Synthetic Studies on Heteropolycyclic Natural Products: Strategies via Novel Reactions and Reactivities

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(Received July 18, 2017; E-mail: fukuyama@ps.nagoya-u.ac.jp)

Abstract: Five total syntheses of heteropolycyclic natural products, namely hyalodendrin, tryprostatins, spirotryprostatin, the stemofoline alkaloids, and hinckdentine A, are outlined. These syntheses share common characteristics; the sequences of transformations are facilitated through the development of new synthetic reactions and the discoveries of unknown molecular reactivities. Brief descriptions of new reactions, the mechanistic details of key transformations, and the resulting shortcuts and efficiencies made possible in relation to the overall “picture” of these total syntheses are described.

1. Introduction

Heteropolycyclic natural product synthesis continues to provide us with challenging hurdles that are only overcome by unmasking novel reactions or novel reactivities of the molecules in question. In particular, the construction of these complex molecular structures can be considered to be an important opportunity to explore new ideas in organic synthesis. Our natural-product-synthesis research campaigns have been directed toward the development of two major programs. One has involved single-target total syntheses through novel synthetic routes by the development of new chemical reactions and the discovery of new reactivities. The other has involved divergent-strategy oriented comprehensive syntheses of certain families of natural product. The latter topic will be reviewed elsewhere; this account reviews our efforts toward the former topic, specifically the syntheses of five classes of polycyclic natural product. The target molecules of this research, namely hyalodendrin, tryprostatins, spirotryprostatin, the stemofoline alkaloids, and hinckdentine A are characteristic in that they cannot be accessed by simple combinations of conventional synthetic transformations. Novel key transformations and new reactivities that facilitated the total syntheses of these remaining transformations required to achieve stereoselective total syntheses of the targets is described.

2. Hyalodendrin

The broad spectrum of bioactivities of the disulfide-bridge-containing epidithiodioxopiperazine (ETP) alkaloids is generally ascribed to their common central bicyclo[2.2.2]octane moieties (Figure 1). Consequently, the development of synthetic strategies for the preparation of the core bicyclo[2.2.2]octane structure has drawn considerable interest among the synthetic community. We also began our research into these ETP natural products in an effort to develop novel methodology for the enantioselective construction of the ETP core structure, and hyalodendrin (1) was chosen as our synthetic target for this project. Bicycle 1 was isolated in 1974 from Hyalodendron sp. (FSC-601) by Strunz et al. and is known to be one of the simplest members of this class of alkaloid.

![Figure 1. Synthetic targets to be described in this review.](image-url)
benzylated product 15 followed by ring cleavage of the bridgehead anion 17 and benzylolation of the resultant thiolate 18.

We circumvented this untimely ring opening through the use of benzaldehyde as the electrophile, which was expected to lead to the formation of the electron–rich alkoxide 19, thereby retarding deprotonation at the opposite bridgehead (Scheme 1c). This strategy exclusively gave the desired secondary alcohol 20. The benzyl hydroxy group was activated as mesylate 21 and was reduced by treatment with TMSOTf and Et3SiH. Upon treatment with 1.0 equivalent of LDA at −78 °C, 15 underwent facile ring cleavage to give thiolate 18 that was then tritylated to furnish the stable trityl disulfide 22. Dithydroxylation afforded a diastereomeric mixture of diols that was treated with BF3·OEt2 as a uniquely effective cyclization reagent. The acyliminium ion, generated that was subsequently treated with Zn/LiCuBr2 in ethanol and was reduced by treatment with TMSOTf and diimide 23, resulted in no reaction or over reduction, treatment with Zn/LiCuBr2 in ethanol23 gave the desired Z—isomer with solvolysis of the formate. The solvent was accordingly changed to 2,2,2-trifluoroethanol24 to suppress the undesired solvolysis, which improved the yield of 26 to as high as 99%. Subsequent dehydration with triphosgene gave the ortho–alkenyl isocyanide 27, thereby setting the stage for a radical–mediated cyclization.

When isocyanide 27 obtained in this manner was subjected to radical cyclization under our established conditions,14 the desired 5-exo adduct 28 was obtained in moderate yield with concomitant formation of a considerable amount of 6-endo cyclization/cleavage products (29, 30) after acidic treatment with silica gel. We were aware of the tendency of imidoyl radicals 31 to cyclize to form a mixture of the 5-exo (32) and 6-endo (33) intermediates because the kinetically favored 32 is not stabilized by a neighboring substituent. Thus, V−70 (2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile), 34) was
employed as a radical initiator because of its lower decomposition temperature.\(^9\)

To our delight, the radical cyclization of isocyanide 27 at low temperature (30°C) showed complete selectivity for cyclization of the imidoyl radical and gave 2-stannylindole 35 as the sole product. Extensive investigation into the coupling reaction with prenyl acetate 36 revealed that the use of Pd(PPh\(\text{3}\))\(_4\) or the Pd/trifurylphosphine system gave low to moderate yields of 37. The combination of Pd,\(_2\)(dba),\(_3\), triphenylarsine, and lithium chloride\(^{21}\) eventually gave the best results, affording the desired 2-allylated tryptophan derivative 37 in 92% yield in a one-pot process from isocyanide 27.

With the indole moiety constructed, 37 was converted to the corresponding amino acid 39 in a three-step sequence that included Boc protection of the indole, hydrolysis of the acetone, and TEMPO oxidation of the resulting alcohol 38 to carboxylic acid 39. After condensation with L-proline methyl ester (40) the Boc groups were removed thermally\(^{17}\) by heating the substrate under reflux in N-methylpyrrolidinone (230°C) the two Boc groups in 41 were removed, which, to our delight, was followed by the concomitant formation of the diketopiperazine core structure. These transformations gave tryprostatin B (2b) in 89% yield, thereby establishing a synthetic route in ten steps from 24 in 33% overall yield on a half-gram scale. We also synthesized tryprostatin A (2a) bearing a methoxy group at the 6-position of the indole following an almost identical synthetic route; tryprostatin A (2a) was obtained in 30% overall yield on a half-gram scale.

Our optimization of the radical-mediated indole synthesis at reduced temperature by means of V\(\text{70}\) facilitated selective access to 2-stannyl-3-stibulated indoles in which the substituent at C3 cannot effectively stabilize the initially formed radical. In combination with a subsequent palladium-mediated coupling reaction at C2, this route constitutes a powerful strategy for the preparation of a variety of 2,3-disubstituted tryptophan derivatives, including tryprostatins A and B.

4. Spirotryprostatin A\(^{23}\)

One of the representative spirocyclic natural products, spirotryprostatin A (3), was isolated in 1996 from the fermentation broth of \textit{Aspergillus fumigatus}.\(^{24}\) Primarily due to its highly challenging spirocyclic structure, various synthetic analogues of this compound have been extensively explored.\(^{25}\) Spirotryprostatin A (3) is structurally characterized by an annulated diketopiperazine moiety and a multiply substituted proline core that is connected to a 6-methoxyindolinone moiety through a spiro quaternary stereogenic center. Through various synthetic efforts and previous total syntheses of the spirotryprostatins\(^{26,27}\) that were aimed at constructing the highly substituted proline moiety, it is understood that the selective construction of the contiguous stereocenters is exceedingly difficult. We envisioned a synthesis of spirotryprostatin A (3) that emphasized the selectivity of each transformation, especially the preparation of the spiro quaternary center.

Scheme 3 details our synthetic approach to spirotryprostatin A. We planned to deliver the aryl group of the indolinone via an intramolecular Heck reaction with an aryl halide tethered to the latent isopropylidene moiety, which was expected to yield the spiro quaternary center of the target with high diastereoselectivity. Our synthesis commenced with the condensation of L-proline methyl ester p-toluenesulphonate 42 with N-Cbz-4-trans-hydroxyproline 43 followed by oxidative transformations that successfully afforded intermediate 44 on a 5-g scale.
Subsequent functionalization of the diketopiperazine moiety required a regio- and stereoselective transformation for the introduction of the latent isobutenyl side chain at C18. So far, known methods for the enolization of 4-pyrrolidine systems, as in the first example of the construction of the opposite regioselectivity in the 4/5f$_1$irst example of the construction of the opposite regioselectivity of the diketopiperazine moiety, which, to the best of our knowledge, pleasingly constitutes the only given silyl enolates or enamines of the 3,4-f$	extsubscript{2}$ only gave silyl enolates or enamines of the 3,4-$K^\text{O}_2$oxoproline derivatives $K^\text{O}_2$oxoproline derivatives. This result highlights the significance of the construction of the opposite regioselectivity of the diketopiperazine moiety. Here we treated ketone 44, which was oxidized to the aldehyde, and reacted with the aryl Grignard reagent in situ using Knochel’s technique. Subsequent oxidation using the Dess–Martin reagent gave the desired ketone 51 as the substrate for the intramolecular Heck reaction. The crucial Heck cyclization proceeded uneventfully with the aid of the ketone tether, to afford tetralone 52 in 96% yield. Successful intramolecular control of the stereochemistry at the newly generated C3 quaternary carbon center was consequently achieved. The nitrogen atom on the aryl group was required for the construction of the spiroindolinone moiety. Our attempt to achieve this transformation using the Beckmann rearrangement was first met with failure. The activation of the oxime intermediate with various acids did not mediate the required rearrangement; consequently, 52 was converted to oxime mesylate 53. Our trial experiments revealed that the Beckmann rearrangement proceeded to afford the desired lactam 54 in 86% yield only when mesylate 53 was treated with TiCl$_4$. Introduction of the Boc group onto the amide and ring opening of the imide with CH$_3$Li successfully introduced two methyl groups to give tertiary alcohol 55 in 59% yield. Subsequent ozonolysis of the vinyl group and oxidation gave the lactam intermediate. Elimination of the tertiary hydroxy group and removal of the Boc group were performed concurrently under acidic conditions to selectively give spiropyrostatin A (3).

The characteristic feature of this asymmetric synthesis of spiropyrostatin A lies in the intriguing application of the stereochemical propensity of the cyclo-(Pro–Pro) diketopiperazine scaffold to stereoselectively introduce functionality. It could be said that by understanding the intrinsic properties of the cyclo-(Pro–Pro) intermediate the highly selective formation of the quaternary spirocenter of indolinone was realized, as well as the total synthesis of the target.

5. Core Structure of the Stemofoline Alkaloids

The stemofoline alkaloids contain the highest levels of complexity within the large family of Stemona alkaloids that share the common pyrrolo[1,2-a]azepine core (Figure 1). A representative member of these alkaloids is stemofoline (56), isolated by Uyeo and coworkers in 1970. Inspired by past
total syntheses of these alkaloids by Kende and Overman, as well as the formal synthesis by Martin, and Pyne’s versatile semisyntheses, we launched our synthetic campaign toward the stemofoline alkaloids, bearing in mind that our strategy should also allow extensive late-stage derivatization of these alkaloids. Since the introduction of a γ-ylidene tetronate into a lactone, as well as the C–3 side chain of the C–3 formyl intermediate were previously reported, we targeted lactone 4 bearing a C10 methyl group (Scheme 4a).

Details of the synthesis are shown in Scheme 4b. N–H insertion in 57 was performed by Che’s methodology employing [RuCl2(p-cymene)], as the catalyst, following by the in situ NaBH4 reduction of ketone provided 58 in good yield with good diastereoselectivity. The secondary alcohol in 58 was then acylated with fumaric acid monomethyl ester to furnish 59. Attempts to remove the Boc group and the transformation into the nitrone were initially hampered by the β-elimination of the fumarate moiety. This facile elimination was suppressed by first isolating the secondary amine as the trifluoroacetate salt. This salt was then subjected to m-CPBA oxidation with slow neutralization using solid NaHCO3, thereby affording the desired nitrone 62 regioselectively and in good conversion. While the intramolecular 1,3-dipolar cycloaddition reaction partially proceeded during oxidation, it was driven to completion by heating in toluene to exclusively afford the desired diastereomer 63 in 62% overall yield through transition state 64. Formation of the undesired isomer 65 via transition state 66 was not observed because of molecular strain, which hampers overlap between the nitrone moiety and the double bond of the fumarate. The high selectivity of this cycloaddition allows for the successful construction of the C7 stereochemistry of the target molecule. Preliminary studies at this stage suggested that the additional ring strain caused by the planar amide hampers the formation of the bond between C8 and C9; hence, reduction of the lactam and subsequent functional group transformations to give 69 were achieved in 8 steps. The transformation of 69 into the homoenoalate or its equivalent was vital for the construction of the caged structure and concomitant γ-lactone formation leading to the intended lactone 4. We envisioned utilizing allylic sulfoxide as a three-carbon homologation substrate; Mislow–Evans rearrangement of 69 gave this desired allylic sulfoxide. Inspired by the pioneering work of Evans, the lithiated allylic sulfoxide 71 attacked the carbonyl group at C9 from its γ-position; silylation of the resulting alkoxide and the second deprotonation of the alkenylsulfoxide to 73, followed by silylation gave the α-silylalkenyl sulfoxide adduct. These sequential reactions provided isolated isomers E-74 and Z-74 with C8–C9 transannular bonds in a 2:1 ratio, which was then transformed through a sila-Pummerer rearrangement into the thioester 75 by heating with TMSOH in toluene. Collectively, this reaction sequence facilitated the transformation of allylic sulfoxide 71, as the homoenoalate equivalent, to the ring-closed thioester 75. With the thioester 75 in hand, the remaining tasks for the construction of the core included the formation of the lactone moiety and the stereoselective introduction of the C10 methyl group.

Scheme 4. Synthesis of the common core structure of the stemofoline alkaloids.
While acid treatment of thioester 75 provided the corresponding lactone in 73% yield, C-10 methylation via the lithium enolate provided the undesired stereoisomer at C10. Consequently, we decided to employ an approach patterned after Overman’s protocol for the synthesis of a similar natural product.\(^{38}\) Hence, thioester 75 was transformed\(^{49}\) into aldehyde 76, followed by a Mannich reaction and catalytic hydrogenation. Isomerization of the stereochemistry of the resultant saturated aldehyde at the C10 methyl group through treatment with silica gel gave only the desired S-isomer. Selective removal of the TMS moiety and subsequent Swern oxidation gave the projected lactone 4 with entirely the desired stereochemistry. The key motif 4 bears seven stereocenters and potentially provides access to the other stemofoline alkaloid members and their analogues.

Accordingly, we developed a synthetic route to the common core motif of the stemofoline alkaloids. An intramolecular 1,3-dipolar cycloaddition reaction of a highly functionalized pyrroline intermediate successfully provided a set of stereochemistries on the core structure. We also demonstrated the potency of a lithiated allylic sulfoxide as a novel homoeno-late equivalent to a thioester via an \(\alpha\)-silylalkenyl sulfoxide. A sila-Pummerer reaction and acid-mediated cyclization facilitated a powerful lactone formation strategy that eventually realized the formation of the complex caged structure of the stemofoline alkaloids.

6. Hinckdentine A\(^{57}\)

The development of a dearomatization strategy offers a potent solution to the rapid construction of architecturally complex poly cyclic systems. Functionalized planar aromatic frameworks are accordingly able to acquire three-dimensional characteristics that are increasingly important for the development of future pharmaceuticals.\(^{60}\) Substantial effort has been devoted to this field\(^{11}\) after the pioneering works of Buchwald,\(^{45}\) Bedford,\(^{55}\) and You.\(^{54}\) These strategies have also been applied toward the total syntheses of natural products, demonstrating their potential for constructing complex structures with rich structural information.\(^{31}\) We hypothesized that this strategy is advantageous for the synthesis of the screw-shaped hinckdentine A (5), which was isolated from the marine bryozoan *Hincksinoflustra denticulata* in 1987.\(^{56}\) The structure, unambiguously determined by single-crystal X-ray crystallographic analysis, is characterized by a highly brominated indolo[1,2-c]quinazoline core fused to a seven-membered lactam unit through consecutive stereogenic centers at C12 and C17a, and a cyclic amidine moiety. The biological activity of this compound has not been reported due to a shortage of naturally isolated 5; the synthetic supply of this material\(^{37}\) is clearly important for uncovering its biological activities and those of its derivatives.

Scheme 5 shows our retrosynthetic analysis of 5. McWhorter’s synthetic study\(^{16b}\) indicated that brominations at the C2 and C10 positions are selective, while the C8-selective bromination of 8-desbromohinckdentine A, bearing an amidine substructure, is problematic, affording an inseparable mixture of various tribromides and tetrabromides. Kawasaki accordingly employed a protected cyclic aminal intermediate for selective C2, C8, and C10trimbromination, and succeeded in the first racemic total synthesis of 5.\(^{38}\) Hence, we selected indoline/anilide 77 as our key intermediate. Compound 77 was expected to favor *ortho–para* dibromination at C8 and C10 on the left-hand indoline (as shown in Scheme 5) as well as single *para* bromination at C2 on the right-hand anilide prior to the introduction of the amidine unit. Indoline in 77 is a dearamatized indole, bearing an aromatic moiety introduced at C17a (the indole 2-position) and can be disconnected into two planar synths 78 and 79. The nitrogen functionalities in the azepane moiety of 78 and the acylamino group of 79 were retrosynthetically removed and strategically tethered through the carbonyl group. The simple *N*-acyl tetrahydrocarbazole 80 was consequently chosen for the execution of the crucial asymmetric dearomatative cyclization.

![Scheme 5. Retrosynthetic analysis of hinckdentine A.](image)

The palladium-catalyzed asymmetric dearomatative Heck-type cyclization of 80 to 81 was first investigated (Scheme 6). A non-asymmetric variant using related *N*-acyl indoles was originally reported by Grigg\(^{61}\) in 2001 and later developed by Wu,\(^{46}\) Jia,\(^{41}\) and Lautens.\(^{42}\) We attempted to induce asymmetry through the use of an appropriate chiral ligand. Extensive investigations revealed that Feringa’s phosphoramidite ligand\(^{83b}\) exhibited the best results in our study. Hence, we used the following optimized conditions: 80 (100 μmol), Pd2(dba)3·CHCl3 (2.5 mol %), ligand 82 (25 mol %), NaOAc (1.5 equiv.), i-PrOH (1.5 mL), 100 °C, and 18 h. This reaction can be reproducibly scaled up to 10 g scale under these optimized conditions (98% isolated yield, \(R/S=93/7\)). The absolute stereochemistry of 81 was determined through the CD/VCD technique.\(^{58}\) Other phosphoramidite ligands bearing substituents on nitrogen atoms, or the \(3,3^{\prime}\)-position of BINOL, result in slightly slower reaction rates and lower enantiomeric ratio (er) values. Bidentate ligands (BOX and BINAP) resulted in almost racemic reactions, or sluggish reaction (PHOX). Other solvent system decreased the er (DMA and DMCO), or slowed down the reaction while decreasing the er (1,4-dioxane, CH2CN, 1,2-dichloroethane, and toluene).

Subsequent transformations required the ring expansion of the cyclohexenone moiety via the introduction of a nitrogen atom. Our initial attempts at the Beckmann rearrangement\(^{17b}\) did not afford the desired seven-membered lactam. Consequently, a Beckmann fragmentation strategy was employed. An oxime functionality was introduced at the \(\alpha\)-position to the ketone by reaction of the intermediary silyl enolate with NOCl that was generated *in situ* from TMSCI and \(i\)-AmONO.\(^{65}\) The Beckmann fragmentation of 83 was efficiently mediated by SOCl2; subsequent treatment with CF3CO2H gave a 1:11 E/Z mixture of the \(\alpha\),\(\beta\)-unsaturated 2,2,2-trifluoroethyl esters 84 bearing a cyanomethyl group at C17a. The
C12 tertiary stereogenic center was installed by hydrogenation of the olefin in 84. Hydrogen atoms were introduced with perfect diastereoselectivity from the face opposite to the blocking cyanomethyl group, to afford 85 in 98% yield with 93:7 er. The enantiomerically pure 85 was obtained in 81% yield by simply rinsing the crystals with ice-cold ethanol; the heterochiral racemic crystals of 85 appear to be more soluble than the homochiral crystals in ethanol. The nitrile functionality in 85 was hydrogenated over Raney nickel to provide the corresponding amine, which spontaneously reacted with the 2,2,2-trifluoroethyl ester group to give the seven-membered lactam intermediate 86.

The remaining obstacles to be cleared toward 5 involve the introduction of the nitrogen atom of the indoline/anilide intermediate prior to selective tribromination and formation of the amidine moiety. The most direct route for the introduction of the nitrogen atom is hydrolysis followed by Curtius rearrangement. Here, the hydrolysis of the five-membered lactam in 86 proceeded very quickly to give 87, but easily cyclized again during workup. Ring opening was also difficult by alcoholysis or aminolysis. This propensity for the formation of the five-membered structure was also observed during the partial reduction of the lactam by LiAlH4, affording only hemiaminal 88. Activation of this hemiaminal resulted only in the substitution of the hydroxy group; we duly reduced the tertiary lactam to the hydroxy amine. The chemoselective reduction of the tertiary amide functionality in 86 was a difficult task, but was eventually achieved by a modification of Soai’s method56 (NaBH4-CH3OH-THF) that left the secondary amide of the seven-membered lactam intact to give amino alcohol 89 in 78% yield. Conventional reduction conditions did not give the desired hydroxy amine and mostly gave the tertiary amine or mediated the competitive reduction of the seven-membered lactam. After protection of the amine and alcohol moieties as a TFA amide and a TES ether, respectively, the resulting 90 was oxidized using Jones reagent to provide an aldehyde, which was immediately transformed to aldoxime 91, setting the stage for a modified Kim’s reaction.57

Introduction of the anilinic nitrogen functionality was next pursued (Scheme 7). The conversion of 91 into the nitrile oxide...
was performed by treatment with NCS in situ, followed by reaction with tetrahydro-2-pyrimidinethione (92) to afford the cycloaddition/rearrangement product, the isothiocyanate 93, as the sole product in 72% yield. The TFA group in 93 formed under these conditions was labile under basic conditions, readily forming the cyclic thiourea 94. Extensive screening of the reaction conditions revealed that the undesired removal of the TFA group could be suppressed by the initial treatment of 93 with KSAc in CH₂OH at 40 °C for 4 h followed by a hydrolytic workup with aqueous NaHCO₃. KSAc seems to selectively attack the isothiocyanate to give 95, followed by acyl transfer to 96, which was then hydrolyzed to afford 97. The use of KS(CO)H was expected to shorten the transformations during the later stages but it was found that the anilinic secondary amine easily cyclizes to the resultant formamide to give the untimely cyclic amidine moiety. Bromination following construction of the amidine moiety was already known to disrupt the regioselective tribromination, hence the use of this reagent was avoided.

The indoline/acetanilide intermediate 97 was equipped with the electronic properties required for the next crucial tribromination. However, this bromination was delicate probably due to the low solubility of 97 and the reaction intermediates in the solvents typically used for bromination (CH₂Cl₂, CHCl₃), resulting in facile cyclization to methylquinazoline 98 even at rt. The use of CH₃CN as a solvent seemed to provide the required solubility and reactivity, but the formation of the Ritter-type reaction product (2,4,4,5-tetramethyl-4,5-dihydrooxazole) complicated the purification process, and was consequently not employed. The undesired pathway was able to be avoided by dissolving substrate 97 in CH₃NO₂. Treatment of a clear solution of 97 in CH₃NO₂ at ~20 °C with 3.0 equiv. of Br₂ resulted in selective bromination at C2 and C10 (99). Under these conditions the brominated intermediate did not form the methylquinazoline structure, and further bromination was performed with 8.0 equiv. of Br₂ at rt that slowly proceeded selectively at C8. Conventional workup of intermediate 100 facilitated the oxidative formation of the N–N bond to afford 101; the reaction was quenched with 2-methyl-2-butenone to reproducibly furnish the penultimate tribromide 102 in 64% yield from isothiocyanate 93. Construction of the amidine moiety was finally examined. The introduction of a carbon unit between the two nitrogen atoms was necessary to achieve this transformation. Since the replacement of the acetyl group with a formyl group was tedious, and formylation of the anilinic nitrogen was difficult because of steric hindrance, we envisioned the activation of a formyl group equivalent between the two nitrogen atoms. This would generate an amidine intermediate 103 that would also assist the removal of the acetyl group. Eventually, the amidine moiety of 5 was constructed in 88% yield by the treatment of 102 with an excess amount of HCO(OCH₃)₂, (50 equiv.) and TFA (50 equiv.). This final process provided hinckdentine A (5) on a 300 mg scale.

We carried out the first enantioselective total synthesis of hinckdentine A (5) in 14 steps and in 8.8% total yield from the readily available indole 80. Our unique synthetic strategy consisted of five effective key processes: i) palladium-catalyzed asymmetric dearomatative cyclization of 80 to 81; ii) a Beckmann fragmentation/lactamization sequence leading to the seven-membered lactam 86; iii) the rearrangement-based introduction of a nitrogen atom into anilide 97; iv) regioselective tribromination; and v) the formation of the amidine moiety to afford the indolo[1,2-c]quinazoline core.

7. Conclusion

This review provides an overview of the syntheses of five groups of natural products that we have successfully accomplished. The keys to these syntheses are the development of novel reactions and the discoveries of intrinsic reactivities of molecules unearthed during our synthetic research. H yaloden din was synthesized via the development of a novel L-cysteine-derived bridgehead carbanion and its alkylation with a benzyl group equivalent. The syntheses of tryprostatins A and B were accomplished by low temperature radical cyclizations that constructed the indole core through the use of V70 as a room temperature radical initiator. Combined with the palladium-mediated coupling reaction of the resulting 2-stannyl indole and the prenyl moiety, these transformations are useful for the syntheses of related substituted tryptophan derivatives. Our synthesis of spiriotryptostatin A exploited the intrinsic utility of cyclo–(Pro–Pro) for the selective introduction of functional groups. In combination with an intramolecular Heck reaction and a Beckmann rearrangement for the late-stage introduction of nitrogen functionality, this synthesis represents a unique example of the construction of a spirindolino-mone moiety. The highly caged core structure of the stemonoline alkaloids was constructed using intramolecular 1,3-dipolar cycloaddition sequences followed by a novel strategy that employed an allylic sulfoxide as a homoenoate equivalent. Finally, novel catalytic asymmetric dearomatative cyclization of an indole substrate afforded the core screw-shaped structure of hinckdentine A. Original regio- and stereoselective methods for the introductions of two nitrogen atoms and three bromine atoms provided the natural product.

Collectively, we encountered many opportunities to develop new synthetic transformations and gain new insight into the syntheses of complex molecules during these five total–synthesis endeavors. We believe that our efforts in reaching the summits of “mountains” will continue to inspire synthetic organic chemists in the future.

Acknowledgment

The authors thank Prof. Masato Kitamura (Nagoya University) for fruitful discussions and helpful support. We also appreciate the following collaborators for their invaluable efforts: Ren Takeuchi, Dr. Takayuki Yamakawa, Dr. Eiji Ideue, Dr. Katsushi Kitahara, Dr. Hiroyuki Ono, and Kazuya Douki. Dr. Tohru Taniguchi (Hokkaido University) is acknowledged for his work on the CD/VCD experiments. This work was supported by the Kato Memorial Bioscience Foundation, a Mitsubishi Tanabe Pharma Award in Synthetic Organic Chemistry Japan, JSPS KAKENHI Grant Numbers 21790009, 20020024, 23590003, 25221301, 15H05641, the Platform for Drug Discovery, Informatics, and Structural Life Science from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and the Advanced Catalytic Transformation Program for Carbon Utilization (ACT–C) from the Japan Science and Technology Agency (JST).

References

PROFILE

Jun Shimokawa was born in 1980 in Tokyo, Japan. He received his B.S. (2003) and M.S. (2005) degrees at the University of Tokyo under the direction of Professor Yuichi Hashimoto. He performed his Ph.D. studies under the direction of Professor Toshu Fukuyama at the University of Tokyo where he conducted the research on total syntheses of complex natural products. In 2006, he started his academic career as an Assistant Professor in the same group. In 2012, he moved to Nagoya University, where he is appointed Assistant Professor in Professor Masato Kitamura’s group. He has received Young Scientist’s Research Award in Natural Product Chemistry (2012) and The Pharmaceutical Society of Japan Award for Young Scientists (2017). His research efforts focus on the development of novel synthetic methodology and applications to the multistep synthesis of complex molecule.

Toshu Fukuyama was born in 1948 in Anjo, Japan and received his B.S. and M.S. degrees at Nagoya University. He then earned his Ph.D. in 1977 at Harvard University under the direction of Professor Yoshito Kishi. He began his independent career at Rice University in 1978 and rose to the rank of Professor in 1988. He returned to his home country and joined the faculty of the University of Tokyo in 1995 and then moved to Nagoya University where he is currently Designated Professor of Pharmaceutical Sciences. His main research interest is total synthesis of natural products and development of synthetic methodology.