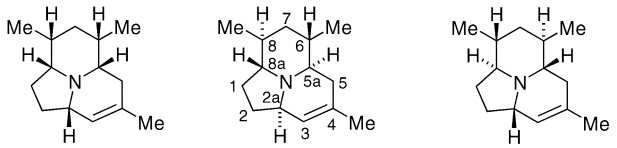


1 **2** **3**

Figure 1. Original (**1**) and revised (**2**) structures of alkaloid 205 B, and the structure of its antipode, **3**.

Alkaloid Total Synthesis

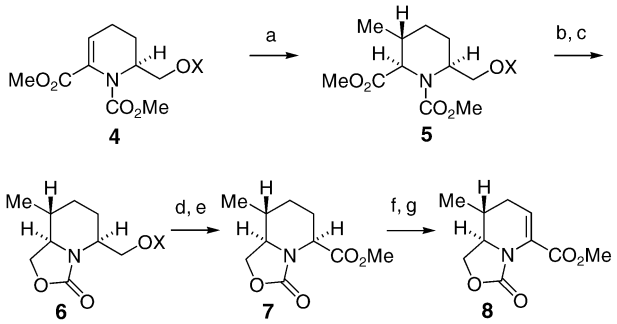
Total Synthesis of the Antipode of Alkaloid 205 B**

Naoki Toyooka, Ayako Fukutome, Hiroyuki Shinoda, and Hideo Nemoto**

A remarkably diverse array of biologically active alkaloids, for example, blockers of neuromuscular-type, ganglionic-type, and nicotinic receptor channels, occurs in amphibian skin, and over 500 alkaloids have been isolated to date.[1] The structural diversity and pharmacological activity associated with these alkaloids have stimulated research in numerous synthetic groups.[2] Alkaloid 205 B, one of the compounds isolated from skin extracts of the Panamanian frog *Dendrobates pumilio*, possesses an unusual and unique 8b-azaacenaphthylene ring system (Figure 1). The structure of alkaloid 205 B was first reported to be **1**,[3] and recently revised to be **2** based upon FTIR, NMR, and MS data.[4] This alkaloid contains five asymmetric centers in its compact, fourteen-carbon-atom frame; however, no synthesis of this unique alkaloid has been reported, and its absolute stereochemistry is still unknown.

As part of a program directed at studying the synthesis of biologically active alkaloids,[5] we report here the first total synthesis of **3** (see Figure 1), the antipode of natural 205 B, and the determination of the absolute stereochemistry of natural 205 B.

The synthesis began with enaminoester **4**,[6] which was treated with lithium dimethylcuprate to give adduct **5** as a single isomer (Scheme 1).[7] The oxazolizinone ring was constructed in a two-step sequence to provide **6**, which was transformed into the desired cyclic carbamate **8** via ester **7** by using the protocol developed by Matsumura et al.[8]



4 **5** **6** **7** **8**

Scheme 1. Synthesis of enaminoester **8**. Reagents and conditions: a) $(Me)_2CuLi$, Et_2O, −78 to −30 °C (98 %); b) Lithium triethylborohydride, THF, 0 °C (92 %); c) NaH, THF, 0 °C (99 %); d) TBAF, THF, 0 °C–RT (99 %); e) 1. Swern oxidation, −78 °C to 0 °C, 2. $NaClO_2$, NaH_2PO_4, *t*BuOH/H_2O, 3. CH_2N_2, EtOAc (86 % over 3 steps); f) LiHMDS, PhSSPh, THF, −78–0 °C (99 %); g) *m*CPBA, 2,6-lutidine, CH_2Cl_2, RT (85 %). LiHMDS = lithium bis(trimethylsilyl)amide, *m*CPBA = *meta*-chloroperbenzoic acid, RT = room temperature, TBAF = tetrabutylammonium fluoride, X = *tert*-butyldiphenylsilyl.

The second and key Michael reaction of **8** with in situ generated lithium dimethylcuprate proceeded smoothly to afford adduct **9**, again as a single isomer (Scheme 2). The stereochemistry of **9** was confirmed by the NOE interactions indicated. The observed stereoselectivity of the Michael reaction of **8** can be explained by the stereoelectronic effect[9] illustrated in Figure 2.

An Arndt–Eistert sequence was used for carbon-chain extension of **9** to give the homologated ester **10**, which was transformed into ketone **11** by reaction with Weinreb's amide (Scheme 3).[10] Acid-catalyzed protection of the carbonyl group in **11** with ethylene glycol followed by hydrolysis of the oxazolidinone ring with base and protection of the

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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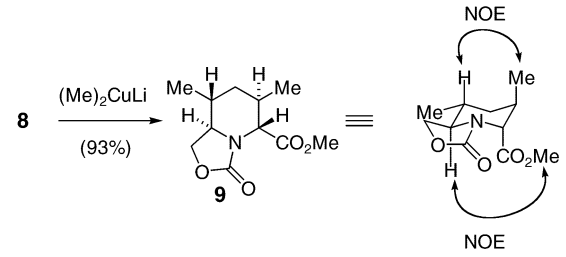


Scheme 2. Synthesis of tetrasubstituted piperidine **9**.

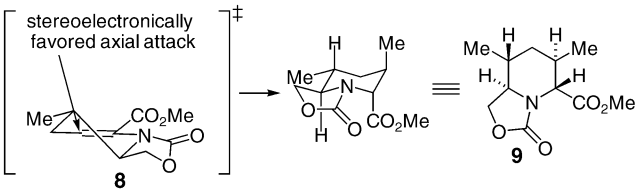
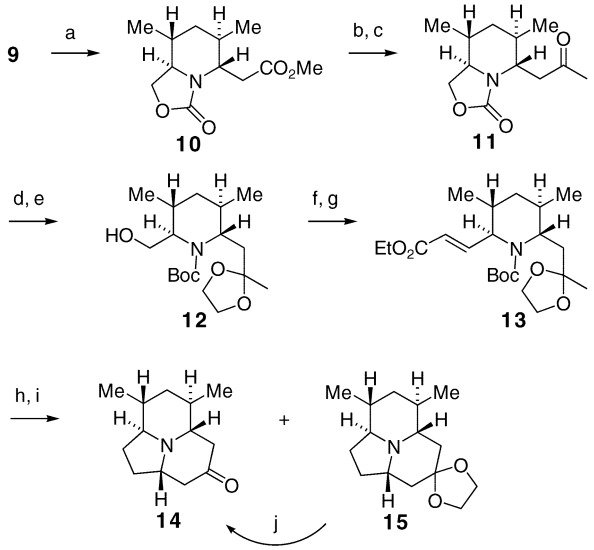


Figure 2. Stereochemical course of the Michael reaction of the enaminoester **8**.



Scheme 3. Synthesis of compound **14** with the tricyclic core. Reagents and conditions: a) 1. LiOH, $MeOH/H_2O$, reflux, 2. $ClCO_2Et$, Et_3N, THF, 0 °C, 3. CH_2N_2, Et_2O, 4. $PhCO_2Ag$, Et_3N, MeOH, RT (71 % over 4 steps); b) 1. LiOH, $MeOH/H_2O$, reflux, 2. 1,1′-carbonyldiimidazole, THF, RT, 3. Et_3N, (MeO)MeNH·HCl, THF, RT (98 % over 2 steps); c) MeMgBr, THF, 0 °C to RT (73 %); d) ethylene glycol, *p*TsOH, benzene, reflux (86 %); e) 1. 2 M KOH in *i*PrOH, 120 °C in a sealed tube, 2. Boc_2O, NaOH, dioxane/H_2O (74 % over 2 steps); f) Swern oxidation, −78 °C to 0 °C; g) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF (74 % over 2 steps); h) 1. 10 % Pd/C, H_2, EtOAc, 2. DIBAL, CH_2Cl_2, −78 °C; i) *p*TsOH, benzene/acetone, reflux (**14**; 62 %, **15**; 15 % over 3 steps); j) *p*TsOH, acetone, reflux (80 %). Boc = *tert*-butoxycarbonyl, DIBAL = diisobutylaluminum hydride, *p*TsOH = *para*-toluenesulfonic acid.

resulting amine with Boc_2O provided alcohol **12** in 74 % overall yield. Swern oxidation of **12** and Wittig–Horner reaction of the resulting aldehyde afforded the α,β-unsaturated ester **13**. Hydrogenation of **13** and reduction of the resulting ester with DIBAL followed by treatment with *p*TsOH in refluxing benzene/acetone provided the key tricyclic compound **14** in 62 % overall yield along with acetal **15** (15 %), which was transformed into **14** by treatment with acid.

The stereochemistry at the newly formed position in **14** was confirmed by the NOE (2 %) between H_{2a} and H_{5a}, and the stereoselectivity of the acid-catalyzed intramolecular Mannich-type cyclization is rationalized as depicted in Figure 3.

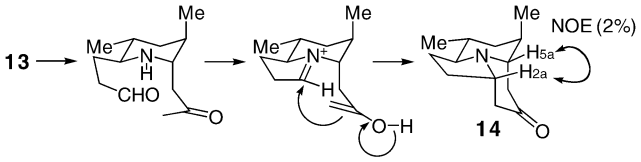
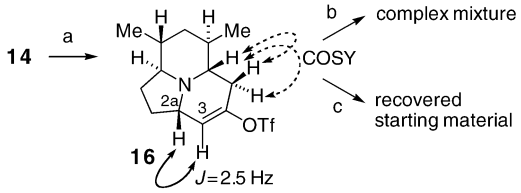


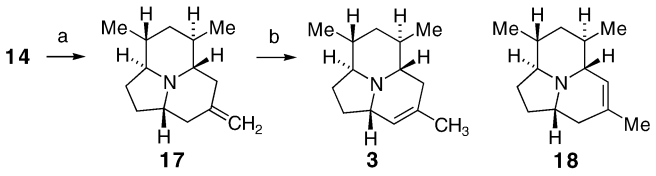
Figure 3. Stereochemical course of intramolecular Mannich-type cyclization reaction of **13** and the stereochemistry of **14**.

With the requisite tricyclic core **14** in hand, we next focused our attention on the final step for the completion of total synthesis of alkaloid 205B. First we examined the formation of the alkene unit by using triflate **16**. Thus treatment of **14** with chiral lithium amide base followed by Comins's triflating agent[11] provided triflate **16** in 54 % yield (Scheme 4). The structure of **16** was confirmed by the H,H COSY experiment and the coupling constant between H_{2a} and H_3. The cross-coupling reaction of **16** with trimethylaluminium in the presence of catalytic amounts of $[Pd(Ph_3P)_4]$[12] afforded a complex mixture and no desired compound was isolated. The coupling reaction with lithium dimethylcuprate[13] resulted in the complete recovery of starting material.



Scheme 4. Attempted synthesis of **3** via triflate **16**. Reagents and conditions: a) 1. *R*-(*R**,*R**)-(+)-bis(α-methylbenzyl)amine, *n*BuLi, THF, 2. [*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (Comins's reagent), −78 to −40 °C (54 %); b) $[Pd(Ph_3P)_4]$, Me_3Al, $ClCH_2CH_2Cl$, 70 °C; c) $(Me)_2CuLi$, THF, 0 °C.

Thus, we were forced to introduce the C–C double bond by using the *exo*-alkene **17**. Wittig reaction of **14** afforded **17** in good yield (Scheme 5). Brief calculations (B3LYP method in Gaussian98, 6-31 + G** basis set) revealed that the desired isomer **3** is lower in energy than the other isomer **18**.[14] Thus, the acid-catalyzed isomerization of **17** provided the isomeric products in a ratio of 6.5:1 (from crude NMR), and the major isomer **3** was isolated in 63 % yield. The spectroscopic data (^1H and ^{13}C NMR, IR, MS) of **3** ($[\alpha]_D^{26} = +8.1$) were identical with those of the natural product ($[\alpha]_D = -8.5$), and the absolute stereochemistry was determined unambiguously to be 2a*R*,5a*R*,6*S*,8*S*,8a*R* by comparison of the optical rotations.



Scheme 5. Completion of the total synthesis of **3**. Reagents and conditions: a) $MeP^{+}Ph_3I^{-}$, *n*BuLi, THF, 0 °C to RT (84 %); b) *p*TsOH, benzene, reflux (63 %).

In summary, we have demonstrated the first enantioselective total synthesis of the antipode **3** of the structurally unique alkaloid 205B. The key step in this synthesis is the stereocontrolled Micheal-type conjugate addition reaction of the enaminoester **8** to form the 2,3,5,6-tetrasubstituted piperidine ring system in **9**. Furthermore, we determined the absolute stereochemistry of the natural product to be 2a*R*,5a*R*,6*S*,8*S*,8a*R*.

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Keywords: alkaloids · Michael addition · natural products · nitrogen heterocycles · stereoelectronic effects

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