A CONVENIENT SYNTHESIS OF PYRROLE- AND N-AMINOPYRROLE-3-PROPIONATE ESTERS*

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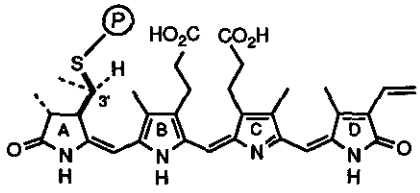
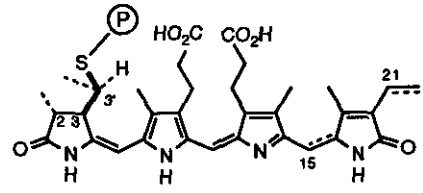
Abstract- Trisubstituted pyrroles having a substitution pattern found in many naturally occurring linear and macrocyclic tetrapyrroles have been prepared in a regiospecific fashion by a two step sequence involving Diels-Alder reaction of 2-oxo-3-butenoate esters (**58**) with 2-alkoxy-1,3-pentadiene derivatives (**46**), followed by ozonolysis and Paal-Knorr cyclization.

Introduction.

The biliproteins are a family of naturally occurring chromophores which are made up of linear tetrapyrrole derivatives covalently bonded to a protein (P).[1] Representative examples include phytochrome (**1**), which functions as the "on-off" switch for photomorphogenesis in higher plants,[2] and the phycocyanins (**2**) and phycoerythrins (**3**).[3,4] These latter materials are commonly found in blue-green, eucaryotic and cryptomonad



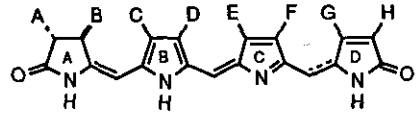
Phytochrome (1)



2 (Δ-15); **3** (Δ-21)

algae and serve as light harvesting proteins in photosynthesis. Along with promoting seed germination and flowering, **1** has also been implicated in the control of potassium uptake, chloroplast movement and water permeability in green plant metabolism.[5] In view of these properties, it is not surprising that species of type **1-3** have attracted considerable synthetic attention.[6]

Synthetic methodology in this area should provide for unequivocal control over both relative and absolute stereochemistry (ring A; C_2, C_3, and $C_{3'}$), as well as regiochemical control along the backbone of the tetrapyrrole skeleton (substituents A-H in **4**). However, these goals are often difficult to achieve. Recently, we



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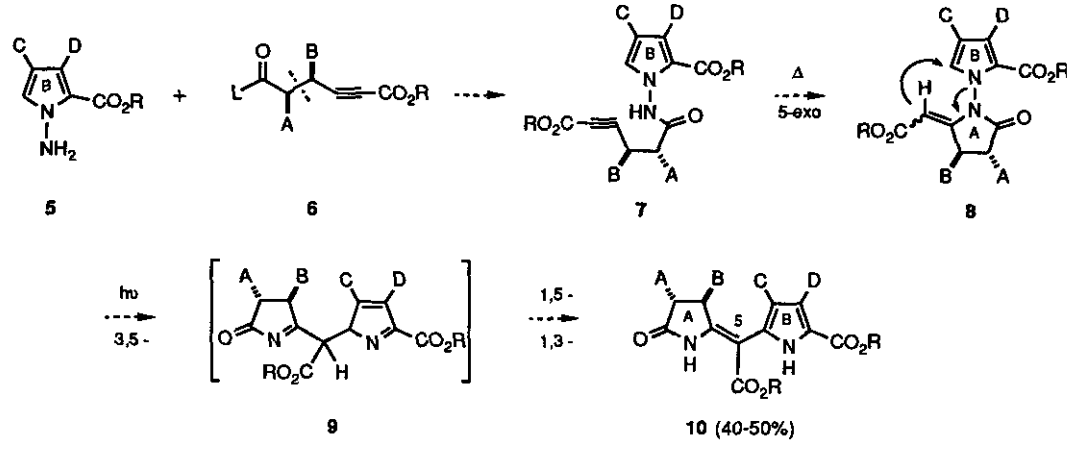
proposed a new strategy for the synthesis of linear tetrapyrroles of type **1-3** which involves an initial acylation of N-aminopyrroles of type **5** with acetylenic acids (**6**) to afford the corresponding hydrazides (**7**) (Scheme

* *Dedicated to my good friend and mentor, Professor Edward C. Taylor, on the occasion of his 70th birthday*

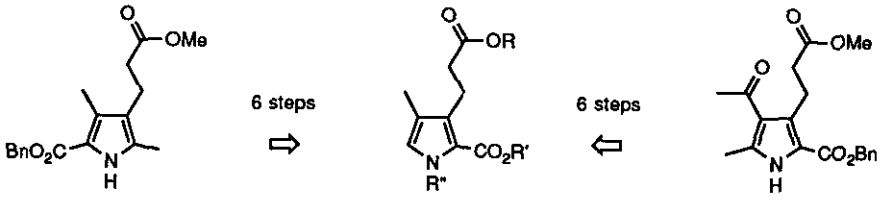
1).[6c,d] These last materials, upon 5-*exo-dig* cyclization, would then afford the *N*-pyrroloenamides (**8**), which upon 3,5-sigmatropic rearrangement would generate dihydropyrromethenones (**10**) directly in their carboxylate protected form. An attractive feature of this approach is the fact that stereochemical and regiochemical features incorporated into **6** are transposed in an unequivocal fashion to the final product (**10**). Importantly, *syn*-substituted acetylenes of type **6** can now be prepared with excellent levels of diastereofacial selectivity using a modified Nicholas reaction (dashed line, L = chiral leaving group).[7] Finally, coupling of **10** with an appropriate C,D-fragment, prepared in analogous fashion, would give the corresponding linear tetrapyrroles in homochiral form.



a) C, D = H; R = Me b) C, D = fused cyclohexyl; R = Me

Scheme 1

The viability of this strategy was initially demonstrated with *N*-aminopyrroles (**5a**) (C,D = H) and (**5b**) (C,D = fused cyclohexyl), which because of their symmetric nature were readily prepared from the appropriate 1,4-dicarbonyl derivatives following standard literature procedures.[6c,8] Dihydropyrromethenones (**10a,b**) (A,B = H, R = Me) were obtained in ~50% yield from **8a,b** upon photolysis at 300 nm in the presence of piperylene (triplet quencher). However, in order for these preliminary studies to be extrapolated to the synthesis of **1-3** it was first necessary to devise an efficient preparation of *N*-aminopyrroles of general structure(**11**). N-*H*-Pyrroles related to **11** have traditionally been prepared by lengthy schemes involving selective degradation of tetra-



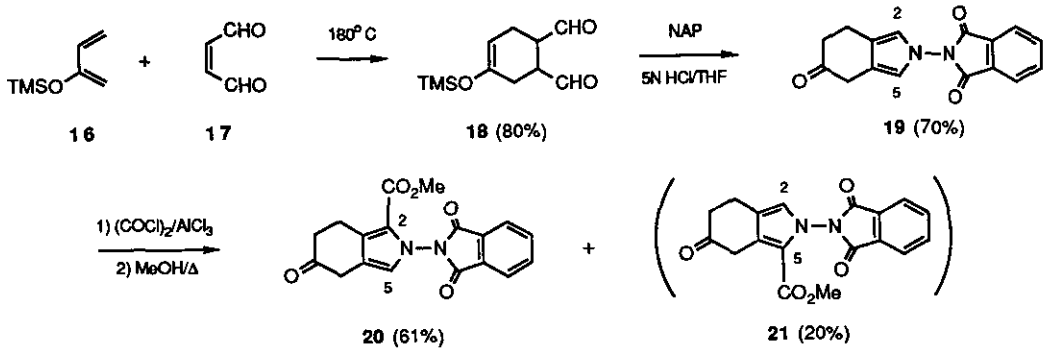
14 **15**

11 (R, R' = alkyl, R" = NH_2)
12 (R' = *t*-Bu, R = Me, R" = H)
13 (R' = Bn, R = Me, R" = H)

substituted derivatives. Thus, pyrrole (**12**) has previously been synthesized in six steps from the dimethyl derivative (**14**), which itself was obtained by a multistep procedure beginning with benzyl acetoacetate.[9a] In similar fashion, **13** was prepared by extensive manipulation of **15**.[9b] Neither approach is amenable to the preparation of *N*-aminopyrroles.

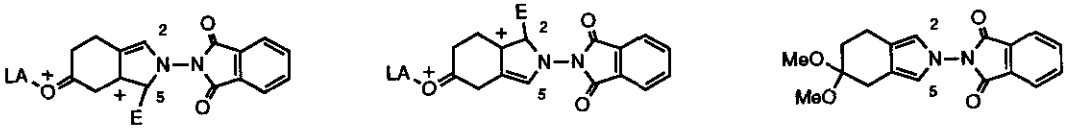
Preliminary Studies.

Our initial efforts at developing an efficient synthesis of **11** took advantage of the ready availability of the pyrrolo ketone (**19**) (Scheme 2). This material was obtained in >50% overall yield by Diels-Alder cyclization of 2-trimethylsilyloxybutadiene (**16**) with malealdehyde (**17**), followed by acid catalyzed condensation of the resulting dialdehyde (**18**) with *N*-aminophthalimide (NAP). As the key step in this approach, **19** was converted to the 2-carbomethoxy derivative (**20**) in 61% yield, with ~3:1 selectivity, by Friedel-Crafts acylation with oxaloyl chloride/$AlCl_3$ followed by methanolysis.[10] Selectivity in this transformation is presumably due to the

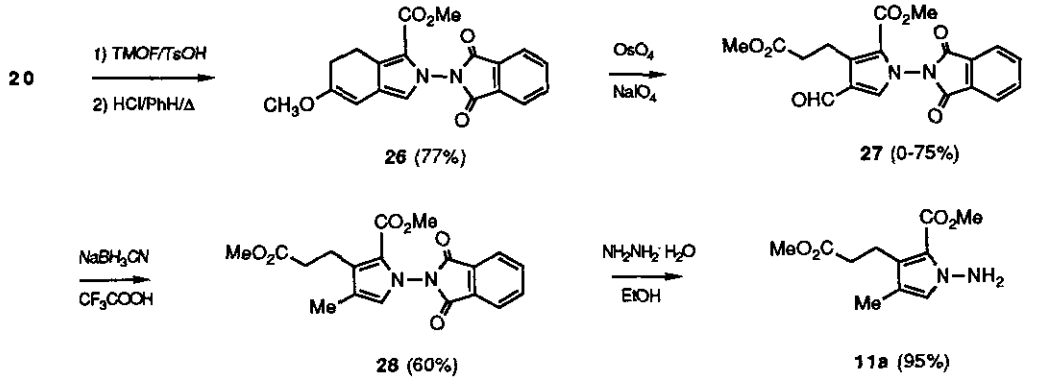


Scheme 2

inductive influence of the Lewis acid-complexed ketone functionality, which should exert a substantially greater destabilizing effect on carbocation intermediates of type **22**, arising from initial electrophilic attack at C_5, as compared to **23**. In agreement with this suggestion, ketal derivative (**24**) underwent Friedel-Crafts acylation



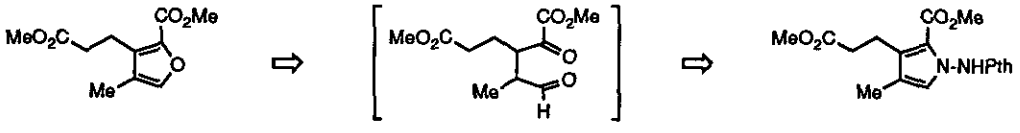
under identical conditions to afford ~1:1 mixtures of the dimethylketals corresponding to **20** and **21**. Next, keto ester (**20**) was cleanly converted to the enol ether (**26**) by a two step sequence involving initial conversion to dimethyl ketal (**25**) (96%, not shown), followed by acid catalyzed elimination in refluxing benzene (80%) (Scheme 3). Numerous conditions were explored to effect the oxidative cleavage of **26** to the ester aldehyde



Scheme 3

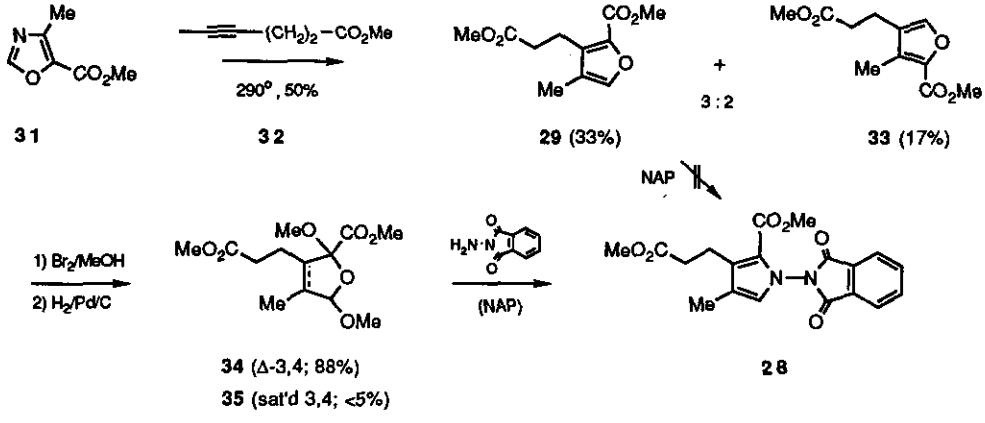
(27). Of these, the reagent system $OsO_4/NaIO_4$ was most satisfactory, although yields were highly variable (0-75%). Reduction of **27** with sodium cyanoborohydride in TFA then afforded the fully reduced derivative (**28**) (60%), and finally, hydrazinolysis of **28** gave a 95% yield of **11a**, which proved to be a stable, colorless oil. The difficulties with this approach centered mainly around the unpredictable nature of the conversion of **26** to **27**. Although this reaction worked well on small scales (<50 mg), it could not be carried out with sufficient material to give reasonable quantities of **11a**.

Furan derivatives have been employed as convenient precursors to pyrroles,[8] and this transformation formed the basis for our second approach to *N*-aminopyrroles of type **11**. Thus, we expected that furano diester (**29**) might be hydrolyzed either directly, or *via* a suitably activated derivative, to keto aldehyde (**30**), which upon condensation with *N*-aminophthalimide (NAP) would afford the identical pyrrolo diester (**28**) as described above in Scheme 3. Alternatively, it is sometimes possible to convert furans directly to pyrroles with



29 **30** **28**

sufficiently eactive amines. The requisite furan (**29**) was readily prepared by (Diels-Alder)-(*retro*-Diels-Alder) cyclization of 4-methyl-5-carbomethoxyoxazole (**31**) with acetylenic ester (**32**), which afforded a 50% yield of the furan derivatives (**29**) and (**33**) (Scheme 4).[11] The desired isomer (**29**) predominated by ratios varying from 2:1 to 3:2, and this reaction could be carried out on relatively large scales (0.5-1.0 g). However, all



31 **32** **29** (33%) **33** (17%)

34 (Δ-3,4; 88%)
35 (sat'd 3,4; <5%)

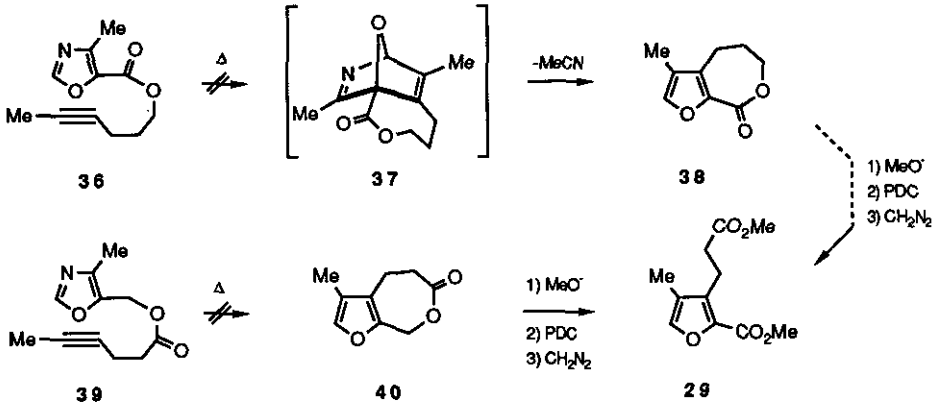
28

Scheme 4

attempts at the direct conversion of **29** to **28** by reaction with *N*-aminophthalimide (NAP) were unsuccessful, as were efforts aimed at the direct hydrolysis of **29** to the keto aldehyde (**30**) (*vide supra*). Therefore, we focused our attention next on the preparation of the more reactive 2,5-dimethoxytetrahydrofuran derivative (**35**), which we expected would be available from **29** by well precedented procedures involving bromination in MeOH, followed by catalytic hydrogenation.[12] In practice, bromination of **29** proceeded smoothly to give an 88% yield of the corresponding 2,5-dimethoxy-2,5-dihydrofuran (**34**) (Δ-3,4). Unfortunately, however, hydrogenation of **34** afforded < 5% of the desired tetrahydro derivative (**35**), from which only trace amounts of **28** were obtained upon reaction with *N*-aminophthalimide (NAP).

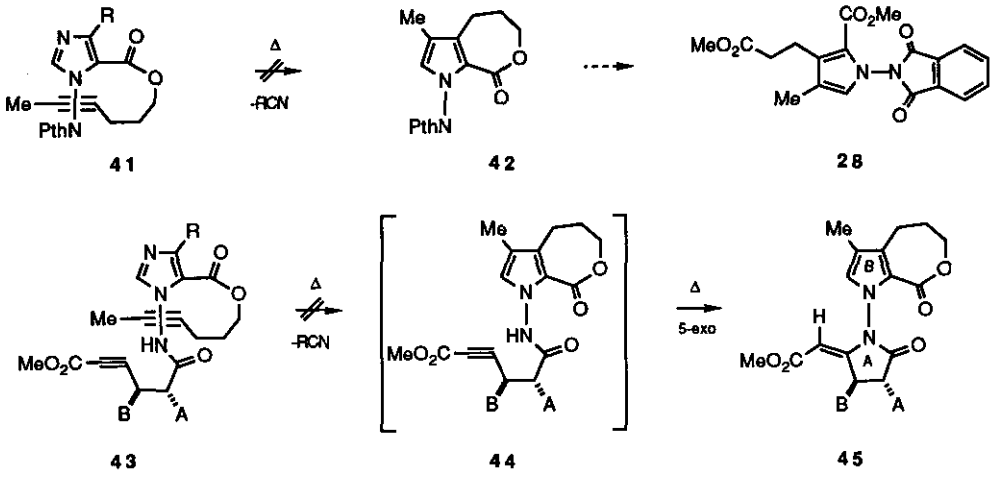
In an effort to avoid the regiochemical ambiguity associated with the intermolecular Diels-Alder reaction of **31** with **32**, attention was also devoted to the preparation and cyclization of the acetylenic oxazoles (**36**) and (**39**) (Scheme 5, following page). We have had considerable success with closely related intramolecular

cyclizations,[13] and in principle, both **36** and **39** should be convertible to the desired furano ester (**29**) by a straightforward sequence of transformations. Unfortunately, however, although readily prepared, **36** and **39** gave *none of the requisite lactones* (**38**) and (**40**), respectively, upon thermolysis under a variety of conditions. This lack of reactivity is most likely due to the fact that esters (**36**) and (**39**) strongly prefer the *E*-conformation, as previously noted by Jung and others for related examples.[14]



Scheme 5

Finally, in a related series of studies, we investigated the possibility that *N*-substituted imidazoles of general structure (**41**) and (**43**) might undergo an intramolecular Diels-Alder reaction to afford *N*-substituted pyrroles of type **42** and **44** directly (Scheme 6). The advantages to such an approach are considerable, and we

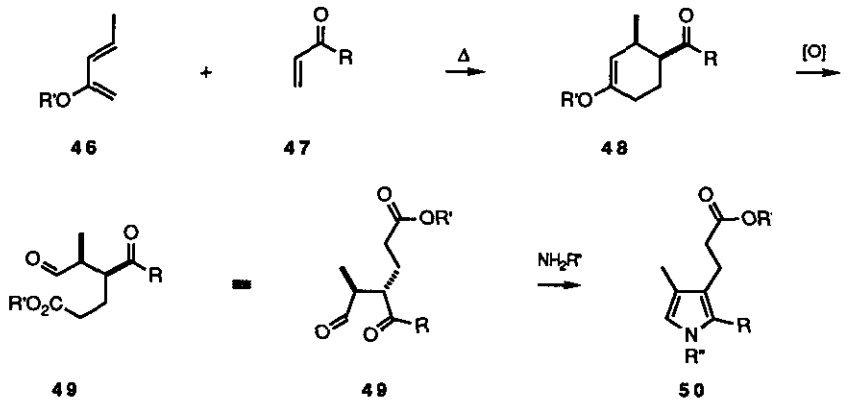


Scheme 6

were particularly attracted to the possibility that **43** might provide the key pyrromethenone precursor (**45**) in a single step by sequential (Diels-Alder)-(*retro*-Diels-Alder) reaction followed by 5-*exo-dig* cyclization. Although imidazoles, in contrast to oxazoles, are normally unreactive in Diels-Alder reactions, we were encouraged in this approach by closely related precedent in the literature. Thus, in a noteworthy series of papers, Schultz *et al.* reported that *N*-aminopyrroles, in contrast to simple pyrroles, function as highly reactive dienes in Diels-Alder reactions.[15] Notwithstanding this analogy, however, both **41** and **43** proved to be unreactive species.

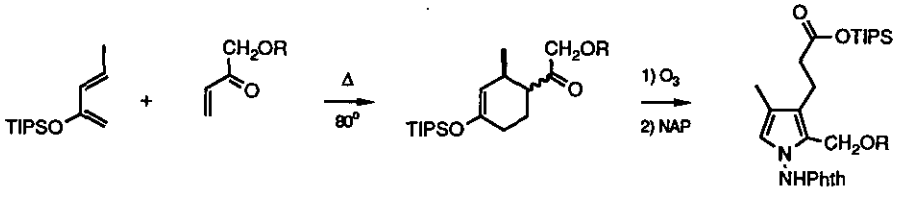
Vinylketones as Dienophiles in a Versatile Synthesis of Pyrroles.

It seemed likely that Diels-Alder cyclization of 2-alkoxy-1,3-pentadiene derivatives of type **46** with vinyl ketones (**47**) would provide a facile route to cyclohexene derivatives of general structure (**48**), which in principle are attractive intermediates for the synthesis of highly substituted pyrroles of type **50** (Scheme 7). Thus,



Scheme 7

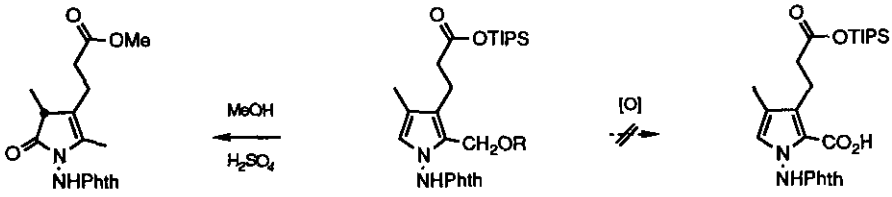
cyclohexene (**48**), upon ozonolysis, could be expected to afford keto-aldehyde derivatives of type **49**, which upon Paal-Knorr cyclization would give **50** in unequivocal fashion.[8] This approach takes advantage of the highly regiospecific nature of Diels-Alder reactions to establish the desired orientation of substituents destined to occupy the pyrrole nucleus. The viability of this strategy was initially tested with the known dienophiles (**51**) and (**52**),[16a,b] which underwent clean cyclization with **46d** to afford the corresponding "ortho" adducts (**53a**) and (**53b**) as mixtures of *endo* and *exo* stereoisomers. Importantly, no trace of regioisomeric adducts derived



from "para" cycloaddition could be detected in the crude reaction mixtures. The utility of these cyclohexene derivatives for the synthesis of pyrroles was then demonstrated by ozonolysis, followed by condensation with *N*-aminophthalimide (NAP), which afforded the corresponding *N*-aminopyrroles (**55a**) (54%) and (**55b**) (71%) with 100% selectivity.

For the purpose of preparing *N*-aminopyrroles of type **11**, containing a 2-carboalkoxy substituent (*vide supra*), it was necessary to effect the oxidation of either **55a** or **55b** to the corresponding carboxylic acid (**56**) (see below). This transformation required an initial deprotection of **55a,b** (R = Ac, Me) to the hydroxymethyl derivative (**55c**) (R = H). Unfortunately, however, both **55a** and **55b** turned out to be very unstable species, which rapidly decomposed under both acidic and basic conditions. In most cases the products of attempted deprotection were polymeric materials. With MeOH/H_2SO_4, however, both **55a** and **55b** afforded moderate yields of a product whose nmr spectrum was consistent with the rearranged pyrrole derivative (**57**), the product

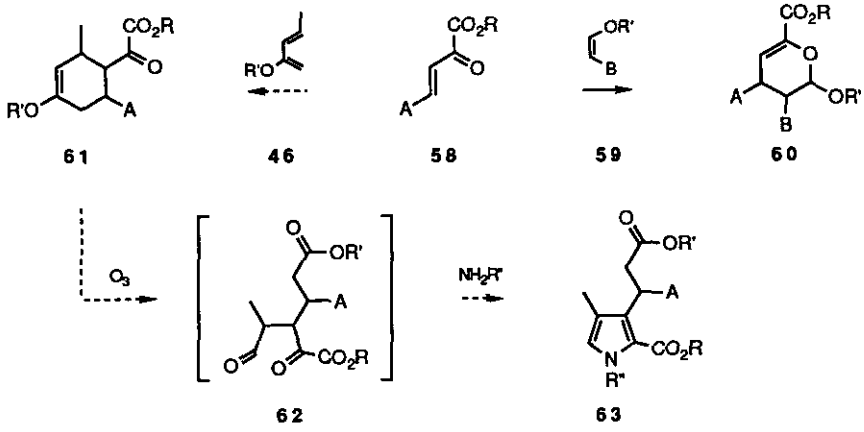
of S_N2' displacement. In no case were we able to obtain any evidence for the formation of **56** under a variety of oxidation conditions. These results forced a re-evaluation of our synthetic scheme.



57 **55a,b,c** **56**

a) R = Ac; b) R = Me; c) R = H

In a recent series of papers Boger[17a-c] and Tietze[17d] reported that 2-oxo-3-butenoate derivatives of general structure (**58**) (R = Me; A = Ph, OMe[17a], NPhth[17d]) undergo a $LUMO_{diene}$ controlled hetero-Diels-Alder reaction with electron rich dienophiles of type **59** (R' = alkyl; B = alkyl, alkoxy, acyl), affording 2-alkoxy-3,4-dihydro-2*H*-pyran-6-carboxylates (**60**) under either thermal, Lewis acid catalyzed or high pressure conditions



61 **46** **58** **59** **60**

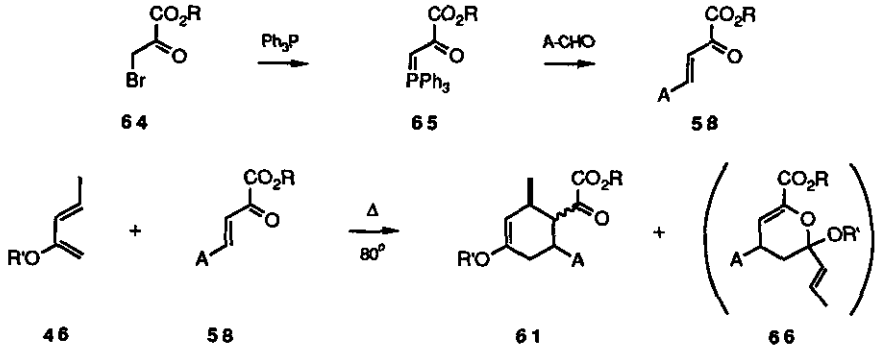
62 **63**

Scheme 8

(Scheme 8). The utility of these highly electron deficient heterodienes as 4π components in Diels-Alder reactions is thus well established. It seemed reasonable to expect that 2-oxo-3-butenoate esters of type **58** might also function as 2π components in Diels-Alder reactions, affording cyclohexene derivatives of general structure **61** upon reaction with alkoxydienes of type **46**. Cyclohexenes (**61**), in turn, have both the proper substitution pattern and oxidation state to afford pyrrole-2-carboxylic esters following the general route oulined in Scheme 7. Thus, for example, ozonolysis of **61** would be expected to give keto aldehydes of type **62**, which upon Paal-Knorr cyclization would afford pyrroles (**63**) in unequivocal fashion. As attractive as this scheme appeared, however, little was known about the reactivity of species such as **58** as dienophiles in Diels-Alder reactions. To the best of our knowledge, the only report which addressed this issue was the observation that methyl *trans*-4-methoxy-2-oxo-3-butenoate (**58a**, A = OMe, R = Me) undergoes dimerization at 13 kbar pressure in the absence of a suitably reactive dienophile.[17a,b] It was therefore necessary to investigate the feasibility of this cycloaddition, in particular with regard to substituent effects in both the diene and dienophile components.

2-Oxo-3-butenoates (**58b**) (R = Et, A = H) and (**58c**) (R = Bn, A = H) were readily prepared from the corresponding Wittig reagents (**65**) following the general procedure of Le Corre for the synthesis of **58d** (R = Et, A = Ph) (Scheme 9, below).[18,19] Each of these materials was then subjected to Diels-Alder cyclization with

a variety of 2-alkoxy-1,3-pentadiene derivatives (**46**), and the resulting product mixtures were analyzed for the presence of the regioisomeric adducts (**61**) and (**66**). Adducts (**61a-e**) were obtained as mixtures of *endo* and *exo* isomers which readily enolized upon exposure to acid or upon prolonged contact with silica gel. In most cases **61** and **66** were the only products which could be identified. However, with **61f,g** (A = Ph, *entries 6* and *7*) the competing directing influence of the phenyl ring also led to the formation of varying amounts of products tentatively identified as *meta* isomers. Not surprisingly, these last two examples also required considerably longer times for complete reaction (26 h *vs* 2-4 h in refluxing benzene).

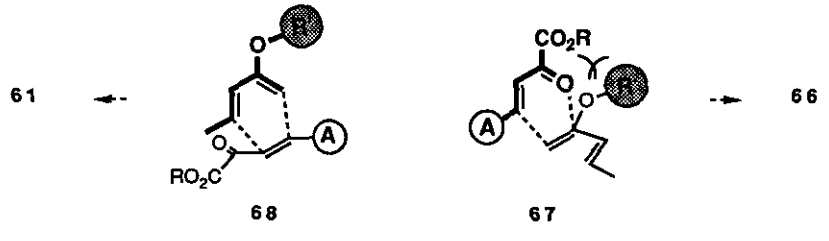


Entry	Experiment	R'	R	A	% yield 61	% yield 66
1	**46a + 58b**	Et	Et	H	40% (**61a**)[a]	14% (**66a**)[a]
2	**46b + 58b**	TMS	Et	H	45% (**61b**)[a]	10% (**66b**)[a]
3	**46c + 58b**	TBDMS	Et	H	61% (**61c**)[a]	8% (**66c**)[a]
4	**46d + 58b**	TIPS	Et	H	81% (**61d**)[a]	<1% (**66d**)[a]
5	**46d + 58c**	TIPS	Bn	H	60% (**61e**)[a]	<1% (**66e**)[a]
6	**46c + 58d**	TBDMS	Et	Ph	41% (**61f**)[b,c]	19% (**66f**)[b]
7	**46d + 58d**	TIPS	Et	Ph	49% (**61g**)[b,c]	4% (**66g**)[b]

a) 2-4 h, 80° C. b) 26h, 80° C. c) combined yield of *o*- and *m*-isomer

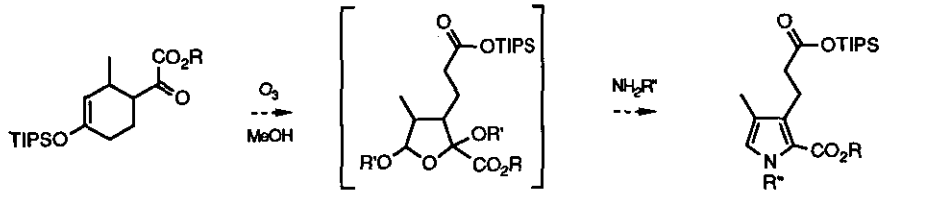
Scheme 9

In general, yields of **61** increased in the order R' = Et < trimethylsilyl (TMS) < *t*-butyldimethylsilyl (TBDMS) < tri-isopropylsilyl (TIPS), ranging from 40% (R' = Et, *Entry 1*) to 80-95% (R' = TIPS, *Entry 4*). This trend may be partly due to the stability of adducts **61**, since both **61a** and **61b** were extremely sensitive to hydrolysis upon attempted purification. Of greater interest, the relative yields of **61** and **66** were also markedly influenced by substituent R', ranging from ~3:1 (A = H, R' = Et, *Entry 1*) to ~99:1 (A = H, R' = TIPS, *Entries 4* and *5*). Similarly, with A = Ph, greater selectivity for **61** was observed with R' = TIPS (~12:1, *Entry 7*) as compared to R' = TBDMS (~2:1, *Entry 6*). These selectivity patterns closely parallel the relative size of R', and we believe that the observed product ratios can be rationalized by considering steric interactions in the competing transition states (**67**) and (**68**) leading to adducts **66** and **61**, respectively.[17e] Thus, one would expect that R' would



exert little effect on the rate of cyclization leading from **68** to the desired adducts (**61**). In contrast, steric effects in **67** should be much more important and the rate of formation of **66** would be expected to decrease with increasing size of R'.

In any event, adducts (**61d**) and (**61e**) were readily converted to the desired pyrroles (**70**) by ozonolysis followed directly by Paal-Knorr cyclization. It proved to be neither necessary nor desirable to purify the intermediate cleavage products (**69**), which by nmr analysis appeared to exist as complex mixtures of cyclic acetals and hemi-acetals (R' = H, Me). Cyclization of **69d,e** with ammonium carbonate (R" = H) afforded the corresponding pyrroles (**70d,e**) in 60-70% overall yield,[8] while cyclization of **69d** with *N*-aminophthalimide (R" = Phth) afforded **70f** in ~65% yield. This last material then gave a 90% yield of the corresponding *N*-aminopyrrole (**70g**) upon hydrazinolysis with hydrazine hydrate. We are confident that this methodology can be readily extended to a wide variety of pyrroles and *N*-aminopyrroles of biological importance.[20]



61d (R = Et)
61e (R = Bn)

69d (R = Et)
69e (R = Bn)

70d (R = Et, R" = H)(66%)
70e (R = Bn, R" = H)(60%)
70f (R=Et, R" = Phth)(64%)
70g (R=Et, R" = NH_2)(90%)

EXPERIMENTAL SECTION

1. General.

^{1}HNmr and ^{13}C nmr spectra were recorded on a Varian XL-400 spectrometer. Infrared spectra were recorded on either a Perkin-Elmer 1500 FT-IR or 1600 FT-IR spectrophotometer. Mass Spectra were recorded on a Hewlet Packard HP 38890 GC-MS system. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Exact mass determinations were carried out on a Kratos MS-80 RFA mass spectrometer at the Yale University Instrument Center, New Haven, CT. Elemental analyses were carried out by Atlantic Micro Labs, Inc., Atlanta, GA.

Unless otherwise noted, materials obtained from suppliers were used without further purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. Methanol (MeOH) was distilled from CaH. Methylene chloride (CH_2Cl_2) was distilled from P_2O_5 immediately prior to use. Aromatic solvents were distilled from sodium immediately prior to use. Dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were distilled from CaH and stored over activated 4 Å sieves. Reactions were generally performed under a nitrogen atmosphere. Chromatography refers to flash chromatography according to the procedure of Still.[21]

2. *Ozonolysis conditions.*

Ozone was generated in the usual fashion employing a Welsbach T-408 laboratory ozonator using commercial-grade oxygen as a source. Ozonolyses were carried out in round-bottomed flasks nearly filled with solvent and cooled in dry ice acetone baths. Commercial dyes (Aldrich Chemical Co.) were used without further purification in the form of 0.05-0.10% solutions in the reaction solvent. A sufficient amount (usually a few drops) of dye was added to impart a definitive color to the reaction mixture, and the end point was indicated by

total discoloration. After flushing with nitrogen for at least 15 min, the ozonolysis product was cleaved with excess dimethyl sulfide (DMS) at -78 °C.

3. Sealed tube reactions.

An appropriate reaction vessel was prepared by sealing one end of a 15 mm pyrex standard wall tube and constricting the other end ~20 cm from the bottom. The tube was washed with saturated aqueous $NaHCO_3$, rinsed with distilled H_2O and absolute ethanol, thoroughly dried in an oven and cooled in an inert atmosphere. A reaction solution was injected into the tube by means of a syringe equipped with a needle which was long enough to extend beyond the constriction. The tube was then attached to a vacuum manifold which was connected to a nitrogen line *via* a Firestone valve.[22] Three successive degassing cycles were performed according to the procedure of Firestone, followed by three freeze-thaw cycles employing liquid nitrogen. The degassed reaction mixture was then evacuated and the tube was sealed at the constriction with a flame. After warming to ambient temperature, the tube was placed in an oven and heated as required.

Phthalimide Esters 20 and 21. A supension of 1.2 g (9.0 mmol, 6 eq) of anhydrous $AlCl_3$ in 20 ml of 1,2-dichloroethane was treated in dropwise fashion, at 0 °C, with 0.4 ml (4.6 mmol, 3 eq) of oxaloyl chloride. The resulting mixture was then stirred for an additional 0.5 h at 0 °C before adding a solution of 400.0 mg (1.4 mmol) of pyrroloketone(**19**)[23] in 10 ml 1,2-dichloroethane over a period of 15-25 min at 0 °C. Stirring was continued for 1 h at at 0 °C and then at ambient temperature for two and one-half days. The resulting black solution was poured into 100 ml of crushed ice/pH 7 buffer solution and extracted with 3x30 ml of CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford a black residue consisting of crude acid chloride. This residue was taken up in 30 ml of MeOH, and the resulting solution was heated at reflux for 1 h before cooling to room temperature and concentrating under reduced pressure.[10] Chromatography (silica gel, 50% EtOAc/hexanes) then afforded 393 mg (81%) of an inseparable 3:1 mixture of regioisomers (**20**) and (**21**) as a white solid. Recrystallization from EtOAc/hexanes gave 120 mg of pure **20** as colorless crystals, mp 202-205 °C: R_f 0.4 (silica gel, 50% EtOAc/hexanes); ms: m/z (%) 338 (M^+, 79); ^1H nmr ($CDCl_3$) δ 2.63 (t, 2H, J=8.0 Hz), 3.25 (t, 2H, J=8.0 Hz), 3.46 (s, 2H), 3.66 (s, 3H), 6.77 (s, 1H), 7.82 (m, 2H), 7.97 (m, 2H). Anal. Calcd for $C_{18}H_{14}N_2O_5$: C, 63.94; H, 4.17; N, 8.28. Found: C, 63.83; H, 4.21; N, 8.19.

Dimethylketal 25. A solution of 110.0 mg (0.33 mmol) of ester (**20**) in 10 ml of MeOH was treated with 80 µl of $HC(OMe)_3$, and a catalytic amount of *p*-toluenesulfonic acid, at 0 °C with vigorous stirring. After stirring a total of 2 h at 0 °C, followed by 1 h at ambient temperature, the reaction was quenched with 20 ml of H_2O and extracted with 3x20 ml of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatography (silica gel, 25% EtOAc/hexanes) then afforded 121 mg (96%) of **25** as a white solid: R_f 0.35 (silica gel, 50% EtOAc/hexanes; ms: m/z (%) 352 (M-32); ir (CH_2Cl_2) 2960, 1746, 1700, 1256 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.00 (t, 2H, J=8.0 Hz), 2.81 (s, 2H), 2.90 (t, 2H, J=8.0 Hz), 3.28 (s, 6H), 3.64 (s, 3H), 6.70 (s, 1H), 7.81 (m, 2H), 7.96 (m, 2H).

Enol Ether 26. A solution of 400.0 mg (1.04 mmol) of dimethylketal (**25**) in 30 ml of benzene was heated to 40 °C and treated with 4 drops of acetyl chloride and 3 drops of pyridine. The reaction mixture was then heated at reflux for 2 h, cooled, and diluted with 10 ml of CH_2Cl_2. Crushed ice/5% $NaHCO_3$ solution was added and the mixture was extracted with 3x10 ml of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatography (silica gel, CH_2Cl_2) then afforded 290 mg (80%) of enol ether (**26**) as a yellow solid, mp 165-169 °C: R_f 0.55 (CH_2Cl_2); ms: m/z (%) 352 (M^+, 100); ir (CH_2Cl_2) 1750, 1695 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.45 (t, 2H, J=8.0 Hz), 3.07 (t, 2H, J=8.0 Hz), 3.65 (s, 3H), 3.68 (s, 3H), 5.42 (s, 1H), 6.65 (s, 1H), 7.82 (m, 2H), 7.98 (m, 2H).

Aldehyde 27. A solution of 11.6 mg (0.03 mmol) of enol ether (**26**) in 1 ml of *t*-BuOH, 0.5 ml of CH_2Cl_2, and 1 ml of H_2O was treated with 40.0 mg (0.18 mmol, 6 eq.) of $NaIO_4$ and a total of 5 drops of 0.4% OsO_4/H_2O solution. The reaction mixture was stirred vigorously at ambient temperature for 1 day, and then diluted with 2 ml H_2O and extracted with 3x3 ml of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Preparative tlc (silica gel, 50% EtOAc/hexanes) then gave 9.2 mg (73%) of aldehyde(**27**)as an unstable yellow oil: R_f 0.66 (silica gel, 50% EtOAc/hexanes); ^{1}H nmr ($CDCl_3$) δ 2.64 (t, 2H, J=8.0 Hz), 3.42 (t, 2H, J=8.0 Hz), 3.66 (s, 3H), 3.69 (s, 3H), 7.51 (s, 1H), 7.87 (m, 2H), 7.99 (m, 2H), 9.95 (s, 1H).

Methylpyrrole 28. A solution of 14.0 mg of aldehyde (**27**) in 8 ml of CF_3CO_2H was treated with an excess amount of $NaCNBH_3$ at 0 °C. After stirring at 0 °C for 15 min, reaction was complete as judged by tlc. The reaction mixture was then brought to pH=7 with saturated aqueous $NaHCO_3$, and extracted with 3x5 ml of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Preparative tlc (silica gel, 50% EtOAc/hexanes) then gave 8.1 mg (60%) of **28** as a white solid: R_f 0.56 (50% EtOAc/hexanes); ms: m/z (%) 370 (M^+); ir (CH_2Cl_2) 1750, 1700, 1420, 1275 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 2.08 (s, 3H), 2.55 (t, 2H, J=8.0 Hz), 3.05 (t, 2H, J=8.0 Hz), 3.65 (s, 3H), 3.68 (s, 3H), 6.70 (s, 1H), 7.81 (m, 2H), 7.96 (m, 2H). Exact mass (EI): Calcd for $C_{19}H_{18}N_2O_6$: 370.1165. Found: 370.1160.

N-Aminopyrrole 11a. A suspension of 8.1 mg (0.02 mmol) of methylpyrrole (**28**) in 0.7 ml of EtOH was treated with 12.0 μl (0.026 mmol, 1.2eq) of hydrazine monohydrate. After stirring at ambient temperature for 15 min all starting materials had dissolved and a white precipitate of phthaloylhydrazide began to form. After stirring an additional 4 h at ambient temperature, the solid was filtered and the filtrate was concentrated under reduced pressure. Preparative tlc (silica gel, 50% EtOAc/hexane) then afforded 5.0 mg (95%) of **11a** as a colorless oil: R_f 0.62 (silica gel, 50% EtOAc/hexane); ms (EI): m/z 240 (M^+); ^{1}H nmr ($CDCl_3$) δ 1.98 (s, 3H), 2.48 (t, 2H, J=8 Hz), 2.96 (t, 2H, J=8 Hz), 3.67 (s, 3H), 3.84 (s, 3H), 5.46 (br s, 1H), 6.70 (s, 1H).

Furanoesters 29 and 33. A solution of 300.0 mg (2.1 mmol) of 4-methyl-5-carbomethoxyoxazole (**31**) and 540.0 mg (4.7 mmol, 2.4 eq) of acetylenic ester(**32**)in 4 ml of freshly distilled mesitylene, containing 5-10 mg of methylene blue, was heated in a sealed tube at 260 °C for 26 h. Removal of solvent under reduced pressure and purification of the crude oil by preparative tlc afforded 196 mg (33%) of furan (**29**) as the major product along with 102 mg (17%) of regioisomer (**33**).

29: R_f 0.49 (silica gel, 1:8 Et_2O/hexanes, developed three times); ^{1}H nmr ($CDCl_3$): δ 2.01 (s, 3H), 2.55 (t, 2H, J=8 Hz), 2.99 (t, 2H, J=8 Hz), 3.66 (s,3H), 3.88 (s,3H), 7.25 (s, 1H).

33: R_f 0.43 (silica gel, 1:8 Et_2O/hexanes, developed three times); ^{1}H nmr ($CDCl_3$): δ 2.25 (s, 3H), 2.52 (t, 2H, J=8 Hz), 2.64 (t, 2H, J=8 Hz), 3.63 (s,3H), 3.83 (s,3H), 7.25 (s, 1H).

Dihydrofuran 34. A solution of 180.0 mg (0.8 mmol) of furan (**29**) in 12 ml of MeOH was treasted with excess powdered Na_2CO_3 and 10 drops of Br_2 at 0 °C with vigorous stirring. The resulting solution was stirred at 0 °C for 0.5 h and at ambient temperature for 2 h. An additional 10 drops of bromine were then added and stirring was continued at ambient temperature for 4 h, at which point all **29** had been consumed. The reaction mixture was then quenched with 20 ml of brine and extracted with 3x15ml of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatagraphy afforded 202 mg (88%) of **34** as colorless oil: R_f 0.43 (silica gel, 1:2 EtOAc/hexane); ms (EI): m/z 287 (M^+-1); ir (CH_2Cl_2): 1749 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.76 (s, 3H), 2.42 (m, 4H), 3.23 (s, 3H), 3.46 (s, 3H), 3.64 (s, 3H), 3.76 (s, 3H), 5.41 (s, 1H).

Oxazole Ester 36. A solution of 378.0 mg (2.7 mmol) of 4-methyl-5-carbomethoxyoxazole (**31**) and 615.0 mg (6.3 mmol, 2.3 eq) of 4-hexyn-1-ol in 6 ml of freshly distilled toluene was heated at reflux for 44 h in the presence of 40 mg of SCN-Bu_2Sn-O-SnBu_2OH as transesterification catalyst. The reaction solution was then cooled to

ambient temperature and concentrated under reduced pressure. Preparative tlc afforded 599 mg (87%) of **36** as a colorless oil: *Rf* 0.42 (silica gel, 1:2 EtOAc/hexanes); ms (EI): m/z 207 (M^+); ir (CH_2Cl_2): 1723 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.75 (s, 3H), 1.91(t, 2H, J=7.2 Hz), 2.28 (m, 2H), 2.48 (s, 3H), 4.40 (t, 2H, J=7.2 Hz), 7.86 (s, 1H). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76, H, 6.32, N, 6.40. Found: C, 63.91, H, 6.40, N, 6.80.

Oxazole Ester 39. A solution of 200.0 mg (1.8 mmol) of 4-methyl-5-hydroxymethyloxazole and 480.0 mg (3.8 mmol, 2.1 eq) of acetylenic ester (**32**) in 10 ml of freshly distilled toluene was heated at reflux for 15 h in the presence of 34 mg of SCN-Bu_2Sn-O-SnBu_2OH as transesterification catalyst. After cooling to ambient temperature, the resulting solution was concentrated under reduced pressure and the residue was purified by preprative tlc to afford 360 mg (88%) of **39** as a colorless oil: *Rf* 0.4 (silica gel, 1:2 EtOAc/hexanes); ir (CH_2Cl_2): 1744, 1506 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.70 (s, 3H), 2.19 (s, 3H), 2.39 (m, 2H), 2.47 (t, 2H, J=8.0 Hz), 5.10 (s, 2H), 7.75 (s, 1H). Exact mass (CI): Calcd for $C_{11}H_{13}NO_3$: 208.1052. Found: 208.0896.

2-Triisopropylsilyloxy-1,3-pentadiene (46d). A stirring solution of 55.0 ml (27.5 mmol, 1.13 eq) of 0.5 M $KN(TMS)_2$/toluene in 20 ml of anhydrous THF, maintained at -78 °C under an inert atmosphere, was treated in dropwise fashion, during a period of 1.5 h, with a solution of 2.0 g (23.8 mmol) of 3-penten-2-one in 15 ml anhydrous THF. After addition was complete, stirring was continued at -78 °C for an additional 1 h. The resulting enolate solution was then quenched with 7.25 ml (27.0 mmol, 1.13 eq) of triisopropylsilyl triflate at -78 °C, and stirring was continued at -78 °C – -40 °C for 1 h. The reaction mixture was then allowed to warm to room temperature, quenched with 40 ml of saturated NH_4Cl, and extracted with 3x30 ml of Et_2O. The combined extracts were washed with 2x10 ml brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Distillation of the residue then afforded 5.5 g (95%) of **13d** as colorless oil, bp 88-95 °C/0.8 mm Hg. *Rf* 0.80 (silica gel, 10% Et_2O/petroleum ether); ms (EI): m/z 240 (M^+); ir (CH_2Cl_2) 1586.6, 1464.1 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.07 (d, 18H, J=7.2 Hz), 1.20 (m, 3H), 1.74 (d, 3H, J=6.8 Hz), 4.11 (s, 1H), 4.16 (s, 1H), 5.86 (d, 1H, J=15 Hz), 6.05 (m, 1H); Exact mass (CI): Calcd for $C_{14}H_{28}OSi$: 241.1988. Found, 241.1989; Anal. Calcd for $C_{14}H_{28}OSi$: C, 69.93; H, 11.74. Found: C, 69.67; H, 11.69.

2-*t*-Butyldimethylsilyloxy-1,3-pentadiene (46c). This material was prepared in 75% yield as a colorless oil, bp 87-88 °C/22 mm Hg, from 3-pentene-2-one and *t*-butyldimethylsilyl chloride, following an identical procedure as that described above for **46d**. *Rf* 0.61 (silica gel, 1:9 Et_2O/petroleum ether); ms (EI): m/z 198 (M^+); ir (CH_2Cl_2) 1593 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.18 (s, 6H), 0.96 (s, 9H), 1.75 (d, 3H, J=7.0 Hz), 4.17 (s, 2H), 5.88 (d, 1H, J=17 Hz), 6.00 (m, 1H); Anal. Calcd for $C_{11}H_{22}OSi$: C, 66.60; H, 11.18. Found: C, 66.72; H, 11.13.

Diels-Alder Adduct 53a (R=Ac). A solution of 140.0 mg (0.6 mmol) of 2-triisopropylsilyloxy-1,3-pentadiene (**46d**) and 110.0 mg (0.9 mmol, 1.5 eq) of 1-acetoxy-3-buten-2-one (**51**)[16a] in 1.5 ml of benzene containing a catalytic amount of *t*-butylcatechol was heated at reflux under N_2 for a period of 8 h. The reaction was then allowed to cool to ambient temperature and concentrated under reduced pressure to afford a viscous oil. Chromatography (silica gel, 5-10% Et_2O/hexanes) then afforded 194 mg (91%) of **53a** as a colorless oil (mixture of *endo* and *exo* isomers): *Rf* 0.59 (silica gel, 1:2 Et_2O/petroleum ether); ms (EI): m/z 368 (M^+); ir (CH_2Cl_2) 1754.9, 1730.9, 1688, 1667.6, 1463.6, 1370.2 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.84 (d, 3H, J=6.8 Hz, *exo*-CH_3), 0.90 (d, 3H, J=7.0 Hz, *endo*-CH_3), 1.04 (d, 18H, J=6.0 Hz), 1.12 (m, 3H), 1.70 (m, 1H), 1.88 (m, 1H), 2.08 (m, 2H), 2.14 (s, 3H), 2.64 (m, 2H), 4.62 (d, 1H, J=16 Hz), 4.63 (s, 1H, *exo*-vinyl), 4.79 (d, 1H, J=16 Hz), 4.79 (d, 1H, J=5 Hz, *endo*-vinyl); Exact mass (CI): Calcd for $C_{20}H_{36}O_4Si$: 369.2462. Found, 369.2462.

Diels-Alder Adduct 53b (R=Me). This material was prepared in 63% yield as a viscous, colorless oil (mixture of *endo* and *exo* isomers) from 2-triisopropylsilyloxy-1,3-pentadiene (**46d**) and 1-methoxymethyl-3-buten-2-one (**52**)[16b] following an identical procedure as that described above for Diels-Alder adduct **53a**. *Rf*

0.66 (silica gel, 1:2 EtOAc/hexanes); ms (EI): m/z (%) 340 (M^+, 9), 295 (25), 265 (59), 145 (67), 117 (81), 75 (100); ir (CH_2Cl_2) 1725.6, 1667.2 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.81 (d, 3H, J=7.5Hz, *endo*-CH_3), 0.88 (d, 3H, J=7.5 Hz, *exo*-CH_3), 1.05 (d+m, 21H), 1.67 (m, 1H), 1.84 (m, 1H), 2.12 (m, 2H), 2.65 (m, 2H), 2.65 (m, 2H), 3.38 (s, 3H), 3.40 (s, 1H), 4.10 (m, 2H), 4.49 (s, 1H), 4.86 (d, 1H, J=5 Hz).

***N*-Phthalimidopyrrole 55a** (R=Ac). A solution of 700.0 mg (1.9 mmol) of **53a** in 20 ml of MeOH was cooled to -78 °C, and subjected to ozonolysis (O_3, 1.5 PSI) at -78 °C for ~5 min (see general procedure). After flushing with N_2 at -78 °C for 10 min, the resulting peroxide solution was treated with 4 ml dimethyl sulfide (DMS) and stirring was continued at -78 °C for 1 h, at 0 °C for 1h, and at ambient temperature for 30 min. The reaction mixture was then concentrated under reduced pressure, and chromatographed through a short silica gel column to afford 686 mg (90%) of ozonolysis product as a colorless oil (mixture of ketal derivatives).

A solution of 184.0 mg (0.46 mmol) of the above ozonolysis product in 10 ml of THF was treated with 79.0 mg (0.44 mmol) of *N*-aminophthalimide and 1 drop of 2.5 N HCl solution, and stirred at ambient temperature overnight. The reaction mixture was then quenched with 10 ml of saturated NH_4Cl solution and extracted with 2x15 ml ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Preparative tlc afforded 196 mg (81%) of **55a** along with a methyl migrated product in a ratio of ~2:1. Crystallization from ethyl acetate/hexanes then gave a 54% yield of **55a** as a colorless crystalline solid: *Rf* 0.82 (silica gel, 1:1 EtOAc/hexanes); ir (CH_2Cl_2) 1753.4, 1713.1, 1469.9, 1371.7 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.08 (d, 18H, J=7.2 Hz), 1.28 (m, 3H), 1.85 (s, 3H), 2.05 (s, 3H), 2.57 (t, 2H, J=8 Hz), 2.83 (t, 2H, J=8.0 Hz), 4.92 (s, 2H), 6.48 (s, 1H), 7.83 (m, 2H), 7.95 (m, 2H). Anal. Calcd for $C_{28}H_{38}N_2O_6Si$: C, 63.86; H, 7.27; N, 5.32. Found: C, 63.87; H, 7.32; N, 5.29.

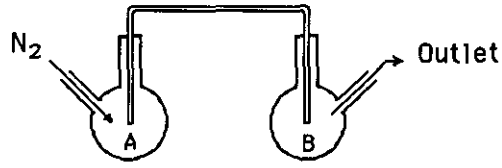
Methyl migrated product: *Rf* 0.82 (silica gel, 1:1 EtOAc/hex); ms (EI): m/z (%) 526 (M^+, 6), 379 (17), 297 (37), 253 (36); ir (CH_2Cl_2) 1749.4, 1713.5 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.08 (d, 18H, J=7.2 Hz), 1.29 (m, 3H), 1.87 (s, 3H), 2.58 (dd, 2H, J=18, 10 Hz), 2.72 (dd, 2H, J=17, 6 Hz), 5.00 (dd, 1H, J=46, 14 Hz), 6.20 (d, 1H, J=3.2 Hz), 6.63 (d, 1H, J=3.2 Hz), 7.89 (m, 2H), 7.98 (m, 2H). Exact mass (EI): Calcd for $C_{28}H_{38}N_2O_6Si$: 526.2525. Found: 526.2520.

***N*-Phthalimidopyrrole 55b** (R=Me). This material was prepared in 71% yield as a colorless, crystalline solid (EtOAc/hexanes) by ozonolysis of Diels-Alder adduct (**53b**), followed by condensation with *N*-aminophthalimide, by an identical procedure as that described above for *N*-phthalimidopyrrole(**55a**) *Rf* 0.66 (silica gel, 1:1 EtOAc/hexanes); ir (CH_2Cl_2) 1798.0, 1752.4, 1711.8, 1469 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.08 (d, 18H, J=7.2 Hz), 1.29 (h, 3H, J=7.2 Hz), 2.07 (s, 3H), 2.53 (t, 2H, J=8 Hz), 2.79 (t, 2H, J=8.0 Hz), 3.08 (s, 3H), 4.27 (s, 2H), 6.49 (s, 1H), 7.81 (m, 2H), 7.94 (m, 2H). Anal. Calcd for $C_{28}H_{36}N_2O_5Si$: C, 65.04; H, 7.68; N, 5.62. Found: C, 65.09; H, 7.70; N, 5.60.

Wittig Reagent 65c (R=Bn). A solution of 3.87 g (10.0 mmol) of Wittig reagent (**65b**) (R=Et)[18] in 30 ml of freshly distilled toluene was treated with 1.28 ml (12.0 mol) of benzyl alcohol and 490 mg (3.0 mmol) of 4-pyrrolidinopyridine. The reaction mixture was then heated at reflux for a period of 48 h. After cooling to ambient temperature, the resulting solution was treated with 20 ml of saturated NH_4Cl solution and extracted with 3x25ml of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatography then afforded 2.05 g (47%) of Wittig reagent (**65c**) (R=Bn) as a pale yellow solid. Recrystallization from EtOAc afforded **65c** as colorless crystals, mp 193-194 °C. *Rf* 0.32 (silica gel, 80% EtOAc/hexanes); ir (CH_2Cl_2) 1711.7, 1562.3 cm^{-1}; ^1H nmr ($CDCl_3$) δ 5.25 (s, 2H), 7.2-7.8 (br m, 21H); Anal. Calcd for $C_{28}H_{23}O_3P$: C, 76.70; H, 5.29; Found: C, 76.67; H, 5.32.

Enone Ester 58b (R=Et, A=H). A solution of 6.8 g (18.0 mmol) of Wittig reagent (**65b**) (R=Et)[18] in 100 ml of CH_2Cl_2 was cooled to 0 °C in a two-necked round bottom flask equipped with a N_2 inlet and an exit trap filled with 10% NaOH to trap excess HCHO (flask B, below). The reaction solution was then treated at 0 °C, and with vigorous stirring, with gaseous HCHO carried by dry N_2 and generated during the course of 3-4 h by

heating 30 g of paraformaldehyde to 120 °C under N_2 in a second two-necked flask connected by tygon tubing (flask A, below; tubing diameter >12 mm; N_2 flow rate ~25 bubbles/min; the inlet tube should be maintained slightly above the surface of the **65b** solution in order to minimize clogging). After reaction was complete, as judged by tlc, a total of 50 ml of petroleum ether was added at 0 °C and the resultant precipitate was filtered. The filtrate was concentrated under reduced pressure and the residue was passed through a short silica gel column (2.5x6 cm, 5% Et_2O/petroleum ether) to afford 1.88 g (82%) of enone ester(**58b**)as an unstable pale yellow oil. *Rf* 0.88 (silica gel, 20% EtOAc/hexanes); ms (EI): 128 (M^+); ir (CH_2Cl_2) 1734.1, 1707.8, 1686.9 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.37 (t, 3H, J=7.0 Hz), 4.34 (q, 2H, J=7.0 Hz), 6.10 (d, 1H, J=11 Hz), 6.55 (d, 1H, J=18 Hz), 6.90 (dd, 1H, J=18, 11 Hz); ^1H nmr (C_6D_6) δ 0.83 (t, 3H, J=6.8 Hz, $OCH_2\underline{CH_3}$), 3.84 (q, 2H, J=6.8 Hz, OCH_2), 5.30 (d, 1H, J=10.8 Hz), 6.18 (d, 1H, J=17.6 Hz), 6.57 (dd, 1H, J=17.6, 10.8 Hz); ^{13}C nmr (C_6D_6) δ 13.78 ($OCH_2\underline{C}H_3$), 61.92 (OCH_2), 131.46 (C_3), 133.12 (C_4), 162.31(C_2), 183.6 (C_1).



Enone Ester 58c (R=Bn, A=H). Enone ester (**58c**) (R=Bn, A=H) was prepared from Wittig reagent(**65c**) (R=Bn) and HCHO in 61% yield as an unstable yellow oil following an identical procedure as that described above for enone ester(**58b**)(R=Et, A=H). *Rf* 0.88 (Silica gel, 20% EtOAc/hexanes); ms (EI): m/z 190 (M^+); ir (CH_2Cl_2) 1782.8, 1708.2, 1687.5 cm^{-1}; ^1H nmr (C_6D_6) δ 5.30 (s, 2H, OCH_2), 6.09 (d, 1H, J=10.8 Hz), 6.51 (d, 1H, J=16 Hz), 6.88 (dd, 1H, J=16, 10.8 Hz), 7.36 (m,5H). ^{13}C nmr (C_6D_6) δ 67.96 (OCH_2), 128.62, 128.70, 128.79 ($C_{2'}$, $C_{3'}$, $C_{4'}$ of Ph), 131.17 (C_3), 134.44 ($C_{1'}$ of Ph), 134.48 (C_4), 161.48 (C_2), 183.33 (C_1).

Diels-Alder Adduct 61d (R=Et, R'=TIPS, A=H). A solution of 2.80 g (11.6 mmol) of 2-triisopropylsilyloxy-1,3-pentadiene (**46d**) (R'=TIPS) and 1.28 g (10.0 mmol, 0.9 eq) of enone ester (**58b**) (R=Et, A=H) in 30 ml of benzene containing a catalytic amount of *t*-butylcatechol was heated at reflux under N_2 for a period of 4 h. The resulting colorless solution was then cooled to ambient temperature, concentrated under reduced pressure and chromatographed (three times, silica gel, 5%-10% Et_2O/hexanes) to afford 3.03 g (81%) of Diels-Alder adduct (**61d**) (R=Et, R'=TIPS, A=H) as a ~2:3 mixture of *endo*- and *exo*-isomers (pale yellow oil), and 32 mg (0.86%) of dihydropyran (**66d**) (R=Et, R'=TIPS, A=H) (pale yellow oil). *Endo*-**61d** and *exo*-**61d**: *Rf* 0.53 (silica gel, 1:9 Et_2O/petroleum ether); ms (EI): m/z (%) 368 (M^+, 22), 325 (18), 266 (100), 213 (14); ir (CH_2Cl_2) 1725.4, 1668.1, 1464.1, 1366.5 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.79 (d, 3H, J=6.8 Hz, *endo*-Me), 0.92 (d, 3H, J=6.8 Hz, *exo*-Me), 1.05 (d, 18H, J=6.0 Hz), 1.13 (m, 3H), 1.34 (t, 3H, J=7.2 Hz), 1.80 (m, 2H), 2.12 (m, 2H), 2.65 (m, 0.5H, *exo*-H_3), 2.89 (m, 1.5H, *exo*-H_4, *endo*-H_3), 3.31 (ddd, 1H, J=12 Hz, 5.2 Hz, 3.2 Hz, *endo*-H_4), 4.30 (q, 2H, J=7.2 Hz), 4.69 (s, 1H), 4.86 (d, 1H, J=5.2 Hz, *endo*-H_2); ^{13}C nmr (C_6D_6) δ 12.77 (Me), 13.02 (Me's of *i*-Pr), 13.90 (Me), 17.63 (Me), 18.03 (Me), 18.27 (CH_2), 18.74 (CH_2), 21.44 (CH_2), 24.97 (CH_2), 29.23 (*i*-PrCH), 29.32 (*i*-PrCH), 29.93 (CH), 30.92 (CH), 47.23 (CH), 50.38 (CH), 61.81 (OCH_2), 61.92 (OCH_2), 108.31 (CH=), 108.28 (CH=), 150.02 (=COTIPS), 150.76 (=COTIPS), 162.71 (CO), 162.46 (CO), 196.57 (CO), 197.08 (CO); Exact mass (CI): Calcd for $C_{20}H_{32}O_4Si$: 369.2462. Found, 369.2478; Anal. Calcd for $C_{20}H_{32}O_4Si$: C, 65.17; H, 9.87. Found: C, 64.93; H, 9.87. **Dihydropyran 66d** (R=Et, R'=TIPS, A=H): *Rf* 0.65 (silica gel, 1:9 Et_2O/petroleum ether); ms (EI): m/z (%) 368 (M^+, 12), 325 (34), 266 (22), 213 (100); ir (CH_2Cl_2) 1725.4, 1652.8 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.01 (d, 18H, J=6.0 Hz), 1.05 (m, 3H), 1.27 (t, 3H, J=7.2 Hz), 1.69 (d, 3H, J=6.4 Hz), 1.65 (m, 1H), 1.90 (m, 1H), 2.10 (m,

1H), 2.30 (m, 1H), 4.21 (m, 2H), 5.62 (d, 1H, J=16 Hz), 5.85 (m, 1H), 6.10 (t, 1H, J=4.5 Hz); Exact mass (EI): Calcd for $C_{20}H_{32}O_4Si$: 368.2384. Found: 368.2397.

Diels-Alder Adduct 61a (R=Et, R'=Et, A=H). This material was prepared in 40% yield from diene (**46a**) (R'=Et) and enone ester (**58b**) (R=Et, A=H) as a 2.4:1 mixture of *endo*- and *exo*-isomers by a procedure identical to that described above for Diels-Adduct (**61d**). Pale yellow oil, R_f 0.58 (silica gel, 1:9 Et_2O/hexane); ms (EI): m/z 240 (M^+); ir (CH_2Cl_2) 1725.3, 1666.1 cm^{-1}; ^1H nmr (C_6D_6) δ 0.86 (t, 3H, J=7.2 Hz), 0.88 (2t, 3H, J=7.2 Hz), 0.97 (t, 3H, J=7.2 Hz), 1.07 (t, 3H, J=7.2 Hz), 1.08 (t, 3H, J=7.2 Hz), 0.90 (d, 3H, J=6.8 Hz, *endo*-Me), 0.99 (d, 3H, J=6.8 Hz, *exo*-Me), 1.50 (dd, 3H, J=6.6, 1.4 Hz, Pyran-Me), 1.6-2.1 (3 sets, m, 4H), 2.84 (m, 1H, *exo*-H_3), 2.90 (dd, 1H, J=17.2, 6.8 Hz, *exo*-H_4), 3.01 (bt < 1H, J=6.8 Hz, *endo*-H_3), 3.22 (ddd, 1H, J=12, 5.2, 2.8 Hz, *endo*-H_4), 3.36 (q, 2H, J=7.2 Hz) 3.66 (m, 2H, Pyran-OCH_2Me), 3.87 (q, 2H, J=7.2 Hz), 3.87 (q, 2H, J=7.2 Hz), 4.05 (q, 2H, J=7.2 Hz), 4.06 (q, 2H, J=7.2 Hz), 4.25 (s, 1H, *exo*-H_2), 4.36 (d, 1H, J=4 Hz, *endo*-H_2), 5.44 (dd, 1H, J=15.6, 1.6 Hz), 6.09 (dd, 1H, J=15.6, 6.8 Hz), 6.27 (m, 1H). **Dihydropyran 66a** (R=Et, R'=Et, A=H): Yield, 14%, pale yellow oil; ^1H nmr (C_6D_6) δ 1.16 (d, 18H, J=2.4Hz), 1.18 (m,3H), 1.46 (dd, 3H, J=6.8, 1.6Hz), 1.75 (m, 2H), 2.10 (m, 2H), 5.58 (dd, 1H, J=15.2, 1.6Hz), 5.95 (m, 1H), 6.19 (t, 1H, J=4.4Hz); Exact mass (EI): Calcd for $C_{13}H_{20}O_4$: 240.1362 Found: 240.1383.

Diels-Alder Adduct 61b (R=Et, R'=TMS A=H). This material was prepared in 45% yield from diene (**46b**) (R'=TMS) and enone ester (**58b**) (R=Et, A=H) as a 2:3 mixture of *endo*- and *exo*-isomers by a procedure identical to that described above for Diels-Adduct (**61d**). Pale yellow oil, R_f 0.39 (silica gel, 1:9 EtOAc/hexane); ms (EI): m/z (%) 284 (M^+, 45), 311 (10), 297 (17), 269 (24), 224 (100); ir (CH_2Cl_2) 1725.4, 1668.3 cm^{-1}; ^1H nmr (C_6D_6) δ 0.13 (s, 9H, TMS), 0.87 (m, 6H, $OCH_2\underline{C}H_3$, *endo*- and *exo*-Me), 1.59-1.98 (m, 4H), 2.82 (m, 0.2H, *exo*-H_3), 2.89 (m, 1.2H, *exo*-H_4, *endo*-H_3), 3.19 (m, 1H, *endo*-H_4), 3.88 (q, 2H, J=6.8 Hz), 4.73 (s, 0.2H, *exo*-H_2), 4.83 (d, 1H, J=5.2 Hz, *endo*-H_2); ^{13}C nmr (C_6D_6) δ 0.41 (2 TMS), 13.83 (Me), 13.99 (Me), 17.72 (Me), 17.86 (Me), 18.78 (2 CH_2), 29.38 (2 CH_2), 29.87 ($\underline{C}$H-Me), 30.11 ($\underline{C}$H-Me), 47.22 ($\underline{C}$H-CO), 47.35 ($\underline{C}$H-CO), 61.81 (OCH_2), 61.93 (OCH_2), 108.59 (CH=), 108.95 (CH=), 150.54 (2 =COTMS), 162.53 (CO), 162.6 (CO), 196.58 (CO), 196.8 (CO); Exact mass (EI): Calcd for $C_{14}H_{24}O_4Si$: 284.1444. Found: 284.1437. **Dihydropyran 66b** (R=Et, R'=TMS, A=H): Yield, 10%, pale yellow oil; R_f 0.46 (silica gel, 1:9 Et_2O/hexane); ms (EI): m/z (%) 284 (M^+, 13), 269 (13), 255 (16), 182 (56), 141 (100); ir (CH_2Cl_2) 1723.6, 1662 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.08 (s, 9H), 1.23 (m, 1H), 1.28 (t, 1H, J=8.0 Hz), 1.69 (d, 3H, J=6.8 Hz), 1.78 (m, 1H), 2.06 (m, 1H), 2.25 (m, 1H), 4.23 (m, 2H), 5.60 (d, 1H, J=15.2 Hz), 5.84 (m, 1H), 6.10 (br s, 1H); Exact mass (EI): Calcd for $C_{17}H_{30}O_4Si$: 284.1444. Found, 284.1423.

Diels-Alder Adduct 61c (R=Et, R'=TBDMS A=H). This material was prepared in 61% yield from diene (**46c**)(R'=TBDMS) and enone ester (**58b**)(R=Et, A=H) as a 2:3 mixture of *endo*- and *exo*-isomers by a procedure identical to that described above for Diels-Adduct (**61d**). Pale yellow oil, R_f 0.53 (silica gel, 1:6 EtOAc/hexane); ms (EI): m/z (%) 326 (M^+, 45), 311 (10), 297 (17), 269 (24), 224 (100); ir (CH_2Cl_2) 1725.4, 1668.3 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.11 (s, 6H), 0.80 (d, 3H, J=6.8 Hz, *endo*-Me), 0.89 (s, 9H), 0.93 (d, 3H, J=6.8 Hz, *exo*-Me), 1.35 (2 t, 3H, J=7.2 Hz), 1.70-3.71 (m, 4H), 2.74 (m, 1H, *exo*-H_3), 2.89 (m, 2H, *exo*-H_4, *endo*-H_3), 3.30 (ddd, 1H, J=9.2 Hz, 5.2 Hz, 2.8 Hz, *endo*-H_4), 4.32 (q, 2H, J=7.2 Hz), 4.68(s, 1H, *endo*-H_2), 4.85 (d, 1H, J=5.2 Hz, *exo*-H_2); ^1H nmr (C_6D_6) δ 0.09 (s, 6H), 0.87 (m, 6H, $OCH_2\underline{C}H_3$, *endo*- and *exo*-Me), 0.97 (s, 9H), 1.59-1.98 (m, 4H), 2.82 (m, 0.5H, *exo*-H_3), 2.92 (m, 1.5H, *exo*-H_4, *endo*-H_3), 3.19 (m, 1H, *endo*-H_4), 3.88 (q, 2H, J=6.8 Hz), 4.73 (s, 0.5H, *exo*-H_2), 4.83 (d, 1H, J=5.2 Hz, *endo*-H_2); ^{13}C nmr (C_6D_6) δ -4.23 (2 Me-Si), 13.83 (Me), 13.98 (Me), 17.66 (Me), 17.80 (Me), 18.27 (CH_2), 18.75 (CH_2), 25.85 (Me of *t*-Bu), 26.00 (Me of *t*-Bu), 29.21 (CH_2), 29.31 (CH_2), 29.85 ($\underline{C}$H-Me), 30.09 ($\underline{C}$H-Me), 47.24 (2 $\underline{C}$H-CO), 61.82 (OCH_2), 61.92 (OCH_2), 108.84 (CH=), 109.20 (CH=), 149.85 (=CHOTBDMS), 150.60 (=CHOTBDMS), 162.52 (CO), 162.74 (CO), 196.58 (CO), 197.1 (CO); Exact mass (EI): Calcd for $C_{17}H_{30}O_4Si$: 326.1913. Found, 326.1908. **Dihydropyran 66c** (R=Et, R'=TBDMS, A=H): Yield, 8%, pale

yellow oil; R_f 0.60 (silica gel, 1:6 EtOAc/hexane); ms (EI): m/z (%) 326 (M^+, 20), 297 (12), 269 (100), 224 (57); ir (CH_2Cl_2) 1725.9, 1662.3 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.03 (s, 3H), 0.11 (s, 3H), 0.83 (s, 9H, isomer-1), 0.92 (s, 9H, isomer-2), 1.31 (t, 3H, J=8.0 Hz), 1.56 (m, 1H), 1.72 (d, 3H, J=7.0 Hz), 1.88 (m, 1H), 2.10 (m, 1H), 2.32 (m, 1H), 4.25 (m, 2H), 5.64 (d, 1H, J=14 Hz), 5.91 (m, 1H), 6.13 (m, 1H); Exact mass (EI): Calcd for $C_{17}H_{30}O_4Si$: 326.1913. Found: 326.1908.

Diels-Alder Adduct 61e (R=Bn, R'=TIPS, A=H). This material was prepared in 60% yield from diene (**46d**)(R'=TIPS) and enone ester(**58c**)(R=Bn, A=H) as a 1:1 mixture of *endo*- and *exo*-isomers by a procedure identical to that described above for Diels-Adduct (**61d**). Pale yellow oil, R_f 0.52 (silica gel, 1:9 Et_2O/hexanes); ms (EI): m/z 430 (M^+); ir (CH_2Cl_2) 1726.4, 1667.7, 1463.0, 1366.5 cm-1; ^1H nmr (C_6D_6) δ 0.81 (d, 3H, J=7 Hz, *endo*-Me), 0.92 (d, 3H, J=7 Hz, *exo*-Me), 1.10 (d, 18H, J=6.0 Hz), 1.20 (m, 3H), 1.57 (m, 1H), 1.80 (m, 1H), 1.96 (m, 2H), 2.81 (m, 1H, *exo*-H_3), 2.90 (m, 2H, *endo*-H_3, *exo*-H_4), 3.15 (m, 1H, *endo*-H_4), 4.81 (d, 1H, J=5.2 Hz), 4.94 (s, 2H), 7.02 (m, 3H), 7.15 (m, 2H, overlap with C_6H_6); ^{13}C nmr (C_6D_6) δ 13.0 (2 Me), 18.3 (2x6 Me of *i*-Pr), 17.6 (CH_2), 18.7 (CH_2), 21.4 (CH_2), 24.8 (CH_2), 29.1 (*i*-PrCH), 29.3 (*i*-PrCH), 29.9 (C<u>H</u>-Me), 30.9 (C<u>H</u>-Me), 47.4 (C<u>H</u>-CO), 50.5 (C<u>H</u>-CO), 67.4 (OCH_2), 67.5 (OCH_2), 108.2 (CH=), 108.3 (CH=), 127.5-128.8 (2 sets $C_{2'}$, $C_{3'}$, $C_{4'}$-Ph, overlap), 135.3 ($C_{1'}$-Ph), 135.2 ($C_{1'}$-Ph), 150.0 (=COTIPS), 150.7 (=COTIPS), 162.2 (CO), 162.5 (CO), 196.2 (CO), 196.8 (CO); Exact mass (EI): Calcd for $C_{25}H_{38}O_4Si$: 430.2539. Found: 430.2533. **Dihydropyran 66e** (R=Bn, R'=TIPS, A=H): Yield, <1%, pale yellow oil; R_f 0.52 (silica gel, 1:10 Et_2O/hexanes); ms (EI): m/z (%) 430 (M^+, 1), 387 (9), 339 (19), 303 (8), 91 (100); ir (CH_2Cl_2) 1723.6, 1662 cm^{-1}; ^1H nmr (C_6D_6) δ 1.16 (d, 18H, J=2.4 Hz), 1.18 (m, 3H), 1.46 (dd, 3H, J=6.8, 1.6 Hz), 1.75 (m, 2H), 2.10 (m, 2H), 5.58 (dd, 1H, J=15.2, 1.6 Hz), 5.95 (m, 1H), 6.19 (t, 1H, J=4.4 Hz); Exact mass (CI): Calcd for $C_{25}H_{38}O_4Si$: 431.2617. Found: 431.2617.

Pyrrole 70d (R=Et, R"=H). A solution consisting of 140.0 mg (0.38 mmol) of Diels-Alder adduct(**61d**) (R=Et) and 2 drops of 0.1% Sudan Red 7B/MeOH in 12 ml of MeOH was cooled to -78 °C and subjected to ozonolysis until the color was totally discharged (~5 min, see general conditions). The resulting peroxide was reduced by adding 1 ml of dimethylsulfide (DMS) at -78 °C, and stirring was continued at -78 to 0 °C for 2 h and finally at ambient temperature for 0.5 h. After concentrating under reduced pressure, the crude ozonolysis product (viscous oil) was treated directly with 500 mg of NH_4CO_3 in 5 ml of freshly distilled benzene and 1 ml of distilled *t*-BuOH. The resulting suspension was then heated at reflux for a period of 2 h. After cooling to ambient temperature, the reaction mixture was diluted with 10 ml of Et_2O, washed with 10 ml of pH 7 buffer solution, and the aqueous layer was extracted with 3x5 ml of Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography (silica gel, 10% EtOAc/hexane) then afforded 99 mg (66%) of **70d** as a colorless oil, R_f 0.66 (silica gel, 1:2 EtOAc/hexane). ms (CI): m/z 382 (M^++1); ir (CH_2Cl_2) 3454.4, 1708, 1686 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.06 (d, 18H, J=7.6 Hz), 1.30 (m, 3H), 1.32 (t, 3H, J=6.4 Hz), 2.03 (s, 3H), 2.54 (t, 2H, J=8.4 Hz), 3.01 (t, 2H, J=8.4 Hz), 4.29 (q, 2H, J=6.4 Hz), 6.64 (s, 1H), 8.86 (br s, 1H); ^{13}C nmr ($CDCl_3$) δ 9.86 (pyrrole-C<u>H</u>$_3$), 11.91 (SiC<u>H</u>), 14.45 ($OCH_2C\underline{H}_3$), 17.79 (CH(C<u>H</u>$_3$)$_2$), 20.83 (C<u>H</u>$_2$), 36.54 (C<u>H</u>$_2$), 60.01 (O<u>C</u>H$_2$), 119.14 (pyrrole-C_4), 120.07 (pyrrole-C_3), 120.40 (pyrrole-C_5), 128.98 (pyrrole-C_2), 161.43 (<u>C</u>OOEt), 173.36 (<u>C</u>OOTIPS); Exact mass (CI): Calcd for $C_{20}H_{35}NO_4Si$: 382.2413. Found, 382.2415.

Pyrrole 70e (R=Bn, R"=H). This material was prepared in 60% yield from Diels-Alder adduct(**61e**)(R=Bn) and NH_4CO_3 by an identical procedure as that described above for pyrrole(**70d**). Colorless oil, R_f 0.5 (silica gel, 1:2 EtOAc/hexanes); ir (CH_2Cl_2) 3455.4, 1708.9, 1680 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.04 (d, 18H, J=7.6 Hz), 1.27 (m, 3H), 2.02 (s, 3H), 2.54 (t, 2H, J=8.4 Hz), 3.03 (t, 2H, J=8.4 Hz), 6.12 (s, 1H), 7.34 (m, 5H), 8.86 (br s, 1H); ^{13}C nmr ($CDCl_3$) δ 9.84 (pyrrole-C<u>H</u>$_3$), 11.91 (SiC<u>H</u>), 17.79 (CH(C<u>H</u>$_3$)$_2$), 20.74 (C<u>H</u>$_2$), 36.44 (C<u>H</u>$_2$), 60.01 (O<u>C</u>H$_2$), 118.75 (pyrrole-C_4), 120.31 (pyrrole-C_3), 120.60 (pyrrole-C_5), 128.14 (Ph-C), 128.17 (Ph-C), 128.54 (Ph-C), 129.68 (pyrrole-C_2), 136.19 (Ph-C), 160.84 (<u>C</u>OOEt), 173.36 (<u>C</u>OOTIPS); Exact mass (CI): Calcd for $C_{25}H_{37}NO_4Si$: 444.2571. Found: 444.2571.

Pyrrole 70f (R=Et, R"=Phthalimide). A solution consisting of 368.0 mg (1.0 mmol) of Diels-Alder adduct (**61d**)(R=Et) and 5 drops of 0.1% Sudan Red 7B/MeOH in 30 ml of MeOH was cooled to -78 °C and subjected to ozonolysis until the color was totally discharged (~5 min, see general conditions). The resulting peroxide was reduced by adding 5 ml of dimethylsulfide (Dm/z) at -78 °C, and stirring was continued at -78 to 0 °C for 2 h and finally at ambient temperature for 0.5 h. After concentrating under reduced pressure, one-half of the crude ozonolysis product (0.50 mmol, viscous oil) was treated directly with a solution of 101.0 mg (0.56 mmol, 1.12 eq) of *N*-aminophthalimide and 8.0 mg of TsOH (recrystallized from CH_2Cl_2) in 10 ml of freshly distilled benzene and 2 ml of distilled *t*-BuOH. The resulting solution was then heated at reflux under a N_2 atmosphere for a period of 2.5 h. After cooling to ambient temperature, the reaction mixture was diluted with 10 ml of Et_2O, washed with 10 ml of pH 7 buffer solution, and the aqueous layer was extracted with 3x10 ml of Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography (silica gel, 10-30% EtOAc/hexane) then afforded 150 mg of **70f** (57%) as a white solid. The analytical sample, prepared by crystallization from EtOAc/hexanes, had mp 164-165 °C. *Rf* 0.59 (silica gel, 1:2 EtOAc/hexanes); ir (CH_2Cl_2) 1753.7, 1712.7, 1688.5 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.08 (d, 18H, J=7.2 Hz), 1.29 (pentuplet, 3H, J=7.2 Hz), 2.07 (s, 3H), 2.53 (t, 2H, J=8 Hz), 2.79 (t, 2H, J=8.0 Hz), 3.08 (s, 3H), 4.27 (s, 2H), 6.49 (s, 1H), 7.81 (m, 2H), 7.94 (m, 2H). Anal. Calcd for $C_{28}H_{38}N_2O_6Si$: C, 63.86; H, 7.27; N, 5.32. Found, C, 63.80; H, 7.26; N, 5.32.

***N*-Aminopyrrole 70g** (R=Et, R"=NH_2). This material was prepared in 90% yield from pyrrole (**70f**) (R=Et, R"=Phthalimide) and hydrazine monohydrate by an identical procedure as that described above for *N*-aminopyrrole (**11a**). *N*-Aminopyrrole (**70g**) (R=Et, R"=NH_2) was obtained as a colorless oil which solidified upon freezing. The analytical sample, prepared by crystallization from petroleum ether at T < O °C, was a colorless solid with mp < 20 °C. *Rf* 0.61 (silica gel, 1:2 EtOAc/hexane); ms (EI): m/z (%) 396 (M^+, 11), 353 (100), 281 (8), 181 (70); ir (CH_2Cl_2) 3683.4, 3441.9, 1709.6, 1678.6 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.06 (d, 18H, J=7.6 Hz), 1.30 (m, 3H), 1.33 (t, 3H, J=7.2 Hz), 2.01 (s, 3H), 2.47 (t, 2H, J=8 Hz), 2.96 (t, 2H, J=8 Hz), 4.31 (q, 2H, J=7.2 Hz), 6.92 (s, 1H), 8.71 (br s, 1H); ^{13}C nmr ($CDCl_3$) δ 9.49 (pyrrole-$\underline{C}H_3$), 11.93 (Si$\underline{C}$H), 14.35 (OCH$_2\underline{C}H_3$), 17.78 (CH($\underline{C}H_3$)$_2$), 21.68 ($\underline{C}H_2$), 36.82 ($\underline{C}H_2$), 59.86 (O$\underline{C}H_2$), 117.23 (pyrrole-C_4), 118.2 (pyrrole-C_3), 126.76 (pyrrole-C_5), 128.85 (pyrrole-C_2), 162.14 ($\underline{C}$OOEt), 173.21 ($\underline{C}$OOTIPS). Exact mass (EI): Calcd for $C_{20}H_{36}N_2O_4Si$: 396.2444. Found, 396.2450. Anal. Calcd for $C_{20}H_{36}N_2O_4Si$: C, 60.57; H, 9.15; N, 7.07. Found, C, 60.49; H, 9.19; N, 7.00.

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