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A SHORT STEREOSPECIFIC TOTAL SYNTHESIS OF dl-PUMILIOTOXIN C

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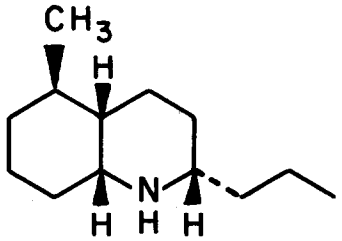
Pumiliotoxin C (1) is one of a large group of structurally related toxins which have been isolated from skin extracts of the colorful Central American poison arrow frog Dendrobates pumilio.[2, 3, 4, 5c] Synthetic investigations in several laboratories culminated in 1975 in three total syntheses of this unusual cis-decahydroquinoline alkaloid.[5, 6] In this letter we



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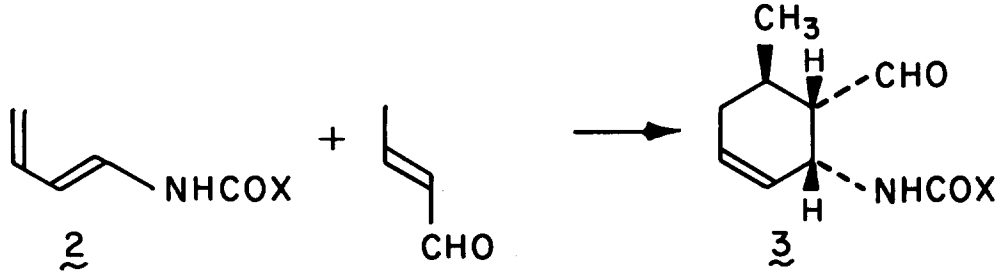
report a short, stereospecific, construction of racemic pumiliotoxin C, which proceeds in greater than 45% overall yield, and which should be easily adapted for the preparation of other pumiliotoxins.

Our synthetic analysis of 1 suggested that the construction of the three chiral centers in the carbocyclic ring would be pivotal. In principle these three chiral centers could be established in a single step, from readily available starting materials, if the endo adduct 3 were preferentially formed from the cycloaddition of dienamide 2[7] and trans-crotonaldehyde.

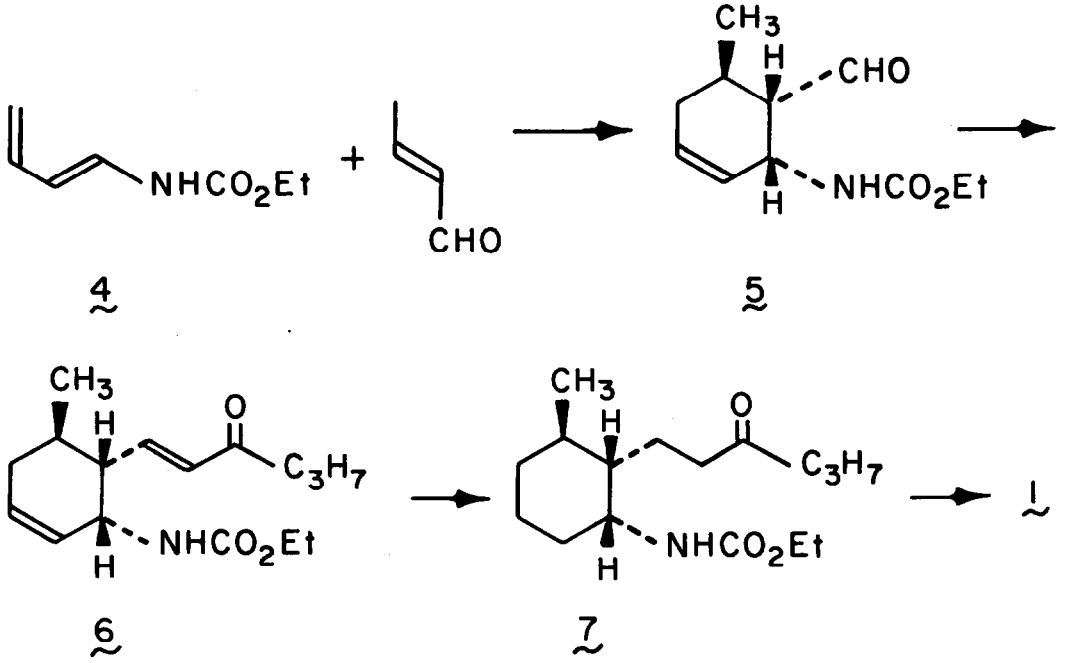


2 3

This represents a demanding test for the stereoselectivity of dienes such as 2, since trans crotonate derivatives typically exhibit notoriously low endo stereoselectivities in the Diels-

Alder reaction.[8] A reactive diene most certainly would be required.[7,9] The successful implementation of this strategy is outlined below.[10]

Cycloaddition of ethyl trans-1, 3-butadien-1-carbamate (4)[7a] and trans-crotonaldehyde (0.14 g/ml, 4-tert-butylcatechol added as an inhibitor) for 2 1/2 hr at 110° (ca. 90% conversion of the diene), and purification of the crude product by column chromatography on silica gel (hexane-ethyl acetate) afforded adduct 5,[11] mp 56-58°, in 61% yield (68% based on consumed diene). Analysis of the crude reaction mixture by hplc indicated that less than 5% of isomeric Diels-Alder adducts were present at 2 1/2 hr, however, they became increasingly important at longer reaction times. Reaction of 5 with the sodium salt of dimethyl 2-oxopentylphosphonate[12] (2 equiv) in THF proceeded smoothly to afford the crystalline enone 6,[11] mp 102.5-104°, in 83% yield, after filtration of the crude reaction product through a short column of silica gel and recrystallization from hexane-ether. Hydrogenation (1 atm, Pd/C) of dienone 6 yielded 7 quantitatively. Treatment of 7 with freshly prepared saturated HBr in acetic acid (30 mg/ml, 3 hr at reflux, in the presence of copper powder -0.1 g/ml) resulted in cleavage of the carbamate group and afforded the sensitive $\Delta^{1,2}$ imine after concentration (aspirator, 25°) and partitioning of the residue between ether and saturated aqueous bicarbonate. The crude imine was immediately hydrogenated (1 atm, PtO_2, ethanol-2NHCl)[6a] to yield nearly pure 1 (ca. 90% from 7) after basification and extraction with dichloromethane. Purification was accomplished by conversion to the hydrochloride to afford



dl-pumiliotoxin C hydrochloride,[11] mp 232-234°, homogeneous by GC, in 83% overall yield from 7. This material exhibited the expected ^{1}H and ^{13}C NMR spectra,[13] and was identical (mixture mp, IR, ^{1}H NMR, GC, mass spec) with an authentic sample of racemic pumiliotoxin C hydrochloride.[14]

Further studies on related approaches to pumiliotoxin C, and other pumiliotoxins, will be reported in due course.

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8. Cf. Y. Kobuke, T. Fueno, and J. Furukawa, J. Am. Chem. Soc., 92, 6548 (1970).
9. Cf. K. Seguchi, A. Sera, Y. Otsuki, and K. Maruyama, Bull. Chem. Soc. Jap., 48, 3641 (1975).

10. This approach is clearly related to the intramolecular Diels-Alder approach of Oppolzer.[5a]

11. Selected data on analytical specimens are summarized here: 5: mp 59.5-60°; mass spectrum 211.120 (10%, $C_{11}H_{17}NO_3$ requires 211.121), 141 (100%); IR (nujol) 3280, 1710, 1670, and 1530 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 9.69 (d, CHO, J = 1.9), 4.8-5.2 (m, NH), 4.3-4.7 (m, NHCH), 2.4-2.6 (m, CHCHO), 1.09 (d, CH_3, J = 6.3); ^{13}C NMR ($CDCl_3$, δ) 203.0, 156.0, 129.2, 126.2, 61.2, 56.4, 45.1, 31.5, 25.3, 19.3, 14.6. 6: mp 102.5-104°; mass spectrum 279.181 (4%, $C_{16}H_{25}NO_3$ requires 279.183), 141 (100%); IR (nujol) 3310, 1715, 1660, 1525, and 1460 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 6.70 (dd, CH=CHC=O, J = 9.4, 16.1), 6.15 (d, CH=CHC=O, J = 16.1); ^{13}C NMR ($CDCl_3$, δ) 200.4, 156.0, 146.2 132.4, 129.6, 126.4, 61.0, 48.3 (2 carbons), 42.0, 32.4, 28.5, 19.9, 17.7, 14.6, 13.8. dl-1 hydrochloride: mp 242.5-243.5° (sealed capillary, after one recrystallization from isopropanol or 1:3 ethanol: ethyl acetate); mass spectrum 195.200 (5%, $C_{13}H_{25}N$ requires 195.199), 152(100%); ^1H NMR ($CDCl_3$-D_2O, δ) 3.30 (m, W h/2 = 9 Hz, C_9-H), 2.95 (m, W h/2 = 20 Hz, C_2-H); ^1H NMR (free base, $CDCl_3$, δ) 2.95 (m, W h/2 = 7 Hz, C_9-H), 2.64 (m, W h/2 = 18 Hz, C_2-H); ^{13}C NMR ($CDCl_3$, δ) 60.1, 58.1, 41.0, 35.0, 34.6, 29.2, 27.4, 25.3, 23.3, 20.7, 19.7, 19.2, 13.7.

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14. Kindly provided by Professor T. Ibuka.