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The first total synthesis and reassignment of the relative stereochemistry of 16-hydroxy-16,22-dihydroapparicine

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ABSTRACT

We report the first total synthesis and reassignment of the relative stereochemistry of naturally occurring 16-hydroxy-16,22-dihydroapparicine. Our novel route proceeds by a cascade reaction to efficiently construct a 1-azabicyclo[4.2.2]decane core, along with two stereocenters (C-15 and C-16). The C-16 quaternary carbon was constructed through stereospecific 1,2-addition using an indole nucleophile to an aldehyde or a methylketone. The stereospecific synthesis of two diastereomers of the target product has revealed the true relative stereochemistry of the natural compound.

Plants of the genus *Tabernaemontana* have a widespread distribution and are known to provide alkaloids of intriguing molecular structure and novel biological activity. Apparicine (**1**) was the first monoterpenoid indole alkaloid, initially isolated from *Aspidosperma dasycarpon* more than 45 years ago.[1] It is the main representative of a small group of 5-nor stemmadenine alkaloids of which there are 16 known species (including apparicine (**1**),[1] 16-hydroxy-16,22-dihydroapparicine (**2**),[2] ervaticine (**3**),[3] conolidine (**4**),[4] and isobrafouedine (**5**)[5]) (Fig. 1).

The main structural and defining feature of these alkaloids is the strained 1-azabicyclo[4.2.2]decane skeleton, including a single carbon connection between the indole 3-position and aliphatic

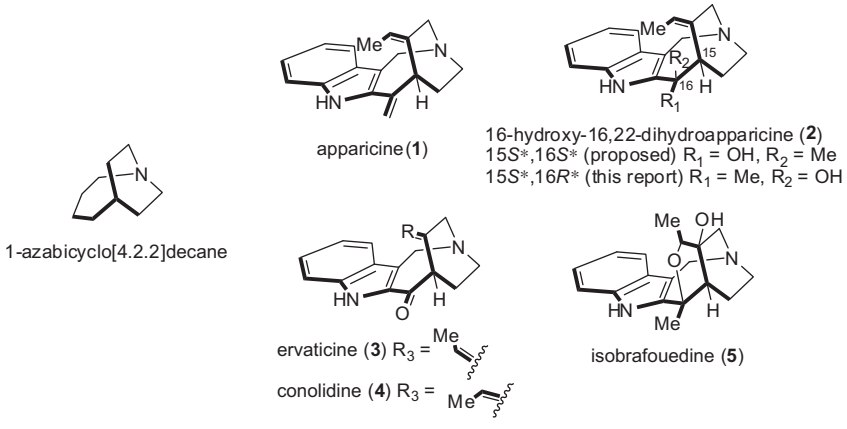

Figure 1. Structure of some 5-nor stemmadenine alkaloids.

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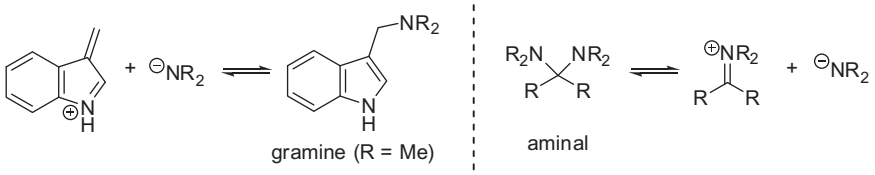


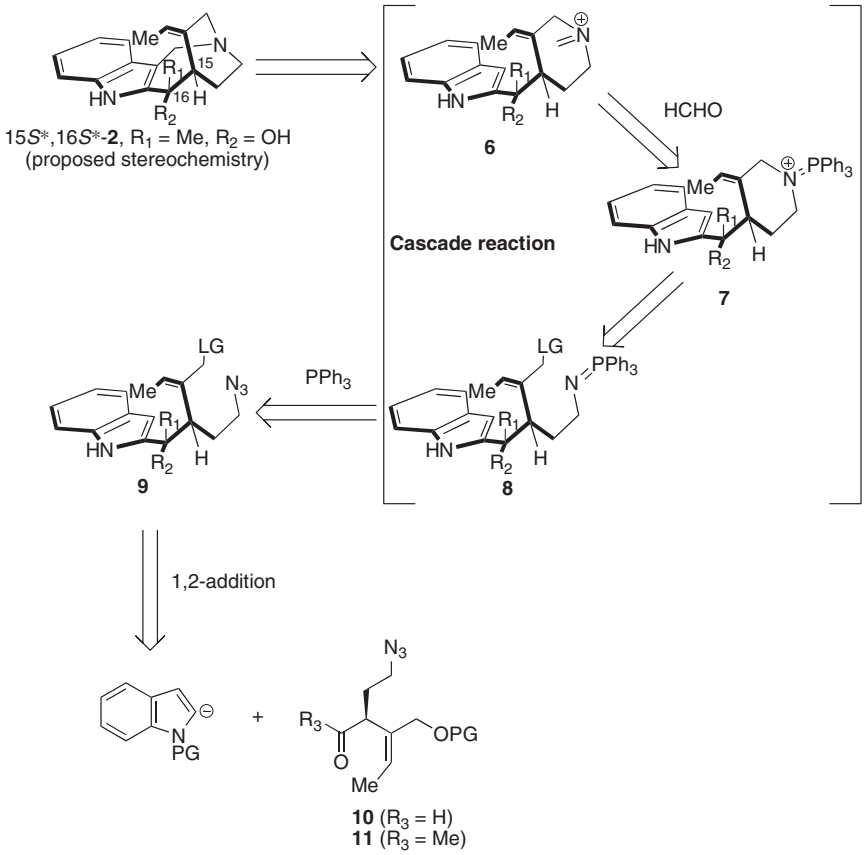
Scheme 1. Gramine as a versatile pseudo-aminal type compound.

nitrogen moiety. The characteristic moiety of the single carbon-aliphatic nitrogen of the 5-nor stemmadenine alkaloids are like gramine (Scheme 1). In gramine, the single carbon-aliphatic nitrogen bond is easily cleaved by retro-Mannich reaction to generate the imine under acidic,[6] basic,[7] or thermic[8] conditions. Therefore, we anticipated that the aminomethyl moiety on 3-position of indole was an indicator of reactivity similar to the aminal.

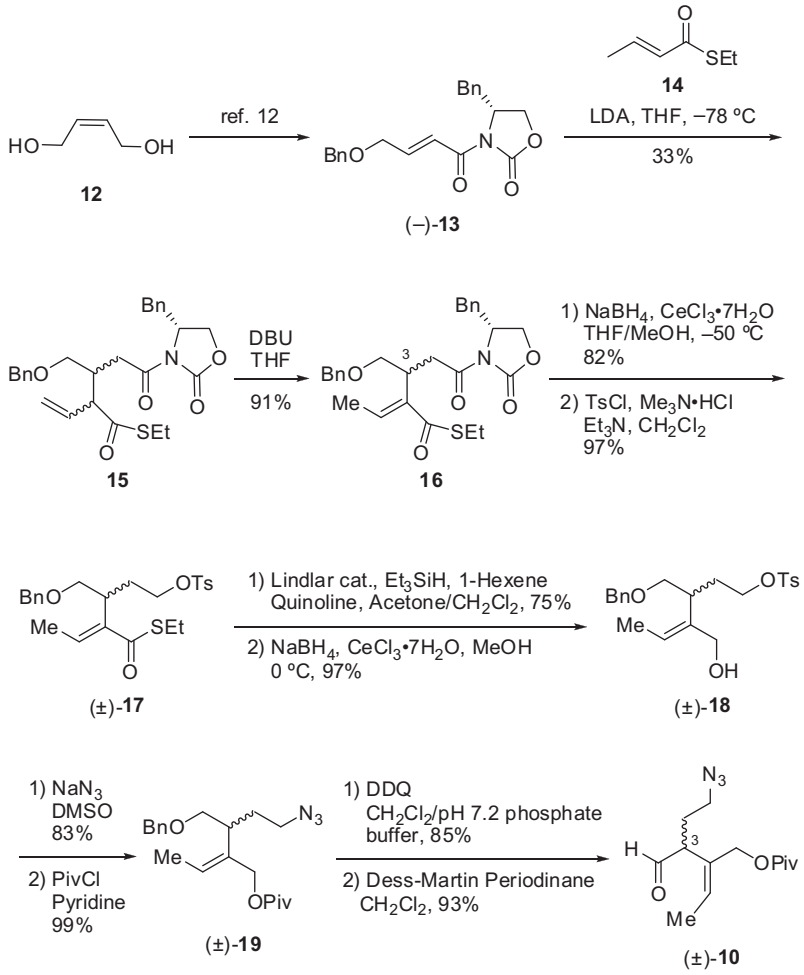
Recently, the total synthesis of simple 5-nor stemmadenine alkaloids were reported by the Bennasar group[9] and the Micalizio group.[10] Herein, we report the total assignment of the configuration of 16-hydroxy-16,22-dihydroapparicine (**2**) identified through the first stereospecific total synthesis of two diastereomers of **2**. 16-Hydroxy-16,22-dihydroapparicine (**2**) was isolated from *Tabernaemontana dichotoma* in 1984.[2] Based on spectral analysis, the relative stereochemistry of **2** was proposed to be a 15*S**,16*S**-configuration. The total synthesis of **2**, has not previously been accomplished to help accurately determine the relative and absolute stereochemistry.

Our synthesis pathway to the 1-azabicyclo[4.2.2]decane skeleton was guided by the hypothesis that pseudo-aminal type alkaloids occur via a biogenetic intermediate. We envisaged the in situ preparation of the iminium cation (**6**), which could be constructed by a cascade reaction (Scheme 2). Given the reactivity of phosphineimine, we designed a novel phosphineimine-mediated cascade reaction, the sequence of which was; (1) Staudinger reaction[11] with triphenylphosphine and an azido group to generate phosphineimine (**8**); (2) compound **8** was converted to aminophosphinium (**7**) by intramolecular N-allylation with an appropriate electrophile; (3) aza-Wittig reaction of **7** with formaldehyde; (4) intramolecular Mannich reaction. Consequently, nucleophilic attack might be performed from the indole 3-position to iminium cation (**6**) (see Scheme 2).

Our synthesis commenced with preparation of the azidoaldehyde (**10**) (Scheme 5). *cis*-Butenediol (**12**) was elaborated to the α,β-unsaturated imide (−)-**13** using the robust four-step procedure described by Martinelli.[12] Subsequently, remote asymmetric Michael reaction of (−)-**13** was attempted to convert the desired β-substituted product (**15**). However, the desired Michael addition product (**15**) appeared in low yield, along with other diastereomers and γ-addition regioisomers of **14** under any extensive conditions. Subsequently, DBU mediated isomerization of **15** afforded the sole *E*-olefin product (**16**) as a 1:1 mixture (of diastereomer at C-3), in a 91% yield. The *E*-olefin product (**16**) was reduced to alcohol in an 82% yield, without further reduction.[13]



Scheme 2. Retrosynthetic analysis of 15*S**,16*S**-**2**.



Scheme 3. Synthesis of azidoaldehyde (±)-**10**.

The alcohol was converted to tosylate (±)-**17** via the process reported by Tanabe and co-workers.[14] Subsequently, α,β-unsaturated thioester was transformed to the allyl alcohol (±)-**18**. The Fukuyama reduction caused high chemoselectivity, causing the thioester group to be converted to the conjugated aldehyde[15] which was then converted to the desired allyl alcohol (±)-**18** under Luche condition[12] in a 97% yield. Furthermore, azidation of (±)-**18**, followed by protection of the hydroxy group, afforded the allyl pivalate (±)-**19** in excellent yield. In the next step, the benzyl group was removed from (±)-**19** under oxidative deprotection using DDQ, as reported by Ikemoto and Schreiber.[16] The obtained alcohol was oxidized to azidoaldehyde (±)-**10** using Dess–Martin periodinane[17] in a 93% yield (Scheme 3).

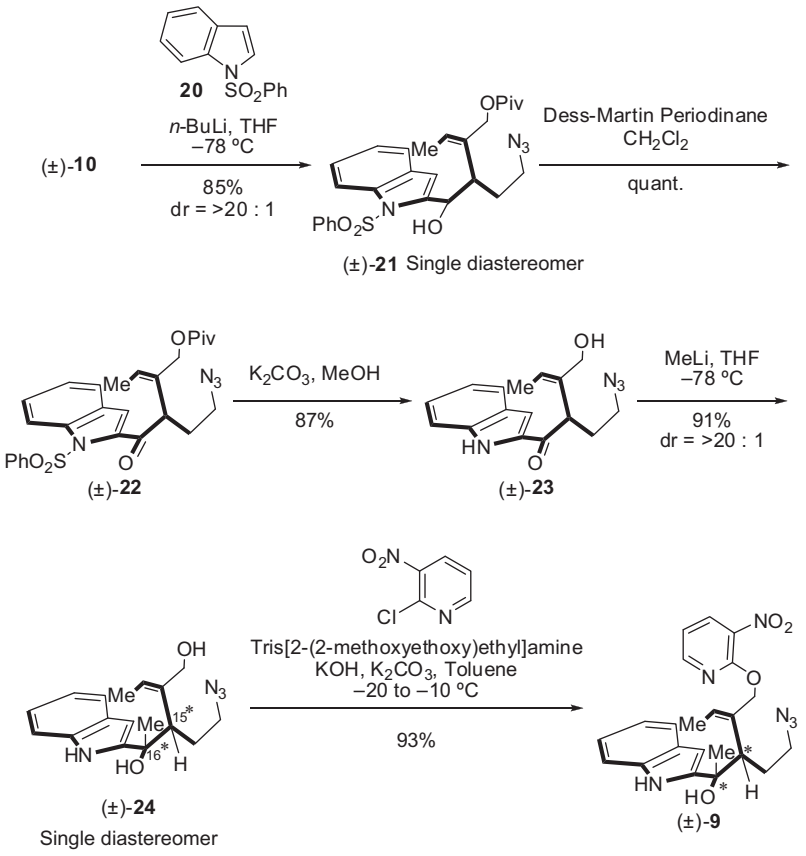
With the azidoaldehyde (±)-**10** in hand, 1,2-addition of the indole nucleophile (**20**), protected by phenylsulfone,[18] provided the hydroxyindole (±)-**21** (as a single diastereomer) in an 85% yield. Dess–Martin oxidation[17] of (±)-**21** was performed to give the ketoindole (±)-**22**, following removal of the phenylsulfone and pivaloyl groups under basic solvolysis, which was converted to the hydroxyketoindole (±)-**23** in an 87% yield.

Subsequently, diastereoselective methylation of (±)-**23** was converted to dihydroxyindole (±)-**24** as a single diastereomer in excellent yield. The C-16 stereocenter of (±)-**24** was not confirmed at this point. Preparation of full carbon and nitrogen skeletons was completed and introduction of a suitable leaving group on the primary alcohol to attempt the cascade reaction was all that was now required. After many attempts to find a suitable leaving group, we finally opted for a 3-nitropyridyl group,[19] and prepared (±)-**9** in a 93% yield under Ballesteros's condition[20] (Scheme 4).

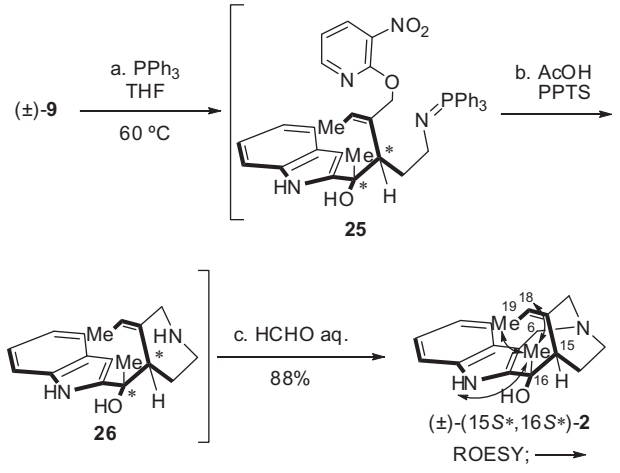
In the final stage, we attempted a cascade reaction for construction of the 1-azabicyclo[4.2.2]decane skeleton, including the pseudo-aminal type moiety. Thus, (±)-**9** was treated with PPh_3 at 60 °C. Subsequently, the reaction mixture was acidified using AcOH for activation of the 3-nitropyridyl group. Finally, formaldehyde and PPTS were added to the reaction mixture, and synthesis of (±)-**2** was completed in an 88% yield (Scheme 5).

However, the spectral data of synthetic (±)-**2** did not agree with that of natural **2**.[2] In particular, ROESY analysis of synthetic (±)-**2**, showed a relationship between H-18 or H-19 and 16-Me. Thus the relative stereochemistry of synthetic (±)-**2** was determined to be a 15*S**,16*S**-configuration, which was the configuration proposed by Verpoorte's group.[2] As a result, the C-16 stereocenter outcome reflected the Felkin–Anh transition state. Comparison of ^1H and ^{13}C NMR indicated 16-Me and H-6a,b proton difference (as shown in the Supplementary data). Furthermore, the ^{13}C signals of the piperidine ring were greatly shifted from those seen in naturally occurring **2**. Therefore, we expected that the 16-Me group in natural **2** was on the opposite face of the trisubstituted *exo*-cyclicolefin. Thus, the relative stereochemistry was anticipated to be the 15*S**,16*R**-configuration. To confirm this, we turned our attention to completing the synthesis of 15*S**,16*R**-isomer **33** with methylketone (**27**).

Construction of the stereocenter of 16*R** of C-16 position was adapted to our 1,2-addition procedure through the Felkin–Anh



Scheme 4. Synthesis of the cascade reaction precursor (±)-**9**.



Scheme 5. Total synthesis of (±)-(15*S**,16*S**)-16-hydroxy-16,22-dihydroapparicine (**2**).

transition state (Scheme 6). The methylketone was prepared from the aldehyde (±)-**10** by the addition of methyl anion, plus subsequent oxidation using Dess–Martin periodinane, in good yields. Access to the isomer, 16*R**-**33** was obtained by applying an identical reaction sequence with an improvement for 1,2-addition by the use of SEM protected indole nucleophile,[21] similar to that used for the preparation of 16*S**-**2** from methylketone (±)-**27**. Actually, 1,2-addition of $PhSO_2$-protected indole (**20**) to (±)-**27** not only produced the 1,2-adduct product in a 20% yield, but also the deprotection of $PhSO_2$ group could not proceed under any conditions without decomposition of the substrate. Characterization data provided for synthetic (±)-(15*S**,16*R**)-**33** were fully consistent with the data for the natural compound reported by Verpoorte's group.[2] In addition, NOE relationship was observed between H-14a and H-22 (i.e., 16-Me). As the result, the relative stereochemistry of C15 and C16 was determined to be the 15*S**,16*R**-configuration. Furthermore, we also analyzed (±)-(15*S**,16*S**)-**1**, (±)-(15*S**,16*R**)-**33** and natural product via HPLC. Both diastereomer **1** and **33** were separated, and the natural product was identical to synthetic **33**.

In conclusion, we have achieved the first total synthesis of 16-hydroxy-16,22-dihydroapparicine and determined the true relative stereochemistry of the naturally occurring compound (±)-(15*S**,16*R**)-16-hydroxy-16,22-dihydroapparicine (**33**). Synthesis involved a novel cascade reaction allowing efficient construction of the 1-azabicyclo[4.2.2]decane, including a pseudo-aminal type moiety, plus a Staudinger reaction, N-allylation, aza-Wittig reaction and Mannich reaction. In addition, we developed a novel method employing diastereoselective 1,2-addition of aldehyde or methylketone using N-protected indole-nucleophiles. Further detailed study of the cascade reaction mechanism and development of asymmetric total synthesis is in progress, and the results of these and related investigations will be reported in due course.

Acknowledgments

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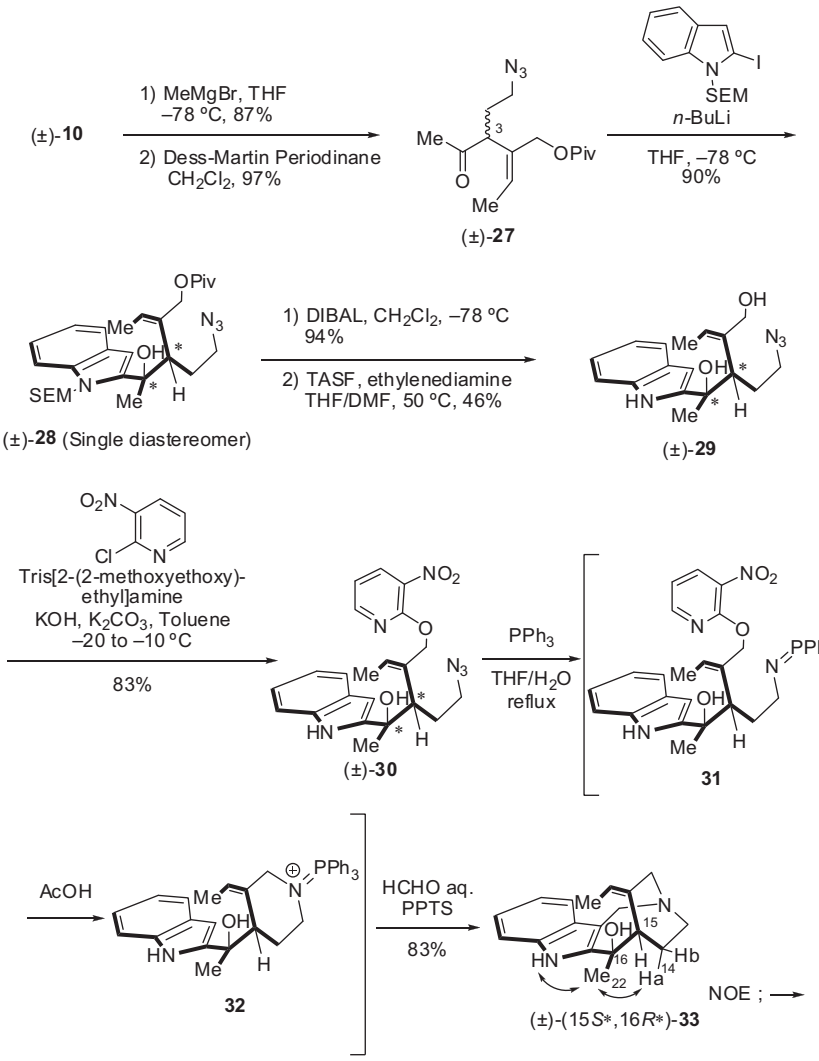

Scheme 6. Total synthesis of (±)-(15*S**,16*R**)-isomer (**33**).

of Pharmacy, Kitasato University) for various instrumental analyses. We are grateful to Dr. Kam for providing the authentic sample of 16-hydroxy-16,22-dihydroapparicine.

Supplementary data

Supplementary data (representative experimental procedure and characterization data of compound ((±)-15*S**,16*S**-**1** and (±)-15*S**,16*R**-**33**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.110.

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