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APPLICATIONS OF C-H INSERTION REACTION IN TOTAL SYNTHESIS OF BIOLOGICALLY ACTIVE HETEROCYCLIC NATURAL PRODUCTS

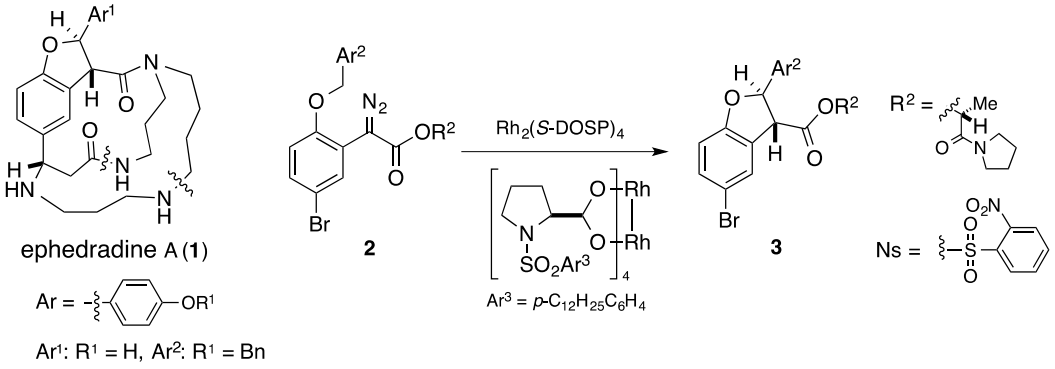
Toshiyuki Kan,* Tomohiro Asakawa, and Makoto Inai

School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan

Abstract – Here, we summarize our work on applications of the Rh-catalyzed C-H insertion reaction to syntheses of heterocyclic natural products. Total synthesis of racemic serotobenine (**4**) was achieved in an optical active form. Enantioselective synthesis of SB-203207 (**25**) was accomplished via desymmetric C-H insertion reaction of **33** to construct the bicyclo[3.3.0] framework. Stereoselective synthesis of MFPA (**53**) was accomplished with the aid of an intermolecular C-H insertion reaction. Synthesis of aperidine (**70**) featured *cis*-selective construction of the dihydrobenzofuran ring of **81** by utilizing Hashimoto's catalyst.

INTRODUCTION

During the course of our development of the Ns-strategy[1,2] for the construction of medium-size rings, we completed a total synthesis of ephedradine A (**1**).[3] During the synthesis, we found that Rh-carbenoid-mediated C-H insertion reaction[4] enabled efficient construction of the dihydrobenzofuran ring. As shown in Scheme 1, treatment of diazoester **2** bearing a chiral auxiliary with Rh_2(*S*-DOSP)$_4$ catalyst[5] resulted in efficient C-H insertion to provide the desired dihydrobenzofuran **3**.[6] This transformation can easily be scaled up to the level of hundreds of grams. Furthermore, there was no requirement for an electrophilic functional group for the carbon-carbon bond formation. Thus, the introduction of our C-H insertion reaction considerably streamlined the synthetic strategy. Inspired by this finding, we subsequently employed the C-H insertion reaction in the synthesis of several other complex natural products.



Scheme 1. Total synthesis of ephedradine A (**1**)

RESULTS AND DISCUSSION

1. Total synthesis of serotobenine (**4**)

Serotobenine (**4**) was isolated from safflower seeds as a racemic natural product in 1985.[7] Recently, another related natural product, decursivine (**5**),[8] was isolated in optically active form from *Rhaphidophora decursiva*. Because the biosynthetic pathways of **4** and **5** should be similar, a special mechanism may operate for racemization of **4**. We hypothesized that serotobenine (**4**) might racemize through the quinonemethide intermediate **6**, and aimed to synthesize optically active **4** and **5** to solve the mystery.

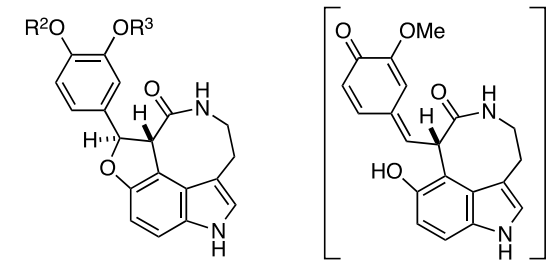
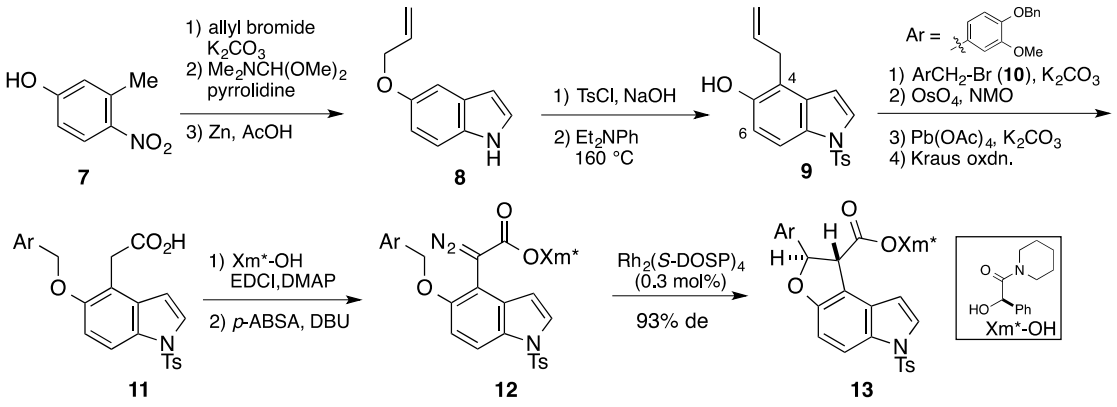


Figure 1. Serotobenine (**4**) and decursivine (**5**)

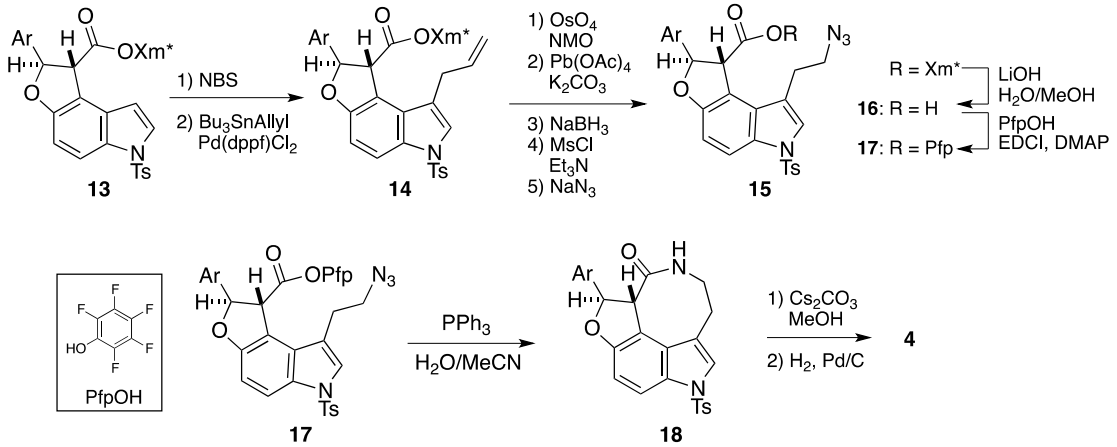
Serotobenine (**4**) and decursivine (**5**) are composed of an indole, an eight-membered lactam, and a dihydrobenzofuran ring, and the order of construction of the heterocyclic ring is likely to be important. As shown in Scheme 2, the synthesis was started with construction of the indole skeleton. After *O*-allylation of 3-methyl-4-nitrophenol (**7**), the Leimgruber-Batcho procedure[9] provided 5-allyloxy-1*H*-indole (**8**). After protection of **8** with a Ts group, thermal Claisen rearrangement provided **9** in a regio-selective manner.[10] Benzyl halide derivative **10** was incorporated into the resultant phenol, and then oxidative cleavage of the olefin and $NaClO_2$-mediated oxidation furnished carboxylic acid **11**. After incorporation of a chiral auxiliary (Xm) into **11**, ABSA-mediated diazotransfer reaction afforded **12**. The key C-H insertion reaction was accomplished by treatment of diazoester **12** with Rh_2(*S*-DOSP)$_4$ catalyst to provide dihydrobenzofuran ring **13**. In this reaction, we found that

mandelate-amide (Xm*) was superior to lactate-amide as a chiral auxiliary.



Scheme 2. Preparation of *trans*-dihydrobenzofuran **13**

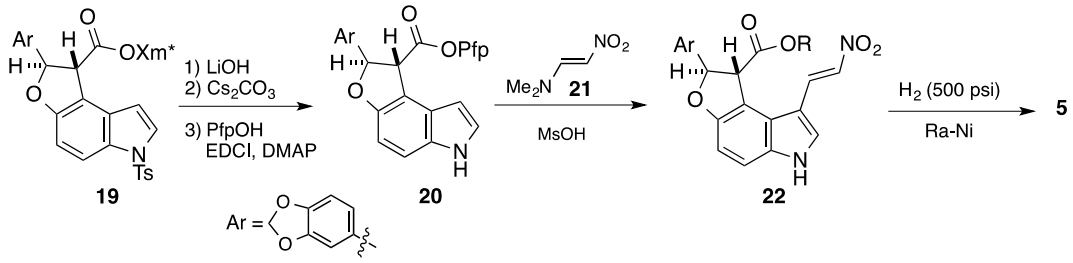
Next, incorporation of a side chain at the 3-position of indole **13** was achieved by bromination, and Pd-mediated Stille-type coupling reaction provided the desired **14**. The allyl group was converted to ethyl azide **15** *via* a five-step sequence. Removal of the chiral auxiliary and condensation of the resultant carboxylic acid **16** with pentafluorophenol gave activated ester **17**. Upon treatment of azide **17** with PPh_3 in the presence of H_2O, reduction to the amine and simultaneous cyclization proceeded to afford eight-membered lactam **18**. Removal of the Ts group and cleavage of the benzyl ether under hydrogenolysis conditions yielded (–)-serotobenine (**4**).[11]



Scheme 3. Completion of synthesis of serotobenine (**4**)

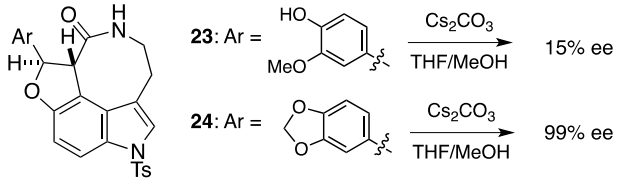
Synthesis of decursivine (**5**) was also accomplished, as shown in Scheme 4. Construction of the dihydrobenzofuran ring of **19** again utilized the C-H insertion reaction. After hydrolysis of the chiral auxiliary and Ts group of **19**, condensation with Pfp-OH provided the activated ester **20**. Treatment of indole **20** and nitro-olefin **21** in the presence of methanesulfonic acid, followed by Michael reaction, and elimination of dimethylamine proceeded smoothly to give **22**. Subsequent treatment of **22** under hydrogenolysis conditions, reduction of both the nitro functionality and double bond, and subsequent

amide bond formation proceeded to provide decursivine (**5**) in a single step.



Scheme 4. Completion of synthesis of decursivine (**5**)

With optically active **4** and **5** in hand, we examined their optical stability under various conditions. Neither racemization nor epimerization occurred upon exposure of **1** to acidic or basic conditions. On the other hand, on treatment of *N*-Ts derivative **23** with Cs_2CO_3, a remarkable decrease of the enantiomeric excess was observed. Since incorporation of the Ts group increased the leaving ability of the 5-hydroxyindole group, the ring-opening reaction of dihydrobenzofuran would readily occur to afford *p*-quinonemethide intermediate **6**. Furthermore, the acidic *a*-proton of the amide should equilibrate. On the other hand, the methylenedioxy bridge likely prevents conversion of **24** to the *p*-quinonemethide intermediate, which may be the reason why **5** is optically active, whereas natural **4** exists as a racemic mixture.[11]



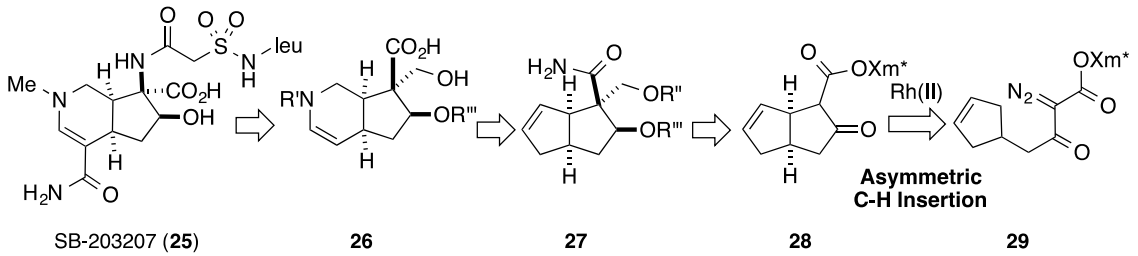
Scheme 5. Comparison of optical stability of **23** and **24**

2. Total synthesis of SB-203207 (**25**)

SB-203207 (**25**) was isolated from a *Streptomyces* species by a SmithKline Beecham group. It strongly inhibits isoleucyl *t*RNA synthetase.[12] A unique structural feature of **25** is the β-hydroxyl α-disubstituted-α-amino acid moiety on the 6-aza indene skeleton. In 1995, Kende and co-workers reported a total synthesis of altemicidin, the core compound of **25**,[13] but **25** itself has not been synthesized.

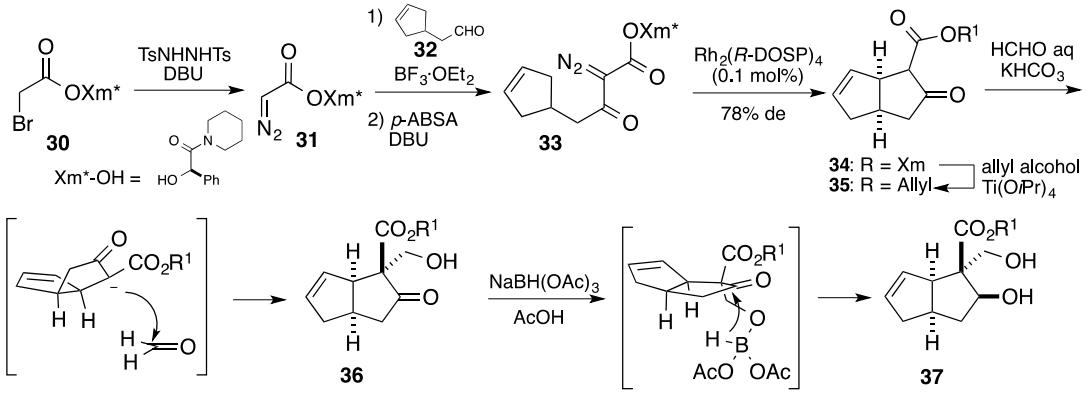
The heart of our synthetic plan for **25** is illustrated in Scheme 6. The highly polar sulfonamide and vinylogous urea of **25** would be introduced at a later stage of the synthesis. Because incorporation of nitrogen onto the quaternary carbon would be performed by Curtius rearrangement, the azabicyclo[4.3.0]skeleton **26** would serve as a key intermediate. The cyclic enamide of **26** would be constructed from cyclopentene **27** by oxidative cleavage of the double bond followed by regioselective introduction of nitrogen and re-cyclization. The quaternary carbon and the secondary alcohol would be

stereoselectively installed by employing β-ketoester **28**. Synthesis of the optically active bicyclo[3.3.0] framework **28** would be accomplished by using our Rh-carbenoid mediated intramolecular C-H insertion reaction[14] of **29**.



Scheme 6. Synthetic strategy of SB-203207 (**25**)

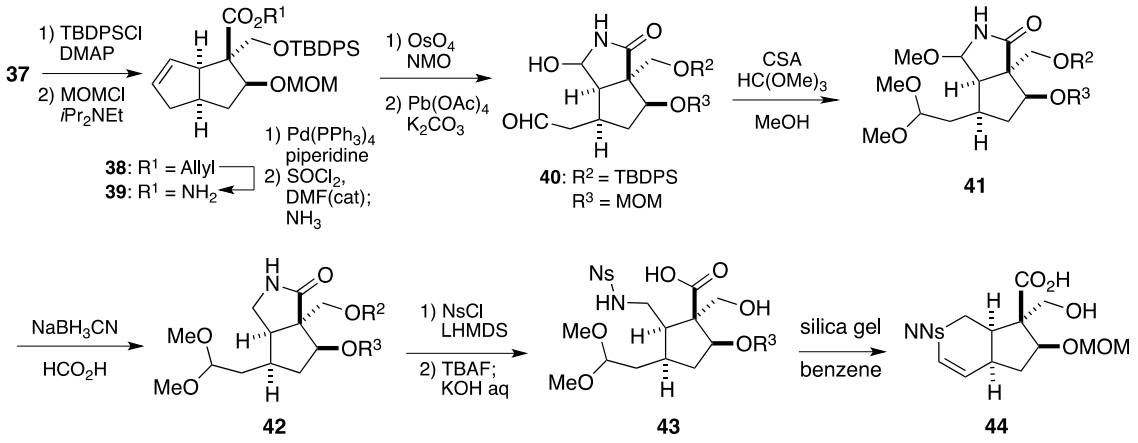
Since direct incorporation of a chiral auxiliary (Xm*-OH) into β-ketoester **33** was difficult, we started the synthesis from **30**, as shown in Scheme 7. According to Fukuyama's procedure,[15] preparation of the diazo group was performed by treatment of α-bromoester **30** and bistosyl hydrazine with DBU to give **31**. Then, condensation of **31** and aldehyde **32**[14] by means of a modified Roskamp reaction[16] provided the C-H insertion precursor **33**. Treatment of **33** with 0.1 mol% Rh_2(*R*-DOSP)$_4$ resulted in desymmetric C-H insertion to afford the bicyclo[3.3.0]octane ring compound **34**. This transformation had the advantage of enabling one-step generation of the two chiral centers at the ring fusion. After conversion to the allyl ester **35**, stereoselective hydroxymethylation was achieved by treatment with formalin and a catalytic amount of $KHCO_3$ to give **36**. Subsequent stereoselective reduction of **36** with NaBH(OAc)$_3$[17] gave **37**. As expected, alkylation occurred from the convex face of **35** and reduction proceeded via chelation with the primary hydroxyl group of **36**.



Scheme 7. Synthesis of key intermediate **36** of SB-203207 (**25**)

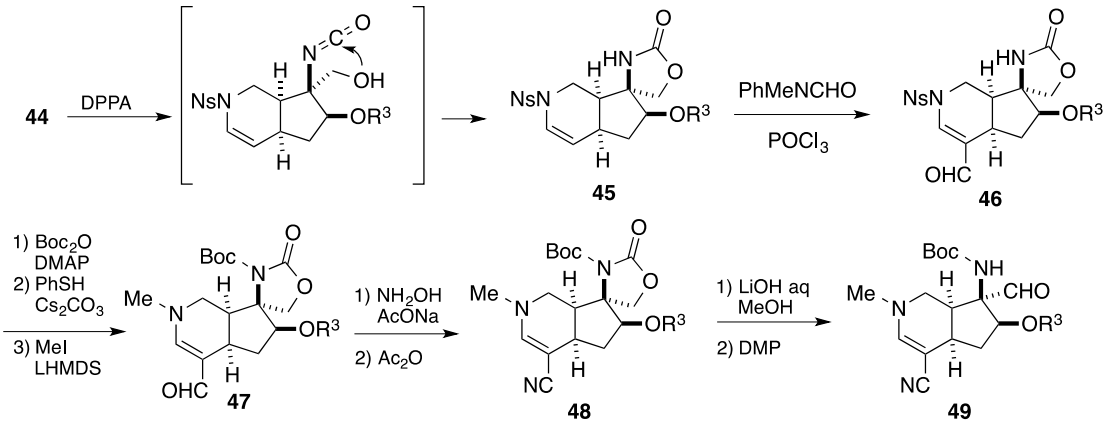
As shown in Scheme 8, the primary alcohol and secondary alcohol were protected as TBDPS and MOM ether, respectively. Because directly installing the nitrogen group is difficult, oxidative cleavage of the double bond of **38** and intermolecular delivery of nitrogen were employed. Deprotection of the allyl group of **38**,[18] conversion to the acid chloride, and treatment with ammonia gave amide **39**. After

dihydroxylation of **39**, treatment with $Pb(OAc)_4$ generated dialdehydes, where the amide nitrogen selectively attacked the closer aldehyde to provide hemiaminal **40**. After conversion to the dimethyl acetal and methyl hemiaminal, selective reduction of hemiaminal **41** was achieved by treatment with $NaBH_3CN$ in the presence of formic acid to give lactam **42**. Opening of the gamma lactam of **42** was achieved by combining activation by Ns imide and participation of the neighboring primary alcohol through the lactam intermediate to provide **43**. Cyclic enamide **44** was obtained by heating **43** with silica gel.



Scheme 8. Synthesis of key intermediate **44** of SB-203207 (**25**)

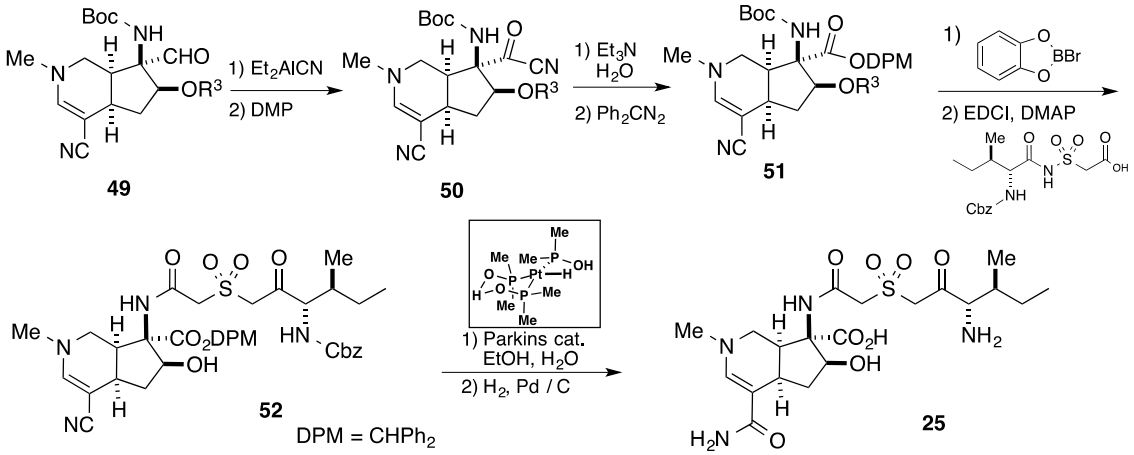
Next, introduction of a nitrogen atom onto the quaternary carbon of **44** was performed by treatment with DPPA[19] to give **45**, as shown in Scheme 9. After incorporation of a C1 unit into enamide **45** *via* modified Vilsmeier reaction[20] and protection of **46** with a Boc group, deprotection of the Ns group and *N*-methylation afforded **47**. Conversion of aldehyde **47** to nitrile **48** was performed by treatment with hydroxylamine, followed by addition of acetic anhydride. Although conversion to aldehyde **49** proceeded smoothly via hydrolysis of the oxazolidinone ring and Dess-Martin periodinane (DMP) oxidation, further oxidation to the corresponding acid derivative was difficult.



Scheme 9. Synthesis of key intermediate **49** of SB-203207 (**25**)

Since typical $NaOCl_2$-mediated Kraus oxidation, as well as TEMPO- or AZADO-catalyzed oxidation,

resulted in decomposition of the reactive cyanoenamide group, oxidation of **49** required non-nucleophilic reaction conditions. We found that oxidation of the cyanohydrin intermediate was suitable. After conversion to cyanohydrin by treatment with Et_2AlCN,[21] DMP-mediated oxidation provided **50** without any decomposition of the enamide group. After hydrolysis of acylcyanide **50**, treatment with diphenyldiazomethane provided **51**. Simultaneous removal of the Boc and MOM groups of **51** was achieved by treatment with *B*-bromocatechol borane and incorporation of the side chain gave **52**. Conversion of the cyanoenamide **52** to carbamoylenamide was performed in the presence of Parkins catalyst.[22] Finally, simultaneous cleavage of the Cbz and diphenylmethyl ester groups under hydrogenolysis conditions yielded SB-203207 (**25**).



Scheme 10. Completion of synthesis of SB-203207 (**25**)

3. Total synthesis of methoxyphenylkainic acid (MFPA: **53**)

Kainoids have received significant attention due to their binding affinity for ionotropic glutamate receptors (iGluRs), which are involved in important neurophysiological processes, including memory and learning.[23] Although many synthetic investigations of kainoids have been reported to date, efficient synthetic methods are still urgently required. During pioneering investigations of the potent natural product acromelic acid A (**53**), discovered by the Shirahama group,[24] it was discovered that a synthetic MFPA (**54**) possessed more potent activity than **53**.[25] Inspired by this interesting structure–activity relationship information, we launched an investigation with the aim of developing efficient synthetic methods for **53**.

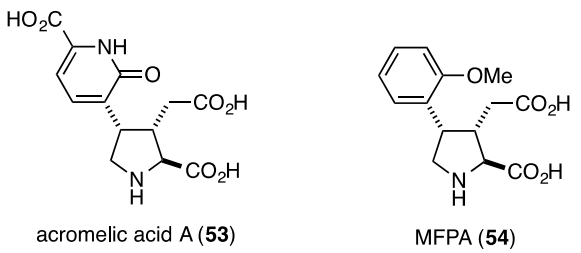
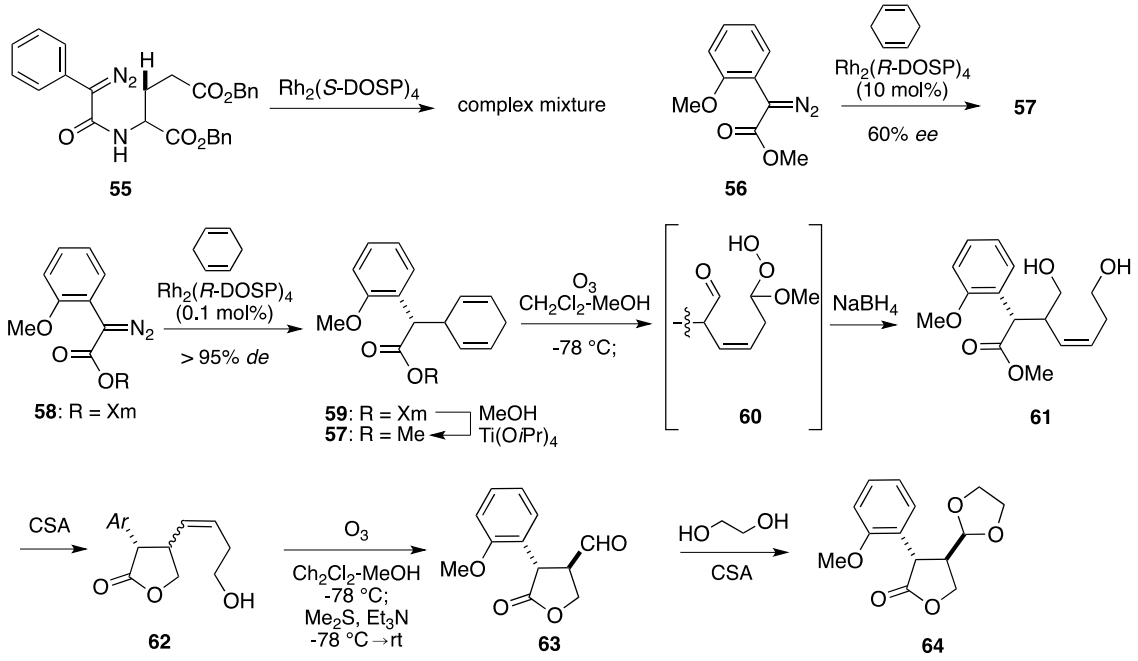


Figure 2. Acromelic acid A (**53**) and MFPA (**54**)

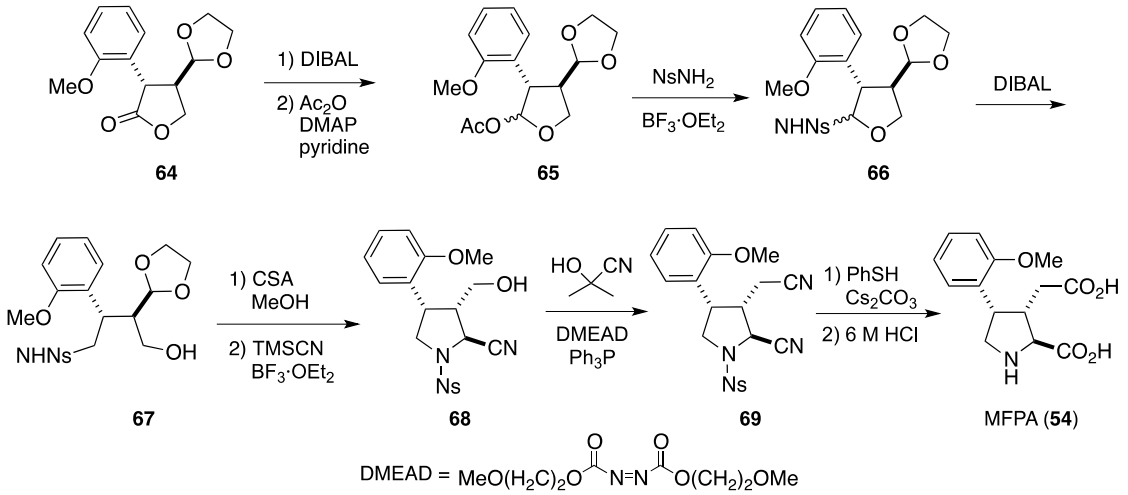
Initially, we examined intramolecular C-H insertion reaction of diazoester **55**, which was derived from condensation of phenylacetic acid and glutamic acid. However, the desired C-H insertion reaction did not proceed on treatment of **55** with Rh catalyst, and a complex mixture was formed. On the other hand, intermolecular C-H insertion reaction of the similar aryl diazoester **56** with cyclohexadiene proceeded smoothly to give **57**, though the enantioselectivity was not satisfactory.[26] In order to improve the selectivity, we prepared diazoester **58** bearing our chiral auxiliary. Upon treatment of **58** and cyclohexadiene with Rh_2(*R*-DOSP)$_4$ catalyst, the C-H insertion reaction proceeded smoothly to afford **59** exclusively. After conversion of **59** to the corresponding methyl ester, mono-selective oxidative cleavage of the diene was accomplished by ozonolysis at –78 °C. After confirmation of disappearance of the starting material, addition of $NaBH_4$ to the ozonide intermediate **60** gave the corresponding primary alcohol **61** as a 1:1 mixture. This was converted to the lactone **62**, and oxidative cleavage of the olefin proceeded with concomitant epimerization at the α-position of the aldehyde to give **63** predominantly. In this reaction, the absence of triethylamine base resulted in a 1:1 mixture. Without purification, aldehyde **63** was protected with ethylene glycol to give **64**.



Scheme 11. Synthesis of key intermediate **64** of MFPA (**54**)

Reduction of the lactone **64** with DIBAL and conversion to the acetate gave **65**. Upon treatment of **65** with Ns-NH_2[27] in the presence of BF_3·OEt_2, amination reaction proceeded smoothly to afford **66**. Selective reduction of the aminal of **66** was performed by treatment with DIBAL to give **67**. Treatment of **67** under acidic conditions, alcoholysis of the acetal, and subsequent cyclization with the Ns-amide smoothly afforded the aminal as a single isomer. On treatment of the aminal with BF_3·OEt_2 and TMSCN, Strecker-type reaction occurred from the less-hindered b-face of the pyrrolidine ring to provide

the aminonitrile **68** as a single diastereomer. Next, another nitrile group was incorporated by Mitsunobu reaction of acetone cyanohydrin and DMEAD,[28] to afford **69**. After deprotection of the Ns group by treatment with PhSH and base, acidic hydrolysis of the cyano groups was carried out in a sealed tube to give the desired MFPA (**54**).[29]



Scheme 12. Completion of total synthesis of MFPA (**54**)

4. Total synthesis of aperidine (**70**)

From ancient times, beer has been a familiar drink with well-known gastrointestinal prokinetic effects. Professor Wakimoto, a former group-member and colleague of ours, isolated aperidine (**70**) and hordatine (**71**)[30] from beer as compounds with muscarinic M_3 receptor-binding activity.[31] These compounds also exhibited α_1 adrenoceptor antagonist activity. Although a total synthesis of hordatine (**71**) has been reported by Wakimoto et al.,[32] they found difficulty in synthesizing **70**, which was unstable due to its ready isomerization to the *trans* isomer **71**.

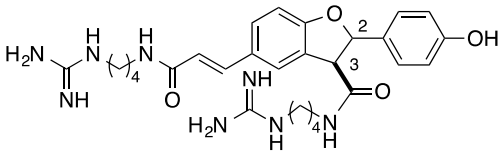
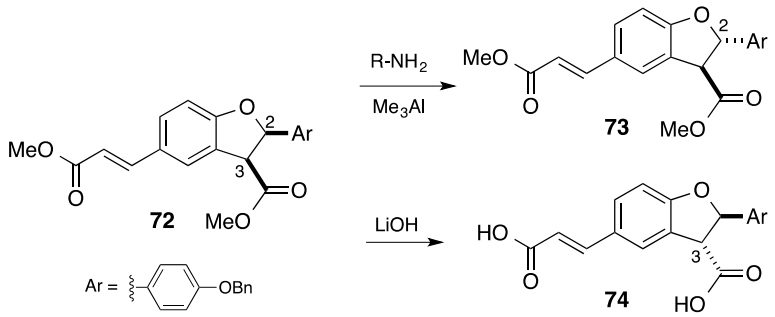


Figure 3. Structures of aperidine (**70**) and hordatine (**71**)

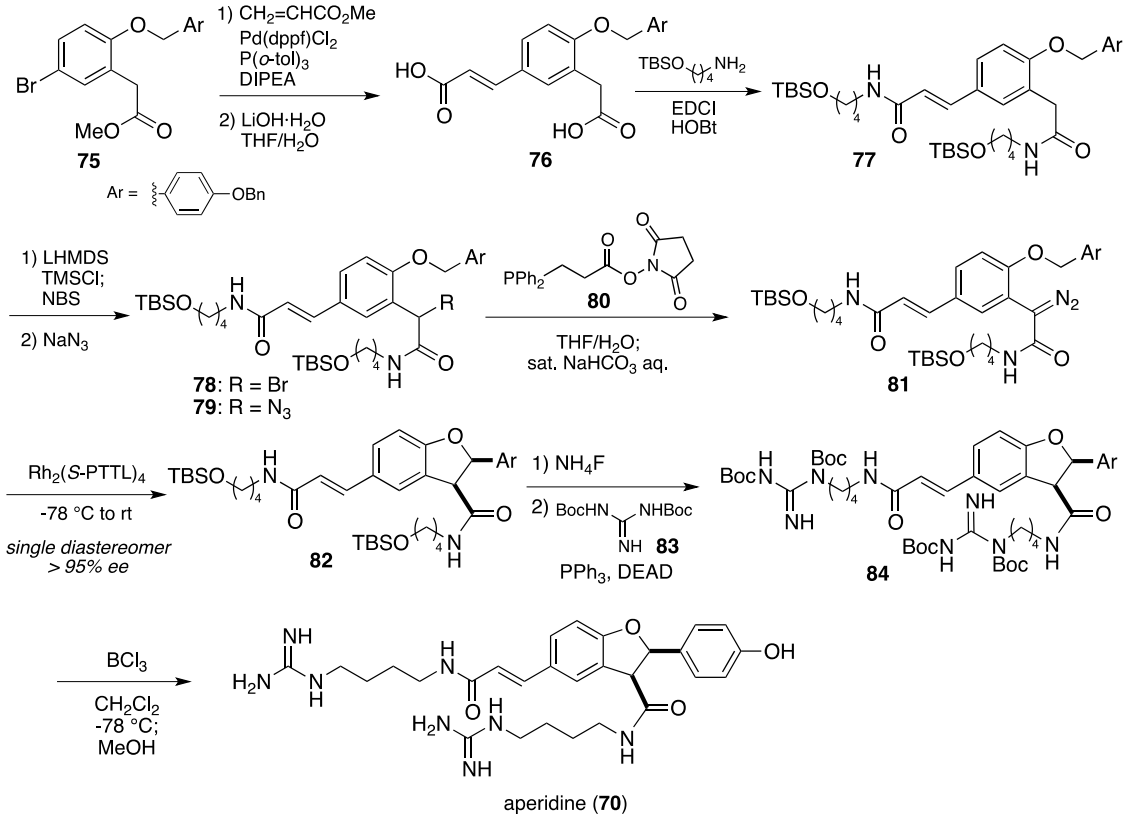
Initially, we attempted to incorporate the side chain after construction of the dihydrobenzofuran ring by C-H insertion reaction, as shown in Scheme 13. Treatment of dihydrobenzofuran **72** and amine (R-NH_2) with Me_3Al resulted in epimerization at the C-2 position prior to the desired amide bond formation to give **73**. This reaction presumably proceeded through Lewis acid-mediated *p*-quinonemethide intermediate formation. Next, hydrolysis of **72** by treatment with LiOH proceeded, with concomitant epimerization at the a-position of the ester group, to give **74**. Therefore, we concluded that the labile

cis-dihydrobenzofuran ring should be constructed in a late stage of the total synthesis.



Scheme 13. Epimerization of dihydrobenzofuran ring (**72**)

As shown in Scheme 14, the *cis*-dihydrobenzofuran ring was constructed after incorporation of side chains. After Heck reaction of methyl ester **75** and methyl acrylate and hydrolysis of the diester, condensation of the resultant carboxylic acid **76** with butanol amine gave the amide **77**. ABSA-mediated diazo transfer reaction of **77** did not proceed smoothly due to the lower pKa of the a-position of the amide group. Recently, Raines and coworkers reported an efficient conversion of an azide functionality to a diazo group using a novel phosphine reagent **80**.[33]



Scheme 14. Total synthesis of aperidine (**70**)

Incorporation of an azide group was performed by introduction of a bromine atom into **77** and displacement of bromide with NaN_3. Upon treatment of **79** with **80**, phosphine-mediated activation of

the azide group and subsequent diazoamide formation proceeded to provide **81**. Construction of the *cis*-dihydrobenzofuran **82** was accomplished by treatment of **81** with Hashimoto catalyst Rh_2(*S*-PTTL)$_4$,[34] to provide **82** in 75% yield. After deprotection of both TBS ethers of **82** by NH_4F, a guanidine moiety was incorporated by means of the Mitsunobu reaction. Upon treatment of the di-Boc guanidine **(83)** in the presence of the corresponding alcohol with DEAD and PPh_3, smooth amination proceeded to provide the protected aperidine **84**. Finally, simultaneous removal of the Bn ether and Boc groups was performed by treatment with BCl_3 at –78 °C. Careful work-up afforded **70**.[35]

In this review, we have summarized our work on applications of the Rh-carbenoid-mediated C-H insertion reaction as a key step in total syntheses of several biologically active natural products. These synthetic studies have not only contributed to our understanding of the biological activities of the natural products, but also have uncovered the factors underlying other chemical behaviors of the compounds.

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Professor Toshiyuki Kan was born in Kushiro, Hokkaido, in 1964. He received his Ph.D. in 1993 from Hokkaido University under the direction of Professor H. Shirahama. After spending three years (1993-1995) at the Suntory Institute for Bioorganic Research, he was appointed Assistant Professor of Pharmaceutical Sciences in Professor Fukuyama's group at the University of Tokyo, and rose to the rank of Associate Professor in 2004. In 2005, he moved to University of Shizuoka, where he is currently Full Professor of Pharmaceutical Sciences. He is the recipient of the Incentive Award in Synthetic Organic Chemistry, Japan (2002), Research Vision Division Award, 2003, Pharmaceutical Society of Japan (2004), Pfizer Distinguished Lecture, Colorado State University (2012) and Asteras Life Science Award in the Society of Synthetic Organic Chemistry, Japan (2012). His research interest is focused on the total synthesis of bioactive natural products and chemical biology.

Tomohiro Asakawa was born in Nara (Japan), in 1979. He received his Ph.D. degree in 2007 at University of Shizuoka under the direction of Professor T. Kan. He was a post-doctoral fellow at Columbia University (Centennial professor K. Nakanishi) in 2007-2009. He joined School of Pharmaceutical Sciences, University of Shizuoka as an Assistant Professor (Professor T. Kan group) in 2010. He is interested in the total synthesis of biologically active natural product from food and chemical biology.

Makoto Inai was born in Ehime (Japan) in 1981 and attended Tokushima Bunri University where he received the B.A. degree in 2004. He obtained the Ph.D. degree in 2009 at University of Shizuoka under the direction of Professor T. Kan. He was a post-doctoral fellow at Colorado State University (Professor R. M. Williams, Finical support from Uehara Memorial Foundation) in 2009 and Tokushima Bunri University (Professor T. Tsunoda) in 2010. He joined Tokushima Bunri University as an Assistant Professor (Professor T. Tsunoda group) in 2011, and moved to University of Shizuoka as an Assistant Professor (Professor T. Kan group) in 2011. He is interested in the total synthesis of biologically active natural product, the development of useful synthetic reaction and chemical biology.