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THE SYNTHESIS OF INDOLIZIDINES BY INTRAMOLECULAR ENE CYCLIZATIONS. PREPARATION OF (E)-ALKYLIDENE ANALOGS OF PUMILIOTOXIN A.

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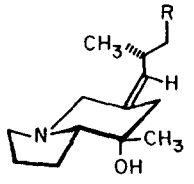
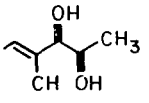
Summary: 6-Alkylidene-8-hydroxyindolizidines 4 can be prepared by Lewis acid-catalyzed intramolecular ene cyclization of proline-derived ketones 3.

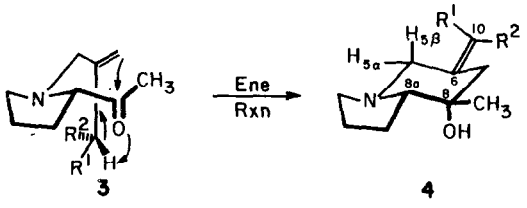
The (Z)-6-alkylideneindolizidine ring is the common structural feature of the pumiliotoxin A alkaloids,[1] e.g. 1 and 2. As a result of the significant cardiotonic activity of pumiliotoxin B[1,2] and simpler analogs,[2] and the scarcity of these natural products in nature,[1] chemical synthesis[3] of indolizidines



1; R =  pumiliotoxin B

2; R = n-Pr pumiliotoxin 251D

of this type is important. The 3-alkylidenecyclohexanol portion of the pumiliotoxin A alkaloids, in particular the axial nature of the C-8 hydroxyl group,[1] suggests that these alkaloids might be prepared by a Type II intramolecular ene reaction.[4,5] In this communication, we report the successful synthesis

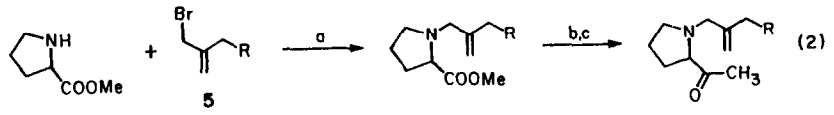


(1)

3 4

of indolizidines 4 by the intramolecular ene strategy of eq 1.

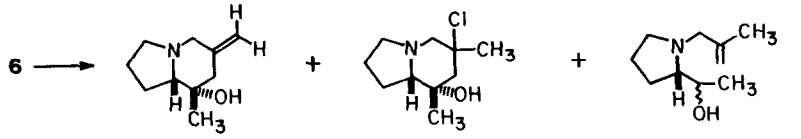
The cyclization substrates 6-8[6] were prepared (30-45% overall yield) from proline and the corresponding allylic bromide 5[7] as summarized in eq 2. Unsaturated ketone 6 was best cyclized in the presence of 2 equiv of freshly sublimed $AlCl_3$ (CH_2Cl_2, 25°C, 1.5 h)[8]. Basic workup, followed by chromatography on alumina (activity III, 9:1 hexane-ethyl acetate) gave[9] alkylidene indolizidine 9[10] and chloride 10[10] in yields of 27% and 39%, respectively. The stereostructure of 9, followed from the close similarity of its ^1H and ^{13}C NMR spectra with those of pumiliotoxin 251D (2),[11] see Table. On the basis of the ^{13}C NMR spectra, chloride 10 likely has the same relative stereochemistry at C-8 and C-8a, although we have no experimental evidence for the stereochemistry at



6; R = H
7; R = $CH_2CH_2CH_2CH_3$
8; R = $CH_2CH(CH_3)_2$

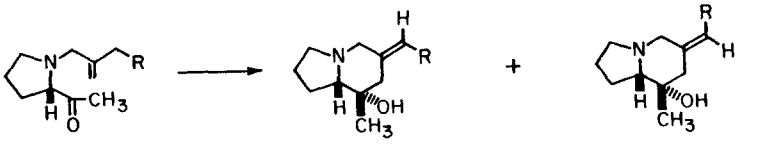
(a) K_2CO_3, DMF, rt; (b) LiOH (1 eq), THF-H_2O, rt; toluene azeotrope; (c) CH_3Li (1 eq), Et_2O, 25-40°C.

C-6. A variety of other Lewis acids were ineffective (e.g. $BF_3.OEt_2$, Me_2AlCl) or afforded complex product mixtures (e.g. $EtAlCl_2$ gave significant amounts of reduction product 11).



9 **10** **11**

Cyclization of unsaturated ketone 7 was accomplished in significantly higher yield (91% after chromatography on silica gel) under identical conditions (2 eq $AlCl_3$, 1.5 h, 25°C) to provide a 3:1 mixture of alkylidene isomers 12 and 13. This clean reaction demonstrates that intramolecular ene cyclization in this series is highly diastereoselective in forming the new C-8 stereocenter and that it is not essential to use alkyl aluminum halide catalysts[8] to obtain tertiary alcohol products[8b] in high yield from Lewis acid - catalyzed ene cyclizations of ketones. The alkylidene isomers could be separated on alumina (activity III, 9:1 hexane-ethyl acetate) and the minor isomer 13[10] was identical with a sample of pumiliotoxin "nor-11-methyl-237A" that we had previously prepared[3b] by stereospecific iminium ion-vinylsilane cyclization. The major (E)-isomer 12[10] showed a diagnostic upfield shift[12] for C-7 (6.2 ppm relative to 9) in the ^{13}C NMR spectrum.



7; R = n-Bu
8; R = i-Pr

12; R = n-Bu
14; R = i-Pr

13; R = n-Bu
15; R = i-Pr

In an identical fashion, 8 was cyclized to give alkylidene indolizidines 14 and 15 in a 6:1 ratio, together with two uncharacterized minor products.

Table: ^{13}C and ^{1}H NMR Data for Alkylideneindolizidines 4 and Chloride 10.[a]

Compound	R^1	R^2	^{13}C NMR C-1	C-2	C-3	C-5	C-6	C-7	C-8	C-8a	^{1}H NMR[b] H-5α	H-5β	H-10	Ref.
9	H	H	23.3	21.3	54.5	59.3	142.1	47.5	65.8	71.3	3.45(11)	2.62(11	4.92,4.84	
251D(2)	(R)-1-Me-pentyl	H	23.3	21.1	54.6	53.2	129.8	48.9	68.3	71.8	3.78(12)	2.34(12)	5.05(9.5)	3a
nor-11-Me-237A (13)	n-Bu	H	23.3	21.1	52.8	54.6	128.0	48.9	68.4	71.7	3.80(12)	2.34(12)	5.26(8)	3b
15	i-Pr	H	23.6	21.3	54.7	53.1	129.5	48.9	68.5	71.9	3.79(12)	2.32(12)	5.10(9.8)	
12	H	n-Bu	23.5	21.2	54.6	61.1	128.6	41.3	68.5	72.2	3.35(11)	2.62(11)	5.44(6.4)	
14	H	i-Pr	23.4	21.2	54.5	61.0	129.4	41.4	68.4	72.1	3.30(11)	2.59(11)	5.25(9.3)	
10	HCl	adduct	23.1	21.2	54.3	66.3	68.5	50.9	68.5	71.6	3.24(11)			

[a] In $CDCl_3$; ppm rel to TMS. [b] Coupling constants (J) in Hz are in parentheses.

Chromatography on alumina (activity IV, 20:1 hexane-ethyl acetate) provided pure samples of 14[10] and 15[10] in yields of 50% and 9%, respectively. Stereochemical assignments again followed unambiguously from NMR spectra (Table). Particularly diagnostic was the upfield[12] shift of carbon-7 in the (E)-isomer 14, and the upfield shift of carbon-5, and the corresponding downfield shift[13] for hydrogen-5α, in the (Z)-isomer 15.

The stereoselectivity of the cyclization reaction appears to increase with the steric bulk of the alkylidene side chain. This result suggests that ene cyclization of the $AlCl_3$ complex of 3[14] occurs in an essentially concerted manner.[15] Such a process would favor loss of the diastereotopic hydrogen which would place the alkyl group in the less sterically congested R^2 position of 3. We consider a stepwise process proceeding via a discrete C-6 cation to be much less likely, since there is no obvious reason that such a cation should undergo stereoselective deprotonation.

In conclusion, a new synthesis of indolizidines is reported that affords, with modest stereoselectivity, (E)-alkylidene analogs of the pumiliotoxin A alkaloids. Significantly, these syntheses demonstrate that Lewis-acid catalyzed intramolecular ene reactions can be successfully employed with strongly basic substrates.

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2. See Daly, J.W.; McNeal, E.T.; Overman, L.E.; Ellison, D.H. J. Med. Chem. 1985, in press; and references therein.
3. (a) Overman, L.E.; Bell, K.L.; Ito, F. J. Am. Chem. Soc. 1984, 106, 4192. (b) Overman, L.E.; Bell, K.L. ibid. 1981, 103, 1851. (c) Overman, L.E.; Goldstein, S.W. ibid. 1984, 106, 5360.
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5. For earlier demonstrations of this strategy for preparing axial cyclohexanols in the terpene series, see Andersen, N.H.; Uh, H.-S.; Smith, S.E.; Wutz, P.G.M. J. Chem. Soc., Chem. Commun. 1972, 956. McCurry, P.M.; Singh, R.K. Tetrahedron Lett. 1973, 3325. Andersen, N.H.; Ladner, D.W. Synthetic Commun. 1978, 8, 449.
6. The ketones prepared in this investigation were racemic. However, the preparation of ketones of this type with high enantiomeric purity should be possible, see ref. 3c.
7. Halides 5 (R=n-Bu, i-Bu) were prepared in 30-40% overall yield from 2,3-dibromopropene in 4 steps: (a) RMgBr, Et_2O, refl; (b) t-BuLi (2 eq), THF, -78°C; DMF, rt; 0.1 N HCl; (c) $NaBH_4$, $CeCl_3$, MeOH-H_2O, rt; (d) Ph_3P, CBr_4, CH_2Cl_2, refl.
8. (a) For a review of the Lewis acid-catalyzed ene reactions, see Snider, B. Accts. Chem. Res. 1980, 13, 426. (b) For recent examples of Lewis acid-catalyzed intramolecular ene cyclizations of ketones, see Jackson, A.C.; Goldman, B.E.; Snider, B. J. Org. Chem. 1984, 49, 3988.
9. The ratio of 9 and 10 was extremely sensitive to the reaction conditions suggesting that 10 is a secondary product formed by HCl addition to 9.
10. New compounds were homogeneous by TLC analysis and showed appropriate 250 MHz ^1H NMR, 63 MHz ^{13}C NMR, IR and mass spectra. Molecular composition of key intermediates was confirmed by high resolution MS.
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13. Jackman, L.M.; Sterhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd Ed.; Pergamon Press: Oxford, 1969; pp 71-72, 204-207.
14. Under the conditions employed it is likely that the nitrogen and the carbonyl oxygen are coordinated to separate molecules of $AlCl_3$.
15. For a recent unambiguous demonstration of concert in a quite different Lewis acid promoted ene cyclization, see Oppolzer, W.; Mirza, S. Helv. Chem. Acta 1984, 67, 730.

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