Academic Program [Oral B] | 16. Natural Products Chemistry, Chemical Biology：Oral B

Tue. Mar 19, 2024 1:00 PM - 2:50 PM JST | Tue. Mar 19, 2024 4:00 AM - 5:50 AM UTC H933(933, Bldg. 9 [3F])

[H933-2pm] 16. Natural Products Chemistry, Chemical Biology

Chair: Masahito Yoshida, Okano Kentaro

English
1:00 PM - 1:20 PM JST | 4:00 AM - 4:20 AM UTC
[H933-2pm-01]
Efficient isolation and purification of monoglucosyl ginsenoside G-Rh_2 with CNS protective activity from an extract of Chikusetsu ginseng

○Yoshiki Ooshima[1,2], Hiroko Koyama[1,3], Aya Ogata[2,4], Hiroshi Ikenuma[2], Yasuyuki Kimura[1,2], Takashi Kato[1,2], Masaaki Suzuki[2,3] (1. United Graduate School of Drug Discovery and Medical Information Sciences, Gifu University, 2. National Center for Geriatrics and Gerontology, 3. Faculty of Engineering, Gifu University , 4. Gifu University of Medical Science)

English
1:20 PM - 1:40 PM JST | 4:20 AM - 4:40 AM UTC
[H933-2pm-02]
Gram-Scale Synthesis of Carbazomycin A–D

○Yuxuan Feng[1], Kentaro Okano[1], Atsunori Mori[1,2] (1. Department of Chemical Science and Engineering, Kobe University, 2. Research Center for Membrane and Film Technology, Kobe University)

1:40 PM - 1:50 PM JST | 4:40 AM - 4:50 AM UTC
Break

Japanese
1:50 PM - 2:10 PM JST | 4:50 AM - 5:10 AM UTC
[H933-2pm-03]
Development of Novel Synthetic Method for Hydroindole Skeleton and Its Application for Total Synthesis of Natural Product

○Tomohiro Tsutsumi[1], Ryui Yamagami[1], Ichiro Hayakawa[1] (1. Graduate School of Integrated Basic Sciences, Nihon University)

Japanese
2:10 PM - 2:30 PM JST | 5:10 AM - 5:30 AM UTC
[H933-2pm-04]
Synthetic studies on Cristaxenicin A.

○Wataru Kiuchi[1], Yuko Tsunoda[1], Kosuke Kato[1], Keiji Tanino[2] (1. Grad. Sch. Chem. Sci. & Eng., Hokkaido Univ., 2. Dept. Chem., Fac. Sci., Hokkaido Univ.)

English
2:30 PM - 2:50 PM JST | 5:30 AM - 5:50 AM UTC
[H933-2pm-05]
Synthesis and Structure Revision of a Marine Cyanobacteria-Derived Natural Product Lagunamide C

○Kazuki Hagimoto[1], Toshiaki Teruya[2], Masahito Yoshida[1], Hideo Kigoshi[1] (1. Univ. of Tsukuba, 2. Univ. of the Ryukyus)

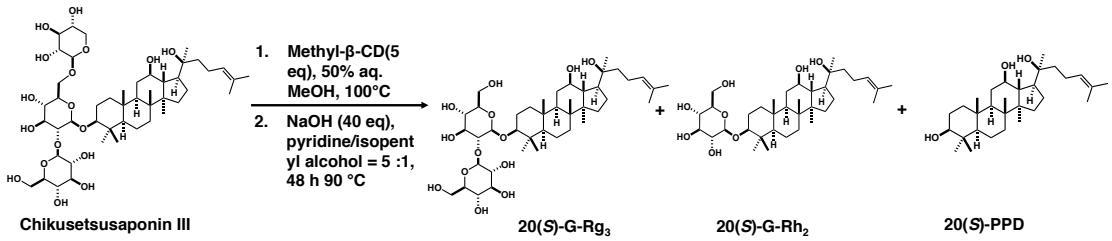
Efficient Isolation and Purification of Monoglucosyl Ginsenoside G-Rh_2 with CNS Protective Activity from an Extract of Chikusetsu Ginseng

([1]*United Graduate School of Drug Discovery and Medical Information Sciences, Gifu University,* [2]*National Center for Geriatrics and Gerontology,* [3]*Faculty of Engineering, Gifu University,* [4]*Gifu University of Medical Science*) ○ Yoshiki Ooshima,[1,2] Hiroko Koyama,[1,3] Aya Ogata,[2,4] Hiroshi Ikenuma,[2] Yasuyuki Kimura,[1,2] Takashi Kato,[1,2] Masaaki Suzuki[2,3]

Keywords: Ginsenoside; Cyclodextrin; Hydrolysis of sugar

Ginsenosides, active components of Korean ginseng as medicinal resources in traditional Chinese medicine, have recently been considered as a potential therapy for central nervous system diseases.[1] We planned to evaluate the brain uptake of highly active metabolites, prosapogenols distinguished as Compound-K, Ginsenoside-Rh_2 (G-Rh_2) and the sapogenin 20(*S*)-protopanaxadiol (PPD) by non-invasive molecular imaging technology positron emission tomography. In this study, we attempted to synthesize and isolate enough amounts of G-Rh_2 and PPD from ginseng extract, which contains various ginsenosides, in order to synthesize the precursors for labeling.

Chikusetsusaponin III contained a three glucose residue in the structure, isolated from Japanese ginseng (Panax japonicus C.A. Meyer), was used to optimize the conditions of glucose hydrolysis. Following the reported conditions, PPD was obtained from Chikusetsusaponin III at 90% yield under NaOH (40 eq)/1-butanol conditions at 90 °C for 24 hours.[2] To selectively obtain the partial hydrolysis intermediate G-Rh_2, we controlled the reaction rate by using co-solvent of non-protonic polar solvent, and protected the resulted structure with cyclodextrin. Actually, the inclusion complex between Chikusetsusaponin III and methyl-β-cyclodextrin was reacted in the presence of NaOH (40 eq) in pyridine/isopentyl alcohol (5:1, *v*/*v*) at 90 °C for 48 hours, resulted in the selective improvement and the 61% isolation yield of objective G-Rh_2.



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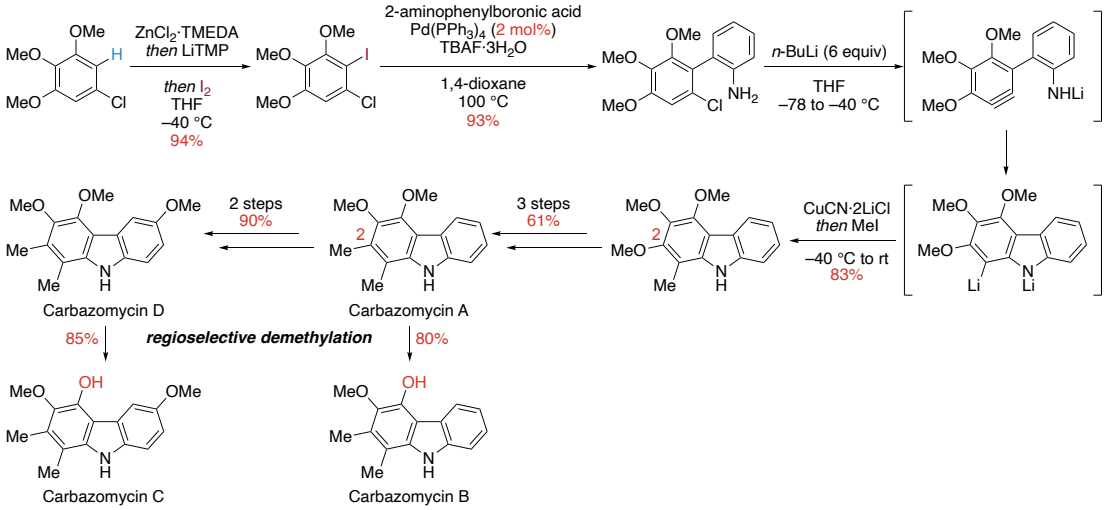
Gram-Scale Synthesis of Carbazomycin A–D

([1]*Department of Chemical Science and Engineering, Kobe University*, [2]*Research Center for Membrane and Film Technology, Kobe University*) ○Yuxuan Feng,[1] Kentaro Okano,[1] Atsunori Mori[1,2]

Keywords: Carbazole alkaloids; Aryne intermediate; Regioselective demethylation; Protecting-group-free synthesis

Carbazomycins A–D, isolated from *Streptoverticillium ehimense* by Nakamura and co-workers in the 1980s, are the first class of antibiotics containing a carbazole framework.[1] These compounds were characterized by a highly unsymmetrical structure, in which one of the benzene rings carries four electron-donating groups to form the fully substituted aromatic ring.

Herein, we achieved the total synthesis of carbazomycins A–D on gram scales. Iodination of the symmetrical trimethoxychlorobenzene and subsequent Suzuki–Miyaura coupling sequence gave the aminobiaryl bearing the chlorine atom. Treatment of this compound with six equivalents of *n*-BuLi led to the formation of the aryne, which underwent the intramolecular nucleophilic addition with the lithium amide tether to construct the carbazole framework. The use of the carbazole dianion enabled the synthesis of 1-methylcarbazole without protecting groups. Carbazomycin A was obtained by transforming the methoxy group at the C-2 position into the methyl group over three steps.[2] Subsequently, carbazomycin D was provided via the regioselective methoxylation from carbazomycin A over two steps. Finally, total synthesis of carbazomycins B and C was achieved through the regioselective demethylation of carbazomycins A and D, respectively.



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新規ヒドロインドール骨格の合成法の開発と全合成への応用

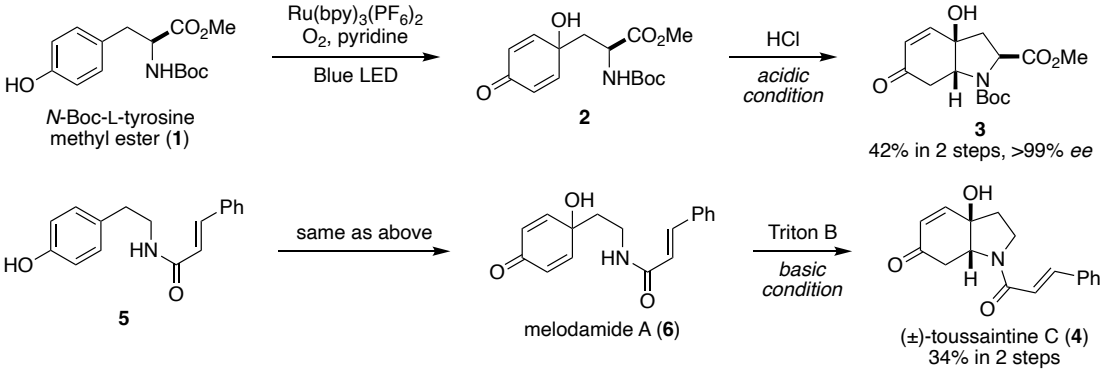
（日大院総合基）○堤 大洋・山上 龍威・早川 一郎
Development of Novel Synthetic Method for Hydroindole Skeleton and Its Application for Total Synthesis of Natural Product (*Graduate School of Integrated Basic Sciences, Nihon University*) ○Tomohiro Tsutsumi, Ryui Yamagami, Ichiro Hayakawa

Hydroindole skeleton which contains fused six membered ring and pyrrolidine ring is usually prepared by using hypervalent iodine reagent. In this study, we developed the novel synthetic method of hydroindole skeleton by dearomatization reaction using singlet oxygen and cyclization cascade reaction. Moreover, we achieved the total synthesis of toussaintine C using our synthetic method. We will report the optimization of reaction conditions and detail of substrate scope of this synthetic method.
Keywords : Hydroindole; Dearomatization Reaction; Singlet Oxygen; Toussaintine C

ヒドロインドール骨格は六員環とピロリジン環が縮環した構造であり、フェノールに対して超原子価ヨウ素試薬を用いる合成法が報告されている[1]。本合成法は多くの研究者が利用しているが、強塩基による異性化が懸念されることから、新たなヒドロインドール骨格の合成法の開発が望まれていた。今回我々は、一重項酸素を用いた新たな手法によるヒドロインドール骨格の合成法の開発を行なったので報告する。

N-Boc-L-チロシンメチルエステル(**1**)を用いて、O_2 雰囲気下、Ru 錯体に対して青色 LED を照射することで[2]、一重項酸素の発生とフェノールの脱芳香族化反応が進行しジエノン **2** を得た。**2** に対して、酸性条件でアザマイケル付加反応による環化を行ったところ、光学純度を損なうことなくヒドロインドール **3** を合成することができた。

この合成法をトウサインチン C (**4**)の全合成へ適用した。すなわちチラミン誘導体 **5** に対して、確立した一重項酸素を用いたフェノールの脱芳香族化反応を行うことでメロダミド A (**6**)を合成した。得られた **6** に対して、塩基性条件で環化反応を行い、ラセミ体のトウサインチン C (**4**)全合成を達成した。現在、**4** の不斉全合成を検討している。本発表では反応条件の最適化および基質適用範囲の詳細を報告する。



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Cristaxenicin A の合成研究

（北大院総化[1]・北大院理[2]）○城内 航[1]・角田 祐子[1]・加藤 港介[1]・谷野 圭持[2]
Synthetic Studies on Cristaxenicin A ([1]*Graduate School of Chemical Sciences and Engineering, Hokkaido University*, [2]*Faculty of Science, Hokkaido University*) ○Wataru Kiuchi,[1] Yuko Tsunoda,[1] Kosuke Kato,[1] Keiji Tanino[2]

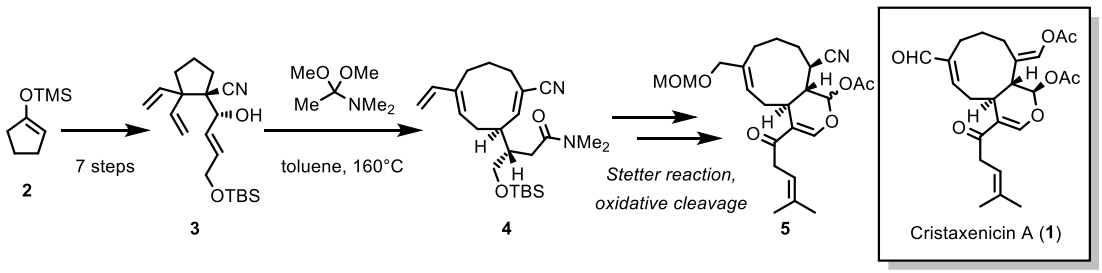
Cristaxenicin A (**1**) is a marine natural product which possesses the core structure consisting of a nine-membered carbocycle and a trans-fused dihydropyran ring. For its high antiprotozoal activity, this compound is anticipated to be a lead compound for a treatment drug against leishmaniasis. Therefore, **1** has been considered as an attractive synthetic target.

We began our synthesis with readily available silyl enol ether **2** which was converted to five-membered nitrile **3** having a geminal divinyl group. This nitrile was subjected to a sequential Claisen-Cope rearrangement reactions to afford the key nine-membered nitrile **4.** Then compound **4** was converted to dihydropyran **5** through a stereoselective construction of a 9-5 fused bicyclic skeleton by an intramolecular Stetter reaction followed by an oxidative cleavage of the five-membered ring.

Keywords : Total synthesis, Diterpenoid, Tandem reaction

Cristaxenicin A（**1**）は、中尾らによって軟体サンゴより単離・構造決定された海洋性ジテルペノイドであり[1)]、炭素 9 員環とジヒドロピランが縮環した xenican 骨格上に多数の酸素官能基を有する。**1** は、リーシュマニア症の原因原虫に対して高い抗原虫活性を示すことから、その治療薬のリード化合物として期待されているが、天然からの供給量は微量であり、合成研究も細川らによる 1 例があるのみある[2)]。このような背景から我々は、本化合物の合成法の確立を目指した。

市販のシリルエノールエーテル **2** から出発し、7 工程で *gem*-ジビニル基を有する 5 員環ニトリル **3** を合成した。このものをジメチルアセトアミドジメチルアセタールと共に加熱すると、Eschenmoser-Claisen 転位反応と、Cope 転位反応が連続的に進行し、アミド側鎖を有する 9 員環ニトリル **4** が得られた。さらに、分子内ステッター反応による立体選択的な 9-5 縮環骨格の構築と 5 員環の酸化的開裂を含む数工程の変換を経て、ジヒドロピラン環を有する化合物 **5** の合成に成功した。



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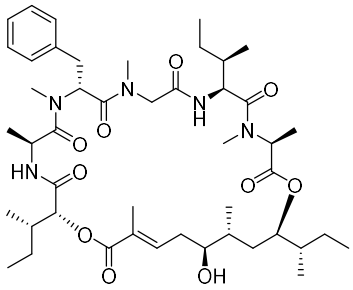
Synthesis and Structure Revision of Marine Cyanobacteria-Derived Natural Product Lagunamide C

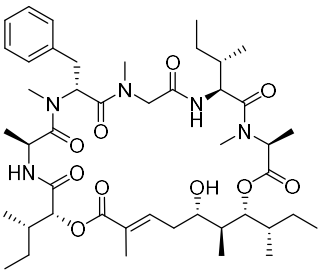
([1]*Degree Programs in Pure and Applied Sciences, University of Tsukuba*, [2]*Faculty of Education, University of the Ryukyus*) ○Kazuki Hagimoto,[1] Toshiaki Teruya,[2] Masahito Yoshida,[1] Hideo Kigoshi[1]

Keywords: Natural Product; Total Synthesis; Peptide; Polyketide; Cyclodepsipeptide

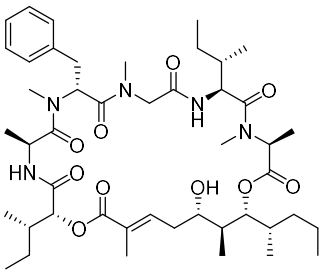
Lagunamide C, a 27-membered cyclodepsipeptide, was isolated from the marine cyanobacteria *Lyngbya majuscule* in 2011 by Tripathi et al.[1] and exhibits potent cytotoxicity against several cancer cells, comparable to that of the 26-membered analog lagunamide A.[2] The structural difference between the above compounds lies only in the presence or absence of a methylene carbon in the aliphatic acid moiety. However, it is known that the biological activity of cyclopeptides is strongly dependent on the conformation of their structure[3]. It should be interesting that the lagunamide families show comparable cytotoxicity regardless of the difference in the ring size of the cyclopeptide structure. Therefore, we planned the total synthesis of lagunamide C to elucidate its relationships between conformation and biological activity. In this presentation, we will report the total synthesis of the putative structure of lagunamide C and structure revision of lagunamide C to the related analog odoamide.



Lagunamide C (**1**, Putative structure)
IC_{50} 2.4 nM against A549



Lagunamide A
IC_{50} 2.9 nM against A549



Odoamide
(Revised structure of Lagunamide C)

Referrences

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