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Asymmetric Radical Cyclizations: The Synthesis of 6-Alkyl Pyrrolizidin-2-ones

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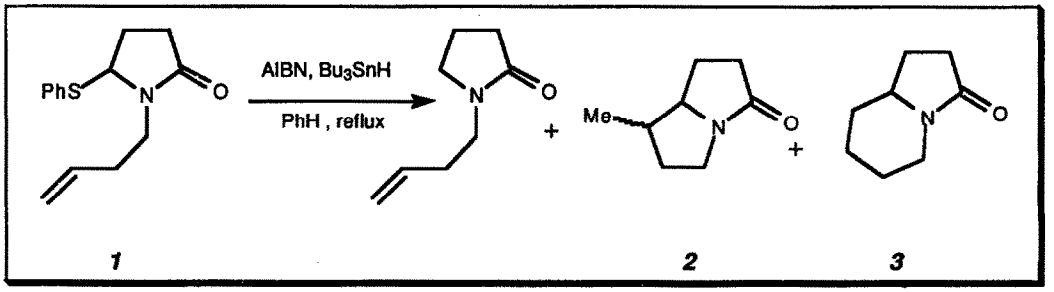
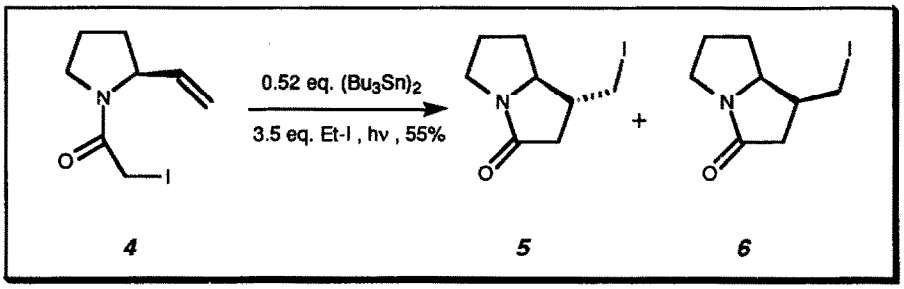
Abstract: This work describes the use of ethyl (5S)-carboethoxy-2-pyrrolidinone (ethyl pyroglutamate) as a chiral starting material for use in radical cyclization reactions. Pyroglutamate is converted to a 5-iodomethyl-N-allylic-2-pyrrolidinone that undergoes radical cyclization under mild conditions. The products are 6-substituted pyrrolizidinone derivatives, produced with high diastereoselectivity.

We previously communicated the radical cyclization of S-5-iodomethyl-1-alkenyl-2-pyrrolidinone derivatives.[2] This method generated pyrrolizidine type alkaloids that were not naturally occurring and is general for the synthesis of 6-substituted and 6,5-disubstituted derivatives. That communication showed the ability of the reaction to produce pyrrolizidinones with high diastereoselectivity and high enantioselectivity from pyroglutamate. The purpose of this report is to provide a full account of the work, describe the problems that were overcome to make pyroglutamate a useful chiral precursor for these compounds, and to describe the NMR characteristics of the compound that allowed facile identification by two-dimensional NMR techniques.

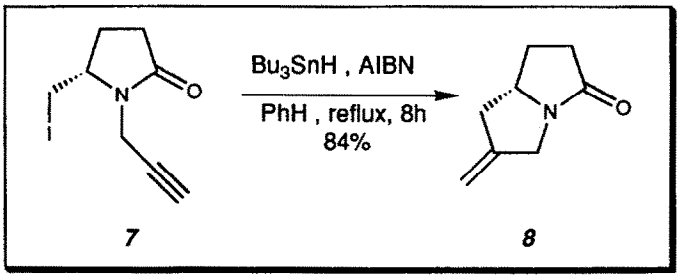
Over 300 plant and plant products are known to contain pyrrolizidine alkaloids. Pharmacologic properties include hepatatoxic effects, mutagenesis, and carcinogenesis.[3] Secondary metabolites activated in the liver are known to be antimiotigens, carcinogens, teratogens, and mutagens in animals.[3a] Efforts to synthesize pyrrolizidine alkaloids has been mainly directed towards the total stereoselective syntheses of simple necine bases such as retronecine[3] or hastanecine.[3] Most of the earlier synthetic routes to pyrrolizidine alkaloids (and to 1-azabicyclo alkaloids in general) rely on nucleophilic ring closures using Dieckmann or Aldol condensations. A few strategies use acid catalyzed ring closure routes. 3 + 2 cycloaddition strategies with nitrone derivatives have also led efficient syntheses of these alkaloids.[3b] A more recent approach introduced reductive, single electron transfer processes for the generation and cyclization of ω-unsaturated α-amino radicals for the syntheses of pyrrolizidine and piperidine rings,[4] (radical π-cyclization).[5]



Radical cyclization of molecules containing nitrogen has recently been used to prepare 'izidine' type alkaloids. Two syntheses of pyrrolizidine alkaloids were reported independently by Hart and Livinghouse. In Hart's work, N-butenyl-5-thiophenyl-2-pyrrolidinone, *1* cyclizes to give a mixture of pyrrolizidines, *2* indolizidines, *3*



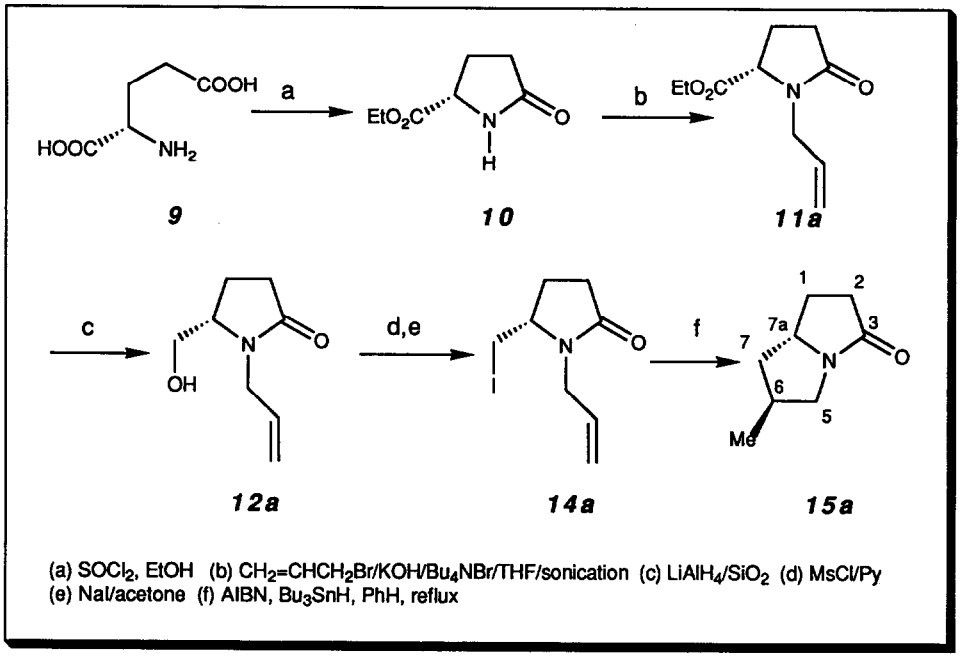
and reduced lactam, N-(1-but-3-enyl)-2-pyrrolidinone (84% combined yield).[6] The cyclized products were inseparable by chromatography but were isolated as their picrate salts (as a 2:1 ratio of *2* and *3*). The cyclization step was stereoselective (10:1), and the 5-exo-trig ring closure was favored over the 6-endo-trig process. Keck has reported a radical similar cyclization process.[7] In more recent work, Hart reported an asymmetric synthesis of swainsonine[8] and developed a general route to tri-hydroxylated indolizidines.



In Livinghouse's work, the pyrrolizidine derivative was formed by cyclization of 2-vinyl-iodoacetamide (*4*) via the action of (n-$Bu_3Sn)_2$ in moderate yields, with high diastereoselectivity (*5*:*6* = >30:1).[9] Cyclization of

iodoacetamide ***4*** using tributyltin hydride was sluggish, and led to a 2:1 ratio of hydrogen transfer product:***5/6*** in an 80% yield, favoring the reduced product. The use of $(n\text{-}Bu_3Sn)_2$ diminished the hydrogen transfer reaction and perhydroindolone ***6*** was formed in 58% yield.[9]

We wanted to explore the possibility that pyroglutamate (***10***) was a useful chiral precursor for the asymmetric synthesis of pyrrolizidine alkaloids. A pyroglutamate cyclization strategy would retain the advantages of but remove the difficulties inherent to prolinol cyclization. The pyroglutamate nitrogen is internally 'protected' as the lactam whereas prolinol must usually be protected as a carbamate or benzyl derivative, limiting the synthetic



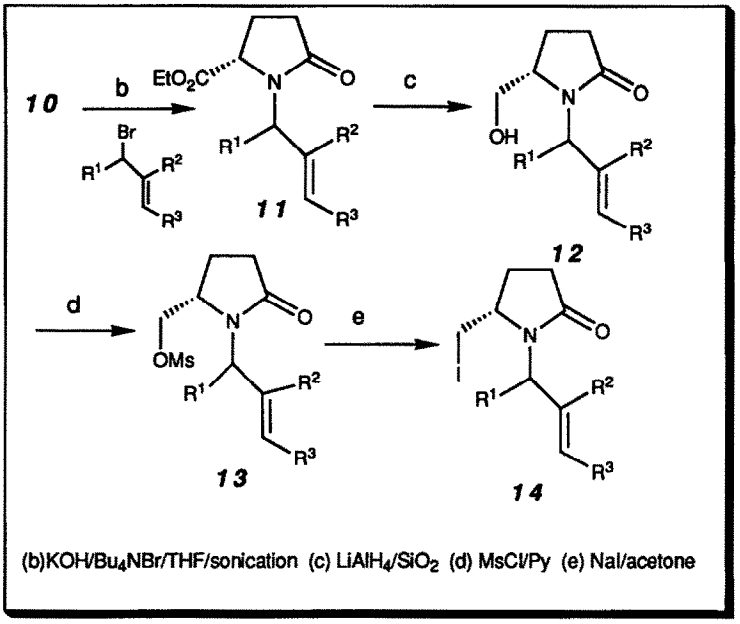
versatility. Pyroglutamate can be easily converted to the C_5 alkenyl derivative and cyclized with N-haloethyl or halopropyl substituents to give both pyrrolizidines and indolizidines. The C_5 ester of pyroglutamate can be converted to the halomethyl derivative, and cyclization via an N-alkenyl derivative provides an alternative cyclization mode for pyrrolizidines and indolizidines unavailable to prolinol based cyclizations.

Shortly after our initial communication, Knapp published a synthesis of pyrrolizidine alkaloids based on radical cyclization with pyroglutamate as a staring material.[10] A typical example of this cyclization is the conversion of ***7*** to pyrrolizidinone ***8***, in 84% yield. Knapp examined more complex substrates and extended the methodology to forming tricyclic alkaloids. The work described in our paper generated relatively simple bicyclic molecules.[2]

Silverman,[11] based on the method of Adkins and Billica,[12] showed that *L*-glutamic acid can be readily converted to S-ethyl pyroglutamate (***10***) by treatment with thionyl chloride and subsequent cyclization at 150°C.[2] Silverman's synthesis was modified by refluxing for an hour followed by Kugelrohr distillation (oven

temperature, 150°C at 3 mmHg) to give ***10***. The pyroglutamate could be further purified by recrystallization from ethyl acetate, but was usually used directly after Kugelrohr distillation.

Table 1. Preparation of 5-Iodomethyl-N-allyl-2-pyrrolidinones



	R^1	R^3	R^2	%11	%12	%13	%14
a	H	H	H	78	87	86	90
b	H	H	Ph	36	76	80	80
c	Me	H	H	38	91	85	73
d	$-CH_2CH_2CH_2-$		H	38	72	79	79
e	H	H	Me	40	66	75	83
f	H	Me	H	49	75	57	82

The next step was introduction of the N-allyl substituent. Attempts at alkylation with various bases proved ineffective. Takahata described a phase transfer method for the alkylation of simple lactams using tetrabutylammonium iodide and crushed potassium hydroxide in THF.[13] When this methodology was applied to the reaction of allyl bromide and ethyl pyroglutamate, the yields were less than 20 %. Improved yields were observed when the KOH was finely ground with mortar and pestle, and higher concentrations of tetrabutylammonium iodide (about 20%) also increased yields. The lactam and bromide had to be added to the basic solution very slowly (over a period of an hour), but these modifications increased yields to only 30 - 35%. Problems with the yield were finally circumvented when the reaction was done in an ultrasonic cleaning bath. Presumably, the ultrasound assists the phase transfer catalysts to better solvate the base.[14] Slow addition of ***10*** and allyl bromide to a rapid mechanical stirring mixture of KOH and tetrabutylammonium iodide in dry THF immersed in a sonic bath increased yields to 80 %. If excess KOH was used, however, saponification of the ethyl ester led to a small amount of N-allyl allyl ester pyrrolidinone.

The next step in the sequence required reduction of the pyroglutamate ester moiety to the C_5 hydroxymethyl derivative. Reduction of ***11a*** with $LiBH_4$ was very slow, required large excess of lithium borohydride and yielded less than 20% of the desired alcohol. A paper by Hojo suggested that $LiAlH_4$ on silica gel could lead to a less reactive and more selective reagent. Hojo reduced esters and ketones without reducing nitro and cyano groups in the same molecule.[15] Lithium aluminum hydride alone was known to reduce the lactam and the ester to the hydroxymethyl amine. When lactam ***11a*** was reacted with $LiAlH_4$ on silica gel, only the ester was reduced yielding the corresponding alcohol, ***12a***. Larger mesh silica worked better than finer grade TLC silica, and did not observe overreduction of the lactam. Yields were generally 80 - 90% and the resulting lactam alcohol showed a strong absorbance at both 3400 and 1680 cm^{-1} in the infrared, corresponding to an alcohol and a lactam carbonyl group, respectively.

Although it would have been desirable to go directly from the alcohol to the iodide, direct conversion was not facile. Conversion first to mesylate ***13a***, however, allowed conversion to the iodide ***14a*** by a normal Finkelstein exchange. The alcohol-iodide conversion proceeded in very high yields (>90%), and the iodide was easily isolated by chromatography. Both ***13a*** and ***14a*** were stable, with shelf lives of over two months.

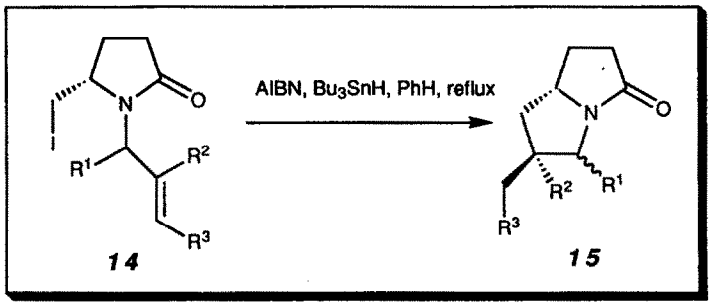
When ***14a***, AIBN and tributyltin hydride (in benzene) were refluxed overnight, radical cyclization of the N-allyl-5-iodomethyl-2-pyrrolidinone led to 6-methyl-3-pyrrolizidinone, ***15a***. The chiral center at C_5 had been preserved ($[\alpha]_D^{25}$ = +20.8 (dichloromethane, c = 0.0288g/mL)) and analysis by capillary GC/MS showed a single product, with no other detectable diastereomers. Using NMR techniques, we determined the selectivity of the ring closure by analysis of the stereochemical position of the methyl group at C_6 relative to the bridgehead hydrogen at C_{7a}.

The bridgehead hydrogen at C_{7a} showed up clearly as a pentet (J = 9 Hz) at 4.04 ppm relative to tetramethylsilane, and the exocyclic methyl at C_6 appeared as a doublet (J = 7.0 Hz) at 1.09 ppm. The C_6 proton was buried in a large multiplet around 2.3 ppm. That multiplet was comprised of four protons from the pyrrolidinone ring, a single methylene proton from the carbon α to the nitrogen, and the C_{7a} methine proton. The two methylene protons on C_5 showed very different chemical shifts. The *endo* proton appeared at 2.52 ppm and the *exo* proton was shifted downfield to 3.81 ppm. This difference in chemical shifts can be explained by diamagnetic anisotropy. The effect of an applied magnetic field for a carbonyl is greatest along the transverse axis of the C=O bond and extends in a cone shaped fashion outward.[16] The exo proton at the C_5 position is in a (-) region and is,therefore, deshielded (3.81 ppm). The *endo* proton is slightly shielded and appears at 2.3 ppm. similar behavior has been reported previously for quinolizidinones, with similar shifts for the appropriate protons. Although the *exo* C_5 proton appeared as a doublet of doublets and the coupling of the C_6 proton and the methyl was clear, the coupling constants could not be used to correlate the geometry of the C_6 proton since both *cis- and trans-* protons on five-membered rings give J values in the 4-5 Hz range.

A COSY experiment was employed to identify individual protons and their couplings. The strongest coupling observed in the 2-D spectra was between the endo and exo protons at C_5. The methyl showed strong coupling with the proton at C_6 which was buried in the large multiplet with the C_7 protons, as mentioned above. The bridgehead proton was clearly coupled to C_7 and C-1 as expected. Strong coupling within the large multiplet between 2.3 ppm and 2.6 ppm was due to the C_1 and C_2 protons. The relative position of every proton was established. No long range couplings were apparent between the C_6 proton and the C_{7a} proton. By inserting a fixed delay after each 90° pulse, the COSYLR experiment showed long range coupling between the exo C_5 proton and the bridgehead hydrogen, clearly a W-coupled enhanced signal. The *endo* C_5 proton was also

weakly coupled to the methyl (presumably by a W-type coupling) but not the *exo* C_5 proton. This suggests the methyl at C_6 is *exo* relative to the *endo* C_5 proton, which is the only way W type coupling could occur with the methyl If the methyl was down (*anti*) relative to the bridgehead hydrogen, the C_6 proton would be expected to show long range coupling with the bridgehead proton at C_{7a} because of a similar W-type orientation. On close inspection, none was evident. This was taken as additional evidence that the methyl must be up (*syn*) relative to the C_{7a} proton, i.e. the C_{7a} proton and the C_6 proton are *anti*. The NOESY experiment confirmed this stereochemistry, showing no evidence of spatial dipolar couplings for these protons. The NMR data showed that the radical cyclization is highly diastereoselective for the anti ring closure. When the methyl is down, the alkenyl carbons are almost "inside" the pyrrolidinone ring and the steric hindrance is too high for this to be a competitive mode of attack. Conversely, when the methyl is orientated up, the alkenyl carbons are out of the way, and the radical is free to attack the double bond. This *exo* selectivity was also observed by Livinghouse in *5*, relative to the C_{7a} proton.[9]

Table 2. Radical Cyclization of *14* to Pyrrolizidinone *15*.



14	Time (h)	Conc (mM)	%*15*
14a	4	10	70
14b	3	3.7	72
14c	12	4.3	54
14d	12	0.74	58
14e	12	0.22	72
14f	12	0.30	52

Carbon-13 spectroscopy, capillary GC/MS, and 2-D spectra all indicated high diastereoselectivity and high regioselectivity. HPLC (C-18 - reverse phase, acetonitrile) also showed a single sharp peak with a small peak (less than 1%) that would seem to suggest diastereoselectivity of greater than 100:1 for the *exo* isomer over the endo isomer. Comparable *exo* diastereoselectivity was observed by Livinghouse for the prolinol based cyclization. Formation of the indolizidinone was not observed for the allyl derivative under normal conditions. Using very dilute conditions (< 1 mM benzene), a small amount (less than one percent) was observed identified by a characteristic M - 1 peak in the mass spectrum.

In order to study the effect of substituted allylic moieties on ring cyclization, a number of derivatives were prepared. The crotyl and cinnamyl derivatives, ***14f*** and ***14b*** reacted similarly to ***14a***. Both derivatives gave

comparable yields of the N-allyl-2-pyrrolidinone and showed similar diastereoselectivity and regioselectivity in the cyclization reaction. The allylic substitution pattern on lactam ***11c*** introduced a new chiral center α to the nitrogen as a mixture of diastereomers. The iodo radical precursor, ***14c***, was shown to be a 60:40 mixture of diastereomers before cyclization. Cyclization of ***14c*** in 4.3 mM benzene gave a 65:35 mixture of cyclized diastereomers in 54% yield and the chiral center at C_5 reflected the lack of stereocontrol in the precursor, as expected. It would seem that the conformational bias for the equatorial isomer leads to some selectivity for the trans fused B-C ring in the cyclized product. The cyclization was highly diastereoselective with the C_6 position showing the expected preference for the alkyl group *anti* to the hydrogen at C_{7a}.

Substitution β to the nitrogen, at the point of annulation, leads to a number of interesting effects. Initially, ***14e*** was run in 20 mM in benzene and the major product was 5-methyl pyrrolidinone. By decreasing the concentration to 3 - 5 mM in benzene, reduction was minimized and radical cyclization was observed. If the solution were too dilute, decreased yields of cyclized product were observed. At 5 mM in benzene, cyclization of N-(2-methyl-1-propenyl)-pyrrolidinone (***14e***) led to a 60:40 mixture of two products, but the major peak in the mass spectrum of these products showed a M-1 peak not seen before in the pyrrolizidines. The minor product shows a mass spectrum similar to an expected pyrrolizidine. This strong M - 1 peak has been reported as being characteristic of indolizidines. Indolizidines can be formed from a disfavored 6-endo-trig ring closure and were observed in Hart's pyrrolizidine ring closures as minor products (less than 5%). Obviously the 3-methyl group hinders the preferred mode of attack forcing a 6-endo ring closure. From three dimensional models it appeared that with the methyl exo to the incoming radical, the radical is in closer proximity to the outlying alkenyl carbon because the adjacent carbon is now more distant.

Experimental Procedures

Melting points were determined with a Thomas-Hoover capillary melting point apparatus. All melting points are uncorrected. Infrared spectra were recorded with a Perkin Elmer Infrared Spectrophotometer Model 283 and recorded in reciprocal centimeters. ^1H NMR and ^{13}C NMR spectra were taken in d-chloroform on a IBM 270 MHz Spectrometer at 270.13 MHz and 67.3 MHz respectively, and reported in ppm using tetramethylsilane (TMS) as an internal standard. Multiplicities were determined either by off-resonance decoupling or INEPT experiments. High resolution mass spectra were measured on an AEI MS-902 mass spectrometer and are accurate to ±5 ppm. Apparatus for experiments requiring anhydrous conditions were flame dried, allowed to cool in a desiccator over calcium chloride and flushed with argon prior to use. Sonication was done in a Bransonic 220 cleaning bath that had been previously mapped for optimum sonication by floating aluminum foil 1 cm above the floor of the bath and recording where the aluminum had been disintegrated, and repeated with the aluminum foil suspended one cm below the surface of the water in the bath.

(S)-(+)-5-Carbethoxy-2-pyrrolidinone, *10*

The procedure of Adkins and Billica was modified to addition of 60 mL (0.8 mol) of freshly distilled thionyl chloride added to a suspension of *L*-glutamic acid (***9***, 51.2 g, 348 mmol) in 500 mL of commercial absolute ethanol cooled in an ice bath. The solution was stirred at room temperature for one hour and refluxed for a half an hour. Ethanol was removed *in vacuo*, and the viscous oil was heated under reduced pressure (140-150°C, 3 mm Hg) for three hours. The ester was purified by Kugelrohr distillation to yield colorless needles, of

10 mp 50-51°C (Lit. Mp., 51-52°C, 48-50°C)[11,12] (47.8 g, 303 mmol, 87%): ^{1}H NMR ($CDCl_3$): δ 7.2(1H, br),4.1(3H, m), 2.3(4H, m),and 1.3 ppm(3H, t); ^{13}C NMR ($CDCl_3$): δ 180(s),152(s), 61.6(t),56(d), 29.5(t), 22(t) and 14.4 ppm(q). Infrared (neat), 3230(br), 1740(s), 1700(s),1200(s), 1100(m), 1040(m),and 740(br) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 157(14), 135(8), 129(80),127(6), 99(8), 84(10), 83(100), 73(8), 56(44) and 55(6).

General Procedure for the Preparation of Allylic Lactams

A suspension of pulverized KOH (1.1 equivalents) and tetrabutyl ammonium iodide (0.20 equivalents)in 100 mL of dry THF was stirred by mechanical stirrer. The 3-neck round bottom flask was submerged in a sonic bath (Bransonic 220), and a solution of the allyl halide (1.1 equivalents) and lactam (1 equivalent) in 100 mL dry THF was added over one hour at room temperature with sonication. On completion of addition, the reaction mixture was stirred for 1-3 hours with sonication at room temperature. The precipitate was filtered off and the filtrate was evaporated in vacuo to leave an oil. On addition of ether, the phase catalyst crystallized and was filtered off. The filtrate was washed with water and brine. Solvent was evaporated and the product was isolated by column chromatography (ether/SiO2).

1-(2-Propenyl)-5-carboethoxy-2-pyrrolidinone, *11a*.

After addition of allyl bromide (22 mL, 25 mmol) and pyroglutamate *10* (38.8 g, 247 mmol) to the KOH (15.5 g, 28.0 mmol) and tetrabutylammonium iodide (TBAI) (16.2 g, 50.0 mmol), the reaction was checked by TLC every hour.When complete, *11a* (21 g, 11 mmol, 78%) was isolated and purified by column chromatography (R_f 0.52): ^{1}H NMR ($CDCl_3$): δ 5.7(1H, br), 5.17(2H, m), 4.22(4H, m), 3.6(1H, m), 2.40(4H, m) and 1.29(3H, t) ppm; ^{13}C NMR ($CDCl_3$): δ 174(s), 171(s), 131(d), 118(t), 61(t), 58.5(d), 44(t), 29(t), 22.5(t) and 14 ppm(q); Infrared(neat): 3500(br), 3073(m), 2982(s), 1733(s), 1697(s), 1411(m), 1190(s) and 924(m) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 197(8), 169(1), 142(1), 124(100), 96(7), 84(8) and 68(5); $[\alpha]_D^{25}$ = +1.88, c = 0.10 g/5 mL dichloromethane; HRMS Calcd for $C_{10}H_{15}NO_3$ m/z 197.1052, Observed m/z 197.1055 (±1.0 mmu).

1-(3-Phenyl-2-propenyl)-5-carboethoxy-2-pyrrolidinone, *11b*

Cinnamyl bromide (10 g, 51 mmol) and pyroglutamate *10* (16.0 g, 100 mmol) were added over forty minutes to a mechanically stirred suspension of KOH (6.00 g, 100 mmol) and TBAI (5 g). After two hours of sonication, *11b*, was isolated as a mixture of cis/trans isomers, (9.7 g, 36 mmol, 36%) was isolated and purified by column chromatography (R_f 0.42): ^{1}H NMR ($CDCl_3$): δ 7.28(5H, m), 6.45(1H, m),6.08(1H, m), 4.15(5H, m), 2.39(4H, m)and 1.21(3H, m) ppm; ^{13}C NMR ($CDCl_3$): δ 174.5(s), 171.7(s),134.8(s), 133.8(d), 133.6(d), 128.3(d), 128.2(d), 128.0(d), 127.6(d), 126.3(d), 126.1(d), 123.0(d), 123.0(d), 121.9(d), 65.6(t), 61.1(t), 58.9(d), 58.5(d), 43.7(t),43.7(t), 29.2(t), 22.6(t) and 13.8(q) ppm; Infrared (neat) 3466(br), 3030(m), 2975(m), 1959(w),1888(w), 1735(s), 1692(s), 1409(s), 1180(s), 967(s), 749(s)and 689(s) cm^{-1}. Mass Spectrum (m/z, rel. intensity): P^+ 273(30), 245(8), 200(27), 172(25), 144(15),117(100), 115(60), 91(25) and 85(10); $[\alpha]_D^{25}$ = -26.2, c = 0.17, dichloromethane; HRMS Calcd for $C_{16}H_{19}NO_3$ m/z 273.1365. Observed m/z 273.1371 (± 0.6 mmu).

1-(1-Methyl-2-propenyl)-5-carboethoxy-2-pyrrolidinone, *11c*

1-Bromo-2-methyl-propene (16.2 g, 120 mmol) and pyroglutamate *10* (15.0 g, 100 mmol) were added dropwise over thirty minutes to a mechanically stirred suspension of KOH (5 g) and TBAI (5 g). After three hours of sonication, *11c* (8.0 g, 38 mmol, 38%) was isolated and purified by column chromatography (R_f

0.42): ^{1}H NMR ($CDCl_3$): δ 4.71(2H, d),4.10(4H, m), 2.24(5H, m), 1.61(3H, s) and 1.21(3H, t) ppm; ^{13}C NMR ($CDCl_3$): δ 175.4(s), 172.1(s), 140.0(s), 113.3(t), 60.1(t),58.5(d), 45.2(t), 30.1(t), 23.5(q), 22.2(t), 17.6(q) ppm; Infrared (neat) 3490(br), 3070(w), 2980(m), 1738(s), 1699(s), 1410(s), 1243(br), 1290(m) and 900(m) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 211(25), 183(1),156(1), 138(100), 120(1), 94(30), 82(10) and 55(50); $[\alpha]_D^{25} = \pm 12.4$, c = 0.017 g/5 mL, dichloromethane; HRMS Calcd for $C_{11}H_{17}NO_3$ m/z 211.1208. Observed m/z 211.1212 (±0.4 mmu).

1-(2-Cyclohexenyl)-5-carboethoxy-2-pyrrolidinone, *11d*

3-Bromocyclohexene (57.3 g, 330 mmol) and pyroglutamate ***10*** (50.0 g, 320 mmol) were added dropwise to a mechanically stirred suspension of KOH (18.0 g, 330 mmol) and TBAI (10 g).After six hours of sonication ***11d***, isolated as a mixture of diastereomers, (28.0 g, 120 mmol, 38%) was isolated and purified by column chromatography (R_f = 0.42): ^{1}H NMR ($CDCl_3$): δ 5.81(1H, m), 5.24(1H, m), 4.12(3H, m), 2.25(4H, m), 1.93(7H, m) and 1.21(3H, t) ppm; ^{13}C NMR ($CDCl_3$): δ 178.7(s),175.2(s), 132.1(d), 131.7(d), 126.9(d), 126.1(d), 61.3(t), 61.3(t), 58.1(d), 57.6(d), 48.6(d), 48.0(d), 29.8(t), 26.9(t), 26.9(t), 24.7(t), 24.4(t), 24.0(t), 21.1(t), 20.7(t) and 14.0(q) ppm. Infrared (neat): 3325(br), 3031(w), 2925(s), 1734(s), 1693(s), 1446(m), 1193(s), 1023(m) and 741(s) cm^{-1}; Mass Spectrum (m/z, rel. intensity): 237(15), 209(30), 181(5),164(35), 136(40), 109(5), 84(100), 82(40), 79(25) and 53(10). $[\alpha]_D^{25}$ = +11.0, c = .043 g/5 mL, dichloromethane; HRMS Calcd for $C_{13}H_{19}NO_3$ m/z 237.1365, Observed m/z 237.1375 (±1.0 mmu).

1-(2-Methyl-2-propenyl)-5-carboethoxy-2-pyrrolidinone, *11e*

1-Chloro-3-methylbut-1-ene (11.0 g, 120 mmol) and pyroglutamate ***10*** (15.0 g, 100 mmol) were added dropwise to a mechanically stirred suspension of KOH (5.0 g, 90 mmol) and TBAI (5 g). After three hours of sonication, ***11e***, isolated as a mixture of diastereomers, (8.4 g, 40 mmol, 40%) was isolated and purified by column chromatography (R_f = 0.39): ^{1}H NMR ($CDCl_3$): δ 5.62(1H, m), 5.24(2H, m), 4.13(4H, m), 2.31(4H, m), 1.61(3H, dd) and 1.23(3H, t) ppm; ^{13}C NMR ($CDCl_3$): δ 175(s), 172.0(s), 130.5(d), 129.5(d), 124.7(t), 123.7(t), 61.3(t), 59.0(d), 58.9(d), 43.8(d),38.0(t), 29.7(t), 29.6(t), 22.9(q), 17.6(t) and 14.2(q) ppm; Infrared (neat) 3380(br), 2990(m), 2925(m), 1740(s), 1699(s), 1410(m), 1185(s), 1040(m) and 945(m) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 211(20), 183(5), 155(1), 138(50), 114(1), 110(10), 84(100) and 55(25). $[\alpha]_D^{25}$ = +16.3, c = 0.015 g/5 mL, dichloromethane; HRMS Calcd for $C_{11}H_{17}NO_3$ m/z 211.1208, Observed m/z 211.1210 (±0.2 mmu).

1-(3-Methyl-2-propenyl)-5-carboethoxy-2-pyrrolidinone, *11f*

Crotyl bromide (16.2 g, 120 mmol) and pyroglutamate ***10*** (15.0 g, 100 mmol) were added dropwise to a mechanically stirred suspension of KOH (5.0 g, 90 mmol) and TBAI (5 g). After six hours of sonication, ***11f***, isolated as a mixture of cis/ trans isomers, (10 g, 41 mmol, 49%) was isolated and purified by column chromatography (R_f = 0.39); ^{1}H NMR ($CDCl_3$): δ 5.55(1H, m),5.38(1H, m), 4.20(4H, m), 2.31(3H, M), 2.1(1H, m), 1.69(4H, m) and 1.29(3H, t) ppm; ^{13}C NMR ($CDCl_3$): δ 175.2(s), 172.0(s),130.5(d), 124.7(d), 123.7(d), 61.4(t), 59.0(d), 58.9(d), 43.7(d), 29.6(t),23.3(t), 22.9(q), 17.6(t) and 14.2(q) ppm; Infrared (neat) 3390(br), 2990(s), 2970(s), 1730(s), 1695(s), 1420(s), 1190(s), 1040(s), 970(m) and 800(m) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 211(15), 183(5), 155(5), 138(50), 110(10), 84(100) and 55(35); $[\alpha]_D^{25}$ = +15.1, c = 0.021 g/5 mL, dichloromethane; HRMS Calcd for $C_{11}H_{17}NO_3$ m/z 211.1208, Observed m/z 211.1212 (±0.4 mmu).

General Procedure for the Reduction of N-Allyl-2-pyrrolidinones

100 mL of dry ether was added to oven dried silica gel (.063-.200 mesh) and then $LiAlH_4$ was slowly added to this mechanically stirred slurry. The slurry was stirred for one hour. The ester was added dropwise and the reaction mixture was stirred at room temperature for three hours. The mixture was cooled in an ice bath and quenched using Fieser's method.[28] The slurry was filtered and washed with copious amounts of ether, dried with magnesium sulfate and solvent evaporated to yield alcohol.

1-(2-Propenyl)-5-hydroxymethyl-2-pyrrolidinone, *12a*

N-Allyl-5-Carbethoxy-2-pyrrolidinone, ***11a*** (8.8 g, 44 mmol) was added dropwise to a mechanically stirred solution of $LiAlH_4/SiO_2$ (2 g/ 50 g)in 100 mL of ether. The slurry was filtered and alcohol ***12a*** (5.9 g, 38 mmol, 87%) was purified by column chromatography (ether, SiO_2, $R_f = 0.12$): ^1H NMR ($CDCl_3$): δ 5.65(1H, m),5.11(2H, m), 4.17(1H, dd), 3.58(4H, m), 2.25(3H, m) and 2.00(2H, m); ^{13}C NMR ($CDCl_3$): δ 175.6(s), 132.4(d), 117.5(t), 61.9(t), 58.8(d), 43.1(t), 30.2(t) and 20.9(t); Infrared (neat) 3350(br), 3030(w),2990(m), 1667(vs), 1414(m) and 1054(m) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 155(5), 126(7), 124(100), 96(5), 84(9), 68(5) and 55(5); $[\alpha]_D^{25}$ = = +37.6, c = 0.32 g/5 mL, dichloromethane; HRMS Calcd for $C_8H_{13}NO_2$ m/z 155.0946, Observed m/z 155.0945 (±0.8 mmu).

1-(3-Phenyl-2-propenyl)-5-hydroxymethyl-2-pyrrolidinone, *12b*

N-Cinnamyl-5-carboethoxy-2-pyrrolidinone, ***11b*** (1.0 g, 3.7 mmol) was added dropwise to a mechanically stirred suspension of $LiAlH_4/SiO2$ (1.5 g/ 10 g)in 100 mL of ether. The slurry was filtered and alcohol ***12b*** was isolated as a mixture of isomers (0.65 g, 2.8 mmol, 76%), purified by column chromatography (ether/SiO_2, $R_f = 0.10$): ^1H NMR ($CDCl_3$): δ 7.31(5H, m), 6.51(1H, d), 6.32(1H, m), 3.66(3H, m), 3.20(2H, m), 2.39(1H, br) and 1.77(4H, m) ppm; ^{13}C NMR ($CDCl_3$): δ 175(s),136.9(s), 132.3(d), 128.5(d), 127.5(d), 127.0(d), 126.3(d), 64.2(t), 62.1(t), 56.6(d), 54.4(d), 27.8(t) and 23.5(t) ppm; Infrared (neat) 3390(br), 3020(w), 2930(m), 1667(s), 1441(m), 1410(m), 1235(m) and 956(m) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 186(40), 117(100), 91(10), 70(5) and 65(5); $[\alpha]_D^{25}$ = = +51.6, c = 0.19 g/5 mL, dichloromethane; HRMS Calcd for $C_{14}H_{17}NO_2$ m/z 231.1259, Observed m/z 231.1260 (±1.2 mmu).

1-(1-Methyl-2-propenyl)-5-hydroxymethyl-2-pyrrolidinone, *12c*

N-2-Methylprop-1-ene-5-carb, ***11c*** (1.0 g, 4.7 mmol) was added dropwise to a mechanically stirred suspension of $LiAlH_4/SiO_2$ (0.5 g/ 5 g)in 100 mL of ether. The slurry was filtered and alcohol ***12c*** (0.73 g, 4.3 mmol, 91%) was isolated by column chromatography (ether/SiO_2, $R_f = 0.12$): ^1H NMR ($CDCl_3$): δ 4.85(2H, d), 4.28(1H, br), 3.54(5H, m), 2.45(2H, m), 2.08(2H, m) and 1.67(3H, s) ppm; ^{13}C NMR ($CDCl_3$): δ 176.0(s), 140.0(s), 112.6(t), 61.7(t), 58.7(d), 46.3(t), 30.3(t), 20.9(t) and 19.8(q) ppm; Infrared (neat) 3378(br), 3073(m), 2953(s), 2833(m), 1670(s), 1432(s), 1283(m), 1077(br), 892(s) and 738(s) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 169(10), 140(10), 138(100), 110(5), 95(10), 84(30), 68(10) and 55(50); $[\alpha]_D^{25}$ = +41.8, c = 0.12 g/5 mL, dichloromethane; HRMS Calcd for $C_9H_{15}NO_2$ m/z 169.1103, Observed m/z 169.1110 (±0.8 mmu).

1-(2-Cyclohexenyl)-5-hydroxymethyl-2-pyrrolidinone, *12d*

N-Cyclohex-3-ene-5-carboethoxy-2-pyrrolidinone, ***11d*** (7.7 g, 32 mmol) was added dropwise to a mechanically stirred suspension of $LiAlH_4/SiO_2$ (5 g/45 g)in 100 mL of ether. The slurry was filtered and alcohol ***12d*** was isolated as a mixture of diastereomers (4.5 g, 23 mmol, 72%), purified by column chromatography (ether/SiO_2, $R_f = 0.12$): ^1H NMR ($CDCl_3$): δ 5.85(1H, m), 5.53(1H, m), 4.69(1H, br), 3.67(4H, m) and 2.04(10H, m) ppm; ^{13}C NMR ($CDCl_3$): δ 175.9(s), 131.4(d), 130.2(d), 129.2(d), 126.8(d),

64.3(t), 58.4(d), 58.3(d), 49.6(d), 48.4(d), 30.5(t), 28.5(t), 26.1(t), 24.7(t), 24.5(t), 22.3(t), 22.0(t), 21.8(t) and 21.6(t); Infrared (neat) 3388(br), 3004(w), 2934(s), 2860(m), 1664(m), 1448(m), 1207(m), 1076(m) and 798(m) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 195(30), 164(45), 136(27), 116(15), 94(5), 84(100) and 59(10). $[\alpha]_D^{25}$ = = -28.1, c = 0.024 g/5 mL, dichloromethane; HRMS Calcd for $C_{11}H_{17}NO_2$ m/z 195.1259, Observed m/z 195.1257 (±1.0 mmu).

1-(2-Methyl-2-propenyl)-5-hydroxymethyl-2-pyrrolidinone, *12e*

N-2-But-3-ene-5-carboethoxy-2-pyrrolidinone, ***11e*** (1.0 g, 4.7 mmol) was added dropwise to a mechanically stirred suspension of $LiAlH_4/SiO_2$ (0.5 g/5 g) in 100 mL of ether. The slurry was filtered and alcohol ***12e*** was isolated as a mixture of diastereomers (0.52 g, 3.1 mmol, 66%), purified by column chromatography (ether/SiO_2, R_f = 0.10): ^1H NMR ($CDCl_3$): δ 5.63(1H, m), 5.31(1H, m), 4.21(1H, m), 3.75(5H, m), 2.19(4H, m) and 1.70 ppm (3H, d); ^{13}C NMR ($CDCl_3$): δ 175.7(s), 129.5(d), 128.3(d), 125.5(t), 124.9(t), 62.5(t), 62.4(t), 59.1(d),58.9(d), 42.7(d), 37.5(t), 30.5(t), 21.0(t) and 17.6(q) ppm; Infrared (neat) 3400(br), 2974(s), 1654(s), 1451(m), 1045(s) and 880(m) cm^{-1}. Mass Spectrum (m/z, rel. intensity): P^+ 169(8), 138(55), 84(100) and 55(35). $[\alpha]_D^{25}$ = +55.4, c = 0.026 g/5 mL, dichloromethane; HRMS Calcd for $C_9H_{15}NO_2$ m/z 169.1103, Observed m/z 169.1110 (±0.8 mmu).

1-(3-Methyl-2-propenyl)-5-hydroxymethyl-2-pyrrolidinone, *12f*

N-Crotyl-5-carboethoxy-2-pyrrolidinone, ***11f*** (1.2 g, 5.7 mmol) was added dropwise to a mechanically stirred suspension of $LiAlH_4/SiO_2$ (0.8 g/ 6 g) in 100 mL of ether. The slurry was filtered and alcohol ***12f*** was isolated as a mixture of isomers (0.72 g, 4.3 mmol, 75%), purified by column chromatography (ether/SiO_2, R_f = 0.10): ^1H NMR ($CDCl_3$): δ 5.61(1H, m), 5.53(1H, m), 3.84(5H, m), 1.81(4H, m) and 1.26(3H, d) ppm; ^{13}C NMR ($CDCl_3$): δ 175.6(s), 130.6(d), 118(d), 62.4(t), 59.6(d), 42.7(t), 36.5(t), 30.8(t), 21.2(q) ppm; Infrared (neat) 3357(br), 2964(s), 2877(s), 1665(s), 1481(m), 1376(m), 1785(m), 1049(s), 880(m) and 738(m) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 138(50), 84(100), 55(40); $[\alpha]_D^{25}$ = +38, c = 0.005 7 g/5 mL, dichloromethane; HRMS Calcd for $C_9H_{15}NO_2$ m/z 169.1103, Observed m/z 169.1107 (±0.8 mmu).

General Procedure for the Conversion of Alcohol to Mesylate

To a stirred solution of alcohol (one equivalent) and methanesulfonyl chloride (1.1 equivalents) in 100 mL dry dichloromethane, triethylamine was added via syringe over 45 minutes under argon at -78°C. The solution was allowed to warm to room temperature over a period of two hours. The solution was washed with 50 mL 1N HCl, 50 mL water , 50 mL $NaHCO_3$, respectively. The combined aqueous layers were extracted once with dichloromethane and the combined organic layers were dried with magnesium sulfate. The solvent was removed under vacuum to give a yellow oil. Column chromatography (ether/SiO_2) yielded pure product.

1-(2-Propenyl)-5-hydroxymethyl-2-pyrrolidinone methanesulfonate, *13a*.

A solution of triethylamine (4.6 mL, 33 mmol) was added to a stirred solution of mesyl chloride (2.5 mL, 32 mmol) and the alcohol, ***12a*** (4.62 g, 30.0 mmol) at -78°C. After three hours, the mesylate (***13a***, 6.0 g, 26 mmol, 86%) was isolated (R_f = 0.10) and purified: ^1H NMR ($CDCl_3$): δ 5.68(1H, m),5.18(2H, dd), 4.24(3H, m), 3.84(1H, m), 3.50(1H, m), 2.98(3H, m) and 2.32(4H, m) ppm; ^{13}C NMR ($CDCl_3$): δ 174.6(s),132.2(d), 118.1(t), 68.2(t), 55.9(d), 43.4(q), 37.4(t), 29.5(t) and 21.0(t) ppm; Infrared (neat): 3358(br), 3030(w), 2938(s), 1686(s), 1415(m), 1356(s), 1176(s), 951(m) and 528(m) cm^{-1}; Mass Spectrum (m/z,rel. intensity): P^+ 233(10), 206(1), 154(1), 124(100), 96(10), 70(10) and 55(10). $[\alpha]_D^{25}$ = +23.2, c = 0.0995 g/5 mL, dichloromethane. HRMS Calcd for $C_9H_{15}NO_4S$ m/z 233.0722, Observed m/z 233.0723 (±1.2 mmu).

1-(3-Phenyl-2-propenyl)-5-hydroxymethyl-2-pyrrolidinone methanesulfonate, *13b*

A solution of triethylamine (1.4 mL, 9.8 mmol) was added slowly to a stirred solution of mesyl chloride (0.70 mL, 9.1 mmol) and the alcohol, ***12b*** (1.9 g, 8.2 mmol) at -78°C. After three hours, the mesylate, a mixture of isomers, (***13b***, 2.0 g, 6.6 mmol, 80%) was isolated and purified (R_f = 0.10): ^{1}H NMR ($CDCl_3$): δ 7.25(5H, m), 6.50(1H, d), 6.06(1H, m),4.15(3H, m), 3.88(2H, m), 2.92(3H, s) and 2.1(4H, m) ppm; ^{13}C NMR ($CDCl_3$): δ 174.8(s),137(s), 133.8(d), 128.6(d), 128.0(d), 126.4(d), 123.5(d), 66.2(t), 56.1(d), 43.1(q), 37.6(t), 29.7(t) and 21.2(t) ppm; Infrared (neat) 3410(br), 3030(w), 2948(m), 1676(s), 1450(m), 1358(s), 1176(s), 972(m), 909(s) and 732(s) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 309(50), 218(25), 200(30), 192(15), 172(20), 117(100), 115(70), 96(25) and 55(10); $[\alpha]_D^{25}$ = +29.4, c = 0.0252 g/5 mL, dichloromethane; HRMS Calcd for $C_{15}H_{19}NO_4S$, m/z 309.1035, Observed m/z 309.1035 (±1.5 mmu).

1-(1-Methyl-2-propenyl)-5-hydroxymethyl-2-pyrrolidinone methanesulfonate, *13c*

A solution of triethylamine (5.0 mL, 34 mmol) was added slowly to a stirred solution of mesyl chloride (2.5 mL, 32 mmol) and the alcohol, ***12c*** (5.0 g, 30 mmol) at -78°C.After three hours, the mesylate (***13c***, 6.4 g, 26 mmol, 85%) was isolated and purified (R_f = 0.10): ^{1}H NMR ($CDCl_3$): δ 4.82(2H, d), 4.18(3H, m), 3.7(2H, m), 2.98(3H, s), 2.1(4H, m) and 1.62(3H, s) ppm; ^{13}C NMR ($CDCl_3$): δ 174.9(s), 139.9(s), 113.3(t), 68.0(t), 55.9(d), 46.7(q), 37.6(t), 29.6(t), 21.2(t) and 19.8(t) ppm; Infrared (neat): 3350(br), 3030(w),2930(s), 1665(s), 1410(s), 1340(s), 1170(s), 947(br) and 850(m) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 247(20), 206(3), 192(2), 152(3), 138(100), 110(8), 94(25), 82(4) and 55(55); $[\alpha]_D^{25}$ = +7.5, c = 0.0057 g/5 mL, dichloromethane; HRMS Calcd for $C_{10}H_{17}NO_4S$, m/z 247.0878 mmu, Observed m/z 247.0884 (±1.2 mmu).

1-(2-Cyclohexenyl)-5-hydroxymethyl-2-pyrrolidinone methanesulfonate, *13d*

A solution of triethylamine (17 mmol) was added slowly to a stirred solution of mesyl chloride (13 mmol) and the alcohol, ***12d*** (2.0 g, 11 mmol) at -78°C. After three hours, the mesylate, a mixture of diastereomers, (***13d***, 2.37 g, 8.70 mmol, 79%) was isolated and purified (R_f = 0.10): ^{1}H NMR ($CDCl_3$): δ 5.92(1H, m), 5.43(1H, m), 4.58(1H, m),4.00(3H, m), 2.98(3H, s) and 1.99(10H, mm) ppm; ^{13}C NMR ($CDCl_3$): δ 175.4(s), 132.2(d), 130.4(d),128.6(d), 126.1(d), 69.1(t), 69.0(t), 55.19(d), 49.3(q), 37.6(t), 29.9(t), 28.5(t), 24.5(t), 22.2(t) and 21.4(t) ppm; Infrared (neat) 3010(w), 2940(m), 1673(s), 1420(m), 1355(s), 1170(s), 970(m), 937(m) and 840(m) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 273(40), 245(6), 200(35), 172(30), 144(10), 117(100), 115(50), 91(25) and 65(4); $[\alpha]_D^{25}$ = -36.9, c = 0.0467 g/5 mL, dichloromethane; HRMS Calcd for $C_{12}H_{19}NO_4S$, m/z 273.1035, Observed m/z 273.1039 (±1.4 mmu).

1-(2-Methyl-2-propenyl)-5-hydroxymethyl-2-pyrrolidinone methanesulfonate, *13e*

A solution of triethylamine (3.3 mmol) was added slowly to a stirred solution of mesyl chloride (3.1 mmol) and the alcohol, ***12e*** (0.50 g, 3.0 mmol) at -78°C. After three hours, the mesylate, a mixture of diastereomers, (***13e***, 0.55 g, 2.2 mmol, 75%) was isolated and purified (R_f = 0.10): ^{1}H NMR ($CDCl_3$): δ 5.75(1H, m), 5.35(1H, m), 4.32(3H, m),3.8(2H, m), 3.05(3H, s), 2.3(4H, m) and 1.70(3H, dd) ppm; ^{13}C NMR ($CDCl_3$): δ 174.8(s), 130.1(d), 128.9(d), 125.0(t), 124.4(t), 68.3(t), 56.0(d), 55.6(d), 42.7(q), 37.6(t), 29.8(t), 21.1(t) and 17.7(t) ppm; Infrared (neat) 3461(br), 3008(w), 2936(m), 1682(s), 1447(m)m 1419(m), 1349(s), 1169(s), 945(s) and 858(m) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 247(30), 206(3), 168(2), 138(60), 110(10), 84(100) and 55(50); $[\alpha]_D^{25}$ = -13.6, c = 0.0182 g/5 mL, dichloromethane; HRMS Calcd for $C_{10}H_{17}NO_4S$, m/z 247.0878, Observed m/z 247.0878(±1.2 mmu).

1-(3-Methyl-2-propenyl)-5-hydroxymethyl-2-pyrrolidinone methanesulfonate, *13f*

A solution of triethylamine (7.0 mL) was added slowly to a stirred solution of mesyl chloride (5 mL) and the alcohol, ***12f*** (9.0 g, 53 mmol) at -78°C. After three hours, the mesylate was isolated as a mixture of isomers, (***13f***, 7.5 g, 30 mmol, 57%) and purified (R_f = 0.10): ^{1}H NMR ($CDCl_3$): δ 5.66(1H, m), 5.35(1H, m), 4.23(3H, m), 3.93(1H, m), 3.58(1H, m), 3.05(3H, s), 2.22(4H, m) and 1.69(3H, d) ppm; ^{13}C NMR ($CDCl_3$): ∂ 175.3(s), 130.3(d), 124.8(d), 68.5(t), 56.1(d), 42.8(q), 37.6(t), 29.9(t) and 17.7(q) ppm; Infrared(neat) 3422(br), 3019(w), 2932(m), 1670(s), 1458(m), 1419(m), 1354(s), 1169(s) and 945(s) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 246(100), 206(10), 194(2), 150(4), 133(1), 122(2), 84(40) and 53(20); $[\alpha]_D^{25}$ = -19.1, c = 0.0530 g/5 mL, dichloromethane; HRMS Calcd for $C_{10}H_{17}NO_4S$, m/z 247.0878, Observed m/z 247.0883 (±1.2 mmu).

General Procedure for the Conversion of the Mesylate to the Iodide

The mesylate (one equivalent), NaI (oven dried under vacuum), and anhydrous acetone were stirred twelve hours under argon,then refluxed for one hour. The solution was filtered, washed with acetone, and the solvent evaporated *in vacuo* to yield yellow oil. Ether was added, and the ether layer was washed with water, saturated sodium sulfite, and brine. Ether was removed under vacuum, and the product was purified by column chromatography (ether/SiO_2).

1-(2-Propenyl)-5-iodomethyl-2-pyrrolidinone, *14a*

The mesylate (***13a***, 5.10 g, 22.0 mmol) and NaI (6.6 g, 44 mmol) in 70 mL acetone were stirred overnight and refluxed for one hour yielding the iodide, ***14a*** (5.3 g, 20 mmol, 90%)(R_f = 0.36): ^{1}H NMR ($CDCl_3$): δ 5.75(1H, m), 5.22(2H, dq), 4.3(1H, dq), 3.30(4H, m), 2.37(3H, m) and 1.82(1H, m) ppm; ^{13}C NMR ($CDCl_3$): δ 174.6(s), 132.4(d), 118.4(t), 56.9(d), 43.2(t), 29.7(t), 24.8(t) and 10.8(t) ppm; Infrared (neat) 3487(br), 3084(w), 2953(m), 1686(s), 1643(m), 1447(m), 1409(s), 1348(m), 1251(s), 1209(m), 994(m), 924(m) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 265(20), 210(2), 181(1), 167(1), 124(100), 84(5) and 55(10); $[\alpha]_D^{25}$ = -9.1, c = 0.059 g/5 mL, dichloromethane; HRMS Calcd for $C_8H_{12}NOI$, m/z 264.9966, Observed m/z 264.9970 (±1.3 mmu).

1-(3-Phenyl-2-propenyl)-5-iodomethyl-2-pyrrolidinone, *14b*

The mesylate (***13b***, 1.0 g, 3.2 mmol) and NaI (2.0 g, 12 mmol) in 20 mL acetone were stirred overnight and then refluxed for one hour yielding the iodide, ***14b*** as a mixture of isomers(0.90 g, 26 mmol, 80%, R_f=0.36): ^{1}H NMR ($CDCl_3$): δ 7.31(5H, m), 6.60(1H, d), 6.15(1H, m), 4.51(1H, dd), 3.78(2H, m), 3.42(2H, m), 2.58(2H, m)and 2.0(2H, m) ppm; ^{13}C NMR ($CDCl_3$): δ 174.7(s),136.1(s), 133.6(d), 128.6(d), 128.0(d), 126.5(d), 123.7(d), 57.0(d), 42.8(t), 29.8(t), 24.9(t) and 11.0(t) ppm; Infrared (neat) 3445(br), 3019(w), 2942(m), 2844(m), 1681(s), 1612(w), 1447(m), 1414(m), 1245(m), 1158(w), 967(m), 749(m) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 341(100), 250(45), 226(50), 215(30),200(10), 132(100), 117(75), 115(100), 101(40) and 55(40); $[\alpha]_D^{25}$ = -8.78, c = 0.0390 g/5 mL, dichloromethane; HRMS Calcd for $C_{14}H_{16}NOI$, m/z 341.0279, Observed m/z 341.0227 (±1.7 mmu).

1-(1-Methyl-2-propenyl)-5-iodomethyl-2-pyrrolidinone, *14c*

The mesylate (***13c***, 5.0 g, 20 mmol) and NaI (8.0 g, 53 mmol) in 80 mL acetone were stirred overnight and then refluxed for one hour yielding the iodide, ***14c*** (4.1 g, 15 mmol, 73%, R_f =0.39). ^{1}H NMR ($CDCl_3$): δ 4.88(2H, d),4.30(1H, d), 3.61(1H, m), 3.32(3H, m), 2.42(2H, m), 1.95(2H, m) and 1.68(3H, s) ppm; ^{13}C NMR ($CDCl_3$): δ 175.6(s), 140.0(s), 113.7(t), 56.8(d), 46.5(t), 29.7(t), 24.9(t), 20.1(q) and 10.4(t) ppm; Infrared (neat) 3073(w), 2962(m), 2922(m), 1688(s), 1650(m), 1419(m), 1245(m), 896(m) cm^{-1}; Mass Spectra

(m/z, rel. intensity): P^+ 279(50), 264(10), 238(7), 210(3), 181(1),153(30), 138(100), 110(5), 94(20) and 55(75); $[\alpha]_D^{25}$ = -21.6, c = 0.121 g/5 mL, dichloromethane.

1-(2-Cyclohexenyl)-5-iodomethyl-2-pyrrolidinone, *14d*

The mesylate (***13d***, 1.0 g, 3.7 mmol) and NaI (2.0 g, 14 mmol) in 30 mL of acetone were stirred overnight and then refluxed for one hour yielding the iodide, ***14d*** as a mixture of diastereomers (0.89 g, 29 mmol,79%, R_f = 0.42): ^1H NMR ($CDCl_3$): δ 5.82(1H,m), 5.50(1H, m), 4.75(1H, m), 3.79(1H, m), 3.15(2H, m), 2.50(1H, m) and 1.8(9H,m) ppm; ^{13}C NMR ($CDCl_3$): δ 175.1(s), 131.8(d), 129.7(d), 129.0(d), 126.0(d), 57.2(d), 57.0(d), 49.4(d), 48.0(d),29.7(t), 29.4(t), 29.2(t), 26.3(t), 25.8(t),25.5(t), 24.5(t), 24.3(t), 21.7(t), 21.5(t), 12.3(t) and 12.0(t) ppm; Infrared(neat): 3350(w), 3010(w), 2930(s),1668(s), 1400(s), 1265(m), 1233(m), 1190(m),1162(m), 978(w) and 721(m) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 305(45), 277(10), 264(1), 226(50), 178(100), 164(10), 150(10), 136(20), 123(18), 96(75), 84(25), 80(23) and 55(25); $[\alpha]_D^{25}$ = -80.8, c = 0.118 g/5 mL, dichloromethane; HRMS Calcd for $C_{11}H_{16}NOI$, m/z 305.0279, Observed m/z 305.0276 (±1.5 mmu).

1-(2-Methyl-2-propenyl)-5-iodomethyl-2-pyrrolidinone, *14e*

The mesylate (***13e***, 0.50 g, 2.0 mmol) and NaI (1.0 g, 7.0 mmol) in 10 mL of acetone were stirred overnight and the refluxed for one hour yielding the iodide, ***14e*** as a mixture of diastereomers (0.46 g, 1.6 mmol, 83%, R_f = 0.40): ^1H NMR ($CDCl_3$): δ 5.68(1H,m), 5.41(1H, m), 4.35(1H, m), 3.6(2H, m), 3.34(2H, m),2.37(3H, m), 1.83(1H, m) and 1.72(3H, s) ppm; ^{13}C NMR ($CDCl_3$): δ 174.7(s), 130.0(d), 128.9(d), 125.2(t), 124.4(t), 57.1(d), 56.9(d), 42.6(d), 29.9(t), 24.9(t), 17.7(q), 11.0(t) and 10.9(t) ppm; Infrared (neat) 3455(br), 3019(w), 2921(m), 1681(s), 1414(m), 1196(m), 1147(m), 1048(m) and 967(m) cm^{-1}; $[\alpha]_D^{25}$ = -20, c = 0.0016 g/5 mL, dichloromethane; HRMS Calcd for $C_9H_{14}NOI$, m/z 279.0122, Observed m/z 279.0119 (±1.4 mmu).

1-(3-Methyl-2-propenyl)-5-iodomethyl-2-pyrrolidinone, *14f*

The mesylate (***13f***, 0.40 g, 1.6 mmol) and NaI (1.0 g, 7.0 mmol) in 10 mL of acetone were stirred overnight and then refluxed for one hour yielding the iodide, ***14f*** as a mixture of isomers (0.37 g, 1.3 mmol, 82%, R_f = 0.42): ^1H NMR ($CDCl_3$): δ 5.65(1H,m), 5.37(1H, m), 4.27(1H, m), 3.62(1H, m), 3.33(3H, m), 2.35(3H, m), 1.80(1H, m) and 1.71(3H, d) ppm; ^{13}C NMR ($CDCl_3$): δ 174.6(s), 129.9(d), 125.0(d), 56.8(d), 42.5(t), 29.8(t), 24.8(t), 17.7(q) and 11.0(t) ppm; Infrared (neat) 3422(br), 3010(w), 2929(m), 1681(s), 1442(m), 1196(m) and 962(m) cm^{-1};$[\alpha]_D^{25}$ = -9.1, c = 0.0016 g/5 mL, dichloromethane; HRMS Calcd for $C_9H_{14}NOI$,m/z 279.0122, Observed m/z 279.0123 (±1.4 mmu).

General Procedure for Radical Ring Closure

The iodide (3-6 mM) and 1.1 equivalents of tributyltin hydride were dissolved in benzene and a catalytic amount of AIBN was added. The solution was degassed and then refluxed for 3-12 hours under argon. Solvent removal and chromatography (ether/SiO_2) gave pure cyclized product.

6-Methyl-Tetrahydropyrrolizin-3-one, *15a*

Refluxing iodide ***14a*** (1.3 g, 4.9 mmol, 10 mM), Bu_3SnH (2.64 mL, 9.80 mmol) and a catalytic amount of AIBN for four hours yielded ***15a*** (0.48 g, 3.5 mmol, 70%, R_f 0.38): ^1H NMR ($CDCl_3$): δ 4.07(1H, q), 3.93(1H, dd), 2.52(3H, m), 2.37(2H, m), 1.61(3H, m), 1.01(3H, m) ppm; ^{13}C NMR ($CDCl_3$): δ 175.3(s), 60.2(d), 49.3(t),39.7(t), 34.9(t), 34.5(d), 28.3(t), 19.6(q) ppm; Infrared (neat) 3365(br), 2966(m), 2880(m), 1672(s), 1414(m), 1302(m), 1178(m), 908(s) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 139(50), 124(3),110(2), 97(100), 84(12), 69(50), 55(40), 41(45); $[\alpha]_D^{25}$ = +20.8, c = 0.144 g/5 mL, dichloromethane; HRMS Calcd for $C_8H_{13}NO$, m/z 139.0997, Observed m/z 139.1005 (±0.8 mmu).

6-Benzyl-Tetrahydropyrrolizin-3-one, *15b*

Refluxing iodide ***14b*** (0.84 g, 2.5 mmol, 25 mM), Bu_3SnH (1.0 mL, 3.7 mmol) and a catalytic amount of AIBN for three hours yielded ***15b***(0.38, 1.8 mmol, 72%). ^1H NMR ($CDCl_3$): δ 7.30(5H, m), 4.00(1H, q), 3.82(1H, dd), 3.62(2H, m), 2.58(2H, m), 2.35(3H, m), 1.67(3H, m); ^{13}C NMR ($CDCl_3$): δ 176(s), 136.5(s), 130.0(d), 126.9(d), 124.2(d), 60.2(d), 45.1(t), 42.1(t), 36.0(d), 34.4(t), 28.0(t); Infrared (neat) 3433(br), 3019(w), 2932(m), 2877(m), 1686(s), 1490(m), 1452(m), 1414(m), 1294(m), 1191(w), 1027(w), 913(w) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 215(85), 187(5),160(5), 137(100), 124(90), 97(75), 91(70), 69(30), 68(29), 55(10); $[\alpha]_D^{25}$ = -8.39, c = 0.0408 g/5 mL, dichloromethane; HRMS Calcd for $C_{14}H_{17}NO$, m/z = 215.1310, Observed m/z = 215.1308 (±1.1 mmu).

5, 6-Dimethyltetrahydropyrrolizin-3-one, *15c*

Refluxing iodide ***14c*** (0.050 g, 0.18 mmol, 4.3 mM), Bu_3SnH (0.060 mL, 0.22 mmol) and a catalytic amount of AIBN for twelve hours yielded cyclized product, ***15c*** (0.015 g, 0.10 mmol, 54%) as a 65:35 mixture of diastereomers: ^1H NMR ($CDCl_3$): δ 4.00(1H, m), 3.85(1H, dd), 2.56(2H, m), 2.33(2H, m), 1.70(3H, m), 1.4(2H, m), 0.93(6H, m); ^{13}C NMR ($CDCl_3$): δ 174.5(s), 60.1(d), 47.4(d), 41.9(t), 39.3(d), 35.1(t), 28.5(t), 27.2(q), 12.5(q) ppm; Infrared (neat) 3394(br), 2957(m),2929(m), 1692(s), 1408(s), 1297(m), 1129(w) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 153(40), 138(5), 124(7), 110(5), 97(100), 84(7), 69(50), 68(25), 55(30); $[\alpha]_D^{25}$ = -6.3, c = 0.0013 g/5 mL, dichloromethane; HRMS Calcd for $C_9H_{15}NO$, m/z = 153.1154, Observed m/z = 153.1157 (±0.8 mmu).

Hexahydro-3-oxo-pyrrolo[1,2-a]indole, *15d*

Refluxing iodide ***14d*** (0.15 g, 0.49 mmol, 6 mM), Bu_3SnH (0.20 mL, 0.74 mmol), and a catalytic amount of AIBN for twelve hours yielded ***15d*** (0.051 g, 0.29 mmol 58%, R_f 0.38): ^1H NMR ($CDCl_3$): δ 3.94(1H, m), 3.57(1H, q), 2.43(5H, M), 1.75(6H, m), 1.25(4) ppm; ^{13}C NMR ($CDCl_3$): δ 173.4(s), 63.1(d), 53.1(d), 41.1(t), 37.0(d), 33.8(t), 29.9(t), 28.0(t), 26.7(t), 23.1(t), 21.5(t) ppm; Infrared (neat) 3373(br), 2925(m), 2854(m), 1684(s), 1455(m), 1404(m), 1297(m), 1170(m), 1119(m), 758(w), 667(m) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 179(50), 150(10), 138(100), 124(10), 100(5), 95(7), 85(15), 84(15), 68(20), 55(18); $[\alpha]_D^{25}$ = -15.5, c = 0.0119 g/5 mL, dichloromethane; HRMS Calcd for $C_{11}H_{17}NO$, m/z = 179.1310, Observed m/z = 170.1314 (±0.9 mmu).

6, 6-Dimethyltetrahydropyrrolizin-3-one, *15e*

Refluxing iodide ***14e*** (0.055 g, 0.20 mmol, 5 mM), Bu_3SnH (0.060 mL, 0.22 mmol) and a catalytic amount of AIBN for twelve hours yielded a 60:40 mixture of 5, 6-dimethylindolizidin-2-one and pyrrolizidine, ***15e***, respectively and 23 % of N-(2-methyl-2-propenyl)-5-methyl-2-pyrrolidinone (0.022 g, 0.14 mmol, 72 %, R_f 0.36): ^1H NMR ($CDCl_3$): δ 5.68(2H, m), 4.23(1H, m), 4.00(1H, m), 3.85(1H, dd), 2.56(2H, m), 2.33(2H, m), 1.70(3H, m), 1.4(2H, m) and 0.93 ppm (6H, m); ^{13}C NMR ($CDCl_3$): δ 174.2, 173.5, 116.4, 62.5, 60.1, 58.1, 49.4, 48.2, 47.4, 46.1, 41.9, 39.3, 38.7, 36.3, 36.0, 35.1, 34.9, 34.8, 34.2, 34.0, 32.7, 32.1, 29.3, 28.5, 27.2, 26.5, 25.8, 24.3, 21.5, 17.8, 16.8, 15.9. 12.5 ppm; Infrared (neat) 3394(br), 2957(m),2929(m), 1692(s), 1408(s), 1297(m), 1129(w) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 153(40), 138(5), 97(100), 82(7), 69(50), 68(25), 55(30) and P^+ 153(90), 152(100), 138(70), 124(32), 110(75), 98(85), 84(90), 68(39), 55(82); $[\alpha]_D^{25}$ = -2.3, c = 0.0012 g/5 mL, dichloromethane; HRMS Calcd for $C_9H_{15}NO$, m/z = 153.1154, Observed m/z = 153.1157 (±0.8 mmu).

6-Ethyltetrahydropyrrolizin-3-one, *15f*

Refluxing iodide ***14f*** (0.070 g, 0.25 mmol, 3 mM), Bu_3SnH (0.08 mL, 0.3 mmol), and a catalytic amount of AIBN for twelve hours yielded ***15f***(0.020 g, 0.13 mmol, 52%): ^1H NMR ($CDCl_3$): δ 3.98(1H, q), 3.85(1H, dd), 2.60(2H, m), 2.37(3H, m), 1.66(3H, m), 1.43(2H, q), 0.92(3H, t) ppm; ^{13}C NMR ($CDCl_3$): δ 175(s), 60.2(d), 47.5(t), 41.9(t), 37.6(d), 34.6(t), 28.6(t), 27.3(t), 12.5(q) ppm; Infrared (neat) 3443(br), 2956(m), 2925(m), 2866(m), 1689(s), 1466(m), 1409(m), 1292(m), 1130(m), 1028(w) cm^{-1}; Mass Spectrum (m/z, rel. intensity): P^+ 153(30), 138(3), 124(5), 110(5), 97(100), 84(7), 69(50), 55(30); HRMS Calcd for $C_9H_{15}NO$, m/z = 153.1154, Observed m/z = 153.1154 (±0.8 mmu).

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