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Total Synthesis of the Neotropical Poison-Frog Alkaloid (−)-205B

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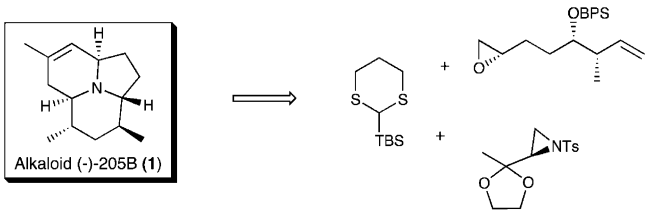
ABSTRACT



A stereocontrolled total synthesis of the neotropical poison-frog alkaloid (−)-205B (1) has been achieved, employing a dithiane three-component linchpin coupling, a one-pot sequential construction of the embedded indolizidine ring, and ring-closing metathesis (RCM) to arrive at the novel 8b-azaacenaphthylene ring system comprising the alkaloid. The synthesis proceeded with a longest linear sequence of 19 steps, affording (−)-1 in 5.6% overall yield.

For nearly forty years the Daly Laboratory at the National Institutes of Health has provided the biomedical community with an almost bewildering array of architecturally diverse alkaloids, isolated from the skin of neotropical poison-frogs; examples include the steroidal batrachotoxins, the histrionicotoxins, the gephyrotoxins, and the pumiliotoxins.[1] One such extract from the Panamanian frog *Dendrobated pumilo* yielded alkaloid (−)-205B (**1**), possessing the unusual 8b-azaacenaphthylene ring system.[2] The structure, provisionally reported in 1987,[2a] was assigned by Daly et al. in 1998, based on an extensive series of FTIR, NMR, and HRMS studies, in conjunction with molecular modeling, to comprise (−)-**1**.[2b] The absolute stereochemistry was subsequently reported in 2003 by Toyooka et al. based on their total synthesis of the unnatural (+)-antipode.[3a] The central feature of the Toyooka synthesis entailed a series of Michael-type additions to enaminoesters; the longest linear sequence required 30 steps from known (*S*)-6-(*tert*-butyldiphenylsilyloxymethyl)-piperidin-2-one.[3b] Although biological studies of the naturally occurring alkaloid have not as yet been reported, due presumably to lack of material, the unnatural (+)-antipode was recently reported to block selectively the α7 nicotinic receptor.[4]

Intrigued both by the architecture of alkaloid (−)-205B (**1**) and the opportunity to provide material for biological evaluation, we recently initiated a program to construct (−)-**1**, as well as a small family of congeners. In this paper, we report completion of the initial phase of this program: the first total synthesis of the natural (−)-antipode of alkaloid 205B (**1**).

Our synthetic strategy calls upon our recently successful three-component linchpin construction of the indolizidine ring system (Scheme 1),[5] employing an *N*-Ts aziridine as

(1) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspective*; Pelletier, S. W., Ed.; Pergamon: New York, 1999; Vol. 13, p 1.

(2) (a) Tokuyama, T.; Nishimori, N.; Shimada, A.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1987**, *43*, 643. (b) Tokuyama, T.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *An. Asoc. Quim. Argent.* **1998**, *86*, 291.

(3) (a) Toyooka, N.; Fukutome, A.; Shinoda, H.; Nemoto, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 3808. (b) Toyooka, N.; Fukutome, A.; Shinoda, H.; Nemoto, H. *Tetrahedron* **2004**, *60*, 6197. The known piperidone was prepared in five steps and 35% overall yield from 4-methoxyphenylmethylhex-5-enoate; see: Hodgkinson, T. J.; Shipman, M. *Synthesis* **1998**, 1141.

(4) Tsuneki, H.; You, Y.; Toyooka, N.; Kagawa, S.; Kobayashi, S.; Sasaoka, T.; Nemoto, H.; Kimura, I.; Dani, J. A. *Mol. Pharmacol.* **2004**, *66*, 1061.

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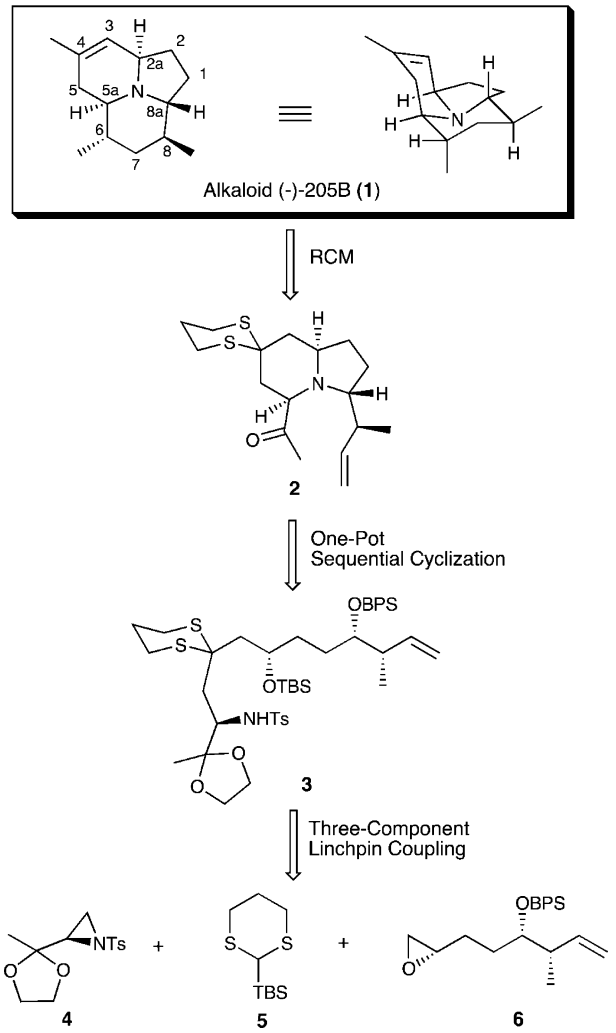
Scheme 1

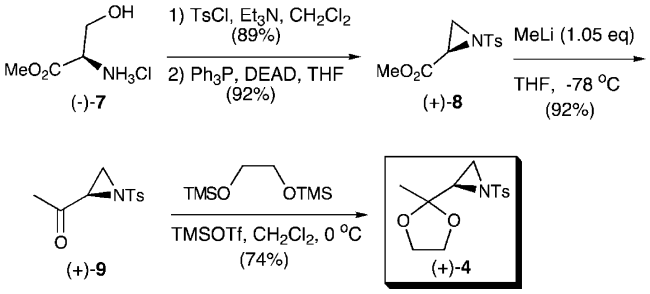


the second electrophile, followed by a one-pot sequential cyclization to complete elaboration of the indolizidine ring encased within the 8b-azaacenaphthylene ring. Ring-closing metathesis (RCM) of the derived kinetic silyl enol ether would then afford the 205B azaacenaphthylene skeleton. Assuming success, this synthetic scenario would also hold the promise of numerous readily available synthetic congeners, requiring only alternation of the structure and/or configuration of the epoxide and aziridine coupling partners.

An additional site for structural diversity of the azaacenaphthylene skeleton in the C(4) carbonyl would be available after RCM and removal of the dithiane.

We initiated the synthesis of alkaloid (−)-205B (**1**) with construction of aziridine **4** (Scheme 2). Tosylation of the nitrogen of commercially available serine methyl ester hydrochloride (−)-**7**, followed by Mitsunobu ring closure, furnished aziridine (+)-**8**,[6] which upon treatment with MeLi

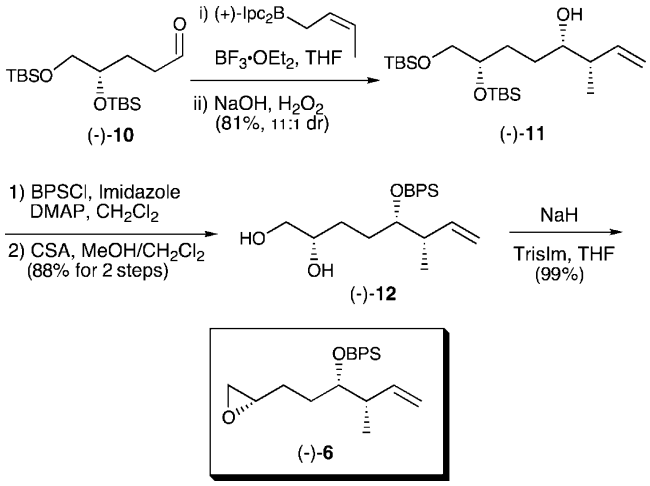
Scheme 2



(1.05 equiv) at −78 °C led to ketone (+)-**9** in excellent yield (92%). Protection of the carbonyl as the ethylene ketal employing the Noyori conditions[7] then furnished (+)-**4**.

For epoxide **6** (Scheme 3), Brown asymmetric crotylation[8] of known aldehyde (−)-**10**[9] led to alcohol (−)-**11** both in good yield and with excellent diastereoselectivity (ca. 11:1). Protection of the resulting secondary alcohol, followed by removal of the TBS groups next afforded diol (−)-**12**. Completion of (−)-**6** was achieved via a one-flask Fraser-Reid epoxide protocol.[10] The overall yield for the four-step sequence was 65%.

Scheme 3



With ample quantities of aziridine (+)-**4** and epoxide (−)-**6** in hand, we executed the multicomponent linchpin coupling (Scheme 4). Pleasingly, lithiation of **5** in Et_2O, followed in turn by addition of epoxide (−)-**6**, warming the reaction mixture to −20 °C over 0.5 h, stirring for an additional 1.5 h at −20 °C, and then addition of aziridine (+)-**4** in THF

(5) (a) Smith, A. B., III; Kim, D.-S. *Org. Lett*. **2004**, *6*, 1493. (b) Smith, A. B., III; Pitram, S. M.; Boldi, A. M.; Gaunt, M. J.; Sfouggatakis, C.; Moser, W. H. *J. Am. Chem. Soc*. **2003**, *125*, 14435. (c) Smith, A. B., III; Boldi, A. M. *J. Am. Chem. Soc*. **1997**, *119*, 6925.

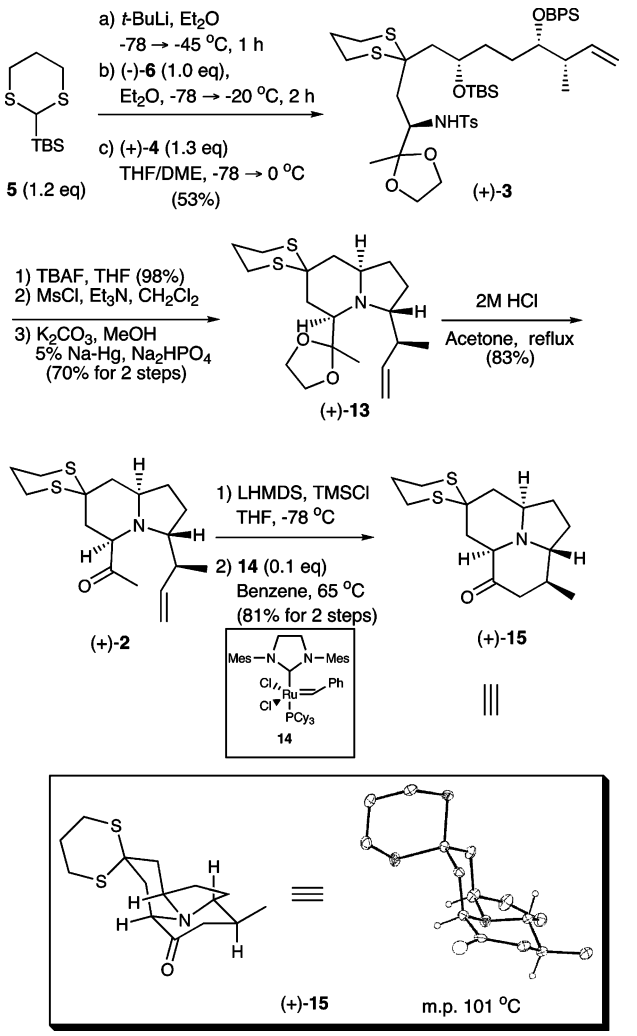
(6) (a) Baldwin, J. E.; Spivey, A. C.; Schofield, C. J.; Sweeney, J. B. *Tetrahedron* **1993**, *49*, 6309. (b) Bergmeier, S. C.; Seth, P. P. *J. Org. Chem*. **1997**, *62*, 2671. (c) Fujii, N.; Nakai, K.; Tamamura, H.; Otaka, A.; Mimura, N.; Miwa, Y.; Taga, T.; Yamamoto, Y.; Ibuka, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1359.

(7) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahederon Lett*. **1980**, *21*, 1357.

(8) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc*. **1986**, *108*, 5919.

containing 1,2-dimethoxyethane (DME) to trigger the Brook rearrangement, led to (+)-**3** in 53% yield.[11]

Scheme 4



Sequential closure of the two rings that comprise the indolizidine ring system, embedded in the 8b-azaacenaphthylene ring system of alkaloid (−)-**1**, was next achieved by removal of the silyl groups (TBAF), bismesylation of the resulting diol, and treatment of the bismesylate with potassium carbonate in MeOH, followed without purification by addition of sodium amalgam (5%); the overall yield of (+)-**13** for the three-step sequence was 69%. Hydrolysis of the acetal with 2 M HCl in acetone at reflux then provided ketone (+)-**2**, which upon treatment with lithium hexamethyldisilazide (LHMDS) in the presence of TMSCl led to the kinetic silyl enol ether. Ring-closing metathesis employing the second-generation Grubbs catalyst (**14**) furnished the requisite advanced tricyclic dithiane (+)-**15** as a crystalline solid (mp 101 °C).[12] Single-crystal X-ray analysis established both the structure and relative stereochemistry.

Having achieved construction of the azaacenaphthylene ring system, we now faced what suprisingly proved to be a difficult task, namely, introduction of an axial methyl group at C(6) in (+)-**15**. From the stereoelectronic persepective, α addition of a methyl nucleophile to the C(6) carbonyl would be expected to furnish the equatorial alcohol. However, deoxygenation of the latter via the Barton−McCombie[13] and/or related protocols[14] involving radical mechanisms would, in all likelihood, lead to the thermodynamically more stable equatorial C(6) methyl substituent as a major product. We therefore turned to the equatorial alcohol, readily available upon reduction of (+)-**15** with $NaBH_4$. Unfortunately, all attempts to displace the derived tosylate with a variety of nucleophiles either proceeded in low yield or furnished elimination products. We also examined the possibility of hydrogenation of both the C(6) exomethylene and C(6)−C(7) trisubstituted olefin congeners. Not suprisingly, in both cases hydrogen was delivered from the less hindered α face to furnish predominately the C(6) equatorial methyl congener (ca. 5:1).

Undaunted, we next explored protonation of the enol or enolate derived from the C(6) aldehyde. To this end, Wittig olefination of (+)-**15** (Scheme 5) with (methoxymethyl)-triphenylphosphonium chloride employing *t*-BuOK to generate the ylide furnished an *E*/*Z* mixture (ca. 4:3) of methyl enol ethers. To our delight, hydrolysis with 6 M HCl at 0 °C for 24 h furnished the desired axial aldehyde as the major diastereomer (4:1; NMR).[15] This result is explained via electrostatic interactions; that is, axial delivery of a proton, presumably the first step in the enol ether hydrolysis, would be more sterically encumbered by electrostatic repulsion between an incoming hydronium ion and the positive charge of the protonated nitrogen than the equatorial delivery.

Without separation, reduction of the mixture of aldehydes with $NaBH_4$ provided alcohol (+)-**16** in 74% isolated yield, after separation from accompanying alcohol (+)-**17** (18%).[16] Mesylation of (+)-**16**, followed in turn by reduction of the

(9) (a) Shimizu, A.; Nishiyama, S. *Tetrahedron Lett*. **1997**, *38*, 6011. (b) Chattopadhyay, S.; Mamdapur, V. R.; Chadha, M. S. *Tetrahedron* **1990**, *46*, 3667. Aldehyde (−)-**10** was prepared in four steps and 95% overall yield from commercially available ethyl (*S*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-propenoate (**i**): see the Supporting Information for details.

(10) (a) Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974**, 203. (b) Cink, R. D.; Forsyth, C. J. *J. Org. Chem*. **1995**, *60*, 8122.

(11) In this case, use of HMPA or DMPU as cosolvents to trigger the Brook rearrangement resulted in poor yield (<10%).

(12) (a) Okada, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett*. **2001**, *42*, 8023. (b) Arisawa, M.; Theeraladanon, C.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett*. **2001**, *42*, 8029. (c) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett*. **1999**, *1*, 953.

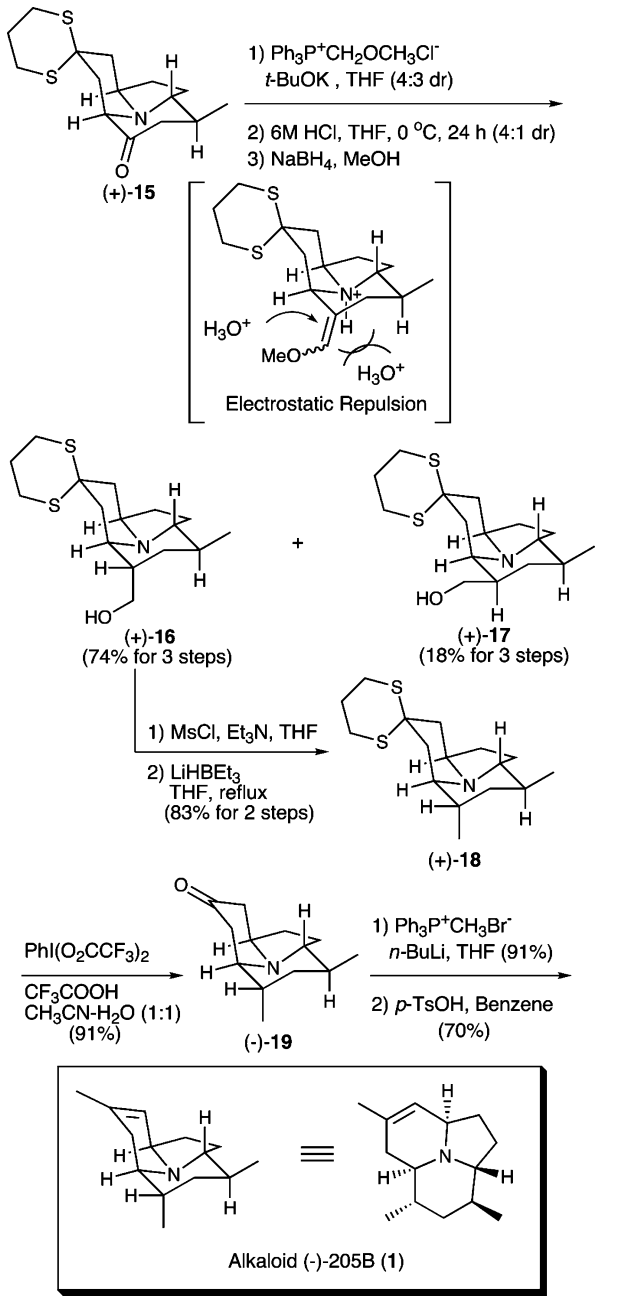
(13) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. (b) Barton, D. H. R.; Parekh, S. I.; Tse, C.-L. *Tetahedron Lett*. **1993**, *34*, 2733.

(14) Zhang, L.; Koreeda, M. *J. Am. Chem. Soc*. **2004**, *126*, 13190 and references therein.

(15) Hydrolysis at room temperature for 12 h led to a mixture (ca. 1:1) of aldehydes.

(16) The stereochemistry at the newly formed position in (+)-**16** was later confirmed by comparison of the NMR data of (−)-**19** with those of known (+)-**19**; see ref 3.

Scheme 5



mesylate with Super-Hydride ($LiHBEt_3$), afforded dithiane (+)-**18**. Removal of the dithiane exploiting the Stork protocol[17] [e.g., bis(trifluoroacetoxy)iodobenzene] then furnished ketone (−)-**19**, which was subjected to the Toyooka endgame sequence.[3] Specifically, Wittig methylenation followed by acid-catalyzed isomerization of the resultant exomethylene alkene to the internal olefin afforded the natural alkaloid (−)-205B as the major isomer (6.2:1; NMR) in an isolated yield of 70%. Synthetic (−)-**1** possessed spectral data {e.g., 400 and 500 MHz ^1H and 125 MHz ^{13}C; $[\alpha]_D = -8.3$ (*c* 0.12, $CHCl_3$) [lit.[2] $[\alpha]_D = -8.5$ (*c* 0.59, $CHCl_3$)]} identical to the data reported for both the natural product[2] and the synthetic antipode {$[\alpha]_D = +8.1$ (*c* 1.05, $CHCl_3$)},[3] except, of course, in the latter case for the chiroptical properties.

In summary, we have achieved an effective, stereocontrolled total synthesis of alkaloid (−)-205B (**1**). Highlights of the synthetic strategy include an indolizidine ring construction tactic, comprising a three-component linchpin coupling of (+)-**4**, **5**, and (−)-**6**, followed by a one-pot sequential cyclization. Ring-closing metathesis completed construction of the tricyclic 8b-azaacenaphthylene ring system of alkaloid (−)-205B. Final stereoselective installation of the axial methyl group at C(6) and application of the Toyooka endgame led to the natural antipode of alkaloid (−)-205B (**1**). The longest linear sequence to (−)-**1** required 19 steps and proceeded in 5.6% overall yield, beginning with known aldehyde (−)-**10**. Biological evaluation of (−)-**1** and the construction of related congeners will be reported in due course.

Acknowledgment. Financial support was provided by the National Institutes of Health (Institute of General Medical Sciences) through Grant No. GM-29028 and an Eli Lilly Foundation Fellowship to D.-S.K. We also thank Dr. John W. Daly, National Institutes of Health, for kindly providing the 400 MHz ^1H NMR and the proton/carbon HMBC spectral data for the natural antipode of alkaloid 205B.

Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) (a) Fleming, F. F.; Funk, L.; Altundas, R.; Tu, Y. *J. Org. Chem.* **2001**, *66*, 6502. (b) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.