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.

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(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.

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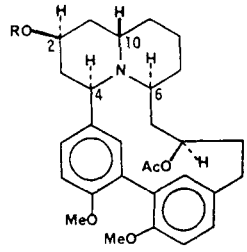
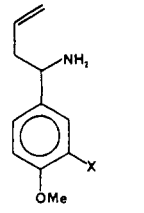
nolizidine metacyclophanes, typified by lythrancepine II (1).[2] We report here the preparation of (±)-lythrancepine II, the first total synthesis of this type of Lythraceae alkaloid.

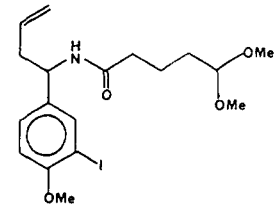


1 R = H
23 R = CH_2Ph

Our first key intermediate (12) was prepared by using a strategy employed in our earlier route to vertaline, a macrocyclic lactonic Lythraceae alkaloid.[3] Thus, sequential treatment of *m*-iodoanisaldehyde[4] with lithium hexamethyldisilazide and allylmagnesium bromide gave homoallylic amine **2** (76%) along with 9% of amine **3**.[5]



2 X = I
3 X = H



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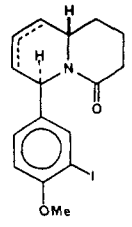

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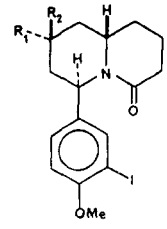
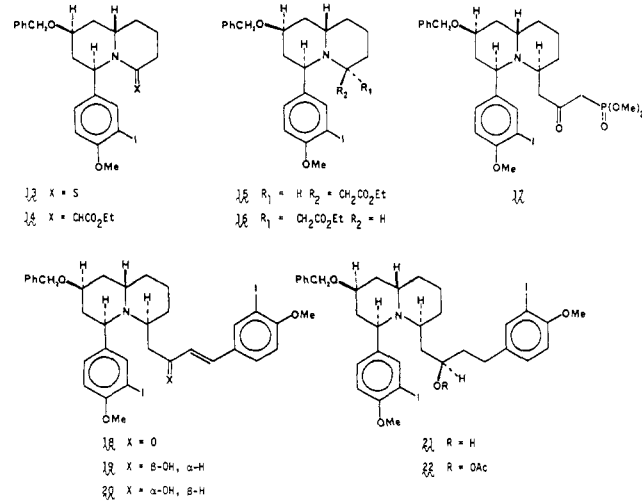


5 R_1 = OCHO R_2 = H
6 R_1 = H R_2 = OCHO
7 R_1 = OH R_2 = H
8 R_1 = H R_2 = OH
10 R_1, R_2 = O
11 R_1 = H R_2 = OCH_2Ph
12 R_1 = OCH_2Ph R_2 = H

Treatment of **2** with trimethylaluminum followed by methyl 5,5-dimethoxypentanoate[6] gave amide **4** (mp 74–75 °C, 96%).[7] When **4** was stirred with 98% formic acid in dichloromethane at room temperature for 2 h, formate **5** (mp 162–163 °C, 48%), formate **6** (mp 48–50 °C, 5%), alcohols **7** (mp 158–160 °C) and **8** (22%), olefins **9** (9%), and *m*-iodoanisaldehyde (mp 105–107 °C, 9%) were obtained.[8] Treatment of the mixture of **5**–**8** with sodium hydroxide in aqueous methanol followed by a Swern oxidation gave quinolizidindione **10** (mp 136–137 °C, 98%).[9] Ketone **10** was reduced with lithium triethylborohydride,[10] and the resulting inseparable mixture of **7** and **8** was treated with sodium hydride and benzyl bromide in *N,N*-dimethylformamide to afford a separable mixture of quinolizidines **11** (66%) and **12** (10%).

Having established the appropriate stereochemistry at C(2), C(4), and C(10), we turned to introduction of the C(6) side chain. Treatment of **11** with Lawesson's reagent gave thiolactam **13** (mp 175–176 °C, 98%).[11] Attempts to



13 X = S
14 X = $CHCO_2Et$
15 R_1 = H R_2 = CH_2CO_2Et
16 R_1 = CH_2CO_2Et R_2 = H
17
18 X = O
19 X = β-OH, α-H
20 X = α-OH, β-H
21 R = H
22 R = OAc

introduce the entire C(6) side chain using an Eschenmoser sulfide contraction met with failure, and thus, a stepwise procedure was used.[12,13] Treatment of **13** with ethyl iodoacetate in chloroform (25 °C, 24 h) followed by DABCO and triphenylphosphine under reflux gave vinylogous urethane **14** (92%). Reduction of **14** with sodium cyanoborohydride (MeOH, pH 4) gave amino esters **15** (88%) and **16** (10%).[14] Although NMR arguments based on model compounds allowed us to make a tentative C(6) stereochemical assignment at this point, proof of stereo-

(2) Isolation: Fujita, E.; Bessho, K.; Saeki, Y.; Ochiai, M.; Fuji, K. *Lloydia* **1971**, *34*, 306. Structure: The structure assignment for **1** is based on spectral data and a chemical correlation with lythrancine II (1β-hydroxylythrancepine II), whose structure was determined by X-ray crystallographic analysis of a derivative; see ref 1 and the following. Fujita, E.; Saeki, Y. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2141. Barrow, M. J.; Cradwick, P. D.; Sim, G. A. *J. Chem. Soc., Perkin Trans 1* **1974**, 1812. Synthesis: For model studies toward a related alkaloid, see the following. Quick, J.; Khandelwal, Y.; Meltzer, P. C.; Weinberg, J. S. *J. Org. Chem.* **1983**, *48*, 5199.

(3) Hart, D. J.; Kanai, K. *J. Org. Chem.* **1982**, *47*, 1555.

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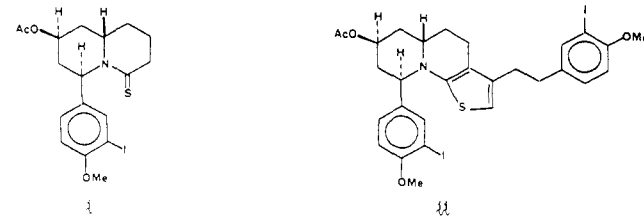
(13) For example, sequential treatment of **i** with 1-bromo-4-(3-iodo-4-methoxyphenyl)-2-butanone and triphenylphosphine–DABCO gave thiophene **ii** in 75% yield.



i ii

(14) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

chemistry was obtained at a later stage of the synthesis. The major amino ester (**15**) was converted to β-keto phosphonate **17** [$(MeO)_2P(O)CH_2Li$, 99%][15] and a Horner–Wadsworth–Emmons reaction (NaH, DME) with *m*-iodoanisaldehyde gave unsaturated ketone **18** (mp 201–202 °C, 81%).[16] Treatment of **18** with lithium triethylborohydride gave an easily separable mixture of allylic alcohols **19** (mp 100–102 °C, 71%) and **20** (25%). The major alcohol (**19**) was reduced with diimide ($TsNHNH_2$, NaOAc, H_2O–DME) to afford **21** (mp 163.5–165.5 °C, 95%), whose structure was established by X-ray crystalography.[18]

With the C(6) side chain in place, we were set for the critical biaryl construction using methodology developed by Semmelhack and co-workers.[19] Thus, alcohol **21** was converted to acetate **22** (mp 61–64 °C, 85%; Et_3N, Ac_2O, 4-DMAP).[20] Treatment of **22** with 1.5 equiv of freshly prepared tetrakis(triphenylphosphine)nickel(0) in *N,N*-dimethylformamide at 55 °C for 48 h gave biaryl **23** (mp 169–169.5 °C, 20%). Cleavage of the benzyl ether (BBr_3, CH_2Cl_2, 1 min, 0 °C)[21,22] gave (±)-lythrancepine II (mp 139–142 °C, 60%), which was identical (500-MHz ^1H NMR, IR, MS, TLC) with an authentic sample of natural 1.[23]

In summary, we have completed the first total synthesis of a member of the largest structural family of Lythraceae alkaloids. The synthesis requires 17 steps from *m*-iodoanisaldehyde and proceeds in approximately 1% overall yield. Furthermore, the basic strategy should allow the synthesis of all other members of this family of Lythraceae alkaloids.

Acknowledgment. We thank the National Institutes of Health for their support of this research (GM-27647). We thank Richard Weisenberger and Dr. Chuck Cottrell for recording mass and 500-MHz ^1H NMR spectra, respectively, at The Ohio State University Chemical Instrumental Center.

(15) Dauben, W. G.; Beasley, G. H.; Broadhurst, M. D.; Muller, B.; Peppard, D. J.; Pesnelle, P.; Suter, C. *J. Am. Chem. Soc.* **1975**, *97*, 4973.
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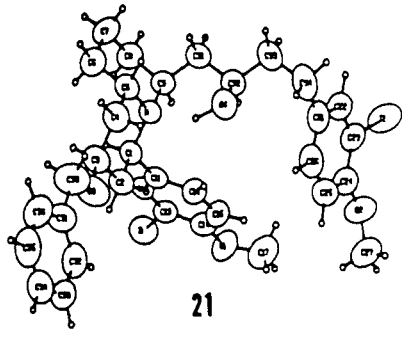
(17) Footnote deleted in proof.
(18) We thank Dr. Ruth Hsu for performing this analysis at the Ohio State University Department of Chemistry X-Ray Crystallographic Facility. Questions regarding the structure determination should be directed to Dr. Hsu.



21

(19) Semmelhack, M. F.; Helquist, P.; Jones, L. D.; Keller, L.; Mendelson, L.; Speltz Ryono, L.; Gorzynski Smith, J.; Stauffer, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 6460.
(20) Steglich, W.; Holfe, G. *Angew, Chem., Int. Ed. Engl.* **1969**, *8*, 981.
(21) Kutney, J. P.; Abdurahman, N.; LeQuesne, P.; Piers, E.; Vlattas, I. *J. Am. Chem. Soc.* **1966**, *88*, 3656.
(22) Hydrogenolysis of **23** under a variety of conditions gave benzylic C–N bond cleavage in addition to benzyl ether cleavage.
(23) We thank Professor Eiichi Fujita for graciously supplying a sample of authentic (+)-lythrancepine II. Further proof of structure has obtained by acetylation of (±)-1 to give (±)-lythrancepine III (mp 82–84 °C).[2] This material was also identical with a sample of (+)-lythrancepine III supplied by Professor Fujita.

(24) Fellow of the Alfred P. Sloan Foundation, 1983–1987.

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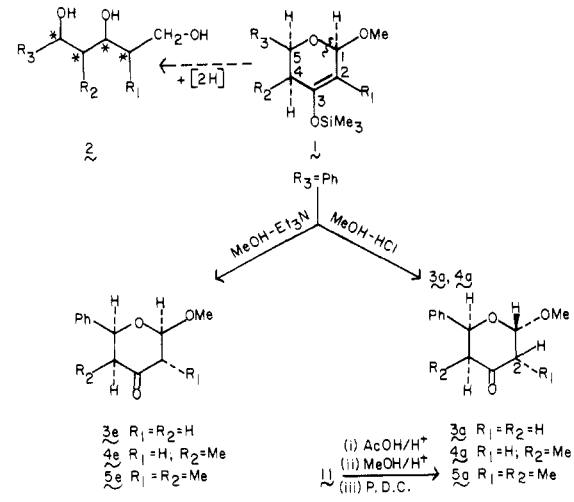
On the Steric Course of the Reduction of 2-Alkoxy-4-pyranones: A Remarkable Demonstration of Anomeric Control

Summary: The stereochemistry about the anomeric alkoxy center governs the facial selectivity of reduction of the title compounds with metal hydrides.

Sir: Recently developed chemistry provides access to compounds of the type implied in formula **1**.[1] In addition to their pertinence to the synthesis of complex saccharides, such systems, upon suitable disconnection of the pyran ring at the acetal carbon, could well serve as useful intermediates in the synthesis of polypropionates (viz., **1** → **2**).[2,3]



Of course, the efficacy of such a strategy would depend, to no small extent, on the stereochemical control that can be exercised during the rehybridization of unsaturated carbons 2 and 3. Treatment of such systems with triethylamine in methanol leads to axial protonation. Thus, in the case of cycloadduct **1** (R_1 = R_2 = Me; R_3 = Ph) compound **5e** is obtained stereospecifically. As a consequence of de facto endo addition[4] in the cycloaddition step, a cis stereochemical relationship is established between the "glycosidic" center and C_5. Examination of the ^1H NMR spectra of these "cis–cis" compounds establishes the methoxy, phenyl, and R^1 centers (see compound **5e**) to be equatorial, while the R_2 methyl group (see compounds **4e** and **5e**) is axial.[5]

(1) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716.
(2) For an important demonstration of polypropionate synthesis, see: Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.
(3) For a recent description of a new strategy in this area, see: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.
(4) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246.

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