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CYCLOPEPTIDE ALKALOID MODEL STUDIES.

A TWO-STEP CONVERSION OF 5-AMINOISOXAZOLES

TO AMINO ACID BIS-AMIDES

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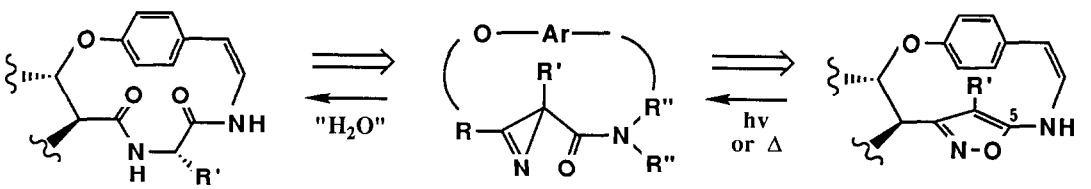
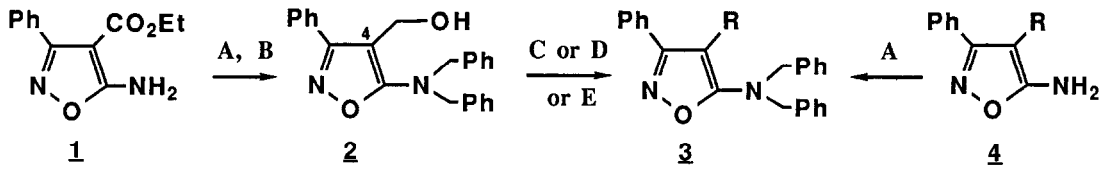
Abstract: Thermolyses of substituted 5-aminoisoxazoles, readily available from common starting materials, lead to azirines in good yields. Subsequent hydration affords bis-amide derivatives of amino acids.

At the heart of any efficient route to the specific ion sequestering cyclopeptide alkaloids[2] must lie a solution to the problem of 14-membered ring macrocycle formation. The difficulties encountered by others[2,3] in attempting to realize this goal have lead us to pursue a quite different strategy which, rather than invoking macrolactamization, relies on heteroaromatics as latent functionality,[4] in this case as amino acid (AA) derivatives. Previous reports discussing ongoing projects have revealed the AA content present in both oxazole[5] and imidazole rings.[6] By virtue of a thermal or photochemical reorganization/hydration sequence (below), isoxazoles[7] were perceived as AA equivalents as well. We now describe model studies on the development of substituted 5-aminoisoxazoles as a third inroad to the key functionality present in these alkaloids.



The educts 3 were arrived at in short order by standard literature procedures[8] in 60-80% overall yields. The initially formed primary amines 1 and 4 were then smoothly dibenzylated (before reduction to alcohol 2 beginning with 1). Modifications at C-4 in 2 thereby generated a series of suitable test cases (Scheme 1).



A: NaH, DMF; 2.5 $PhCH_2Br$, 0° to rt
B: 3 LAH, THF, 0° to rt
C: NaH, DMF, $PhCH_2Br$, 0°
D: NaH, DMF, CH_3I, 0°
E: Tf_2O, pyr.; NaSPh, DMF, 0°

3a, R = CH_2SPh
3b, R = CH_2OCH_2Ph
3c, R = CH_2OCH_3
3d, R = CH_3
3e, R = Ph
3f, R = H
3g, R = CH_2Ph
3h, R = $(CH_2)_2CH_3$

4d, R = CH_3
4e, R = Ph
4f, R = H
4g, R = CH_2Ph
4h, R = $(CH_2)_2CH_3$

Scheme 1

It was originally thought that photolyses of 3, under the proper conditions, would afford the desired azirines 5.[9] While with a few examples 5 was indeed isolated, yields were low and highly variable from run to run. It was later found that thermolyses[9a,10] using neat samples placed in a pear-shaped flask under argon and positioned in a sand bath at appropriate temperatures (175-260°) rapidly (10-12 min) lead to synthetically useful yields of rearranged materials 5 (Scheme 2 and Table I). Performing the reactions in inert media (e.g., mineral oil, toluene) gave inferior results.

Scheme 2

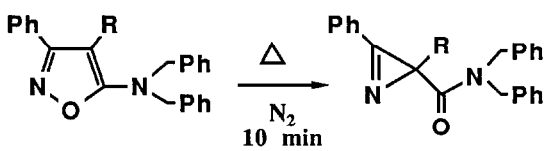
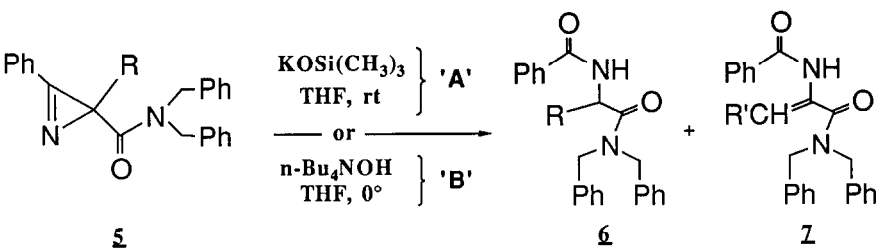


Table I

Isoxazole	Δ (°C)	Yield(%)
3a	175	70 (77)*
3b	250	68
3c	255	86
3d	230	69
3e	215	76 (84)*
3f	230	52 (72)*
3g	260	90 (92)*
3h	215	54 (78)*

*Yield based on recovered educt.

Hydrations of azirines 5 were anticipated to be straightforward, so long as mildly basic, rather than acidic, conditions were pursued.[11] Exposure of 5a-c to n-Bu_4NOH in THF (method 'B'), gave varying amounts of the desired products 6, along with by-products 7a-c (R' = H) resulting from what was originally ascribed to competing β-elimination. The identity of the by-product became less certain when traces were observed arising from the ring opening of azirine 5d (i.e., R = CH_3), where the leaving group (by analogy to 5a-c) is hydride. Switching to K^+TMSO^- as an equivalent[12] of HO^- (method 'A') dramatically increased the amount of this material (i.e., 7d) to ca. 27%. Although NMR data were fully in accord with compound 7d (R' = H) as the by-product (mp 131-133°), an X-ray analysis was performed to unequivocally confirm its structure (Figure 1). Interestingly, while the n-propyl case also gave the unsaturated product 7h (i.e., R' = Et), the benzyl substituted azirine 5g did not afford a similar product of oxidation, and in fact, an excellent yield of bis-amide 6g was obtained with either reagent (Table II).[13]



5 6 7

Table II

	'A'	'B'	'A'	'B'	Total(%) 'A'	'B'
a: R = CH_2SPh	--	trace	67	50	67	50
b: R = CH_2OCH_2Ph	27	27	70	70	97	97
c: R = CH_2OCH_3	--	49	--	13	--	62
d: R = CH_3	51	65	27	trace	78	65(84)*
e: R = Ph	--	85	--	--	--	85
f: R = H	--	69	--	--	--	69
g: R = CH_2Ph	97	80	--	--	97	80
h: R = $(CH_2)_2CH_3$	61	71	23	--	84	71(75)*

*Based on recovered starting material.

In summary, a two-step protocol which converts 5-aminoisoxazoles to amino acid bis-amides the key structural unit of the cyclopeptide alkaloids, has been demonstrated.

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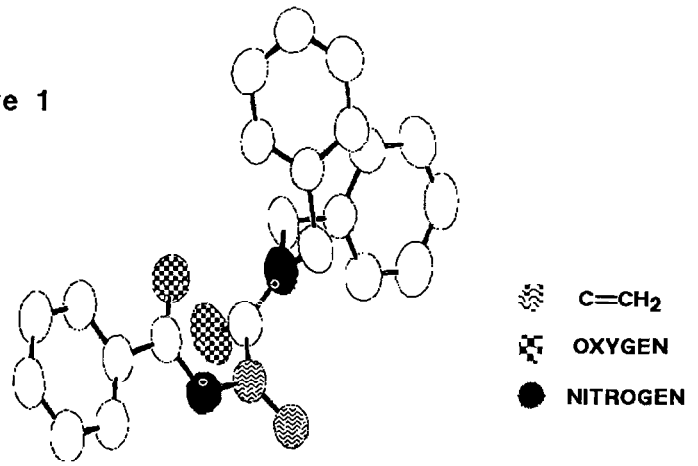
Figure 1



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