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Supplementary Material Available: A table of melting points and ^1H NMR spectral and elemental analyses data for compounds **2a–j** (2 pages). Ordering information is given on any current masthead page.

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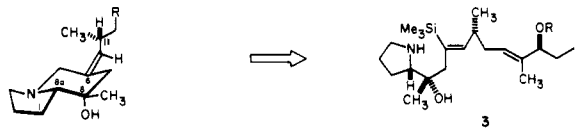
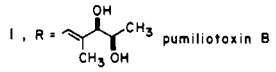
Enantioselective Total Synthesis of (+)-Pumiliotoxin A

Summary: (+)-Pumiliotoxin A (**2**), the parent alkaloid of the cardiac-active pumiliotoxin A class, can be prepared in 13 steps and 5% overall yield from (*S*)-(−)-2-methyl-1-penten-3-ol (**4**). This enantioselective total synthesis establishes, for the first time, the complete stereostructure of **2**.

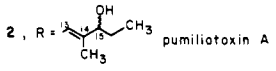
Sir: Daly and co-workers[1] first isolated pumiliotoxins A (**2**) and B (**1**) from the Panamanian poison frog *Dendrobates pumilio* in 1967.[1,2] The structure of the powerful



3



1, R = pumiliotoxin B

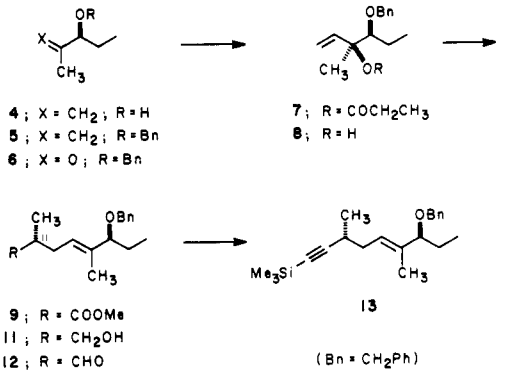


2, R = pumiliotoxin A

cardiotonic agent[1,3] pumiliotoxin B (**1**) has now been rigorously established by a combination of spectroscopic,[4] degradative,[5] and total synthesis[6] studies. In contrast, the stereostructure of pumiliotoxin A,[4,7] the parent alkaloid of the pumiliotoxin A class,[2] is not known. Recent studies[7] indicate that samples of **2** isolated from *Dendrobates pumilio* are mixtures of two isomers that are surmised to be epimers at C-15. In this paper, we report the synthesis of (+)-pumiliotoxin A (**2**) from (*S*)-(−)-2-methyl-1-penten-3-ol (**4**).[8] This enantioselective total synthesis rigorously establishes the complete stereostructure of **2** and demonstrates that the major isomer of (+)-pumiliotoxin A isolated from dendrobatid frogs has the *S* configuration at C-15 (**2**, β-OH). Moreover, the convergent synthesis strategy described herein achieves by far the most efficient entry to the biologically important[2] pumiliotoxin A alkaloids to be developed to date.

The chemical objective of this total synthesis endeavor was to examine whether the iminium ion–vinylsilane cyclization approach[6] for constructing the (*Z*)-6-alkylideneindolizidine ring system of this cardiac toxin class would succeed with a fully functionalized side chain, i.e. **3** → **2**. This strategy is attractive since it is much more convergent than the approach we had previously employed[6] to prepare (+)-pumiliotoxin B.

A key intermediate in the experimental verification of this approach is (−)-silylalkyne **13**, which embodies the fully elaborated side chain of pumiliotoxin A. The synthesis of **13** starts with the *S* alcohol **4**[8] ($[\alpha]^{25}_D$ −4.9° (*c* 0.63, $CHCl_3$); >98% ee[9]), which is readily obtained by Sharpless kinetic resolution.[10] Benzylation of **4** (NaH, BnBr; 86%



4; X = CH_2; R = H
5; X = CH_2; R = Bn
6; X = O; R = Bn

7; R = $COCH_2CH_3$
8; R = H

9; R = COOMe
11; R = CH_2OH
12; R = CHO

13

(Bn = CH_2Ph)

yield) provides **5**,[11] which is successfully cleaved with 1 equiv[12] of O_3 (−78 °C, MeOH; Me_2S; 84% yield) to give α-benzyloxy ketone **6**[11] ($[\alpha]^{25}_D$ −113° (*c* 2.6, $CHCl_3$)). The reaction of **6** with vinylmagnesium bromide (THF, 25 °C) occurs with >99% stereoselectivity[13] to afford the syn

(1) Daly, J. W.; Myers, C. W. *Science (Washington, D.C.)* **1967**, *156*, 970.
(2) For recent reviews of these poison frog alkaloids, see: (a) Daly J. W. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 205. (b) Witkop, B.; Gössinger, E. In "The Alkaloids"; Brossi, A., Ed.; Academic Press: New York, 1983; Vol. 21, Chapter 5.
(3) See, inter alia: Daly, J. W.; McNeal, E. T.; Overman, L. E.; Ellison, D. H. *J. Med. Chem.* **1985**, *28*, 482. Albuquerque, E. X.; Warnick, J. E.; Maleque, M. A.; Kauffman, F. C.; Tamburni, R.; Nimit, Y.; Daly, J. W. *Mol. Pharmacol.* **1981**, *19*, 411.
(4) Daly, J. W.; Tokuyama, T.; Fujiwara, T.; Highet, R. L.; Karle, I. L. *J. Am. Chem. Soc.* **1980**, *102*, 830. Tokuyama, T.; Shimada, K.; Uemura, M.; Daly, J. W. *Tetrahedron Lett.* **1982**, *23*, 2121. Overman, L. E.; McCready, R. J. *Ibid.* **1982**, *23*, 2355.
(5) Uemura, M.; Shimada, K.; Tokuyama, T.; Daly, J. W. *Tetrahedron Lett.* **1982**, *23*, 4369.
(6) Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192.
(7) Tokuyama, T.; Daly, J. W.; Highet, R. J. *Tetrahedron*, **1984**, *40*, 1183.
(8) Catalytic hydrogenation of (−)-**4** gives (*S*)-(−)-2-methylpentan-3-ol whose absolute configuration is established: Büchi, G.; Crombie, L.; Godin, P. J.; Kaltenbronn, J. S.; Siddalingaiah, K. S.; Whiting, D. A. *J. Chem. Soc.* **1961**, 2843.
(9) ^1H NMR analysis of the (+)-MTPA ester: Mosher, H. L.; Dale, J. A.; Dull, D. L. *J. Org. Chem.* **1969**, *34*, 2543.
(10) Martin, V. S.; Woodward, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.
(11) Isolated intermediates showed correct molecular compositions (elemental analysis or high-resolution MS) and appropriate NMR and mass spectra.
(12) Careful monitoring by TLC is necessary to avoid overoxidation to give unwanted benzoate.
(13) See, inter alia: Still, W. C.; McDonald, J. H., III. Tetrahedron Lett., **1980**, 1031.

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alkoxy alcohol 8[11] ($[\alpha]_D$ −21.2° (*c* 0.82, $CHCl_3$)). The intermediate tertiary alkoxide could be acylated in situ (EtCOCl, 2.0 equiv; HMPA, 1.2 equiv; 25 °C) to give 7[11] ($[\alpha]^{25}_D$ −10.2° (*c* 0.95, $CHCl_3$)) in 70% overall yield. Claisen rearrangement of the (*Z*)-silylketene acetal derivative of 7 (LDA, 23 vol % HMPA–THF, −78 °C; *t*-$BuMe_2SiCl$, −78 °C → room temperature) following the Ireland[14] procedure provides, after esterification (MeOH, HCl), 9[11] [^{1}H NMR δ 1.18 d (*J* = 6.8 Hz, C-11 Me) and its C-11 epimer 10 [^{1}H NMR δ 1.19 d (*J* = 6.9 Hz, C-11 Me) in 90% yield. The ratio of isomers obtained from this sequence (9:10 = 7:1, ^{1}H NMR analysis) reflects the expected[14,15] enolization stereoselectivity. Unfortunately, we were unsuccessful in separating these epimers or any acyclic intermediate derived from them, and removal of the unwanted *S* C-11 epimer had to await establishment of the alkylideneindolizidine ring.[16] Reduction of 9 ($LiAlH_4$, 0 °C; 95% yield) provides 11,[11,17] which is best oxidized to aldehyde 12[11,17] with dimethyl sulfoxide activated with SO_3–pyridine[18] (Et_3N, 25 °C; 90% yield). The conversion of 12 to the desired silylalkyne 13[11,17] ($[\alpha]^{25}_D$ −44.4° (*c* 1.2, $CHCl_3$)) is readily accomplished in 87% overall yield by the method of Corey and Fuchs (Ph_3P, CBr_4; BuLi; Me_3SiCl).[19] This overall sequence provides (−)-13[17] in eight steps and 34% overall yield from (*S*)-2-methyl-1-penten-3-ol (4).

Following procedures optimized during our pumiliotoxin B synthesis,[6] 13 is converted to the silylvinyl alanate and coupled with the enantiomerically pure epoxide 14[6] (0.5 equiv, THF, 60 °C) to give bicyclic carbamate 15[11,17] (IR 1744 cm^{-1}) in 52% yield based on epoxide 14. Hydrolysis (KOH, MeOH, 80 °C) of 15, followed by addition of excess formalin affords the crude cyclopentoxazolidine 16[17] in essentially quantitative yield. Cyclization of 16 requires careful control of the acidity of the reaction medium in order to prevent solvolysis of the allylic benzyl ether. The optimum condition proved to be heating 16 at 80 °C in a buffered (pyridine–pyridinium tosylate, pH ~4.5) solution of MeOH, which provides *stereospecifically*[6] the desired (*Z*)-6-alkylideneinodolizidine 17[11] ($[\alpha]_D$ −6.38° (*c* 1.60, $CHCl_3$)) in 71% yield from 15. Debenzylation (Li/NH_3–THF, −78 °C) of 17 followed by chromatographic separation (silica gel, 50:1:0.1 $CHCl_3$–MeOH–12 N NH_4OH) of the unnatural *S* C-11 isomer gave pure[11] (+)-(15*S*)-pumiliotoxin A in 75% yield. Comparison of the ^{1}H NMR spectrum (at 250 and 500 MHz) of this synthetic material [δ 0.99 (d, *J* = 6.6 Hz, C-11 Me), 0.85 (t, *J* = 7.4 Hz, C-17 Me)] with a sample of natural material, which was a 2:1 mixture of isomers,[7,20] showed conclusively the identity of the synthetic material with the major isomer (307 A')[7] obtained from natural sources. Our synthetic (+)-pumiliotoxin A showed $[\alpha]^{25}_D$ +13.9° (*c* 0.80, $CHCl_3$), which compares with a rotation of +14.2° (*c* 0.51, $CHCl_3$) determined for the 2:1 mixture[21] isolated from *Dendrobates pumilio*. Synthetic 2 also showed ionotropic effects on isolated guinea pig atria preparations[22] comparable to those of the natural toxin.[23]

The convergent total synthesis reported here is a practical method for the preparation of (+)-pumiliotoxin A since it requires only 13 steps from 4 and proceeds in 5% overall yield. Of equal importance, this synthesis demonstrates that complex functionality are compatible with iminium ion–vinylsilane cyclizations, thus enhancing the general utility of this useful ring-forming method.[24]

Acknowledgment. We particularly thank Dr. J. W. Daly for the comparison samples of pumiliotoxin A and the biological comparisons. This study was supported by PHS Grant HL-25854. NMR and mass spectra were determined at Irvine with spectrometers purchased with the assistance of NSF Departmental Instrumentation grants, while 500-MHz ^{1}H NMR spectra were determined at the NSF-supported Southern California Regional NMR Facility.

Supplementary Material Available: 250-MHz ^{1}H NMR and IR spectra for 2, 4–9, and 11–17 (28 pages). Ordering information is given on any current masthead page.

(14) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.
(15) Nagatsuma, M.; Shirai, F.; Sayo, N.; Nakai, T. *Chem. Lett.* **1984**, 1393.
(16) We have generally found[6] that C-11 epimers in the pumiliotoxin A alkaloid series having intact (*Z*)-6-alkylideneindolizidine ring systems can be separated by careful flash chromatography on silica gel.
(17) This intermediate was a ca. 7:1 mixture of C-11 epimers.
(18) Parikh, J. R.; Doering, W. Von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(19) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
(20) Kindly provided by Dr. J. Daly. The minor isomer[7] showed characteristic ^{1}H NMR absorptions at δ 1.00 (d, *J* = 6.6 Hz, C-11 Me) and 0.83 (t, *J* = 7.4 Hz, C-17 Me).
(21) Additional experiments, which will be detailed in a full account of this work, have confirmed that the minor isomer in the natural sample of pumiliotoxin A is indeed the 15-*R* epimer.
(22) Mensah-Dwumah, M.; Daly, J. W. *Toxicon* **1978**, *16*, 189.
(23) The biological comparisons were made by Dr. J. Daly.
(24) For other applications of iminium ion–vinylsilane cyclizations, see: Overman, L. E.; Burk, R. M. *Tetrahedron Lett.* **1984**, *25*, 5739. Overman, L. E.; Malone, T. C.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6993. Overman, L. E.; Malone, T. C. *J. Org. Chem.* **1982**, *47*, 5297.

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Lythraceae Alkaloids: Total Synthesis of (±)-Lythrancepine II

Summary: A stereoselective total synthesis of the quinolizidine metacyclophane Lythraceae alkaloid lythrancepine II (1) is described.

Sir: The Lythraceae alkaloids are a large family of natural products that have been classified according to several structural types.[1] The largest structural family are qui-

(1) For reviews, see: Golebiewski, W. M.; Wróbel, J. T. In "The Alkaloids"; Rodrigo, R. G. A., Ed.; Academic Press: New York, 1981; Vol. 18, pp 263–322. Fujita, E.; Fuji, K. In "International Review of Science, Organic Chemistry Series Two"; Wiesner, K., Ed.; Butterworths: London, 1976; p 119.

0022-3263/85/1950-3670$01.50/0