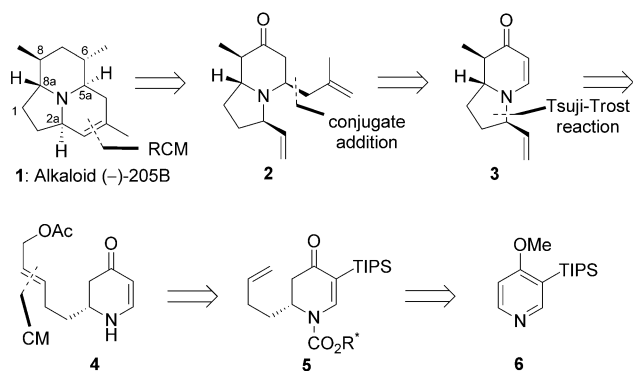


Concise Total Synthesis of the Frog Alkaloid (–)-205B

Sergey V. Tsukanov and Daniel L. Comins*

Tricyclic alkaloid (–)-205B (**1**, Scheme 1) was isolated by Daly and co-workers in 1987 from the skin of the neotropical poisonous frog *Dendrobates*, and its structure was elucidated



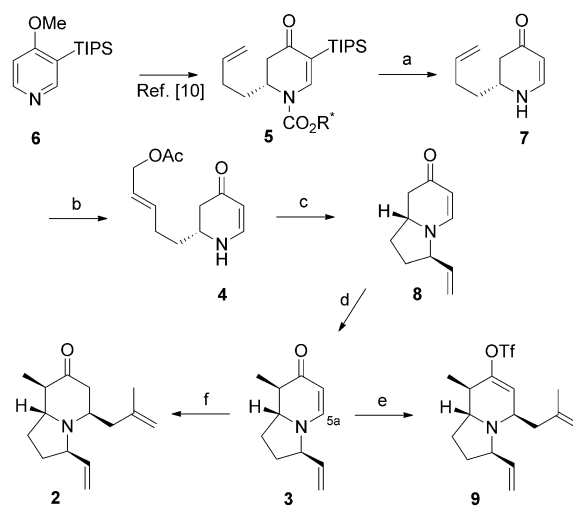
Scheme 1. Retrosynthetic analysis of (–)-205B (**1**). R* = (–)-*trans*-2-(α -cumyl)cyclohexanol (TCC). TIPS = triisopropylsilyl.

a year later by the same group.^[1] Biological studies revealed that the enantiomer of the alkaloid displays selective activity for the inhibition of the α 7-nicotinic acetylcholine receptor, which has been shown to be implicated in several neurological diseases.^[2] From a structural standpoint, with an 8b-azaace-nonaphthylene ring system, (–)-205B has a more complex architecture than most indolizidine alkaloids.^[3,4] In 2003, Toyooka et al. reported the first total synthesis of **1** in 30 steps starting from the known (*S*)-6-(*tert*-butyldiphenylsiloxy-methyl)-piperidin-2-one.^[5] In their synthesis, two stereocontrolled conjugate additions served to elaborate the 2,3,5,6-tetrasubstituted piperidine ring system and introduce four of the five stereocenters in the molecule. The second total synthesis of the natural product required 19 steps and was achieved in 2005 by Smith and Kim, who employed a three-component linchpin union of silyl dithianes for the straightforward construction of the indolizidine portion of the molecule.^[6] With four stereocenters in the piperidine ring, (–)-205B was an attractive target for expanding the scope of dihydropyridone reactions developed by our group.^[7,8] Herein, we report a concise and highly stereocontrolled asymmetric synthesis of (–)-205B.

Our retrosynthetic analysis of (–)-205B is outlined in Scheme 1. We envisioned that a ring-closing metathesis

(RCM) disconnection of the alkene functional group would drastically simplify the molecule to the highly substituted indolizidine core **2**. It was anticipated that the 5a-methallyl and 6-methyl groups could be introduced through consecutive conjugate addition and enolate alkylation. We were intrigued by the possibility that the key pyrrolidine ring could be accessed stereoselectively by an intramolecular Tsuji–Trost reaction.^[9] Furthermore, from previous experience it was expected that 6-substituted piperidone **4** could be obtained from 4-methoxy-3-(triisopropylsilyl)pyridine by exploiting the asymmetric *N*-acylpyridinium salt and cross-metathesis (CM) reactions.

The synthesis commenced with deprotection of known compound **5**,^[10] prepared in one step from 4-methoxy-3-(triisopropylsilyl)pyridine, to give enantiopure dihydropyridone **7** in 81 % yield (Scheme 2).^[11] Cross-metathesis of **7** with (*Z*)-but-2-ene-1,4-diyl diacetate using the Grubbs–Hoveyda second-generation catalyst provided **4** in a good yield.^[12] With these results in hand, we turned our attention to the critical intramolecular Tsuji–Trost allylic amination. To our knowledge, use of a vinylogous amide as a nitrogen nucleophile in metal-mediated allylic amination has not been previously reported. Initial attempts to perform the reaction with [Pd₂(dba)₃]·CHCl₃ and Bu₃P were encouraging, and generated the desired product but as a mixture of two diastereo-



Scheme 2. Synthesis of intermediate **2**. a) MeONa/MeOH, reflux (81 %); b) (*Z*)-but-2-ene-1,4-diyl acetate, Grubbs–Hoveyda 2nd-generation cat., CH₂Cl₂, reflux (88 %); c) [Pd₂(dba)₃]·CHCl₃, P(*t*Bu)₃, Cs₂CO₃, 1,4-dioxane, 75 °C (80 %); d) LDA, THF, –78 °C; MeI, –78 to 0 °C; LDA, –78 °C (82 %, one pot); e) methallyltributylstannane, Tf₂O, CH₂Cl₂, –78 °C (65 %); f) methallyltributylstannane, TFAA, CH₂Cl₂, –50 to 0 °C (69 %). dba = dibenzylideneacetone, LDA = lithium diisopropylamide, Tf = trifluoromethanesulfonyl, TFAA = trifluoroacetic anhydride, THF = tetrahydrofuran.

[*] S. V. Tsukanov, Prof. Dr. D. L. Comins
Department of Chemistry, North Carolina State University
2620 Yarbrough Drive, Raleigh, NC 27695-8204 (USA)
E-mail: daniel_comins@ncsu.edu

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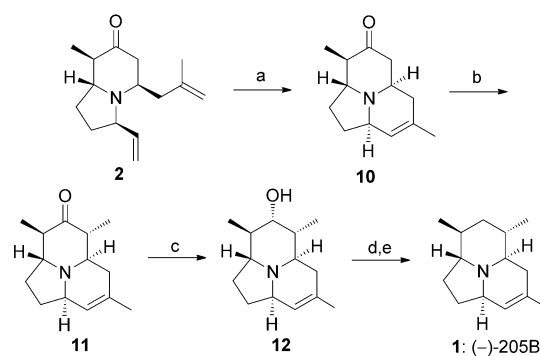
mers (1:1.5). The use of the mild base Cs_2CO_3 appeared to be critical for achieving success in this transformation, as replacement with a stronger base led to significant decomposition. After screening several ligands and sources of palladium, it was found that the sterically encumbered $t\text{Bu}_3\text{P}$ ligand promotes the transformation and gives the desired diastereomer **8** in more than 95 % *de* and 80 % yield.

With a reliable route to the indolizidine intermediate, our efforts were concentrated on the introduction of the C5-methyl group. Our initial plan was to perform a simple methylation of the enolate right after the *N*-acylpyridinium salt reaction. It is common knowledge that an *N*-acyl group in a dihydropyridone generates 1,3-allylic strain, which forces the C6-substituent to occupy the axial position, thus allowing the establishment of a C5 stereocenter with high levels of selectivity through opposite-side axial attack.^[13] Installing the methyl group by enolate alkylation of **5** proved problematic probably owing to the combination of the steric hindrance of both the TCC carbamate and 3-TIPS groups. This prompted us to investigate an alternative route, which incorporates the C5-methyl group at a later stage. The methylation of **8** was carried out using LDA as the base, which resulted in a 3:1 mixture of diastereomers. Gratifyingly, we were able to epimerize the undesired axial diastereomer to the desired isomer **3** through a one-pot process by addition of an extra equivalent of LDA to the reaction mixture.

At this stage, a methyl group needed to be introduced stereoselectively at the 5 α -position. After extensive studies, in which a variety of different reagents including Grignard reagents, cuprates, allylstannane, and allylsilane were examined, we failed to find reaction conditions giving both satisfactory yields and diastereoselectivity. Finally, treatment of vinylogous amide **3** with triflic anhydride at -78°C in the presence of methyltributylstannane furnished vinyl triflate **9** as an exclusive diastereomer in 65 % yield.^[14] The structure of **9** was confirmed unambiguously through multiple NOE correlations. Unable to hydrolyze the triflate, we modified the original reaction conditions by simply substituting trifluoroacetic anhydride for triflic anhydride. To our delight, the reaction proceeded efficiently at a higher temperature to give the intermediate trifluoroacetate, which was easily converted into the desired ketone **2** upon work-up with aqueous sodium bicarbonate. The high levels of stereocontrol in this and the triflic anhydride reaction can presumably be attributed to axial attack from the less-hindered convex face of the generated iminium ion.

The ring-closing metathesis of **2** was conducted with 5 % Grubbs second-generation catalyst at 55°C in *tert*-butyl-methyl ether to afford tricyclic product **10** (Scheme 3).^[15] Axial methylation at C6 was readily accomplished by deprotonation with NaHMDS in THF at -78°C and the addition of MeI to furnish **11** with complete stereocontrol.

Having established all five stereocenters in the molecule in eight steps from **6**, the only remaining transformation was the reductive cleavage of the ketone carbonyl group. Unfortunately, all conventional methods including hydrazone or mesylate reductions, standard Barton–McCombie protocols, and dithiolane formation/reduction were unsuccessful. The presence of two neighboring tertiary centers made the



Scheme 3. Completion of the synthesis of (–)-205B. a) Grubbs 2nd-generation cat., $t\text{BuOMe}$, 55°C (76%); b) NaHMDS, THF, HMPA -78°C ; MeI, -78 to 0°C (82%); c) Li, NH_3/THF , isoamyl alcohol, -78°C (83%); d) TCDI, DMAP, CH_2Cl_2 , reflux (82%); e) AIBN, Bu_3SnH , PhSeSePh , benzene, reflux, (60%). AIBN = 2,2'-azobisisobutyronitrile, DMAP = 4-(dimethylamino)pyridine, HMDS = hexamethyldisilazide, HMPA = hexamethylphosphoramide, TCDI = 1,1'-thiocarbonyl-diimidazole.

ketone group quite unreactive toward various addition/substitution reactions. Also the alcohol and derivatives resulting from the ketone reduction were extremely prone to elimination and formation of a trisubstituted double bond. Ultimately, it was found that conversion of the ketone group into a methylene could be accomplished through a three-step protocol. Ketone **11** was reduced cleanly to the equatorial alcohol **12**, in good yield using lithium in liquid ammonia.^[16] Alcohol **12** was converted into the thiocarbamate by reaction with thiocarbonyl diimidazole and DMAP, and then subjected to a stannane-mediated radical reduction with the addition of 20 mol % of diphenyl diselenide, a method developed by Crich and Yao.^[17] The presence of in situ generated PhSeH results in a significant increase in the rate of the radical trapping, thereby suppressing decomposition of the unstable secondary radical and allowing the formation of (–)-205B in 60 % yield.

In summary, a highly stereoselective, protecting-group-free synthesis of (–)-205B was accomplished in 11 steps from pyridine **6** (8 % overall yield). This synthesis uses a direct and short route to the natural product by employing an asymmetric *N*-acylpyridinium reaction to set the first stereocenter and a novel Tsuji–Trost allylic amination of vinylogous amide **4** for the critical stereoselective formation of the key pyrrolidine ring.

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