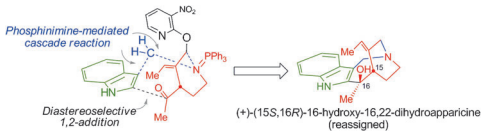

Composed by cascade: A concise method for the construction of an azabicyclo[4.2.2]decone with an indole ring by using a phosphinimine-mediated cascade reaction enabled the structure determination and efficient synthesis of (+)-16-hydroxy-16,22-dihydroapparicine. This synthesis also features a stereospecific 1,2-addition construction of the tetrasubstituted carbon center and an intramolecular chirality-transferring Michael reaction as key steps (see picture).

Total Synthesis

T. Hirose, Y. Noguchi, Y. Furuya, A. Ishiyama, M. Iwatsuki, K. Otoguro, S. Ōmura, T. Sunazuka* …* ▮▮▮▮–▮▮▮▮

Structure Determination and Total Synthesis of (+)-16-Hydroxy-16,22-dihydroapparicine

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Structure Determination and Total Synthesis of (+)-16-Hydroxy-16,22-dihydroapparicine

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Abstract: Herein, we describe the first asymmetric total synthesis and determination of the relative and absolute stereochemistry of naturally occurring 16-hydroxy-16,22-dihydroapparicine. The key steps include 1) a novel phosphinimine-mediated cascade reaction to construct the unique 1-azabicyclo-[4.2.2]decane core, including a pseudo-aminal-type moiety; 2) a highly stereospecific 1,2-addition of 2-acylindole or a methylketone through a Felkin–Anh transition state for the construction of a tetrasubstituted carbon center; and 3) an intramolecular chirality-transferring Michael reaction of the ketoester, with neighboring-group participation, to introduce a chiral center at C15 in the target molecule. In addition, we evaluated the antimalarial activity of synthetic (+)-(15*S*,16*R*)-16-hydroxy-16,22-dihydroapparicine and its intermediate against chloroquine-resistant *Plasmodium falciparum* (K1 strain) parasites.

Keywords: asymmetric synthesis · cascade reactions · dihydroapparicine · Michael reaction · natural products · stereochemistry

Introduction

The *Tabernaemontana* species have a widespread distribution and are known to produce alkaloids with intriguing chemical structures and novel bioactivities. Plant-derived alkaloids are important compounds in medicinal research. Apparicine (**1**; Figure 1) was isolated from *Tabernaemontana cumminsii* in 1970[1] and was originally discovered from *Aspidosperma dasycarpon* in 1965[2] as a 5-nor stemmadenine-type monoterpenoid indole alkaloid. After the discovery of **1**, more than 20 types of 5-nor stemmadenine alkaloids have been reported, and several key compounds in this family are shown in Figure 1.[3] We have focused on the screening of antimalarial agents from natural products, and a crude extraction, including 16-hydroxy-16,22-dihydroapparicine (**4**), originally isolated from the plant *Tabernaemontana dichotoma* in 1984 by Verpoorte and co-workers,[4] was found to possess potent antimalarial activity in our preliminary screening experiments (data not shown). Therefore, we needed to prepare a sufficient amount of **4** to allow proper evaluation of its antimalarial activity.

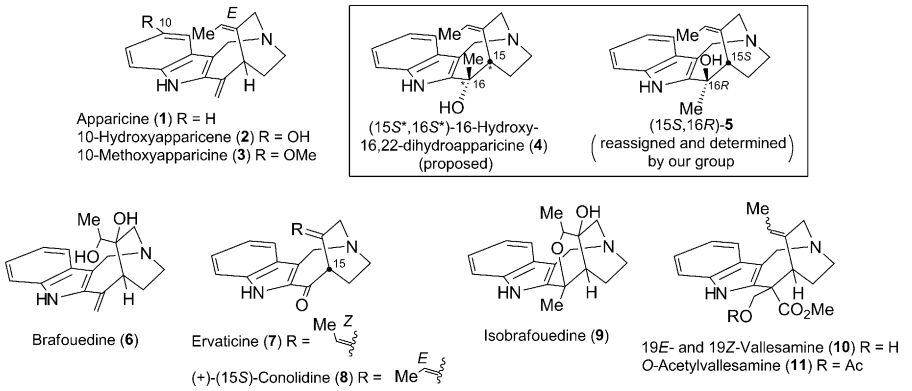

Figure 1. Structure of 5-nor stemmadenine-type indole alkaloids.

The unique structure of **4** consists of a strained 1-azabicyclo[4.2.2]decane structure with a tetrasubstituted carbon center directly connected at the indole 2-position, with a single carbon atom as a connection between the indole 3-position and aliphatic nitrogen atom, which essentially equals the pseudo-aminal-type moiety of gramine compounds (Scheme 1). The pseudo-aminal-type skeleton could convert into the corresponding 3-methylene-3-*H*-indolinium cations, which have proven synthetic utility. The aliphatic nitrogen–carbon bond as a pseudo-aminal-type moiety could be easily cleaved by a retro-Mannich reaction

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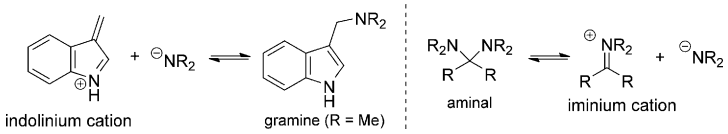


Scheme 1. Gramines as versatile pseudo-aminal-type compounds.

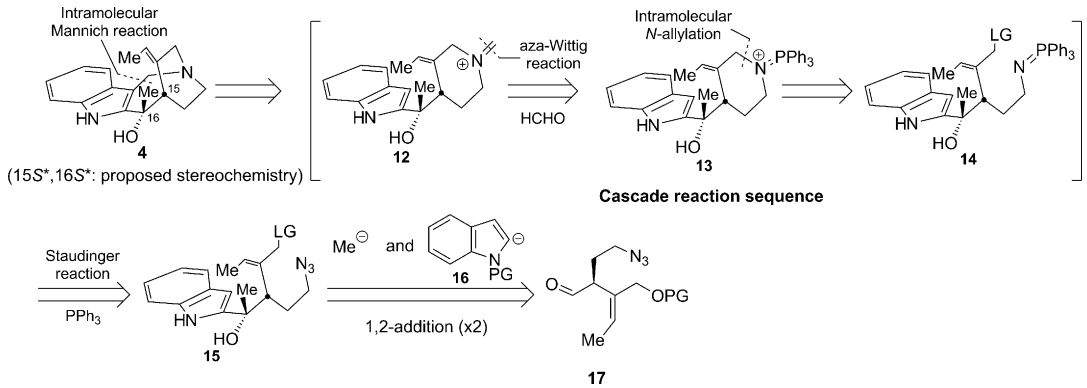
under acidic,[5] basic,[6] or thermal conditions[7] or by using various reagents (e.g., trialkylphosphanes,[8] Lewis acids,[9] phthalimides,[10] thiols,[11] and activated esters)[12] to generate the indolinium cation, which reacts with the various nucleophiles at the 3-methylene position. Therefore, such reactivity and instability for the apparicines, including our target compound, can be predicted. The combination of a remarkable structure, a wide range of biological activity (e.g, antimicrobial,[13] antituberculosis,[3h] opioid,[14] and so forth), and the limited availability from natural sources makes these alkaloids attractive targets. Total synthesis routes toward apparicine (**1**) and (+)-conolidine (**8**) have been reported.[15,16] Although the relative stereochemistry of apparicines is known, at the onset of our investigations, the absolute stereochemistry of apparicines had not been fully established, except for **8**, for which an asymmetric total synthesis was completed by Micalizio and co-workers in 2011.[16]

The relative stereochemistry of 16-hydroxy-16,22-dihydroapparicine was proposed to be a 15*S**,16*S** configuration based on detailed ^{1}H NMR spectroscopic analysis. However, the relative and absolute configuration of 16-hydroxy-16,22-dihydroapparicine has remained undetermined during the 28 years since its isolation. In 2012, we reported the first total synthesis of (±)-**4** and (±)-**5** by using a novel phosphinimine-mediated cascade reaction, and the relative stereochemistry of 16-hydroxy-16,22-dihydroapparicine was reassigned and determined to be **5** (Figure 1).[17] Herein, we report the development of our first- and second-generation total synthesis of 16-hydroxy-16,22-dihydroapparicine, which caused the reassignment of the relative stereochemistry and the determination of the absolute configuration of naturally occurring 16-hydroxy-16,22-dihydroapparicine ((15*S*,16*R*)-**5**), and a better understanding of the mechanism of the phosphane-mediate cascade reaction, which is the key reaction in our pathway to construct the strained 1-azabicyclo-[4.2.2]decane structure. We also confirmed the antimalarial properties of the natural form of 16-hydroxy-16,22-dihydroapparicine and related synthetic intermediates, including activity against chloroquine resistant *Plasmodium falciparum* (K1 strain).

Results and Discussion

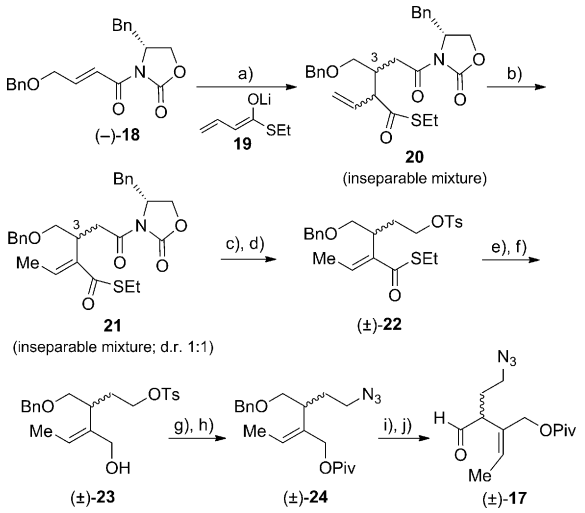
Retrosynthetic analysis of (15*S,16*S**)-4**: Our approach toward the synthesis of the 1-azabicyclo[4.2.2]decane skeleton was guided by the hypothesis that pseudo-aminal-type alkaloids occur via a biogenetic intermediate. In the final step to obtain (15*S**,16*S**)-**4**, we envisaged the preparation of the iminium cation **12** in situ, which could be generated along a cascade sequence from azide **15**. Given the reactivity of the phosphinimine group, we designed a novel phosphinimine-mediated cascade reaction, with the following sequence: 1) Staudinger reaction of **15** with triphenylphosphine to generate phosphinimine intermediate **14**; 2) intramolecular *N*-allylation to the aminophosphinium derivative **13**; 3) aza-Wittig reaction of **13** with formaldehyde, and 4) an intramolecular Mannich reaction, with nucleophilic attack from the indole 3-position to the iminium cation of **12** (Scheme 2).

The designed cascade reaction has two challenging issues: The first was the *N*-allylation of the phosphinimine group, related reactions of which have been reported by Zimmer and Singh[18] and others.[19] Phosphinimine has a relatively high nucleophilicity; however, *N*-alkylation of phosphinimine involves a sensitivity with respect to the electrophilic leaving group, so the choice of the leaving group would be a critical factor in the cascade reaction. The second key issue was the aza-Wittig reaction between the aminophosphonium salt and formaldehyde. Similar reactions have not been reported so far, except for the reaction of aminophosponium salt with excess of DMF to generate the formamidinium salt.[20] Therefore, the reactivity and applicability of the aminophosphonium salt was unknown.



Scheme 2. Retrosynthetic analysis of (15*S*,16*S*)-16-hydroxy-16,22-dihydroapparicine (**4**). LG = leaving group, PG = protecting group.

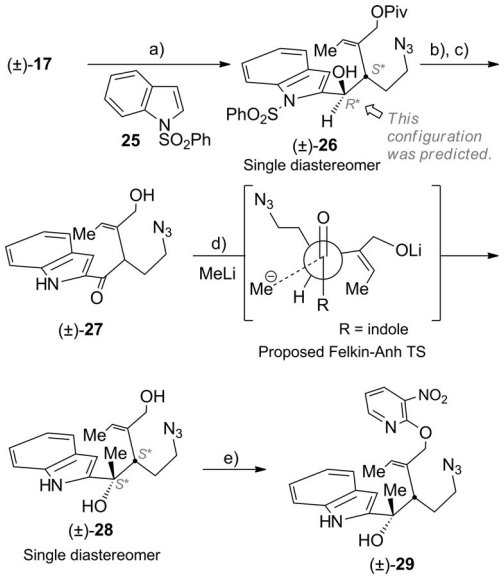
Synthesis of azidoaldehyde 17: Our synthesis commenced with the preparation of azidoaldehyde **17**. The synthesis began from known carboximide (−)-**18**,[21] which was subjected to the remote stereocontrolled Michael reaction, with enolate **19** as a Michael donor, to construct the C15 stereocenter of **4** (corresponding to the C3 position of **20**). However, the desired Michael adduct **20** was obtained as an inseparable diastereomeric mixture in low yield, with no diastereoselectivity at the C3 position, along with the γ-adduct (Scheme 3). Despite extensive optimization by using various



Scheme 3. Reagents and conditions: a) **19**, THF, −78 °C, 1.5 h (44 %; four inseparable diastereomers); b) DBU, THF, RT, 20 h (91 %; two inseparable diastereomers; d.r. = 1:1); c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, THF/MeOH, −50 °C, 45 min (82 %); d) TsCl, $Me_3N{\cdot}HCl$, Et_3N, CH_2Cl_2, RT, 1 h (97 %); e) Lindlar cat., Et_3SiH, 1-hexene, quinoline, acetone/CH_2Cl_2, RT, 3 h (75 %); f) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 5 min (97 %); g) NaN_3, DMSO, RT, 10 h (83 %); h) PivCl, pyridine, RT, 1 h (99 %); i) DDQ, CH_2Cl_2/pH 7.2 phosphate buffer, RT, 58 h (85 %); j) Dess–Martin periodinane, CH_2Cl_2, RT, 15 min (93 %). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMSO = dimethyl sulfoxide, Piv = pivaloyl, Ts = tosyl.

esters of crotonic acid, we could not improve the reaction yield and stereo- or regioselectivities. Further improvements in the diastereoselective Michael reaction were shelved, and our efforts turned toward the preparation of the racemic aldehyde **17** to attempt a diastereoselective 1,2-addition with an indole anion. Subsequently, DBU-mediated isomerization of **20** afforded the sole *E* olefin product **21** as a 1:1 diastereomeric mixture in 91 % yield. Subsequently, imide selective reduction of **21** with $NaBH_4$ with $CeCl_3{\cdot}7H_2O$ in THF/MeOH[22] furnished a primary alcohol in 82 % yield, followed by conversion into tosylate (±)-**22** in 97 % yield by using the protocol developed by Tanabe and co-workers (i.e., TsCl, $Me_3N{\cdot}HCl$, Et_3N).[23] A stepwise reduction of (±)-**22** by using a combination of conditions developed by Fukuyama et al.[24] and Luche et al.[22] were carried out to yield the desired allyl alcohol (±)-**23** in good yield. Subsequently, azidation of (±)-**23**, followed by protection of the hydroxy group with PivCl afforded the allyl pivalate (±)-**24** in excellent yield. In the next two steps, the benzyl group was removed under oxidative deprotection by using DDQ[25] in 85 % yield, followed by the Dess–Martin oxidation[26] of the resultant primary alcohol to yield the azidoaldehyde (±)-**17** in 93 % yield.

Total synthesis of (±)-(15*S,16*S**)-4 and correction of the stereochemistry of the natural product**: With the racemic aldehyde unit (±)-**17** in hand, we turned our attention to completing the synthesis of racemic (15*S**,16*S**)-**4**. A diastereoselective 1,2-addition of the *N*-phenylsulfylindole nucleophile **25** to (±)-**17** was carried out (Scheme 4). In 1993, Nat-



Scheme 4. Reagents and conditions: a) **25**, *n*BuLi, THF, −78 °C, 30 min (85 %; d.r. = > 20:1); b) Dess–Martin periodinane, CH_2Cl_2, RT, 30 min (quant.); c) K_2CO_3, MeOH, RT, 48 h (87 %); d) MeLi, THF, −78 °C, 10 min (91 %; d.r. = > 20:1); e) 2-chloro-3-nitropyridine, tris[2-(2-methoxyethoxy)ethyl]amine, KOH, K_2CO_3, PhMe, −10 °C, 8 h (93 %).

sume and co-workers reported the diastereoselective 1,2-addition of the Garner aldehyde with **25** and *n*BuLi in −75 °C, and the diastereoselectivity obeyed the Felkin–Anh rule.[27] In our case, the 1,2-addition between (±)-**17** and **25** under the conditions developed by Natsume and co-workers provided the 2-substituted indole (±)-**26** in 85 % yield as a single diastereomer. The stereochemistry of the newly constructed secondary alcohol of (±)-**26** was predicted to be the *R** configuration (Scheme 4) on the basis of the Felkin–Anh rule. Subsequently, deprotection of the *N*-phenylsulfonyl group of (±)-**26** was performed under several conditions (i.e., TBAF,[28] basic solvolysis,[29] and reductive condition);[30] however, only decomposition of the substrate was observed. Therefore, (±)-**26** was transformed to 2-acylindole by using Dess–Martin oxidation[26] to reduce the electron density of the indole ring, which would assist in the deprotection of *N*-phenylsulfonyl group from the indole moiety. As expected, the *N*-phenylsulfonyl after oxidation of (±)-**26**, could be easily removed under basic solvolysis by using

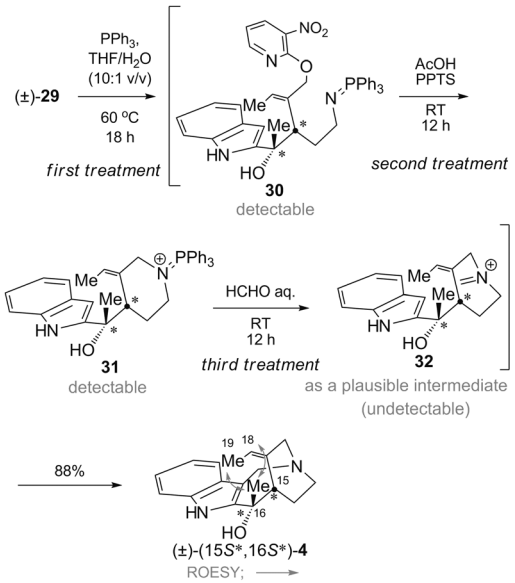
K_2CO_3 in MeOH. Simultaneously, the pivaloyl group was cleaved to afford hydroxyketoindole (±)-**27** in 87% yield, which was converted into dihydroxyindole (±)-**28** by a 1,2-addition reaction of the methyl anion as a single diastereomer in excellent yield. The relative configuration of (±)-**28** was not confirmed at this point, which was expected to be as shown in Scheme 4. The stereoselectivity of this 1,2-addition reaction was defined from the stereochemistry of the final product (±)-**4** after completion of the total synthesis. We also examined a methylation reaction after the oxidation of (±)-**26**, which afforded the *N*-phenylsulfonylated product in 73% yield as a single diastereomer with the same relative configuration as (±)-**28**. These results strongly suggested that the 1,2-addition reaction followed the Felkin–Anh rule, rather than the chelating control model. Next, a leaving group was introduced to the primary alcohol of (±)-**28** to prepare a key intermediate for the cascade reaction to construct the full skeleton of **4**. Firstly, we selected a tosyl group as the leaving group by using the conditions developed by Tanabe and co-workers.[23] However, the product was readily cyclized between the 3-position of the indole skeleton and the allyl position of the tosylate group. After screening suitable leaving groups for this allyl alcohol, we found the 3-nitropyridyl group[31] to be a very suitable leaving group, which was easily introduced into (±)-**28** under basic conditions with 2-chloro-3-nitropyridine[32] to give (±)-**29** in good yield.

For the final key cascade reaction (Scheme 5), (±)-**29** was treated with PPh_3 at 60 °C to generate the phosphinimine intermediate **30**. Continuously, the reaction mixture was acidified with AcOH and PPTS, the addition of which at this time was expected to activate the 3-nitropyridinyloxy function as a leaving group, to form cyclic aminophosphinium **31**. Formaldehyde was added to the resulting solution to promote the intramolecular Mannich reaction, thus forming the target compound (±)-**4**. After purification on a silica gel column chromatography, the synthetic product (±)-**4** was isolated in 88% yield. However, spectral data of (±)-**4** did not agree with that of naturally occurring 16-hydroxy-16,22-dihydroapparicine. Detailed NMR spectroscopic analyses (i.e., ROESY) of synthetic (±)-**4** showed a relationship between H18 or H19 and 16-Me. Thus, the relative stereochemistry of synthetic (±)-**4** was determined to be a 15*S**,16*S** configuration, the configuration proposed by Verpoorte and co-workers (Scheme 5).[4]

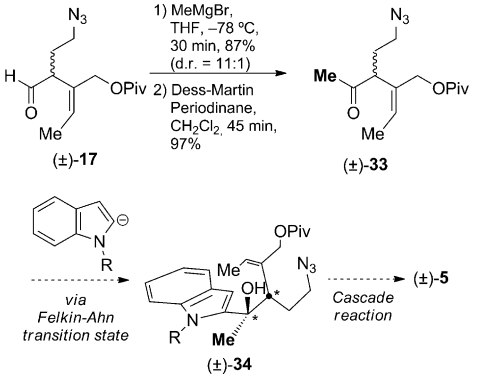
A comparison of synthetic (±)-(15*S**,16*S**)-**4** with the naturally occurring compound found variance in the ^1H and ^{13}C NMR spectra, thus indicating the difference in the chemical shifts in critical positions (see the Supporting Information). In the ^1H NMR spectra, 16-Me and H-6α,β signals were registered with a difference of more than $\Delta\delta = 0.20$ ppm; furthermore, in the ^{13}C NMR spectra, the signals of the piperidine ring were greatly shifted from those seen in naturally occurring 16-hydroxy-16,22-dihydroapparicine. Therefore, we expected that the 16-Me group in the natural product was on the opposite face of the trisubstituted *exo*-cyclic olefin. Thus, the relative stereochemistry of the natural product was anticipated to be the 15*S**,16*R** configuration.

Total synthesis of (±)-(15*S,16*R**)-5 and reassignment of the relative stereochemistry**: Our initial effort achieved the total synthesis of (±)-(15*S**,16*S**)-**4**, which produced spectroscopic data that was not identical with the natural product, thus causing us to believe that the relative stereochemistry of natural 16-hydroxy-16,22-dihydroapparicine was the 15*S**,16*R** configuration. We now turned our attention to complete the synthesis of the 15*S**,16*R** isomer (±)-**5** from methylketone (±)-**33**, which was simply prepared from (±)-**17** by using methylation and Dess–Martin oxidation in good yields (Scheme 6).

Various indole derivatives (i.e., **25** and **35**–**37**) were prepared from the indole skeleton by using a known procedure[33] to examine the diastereoselective 1,2-addition reaction to (±)-**33** (the results are summarized in Table 1). Although the addition of the *N*-phenylsulfonyl indole **25** anion afforded a desired adduct (±)-**38** as a single diastereomer,

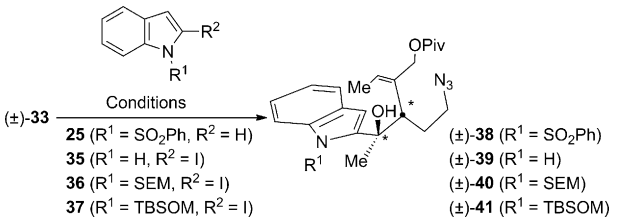


Scheme 5. Conclusion to the synthesis of (±)-(15*S**,16*S**)-**4**.



Scheme 6. Synthetic strategy of (±)-**5** from aldehyde (±)-**17**.

Table 1. Optimization of the stereoselective 1,2-addition reaction of methylketone (±)-**33**.

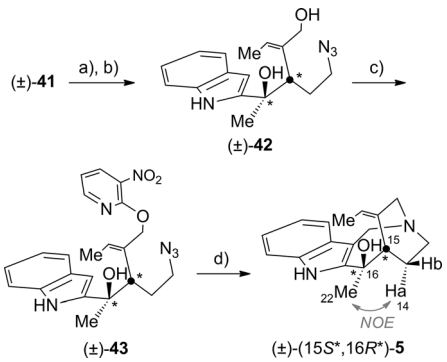


Entry	Compounds	R^1	R^2	Product[e]	Yield [%]
1[a]	**25**	$PhSO_2$	H	(±)-**38**	20
2[b]	**35**	H	I	(±)-**39**	35
3[c]	**36**	SEM	I	(±)-**40**	90
4[d]	**37**[36]	TBSOM	I	(±)-**41**	98

[a] Compound **25** (1.5 equiv), *n*BuLi (1.5 equiv), THF, −78 °C, 1 h. [b] Compound **35** (2.5 equiv), *n*BuLi (5.3 equiv), Et_2O, −78 °C, 1 h. [c] Compound **36** (1.2 equiv), *n*BuLi (1.2 equiv), THF, −78 °C, 1 h. [d] Compound **37** (1.2 equiv), *n*BuLi (1.2 equiv), THF, −78 °C, 1 h. [e] Diastereomeric ratios in all cases was >20:1, as determined by ^{1}H NMR spectroscopic analysis. SEM = 2-(trimethylsilyl)ethoxymethyl, TBSOM = *tert*-butyldimethylsiloxymethyl.

the yield was not satisfactory (Table 1, entry 1). Moreover, deprotection of the *N*-phenylsulfonyl group from (±)-**38** was not successful and led to degradation of the substrate. To improve the efficiency of the conversion from (±)-**33** and *N*-deprotection of the corresponding adducts, nonprotected indole **35** or protected indoles **36** and **37** with acetal groups on the nitrogen atom, which could be deprotected by using a fluoride anion under neutral conditions, were examined. The addition of **35** provided the desired (±)-**39** in 35% yield as a single diastereomer and the starting material was recovered in 14% yield (Table 1, entry 2). The acetal protection group (i.e., SEM and TBSOM)[34] on the indole nitrogen atom were expected to act as a chelator to stabilize the lithium anion at the 2-position of the indole skeleton (Table 1, entries 3 and 4).[35] As a result, the addition of both nucleophiles, derived from **36** and **37**,[36] generated the corresponding desired products (±)-**40** and **41** with satisfactory yields of 90 and 98%, respectively, while maintaining high diastereoselectivity.

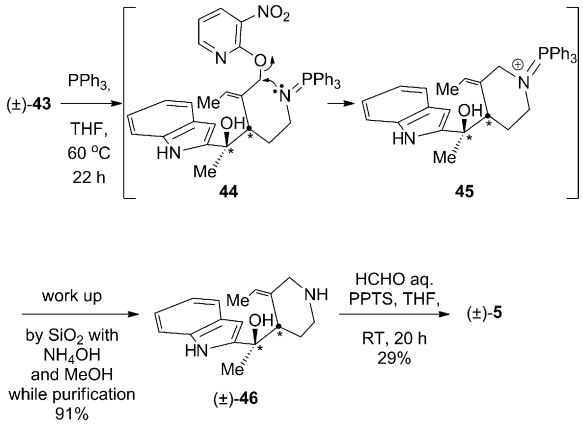
Subsequently, the TBSOM group of (±)-**41** was removed by using TBAF and ethylenediamine in 96% yield, followed by reductive deprotection of the pivaloyl group[37] to give alcohol (±)-**42** in 96% yield (Scheme 7). Following the same reaction sequence as in the synthesis of (15*S**,16*S**)-**4**, 3-nitropyridinylation of (±)-**42** was performed to form (±)-**43** in 83% yield. Finally, the cascade reaction of (±)-**43** furnished the desired product (±)-(15*S**,16*R**)-**5** in 83% yield. The NOE interactions in (±)-**5** were observed between H14a and H22 to support this relative configuration. All data for the synthetic product (±)-**5** were fully consistent with the data for the naturally occurring 16-hydroxy-16,22-dihydroapparicine reported by Verpoorte and co-workers.[4] Furthermore, we also analyzed the synthetic diastereomers (±)-**4** and (±)-**5** and an authentic sample of the natural product by means of HPLC analysis. Both synthetic diastereomers were



Scheme 7. Reagents and conditions: a) TBAF, ethylenediamine, THF, RT, 5 min (96%); b) DIBAL-H, CH_2Cl_2, −78 °C, 5 min (96%); c) 2-chloro-3-nitropyridine, tris[2-(2-methoxyethoxy)ethyl]amine, KOH, K_2CO_3, PhMe, −10 °C, 48 h (83%); d) PPh_3, THF/H_2O (50:1 v/v), 60 °C, 17 h; AcOH, RT, 3.5 h; PPTS, formaldehyde (aq.), RT, 10 h (83%). PPTS = pyridinium *para*-toluenesulfonate, TBAF = tetrabutylammonium fluoride.

separated on a octadecylsilane reverse-phase chromatography system, and the synthetic product (±)-**5** coeluted with the natural product. Thus, the relative stereochemistry of natural 16-hydroxy-16,22-dihydroapparicine was reassigned and defined as a 15*S**,16*R** configuration.

Analysis of the cascade reaction: After achieving the total synthesis of (±)-(15*S**,16*R**)-**5** by using a successful cascade reaction to construct the unique 1-azabicyclo[4.2.2]decane core, we tried to clarify the cascade-reaction mechanism. At first, (±)-**43** was treated with PPh_3 with heating to reflux to isolate the corresponding primary amine, which could be converted from the imine **44**. However, a desired primary amine could not be detected by mass spectrometric analysis during the reaction. Unexpectedly, piperidineindole (±)-**46** was rapidly and directly formed from imine **44**, without acidic activation of the 3-nitropyridinyl group (Scheme 8). Therefore, a desired primary amine from **44** could not be isolated at all. In a time-dependent change from (±)-**43** to **45**, with monitoring by ESI mass-spectrometric analysis, **44**



Scheme 8. Stepwise synthesis of (±)-**5** from (±)-**43**.

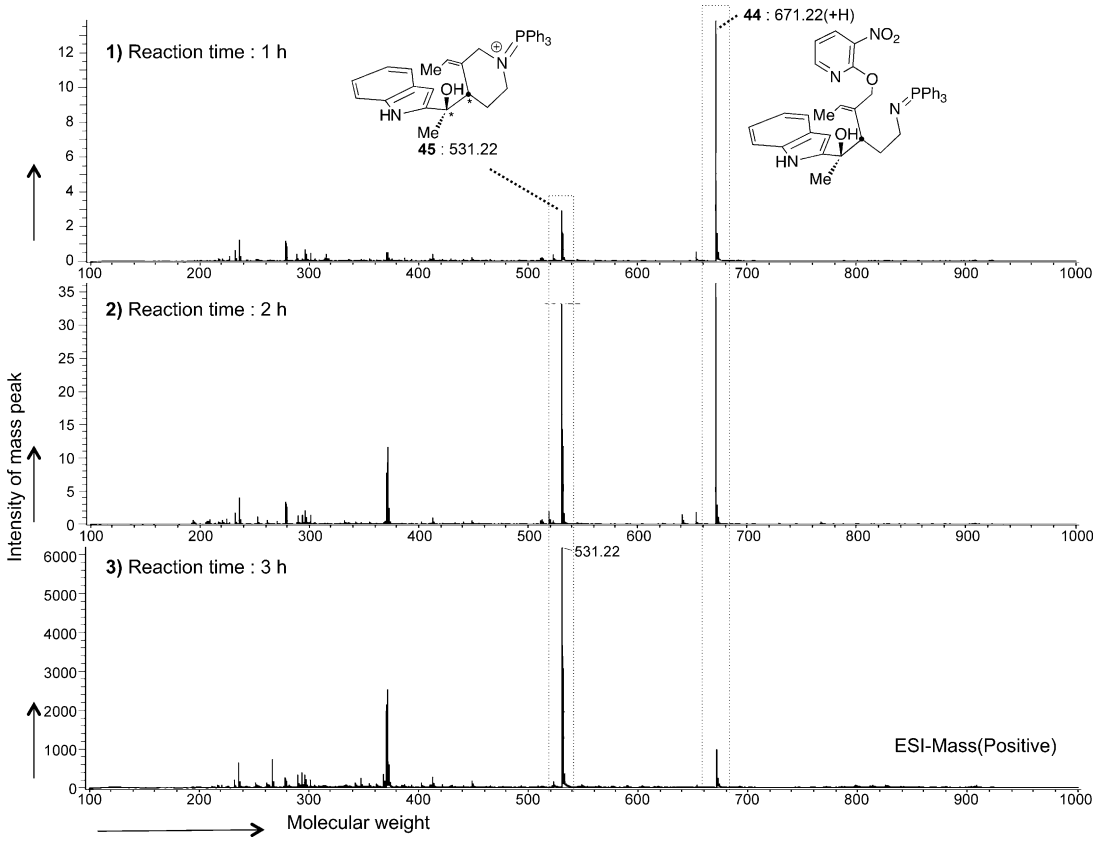
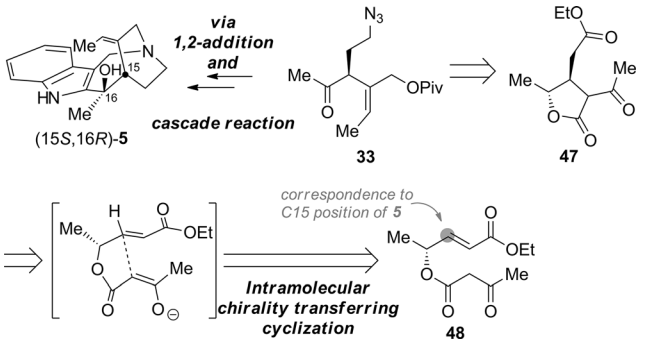


Figure 2. ESI mass spectroscopic analysis of the cascade reaction mechanism.

was smoothly and directly converted into the cyclic aminophosphonium cation **45**, without observation of the primary-amine intermediate (Figure 2). Although the electrophilicity of the 3-nitropyridinyl group is relatively weak under neutral conditions, it was unnecessary for acidic activation, thus showing that the phosphinimine group acts as a very strong nucleophile. We also inferred that the effect of the 1,3-allylic strain in **44**[38] induces the allylic carbon atom at the 3-nitropyridinyl group to get very close to the nitrogen atom of the phosphinimine group. Because of the high reactivity of phosphinimine and the steric effect, autocyclization would occur to form the cyclic aminophosphonium cation. The piperidineindole (±)-**46** could be converted into (±)-**5** by an intramolecular Mannich reaction with formaldehyde under acidic conditions in low yield, which may suggest that the aminophosphonium is a key intermediate in forming an iminium cation through an aza-Wittig reaction in a cascade sequence. However, an iminium intermediate could not be detected by ESI mass-spectrometric analysis.

Asymmetric total synthesis and determination of the absolute stereochemistry of naturally occurring (+)-5: Our synthesis commenced with the preparation of the optically pure methylketone unit **33** to achieve the asymmetric total synthesis of **5** (Scheme 9). The synthesis of chiral methylketone **33** was envisaged from chiral butyrolactone **47**, which possesses the appropriate functional groups and could be pre-

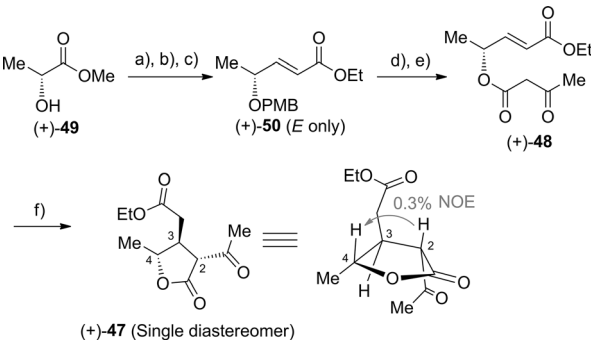


Scheme 9. Retrosynthetic analysis of optically active (15*S*,16*R*)-**5**.

pared from chiral acyclic ketoester **48** through 5-*exo*-cyclization between the acetylacetate and α,β-unsaturated ester moieties. Synthetic pathways for related compounds of butyrolactone **47** are already available,[39] but the enantioselective preparation is limited and has only been reported by Smith et al.[39a,b] We expected that the chiral derivative **47**, including a corresponding C15 stereocenter of **5**, would be formed by the intramolecular chirality-transferring Michael reaction, which should be stereospecifically controlled by the Baldwin rule[40] and Thorpe–Ingold effect.[41]

The synthesis of optically pure **33** began with protection of commercially available (*R*)-methyl lactate (+)-**49** by using *para*-methoxybenzyl (PMB)[42] followed by reduction

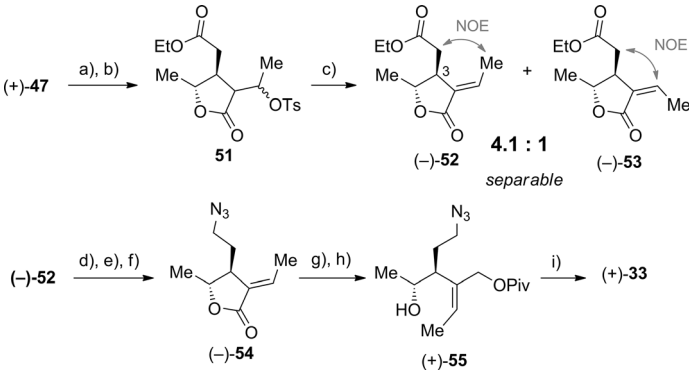
with DIBAL-H and a Horner–Wadsworth–Emmons reaction with ethyl diethylphosphono acetate in the presence of LiCl[43] to provide the (*E*)-α,β-unsaturated ethyl ester (+)-**50** as a sole isomer in good yield over all the steps (Scheme 10). Subsequently, deprotection of the PMB group with DDQ provided the γ-hydroxy-α,β-unsaturated ethyl



Scheme 10. Reagents and conditions: a) $PMBO(=NH)CCl_3$, cat. TfOH, CH_2Cl_2/hexane (1:1 v/v), RT, 30 min (75%); b) DIBAL-H, CH_2Cl_2, −78°C, 1 h; c) ethyl diethylphosphonoacetate, iPr_2NEt, LiCl, MeCN, RT, 1.5 h (63% over 2 steps); d) DDQ, CH_2Cl_2/pH 7.0 phosphate buffer (3:2 v/v), RT, 2.5 h (96%); e) diketene, DMAP, THF, RT, 2 h (quant.); f) K_2CO_3, EtOH, RT, 5 h (91%). DMAP = 4-dimethylaminopyridine, DIBAL-H = diisobutylaluminium hydride, PMB = 4-methoxybenzyl, Tf = trifluoromethanesulfonyl.

ester, the optical rotation of which was compared with that of a reported enantiomer[44] to confirm the *R* configuration of this secondary alcohol. Esterification of this alcohol with diketene in the presence of DMAP[45] afforded the acetoacetyl ester (+)-**48** in quantitative yield. We next attempted the intramolecular chirality-transferring Michael reaction. Through extensive optimization of comparative reaction conditions,[46] we obtained acetylbutyrolactone (+)-**47** under simple basic conditions with K_2CO_3 in 91% yield as a single diastereomer, the relative stereochemistry of which was assigned by comparison with related compounds for the coupling constants[47] and NOE interactions between the α and γ protons of (+)-**47**. The effect of the alcoholic solvent, which would stabilize the anticipated transition state,[41b] was one of the key factors in the intramolecular chirality-transferring Michael reaction. In addition, the substrate benefitted from the Thorpe–Ingold effect[41] by suitable methyl substitution at the γ-position of the α,β-unsaturated ester to promote kinetically favorable cyclization. This reaction can be performed on a large scale (>9 g) without any side reactions or decrease in the diastereoselectivity.

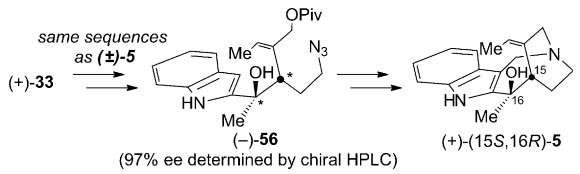
To construct the *E*-ethylidene function, the ketone of the acetyl group of (+)-**47** was reduced with $NaBH_4$ to afford the β-hydroxylactone as an inseparable diastereomixture (d.r. = 3:1), which was subjected to tosylation with TsCl in the presence of Et_3N and *N*-methylimidazole, as reported by Tanabe and co-workers,[48] to provide **51** in excellent yield (Scheme 11). Subsequently, heating of **51** in the presence of DBU[49] facilitated β-elimination of the tosyl group and isomerization of the ethylidene group, thus resulting in produc-



Scheme 11. Reagents and conditions: a) $NaBH_4$, MeOH, 0°C, 10 min (88%; d.r. = 3:1); b) TsCl, Et_3N, *N*-methylimidazole, PhCl, RT, 15 h (96%); c) DBU, PhH, 80°C, 2 h (79 and 19% for (−)-**52** and (−)-**53**, respectively); d) LiOH, THF/MeOH/H_2O (3:1:1), RT, 2.5 h; e) EtOCOCl, Et_3N, THF, 0°C, 45 min; $NaBH_4$ in EtOH, 0°C, 15 min (82% over 2 steps); f) DPPA, DEAD, PPh_3, THF, RT, 2 h (85%); g) DIBAL-H, THF, −78°C, 2 h (51%); h) PivCl, pyridine, CH_2Cl_2, 0°C, 3 h (79%); i) Dess–Martin periodinane, CH_2Cl_2, RT, 30 min (98%; 97% *ee*). DEAD = diethyl azodicarboxylate, DPPA = diphenyl phosphorazidate.

tion of separable isomers (−)-**52** and (−)-**53** (*E*/*Z* = 4.1:1) in 98% yield. The trisubstituted *exo*-cyclic olefin moieties of each product were determined by means of NOE interactions. The *S* configuration of the C3 center of (−)-**52** was determined by means of NOE and ROESY interactions for the hydrogenated product of (−)-**52**[50] because it could not be determined from NOE interactions for (−)-**52**. In the following steps, (−)-**52** was transformed into the targeted methylketone (+)-**33**. Selective hydrolysis of the ethyl ester group under basic conditions afforded a carboxylic acid functionality, followed by formation of the corresponding carboxylic anhydride, which was immediately reduced with $NaBH_4$ to the desired primary alcohol in 82% yield over the two steps.[51] Alternatively, the carboxylic acid group was directly transformed into the primary alcohol by using boron-mediated reduction,[52] although in an unsatisfactory yield. Subsequently, the azidation of the hydroxy group under Mitsunobu conditions[53] produced the azidolactone (−)-**54** in good yield. The lactone moiety was reduced to the diol in 51% yield by using DIBAL-H in THF, followed by the selective protection of the primary alcohol with a Piv group to provide (+)-**55**. Next, oxidation of (+)-**55** by using the Dess–Martin periodinane provided the desired chiral methylketone (+)-**33** in excellent yield without racemization. The optical purity of (+)-**33** (*S* isomer; 97% *ee*) was confirmed by means of chiral HPLC analysis with the comparable *R* isomer of (−)-**33** (see the Supporting Information), which was prepared in the same manner from (−)-(*S*)-methyl lactate.

In the final stage, chiral methylketone (+)-**33** was converted into (+)-(15*S*,16*R*)-**5** by using the same reaction sequences as in the synthesis of racemic **5** (Scheme 12). The optical purity of the substrates after the 1,2-addition reaction was checked for intermediate (−)-**56** by means of chiral HPLC analysis and confirmed as 97% *ee* (see the Supporting Infor-



Scheme 12. Conclusion to the total synthesis of (+)-(15*S*, 16*R*)-**5**.

mation). The characterization data indicated that synthetic (+)-(15*S*,16*R*)-**5** was fully consistent with the data for the natural compound reported by Verpoorte and co-workers.[4] The optical rotation of synthetic (+)-(15*S*,16*R*)-**5** compared well with the values reported for the natural sample ($[\alpha]_D^{24} = +119.2$ ($c = 0.1$ in EtOH) vs $[\alpha]_D^{20} = +129$ ($c = 0.1$ in EtOH), respectively). Otherwise, the optical rotation of synthetic (−)-(15*R*, 16*S*)-**5**, prepared by using the same synthetic pathway, was $[\alpha]_D^{26} = -104.2$ ($c = 0.1$ in EtOH).

Evaluation of antimalarial activity: In 2010, Rottmann and co-workers reported that spiroindolones showed potent antimalarial activity against chloroquine-resistant *Plasmodium falciparum* (K1 strain).[54] Based on this information and with our preliminary results from antimalarial tests, a crude extraction including (+)-**5**, synthetic (±)-(15*S**,16*S**)-**4**, (+)-(15*S*,16*R*)-**5**, (−)-(15*R*,16*S*)-**5**, and some key intermediates in the total synthesis pathway were evaluated against *Plasmodium falciparum* (K1 strain) and for cytotoxicity[55] in vitro in comparison with the clinically used antimalarial drug chloroquine.[56] Belying our expectations, all of the synthetic compounds, including an equivalent of natural 16-hydroxy-16,22-dihydroapparicine did not show sufficient antimalarial activity (see the Supporting Information). Some compounds may have a slight possibility for use as antimalarial agents ($IC_{50} = 8.98 \sim 10.87\ \mu g\,mL^{-1}$), but our results indicated that all the compounds have a weaker activity than that of chloroquine. The selectivity index (cytotoxicity (IC_{50} for the MRC-5 cell)/antimalarial activity (IC_{50} for the K1 strain)), used to compare the antimalarial activity and cytotoxicity, also indicated that the values of all the compounds are very low, thus showing no selectivity between antimalarial activity and cytotoxicity.

Conclusion

We have achieved the first total synthesis and determined the absolute stereochemistry of naturally occurring (+)-(15*S*,16*R*)-16-hydroxy-16,22-dihydroapparicine (**5**) with the (−)-enantiomer **5** and its diastereomer (±)-**4**. The synthesis involved a novel cascade reaction for the efficient construction of the 1-azabicyclo[4.2.2]decane core, including a pseudo-aminal-type moiety, by using a Staudinger reaction, *N*-allylation, aza-Wittig reaction, and Mannich reaction. In addition, we developed a new method that employed a diastereoselective 1,2-addition of a methylketone by using *N*-TBSOM to protect the indole nucleophile and an intramolecular chirality-transferring Michael reaction with neighboring-group participation. In particular, the latter proved a useful method for the synthesis of the chiral trisubstituted butyrolactone. Some synthetic compounds including (±)-(15*S*,16*R*)-**5** were evaluated for bioactivity against the chloroquine-resistant *Plasmodium falciparum* (K1 strain) malaria parasites; however, none of the compounds showed sufficient antimalarial activity. In fact, a crude extraction, including **5**, had been found to possess potent antimalarial activity in our preliminary screening. It is expected that a minor component in the crude extract from plant *Tabernaemontana dichotoma* may be a desirable candidate as a antimalarial agent.

Acknowledgements

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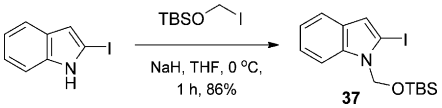

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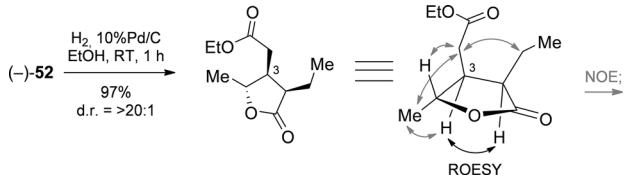

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