J. Org. Chem. **1988**, *53*, 4807–4810

benzene). The mixture was refluxed for 5 h, left to stand overnight, and then treated with an ice-cooled solution of 10% aqueous NaOH (3 mL) in order to decompose the excess of reagent. The mixture was poured into a separatory funnel containing 50 mL of EtOAc and 15 mL of 10% aqueous NaOH, and after rapid equilibration the aqueous phase was separated and reextracted twice with 50 mL of EtOAc. After drying over $MgSO_4$ and evaporation in vacuo at room temperature, the residual gum (about 80% pure) was acetylated (Ac_2O/pyridine) in the usual manner and then chromatographed on silica H, with 15% ethyl acetate in petroleum ether solution as eluant. Pure **14** (10 mg) was eluted in the fourth fraction. Compound **14**: oil; $[\alpha[_D$ +8° (*c* 0.002, $CHCl_3$); IR ($CHCl_3$) 2930, 2870, 1725, 1370, 1240, 1200, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) assigned by COSY 45 experiment: 5.37 (ddd, 6.9, 6.3, 2.1, H-12), 4.83 (d, 2.2, H-20*E*), 4.66 (d, 1.8, H-20*Z*), 4.56 (dd, 12.4, 2.1, H-11), 4.48 (dd, 11.8, 3.3, H-15), 4.21 (d, 6.9, H-16 and 16′), 4.02 (dd, 11.8, 8.5, H-15′), 3.99 (dd, 12.4, 6.9, H-11′), 2.79 (d, 8.8, H-9α), 2.72 (br, dt, 6.3, 6.9, H-13), 2.32 (br dd, 12.7, 3.5, H-1α), 2.09 (s, 3 H), 2.07 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H, 11, 12, 15, and 16-OAc's), 1.87 (br d, 8.5, H-14), 1.86 (m, H-1β), 1.85 (m, H-5α), 1.73 (m, H-2β), 1.68 and 1.65 (m, H-6α,6β), 1.65 and 1.60 (m, H-7α,7β), 1.59 (m, H-3β), 1.36 (m, H-2α), 1.26 (m, H-3α), 0.98 (s, 19-CH_3), 0.94 (s, 18-CH_3), 0.88 (s, 17-CH_3); mass spectrum (CI, ammonia), *m*/*z* (relative intensity) 526 (MNH_4^+, 100), 449 (MH^+ – AcOH, 5), 389 (MH^+ – 2AcOH, 6), 329 (MH^+ – 3AcOH, 4), and 269 (MH^+ – 4AcOH, 2).

Reduction of Shahamin B (3) To Give Compound 14. Compound **4** (1 mg) in toluene (2 mL) was treated with Red-Al solution (1 mL) in the same manner described for **1**. The residue obtained after the usual workup was acetylated to give compound **14** (0.5 mg), identical in all respects with the compound obtained from **1**.

Reduction of Shahamin C (5) To Give Compound 14. Compound **5** (3.6 mg) in toluene (5 mL) was treated with Red-Al (2.6 mL) in the same manner described for **1**. The usual workup followed by acetylation furnished compound **14** (2.5 mg), identical in all respects with the compound obtained from **1**.

Acknowledgment. We express our appreciation to M. Ilan and Prof. J. Vacelet for the identification of the sponge, Y. Abudi for her excellent technical assistance, and to Harbor Branch Oceanographic Institution, SeaPharm Project, for financial support.

Cycloaddition Reactions of 1,1-Dimethylallene with Substituted Alkynes

Daniel J. Pasto* and Wei Kong

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

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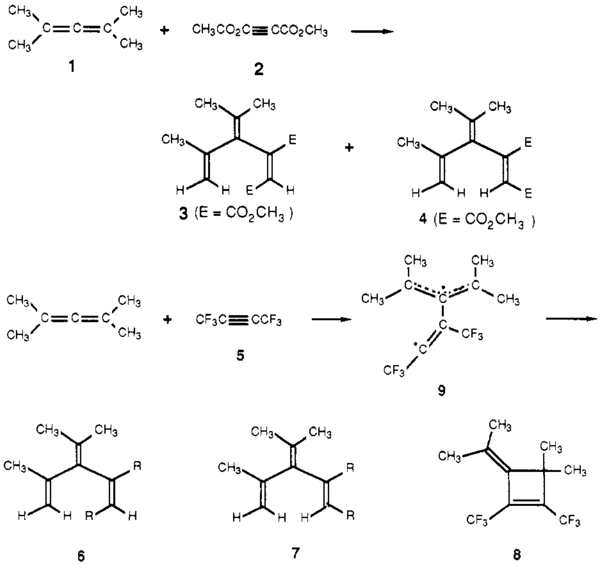
The cycloaddition reactions of 1,1-dimethylallene with ethyl propiolate, ethyl phenylpropiolate, dimethyl acetylenedicarboxylate, and phenylacetylene have been studied. All reactions produce excellent yields of substituted 3-isopropylidenecyclobutenes. Ene products were formed in less than 2% yield. The substituted 3-isopropylidenencyclobutenes are extremely reactive substances, undergoing extensive decomposition or polymerization on exposure to air or attempted purification by chromatographic techniques.

Introduction

One of the major research efforts in our laboratories has focused on the mechanisms of the (2 + 2) cycloaddition reactions of substituted allenes with electronegatively substituted alkenes.[1] These reactions have been shown to proceed via two-step, diradical-intermediate mechanisms. Although ene reactions often compete with cycloaddition reactions, the cycloaddition reactions of the substituted allenes studied in our laboratories have shown that ene reactions, if they occur, result in only very minor product formation.[1] In contrast, a review of the literature of the cycloaddition reactions of substituted allenes with electron-deficient alkynes suggests that ene reactions, when possible, might be the dominant mode of reaction. The reaction of 2,4-dimethyl-2,3-pentadiene (tetramethylallene, **1**) with dimethyl acetylenedicarboxylate (**2**) results in the formation of only the *E* and *Z* ene products **3** and **4**.[2] No (2 + 2) cycloaddition product was apparently formed.[2] The reaction of **1** with hexafluoro-2-butyne (**5**) produced predominantly the *E* and *Z* ene products **6** and **7**, with the (2 + 2) cycloaddition product **8** being formed in only approximately 11% yield.[2] The product distribution of **6**, **7**, and **8** as a function of temperature has been studied; the relative amount of **8** remaining constant leads to the conclusion that **6**, **7**, and **8** are derived from a common intermediate, the diradical **9**.[3]



The reactions of dimethylallene (DMA, **10**) with dimethyl acetylenedicarboxylate and hexafluoro-2-butyne

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[1] (a) Pasto, D. J.; Yang, S.-H. *J. Org. Chem.* **1986**, *51*, 1676. (b) Pasto, D.; Yang, S.-H. *J. Am. Chem. Soc.* **1984**, *106*, 152. (c) Pasto, D. J.; Heid, P. F.; Warren, S. E. *J. Am. Chem. Soc.* **1982**, *104*, 3676. (d) Pasto, D. J.; Warren, S. E. *J. Am. Chem. Soc.* **1982**, *104*, 3670.

[2] Chia, H.-A.; Kirk, B. E.; Taylor, D. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1209.

[3] Kirk, B. E.; Taylor, D. R. *J. Chem. Soc. Perkin Trans. 1* **1974**, 1844.

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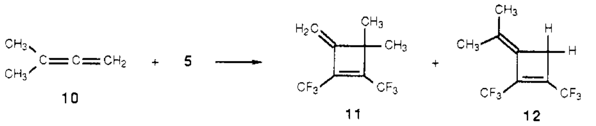
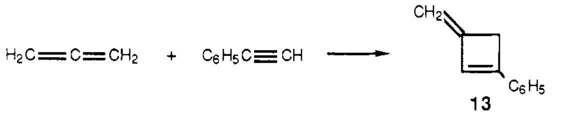
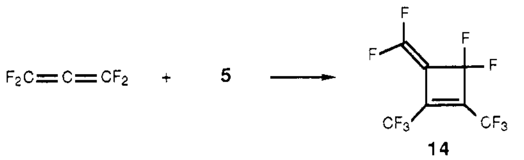
have been studied, the former reaction reported to produce only an "intractable tar", with the latter producing a 3:1 mixture of the cycloadducts **11** and **12**.[3] 1,2-Cyclononadiene is reported to react with **2** and **5** to produce only (2 + 2) cycloaddition products.[4]

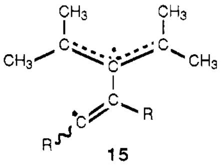


The reaction of allene, which cannot undergo an ene reaction, with phenylacetylene produces **13** in only extremely low yields, polymerization of **13** apparently leading to the disappearance of **13**.[5] Tetrafluoroallene, which also cannot undergo an ene reaction, undergoes cycloaddition with **5** to produce **14**.[6]





There are several factors that might be involved in determining the relative amounts of cycloaddition versus ene reaction in the reactions of substituted allenes with electron-deficient alkenes and alkynes. In the reaction with the electron-deficient alkynes with tetramethylallene (**1**) there is an obvious steric effect which must effect the ratio of the two reactions. In the ring-closure reactions of the diradical intermediates derived from **1**, **15**, severe steric interactions must be generated in the transition states for ring closure and, thus, by default might favor the ene reaction pathway. In the diradical intermediates formed from dimethylallene (**10**), **16**, ring closure to the methylene terminus of the allyl radical is not sterically impeded and should not be retarded. Ring closure at the dimethyl-substituted end of the allyl radical will suffer steric retardation, and attempted ring closure at that end of the allyl radical might be expected to result in ene reaction. Thus DMA provides an excellent example to determine the competition between ring closure (cycloaddition) and hydrogen atom transfer (ene) processes.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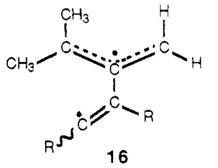
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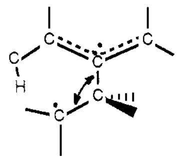
There is also a more subtle aspect to be considered. In the diradical intermediates derived from electron-deficient alkenes (**17**) the saturated radical center is closer to the termini of the allyl radical due to the smaller C–C–C bond angle of approximately 109° (indicated in structure **17**) compared to that of approximately 120° in the diradical intermediate (**18**) derived from an electron-deficient alkyne. This effect should favor the ene reaction over ring closure.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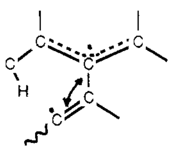
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We have carried out a number of cycloaddition reactions of DMA with electron-deficient alkynes in order to gain a better understanding of the various factors which affect ring-closure versus ene-product formation.

Results

Reaction of 1,1-Dimethylallene (10) with Ethyl Propiolate. The reaction of **10** with a twofold excess of ethyl propiolate in toluene-d_8 was carried out in a sealed NMR tube in the presence of a small amount of hydroquinone. The contents of the tube were triply freeze-degassed, the tube was sealed under reduced pressure, and the tube was heated in a sand bath at 160 °C for 16 h. Direct analysis of the reaction product mixture by NMR indicated the complete disappearance of the DMA, and the formation of essentially (>95%) a single 1:1 cycloadduct. There were no peaks present in the NMR spectrum of the reaction mixture characteristic of the regioisomeric cycloadduct **20**. There was also no evidence of polymerization of reactants or products as indicated by the lack of broad resonances in the vinyl or high-field proton regions. The excess ethyl propiolate was removed under reduced pressure on a vacuum line, and the resulting residue was subjected to rotating-disk, thin-layer chromatography resulting in the isolation of pure **19** in rather low recovered yield. Extensive decomposition and/or polymerization was evident by the isolation of a fraction whose NMR spectrum showed only very broad resonances, none of which were present in the NMR spectrum of the reaction mixture. (This was also the case in the attempt to purify most of the methylenecyclobutene cycloadducts encountered in this study.)

The distinction between the two possible regioisomeric cycloadducts **19** and **20** was accomplished by reduction of the crude reaction mixture with lithium aluminum hydride to the corresponding alcohol and the analysis of the effects of chemical shift reagents on the chemical shifts of the remote methyl groups. The effect of a chemical shift reagent on the chemical shifts of the methyl groups of **22** derived from **19** should be effectively the same, the distance from, and the angle to, the lanthanide metal center being essentially the same for both methyl groups. In contrast, in the alcohol **24** that would be derived from **23** the two methyl groups should show distinctly different changes in chemical shifts in the presence of a chemical shift reagent. The addition of incremental quantities of a chemical shift reagent to the reduction product induced very similar changes in the chemical shifts of the two methyl resonances (see Experimental Section), indicating that the structure of the major cycloadduct is that shown as **19**.

Very low intensity resonances at δ 5.72 and 5.77 in the NMR spectrum of the crude reaction mixture suggested the formation of ~2% of **23**. Compound **23** could not be isolated from the reaction mixture by rotating-disk, thin-layer chromatography. However, a very small quantity (<1%) of a 2:1 adduct assigned structure **21** (on the basis of its NMR spectrum) was isolated. The *E* stereochemistry about the exocyclic double bond is assigned on the basis

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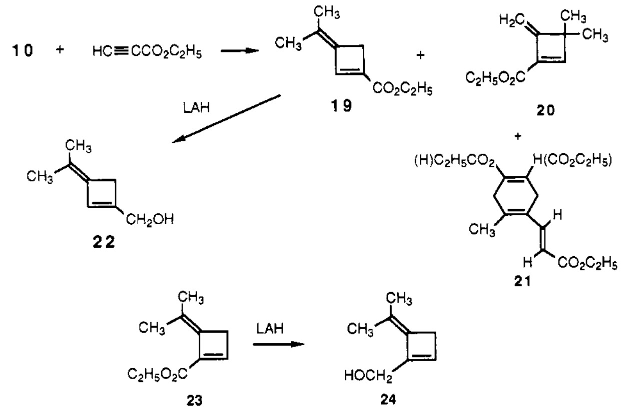
[4] Lee, C. B.; Taylor, D. R. *J. Chem. Res., Synop.* **1977**, 136.

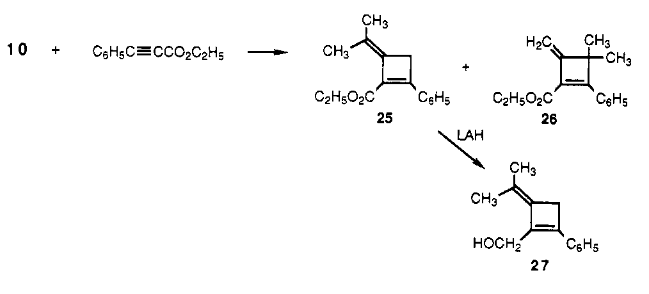
[5] Applequist, D. E.; Roberts, J. D. *J. Am. Chem. Soc.* **1956**, *78*, 4012.

[6] Banks, R. E.; Deem, W. R.; Haszeldine, R. N.; Taylor, D. R. *J. Chem. Soc. C* **1966**, 2051.

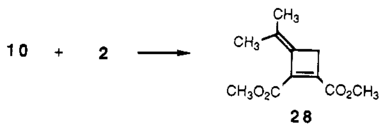


of the magnitude of the H–H coupling constant of 15.7 Hz, which is in the range expected for a trans-disubstituted double bond. This 2:1 adduct is formed by cycloaddition of ethyl propiolate with the ene product. The direction of addition across the ene product could not be unambiguously determined from the NMR spectral data.

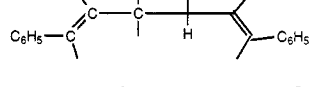
Cycloaddition of 10 with Ethyl Phenylpropiolate. The cycloaddition of **10** with a 35% excess of ethyl phenylpropiolate was carried out in toluene-d_8 at 160 °C for 24 h as described above. Analysis of the NMR spectrum of the solution of the crude reaction mixture indicated the formation of only two (2 + 2) cycloadducts, one containing an isopropylidene group and the other an exocyclic methylene group, formed in a 68:32 ratio. There were no broad resonances present that would be characteristic of polymerization of either reactants or products. Attempts to separate the isomeric cycloadducts by rotating-disk, thin-layer chromatography resulted in the complete decomposition (polymerization) of the cycloadducts. Immediate reduction of the reaction mixture with lithium aluminum hydride gave a mixture of products from which the alcohol **27** was isolated by chromatography. No simple reduction product derived from the isomeric cycloadduct could be isolated, overreduction apparently having occurred as indicated by the mass spectra of the other fractions isolated. The regiochemistry of **27** was assigned on the basis of NMR chemical shift studies. The incremental additions of a chemical shift reagent resulted in substantially different changes in chemical shifts of the two methyl groups (see Experimental Section), unlike the behavior exhibited by alcohol **22**. By analogy, the regiochemistry of the cycloadduct containing the exocyclic methylene group is assigned as shown in **26**.



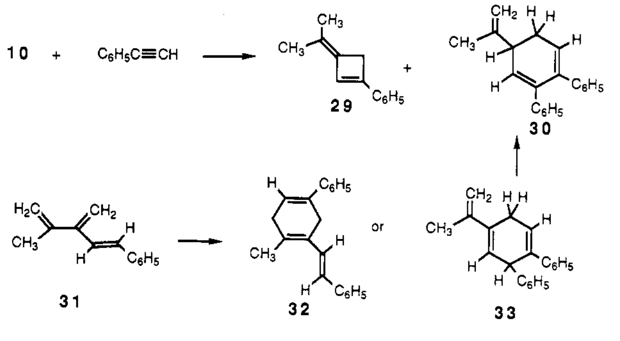
Cycloaddition of 10 with Dimethyl Acetylenedicarboxylate. The NMR spectrum of the reaction mixture derived from **10** with dimethyl acetylenedicarboxylate was very clean, showing essentially only the presence of **28**. There was no NMR evidence for the formation of regioisomer of **28** or polymerization of either reactants or products. The solvent was removed under reduced pressure, and **28** was isolated (10%) by rotating-disk chromatography on silica gel. There was no evidence for the formation of the regioisomer of **28** or an ene product.



Cycloaddition of 10 with Phenylacetylene. The NMR spectrum of the reaction mixture derived from heating **10** with phenylacetylene indicated the formation of one major product along with a very small amount of a second product shown by mass spectrometry to be a 1:2 adduct. There was no evidence of polymerization of either reactants or products. The reaction mixture was separated by rotating-disk, thin-layer chromatography, giving **29** in 26% isolated yield, along with 2% of the 1:2 adduct. The regiochemistry of **29** was assigned as shown on the basis of the NMR spectrum, which showed the vinyl hydrogen as a broadened singlet. The structure of the minor 1:2 adduct has been assigned as **30**. Structure **30** has been assigned on the basis of its NMR spectrum and extensive double resonance studies, which indicates the presence of the spin system shown below,

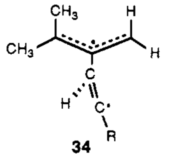


as well as the presence of two conjugated phenyl groups, one vinyl methyl and one terminal methylene. There was no evidence indicating the presence of **32** or **33** that would be derived from the ene product **31** by cycloaddition of phenylacetylene across the methyl-substituted diene or phenyl-substituted diene chromophores. The observed spin system in the 1:2 product is not consistent with either of these structures. The 1:2 adduct **30**, however, can be formed from **33** by a [1,3] hydrogen sigmatropic rearrangement catalyzed by some adventitious acid or base present during the reaction.



Discussion

The cycloaddition reactions of 1,1-dimethylallene (**10**) with a number of alkynes proceed in high yield to form substituted methylenecyclobutenes. The ring closure of the diradical intermediate (**34**) occurs exclusively at the



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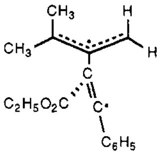
least substituted end of the allyl radical, except with ethyl propiolate in which a minor amount of ring closure occurs at the dimethyl-substituted end of the allyl radical. (The results of prior studies indicate that the largest group attached to the carbon atom of the newly formed bond prefers to be perpendicular to the plane of the allyl radical.[1b]) Ene reactions occurred to only a very minor extent only with ethyl propiolate and phenylacetylene, in the former case producing only the *E* stereochemistry about the newly formed double bond in **21**.

In the cycloaddition reaction with ethyl phenylpropiolate, apparently only the diradical intermediate **35** is formed. In **35** the radical center is stabilized by the phenyl group, whereas in **36** the radical center is stabilized by the ester group. It is obvious that the phenyl group is more capable of stabilizing a radical center than is an ester group.



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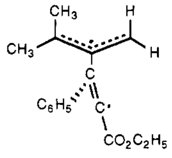

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The substituted methylenecyclobutenes are stable under the cycloaddition reaction conditions, i.e., under an inert atmosphere and in the absence of acids, bases, or radical reagents. They are extremely reactive, however, undergoing polymerization when exposed to air or subjected to chromatography. The chemistry of these substituted methylenecyclobutenes is currently being explored.

Experimental Section

General. All cycloaddition reactions were carried out in toluene-d_8 solution in the presence of a small amount of hydroquinone. The solutions were placed in NMR tubes and the contents were triply freeze-degassed. The tubes were sealed under reduced pressure and were heated in a sand bath at 160 °C. After being heated in the sand bath for 16 h, the sealed NMR tubes were removed and the 300-MHz NMR spectra were recorded.

Cycloaddition of 1,1-Dimethylallene (10) with Ethyl Propiolate. 1,1-Dimethylallene (**10**, 130 μL, 1.3 mmol) was reacted with ethylpropiolate (300 μL, 2.8 mmol) in 0.3 mL of toluene-d_8 as described above. Separation by rotating-disk, thin-layer chromatography on silica gel eluting with methylene chloride gave pure **19** (24%) and **21** (2%). Adduct **20** apparently was not stable under the chromatographic conditions and could not be isolated.

19: colorless liquid; ^{1}H NMR (CDCl$_3$) δ 1.28 (t, J = 7.29 Hz, 3 H), 1.69 (br s, 3 H), 1.78 (br, s, 3 H), 3.03 (br s, 2 H), 4.19 (q, J = 7.29 Hz, 2 H), 6.98 (br s, 1 H); *MS*, *m/e* calcd for $C_{10}H_{14}O_2$ 166.0990, found 166.0993.

21: white crystalline material (insufficient material to determine mp); ^{1}H NMR (CDCl$_3$) δ 1.31 (t, J = 7.07 Hz, 6 H), 2.00 (br s, 3 H), 3.02 (br m, 4 H), 4.23 (q, J = 7.07 Hz, 4 H), 5.79 (d, J = 15.54 Hz, 1 H), 7.03 (m, 1 H), 7.88 (d, J = 15.54 Hz, 1 H); MS, *m/e* calcd for $C_{15}H_{20}O_4$ 264, found 264.

Reduction of 19 to Alcohol 22. The crude reaction mixture derived after removal of the solvent was dissolved in 5 mL of diethyl ether and added to an excess of lithium aluminum hydride in 10 mL of diethyl ether at room temperature. After being stirred for 30 min, the reaction mixture was hydrolyzed by the cautious addition of dilute hydrochloric acid. The ether layer was washed three times with water and 5% NaHCO$_3$ and dried over K$_2$CO$_3$. The solvent was removed and the reaction mixture was subjected to chromatographic separation by thin-layer chromatography on silica gel giving **22** (6.6% overall) as a viscous, colorless liquid: ^{1}H NMR (CDCl$_3$) δ 1.61 (br s, 3 H), 1.68 (br s, 3 H), 2.81 (br s, 2 H), 4.30 (br m, 2 H), 6.31 (br t, J = 1.55 Hz); MS, *m/e* calcd for $C_8H_{18}O$ 125, found 125.

Aliquots of a solution of Eu(fod)$_3$ in CDCl$_3$ were added to the NMR solution and the NMR spectra were recorded. The resulting chemical shifts are given in Table I.

Cycloaddition of 10 with Ethyl Phenylpropiolate. **10** (130 μL, 1.30 mmol) was reacted with ethyl phenylpropiolate (300 μL, 1.78 mmol) as described above. Attempts to separate the reaction mixture by rotating-disk, thin-layer chromatography resulted in the apparent complete decomposition or polymerization of the reaction products. NMR (of the crude reaction mixture in toluene-d_8) of **25**: δ 1.12 (t, 3 H), 1.65 (br s, 3 H), 2.07 (br s, 3 H), 2.91 (br s, 2 H), 4.08 (q, 2 H), 7.07–7.4 (m), 7.91 (d, ortho aromatic H). NMR of **26**: δ 1.17 (t, 3 H), 1.42 (s, 6 H), 4.16 (q, 2 H), 4.80 (br s, 1 H), 5.28 (br s, 1 H), 7.0–7.4 (m), 8.24 (d, ortho aromatic H).

Table I. ^{1}H NMR Chemical Shifts of 22 in the Presence of Eu(fod)$_3$

^{1}H	volume Eu(fod)$_3$/CDCl$_3$ (μL) 0	2.5	5.0
CH$_3$	1.61	1.64	1.68
CH$_3$	1.68	1.73	1.76
-CH$_2$-	2.81	2.93	3.11
-CH$_2$O	4.30	4.75	5.14
=CH-	6.31	6.52	6.68

Table II. ^{1}H NMR Chemical Shifts of 27 in the Presence of Eu(fod)$_3$

^{1}H	volume of added Eu(fod)$_3$ (μL) 0	2.5	5.0	7.5
CH$_3$	1.72	1.85	2.00	2.11
CH$_3$	1.93	2.25	2.57	2.85
-CH$_2$-	3.07	3.25	3.42	3.55
-CH$_2$O	4.55	5.45	6.49	7.15

Reduction of the Reaction Mixture of 10 with Ethyl Phenylpropiolate. The crude reaction mixture derived as described above was dissolved in 5 mL of diethyl ether and added to an excess of lithium aluminum hydride in 10 mL of diethyl ether. After being sitrred for 30 min, the reaction mixture was hydrolyzed by the cautious addition of dilute hydrochloric acid. The organic layer was washed with water and 5% NaHCO$_3$ and dried over K$_2$CO$_3$. Purification by thin-layer chromatography gave **27** as colorless crystals (26% overall yield), which underwent apparent decomposition on attempted recrystallization. MS: *m/e* calcd for $C_{14}H_{16}O$ 200.1198, found 200.1201. Alcohol **27** was dissolved in CDCl$_3$ and the NMR spectrum was recorded with added increments of Eu(fod)$_3$ (see Table II).

Cycloaddition of 10 with Phenylacetylene. **10** (130 μL, 1.31 mmol) and phenylacetylene (300 μL, 2.68 mmol) were reacted as described above. Purification by thin-layer chromatography gave **29** (26%) and **31** (2%).

29: white crystalline solid which underwent apparent decomposition or polymerization on attempted recrystallization; ^{1}H NMR (CDCl$_3$) δ 1.72 (br s, 3 H), 1.79 (br s, 3 H), 3.13 (br s, 2 H), 6.09 (br s, 1 H), 7.20–7.43 (m, 5 H); MS, *m/e* calcd for $C_{13}H_{14}$ 170.1096, found 170.1093.

31: ^{1}H NMr (CDCl$_3$) δ 1.90 (br s, 3 H), 3.19 (m, 2 H), 4.59 (dt, J = 6.16, 4.48 Hz, 1 H), 4.96 (br s, 1 H), 5.05, (br s, 1 H), 6.00 (d, J = 4.48 Hz, 1 H), 6.29 (t, J = 3.80 Hz), 7.2–7.7 (m, 10 H). Irradiation of the δ 6.29 triplet resulted in a broad doublet in the δ 3.1–3.2 region (J = 6.56 Hz). Irradiation of the δ 6.0 doublet caused the double triplet at δ 4.59 to collapse to a triplet. Irradiation of the double triplet at δ 4.59 caused the doublet at δ 6.00 to collapse to a single and the muliplet at δ 3.19 to collapse to a broadened doublet (J = 3.6 Hz). MS: *m/e* 272.

Cycloaddition of 10 with Dimethyl Acetylenedicarboxylate. **10** (130 μL, 1.31 mmol) and dimethyl acetylenendicarboxylate (300 μL, 2.39 mmol) were reacted as described above. The solvent was removed under reduced pressure and the residue was subjected to thin-layer, rotating-disk chromatography on silica gel with methylene chloride as eluent giving **28** (10%) as a viscous liquid: ^{1}H NMR δ 1.71 (s, 3 H), 1.84 (s, 3 H), 3.02 (s, 2 H), 3.75 (s, 3 H), 3.85 (s, 3 H); MS, *m/e* calcd for $C_{11}H_{14}O_4$ 210.0892, found 210.0889.

Acknowledgment. This research was supported by a National Science Foundation grant (CHE87-09725).