Diels–Alder Reactions of 1-(Acylamino)-1,3-dienes

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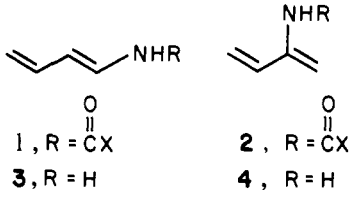
Abstract: A survey of the Diels–Alder reactions of eight 1-(acylamino)-1,3-dienes with thirteen varied dienophiles is reported. These reactions provide convenient access to diversely substituted, amino-functionalized cyclohexanes and octalones. Of particular note are (a) the successful Diels–Alder reactions of diene carbamates **14** and **18** with the notoriously poor dienophiles 2-cyclohexanone, styrene, and 3,4-methylenedioxystyrene, (b) the nearly total regioselectivity observed in reactions of all 1-(acylamino)-1,3-dienes with unsymmetrical dienophiles, and (c) the high endo stereoselectivity observed in the reactions of dienes **5**, **8**, **14**, **16**, and **18** with acrolein, methyl acrylate, *trans*-crotonaldehyde, and methyl *trans*-crotonate.

The Diels–Alder reaction is one of the most useful reactions in preparative organic chemistry.[2,3] It provides the chemist one of his best tools for constructing six-membered rings and has nearly singular capability of establishing large numbers of stereochemical centers in one synthetic step.

Since, in our opinion, nitrogen-substituted dienes had been under exploited as components in the Diels–Alder reaction,[4,5] we initiated in 1975 a study of the preparation and Diels–Alder chemistry of (acylamino)-1,3-dienes.[6,7] We were orginally attracted to this diene class (e.g., **1** and **2**) since they would be synthetic equivalents

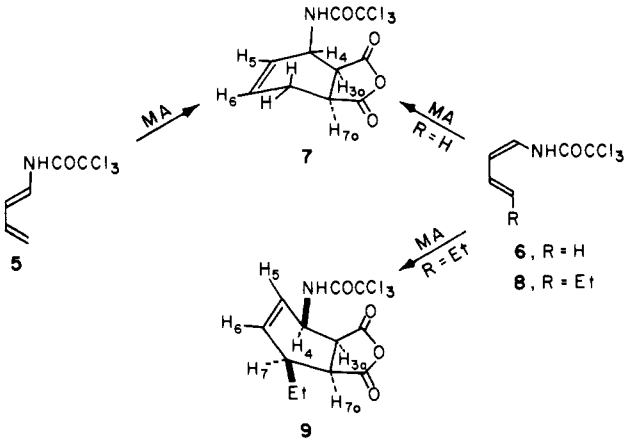


for the unavailable parent amino-1,3-dienes **3** and **4**[8] and also since they embodied the potential to control their Diels–Alder reactivity by modifications of the acyl substituent X.[9] A variety of 1,3-dienes with *N*-acylamino substitution at either the 1- or the 2-position is now available by several procedures developed in our laboratory.[6,7,10]

In this paper we report the details of our survey of the Diels–Alder reactions of a representative group of 1-(acylamino)-1,3-dienes with a variety of dienophiles.

Results and Discussion

(1) Reaction of *cis*- and *trans*-1-(Trichloroacetamido)-1,3-dienes with Maleic Anhydride. Three dienes were examined. *trans*-1-(Trichloroacetamido)-1,3-butadiene (**5**)[10a] reacted with maleic



anhydride (MA) within 2 h in refluxing benzene to give a cyrstalline adduct in 74% yield. The ^{1}H NMR coupling constants observed at 90 MHz for H_4 (δ 4.64, $J_{4,5}$ = 5.6, $J_{4,3a}$ = 2.6 Hz), which indicate near coplanarity for H_4 and H_5 and a gauche rather than an anti disposition of H_4 and H_{3a}, are consistent[11] only with an "extended" boat conformation[12] of endo-adduct **7**. Adduct **7** was also formed in good yield when *cis*-1-(trichloroacetamido)-1,3-butadiene (**6**)[10a] and maleic anhydride were heated in dioxane at 110 °C (sealed tube) for 12 h, since dienes **5** and **6** equilibrate under these conditions.[10a] Diene cis–trans isomerization prior to cycloaddition was also observed with the (1*Z*,3*E*)-diene **8**[10a] which gave in 54% yield the endo-cycloadduct **9** of the corresponding (1*E*,3*E*)-diene when heated with maleic anhydride at 140 °C for 4 h. The structure for cycloadduct **9** followed from ^{1}H NMR coupling constants observed at 250 MHz for H_4 (δ 4.69, $J_{3a,4}$ = 5.9, $J_{4,5}$ = 0 Hz) and H_7 (δ 2.30, $J_{7,7a} \approx$ 6.8, $J_{6,7}$ = 0 Hz), which are consistent only with a "folded-boat" conformation[12] of endo-adduct **9**. *It is thus seen that the (1Z)-1-(trichloroacetamido)-1,3-dienes which are directly available from propargylic trichloroacetimidates[10a] can serve as convenient in situ sources of their more reactive 1E counterparts.*

(1) Camille and Henry Dreyfus Foundation Teacher-Scholar 1976–1981. A. P. Sloan Foundation Fellow, 1975–77.

(2) Onischenko, A. S. "Diene Synthesis"; Israel Program of Scientific Translations; Daniel Davy: New York, 1964. Wollweber, H. "Diels-Alder Reaction"; Georg Thieme Verlag: Stuttgart, 1972. Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 211; **1967**, *6*, 16.

(3) For notable recent examples see: (a) Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *J. Am. Chem. Soc.* **1980**, *102*, 2097. (b) Kukushima, M.; Das, J.; Reid, G. R.; White, P. S.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 3354. (c) Corey, E. J.; Danheiser, R. L.; Chandrasekarin, S.; Keck, G. E.; Gopolan, B.; Larsen, S. D.; Siret, P.; Gras, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 8034.

(4) To date, *N,N*-dialkyl-1-amino-1,3-dienes have been the most widely used Diels–Alder dienes of this type.[2] For a brief review see: Cervinka, O.; Fabrjova, A. *Chem. Listy* **1976**, *70*, 1266.

(5) In recent years the Diels–Alder chemistry of *N*-acyl-*N*-alkyl-1-amino-1,3-dienes has been extensively developed by the Oppolzer school: cf. Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10 and ref 8.

(6) For previous communications of portions of the work described in this paper see: (a) Overman, L. E.; Clizbe, L. A. *J. Am. Chem. Soc.* **1976**, *98*, 2352, 8395. (b) Overman, L. E.; Taylor, G. F.; Jessup, P. J. *Tetrahedron Lett.* **1976**, 3089.

(7) Portions of the work detailed here were briefly discussed in: Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218.

(8) To our knowledge no other synthetic equivalents for 2-amino-1,3-dienes exist. In some cases *trans*-*N*-alkyl-*N*-acyl-1-amino-1,3-butadienes will serve as 1-amino-1,3-butadiene equivalents: Oppolzer, W.; Bieber, L.; Francotte, E. *Tetrahedron Lett.* **1979**, 981, 4537.

(9) For a quantitative study see: Overman, L. E.; Taylor, G. F.; Houk, K. N.; Domelsmith, L. N. *J. Am. Chem. Soc.* **1978**, *100*, 3182.

(10) (a) Overman, L. E.; Clizbe, L. A.; Freerks, R. L.; Marlowe, C. K. *J. Am. Chem. Soc.*, preceding paper in this issue. (b) Overman, L. E.; Taylor, G. F.; Petty, C. B.; Jessup, P. J. *J. Org. Chem.* **1978**, *43*, 2164. (c) Jessup, P. J.; Petty, C. B.; Roos, J.; Overman, L. E. *Org. Synth.* **1979**, *59*, 1. (d) Overman, L. E.; Petty, C. B.; Doedens, R. J. *J. Org. Chem.* **1979**, *44*, 4183.

(11) Cf. Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon: New York, 1969; Chapters 4.2 and 4.4.

(12) Cf. Danishefsky, S.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001.

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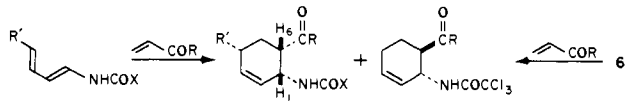
(2) Reaction of 1-(Acylamino)-1,3-dienes with Monosubstituted Ethylenes. Four dienes were examined. Cycloaddition of trans-diene **5** and acrolein occurred readily in dioxane at 110 °C to give an 82:18 mixture of the *endo*-**10** and *exo*-**11** cycloadducts in 95% yield. Other regioisomers were not detected by high-performance LC analysis. The structures for **10** and **11** followed from the 250-MHz ^{1}H NMR spectrum of the cycloadduct mixture which showed characteristic signals[9,11] for H_6: **10**, δ 2.97 ($J_{1,6}$ = 4.5 Hz); **11**, δ 2.69 ($J_{1,6}$ = 6.8 Hz). The cycloaddition (dioxane, 110 °C, 15 h) of **5** with methyl acrylate was also completely regioselective, and only slightly less endo stereoselective, and gave[9] a 77:23 mixture of the endo- and exo-cycloadducts **12** and **13** in 75% yield. An *identical* mixture of cycloadducts **12** and **13** was



5, X = CCl_3, R′ = H
14, X = OEt, R′ = H
15, X = $N(CH_2)_4$, R′ = H
16, X = OEt, R′ = CH_3

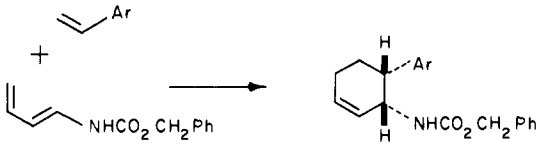
10, R = R′ = H, X = CCl_3
12, R = OMe, R′ = H, X = CCl_3
17, R = OMe, R′ = CH_3, X = OEt

11, R = H
13, R = OMe

formed in 80% yield from the reaction of the cis-diene **6** and methyl acrylate in dioxane at 110 °C for 80 h. The mixture of **12** (76 ± 1%) and **13** (24 ± 1%) which was produced in this reaction was time invariant, thus indicating that cycloaddition occurred *only* with the trans-diene **5**. The much longer time required for the reaction of the cis-diene **6** with methyl acrylate indicated that cis–trans diene isomerization[10a] was the slow step under these conditions. Since we had previously shown[10a] that this equilibration was catalyzed by triethylamine, we examined the reaction of the cis-diene **6** and methyl acrylate in the presence of this base. When this reaction was conducted (110 °C, dioxane) in the presence of 0.7 M triethylamine, diene equilibration was sufficiently rapid that the cycloaddition step was rate limiting and a 76:24 mixture of cycloadducts **12** and **13** was isolated in 83% yield after 15 h.[13-18] In a recently reported[9] quantitative study we compared cycloaddition reactions of diene **5** with those of diene carbamate **14** and diene urea **15**. As anticipated,[9] the more electron-rich dienes **14** and **15** were found[9] to react somewhat faster (2.2 and 3.8 times, respectively) and slightly more endo stereoselectively with methyl acrylate than diene trichloroacetamide **5**.

The reaction of the (*E*,*E*)-diene carbamate **16**[10b] with methyl acrylate allowed the regiochemical directing ability of the carbamate and methyl groups to be compared. Cycloaddition of **16** and methyl acrylate was accomplished at 80 °C and gave a mixture of at least three cycloadducts. Purification by preparative high-performance LC gave the major adduct **17** (~60% yield) as a pure crystalline material. The structure of **17** followed from the 250-MHz ^{1}H NMR spectrum which showed a characteristic absorption for the axial hydrogen H_6 at δ 2.74 ($J_{1,6}$ = 2.8, $J_{5e,6}$ = 4.6, $J_{5a,6}$ = 13.1 Hz).

Although there are many useful Diels–Alder reactions where styrene functions as a diene component, styrene is a notoriously poor dienophile.[1,19,20] Thus some of the more dramatic examples of the high reactivity of (acylamino)-1,3-dienes are the successful cycloadditions of benzyl *trans*-1,3-butadien-1-yl carbamate (**18**)[10b,c]



18

19 Ar = Ph
20 Ar = 3-nitrophenyl
21 Ar = 4-methoxyphenyl
22 Ar = 3,4-methylenedioxyphenyl

with styrene and substituted styrene dienophiles. For example, when diene carbamate **18** and an excess of styrene were heated at 80 °C for 256 h in the presence of the free radical inhibitor 4-*tert*-butylcatechol and in the absence of oxygen, the endo-cycloadduct **19** was formed in >90% yield. When this reaction was conducted at a higher temperature for a shorter time, considerable styrene polymer was formed which complicated isolation of the cycloadduct. The structure of adduct **19** followed from its conversion upon catalytic hydrogenation (Pd/C, HCl, EtOH) to *cis*-2-phenylcyclohexanamine hydrochloride, mp 205–206 °C.[21] Similar results were obtained with substituted styrenes, which gave the endo-cycloadducts **20–22** as the major products from reaction with diene **18**. The structures for adducts **20–22** followed most clearly from ^{13}C NMR spectra which showed characteristic[23] absorptions for the cycloadduct ring carbons which were nearly identical (±1 ppm) to those of styrene adduct **19**. As expected,[9] *m*-nitrostyrene underwent cycloaddition more readily than styrene, while the electron-rich oxygen-substituted styrenes required more vigorous conditions. For example, reaction of diene **18** with an excess of 3,4-methylenedioxystyrene necessitated heating at 140 °C for 156 h and gave the crystalline endo-adduct **22** in 72% yield. *The successful cycloaddition of this electron-rich dienophile with diene carbamate* **18** *is certainly one of the most striking examples of the reactivity of this diene class to be reported to date.*

We briefly examined the reaction of diene **18** with phenyl acetylene but abandoned this effort when the reaction (140 °C, 114 h) of these components was shown by high-performance LC analysis to give more than 13 products.

(3) Reaction of 1-(Acylamino)-1,3-dienes with 1,2-Disubstituted Ethylenes. Another example of the excellent Diels–Alder reactivity of (acylamino)-1,3-dienes is the successful reaction of diene carbamate **14**[10b] with the poor[22] dienophile 2-cyclohexenone. Cycloaddition of diene **14** and 2-cyclohexenone occurred smoothly

23

at 110 °C to afford the crystalline *cis*-octalone **23** in 84% yield. The structure of endo-adduct **23** followed most directly[11] from

(13) It is interesting to note that the endo-adduct **12** is stable to epimerization under these conditions. For the facile epimerization of related crotonaldehyde cycloadducts see ref 14.

(14) Overman, L. E.; Jessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5179; *Tetrahedron Lett.* **1977**, 1253.

(15) In order to explore the possibility of directly catalyzing the cycloaddition of *trans*-1-(acylamino)-1,3-dienes with base,[16] we investigated the reactions of methyl acrylate and the *trans*-dienes **5** and **14** in the presence of triethylamine. No indication of catalysis was observed at Et_3N concentrations up to 1 M.

(16) Although there are many examples[17] of acid-catalyzed Diels–Alder reactions and a few reports of base-promoted Diels–Alder cycloreversions,[18] to our knowledge base catalysis of a Diels–Alder cycloaddition has not been reported.

(17) Recent examples include: Stork, G.; Nakahara, Y.; Greenlee, W. J. *J. Am. Chem. Soc.* **1978**, *100*, 7775. Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *Ibid.* **1980**, *102*, 3554. Reference 3b.

(18) Cf. Bowman, E. S.; Hughes, G. B.; Grutzner, J. B. *J. Am. Chem. Soc.* **1976**, *98*, 8273.

(19) For example, the reactive dienes 2,3-dimethyl-1,3-butadiene[20a] and *trans*-1-(diethylamino)-1,3-butadiene[20b] are reported to react with styrene in yields of 30% (180 °C, 13 h) and 0% (110 °C, 10 h), respectively.

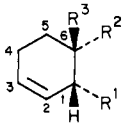
(20) (a) Alder, K.; Rickert, H. F. *Chem. Ber.* **1938**, *70*, 379. (b) Satzinger, G. *Justus Liebigs Ann. Chem.* **1969**, *728*, 64.

(21) (a) Cantavelli, G.; Carissimi, M.; Cattaneo, A.; D'Ambrosio, R.; Grummelli, E.; Milla, E.; Panelli, M.; Ravenna, F. *Farmaco, Ed. Sci.* **1969**, *24*, 123. (b) Treager, W. F.; Vincenz, F. F.; Huitric, A. C. *J. Org. Chem.* **1962**, *27*, 3006.

(22) Cf. Gaddis, A. M.; Butz, L. W. *J. Am. Chem. Soc.* **1947**, *69*, 117. Dauben, W. G.; Rogan, J. B.; Blanz, E. J., Jr. *Ibid.* **1954**, *76*, 6384. Beslin, D.; Bloch, R.; Moinet, G.; Conia, J. M. *Bull. Soc. Chim. Fr.* **1969**, 508. Danishefsky, S.; Kitahara, T. *J. Org. Chem.* **1975**, *40*, 538. Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 3554.

(23) Cf. (a) Wilson, N. K.; Stothers, J. B. *Top. Stereochem.* **1974**, *8*, 25–30, (b) Schneider, H.-J.; Hoppen, V. *J. Org. Chem.* **1978**, *43*, 3866 and references cited therein.

Table I. ^{13}C NMR Spectra for Substituted Cyclohexenes

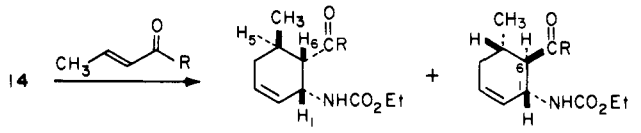


compd no.	R^1	R^2	R^3	chem shift[a] C_1	C_4	C_5	C_6
b,c	$NHCO_2CH_2Ph$	Ph	CO_2Et	49.7	23.0	24.0	53.5
b	$NHCO_2CH_2Ph$	CO_2Et	Ph	53.7	23.5	30.9	54.7
30	$NHCO_2CH_2Ph$	$C_6H_3O_2CH_2$	CO_2Et	50.0	23.3	24.7	53.3
31	$NHCO_2CH_2Ph$	CO_2Et	$C_6H_3O_2CH_2$	54.0	23.6	31.2	54.5
32	$NHCO_2CH_2Ph$	$C_6H_3O_2CH_2$	$COCH_3$	52.5	22.9	25.6	58.6
33	$NHCO_2CH_2Ph$	$C_6H_3O_2CH_2$	CN	45.1	23.5	25.8	52.5
34	$NHCO_2CH_2CCl_3$	$C_6H_3O_2CH_2$	CO_2Et	52.5	22.9	25.6	58.6

[a] In $CDCl_3$; chemical shifts are given in ppm from internal Me_4Si; assignments are consistent with the results of off-resonance decoupled spectra. [b] From ref 9d. [c] Structure determined by single-crystal X-ray diffraction.[10d]

the 90-MHz ^1H NMR spectrum which showed a characteristic absorption for the angular hydrogen H_{8a} at δ 3.05 ($J_{8,8a}$ = 5.1, $J_{4a,8a}$ = 4.4 Hz). This cycloaddition was notably regioselective and endo stereoselective as only traces (<5%) of other products were detected by high-performance LC analysis of the crude reaction mixture.

The cycloaddition of diene carbamate **14** and methyl *trans*-



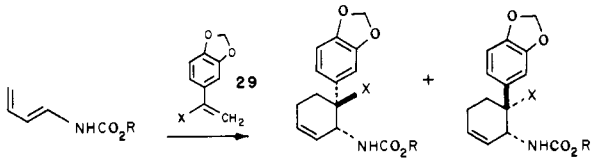
24, R = OMe **25**, R = OMe
26, R = H **27**, R = H

crotonate was carried out in dioxane at 110 °C. The reaction was highly regioselective and gave the stereoisomeric *endo*-**24** and *exo*-**25** cycloadducts in a 61:39 ratio (high-performance LC analysis). A minor product (3%, presumably a regioisomer) was also detected. The stereoisomeric adducts were separated by careful high-performance LC, and the structure of the major adduct **24** was assigned on the basis[11] of ^1H NMR coupling constants observed at 90 MHz for H_6 (δ 2.53, $J_{1,6}$ = 4.7, $J_{5,6}$ = 9.7 Hz), which collapsed to a doublet ($J \approx 10$ Hz) when H_1 (δ 4.5) was irradiated. The structure of *exo*-adduct **25** followed most convincingly from the ^{13}C NMR spectra which showed characteristic absorptions at 51.8 and 54.8 ppm (assigned to carbons-1 and -6, respectively).[9,23] These carbon resonances occurred at lower field than those of the *endo*-adduct **24** (46.3 ppm (C_1), 51.8 ppm (C_6)) as would be expected[23] since the acylamino group would be pseudoequatorial in the exo isomer.[24a] It is important to stress that the ^{13}C NMR spectrum of **25** unambiguously rules out a regioisomeric structure, since the carbomethoxy-bearing carbon would be observed[23,24] between 40 and 45 ppm for either regiochemical stereoisomer. The cycloaddition under identical conditions of diene **14** with the more reactive dienophile *trans*-crotonaldehyde was, as expected,[9] more stereoselective and gave the corresponding *endo*-**26** and *exo*-**27** cycloadducts in a 76:24 ratio[25] (high-performance LC analysis). A minor product (5%, presumably a regioisomer) was also detected. The structure of the major *endo*-adduct **26** followed from our previous[14] conversion of this material to *dl*-pumiliotoxin C, while the structure for the *exo*-adduct **27** followed directly[23,24b] from ^{13}C NMR arguments similar to those utilized to assign the structure of adduct **25**.

It is worth emphasizing that the endo-stereoselectivities (1.5–3:1) observed in the reactions of diene carbamate **14** with methyl *trans*-crotonate and *trans*-crotonaldehyde are unusually high. These dienophiles typically show very low endo preferences[26,27] and, in some cases, exo preferences[26-28] in cycloadditions with other 1-substituted 1,3-butadienes.

Not surprisingly, diene carbamate **14** was found not to cycloadd to cyclohexene (110 °C, 170 h) or 3-acetyl-1-[(trifluoromethyl)sulfonyl]indole (180 °C, 3 h).

(4) Reaction of 1-(Acylamino)-1,3-dienes with 1,1-Disubstituted Ethylenes. In order to explore potential applications of 1-(acylamino)-1,3-dienes for the synthesis of Amaryllidaceae and related alkaloid families, we investigated the reaction of two diene carbamates with a series of 1-substituted 1-(3,4-methylenedioxyphenyl)ethylenes (**29**). The reaction of diene carbamate **18** and



18, R = CH_2Ph
28, R = CH_2CCl_3

30, R = CH_2Ph, X = CO_2Et
32, R = CH_2Ph, X = $COCH_3$
33, R = CH_2Ph, X = CN
34, R = CH_2CCl_3, X = $COCH_3$

31, R = CH_2Ph, X = CO_2Et

acrylate ester **29** (X = CO_2Et) was carried out in refluxing toluene. Cycloaddition occurred cleanly under these conditions and with complete regioselectivity to give, after chromatography, the stereoisomeric adducts **30** and **31** in yields of 64% and 21%, respectively. The reaction of butenone **29** (X = $COCH_3$) and diene **18** under similar conditions afforded a ~4:1 mixture of cycloadducts together with significant amounts of the dienophile dimer, 3,4-dihydro-4-pyran (**35**).[29] Chromatographic purification allowed the major cycloadduct **32** to be isolated in 69% yield. The cycloaddition of unsaturated nitrile **29** (X = CN) and diene **18** was carried out in dioxane at 100 °C and gave a ~3:2 mixture of cycloadducts, from which the major cycloadduct **33** was isolated in 40% yield. Structural assignments for adducts **30–33** followed from ^{13}C NMR spectra (Table I). These assignments rest on a comparison of the ring carbon shifts of **30–33** with those of the

(24) We use the $\Delta\delta$ (=δ(axial) − δ(equatorial)) values reported by Schneider[23b] for the NHMe substituent as a model for the $NHCO_2Et$ substituent. (a) Carbons 1, 4, 5, and 6 of the exo-adduct **25** may then be calculated to absorb at 51.7, 32.2, 31.5, and 54.9 ppm, respectively. These carbons of **25** are observed at 51.8, 33.1, 31.2, and 54.8 ppm, respectively. (b) Carbons 1, 4, 5, and 6 of the exo-adduct **27** may then be calculated to absorb at 50.4, 31.5, 30.1, and 59.4 ppm, respectively. These carbons of **27** are observed at 47.3, 32.7, 28.6, and 61.1 ppm, respectively.

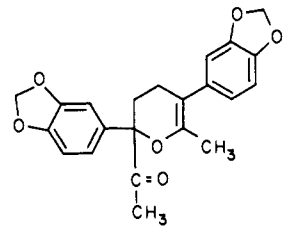
(25) This ratio was incorrectly claimed to be 90:10 in our earlier investigation[14] in which the exo adduct was detected ("high-field" CHO) but not isolated.

(26) Cf. Kobuke, Y.; Fueno, T.; Furukawa, J. *J. Am. Chem. Soc.* **1970**, *92*, 6548. Berson, J. A.; Hamlet, Z.; Mueller, W. A. *Ibid.* **1962**, *84*, 297.

(27) For example, *trans*-1,3-pentadiene reacts with methyl *trans*-crotonate to give a 49:51 mixture of endo and exo cycloadducts under conditions identical with those described for the reaction of this dienophile with diene carbamate **14**: Ono, R. K.; Overman, L. E., unpublished observations.

(28) For a recent example see: Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996.

(29) Cf. Alder, K.; Offermanns, H.; Rüden, E. *Chem. Ber.* **1941**, *74*, 904, 926. Wilson, W.; Kyi, Z. *J. Chem. Soc.* **1952**, 1321. Mulvaney, J. E.; Dillon, J. G.; Laverty, J. L. *J. Polym. Sci., Part A* **1968**, *6*, 1841.



35

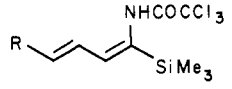
related pair of stereoisomeric adducts formed from the cycloaddition of diene **18** with ethyl 2-phenylacrylate.[10d]

In contrast to the mixture of stereoisomers formed from the cycloaddition of butenone **29** (X = $COCH_3$) with benzyl *trans*-1,3-butadien-1-yl carbamate (**18**), reaction of this dienophile with 2,2,2-trichloethyl *trans*-1,3-butadien-1-yl carbamate (**28**)[10b] gave a *single* (high-performance LC analysis) crystalline cycloadduct **34** which was isolated in 82% yield.

In all of the cases described above and in related reactions described in section 3 of this paper and reported previously[10d] in a phenyl series, the major cycloadducts produced from the reaction of 1-(acylamino)-1,3-dienes with arylethylenes have a cis relationship for the acylamino and aromatic groups. Such results imply a preference for cycloaddition transition states which have the aromatic group in an endo orientation. Unfortunately synthetic endeavors in the Armaryllidaceae alkaloid area require a trans relationship for the amine and aryl functions. However, in related invesitgations[10d] we were able to take advantage of the high stereoselectivity observed in the reaction of ethyl 2-phenylacrylate with diene carbamate **28** to achieve a stereoselective synthesis of the clinically used analgesic Tilidine.

(5) Diels–Alder Reactions of 1-Substituted 1-(Acylamino)-1,3-dienes with Reactive Dienophiles. Acyclic 1,1-disubstituted 1,3-dienes are notoriously poor Diels–Alder dienes, presumably due to their reluctance to adopt *s*-cis conformations.[2] However, a number of successful cycloadditions of electron-rich dienes of this type have been documented in recent years.[30] We examined the Diels-Alder chemistry of three (1*E*)-substituted (1*Z*)-(trichloroacetamido)-1,3-dienes.

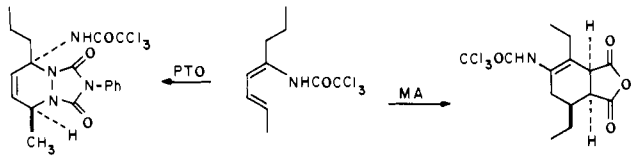
We were totally without success in inducing the Diels–Alder reactions of silyl diene trichloroacetamides **36** and **37**[10a] with



36, R = H

37, R = CH_3

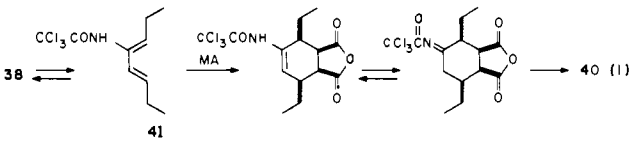
N-phenylmaleimide and methyl acrylate at temperatures up to 100 °C. Diene trichloroacetamide[10a] **38** did react at room tem-



39 38 40

perature with 4-phenyl-1,2,4-triazoline-3,5-dione[31] (PTD) to afford the crystalline cycloadduct **39** in 60% yield. Reaction of **38** with maleic anhydride (110 °C, 36 h) gave a crystalline adduct in 77% yield, which preliminary ^1H NMR examination clearly showed was not the simple Diels–Alder adduct of the two reactants. The material thus produced gave a correct combustion analysis for a 1:1 adduct but did *not* show any vinylic hydrogens in the ^1H NMR spectrum. The off-resonance ^{13}C NMR spectrum confirmed the absence of vinylic hydrogens and showed that the adduct had two methyl carbons, three methylene carbons, three methine carbons, and two vinylic carbons. Structure **40** is consistent with these data, as well as the results of homonuclear ^1H NMR decoupling experiments (see Experimental Section).

The formation of cycloadduct **40** must involve initial tautomeric equilibration of the unreactive 1,1-disubstituted diene **38** with the reactive 2-(trichloroacetamido)-1,3-diene **41**, as summarized in eq 1. Facile proton tautomerization is a characteristic feature



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of the chemistry of (trichloroacetamido)-1,3-dienes,[10a] and related equilibrations prior to Diels–Alder cycloadditions have been reported for isophorone dienamines[32] and dienamides.[33]

Conclusion

1-(Acylamino)-1,3-dienes react with a broad range of dienophiles to provide access to a variety of amino-functionalized cyclic systems. Yields of cycloadducts are generally excellent. These dienes are notably successful in undergoing cycloadditions with poor dienophiles[2,19,20,22] such as methyl *trans*-crotonate, 2-cyclohexenone, styrene, and, perhaps most significantly, electron-rich 3,4-methylenedioxystyrene. The success of these demanding cycloadditions likely derives more from the thermal stability[6,10] of the acylamino dienes than from their cycloaddition reactivity, which is comparable to that of 1-ethoxy-1,3-butadiene.[9,34,35] In rigorously degassed (oxygen-free) solutions diene carbamates such as **14** and **18** are stable for extended periods at 140 °C, and this stability was critical in accomplishing the cycloaddition of diene **18** with 3,4-methylenedioxystyrene which required heating at 140 °C for 6 days.

A most significant feature contributing to the considerable synthesis applications of 1-(acylamino)-1,3-dienes is the high regio- and stereoselectivities these dienes exhibit in cycloadditions with unsymmetrical, and often unreactive,[9] dienophiles. The acylamino substituent is a powerful regiochemical directing group, and only traces of regioisomeric adducts were detected in the many cycloaddition reactions examined in this study. particularly noteworthy are the good endo selectivities observed in the reactions 1-(acylamino)-1,3-dienes with sustituted ethylene and trans-1,2-disubstituted ethylene dienophiles. Dienophiles of this latter type, in particular, typically exhibit very low endo preferences[26,27] and, in some cases, *exo*-preferences,[26–28] in cycloadditions with other *trans*-1-substituted 1,3-butadienes.

The amino equivalency[6a,10cd,14,36,37] of the acylamino group contributes greatly to synthesis applications of 1-(acylamino)-1,3-dienes. Since we originally illustrated the preparative value of these dienes in our total synthesis of *dl*-pumiliotoxin C,[14] 1-(acylamino)-1,3-dienes have been used to achieve total syntheses of *dl*-perhydrogephyrotoxin,[36] *dl*-isogabaculine,[37] and the analgesic Tilidine.[10d] We anticipate that future years will see addtional examples of the synthetic utility of this versatile diene class recorded.

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(34) *trans*-1-(Trichloroacetamido)-1,3-butadiene (**5**) and ethyl *trans*-1,3-butadiene-1-carbamate (**14**) cycloadd wtih methyl acrylate 2.2 and 4.6 times faster, respectively, than *trans*-1-ethoxy-1,3-butadiene.[9,35]

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Table II

time, min	Et_3N, M	adduct yield,[a] M 12	13	conversion, %	endo, %
120		0.053	0.017	7	76
180		0.073	0.021	9	77
300		0.091	0.032	12	74
360		0.093	0.032	12	75
30	0.14	0.071	0.025	10	74
60	0.14	0.138	0.047	18	75
90	0.14	0.135	0.044	18	75
30	0.72	0.068	0.019	9	78
90	0.72	0.197	0.063	25	76
120	0.72	0.162	0.048	21	77

[a] High-performance LC analysis[45] (9:1 hexane–ethyl acetate) with an internal standard.[9]

Experimental Section[38]

Reaction of Dienes 5 and 6 with Maleic Anhydride. Preparation of Endo-Adduct 7. A solution of (*E*)-diene **5** (108 mg, 0.50 mmol), 49 mg (0.50 mmol) of maleic anhydride, and 0.50 mL of dry benzene was heated for 2 h in a sealed ampule at 80 °C. Upon cooling to room temperature, 116 mg (74%) of adduct **7** (mp 136–138 °C) was isolated as fine white needles. Three recrystallizations from benzene gave an analytical specimen: mp 138–140 °C; IR (KBr) 3310, 1860, 1780, 1690, 1530, 1180, 922, 832 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.3–8.8 (m, NH), 5.3–6.3 (m, CH=CH), 4.64 (ddd, J = 9.2, 5.6, 2.6 Hz, C_4 H), 3.2–3.9 (m, C_{3a} and C_{7a} H), 2.0–3.0 (m, CH_2). Anal. Calcd for $C_{10}H_8Cl_3NO_4$: C, 38.43; H, 2.58; N, 4.48. Found: C, 38.48; H, 2.51; N, 4.39.

Adduct **7** was also isolated in 70% yield when a similar mixture of the (*Z*)-diene **6**, and maleic anhydride was heated at 110 °C for 12 h.

Reaction of Diene 8 with Maleic Anhydride. Preparation of Endo-Adduct 9. A solution of (1*Z*,3*E*)-diene **8** (575 mg, 2.3 mmol), 430 mg (4.4 mmol) of maleic anhydride, 20 mg of 4-*tert*-butylcatechol, and 0.6 mL of dioxane was heated at 140 °C in a sealed tube for 4 h. Dilution with benzene precipitated 420 mg (54%) of nearly pure adduct **9**, mp 145–150 °C. Two recrystallizations from $CHCl_3$–CCl_4 (1:2) gave an analytical specimen: white needles, mp 168.5–169.5 °C; IR (KBr) 3340, 1840, 1770, 1720, 1520, 1220, 1040, 945 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.0–8.4 (m, NH), 5.9 (br s, CH=CH), 4.69 (dd, $J_{4,NH}$ = 9.2, $J_{3a,4}$ = 5.9 Hz, C_4 H), 3.65 (dd, $J_{3a,4}$ = 5.9, $J_{3a,7a}$ = 9.6 Hz, C_{3a} H), 3.54 (dd, $J_{3a,7a}$ = 9.6, $J_{7,7a} \approx$ 6.8 Hz, C_{7a} H), 2.30 (apparent q, $J \approx$ 6.8 Hz, C_7 H), 1.7–2.0 (complex m, CH_2), 1.12 (t, J = 7.4 Hz, CH_3). Anal. Calcd for $C_{12}H_{12}Cl_3NO_4$: C, 42.32; H, 3.55; N, 4.11. Found: C, 42.65; H, 3.54; N, 4.18.

Reaction of Diene 5 with Acrolein. Preparation of (*Z*)- and (*E*)-2,2,2-Trichloro-*N*-(6-formyl-2-cyclohexen-1-yl)acetamides (10 and 11). A solution of diene **5** (224 mg, 1.05 mmol), 170 mg (3.0 mmol) of freshly distilled acrolein, and 1 mL of dioxane was heated in a sealed ampule at 110 °C for 3 h. Concentration and bulb-to-bulb distillation (bath temperature 170 °C (0.03 mm)) afforded 270 mg (99%) of adducts **10** and **11**. High-performance LC analysis[45] (9:1 hexane–ethyl acetate) indicated that this sample was >95% pure and that **10** and **11** were present in a 82:18 ratio: IR (film) 3240, 1720, 1510, 1240, 1100, 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) **10** showed characteristic signals at δ 9.77 (d, J = 0.7 Hz, CHO), 6.8–6.6 (m, NH), 5.95–5.85 (m, =CH), 5.7–5.6 (m, =CH), 4.95–4.85 (m, C_1 H), 2.97 (apparent q, $J \approx$ 5 Hz, collapses to a dd, $J_{1,6}$ = 4.5, $J_{6,CHO}$ = 0.7 Hz, when the C_5 hydrogens are irradiated at δ 2.05); **11** showed characteristic signals at δ 9.71 (d, J = 1.5 Hz, CHO), 6.8–6.6 (m, NH), 6.15–5.95 (m, =CH), 5.7–5.6 (m, =CH), 5.85–5.72 (m, C_1 H), 2.69 (apparent dq, collapses to a dd, $J_{1,6}$ = 6.8 Hz, $J_{6,CHO}$ = 1.4 Hz, when the C_5 hydrogens are irradiated at δ 2.05); mass spectrum, m/z (70 eV, relative percent 10% cutoff) 271 (<1), 269 (<1), 236 (15), 234 (25), 108 (35), 96 (16), 81 (25), 80 (75), 79 (100), 78 (12), 77 (31); mol wt ($C_9H_{10}Cl_3NO_2$ requires 268.978) 268.977.

Reaction of Diene 6 with Methyl Acrylate in Dioxane at 110 °C in the Absence and Presence of Triethylamine. The cycloaddition of **6** (1.00 M) and methyl acrylate (3.00 M) was conducted in dioxane at 110 ± 0.2 °C, following the general procedure for kinetic and stereoselectivity experiments detailed in ref 9. Results are summarized in Table II.

Reaction of Diene 16 with Methyl Acrylate. Preparation of Ethyl *cis*-6-(Methoxycarbonyl)-*cis*-4-methyl-2-cyclohexen-1-yl Carbamate 17. A solution of diene **16** (465 mg, 3.0 mmol), 900 mg (10.5 mmol) of methyl acrylate, 20 mg of 4-*tert*-butylcatechol, and 3 mL of dry dioxane was heated at 80 °C for 29 h. Concentration and filtration of the residue through a short pad of silica gel (4:1 hexane–ethyl acetate) afforded a light yellow oil. High-performance LC analysis[45] (9:1 hexane–ethyl acetate) of a comparable sample showed that two major cycloadducts (k' = 3.5 and 4.0) were formed in a ratio of 3:1 (80% combined yield, *p*-dinitrobenzene internal standard). Purification of this mixture by preparative high-performance LC[46] (9:1 hexane–ethyl acetate) gave a chromatographically homogeneous sample of the major cycloadduct **17**: mp 72–76 °C; high-performance LC[45] (9:1 hexane–ethyl acetate) k' = 3.5; ^1H NMR (250 MHz, $CDCl_3$) δ 5.7 (br apparent s, CH=CH), 4.8 (br d, J = 8.9 Hz, NH), 4.6 (m, $W_{1/2}$ = 18 Hz, C_1 H), 4.08 (q, J = 7.0 Hz, OCH_2), 3.67 (s, OCH_3), 2.74 (ddd, J = 13.1, 4.6, 2.8 Hz, C_6 H), 2.1–2.3 (m, C_4 H), 1.94 (ddd, J = 13.5, 5.6, 2.6 Hz, equatorial C_5 H), 1.32 (ddd, J = 13.5, 11, 11 Hz, axial C_5 H), 1.22 (t, J = 7.0 Hz, $CHCH_3$), 1.04 (d, J = 7.0 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$) δ 172.0 (s, COOMe), 154.6 (s, NHCOOR), 135.4 (d, CH=), 124.5 (d, CH=), 60.0 (t, OCH_2), 50.7 (q, OCH_3), 45.4 (d, CHNHR), 43.5 (d, CHCOOMe), 30.1 (d, CHMe), 28.0 (t, C_5), 20.5 (q, equatorial CH_3), 14.0 (q, CH_2CH_3); mass spectrum, m/z (70 eV, relative percent, 10% cutoff), 214.1312 (4, $C_{12}H_{19}NO_4$ requires 241.1314), 209 (9), 199 (10), 181 (30), 168 (33), 155 (64), 93 (100).

Reaction of Diene 18 with Styrene. Preparation of Benzyl *cis*-6-Phenyl-2-cyclohexen-1-yl Carbamate (19). A solution of diene **18** (81.3 mg, 0.400 mmol), 20 mg of 4-*tert*-butylcatechol, and 0.4 mL (3.5 mmol) of freshly distilled styrene was degassed several times (~0.1 mm) and sealed in vacuo. The tube was heated at 80 °C, and the progress of the reaction was monitored by ^1H NMR. After 256 h the reaction mixture was concentrated and purified by filtration through a short plug of silica gel (9:1 hexane–ethyl acetate) to give 123 mg (100%) of nearly pure cycloadduct. High-performance LC analysis[45] (9:1 hexane–ethyl acetate) showed that two products, **19** (k' = 3.3) and an uncharacterized product (k' = 3.0), were present in a 93:7 ratio, respectively. Recrystallization from isooctane–ethyl acetate at −20 °C gave an analytical specimen of the major cycloadduct **19**: mp 56–57 °C; IR (CCl_4) 3460, 1730, 1500, 1460, 1240, 1060, 695 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.0–7.4 (m, Ph), 5.7–5.9 (m, CH=CH), 4.84 (s, CH_2Ph), 4.3–4.7 (m, C*H*N*H*), 2.8–3.0 (m, $W_{1/2}$ = 17 Hz, CHPh); ^{13}C NMR ($CDCl_3$) δ 155.5 (C=O), 142.2, 136.7, 130.4 (C_2*), 128.4 (2 C), 128.2 (2 C), 127.9, 126.5 (C_3*), 66.4 (CH_2O), 49.5 (C_1), 43.4 (C_6), 25.2 and 23.4 (C_4 and C_5); mass spectrum, m/z (isobutane CI, relative percent, 30% cutoff) 308 (MH^+, 67), 247 (85), 203 (36), 157 (88), 152 (51), 91 (100). Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.30; H, 7.00; N, 4.50.

Hydrogenation (1 atm, Pd/C) of a comparable sample of the crude cycloadduct in ethanol containing 1 equiv of HCl, followed by recrys-

(38) Dienes used in this study were prepared as described.[10a,c,d] Commerical samples of methyl acrylate, acrolein, methyl *trans*-crotonate, *trans*-crotonaldehyde, styrene, 4-methoxystyrene, and 3-nitrostyrene were freshly distilled from 4-*tert*-butylcatechol *directly* before use. 3,4-Methylenedioxystyrene[40] was prepared from piperonal; ethyl α-methylene(1,3-benzodioxol-5-yl)acetate,[42] 3-(1,3-benzodioxol-5-yl)-3-buten-2-one, and α-methylene(1,3-benzodioxol-5-yl)acetonitrile were prepared as described.[43] Benzene and toluene were distilled from CaH_2. Dioxane was purified as described[44] and distilled from CaH_2. 4-*tert*-Butylcatechol was purified by sublimation and recrystallization from hexane. ^1H NMR spectra were determined with a Varian EM360 (60 MHz), Bruker WH90 (90 MHz), or Bruker WM250 (250 MHz) spectrometer. ^{13}C NMR spectra were determined at 22.6 MHz with a Bruker WH-90 spectrometer. ^1H and ^{13}C NMR shifts are reported as δ valves in parts per million relative to internal tetramethylsilane. ^1H NMR coupling constants (J) are reported in hertz, and they refer to appparent multiplicities and not true coupling constants; abbreviations used are as follows: s, singlet; d, doublet; t, triplet; and m, complex multiplet. These same abbreviations are used to denote the multiplicities in off-resonance ^{13}C NMR spectra. ^{13}C NMR assignments marked with an asterisk may be reversed. Infrared spectra were determined with a Perkin-Elmer Model 283 spectrometer. Electron-impact and high-resolution mass spectra were determined with a Du Pont 21-498B double-focusing spectrometer at the Caltech Analytical Facility. Chemical ionization mass spectra were determined on a Finnigan 4000 GC/MS/DS. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, or Chemalytics, Inc., Tempe, AZ. TLC and column chromatography utilized E. Merck silica gel. High-performance LC were obtained with Waters components, including a 6000A pump, U6K injector, and R401 differential refractometer. All reactions were run under a nitrogen atmosphere, and concentrations were done by using a rotary evaporator under reduced pressure.

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(42) Tiemann, R. *Chem. Ber.* **1891**, *24*, 2885.
(43) Petty, C. B. Ph.D. Thesis, University of California, Irvine, 1980.
(44) Hess, K.; Frahm, H. *Chem. Ber.* **1938**, *71*, 2627.

(45) A 60 cm × 4 mm μ-Porasil column was used for this analysis.
(46) A 12 ft × $^3/_8$ in. Porasil-A column was used for this separation.

tallization from ethanol–ethyl acetate gave *cis*-2-phenylcyclohexanamine hydrochloride: mp 205–206 °C (lit.[21a] mp 205–207 °C); the ^{1}H NMR spectrum was identical to the published[21b] spectrum and showed $J_{1,6}$ = 3.5 Hz.

Reaction of Diene 18 with *m*-Nitrostyrene. Preparation of Benzyl *cis*-6-(3-Nitrophenyl)-2-cyclohexen-1-yl Carbamate (20). A solution of diene **18** (610 mg, 3.0 mmol), 50 mg of 4-*tert*-butyl-catechol, 450 mg (3.0 mmol) of *m*-nitrostyrene, and 0.6 mL of dioxane was heated in a sealed tube at 110 °C for 25 h. Concentration gave 1.05 g (99%) of ~90% pure cycloadduct **20** (mp 89–120 °C) contaminated with 4-*tert*-butylcatechol. The ^{13}C NMR spectrum of the crude cycloadduct showed that only a single cycloadduct had been formed. Two recrystallizations from chloroform–hexane gave an analytical specimen of cycloadduct **20**: mp 134–136 °C; IR (CCl_4) 3320, 1730, 1530, 1490, 1350, 1210, 1060 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.8–8.0 (m, ArH), 5.6–6.0 (m, CH=CH), 4.78 (s, CH_2Ph), 5.2–5.0 (m, C*H*NH), 3.0–3.3 (m, CHAr, irradiation at δ 1.90 collapses this signal to a d, $J_{1,6}$ = 4 Hz); ^{13}C NMR ($CDCl_3$) δ 155.3 (C=O), 148.1 (CNO_2), 144.5, 136.3, 134.8, 130.8 (C_2*), 128.8, 128.4, 128.1, 127.9, 126.9 (C_3*), 122.9, 121.6, 66.5 (CH_2O), 49.0 (C_1), 44.0 (C_6), 25.4 and 22.7 (C_4 and C_5); mass spectrum, *m/z* (isobutane CI, relative percent, 25% cutoff) 353 (MH^+, 100), 152 (56), 91 (29). Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.33; H, 5.89; N, 8.04.

Reaction of Diene 18 with *p*-Methoxystyrene. Preparation of Benzyl *cis*-6-(4-Methoxyphenyl)-2-cyclohexen-1-yl Carbamate (21). The cycloaddition of diene **18** (81.3 mg, 0.400 mmol) and 0.4 mL of *p*-methoxystyrene was conducted exactly as described for the preparation of **19** to give in 95% yield an 85:15 mixture (high-performance LC[45] analysis) of cycloadducts. Recrystallization from hexane–ether afforded an analytical specimen of the major cycloadduct **21**: mp 76–80 °C; IR (CCl_4) 3460, 1730, 1610, 1510, 1500, 1250, 1040, 690 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.7–7.4 (m, Ar), 5.7–5.9 (m, CH=CH), 4.88 (s, CH_2Ph), 4.4–5.0 (m, C*H*NH), 3.77 (s, CH_3O), 2.9–3.1 (m, CHAr); ^{13}C NMR ($CDCl_3$) 158.3 (COMe), 155.6 (C=O), 136.7, 134.3, 130.3 (C_2*), 129.0, 128.4, 127.9 (C_3*), 113.7, 66.4 (CH_2O), 55.2 (OCH_3), 49.5 (C_1), 43.0 (C_6), 25.2 and 23.7 (C_4 and C_5); mass spectrum, *m/z* (isobutane CI, relative percent, 30% cutoff) 338 (MH^+, 90), 277 (100), 187 (92). Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.74; H, 7.05; N, 4.00.

Reaction of Diene 18 with 3,4-Methylenedioxystyrene. Preparation of Benzyl *cis*-6-(3,4-Methylenedioxyphenyl)-2-cyclohexen-1-yl Carbamate (22). A solution of diene **18** (610 mg, 3.0 mmol), 444 mg (3.0 mmol) of 3,4-methylenedioxystyrene, 80 mg of 4-*tert*-butylcatechol, and 0.9 mL of dioxane was heated in a sealed tube at 140 °C for 144 h. Concentration and purification of the residue by chromatography on silica gel (9:1 hexane–triethylamine) gave 740 mg (70%) of nearly pure cycloadduct **22**. Two recrystallizations from hexane–ether afforded an analytical specimen of **22**: mp 81–83 °C; IR (CCl_4) 3460, 1730, 1610, 1500, 1250, 1040, 690 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.2–7.4 (m, Ph) 6.4–6.7 (m, Ar), 5.90 (s, OCH_2O), 5.8–5.9 (m, CH=CH), 4.91 (s, CH_2Ph), 4.5–4.3 (m, C*H*NH), 3.1–2.9 (m, CHAr); ^{13}C NMR ($CDCl_3$) δ 155.6 (C=O), 147.4, 145.9, 136.7, 136.2, 130.1 (C_2*), 128.4, 128.0, 127.7, 126.8 (C_3*), 121.0, 108.6, 108.0, 100.7 (OCH_2O), 66.6 (OCH_2), 49.5 (C_1), 43.5 (C_6), 25.2 and 23.6 (C_4 and C_5); mass spectrum, *m/z* (isobutane CI, relative percent, 20% cutoff) 352 (MH^+, 20%), 231 (100).

Reaction of Diene 14 and 2-Cyclohexenone. Preparation of Octalone Carbamate 23. A mixture of 2-cyclohexenone (0.4 mL, 4.1 mmol) and 200 mg (1.4 mmol) of diene **14** was degassed and sealed in vacuo in a ^{1}H NMR tube. The reaction was heated at 110 °C for 44 h, at which time the diene was consumed. Concentration and filtration of the residue through a short column of silica gel (9:1 hexane–ethyl acetate) gave 275 mg (88%) of the crystalline adduct **23** (>95% pure by ^{1}H NMR). An analytical specimen was prepared by recrystallization from hexane at −20 °C: mp 71.5–73 °C; IR (CCl_4) 3450, 1725, 1719, 1500, 1330, 1220, 1060 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.6–6.0 (m, NH), 5.6–5.4 (m, CH=CH), 4.6–4.4 (m, C*H*NHR), 4.09 (q, J = 7.0 Hz, OCH_2), 3.05 (dd, J = 5.1, 4.4 Hz; C_{8a} H; irradiation at δ 4.5 collapses this signal to a d, J = 4.4 Hz), 1.5–2.9 (m), 1.23 (t, J = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$) 212.0 (s, C=O), 156.5 (s, NHC=O), 128.4 (d, C=C), 126.1 (d, C=C), 60.7 (t, CH_2O), 52.5 (d, CHNH), 48.5 (d, C_{4a}), 42.3 (t), 37.9 (d, C_{8a}), 29.5 (t), 25.8 (t), 23.9 (t), 14.6 (q, CH_3). Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 7.94; N, 5.90. Found: C, 65.85; H, 8.16; N, 5.93.

Reaction of Diene 14 with Methyl *trans*-Crotonate. Formation of Ethyl 6-*cis*-(Methoxycarbonyl)-5-*trans*-methyl-2-cyclohexen-1-yl Carbamate (24) and Ethyl 6-*trans*-(Methoxycarbonyl)-5-*cis*-methyl-2-cyclohexen-1-yl Carbamate (25). A solution of diene **14** (96.4 mg, 0.680 mmol), 240 mg (2.4 mmol) of *trans*-methyl crotonate, and 1 mL of dioxane was heated in a sealed ampule at 110 °C for 48 h. Concentration and filtration through a plug of silica gel (4:1 hexane–ethyl acetate) gave a mixture of cycloadducts and starting diene **14**. High-performance LC analysis[45] showed that the endo- and exo-cycloadducts **24** and **25** and a third uncharacterized product were formed in a ratio of 18:11:1. This mixture was separated by high-performance LC[47] (4:1 hexane–ethyl acetate) to give chromatographically homogeneous samples of **24** and **25**. Endo-adduct **24**: a colorless oil; IR (film) 3400, 1720, 1660, 1050 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.5–5.9 (m, CH=CH), 4.97 (br d, $J \approx$ 9 Hz, NH), 4.50 (m, Wh/2 = 16 Hz, C*H*NHR), 4.08 (q, J = 7.0 Hz, OCH_2), 3.67 (s, OCH_3), 2.54 (dd, $J_{1,6}$ = 4.7, $J_{5,6}$ = 9.7 Hz, CHCOOMe), 1.4–2.4 (m), 1.23 (t, J = 7.0 Hz, CH_2CH_3), 1.03 (d, J = 5.9 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$) δ 173.4 (C=O), 156.1 (NHC=O), 129.2 (C=C), 126.3 (C=C), 61.0 (OCH_2), 51.8 (C_6), 50.6 (OCH_3), 46.3 (C_1), 32.2 (C_4), 26.7 (C_5), 19.6 ($CHCH_3$), 14.7 (CH_2CH_3); mass spectrum, *m/z* (isobutane CI, relative percent, 10% cutoff) 242 (MH^+, 26), 210 (13), 153 (100), 93 (13), 90 (15).

Exo-adduct **25**: a colorless oil; IR (film) 3360, 1730, 1680, 1430, 1310, 1180 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.2–6.0 (m, CH=CH), 4.3–4.8 (m, C*H*NH), 4.09 (q, J = 7.3 Hz, OCH_2), 3.71 (s, OCH_3), 1.5–2.3 (m), 1.23 (t, J = 7.3 Hz, CH_2CH_3), 0.94 (d, J = 5.3 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$) δ 174.2 C=O), 156.0 (NHC=O), 128.3 (C=C), 128.2 (C=C), 60.9 (OCH_2), 54.8 (C_6), 51.8 (C_1), 51.2 (OCH_3), 33.1 (C_4), 31.2 (C_5), 19.4 ($CHCH_3$), 14.6 (CH_2CH_3); mass spectrum, *m/z* (isobutane CI, realative percent, 20% cutoff) 242 (MH^+, 20), 153 (39), 79 (44), 71 (41), 69 (100).

Reaction of Diene 14 with *trans*-Crotonaldehyde. Preparation of Ethyl 6-*cis*-Formyl-5-*trans*-methyl-2-cyclohexen-1-yl Carbamate (26) and Ethyl 6-*trans*-Formyl-5-*cis*-methyl-2-cyclohexen-1-yl Carbamate (27). A solution of diene **14** (200 mg, 1.42 mmol), 300 mg (4.3 mmol) of *trans*-crotonaldehyde, 10 mg of 4-*tert*-butylcatchol, and 10 mL of dioxane was heated in a sealed tube at 110 °C for 2 h. Concentration and filtration through a plug of silica gel (ethyl acetate) afforded a mixture of cycloadducts and starting diene **14**. Analysis by high-performance LC[45] (9:1 hexane–ethyl acetate) showed that the endo-cycloadduct **26**, exo-cycloadduct **27**, and an uncharacterized minor product were formed in a ratio of 13:4:1, respectively (54% combined yield). Under these reaction conditions no epimer of adduct **26** was produced.[14] This mixture was separated by high-performance LC[47] (9:1 hexane–ethyl acetate) to give chromatographically homogeneous samples of the known[14] endo-adduct **26** and the exo-adduct **27**. Exo-adduct **27**: a colorless oil; IR (film) 3320, 1720, 1690, 1520, 1250 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 9.61 (d, J = 5.1 Hz, CHO), 5.3–6.0 (m, CH=CH), 4.4–4.7 (m, C*H*NH), 4.09 (q, J = 7.0 Hz, OCH_2), 1.3–2.5 (m), 1.22 (t, J = 7.0 Hz, CH_2CH_3), 0.97 (d, J = 5.5 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$) 203.1 (C=O), 128.9 (C=C), 127.2 (C=C), 61.3 (OCH_2), 61.1 (C_6), 47.3 (C_1), 32.8 (C_4), 28.6 (C_5), 14.5 (CH_2CH_3), the $NHCO_2Et$ and $CHCH_3$ carbons were not observed in this very dilute (low signal/noise) spectrum; mass spectrum, *m/z* (isobutane CI, relative percent, 20% cutoff) 212 (MH^+, 14), 182 (100), 153 (22), 123 (35).

Reaction of Diene 18 with Ethyl α-Methylene(1,3-benzodioxol-5-yl)-acetate. Preparation of Benzyl *trans*-6-(Ethoxycarbonyl)-*cis*-6-(1,3-benzodioxol-5-yl)-2-cyclohexen-1-yl Carbamate (30) and Benzyl *cis*-6-(Ethoxycarbonyl)-*trans*-6-(1,3-benzodioxol-5-yl)-2-cyclohexen-1-yl Carbamate (31). A solution of diene **18** (304 mg, 1.50 mmol), 345 mg (1.57 mmol) of ethyl α-methylene(1,3-benzodioxol-5-yl) acetate, 3 mg of 4-*tert*-butylcatchol, and 3 mL of toluene was heated at reflux for 96 h. Concentration and purification of the residue by chromatography on silica gel (9:1 hexane–ethyl acetate) gave 409 mg (64%) of chromatographically pure cycloadduct **30** (TLC, R_f 0.2, 85:15 hexane–ethyl acetate) and 134 mg (21%) of chromatographically pure cycloadduct **31** (TLC, R_f 0.3, 85:15 hexane–ethyl acetate). Two recrystallizations from ether afforded an analytical specimen of the minor cycloadduct **31**: mp 102–103 °C; IR (KBr) 3360, 1730, 1720, 1520, 1490, 1240, 1040, 1020 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 7.2 (apparent s, Ph), 6.7 (apparent d, C_6H_3), 5.9 (apparent s, OCH_2O and NH), 5.7 (apparent s, CH=CH), 4.8 (s, OCH_2Ph), 4.5 (d, J = 10 Hz, C*H*NH), 4.0 (q, J = 7 Hz, OCH_2CH_3), 2.5–1.7 (m), 1.1 (t, J = 7 Hz, CH_2CH_3); mass spectrum, *m/z* (isobutane CI, relative percent, 15% cutoff) 424 (MH^+, 2), 274 (18), 273 (100), 220 (45), 203 (19), 199 (42), 151 (20), 91 (90). Anal. Calcd for $C_{24}H_{25}NO_6$: C, 68.06; H, 5.95; N, 3.31. Found: C, 67.85; H, 6.10; N, 3.10. Two recrystallizations from hexane–ethyl acetate afforded an analytical specimen of the major cycloadduct **30**: mp 98–99 °C; IR (CCl_4) 3400, 1725, 1710, 1520, 1230, 1040 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.4–6.5 (m, Ph and C_6H_3), 5.9 (s, OCH_2O), 5.9–5.8 (m, CH=CH), 5.2–4.5 (m, nonequivalent OCH_2Ph, C*H*NHCOX), 4.1 (q, J = 7 Hz, OCH_2CH_3), 2.7–1.8 (m), 1.1 (t, J = 7 Hz, CH_2CH_3); mass spectrum, *m/z* (isobutane CI, relative percent, 10% cutoff) 424 (MH^+, 12), 274 (16), 273 (100), 220 (21), 199 (44), 151 (16), 91 (76). Anal.

(47) A 55 cm × 4.6 mm Licrosorb 60 column was used for this separation.

Calcd for $C_{24}H_{25}NO_6$: C, 68.06; H, 5.95; N, 3.31. Found: C, 67.98; H, 6.14; N, 3.32.

Reaction of Diene 18 with 3-(1,3-Benzodioxol-5-yl)-3-buten-2-one. Preparation of Benzyl *trans*-6-Acetyl-*cis*-6-(1,3-benzodioxol-5-yl)-2-cyclohexen-1-yl Carbamate (32) and 3,4-Dihydro-4-pyran 35. A solution of diene **18** (200 mg, 0.985 mmol), 283 mg (1.49 mmol) of 3-(1,3-benzodioxol-5-yl)-3-buten-2-one (**29**, X = $COCH_3$), 1 mg of 4-*tert*-butylcatechol, and 1 mL of toluene was heated at reflux for 18 h. Concentration and purification of the residue by chromatography on silica gel (65:35 hexane–ethyl acetate) gave 122 mg (0.321 mmol) of dienophile dimer **35** and 267 mg (69%) of pure crystalline cycloadduct **32**. Two recrystallizations from hexane–ethyl acetate afforded an analytical specimen of **32**: mp 184–185 °C; IR (KBr) 3390, 1720, 1710, 1485, 1220, 1020 cm^{-1}, ^1H NMR (60 MHz, $CDCl_3$) δ 7.3 (apparent s, Ph), 6.7 (apparent s, C_6H_3), 6.0 (s, OCH_2O), 5.8 (apparent s, CH=CH), 5.2 (d, J = 10 Hz, NH), 5.0 (s, OCH_2Ph), 4.8 (d, J = 10 Hz, C*H*NHCOX), 2.3–1.3 (m), 1.9 (s, $COCH_3$); mass spectrum, m/z (isobutane CI, rel percent, 10% cutoff) 394 (MH^+, 10), 244 (16), 243 (100). Anal. Calcd for $C_{23}H_{23}NO_5$: C, 70.22, H, 5.89; N, 3.56. Found: C, 70.28; H, 6.18; N, 3.43.

Two recrystallizations from hexane–ethyl acetate afforded an analytical specimen of dienophile dimer **35**: mp 122–123 °C; IR (CCl_4) 2900, 2785, 1720, 1675, 1500, 1485, 1435, 1250, 1230, 1100, 1045, 942 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.0–6.5 (m, two C_6H_3), 5.96 (s, OCH_2O), 5.93 (s, OCH_2O), 2.6–2.5 (m, CH_2C=C), 2.4–2.3 (m, CH_2), 2.15 (s, CH_3CO), 1.94 (s, CH_3C=C); mass spectrum, m/z (isobutane CI, rel percent, 10% cutoff) 381 (MH^+, 43), 380 (15), 364 (20), 363 (85), 338 (11), 337 (46), 260 (16), 259 (100), 233 (12), 203 (20), 191 (62), 190 (33), 163 (27), 149 (13), 147 (17). Anal. Calcd for $C_{22}H_{20}O_6$: C, 69.54; H, 5.31. Found : C, 69.96; H, 5.43.

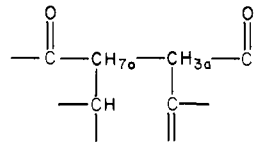
Reaction of Diene 18 with α-Methylene(1,3-benzodioxol-5-yl)acetonitrile. Preparation of Benzyl *trans*-6-Nitrile-*cis*-6-(1,3-benzodioxol-5-yl)-2-cyclohexen-1-yl Carbamate 33. A solution of diene **18** (203 mg, 1.00 mmol), 192 mg (1.11 mmol) of α-methylene (1,3-benzodioxol-5-yl)-acetonitrile, 2 mg of 4-*tert*-butylcatechol, and 1.0 mL of dioxane was heated at reflux for 12 h. High-performance LC analysis indicated that two cycloadducts were formed in a ratio of ~3:2. The major cycloadduct was isolated by chromatography on silica gel (3:1 hexane–ethyl acetate) to give 150 mg (40%) of pure **33**. Two recrystallizations from hexane–ethyl acetate yielded an analytical specimen of **33**: mp 114–115 °C; IR ($CHCl_3$), 3440, 2398, 1728, 1500, 1220, 1040, 935, 720, 670 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.3–6.7 (m, Ph and C_6H_3), 6.00 (d, J = 10 Hz, C*H*=CH), 5.95 (d, J = 1 Hz, OCH_2O), 5.9–5.8 (m, CH=C*H*), 4.92 (d, two lines of AB quartet, J = 12 Hz, OCH*H*Ph), 4.76 (d, two broadened lines of AB quartet, J = 12 Hz, OC*H*HPh), 4.65 (br s, C*H*NHCOX), 4.48 (d, J = 9.2 Hz, N*H*COX, signal moves upfield when sample temperature is increased), 2.6–2.0 (m, two CH_2); mass spectrum, m/z (isobutane CI, relative percent, 10% cutoff) 377 (MH^+, 99), 321 (12), 320 (60), 316 (40), 289 (19), 260 (25), 203 (39), 199 (24), 91 (100). Anal. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.19; H, 5.36; N, 7.45. Found: C, 70.03; H, 5.30; N, 7.39.

Reaction of Diene 28 with 3-(1,3-Benzodioxol-5-yl)-3-buten-2-one. Preparation of 2,2,2-Trichloroethyl *trans*-6-Acetyl-*cis*-6-(1,3-benzodioxol-5-yl)-2-cyclohexen-1-yl Carbamate 34. A solution of diene **28** (269 mg, 1.10 mmol), 315 mg (1.65 mmol) of 3-(1,3-benzodioxol-5-yl)-3-buten-2-one and 2 mg of 4-*tert*-butycatechol was heated at 120 °C for 12 h. As the solution was cooled to room temperature, the reaction mixture was solidified and this solid was purified by chromatography on silica gel (85:15 hexane–ethyl acetate) to afford 82 mg of dienophile dimer **35** and 386 mg (81%) of pure crystalline cycloadduct **34**. Two recrystallizations from hexane–ethyl acetate afforded an analytical specimen of **34**: mp 181–182 °C; IR (KBr) 3340, 1725, 1700, 1500, 1230, 1250, 1130, 820, 712 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.26 (s, NH), 6.72 (apparent d, C_6H_3), 5.95 (s, OCH_2O), 5.75 (apparent s, CH=CH), 4.7 and 4.6 (two lines of AB quartet, nonequivalent CH_2CCl_3), 4.7–4.4 (m, C*H*NHCOX), 2.6–2.0 (m), 1.96 (s, $COCH_3$); mass spectrum, m/z (isobutane CI, relative percent, 10% cutoff) 438 (1), 436 (MH^+, 3), 434 (3), 244 (16), 243 (100). Anal. Calcd for $C_{18}H_{18}Cl_3NO_5$: C, 49.73; H, 4.17; N, 3.22. Found: C, 49.80; H, 4.36; N, 3.20.

Reaction of Diene 38 with 4-Phenyl-1,2,4-triazoline-3,5-dione. Preparation of 2,2,2-Trichloro-*N*-(2,3,5,8-tetrahydro-8-methyl-1,3-dioxo-2-phenyl-5-propyl-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazin-5-yl)acetamide 39. A solution of diene **38** (137 mg 0.5 mmol), 87 mg (0.5 mmol) of 4-phenyl-1,2,4-triazoline-3,5-dione[31] and 5 mL of dioxane was maintained under a nitrogen atmosphere for 1.3 h, at which time the red color of the triazoline dione was discharged. Concentration and recrystallization from absolute ethanol afforded 134 mg (60%) of **39**: mp 156.5–157.5 °C sealed, evacuated capillary); >95% pure by ^1H NMR. An analytical sample was prepared by a further recrystallization from absolute ethanol: mp 158–158.5 °C (sealed, evacuated capillary); IR (KBr) 3320, 1770, 1710, 1700, 1430, 1240, 1140, 758 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.45 (br m, $W_{1/2}$ = 6 Hz, NH and C_6H_5), 6.17 (dd, J = 4.4, 10.3 Hz, C_7 H), 5.85 (dd, J = 1.7, 10.3 Hz, C_6 H), 4.73 (ddq, J = 1.7, 4.4, 6.5 Hz, C_8 H), 2.72 (m, 8 lines, $CH_3CH_2CH_2$), 2.08 (m, 7 lines, $CH_3CH_2CH_2$), 1.42 (d, J = 6.6 Hz, $CHCH_3$), 1.01 (t, J = 6.6 Hz, CH_3CH_2); ^{13}C NMR ($CDCl_3$) δ 160.6, 152.0, 150.1, 131.1, 129.7, 129.4, 128.5, 125.8, 124.3, 92.9, 72.5, 49.2, 41.4, 17.4, 17.2, 13.9. Anal. Calcd for $C_{18}H_{19}Cl_3N_4O_3$: C, 48.50; H, 4.30; N, 12.57. Found: C, 48.49; H, 4.40; N, 12.34.

Reaction of Diene 38 with Maleic Anhydride. Preparation of 2,2,2-Trichloro-*N*-(4,7-diethyl-1,3,3a,6,7,7a-hexahydro-1,3-dioxo-5-isobenzofuranyl)acetamide 40. A solution of diene **38** (504 mg, 1.86 mmol), 182 mg (1.86 mmol) of maleic anhydride, and 1.85 mL of benzene was heated at 110 °C in a sealed tube for 36 h. Concentration and filtration through a small pad of Florisil (CH_2Cl_2) gave 528 mg (77%) of oily **40** (~95% pure by ^1H NMR and ^{13}C NMR). An analytical sample was prepared by three recrystallizations from methylene chloride–hexane to afford white crystalline **40**: mp 150–150.5 °C; IR (KBr) 3330, 1860, 1780, 1720, 1500, 1200, 917, 822 cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) δ 7.8 (br s, NH), 3.83 (d, J = 8.5 Hz, C_{3a} H), 3.50 (m, C_{7a} H), 2.63 (d, J = 17.3 Hz, C_6 H), 2.36 (q, J = 7.5 Hz, C=C-CH_2CH_3), 2.18 (dd, J = 17.6, 10.3 Hz, C_6 H), 1.7–2.0 (m), 1.09 (t, J = 7.2 Hz, CH_3CH_2C=C), 1.03 (t, J = 7.1 Hz, CH_3CH_2CH); ^{13}C NMR ($CDCl_3$) δ 170.6 (C=O, s), 169.6 (C=O, s), 159.9 (C=O, s), 131.2 (s), 126.1 (s), 92.6 (CCl_3, s), 44.9 (d), 43.3 (d), 35.4 (d), 29.6 (t), 24.1 (t), 21.8 (t), 11.8 (q, two CH_3). Anal. Calcd for $C_{14}H_{16}Cl_3NO_4$: C, 45.61; H, 4.38; N, 3.80. Found: C, 45.78; H, 4.38; N, 3.96.

Homonuclear ^1H NMR decoupling experiments confirmed the existence of (a) the =C(—C)-CH_2CH_3 fragment since irradiation of the methyl triplet at δ 1.05 collapsed the allylic methylene (δ 2.36) to a singlet and (b) the



fragment since irradiation of the aliphatic multiplet (δ 1.85) collapsed the C_{7a} methine hydrogen to a doublet.

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