *138*, 5246.

Total synthesis of manginoid D

(*Department of Chemistry for Life Sciences and Agriculture, Tokyo University of Agriculture*)
○Mitsuki Kato, Ryo Katsuta, Ken Ishigami, Shinnosuke Wakamori
Keywords: *Total Synthesis, Meroterpenoid, Manginoid*

Meroterpenoids are a class of natural products produced mainly by plants and fungi and typically represent significant biological activities. However, their complex and diverse molecular structures composed of partial terpenoids demand multistep synthetic processes, posing substantial challenges in organic synthesis. In 2017, manginoid meroterpenoids were isolated from *Guignardia mangiferae* and identified as the first example of spiro meroterpenoids with a tricyclic carbon skeleton, the spiro[cyclohexane-1,5'-indene] ring.[1] While the two elegant syntheses of manginoids A and C have been accomplished,[2,3] the formation of the complex skeleton required the multistep procedure.

In this study, our rapid skeletal construction strategy enabled the total synthesis of manginoid D (**1**). This strategy is a convergent approach that connects two units in a short sequence previously established.[4] Specifically, Knoevenagel condensation/reduction between diketone **2** and meroterpenoid **3** and subsequent the intramolecular cyclization with NIS constructed the tricyclic carbon skeleton to afford **4** successfully. Dehydration of **4** with thionyl chloride, followed by three conversions, formed the olefin and the THF ring, respectively, to achieve the first synthesis of manginoid D (**1**). The synthetic strategy offers the short-step synthesis of other manginoid analogues, addressing key challenges in the synthesis of meroterpenoids.



1) Y. Zhang, *et al. Org. Lett.* **2017**, *19,* 5956. 2) S. A. Snyder, *et al. Angew. Chem. Int. Ed.* **2021**, *60*, 11127. 3) Y. Xu, H. Lou, *et al. Angew. Chem. Int. Ed.* **2021**, *60*, 15286. 4) K. Yamada, K. Murakami, H. Yamada, S. Wakamori, The 101st CSJ Annual Meeting, online, A22-4pm-05, March 2021.

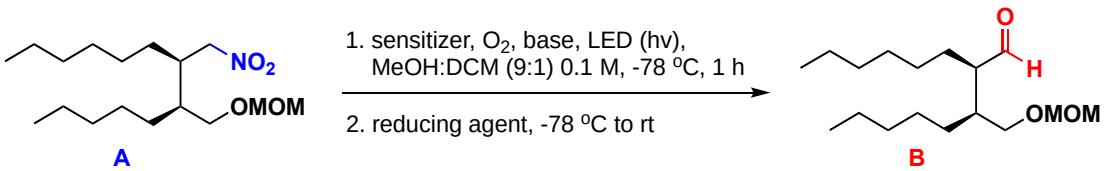
Development of Aldehyde-Forming Nef Reaction Initiated by Singlet Oxygen under Mild Conditions

([1]*Graduate School of Environmental Science, Hokkaido University,* [2]*Faculty of Science, Hokkaido University,* [3]*Faculty of Environmental Earth Science, Hokkaido University*) ○Ira Novita Sari,[1] Bobo Yan[1], Tatsuya Morozumi[2], Yuichi Kamiya[1,3], Taiki Umezawa[1,3]

Keywords: Nef Reaction; Aldehyde Formation; Singlet Oxygen; Mild Conditions; Photoreaction.

The Nef reaction, a transformation that converts nitro groups (NO_2) into carbonyl compounds such as aldehydes, is a valuable tool in organic synthesis. However, the formation of aldehydes via this reaction is less commonly studied compared to ketones and carboxylic acids, due to the challenges of competing side reactions, such as the Henry reaction. Although some aldehyde-forming reactions have been reported, the scope of applicable molecules is limited due to harsh reaction conditions such as strong oxidants and basic or acidic conditions.[1, 2] This study aims to optimize an aldehyde-forming Nef reaction initiated by singlet oxygen under milder conditions to improve reaction efficiency and yield. Previous work by our group demonstrated the aldehyde formation under visible light irradiation but required 48 hours for satisfactory yields.[3]

The current research focuses on refining these conditions to reduce reaction time and increase yield. Various bases, reducing agents, and sensitizers were evaluated for their effectiveness. Results showed that the combination of Cs_2CO_3 (1.5 eq), Rose Bengal (0.05 eq), and Me_2S (3.0 eq) under visible light at 448 nm provided the best conditions, achieving an 85% yield with complete consumption of the starting material. Other conditions, including different wavelengths, bases, and reducing agents, were also examined, and the optimized conditions demonstrated good functional group tolerance, with aldehydes being formed in moderate to high yields. Additionally, the reduction with $NaBH_4$ instead of Me_2S led to alcohol formation in one pot operation, and the reaction with previous substrates yielded products with higher efficiency than earlier methods. The reaction mechanism was also explained based on ion chromatography analysis. This optimized protocol offers a more efficient and versatile approach to aldehyde synthesis via the Nef reaction.



1) H. Muratake, M. Natsume, H. Nakai, *Tetrahedron,* **2004**, *60*, 11783. 2) G. Luo, L. Chen, C. Conway, W. Kostich, J. Macor, G. Dubowchick, *Org. Lett.*, **2015**, *17*, 5982. 3) T. Umezawa, M. Hara, N. Kinoshita-Terauchi, F. Matsuda, F., *Organics,* **2022**, *3*, 187.