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Molecular Cascades. 1. Tandem Cyclopropyl Iminium Ion Rearrangement-[4+2] Cycloaddition Reactions‡

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Abstract: A tandem cyclopropyliminium ion rearrangement-Hofmann elimination affords rapid access to 3-vinyl Δ^2-pyrrolines in some cases bearing an unsaturated tether in good yield. The resulting dienamines subsequently undergo both inter- and intramolecular [4+2] cycloaddition reactions. Good yields were obtained for a number of cases of intramolecular intermolecular cycloaddition reactions affording cycloadducts in good yields with sufficiently reactive dienophiles such as fumarate, acrylate and methacrolein. Evidence suggests a non-concerted pathway for these cycloaddition reactions. © 1997 Elsevier Science Ltd.

INTRODUCTION

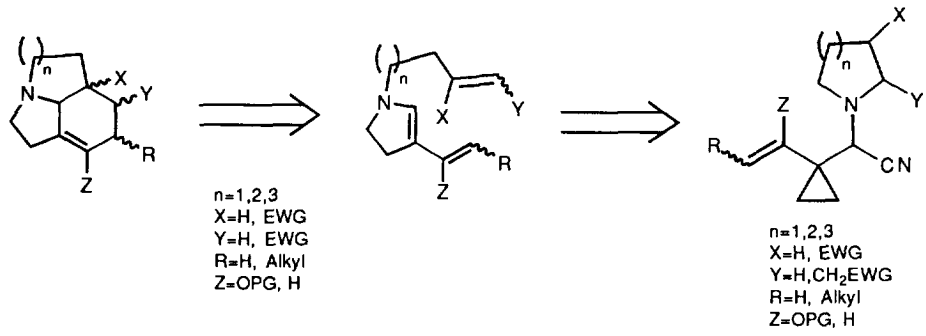
The rearrangement of cyclopropyliminium ions to Δ^2-pyrrolines has a rich history,[1-3] and the value of Δ^2-pyrrolines as intermediates for the synthesis of a variety of structural classes of alkaloids has been amply demonstrated by the late R. V. Stevens in a comprehensive series of papers from his laboratories appearing between 1967-77.[4,5] Somewhat later, Pinnick applied the rearrangement to cyclopropyl Δ^1-pyrrolines also on route to the pyrrolizidine alkaloids.[6] Following Stevens' investigations, Wasserman and coworkers examined the rearrangement of donor stabilized imines derived from cyclopropyl aldehydes, ketones, and dicyclopropyl ketones, finding that the rearrangement took a somewhat different course in these cases, affording five-membered rings via donor-stabilized cyclobutyl cations, and applied the reaction to the synthesis of pyrroles and pyrrolizidine alkaloids.[7,8]

Our interest in this process arose originally from our need to access functionalized 3-vinyl Δ^2-pyrrolines as intermediates for our approach to the Amaryllidaceae alkaloid lycorine.[3,9-11] Our investigations of the alkyl iminium ion variant were stimulated by the expected sensitivity of the dienamines we wished to generate to the high temperatures and harsh acidic conditions required for the proton catalyzed rearrangement.[3] However, it was clear at the outset that this rearrangement would be amenable to coupling with subsequent C-C bond-forming reactions to afford tandem reactions and potentially even more complex molecular cascades if the rearrangement could be conducted under sufficiently mild conditions.

‡Dedicated to Professor Samuel Danishefsky on the occasion of his receipt of the 1996 Tetrahedron Prize.

One such process (Scheme 1) coupled the cyclopropyl iminium ion rearrangement to a variant of the nipecotic acid rearrangement, a Hofmann-like elimination-cyclization described by Rapoport and

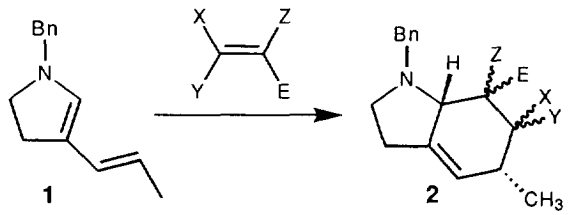
Scheme 1



others, and a [4+2] cycloaddition.[12] Our efforts to reduce such a molecular cascade to practice are described below.

RESULTS AND DISCUSSION

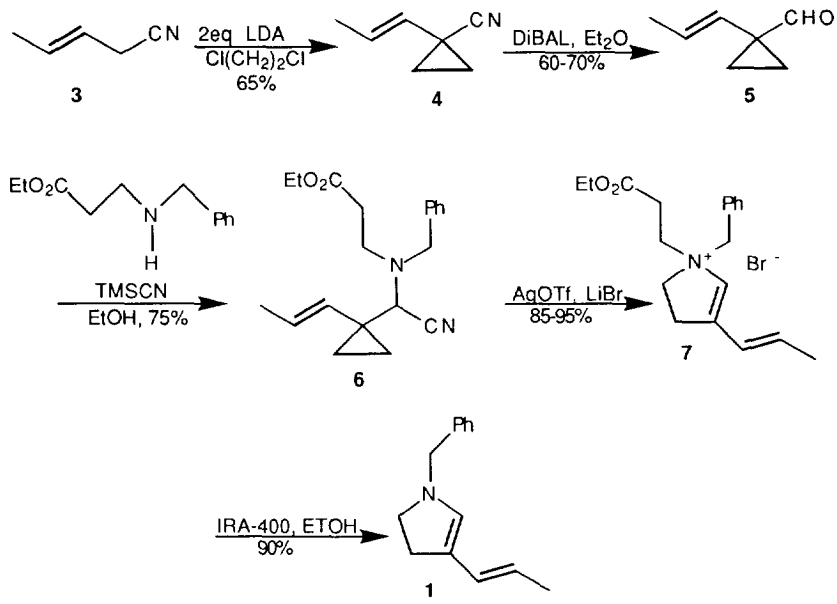
Generation of the a Model Dienamine 1 and Intermolecular Cycloadditions. In order to examine the feasibility of the tandem rearrangement-elimination-cycloaddition cascade, a model system was required which would allow optimization of reaction conditions on a relatively simple substrate. To further simplify matters, we first chose to examine the intermolecular cycloaddition of a Δ^2-pyrroline with various dienophiles such as **1**→**2** as shown in Eqn. 1. This necessitated the construction of a model 3-vinyl Δ^2-pyrroline which could be readily prepared via our cyclopropyliminium ion rearrangement chemistry on multigram scale. Dienamine **1** (Eqn. 1) was chosen based on several criteria. The vinyl methyl group was expected to serve as an inhibitor of polymerization as well as to provide a spectral feature indicative of cycloadduct formation, appearing in the NMR spectrum as an upfield methyl doublet. Incorporation of this methyl group would also reduce the expected volatility of the necessary synthetic intermediates **3** -**5** (Scheme 2).



(1)

The synthesis of **1** began with α,α dialkylation of the commercially available nitrile **3** with 1,2 dibromoethane to afford the cyclopropyl nitrile **4** in 65% yield, a well-precedented transformation for phenylacetonitrile and phenylacetic acid esters but not often described for unsaturated analogs (Scheme 2).[13] Reduction of nitrile **4** with DiBAL-H and acid hydrolysis afforded aldehyde **5**. Employing the conditions reported by Mai, condensation of cyclopropanecarboxaldehyde **5** with ethyl 3-(N-benzylamino) propionate and TMSCN in the presence of ZnI_2 provided the cyanoamine **6** in 75% yield.[14] Treatment of cyanoamine **6** with silver ion and LiBr in THF, according to our previously described protocol, provided the desired enammonium salt **7** in 85-95% yield as a brown solid prone to slow auto-elimination of ethyl acrylate.[9] Treatment of **7** with DBU, or alternatively basic ion exchange resin (IRA-400 pretreated with 50% aq. KOH) in EtOH induced elimination of ethyl acrylate to give the desired dienamine **1** in 90% yield.

Scheme 2

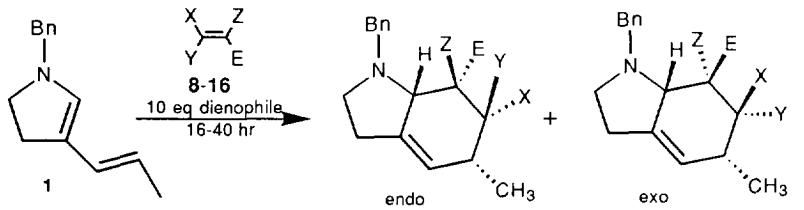


Cycloaddition reactions of simple dienamines have been reported sporadically in the literature over the last 20 years with mixed results.[15] The cycloaddition reactions of a series of common dienophiles **8-16** with dienamine **1** were conducted to establish a benchmark for the reactivity profile of systems such as **1** and provide insight into possible limitations. The results of these cycloaddition reactions are reported in Table 1. Dimethyl fumarate (**8**) rapidly reacted with the diene at room temperature in dichloromethane to afford the adducts **17** and **18** in 65% yield in a ratio of 3.5:1. Preliminary structure assignment for **17** and **18** was based on NMR data and subsequently confirmed by

single crystal X-ray analysis of **17**.[16] When diene **1** was treated with dimethyl maleate (**9**), cycloaddition proceeded more slowly, but afforded a mixture of adducts **17** and **18** (3.5:1) identical to that obtained from **8**. Thus, the stereochemical integrity of the dienophile is not retained strongly implicating a non-concerted cycloaddition pathway. Control experiments established that neither **8** and **9** nor **17** and **18** interconvert under the reaction conditions which suggests that loss of stereochemical integrity occurs by single bond rotation prior to collapse of an intermediate zwitterion.

Reaction of **1** with the less active dienophile methyl acrylate (**10**) occurred much more slowly, requiring 40 hours to achieve completion, affording adducts **19** and **20** (1:3) in 48% yield. Similarly, phenyl vinyl sulfone (**11**) provided a 1:1 mixture of **21** and **22** in 34% yield. Attempts to increase the rate of reaction by increasing the temperature resulted in rapid decomposition of **1**. Reaction with methyl vinyl ketone (**12**) afforded the expected adducts **22** and **23** (1.5:1) in only 10-20% yield, owing to extensive polymerization of the dienophile under the reaction conditions and the sensitivity of the adducts **23** and **24** to chromatographic purification.

Table 1



Dienophile	X	Y	Z	E	Adducts	Endo/Exo	Yield (%)
8	H	CO_2CH_3	H	CO_2CH_3	**17 / 18**	3.5:1	65
9	CO_2CH_3	H	H	CO_2CH_3	**17 / 18**	3.5:1	50
10	H	H	H	CO_2CH_3	**19 / 20**	1:3	48
11	H	H	H	SO_2Ph	**21 /22**	1:1	34
12	H	H	H	$COCH_3$	**23 /24**	1.5:1	10-20
13	H	H	CH_3	CHO	**25 /26**	4:1	52
14	H	H	CH_3	CO_2CH_3	--	--	--
15	H	SO_2Ph	CH_3	CO_2CH_3	--	--	--
16	H	CH_3	H	CO_2CH_3	--	--	--

Formation of cycloadducts with the more highly substituted dienophiles **13-16** did not occur with the exception of the highly reactive methacrolein (**13**) which afforded the expected cycloadducts **25** and **26** (4:1) in 52% yield whose stereochemistry was confirmed by X-ray analysis of **25**.[16] It is unclear whether the lack of reactivity of the more substituted dienophiles toward **1** is based on steric or electronic factors or is the result of the sensitivity of the dienamine **1** to proton catalyzed polymerization. In any case, our model dienamine **1** proved to be significantly less effective as a diene in cycloaddition reactions than had been anticipated. Examination of the UV spectrum of **1** showed a λ_{max} of 285 nm, consistent with delocalization of electron density from the nitrogen into the diene unit. The low efficiency of the dienamine **1** in cycloaddition, thus, does not appear to result from ineffective orbital

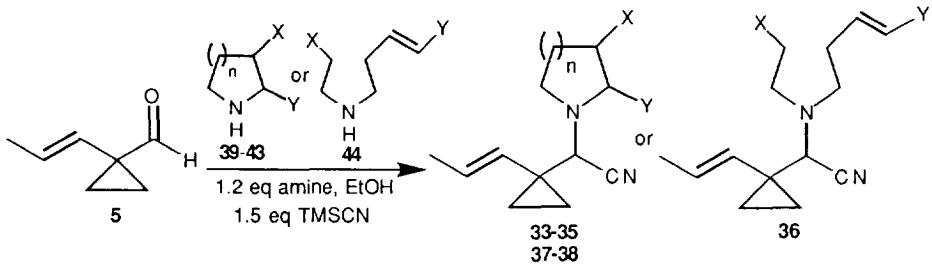
overlap owing to the presence of the nitrogen in a pyrroline ring.

Synthesis of Dienamines 27-32 Bearing Tethered Dienophiles. Since our interest lay principally in the intramolecular variant of such dienamine cycloadditions as part of a molecular cascade which we hoped would provide a general route to the tricyclic core found in a number of classes of alkaloids, we proceeded to examine the analogous intramolecular cycloaddition processes by preparation of a series of dienamines **27-32** bearing tethered dienophiles (Scheme 1 and Table 4). We anticipated that the intramolecular variant of the cycloaddition would prove more favorable owing to the enforced proximity of the dienophile as observed for other intramolecular [4+2] cycloaddition reactions.[17] Although our original intent was to effect the direct conversion of the cyanoamine precursors to the tricyclic [4+2] cycloadducts without isolation of the intermediates **27-32**, it now seemed probable that these intermediates would be isolable based upon our experience with **1**.

Preparation of the desired trienes **27-32** proceeded by way of a series of cyanoamines **33-38** which were obtained by condensation of aldehyde **5** with a series of cyclic and acyclic amino esters **39-44**. Only ethyl nipecotate (**39**) is commerically available, thus the remainder have been prepared by literature procedures or modifications thereof. Amino ester **40** was prepared via 1,3-dipolar cycloaddition,[18,19] while the known tetrahydroazepine ester **41**,[20] was prepared from caprolactam via a reliable but lengthy sequence involving carboxylation of the enolate of caprolactam and reduction. The acyclic analog of the azetidine, amine **42**, was prepared from the adduct of 1,3-aminopropanol and ethyl acrylate by protection, oxidation and olefination using standard methods.[21] Finally, amino esters **43** and **44** were prepared as previously described.[22,23]

The required cyanoamines were readily prepared by the protocol developed for cyanoamine **6** in generally excellent yields (Table 2). The cyanoamines **33-37** were obtained as inconsequential mixtures of diastereomers and were characterized spectroscopically without separation.

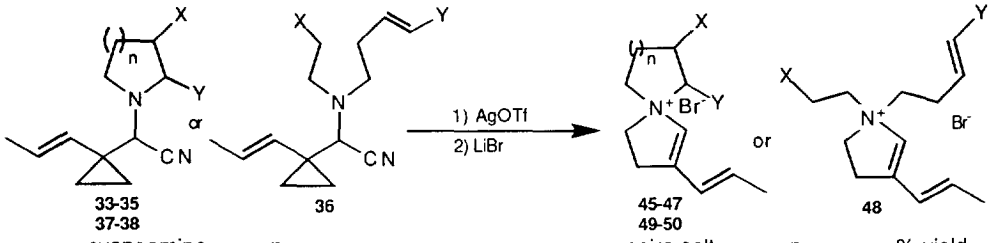
Table 2



amine	n	x	y	cyanoamine	% yield
39	2	CO_2Et	H	**33**	76
40	1	CO_2Et	H	**34**	82
41	3	CO_2Et	H	**35**	86
42	-	CO_2Et	CO_2Et	**36**	37
43	1	H	CH_2CO_2Et	**37**	75
44	2	H	CH_2CO_2Et	**38**	71

The iminium ion rearrangement occurred smoothly to give the corresponding spiro-fused enammonium salts **45-50** as shelf-stable, hygroscopic solids (Table 3). Purification of these salts could be effected by column chromatography on silica gel employing a dichloromethane-methanol gradient. The purification was, however, complicated by the fact that the salts were isolated as a mixture of counterions and diastereomers. For routine purposes, separation of these isomers and salts was unnecessary.

TABLE 3

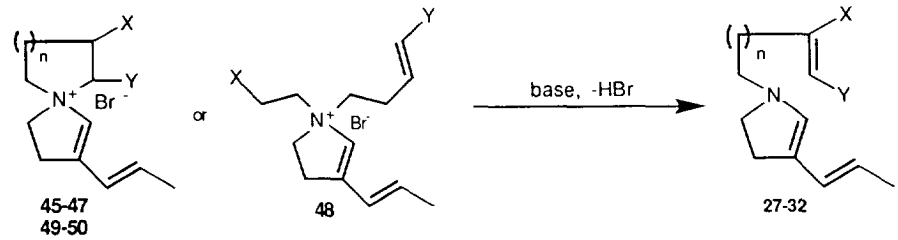


33-35, 37-38 | 36 | 45-47, 49-50 | 48

cyanoamine	n=	x	y	spiro salt	n=	% yield
33	2	CO_2Et	H	**45**	2	93
34	1	CO_2Et	H	**46**	1	83
35	3	CO_2Et	H	**47**	3	89
36	-	CO_2Et	CO_2Et	**48**	-	65
37	1	H	CH_2CO_2Et	**49**	1	88
38	2	H	CH_2CO_2Et	**50**	2	70

Subsequent treatment of the spiro enammonium salts with a strong amine base such as DBU, or passage through a column of ion exchange resin (IRA-400) in ethanol afforded trienes **27-32** in good yield (Table 4).

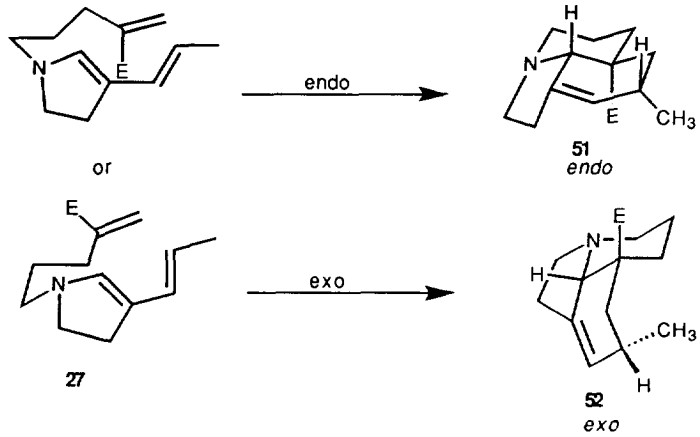
TABLE 4



45-47, 49-50 | 48 | 27-32

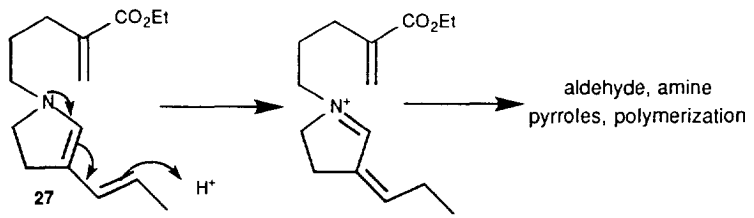
spiro salt	n=	x	y	dienamine	n=	x	y	% yield
45	2	CO_2Et	H	**27**	2	CO_2Et	H	93
46	1	CO_2Et	H	**28**	1	CO_2Et	H	84
47	3	CO_2Et	H	**29**	3	CO_2Et	H	83
48	-	CO_2Et	CO_2Et	**30**	1	H	CO_2Et	54
49	1	H	CH_2CO_2Et	**31**	2	H	CO_2Et	81
50	2	H	CH_2CO_2Et	**32**	3	H	CO_2Et	64

Cycloaddition Reactions of Substrates Bearing Tethered Dienophiles. Our studies began with triene **27** since it was the most readily available (derived from commercially available ethyl nipecotate), and was expected to undergo facile cycloaddition. The length of the tether was predicted to allow good orbital overlap of the diene and dienophile frontier orbitals without significant strain in the transition state according to hand-held models. Both *endo* and *exo* transition states have available a chair-like transition state (Eq. 2). A wide variety of conditions were explored in an effort to induce clean cyclization. As anticipated on the basis of the intermolecular cycloaddition results, reaction did not occur at room temperature with high temperatures required to obtain even traces of cycloadducts.



(2)

The harsh conditions required for cycloaddition resulted in the formation of significant quantities of decomposition products which were not identifiable. Several general spectral features were noted upon examination of the NMR spectra of the crude product mixtures. Signals assigned to olefinic protons of the acrylate residue remained intact, while disappearance of signals associated with the dienamine subunit was observed. The likely pathway for this decomposition is outlined in Eq. 3. Control experiments established that the cycloadducts, when resubjected to the reaction conditions, underwent slow decomposition. However, the cycloadducts were also found to be unstable to purification by chromatography undergoing a retro-Mannich cleavage accounting some additional loss in yield.



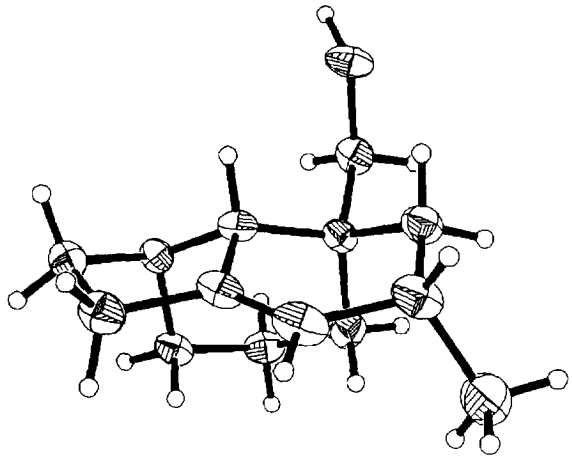
(3)

Decomposition Pathway

One set of optimized conditions, which involved addition of a solution of the triene via syringe

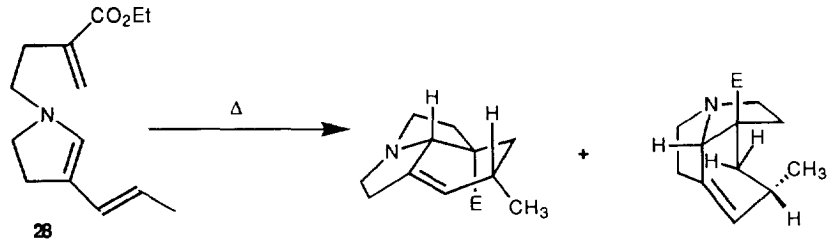
pump to collidine containing potassium carbonate and DBU at reflux (172°C), afforded an ~35% yield of adducts **51-52** as a 1.5:1 mixture (*endo/exo*). While the structure assignment was based on spectral data, the assigned stereochemistry was confirmed by X-ray crystallographic analysis of the alcohol **53** obtained by LAH reduction of the minor diastereomer **52** (Eq. 2), as illustrated by the ORTEP plot of the X-ray crystallographic model for **53** (Figure 1).[16]

FIGURE 1



ORTEP Drawing of **53**

We next chose to examine the cycloaddition of triene **28** with a tether shortened by one carbon atom (Eq. 4). Shortening of the tether was predicted to reduce the degrees of freedom available to the dienophile, making the reaction more entropically favorable. Indeed, thermolysis in collidine under high dilution conditions resulted in 47-53% isolated yields of a single diastereomeric cycloadduct. The structure and stereochemistry of the cycloadduct was assigned as *exo* **55** on the basis of comparison of the spectral data to that of adduct **52**. Adduct **55** was reduced with LAH, as before, and the resulting alcohol fully characterized as the derived *p*-nitrobenzoate ester. It was expected that a large preference should exist for the less strained *exo* isomer **55** which possesses the more stable *cis* ring fusion.

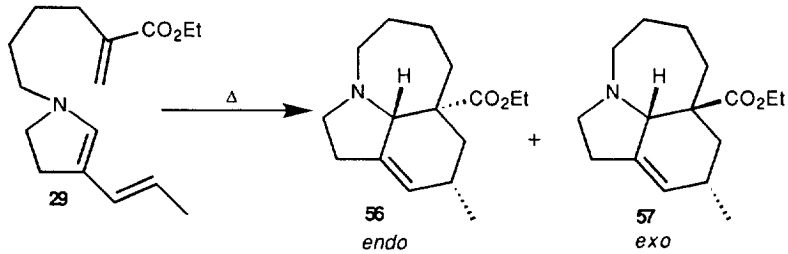


28 **54** *endo* **55** *exo* (4)

The fact that this reaction proved to be so much more efficient was surprising from the standpoint of stereoelectronic considerations although the likely higher stability of adduct **55** to

decomposition by retro-Mannich or other pathways cannot be discounted. In order for overlap of the nitrogen lone pair with the diene to occur in substrate **28**, a more or less planar sp^2 -like nitrogen must be invoked. Molecular models demonstrate that the transition state required for concerted cycloaddition does not permit a planar nitrogen for a 2 carbon tether.

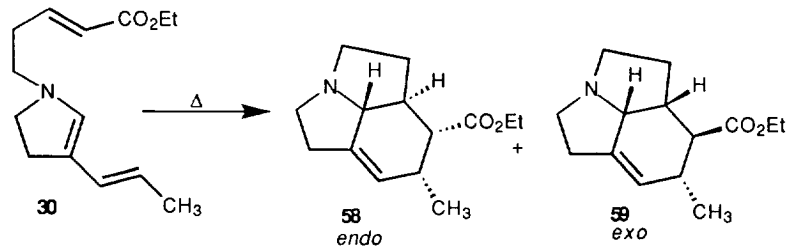
To further explore the effect of tether length on the cycloaddition, triene **29** was subjected to the established reaction conditions (Eq. 5). A low yield (~15%) of adducts tentatively assigned as **56** and **57** were obtained as a 5:1 mixture (*endo/exo*). The remainder of the material was converted to unidentifiable products resulting from dienamine decomposition. This outcome lent further support to the theory that tether length was an important factor in determining the rate of cycloaddition relative to decomposition.



(5)

The scope and limitations of these intramolecular cycloaddition reactions of dienamines were further probed by the examination of a series of crotonate-like dienophiles. We expected to meet with less success here since these reactions should be less favorable electronically according to FMO theory. Experiments conducted in the intermolecular cases also support the lower reactivity of crotonate-like dienophiles toward dienamines such as those under study herein.

Surprisingly, triene **30** underwent spontaneous cyclization at room temperature to form significant quantities of adducts **58** and **59** (50%, ~1:10 ratio of diastereomers) accompanied by unreacted triene (Eq. 6). Unfortunately, attempts to increase the conversion of the substrate to products only resulted in decomposition. The stereochemistry of the major adduct **59** formed was tentatively assigned as *exo* by comparison of spectral data to that of adducts **54** and **55**. The strong *exo* preference is no doubt results owing to the more favorable *cis*-5,6 ring fusion present in that adduct.

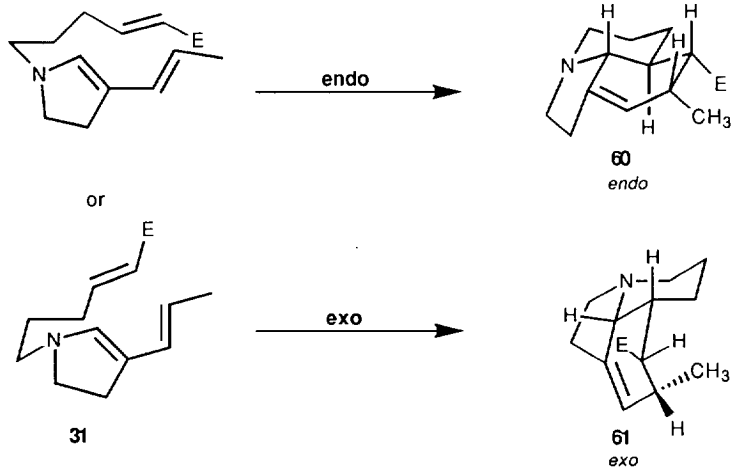


(6)

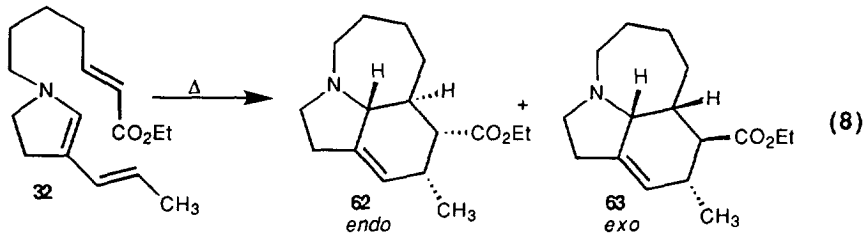
To our delight, thermolysis of triene **31** afforded a 70% yield of crude cycloadducts **60** and **61** as

a 9:1 mixture of diastereomers (Eq. 7). The stereostructures of adducts **60** and **61** were assigned based upon NMR spectroscopy by comparison to the related adducts **52** and **53**. Molecular modeling of the adducts **60** and **61** suggested that **60** was more stable by ~1.6 kcal, a sufficient energy difference to account for the magnitude of the selectivity observed. An interesting observation was made during attempts to further optimize the reaction conditions. Use of dipolar aprotic solvents such as DMF or DMSO resulted in more rapid reaction (qualitatively) when compared to collidine or hydrocarbon solvents. This observation is consistent with the polar solvent effect expected for a non-concerted mechanism as invoked in the intermolecular cases earlier.

Following the cyclization of **31** by NMR, it was noted that conversion to adduct began to occur at ~80°C. As the temperature was raised, the conversion to adduct was qualitatively observed to occur more rapidly, finally reaching preparatively useful rates at 100°C to 120°C. After several hours at this temperature, conversion to adduct fell off precipitously, while starting material continued to be consumed. Slow decomposition of the adduct was also observed to occur. One possible interpretation of this data is that a product-catalyzed decomposition of starting material is occurring. To avoid this possibility, flash pyrolysis was employed for this cycloaddition.[24] The yields and product ratio obtained for **31** by this method were virtually identical to those obtained in solution. Some decomposition was noted using this method in the form of dark material deposited on the walls of the hot tube employed. The reactions were, however, overall cleaner, very rapid, and convenient by this method. This technique was therefore adopted for all the intramolecular cycloaddition reactions discussed herein since it has practical advantages over solution thermolysis.



Finally, the triene **32** was thermolyzed both in solution and by flash pyrolysis, but yielded only ~10% of a pair of adducts (5:1 *endo*/*exo*) tentatively assigned as **62** and **63** (Eq. 8). The low yield was consistent with the idea that tether length affects the relative stability of the resulting adducts to decomposition *via* retro-Mannich or other pathways.



(8)

CONCLUSION

The results discussed demonstrate the synthetic utility of the cyclopropyliminium ion rearrangement/elimination sequence for rapid synthesis of 2-pyrrolines which are not obtainable by other means. Rapid access to functionalized bicyclic and tricyclic heterocycles has been accomplished by, respectively, the inter and intramolecular Diels-Alder cycloaddition of suitably activated dienophiles with 2-pyrrolines. The intramolecular cycloaddition is disfavored relative to the intermolecular reaction due to constraints imposed by the presence of a tethered dienophile. These constraints appear to be both electronic and entropic in nature. The entropic effect is attenuated significantly for tethers of two sp^3 carbons, allowing for more facile cycloaddition. The unanticipated low reactivity of the dienamines in the intramolecular cases may be due to reduced overlap of the lone pair orbital on nitrogen with the diene in order to achieve the transition state for concerted cycloaddition or owe their origin to the instability of the zwitterionic intermediates formed during non-concerted cycloaddition and/or the adducts themselves as the result of facile retro-Mannich reactions.

It is probable that a non-concerted mechanism is operative in at least some, perhaps most, of the cycloadditions reported. This is implicated by facile non stereospecific cycloaddition of **1** with dimethyl maleate, the results of the intramolecular cycloaddition of substrates with very short tethers, and an observed qualitative rate enhancement of several of the cycloadditions in dipolar aprotic solvents.

It would appear at this point that the scope of the intramolecular cycloaddition methodology is limited to the efficient fomation of 5,5,6-tricyclic ring systems unless the retro-Mannich decompostion pathway can be supressed by, for example, deactivation of the nitrogen by installation of either an endocyclic or exocyclic amide carbonyl group. Future studies will be directed toward this end as well as toward the incorporation of oxygen substituents in the core unit **5**.

EXPERIMENTAL SECTION

All reactions were performed in oven or flame dried glassware under Argon. Magnetic stirring was employed unless otherwise noted. Solutions of air sensitive reagents were transferred via needle and syringe or cannula. "Concentrated *in vacuo*" refers to solvent removal on a rotary evaporator at aspirator pressure. All non-volatile samples were pumped on at a vacuum of 0.1 mm Hg until a constant weight was achieved following removal of solvent *in vacuo*. All reagents and solvents employed were used as received except where noted. Lithium bromide was fused just before use and cooled under Argon. Solvents employed in anhydrous reactions were obtained as follows: diethyl ether and tetrahydrofuran were distilled from sodium-benzophenone ketyl under nitrogen; methylene chloride, diisopropyl amine, triethylamine, and N,N-dimethylformamide were distilled from calcium hydride. Collidine, dimethyl sulfoxide, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were distilled from calcium hydride under reduced pressure. 4-Dimethylaminopyridine (DMAP) was used as received from Aldrich Chemical Co.

Infrared spectra were obtained on a Perkin-Elmer 1610 FT-IR spectrophotometer and are reported in wavenumbers (cm^{-1}) calibrated with a polystyrene standard. All spectra were obtained as thin films on a salt plate. Proton Nuclear magnetic resonance (NMR) spectra were obtained on a GE QE-300 (300 MHz) spectrometer. Carbon NMR were obtained on a GE QE-300 (75 MHz) instrument. Chemical shifts are reported in parts per million (d) relative to tetramethylsilane using chloroform as a standard unless otherwise noted. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are reported uncorrected. Elemental analysis was performed by Midwest Microanalytical Laboratories.

1-(1-Propenyl)cyclopropanecarbonitrile (4). A dry 2 L flask equipped with a mechanical stirrer and addition funnel was charged with dry THF (1 L) and diisopropylamine (160 mL, 1.1 mol) was added. The mixture was cooled in a dry ice-acetone bath to an internal temperature of -60°C. A 10M solution of *n*-butyllithium (100 mL, 1.0 mol) in hexane was then added dropwise over 30 min. After the addition was completed, the solution was stirred for an additional 20 min, then DMPU (30 mL) was added. A solution of 3-pentenenitrile **3** (39 mL, 400 mmol) in THF (50 mL) was then added dropwise over 30 min. After a further 30 min, the mixture was allowed to warm gradually to -30°C over 45 min. The orange homogenous anion solution was subsequently recooled to -65°C, and 1,2-dichloroethane (160 mL, 2 mol) was then added rapidly dropwise over 20 mins. The solution was then allowed to warm to -10°C for 1-1/2 h at which time the reaction was judged complete by GC analysis of an aliquot of reaction mixture. The reaction was quenched by the addition of saturated ammonium chloride (200 mL) solution. The mixture was diluted with ether (1L), and the organic phase extracted with diethyl ether, washed with dilute HCl until the washings were acidic, water, saturated sodium bicarbonate, and brine and dried over magnesium sulfate. The solvents were removed *in vacuo* at ice bath temperature to a volume of approximately 100 mL. The brown solution thus obtained was distilled through a 6" Vigreux column at aspirator vacuum (bp 75-79°C / 20 torr) to give 26 g (61%) of **4** as a colorless liquid. ^1H

NMR: δ 0.97 (dd, J_1=7.4 Hz, J_2=5 Hz, 2 H), 1.36 (dd, J_1=7.4 Hz, J_2=5 Hz, 2 H), 1.67 (dd, J_1=6.5 Hz, J_2=1.6 Hz, 3 H), 4.92 (dd, J_1=15.3 Hz, J_2=1.6 Hz, 1 H), 5.85 (m, 1 H); ^{13}C NMR: δ 11.6, 15.8, 17.3, 121.8, 126.9, 127.3. IR (cm^{-1}): 3018, 2920, 2234, 1438, 1380, 1069, 1039, 989, 966.

1-(1-Propenyl)cyclopropanecarboxaldehyde (5). A dry 250 mL flask under Ar was charged with ether (75 mL) and nitrile **4** (5.0 g, 46.7 mmol). This solution was cooled to 0°C and a solution of 1M DiBAL in hexane (50 mL, 50 mmol) was added dropwise over 30 min. The mixture was kept at 0°C for 3 h, then cannulated in a slow stream into a vigorously stirred suspension of 10% sulfuric acid (100 mL) in ether (100 mL) cooled in a large ice bath. The resulting yellow solution was stirred for 30 min at 0°C, and the layers were then separated. The aqueous layer was extracted with ether (100 mL), the ethereal extracts combined and washed with water, saturated sodium bicarbonate, and brine. After drying the extracts over sodium sulfate, the solvents were removed *in vacuo* at 0°C, leaving a small amount of solvent behind. The crude aldehyde was then distilled through a 4" Vigreux column at aspirator vacuum (60-65°C) to give 3.9 g (76%) of aldehyde **5**, (2,4-Dinitrophenylhydrazone, mp 163.5-164.5°C). ^{1}H NMR: δ 1.20 (dd, J_1=7.6 Hz, J_2=3.8 Hz, 2 H), 1.36 (dd, J_1=7.5 Hz, J_2=3.8 Hz, 2 H), 1.73 (dd, J_1=6.3 Hz, J_2=1.4 Hz, 3 H), 5.55 (m, 1 H), 5.93 (dd, J_1=15.5 Hz, J_2=1.4 Hz, 1 H), 8.91 (s, 1 H); ^{13}C NMR: δ 16.3, 17.8, 33.0, 125.7, 126.6, 200.3; IR (cm^{-1}): 2918, 2858, 2723, 1713, 1450, 1294, 1238, 1035, 966, 903.

The following procedure is representative of that employed for all cyanoamine preparations: **(E)-1-(N-benzyl-N-2'-carboethoxyethylamino)-1-(1-propenyl)cyclopropaneacetonitrile (6).** A dry 10 mL flask was charged with aldehyde **5** (0.55 g, 5.0 mmol) and trimethylsilyl cyanide (0.84 mL, 6.0 mmol). A catalytic amount of zinc iodide was added and the resulting pale yellow solution stirred at room temperature for 1 h, by which time it had turned a cloudy white color. The flask was fitted with a condenser and a solution of ethyl 3-benzylaminopropionate (1.20 g, 25 mmol) in dry ethanol (5 mL) was added slowly, causing the reaction to reflux from the vigorous exotherm. The mixture was then heated under reflux for 18 h, cooled, concentrated, and chromatographed on silica gel with 7:1 hexane/ethyl acetate to give 1.22 g (75%) cyanoamine **6** as a colorless oil. ^{1}H NMR: δ 0.62 (m, 1H), 0.74 (m, 1 H), 0.9 (m, 1 H), 1.0 (m, 1 H), 1.27 (t, J=7 Hz, 3 H), 1.68 (dd, J_1=5.7 Hz, J_2=0.9 Hz, 3 H), 2.50 (t, J=7.1 Hz, 1 H), 2.73 (m, 1 H), 3.18 (m, 1 H), 3.35 (d, J=13.6 Hz, 1 H), 4.0 (s, 1 H), 4.13 (m, 3 H), 5.40 (m, 1 H), 5.66 (d, J=15 Hz, 1 H), 7.32 (m, 5 H); ^{13}C NMR: δ 10.1, 12.0, 13.9, 17.4, 20.9, 46.8, 55.6, 59.7, 60.2, 114.9, 124.2, 127.2, 128.1, 128.6, 130.7, 137.4, 171.6; IR (cm^{-1}): 2982, 2839, 1734, 1496, 1258, 1189.

(E)-1-(3-Carboethoxypiperidinyl)-1-(1-propenyl)cyclopropaneacetonitrile (33). Prepared from ethyl nipecotate (**39**) to give 4.5 g (82%) **33.** ^{1}H NMR: δ 0.59-0.74 (m, 3 H), 0.83 (m, 1 H), 1.17 (dt, J_1=7 Hz, J_2=1.9 Hz, 3 H), 1.56 (d, J=6.2 Hz, 3 H), 1.42-1.85 (m, 3 H), 2.08 (m(br), 1 H), 2.30-2.61 (m, 2 H), 2.75 (d, J=8.5 Hz, 1 H), 2.83 (d, J=10.8 Hz, 1 H), 3.04 (dd, J_1=10.9 Hz, J_2=2.2 Hz, 1 H), 3.69 (s, 0.5 H), 3.70 (s, 0.5 H), 4.04 (q, J=7 Hz, 2 H), 5.39 (m, 1 H), 5.52 (m, 1 H); ^{13}C NMR: δ 10.3, 10.4, 12.5, 12.7, 14.0, 14.1, 17.7, 20.9, 20.3, 23.9, 24.0, 26.3, 26.3, 41.3, 41.5, 48.9, 50.8, 51.5, 53.6, 60.2,

64.4, 64.5, 114.6, 114.6, 124.0, 124.1, 130.7, 173.3, 173.4; IR (cm^{-1}):2942, 2814, 2224, 1732, 1467, 1451, 1394, 1306, 1230, 1183, 1156, 1031. HRMS (EI) Calcd for $C_{16}H_{24}N_2O_2$: 276.1832. Found: 276.1837.

(E)-1-(3-Carboethoxypyrrolidinyl)-1-(1-propenyl)cyclopropaneacetonitrile (34). Prepared from 3-carboethoxypyrrolidine (**40**)[18,19] to give 1.2 g of **34** (76%). ^1H NMR: δ 0.69-0.76 (m, 4 H), 1.22 (t, J=7 Hz, 3 H), 1.61 (d, J=6.3 Hz, 3 H), 2.05-2.11 (m, 2 H), 2.63-3.1 (m, 5 H), 3.65 (s, 1 H, 1st diast.), 3.69 (s, 1 H, 2nd diast.), 4.10 (q, J=7 Hz, 2 H), 5.41-5.49 (m, 1 H), 5.62 (dd, J_1=15.5 Hz, J_2=6.3 Hz, 1 H); ^{13}C NMR: δ 11.3, 11.5, 11.6, 13.9, 17.5, 21.8, 26.7, 26.8, 41.5, 50.2, 50.3, 52.7, 52.9, 60.4, 61.1, 61.2, 115.0, 115.1, 124.3, 124.4, 130.1, 130.2, 173.9; IR (cm^{-1}): 2979, 2815, 1734, 1449, 1180; Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.66; H, 8.46. Found: C, 68.39; H, 8.51.

(E)-1-(3-Carboethoxyhexahydroazepinyl)-1-(1-propenyl)cyclopropaneacetonitrile (35). Prepared from 3-carboethoxyhexahydroazepine (**41**)[20] to give 2.5 g of **35** (86%). ^1H NMR: δ 0.48-0.83 (m, 4 H), 1.13 (m, 3 H), 1.53 (d, J=6.1 Hz, 3 H), 1.44-1.61 (m, 5 H), 1.82 (m, 1 H), 2.40 (m, 1 H), 2.50 (m, 1 H), 2.77 (m, 2 H), 2.88 (m, 1 H), 3.88 (s, 0.33 H), 3.91 (s, 0.66 H), 4.02 (m, 2 H), 5.3 (m, 1 H), 5.62 (d, J=15.5 Hz, 1 H); ^{13}C NMR: δ 9.5, 9.8, 12.0, 13.9, 17.3, 17.4, 20.8, 21.1, 23.6, 24.4, 27.8, 28.0, 29.9, 30.1, 44.5, 45.4, 51.0, 51.2, 52.6, 54.1, 59.9, 60.0, 64.6, 64.8, 115.6, 115.6, 123.6, 123.8, 130.6, 130.7, 174.1, 174.3; IR (cm^{-1}): 2934, 2860, 1730, 1449, 1300, 1262, 1193, 1174, 1090, 1033.

(E)-1-N-(2'-Carboethoxyethyl)ethyl-N-4-carboethoxy-3-butenylamino-1-(1-propenyl)cyclopropane acetonitrile (36). Prepared from ethyl 3-propionato-N-4-carboethoxy-3-butenylamine (**42**)[21] to give 0.44 g of **36** (37%). ^1H NMR: δ 0.6-0.9 (m, 4 H), 1.21 (m, 6 H), 1.60 (dd, J_1=17.4 Hz, J_2=6.3 Hz, 3 H), 2.33 (t, J=6.8 Hz, 2 H), 2.40 (t, J=6.7 Hz, 2 H), 2.50 (m, 1 H), 2.66 (m, 1 H), 2.83 (m, 1 H), 3.03 (m, 1 H), 3.92 (s, 1 H), 4.10 (m, 4 H), 5.31 (m, 1 H), 5.53 (d, J=17.4 Hz, 1 H), 5.78 (d, J=16.5 Hz, 1 H), 6.82 (m, 1 H); ^{13}C NMR: δ 10.0, 12.3, 14.0, 17.4, 20.9, 30.0, 32.8, 47.2, 49.5, 59.9, 60.3, 60.5, 115.0, 122.4, 124.2, 130.5, 145.9, 166.0, 171.5; IR (cm^{-1}): 2981, 2938, 1723, 1656, 1448, 1369, 1267, 1225, 1183; Anal. Calcd for $C_{20}H_{30}N_2O_4$: C, 66.26; H, 8.35. Found: C, 66.04; H, 8.37.

(E)-1-(2-Carboxyethylmethyl)pyrrolidinyl-1-(1-propenyl)cyclopropaneacetonitrile (37). Prepared from ethyl 2-pyrrolidylacetate (**43**)[22] to give 1.04 g of **37** (75%). ^1H NMR: δ 0.69-0.87 (m, 4H), 1.26 (m, 3H), 1.63 (dd, J_1=6.4 Hz, J_2=1.6 Hz, 3 H), 1.78 (m, 2 H), 2.01 (m, 1 H), 2.32 (dd, J_1=15.0 Hz, J_2=7.3 Hz, 1 H), 2.51 (m, 2 H), 3.05 (m, 1 H), 3.13 (m, 1 H), 4.01 (s, 0.20 H), 4.13 (m, 2H), 4.16 (s, 0.80 H), 5.40 (m, 1 H), 5.63 (dd, J_1=15.5 Hz, J_2=1.6 Hz, 1 H); ^{13}C: δ 10.2, 11.7, 11.9, 13.7, 13.8, 17.2, 17.3, 21.4, 21.8, 22.5, 22.8, 29.9, 30.8, 39.4, 40.6, 48.7, 53.3, 56.5, 58.5, 59.5, 59.8, 60.1, 61.1, 114.9, 115.00, 123.2, 123.4, 130.8, 131.1, 171.0, 171.2; IR (cm^{-1}): 2970, 2918, 1732, 1448, 1377, 1300, 1270, 1249, 1186, 1095, 1031; Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.52; H, 8.76; N, 10.14. Found: C, 69.29; H, 8.75; N, 10.06.

(E)-1-(2-Carboxyethylmethyl)piperidinyl-1-(1-propenyl)cyclopropaneacetonitrile (38). Prepared from ethyl 2-piperidinylacetate (**44**)[23] to give 2.9 g of **38** (71%). ^1H NMR: δ 0.48-0.9 (m, 4 H), 1.15

(t, J=7 Hz, 3 H), 1.52 (d, J=6 Hz, 3 H), 2.03 (m, 2 H), 2.28-2.36 (m, 1 H), 2.39-2.47 (m, 1 H), 2.6 (m(br), 1 H), 2.96 (d, J=11.3 Hz, 1 H), 3.62 (s, 0.25 H), 3.98-4.17 (m, 2 H), 4.25 (s, 0.75 H), 5.25-5.36 (m, 1 H), 5.51 (d, J=15.3 Hz, 0.75 H), 5.55 (d, J=15.3 Hz, 0.25 H); ^{13}C NMR: δ 9.8, 10.0, 10.1, 11.6, 12.8, 13.9, 17.5, 18.5, 20.0, 23.0, 24.8, 24.9, 29.5, 30.5, 31.4, 37.9, 42.4, 47.2, 56.1, 56.3, 59.0, 60.3, 61.1, 114.6, 117.0, 123.2, 124.6, 127.5, 130.6, 171.2, 172.3; IR (cm^{-1}): 2937, 2858, 1732, 1446, 1160, 1029; Anal. Calcd for $C_{17}H_{26}N_2O_2$: C, 70.3; H, 9.03. Found: C, 70.61; H, 9.33.

The following general procedure was used for preparation of all listed enammonium salts:

(E)-1-Benzyl-1-[(2-carboxyethyl)ethyl]-3-(1-propenyl)-4,5-dihydropyrrolium bromide (7). A dry 25 mL conical flask with a spin vane was charged with silver triflate (0.887 g, 3.4 mmol) and THF (10 mL). A solution of cyanoamine **6** (0.75 g, 2.3 mmol) in THF (2 mL) was added slowly into the silver triflate solution, resulting in a mildly exothermic reaction and precipitation of silver cyanide as a greyish-white suspension. The reaction mixture was allowed to stir an additional 45 min after the addition of cyanoamine was complete. The precipitate of silver cyanide was allowed to settle, and the supernatant transferred via cannula into a solution of lithium bromide (0.70 g, 8.0 mmol, fused immediately before use) in THF (10 mL). The flask was covered with foil and stirred 20 h. Solvents were removed *in vacuo*, and the resulting brown viscous mass was treated with methanol, causing the silver salts to precipitate as a fine yellow solid. The methanolic extract was filtered through a plug of celite, washing solids thoroughly with methanol. The clear brown solution was concentrated *in vacuo* and transferred directly onto a silica gel column and eluted with dichloromethane to remove less polar by-products, then 5% CH_3OH/CH_2Cl_2 to elute product. Removal of solvents yielded 0.765 g (88%) of enammonium salt **7** as a light brown hygroscopic oil which solidified on standing to an amorphous solid, slightly contaminated with excess lithium bromide and triflate. Decomposition occurred on storage with liberation of ethyl acrylate. ^{1}H NMR (CD_3CN): δ 1.23 (t, J=7 Hz, 3 H), 1.80 (d, J=6.5 Hz, 3 H), 2.20 (m(br), 3 H), 2.79 (m, 2 H), 3.79 (m, 2 H), 4.0 (m, 1 H), 4.15 (q, J=6.9 Hz, 2 H), 4.57 (s, 2 H), 5.93 (m, 1 H), 5.95 (s, 1 H), 6.25 (d, J=15.7 Hz, 1 H), 7.49 (m, 5 H); IR (cm^{-1}): 2984, 1732, 1663, 1458, 1377, 1256, 1256 1166, 1099, 1031 965.

(E)-9-carboethoxy-2-(1-propenyl)-5-azoniaspiro[4.5]dec-1-enyl bromide (45). Yield: 0.55 g (83%). ^{1}H NMR (CD_3CN): δ 1.21 (t, J=7.2 Hz, 3 H), 1.63 (m, 2 H), 1.83 (d, J=6.5 Hz, 3 H), 1.97 (s(br), 2 H), 2.95 (m, 3 H), 3.37-3.53 (m, 4 H), 3.83-3.90 (m, 2 H), 4.12 (q, J=7.1 Hz, 2 H), 6.10 (m, 1 H), 6.27 (d, J=15 Hz, 1 H), 6.60 (s, 1 H); IR (cm^{-1}): 3098, 2941, 1728, 1664, 1450, 1370, 1259, 1224, 1156, 1055, 1030.

(E)-8-Carboethoxy-2-(1-propenyl)-5-azoniaspiro[4.4]non-1-enyl bromide (46). Yield: 0.89 g (93%). ^{1}H NMR (CD_3CN): δ 1.25 (m, 3 H), 1.85 (d, J=6.5 Hz, 3 H), 2.39 (m, 1 H), 2.56 (m, 1 H), 2.97 (t, J=7 Hz, 2 H), 3.49-3.67 (m, 3 H), 3.74-3.96 (m, 4 H), 4.17 (m, 2 H), 6.07 (m, 1 H), 6.14 (s, 1 H), 6.28 (d, J=15.7 Hz, 1 H); IR (cm^{-1}): 3081, 2983, 1725, 1475, 1450, 1399, 1381, 1336, 1264, 1157, 1030.

(E)-10-Carboethoxy-2-(1-propenyl)-5-azoniaspiro[4.6]undec-1-enyl bromide (47). Yield: 0.43 g

(89%). ^{1}H NMR (CD_3CN): δ 1.23 (t, *J*=6.9 Hz, 3 H), 1.66 (t, *J*=8.8 Hz, 2 H), 1.85 (d, *J*=6.4 Hz, 3 H), 2.23 (m, 4 H), 2.93 (m(br), 3 H), 3.35 (m, 1 H), 3.4=50 (m(br), 1 H), 3.74 (m, 3 H), 3.98 (m, 1 H), 4.17 (m, 2 H), 6.12 (m, 1 H), 6.29 (d, *J*=16.3 Hz, 1 H), 6.30 (s, 1 H); IR (cm^{-1}): 3109, 2940, 1727, 1632, 1468, 1449, 1371, 1299, 1205, 1059, 966.

(E)-1-(2-Carboethoxyethyl)-1-(4-carboethoxy-3-butenyl)-3-(1-propenyl)-4,5-dihydropyrrolium bromide (48). Yield: 0.23 g (65%). ^{1}H NMR (CD_3CN): δ 1.21 (m, 6 H), 1.84 (d, *J*=6.5 Hz, 3 H), 2.63 (m, 2 H), 2.75 (m, 2 H), 2.93 (t, *J*=7.3 Hz, 2 H), 3.56 (m, 2 H), 3.73 (m, 2 H), 3.92 (m, 2 H), 4.15 (m, 4 H), 5.93 (s, 1 H), 5.97 (d, *J*=6.1 Hz, 1 H), 6.09 (m, 1 H), 6.27 (d, *J*=15.8 Hz, 1 H), 6.78 (m, 1 H); IR (cm^{-1}): 2984, 2941, 1724, 1656, 1449, 1371, 1276, 1225, 1163, 1118, 1096, 1031, 969.

(E)-2-(1-Propenyl)-9-carboethoxymethyl-5-azoniaspiro[4.4]non-1-enyl bromide (49). Yield: 0.88 g (88%). H NMR (CD_3CN): δ 1.19 (m, 3 H), 1.85 (d, *J*=6.4 Hz, 3 H), 1.95 (m, 2 H), 2.07-2.20 (m, 3 H), 2.43-2.63 (m, 3 H), 3.61-3.75 (m, 2 H), 3.88-4.08 (m, 2 H), 4.12 (m, 2 H), 5.92 (s(br), 1 H), 6.11 (m, 1 H), 6.27 (d, *J*=15.7 Hz, 1 H); IR (cm^{-1}): 3081, 2983, 1725, 1666, 1475, 1450, 1399, 1264, 1227, 1157, 1030.

(E)-2-(1-Propenyl)-10-carboethoxymethyl-5-azoniaspiro[4,5]dec-1-enyl bromide (50). Yield: 0.53 g (70%). H NMR (CD_3CN): δ 1.23 (m, 3 H), 1.45-1.74 (m, 3 H), 1.84 (d, *J*=5.9 Hz, 3 H), 1.88-2.02 (m, 2 H), 2.50 (dd, J_1=8.2 Hz, J_2=7.9 Hz, 1 H), 2.69 (d, *J*=6.3 Hz, 2 H), 2.80-3.06 (m, 2 H), 3.45-3.58 (m, 3 H), 3.80 (m, 2 H), 4.02-4.20 (m, 2 H), 5.85 (s, 1 H), 6.09 (m, 1 H), 6.30 (m, 1 H); IR (cm^{-1}): 2945, 1732, 1652, 1456, 1380, 1286, 1190, 1061.

The following general procedure was used for preparation of all listed trienes:

(E)-1-Benzyl-3-(1-propenyl)-4,5-dihydropyrrole (1). A solution of enammonium salt **7** (153 mg, 0.40 mmol) in absolute ethanol (0.5 mL) was added to a column of basic resin IRA-400 and eluted with ethanol. The resulting solution containing the diene was concentrated *in vacuo* in a base washed flask to yield 58 mg (73%) crude diene **1**. The resulting brown oil was extremely acid sensitive and was used immediately without further purification. ^{1}H NMR (CD_3CN): δ 1.78 (d, *J*=7 Hz, 3 H), 2.58 (t, *J*=9.1 Hz, 2 H), 3.10 (t, *J*=9.0 Hz, 2 H), 3.94 (s, 2 H), 5.23 (m, 1 H), 5.98 (s, 1 H), 6.21 (d, *J*=15.3 Hz, 1 H), 7.34 (m, 5 H); IR (cm^{-1}): 2959, 2913, 2848, 1732, 1679, 1644, 1603, 1495, 1453, 1374, 1360, 1300, 1254, 1149, 1075, 1028, 955; UV (EtOH): λ max 285, 230, 205.6.

(E,E)-1-(4-Carbethoxy-4-pentenyl)-3-(1-propenyl)-4,5-dihydropyrrole (27). Yield: 85 mg (93%). ^{1}H NMR (CD_3CN): δ 1.26 (t, *J*=7.1 Hz, 3 H), 1.63 (t, (*J*=7.4 Hz, 2 H), 1.72 (d, *J*=6.4 Hz, 3 H), 2.32 (t, *J*=7.8 Hz, 2 H), 2.46 (t, *J*=9 Hz, 2 H), 2.73 (t, *J*=7.1 Hz, 2 H), 3.05 (t, *J*=9.1 Hz, 2 H), 4.16 (q, *J*=7 Hz, 2 H), 5.14 (m, 1 H), 5.57 (s, 1 H), 5.91 (s, 1 H), 6.09 (s, 1 H), 6.16 (d, *J*=15.3 Hz, 1 H). IR (cm^{-1}): 2934, 2851, 1716, 1678, 1643, 1602, 1445, 1369, 1305, 1256, 1179, 1144.

(E,E)-1-(3-Carbethoxy-3-butenyl)-3-(1-propenyl)-4,5-dihydropyrrole (28). Yield: 21 mg (84%). ^{1}H NMR (CD_3CN): δ 1.19 (t, *J*=7 Hz, 3 H), 1.64 (d, *J*=6.5 Hz, 3 H), 2.41 (m, 4 H), 2.79 (t, *J*=7.6 Hz, 2 H), 3.03 (t, *J*=9 Hz, 2 H), 4.09 (q, *J*=7 Hz, 2 H), 5.05 (m, 1 H), 5.49 (s, 1 H), 5.78 (s, 1 H), 6.03 (s, 1

H), 6.07 (s, 1 H); ^{13}C NMR (CD_3CN): δ 13.6, 17.6, 28.9, 30.6, 51.9, 52.1, 60.2, 117.5, 125.0, 125.6, 137.5, 138.4, 166.3. IR (cm^{-1}): 2976, 1715, 1630, 1444, 1369, 1180.

(E,E)-1-(5-Carbethoxy-5-hexenyl)-3-(1-propenyl)-4,5-dihydropyrrole (29). Yield: 14 mg (83%). ^1H NMR (CD_3CN): δ 1.26 (t, *J*=7.1 Hz, 3 H), 1.48 (m, 4 H), 1.71 (d, *J*=6.5 Hz, 3 H), 2.30 (m(br), 2 H), 2.45 (t, *J*=9 Hz, 2 H), 2.73 (m(br), 2 H), 3.04 (t, *J*=9 Hz, 2 H), 4.16 (q, *J*=7 Hz, 2 H), 5.11 (m, 1 H), 5.56 (s, 1 H), 5.91 (s, 1 H), 6.07 (s, 1 H), 6.15 (d *J*=15.3 Hz, 1 H); IR (cm^{-1}): 2933, 2853, 1717, 1642, 1602, 1446, 1369, 1271, 1177, 1143, 1066, 1028, 953.

(E,E)-1-(3-Carbethoxy-2-propenyl)-3-(1-propenyl)-4,5-dihydropyrrole (30). Yield: 12 mg (54%). ^1H NMR (CD_3CN): δ 1.24 (t, *J*=7.3 Hz, 3 H), 1.72 (d, *J*=6.7 Hz, 3 H), 2.40 (t, *J*=7 Hz, 2 H), 2.46 (t, *J*=8.7 Hz, 2 H), 2.89 (t, *J*=7.1 Hz, 2 H), 3.07 (t, *J*=9.1 Hz, 2 H), 4.13 (q, *J*=7 Hz, 2 H), 5.15 (m, 1 H), 5.87 (m, 1 H), 5.91 (s, 1 H), 6.15 (d, *J*=15.3 Hz, 1 H), 6.92 (m, 1 H); IR (cm^{-1}): 2976, 1722, 1658, 1462, 1444, 1368, 1267, 1182, 1094, 1042, 976.

(E,E)-1-(4-Carbethoxy-3-butenyl)-3-(1-propenyl)-4,5-dihydropyrrole (31). Yield: 47 mg (81%). ^1H NMR (CD_3CN): δ 1.24 (t, *J*=7.2 Hz, 3 H), 1.63 (m, 2 H), 1.72 (d, *J*=6.5 Hz, 3 H), 2.25 (m, 2 H), 2.46 (t, *J*=9.1 Hz, 2 H), 2.73 (t, *J*=7.2 Hz, 2 H), 3.05 (t, *J*=9.1 Hz, 2 H), 4.13 (q, *J*=7.1 Hz, 2 H), 5.13 (m, 1 H), 5.83 (d, *J*=15.5 Hz, 1 H), 5.92 (s, 1 H), 6.15 (d, *J*=15.3 Hz, 1 H), 6.95 (m, 1 H); IR (cm^{-1}): 2935, 2850, 1720, 1644, 1602, 1552, 1446, 1367, 1314, 1261, 1183, 1146, 1095, 1044, 954.

(E,E)-1-(5-Carbethoxy-4-pentenyl)-3-(1-propenyl)-4,5-dihydropyrrole (32). Yield: 34 mg (64%). ^1H NMR (CD_3CN): δ 1.24 (t, *J*=7.4 Hz, 3 H), 1.49 (m(br), 4 H), 1.71 (d, *J*=6.5 Hz, 3 H), 2.25 (m(br), 2 H), 2.45 (t, *J*=9 Hz, 2 H), 2.73 (m, 2 H), 3.04 (t, *J*=9.1 Hz, 2 H), 4.13 (q, *J*=7.3 Hz, 2 H), 5.10 (m, 1 H), 5.82 (d, *J*=15.5 Hz, 1 H), 5.92 (s, 1 H), 6.15 (d, *J*=15.4 Hz, 1 H), 6.92 (m, 1 H); IR (cm^{-1}): 2933, 2854, 1721, 1650, 1602, 1446, 1368, 1267, 1179, 1143, 1096, 1042, 954.

The following general procedure was used to prepare all intermolecular Diels-Alder cycloadducts:

***(endo* and *exo*) N-Benzyl 5-methyl-6,7-dicarbomethoxy-2,3,5,6,7,7a-hexahydroindole (17-18).** Crude diene **1** (58 mg, 0.29 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and 1.1 equiv (44.6 mg, 0.31 mmol) of dimethyl fumarate was added. The solution was stirred for 14 h at room temperature, then concentrated *in vacuo*. Excess fumarate was removed under high vacuum, and the crude adduct was subjected to chromatography on a short (1/2"x1") pad of deactivated silica gel using 9:1 hexane/ethyl acetate as eluant to afford 60 mg (61%) of a mixture of adducts **17** and **18** in a 3.5:1 ratio of diastereomers. For analytical purposes, separation of diastereomers could be achieved with a longer column and less polar solvent, but with a significant loss in yield. The major adduct was crystallized from hexane/ethyl acetate to give X-ray quality crystals (mp 64.5-66°C). Major diastereomer (**17**): ^1H NMR: δ 1.20 (d, *J*=6.9 Hz, 3 H), 2.2(m, 1 H), 2.38-2.49 (m (br), 3 H), 2.66 (dd, J_1=7.6 Hz, J_2=4.2 Hz, 1 H), 2.99 (t (br), *J*=6.9 Hz, 1 H), 3.06 (d (br), 6.7 Hz, 1 H), 3.26 (d, *J*=12.9 Hz, 1 H), 3.46 (dd, J_1=7.5 Hz, J_2=4.2 Hz, 1 H), 3.69 (s, 3 H), 3.74 (s, 3 H), 4.25 (d, *J*=12.9 Hz, 1 H), 5.43 (s, 1 H), 7.3 (m, 5 H); ^{13}C NMR: δ 20.19, 28.25, 31.54, 45.05, 49.31, 51.28, 51.72, 52.87, 58.47, 63.21, 122.40, 126.56,

127.83, 128.36, 138.70, 140.10, 173.17, 175.30; IR (cm^{-1}): 2952, 2793, 1735, 1495, 1434, 1254, 1193, 1164; HRMS (CI, NH_3) Calcd for $C_{20}H_{25}NO_4$: m/e 343.1783. Found: m/e 344.1862 (MH^+).
Minor diastereomer (**18**): ^1H NMR: δ 0.91 (d, *J*=6.9 Hz, 3 H), 2.22 (m, 1 H), 2.35 (m, 2 H), 2.73 (dd, J_1=10 Hz, J_2=5.9 Hz, 1 H), 2.81 (m(br), 1 H), 2.92 (m(br), 1 H), 3.07 (d, *J*=12.4 Hz, 1 H), 3.08 (m, 1 H), 3.17 (dd, J_1=6 Hz, J_2=5.9 Hz, 1 H), 3.72 (s, 3 H), 3.73 (s, 3 H), 3.95 (d, *J*=12.4 Hz, 1 H), 5.43 (s, 1 H), 7.35 (m, 5 H); ^{13}C NMR: δ 17.02, 25.59, 27.18, 31.77, 43.68, 46.81, 51.48, 52.20, 59.34, 67.37, 123.09, 126.72, 127.96, 128.65, 138.65, 138.74, 173.29, 176.35; IR (cm^{-1}): 2952, 2793, 1735, 1495, 1434, 1254, 1193, 1164.

(*endo*/*exo*) N-Benzyl 5-methyl-7-carbomethoxy-2,3,5,6,7,7a-hexahydroindole (19-20). Isolated 21 mg (48%) of a 1:3 mixture of adducts from 30 mg (0.15 mmol) diene **1**. Only the major diasteeomer was characterized. Major diastereomer **20** (*exo*): ^1H NMR: δ 1.13 (d, *J*=6.8 Hz, 3 H), 1.65 (m, 1 H), 1.70 (t(br), *J*=4.3 Hz, 1 H), 2.06 (m, 1 H), 2.14 (m, 1 H), 2.2-2.5 (m(br), 2 H), 2.90 (s(br), 1 H), 3.01 (t, *J*=7.9 Hz, 1 H), 3.14 (m, 1 H), 3.25 (d, *J*=12.9 Hz, 1 H), 3.65 (s, 3 H), 4.19 (d, *J*=12.9 Hz, 1 H), 5.45 (s(br), 1 H), 7.31 (m, 5 H); ^{13}C NMR: δ 21.4, 27.9, 28.2, 31.4, 40.1, 50.8, 52.7, 58.7, 64.6, 123.6, 126.5, 127.8, 128.4, 138.5, 139.0, 174.1; IR (cm^{-1}): 2950, 2869, 2790, 1736, 1678, 1604, 1495, 1453, 1372, 1354, 1244, 1162, 1074, 1029, 973; HRMS (CI, NH_3): Calcd for $C_{18}H_{23}NO_2$: m/e 285.1729. Found: m/e 286.1807 (MH^+).

(*endo* and *exo*) N-Benzyl 5-methyl-7-phenylsulfonyl-2,3,5,6,7,7a-hexahydroindole (21-22). Isolated 72 mg of a 1:1 mixture of adducts (34%) from 114 mg (0.57 mmol) diene **1**. ^1H NMR: δ 0.97 (d, *J*=6.9 Hz, 3 H), 1.17 (d, *J*=7.0 Hz, 3 H), 1.37 (m, 1 H), 2.00-2.50 (m, 5 H), 2.92 (m, 1 H), 3.00 (d, *J*=12.9 Hz, 1 H), 3.20 (d, *J*=13.1 Hz, 1 H), 3.46 (s(br), 1 H), 4.02 (q, *J*=7.3 Hz, 1 H), 4.12 (d, *J*=12.5 Hz, 1 H), 4.22 (d, *J*=13 Hz, 1 H), 5.34 (s, 1 H), 5.48 (s, 1 H), 7.28 (m, 6 H), 7.45-7.70 (m, 2 H), 7.96 (t, *J*=8.3 Hz, 2 H); ^{13}C: δ 21.0, 21.2, 26.6, 27.5, 27.7, 28.1, 29.8, 31.3, 51.5, 52.2, 58.2, 58.7, 60.0, 60.7, 62.4, 63.6, 123.9, 125.9, 126.5, 126.7, 127.7, 127.9, 128.1, 128.4, 128.5, 128.6, 128.9, 129.2, 129.3, 132.4, 133.3, 137.3, 138.1, 139.2, 141.5; IR (cm^{-1}): 3061, 2957, 2927, 2870, 1603, 1495, 1446, 1304, 1143, 1084.

(*endo* and *exo*) N-Benzyl 5,7-dimethyl-7-formyl-2,3,5,6,7,7a-hexahydroindole (25-26). Isolated 21 mg (52%) of a 1.5:1 mixture of adducts from 30 mg (0.15 mmol) diene **1**. Only the major diastereomer was characterized. Major diastereomer (**25**) (*endo*): ^1H NMR: δ 1.04 (d, *J*=7.2 Hz, 3 H), 1.30 (s, 3 H), 1.59 (dd, J_1=13.8 Hz, J_2=3.7 Hz, 2 H), 1.74 (dd, J_1=13.9 Hz, J_2=6.8 Hz, 2 H), 2.26 (m, 1 H), 2.30-2.50 (m, 2 H), 2.94 (s(br), 1 H), 3.26 (d, *J*=13.1 Hz, 1 H), 4.23 (d, *J*=13.1 Hz, 1 H), 5.56 (s, 1 H), 7.28 (m, 5 H), 9.81 (s, 1 H); ^{13}C NMR: δ 21.9, 23.0, 28.0, 28.4, 41.3, 48.3, 52.9, 61.1, 70.3, 126.2, 126.6, 127.9, 128.1, 139.3, 139.9, 207.0; IR (cm^{-1}): 3029, 2967, 2929, 2793, 1720, 1495, 1453, 1340, 1285, 1028.

(*endo*) N-Benzyl 5,7-dimethyl-7-*p*-nitrobenzyloxymethyl-2,3,5,6,7,7a-hexahydroindole. Sodium borohydride (20 mg, 0.45 mmol) was added in one portion to a solution of a 4:1 mixture of adducts **25**

and **26** (121 mg, 0.54 mmol) in CH_3OH (3 mL) at 0°C. After 1 h, solvent was removed *in vacuo* and the residue extracted with dichloromethane and filtered through celite. Upon removal of solvent, the crude alcohols (97 mg, 80%) were redissolved in dichloromethane, and triethylamine was added (81 mL, 0.58 mmol), followed by a catalytic amount of DMAP and 1.1 equiv of *p*-nitrobenzoyl chloride (73 mg, 0.39 mmol). The reaction was allowed to proceed at room temperature for 16 h, then diluted with dichloromethane, washed with saturated sodium bicarbonate solution and brine, and dried over sodium sulfate. Removal of solvent *in vacuo* gave an oil which was chromatographed on deactivated silica gel using 5:1 hexane/ethyl acetate as eluant to give a center cut of 76 mg (50%) of the title *endo p*-nitrobenzoate as a pale yellow solid which was recrystallized from heptane/dichloromethane to give X-ray quality crystals as fine needles (mp 123.5-124°C). ^{1}H NMR: δ 1.03 (d, *J*=7.3 Hz, 3 H), 1.35 (s, 3 H), 1.71 (m, 2 H), 2.25 (m, 2 H), 2.44 (m(br), 2 H), 2.89 (m, 1 H), 2.95 (s, 1 H), 3.38 (d, *J*=13.3 Hz, 1 H), 4.35 (d, *J*=13.3 Hz, 1 H), 4.38 (d, *J*=11.2 Hz, 1 H), 4.63 (d, 11.3 Hz, 1 H), 5.46 (s, 1 H), 7.30 (m, 5 H), 8.21 (d, *J*=8.8 Hz, 2 H), 8.31 (d, *J*=8.8 Hz, 2 H); ^{13}C NMR: δ 21.9, 26.6, 28.3, 28.6, 36.8, 38.3, 52.6, 61.8, 69.4, 72.1, 123.3, 123.6, 126.5, 128.0, 130.2, 135.8, 138.7, 139.7, 150.2, 164.6; IR (cm^{-1}): 3027, 2962, 2926, 2869, 2789, 1724, 1608, 1529, 1494, 1452, 1409, 1346, 1319, 1273, 1117, 1103, 1014; HRMS (CI, NH_3): Calcd for $C_{25}H_{28}N_2O_4$: m/e 420.2049. found: m/e 421.2127 (MH^+).

(*endo* and *exo*) 6a-Carboethoxy-8-methyl-1,2,5,6,7,8,6a,9b-tetrahydro-4H-pyrrolo[3,2,1-i,j]-quinoline (51-52). A solution of triene **27** (190 mg, 0.763 mmol) in xylenes (8 mL) was dripped into a 370°C pyrolysis tube under an Ar flow at a rate of 0.5 mL per minute. The collected pyrolysate was concentrated *in vacuo* to afford 120 mg (63%) crude adduct as a 1.5:1 mixture of diastereomers, containing approximately 50% adduct, 30% unreacted starting material and 20% decomposition products. The reaction mixture was Kugelrohr distilled (85°@ 0.1 mm Hg) to give 86 mg (45%) of the adducts **51-52** as a 1.5:1 mixture of diastereomers, still slightly contaminated with decomposition products. Full characterization is reported for the nitrobenzoate esters. ^{1}H NMR: (Partial) δ 0.94 (d, *J*=7.5 Hz, 3 H), 1.25 (t, *J*=7 Hz, 3 H), 3.24 (m, 2 H), 4.16 (m, 2 H), 5.18 (s, 1 H).

(*exo*)-6a-hydroxymethyl-8-methyl-1,2,5,6,7,8,6a,9b-tetrahydro-4H-pyrrolo[3,2,1-i,j]quinoline (53). To a suspension of $LiAlH_4$ (25.5 mg, 0.69 mmol) in THF (2 mL) at 0°C was added dropwise a solution of esters **51** and **52** (86 mg, 0.345 mmol) in THF (1 mL). The reaction was allowed to warm to room temperature and stirred for 12 h. The mixture was then recooled in an ice bath and ether was added (3 mL). The mixture was then quenched with water (26 mL), 15% NaOH (25 mL) and a second portion of water (25 mL). After 30 min, the white suspension was filtered through a pad of celite, and concentrated *in vacuo* to give 53 mg (74%) crude alcohols as a 1.5:1 mixture of diastereomers. Purification by column chromatography resulted in isolation of the minor diastereomer **53** as a crystalline solid (mp 138-139°C) suitable for X-ray diffraction (*vide supra*).

(*exo*)-6a-*p*-nitrobenzyloxymethyl-8-methyl-1,2,5,6,7,8,6a,9b-tetrahydro-4H-pyrrolo[3,2,1-i,j] quinoline. Alcohol **53** (53 mg, 0.256 mmol) was taken up in dichloromethane (2 mL). To this solution was added triethylamine (71 μL, 0.5 mmol), a catalytic amount of DMAP and *p*-nitrobenzoyl chloride

(57 mg, 0.307 mmol). The light brown solution was stirred at room temperature for 20 h, diluted with dichloromethane and washed with saturated sodium bicarbonate solution and brine and dried over sodium sulfate. Removal of solvent *in vacuo* gave a yellow oil which was purified by chromatography on deactivated silica gel using 5:1 hexane/ethyl acetate as eluant to afford the title *p*-nitrobenzoate ester as a yellow semi-solid. ^{1}H NMR: δ 1.06 (d, J=7.5 Hz, 3 H), 1.27 (m(br), 3 H), 1.53 (dd, J_1=13.7 Hz, J_2=8.7 Hz, 1 H), 1.63 (m(br), 2 H), 1.92 (m, 1 H), 2.05 (m, 2 H), 2.19 (s, 1 H), 2.36 (m(br), 1 H), 2.50 (m, 1 H), 3.11 (m, 1 H), 3.21 (d, J=5.0 Hz, 1 H), 4.15 (d, J=11.9 Hz, 1 H), 4.83 (dd, J_1=11.8 Hz, J_2=1.1 Hz, 1 H), 5.31 (s, 1 H), 8.23 (d, J=8.7 Hz, 2 H), 8.31 (d, J=8.7 Hz, 2 H); ^{13}C NMR: δ 22.6, 23.6, 28.9, 30.1, 33.4, 35.5, 36.5, 54.1, 54.6, 65.8, 73.2, 90.9, 122.0, 124.0, 131.0, 136.6, 136.9, 165.2; IR (cm^{-1}): 2931, 1724, 1607, 1529, 1454, 1348, 1308, 1271, 1163, 1031, 872; HRMS (CI, NH_3): Calcd for $C_{20}H_{24}N_2O_4$; m/e 356.1736. found: m/e 357.1814 (MH^+).

(*exo*)-8a-Carboethoxy-7-methyl-1,2,4,5,7,8,8a,8b-tetrahydropyrrolo[3,2,1-h,i]indole(55). Triene **28** (106 mg) in xylenes (10 mL) was dropped into a 350°C pyrolysis tube under Ar flow at a rate of 0.25 mL per minute. The collected pyrolysate was concentrated *in vacuo* to afford 64 mg (60%) crude adduct **55** as a pale yellow oil. ^{1}H NMR: δ 0.78 (dd, J_1=12.3 Hz, J_2=12.0 Hz, 1 H), 1.04 (d, J=7 Hz, 3 H), 1.27 (t, J=7.1 Hz, 3 H), 1.62 (m, 2 H), 2.09 (s(br), 2 H), 2.22 (dd, J_1=12.9 Hz, J_2=3.2 Hz, 1 H), 2.39-2.68 (m, 3 H), 2.99 (m, 1 H), 3.24 (m, 1 H), 3.83 (s(br), 1 H), 4.19 (q, J=7.2 Hz, 2 H), 5.56 (s, 1 H); ^{13}C NMR: δ 13.9, 20.6, 28.0, 30.7, 38.1, 41.9, 51.2, 51.2, 53.1, 60.5, 66.8, 126.7, 139.1, 176.7; IR (cm^{-1}): 2958, 2871, 1726, 1455, 1367, 1291, 1252, 1191, 1142, 1105, 1083, 1028.

(*exo*)-8a-Hydroxymethyl-7-methyl-1,2,4,5,7,8,8a,8b-tetrahydropyrrolo[3,2,1-h,i]indole. To a suspension of $LiAlH_4$ (9.3 mg, 0.25 mmol) in THF (1 mL) at 0°C was added dropwise a solution of ester **55** (29.7 mg, 0.126 mmol) in THF (1 mL). The reaction was allowed to warm to room temperature and stirred for 2 h. The mixture was then recooled in an ice bath and ether was added (3 mL). The mixture was then quenched with water (9.3 mL), 10% NaOH (14 mL) and a second portion of water (9.3 mL). After 30 min, the white suspension was filtered through a pad of celite, concentrated *in vacuo*, and the residue purified by Kugelrohr distillation (130°C @ 0.05 mm) to afford 17 mg the title alcohol (70%). ^{1}H NMR: δ 0.75 (m, 1 H), 1.03 (d, J=7 Hz, 3 H), 1.48 (m, 1 H), 1.89 (dd, J_1=13.8 Hz, J_2=3.7 Hz, 1 H), 1.96 (m, 1 H), 2.09 (s(br), 1 H), 2.44 (m, 1 H), 2.51 (m, 2 H), 2.65 (m, 1 H), 2.94 (m, 1 H), 3.11 (m, 2 H), 3.56 (s, 2 H), 5.55 (s, 1 H); ^{13}C NMR: δ 21.1, 28.1, 29.8, 36.9, 44.1, 45.9, 50.6, 52.8, 67.5, 68.9, 126.9, 139.5; IR (cm^{-1}): 3279, 2954, 2927, 2869, 1709, 1692, 1460, 1325, 1288, 1154, 1062, 819; HRMS (CI, NH_3) Calcd for $C_{12}H_{19}NO$: m/e 193.1467. found: m/e 194.1544 (MH^+).

(*endo* and *exo*)-8-Carboethoxy-7-methyl-1,2,4,5,7,8,8a,8b-tetrahydropyrrolo[3,2,1-h,i]indole (58-59). A solution of salt **48** (30 mg, 0.095 mmol) in ethanol (5 mL) was allowed to stand for 2 weeks at room temperature, then passed through a plug of ion exchange resin IRA-400. The ethanol eluate was concentrated to afford 12 mg (54%) of adducts **58** and **59** containing less than 10% **30**. ^{1}H NMR: (Partial) δ 1.05 (d, J=7 Hz, 3 H), 1.29 (m, 3 H), 3.22 (s, 1 H), 4.19 (q, J=7 Hz, 2 H), 5.44 (s, 1 H); IR (cm^{-1}): 2930, 1731, 1670, 1446, 1261, 1161, 913.

(*endo* and *exo*)-7-Carboethoxy-8-methyl-1,2,5,6,7,8,6a,9b-tetrahydro-4H-pyrrolo[3,2,1-i,j] quinoline (60-61). A solution of triene **31** (171 mg) in xylenes (18 mL) was dripped into a 350°C pyrolysis tube under an Ar flow at a rate of 0.5 mL per minute. The collected pyrolysate was concentrated *in vacuo* to afford 120 mg (70%) of crude adducts **60** and **61** as a 9:1 mixture of diastereomers, along with small amount of unreacted **31**. The reaction mixture was chromatographed on deactivated silica gel, initially with elution by 9:1 hexane/ethyl acetate, then 2:1 hexane/ethyl acetate to give 82 mg (48%) of the major diastereomer **60**. ^{1}H NMR: δ 0.91 (d, J=7.1 Hz, 4 H), 1.28 (t, J = 6.9 Hz, 3 H), 1.63 (m, 1 H), 1.77 (m(br), 2 H), 1.85 (d, J=8.9 Hz, 1 H), 2.00-2.19 (m, 3 H), 2.42 (m, 2 H), 2.53 (dd, J_1=11.7 Hz, J_2=6.1 Hz, 1 H), 2.70 (s(br), 1 H), 3.14 (m, 2 H), 4.18 (m, 2 H), 5.29 (s, 1H); ^{13}C NMR: δ 14.0, 17.7, 25.7, 27.2, 27.6, 33.4, 34.4, 47.4, 52.9, 53.1, 59.6, 70.1, 121.4, 137.7, 172.9; IR (cm^{-1}): 2930, 2785, 1732, 1456, 1376, 1349, 1322, 1298, 1274, 1255, 1220, 1158, 1147, 1034.

(endo)-7-*p*-Nitrobenzyloxymethyl-8-methyl-1,2,5,6,7,8,6a,9b-tetrahydro-4H-pyrrolo[3,2,1-i,j]quinoline. To a suspension of $LiAlH_4$ (17 mg, 0.46 mmol) in THF (1 mL) at 0°C was added dropwise a solution of ester **60** (57 mg, 0.229 mmol) in THF (1 mL). The reaction was allowed to warm to room temperature and stir for 12 h. The mixture was then recooled in an ice bath and ether was added (3 mL). The mixture was then quenched with water (17 mL), 10% NaOH (24 mL) and a second portion of water (17 mL). After 30 min, the white suspension was filtered through a pad of celite and concentrated *in vacuo* to give 39 mg (82%) crude alcohol. This was taken up in dichloromethane (2 mL). To this solution was added successively triethylamine (35 μL, 0.25 mmol), a catalytic amount of DMAP, and *p*-nitrobenzoyl chloride (37 mg, 0.2 mmol). The light brown solution was stirred at room temperature for 20 h, diluted with dichloromethane and washed with saturated sodium bicarbonate solution and brine and dried over sodium sulfate. Removal of solvent *in vacuo* gave a yellow oil which was purified by chromatography on deactivated silica gel using 5:1 hexane/ethyl acetate as eluant to afford *p*-nitrobenzoate ester **24** as a reddish brown solid. The product could not be obtained in a crystalline form suitable for X-ray analysis. ^{1}H NMR: δ 0.99 (d, J=7.1 Hz, 3 H), 1.14 (dd, J_1=11 Hz, J_2=7.3 Hz, 1 H), 1.43 (m, 1 H), 1.75 (m(br), 3 H), 1.95 (m, 1 H), 2.12 (m, 3 H), 2.44 (m, 2 H), 2.59 (s(br), 1 H), 3.16 (m, 2 H), 4.35 (dd, J_1=11 Hz, J_2=9 Hz, 1 H), 4.57 (dd, J_1=11.1 Hz, J_2=5.6 Hz, 1 H), 5.35 (s, 1 H), 8.21 (d, J=8.7 Hz, 2 H), 8.31 (d, J=8.7 Hz, 2 H); ^{13}C NMR: δ 16.8, 26.6, 28.0, 28.3, 33.8, 33.9, 36.2, 39.9, 53.7, 66.6, 71.7, 123.1, 124.0, 131.1, 136.2, 138.5, 151.0, 165.0; IR (cm^{-1}): 2928, 2788, 1725, 1607, 1528, 1454, 1410, 1349, 1321, 1275, 1167, 1154, 1103; HRMS (CI, NH_3): Calcd for $C_{20}H_{24}N_2O_4$: m/e 356.1736. found: m/e 357.1814 (MH^+).

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