(t, $(CH_2)_2CH_2Me$), 27.83 (t, CH_2CH_2Et), 28.06 (t, $CH_2(CH_2)_2Me$), 62.59 (t, 4-C), 80.55 (d, 5-C), 125.58, 128.11, 128.69 (each d), 141.20 (s), and 168.03 (s, 2-C); MS, *m/e* (relative intensity) 203 (M^+, 5), 161 (96), 118 (32), 97 (65), 68 (39), and 55 (100); HRMS calcd for $C_{13}H_{17}NO$ 203.1309, found 203.1309.

55: pale yellow oil; IR (neat) 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.01 (s, 3 H, 2-Me), 2.29 (s, 3 H, *p*-Me), 3.65 (dd, J = 14.7 and 8.1 Hz, 1 H, one of 4-CH_2), 4.12 (dd, J = 14.7 and 9.9 Hz, 1 H, the other of 4-CH_2), 5.32 (dd, J = 9.9 and 8.1 Hz, 1 H, 5-H), and 7.06 (m, 4 H, Ar); MS, *m/e* (relative intensity) 175 (M^+, 3), 119 (11), 55 (100), and 54 (60); HRMS calcd for $C_{11}H_{13}NO$ 175.0996, found 175.0994.

56: pale yellow oil; IR (neat) 1670 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, $(CH_2)_3CH_3$), 1.13-1.78 (m, 4 H, $CH_2(CH_2)_2Me$), 2.25 (t, 2 H, $CH_2(CH_2)_2Me$), 3.95 (d, J = 8.7 Hz, 2 H, 4-CH_2), 5.34 (t, J = 8.7 Hz, 1 H, 5-H), 6.24 (br s, 2 H, furyl), and 7.29 (br s, 1 H, furyl); ^{13}C NMR ($CDCl_3$) δ 13.69 (q, $(CH_2)_3CH_3$), 22.27 (t, $(CH_2)_2CH_2Me$), 27.73 (t, CH_2CH_2Et), 27.97 (t, $CH_2(CH_2)_2Me$), 58.43 (t, 4-C), 73.53 (5-C), 108.42, 110.37 (each d, 3- and 4-C of furyl), 143.21 (d, 5-C of furyl), and 167.85 (s, 2-C); MS, *m/e* (relative intensity) 193 (M^+, 12), 152 (60), 94 (38), 68 (37), and 55 (100); HRMS calcd for $C_{11}H_{15}NO_2$ 193.1102, found 193.1085.

57: pale yellow oil; IR (neat) 1670 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.98 (s, 3 H, 2-Me), 3.80 (dd, J = 15.0 and 7.8 Hz, 1 H, one of 4-CH_2), 4.14 (dd, J = 15.0 and 10.2 Hz, 1 H, the other of 4-CH_2), 5.59 (dd, J = 10.2 and 7.8 Hz, 1 H, 5-H), and 6.80-7.25 (m, 3 H, Ar); MS, *m/e* (relative intensity) 157 (M^+, 10), 97 (19), 77 (16), and 55 (100); HRMS calcd for C_8H_9NOS 167.0403, found 167.0407.

58: yellow oil; IR (neat) 1650 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.08 (dd, J = 14.4 and 7.5 Hz, 1 H, one of 4-CH_2), 4.45 (dd, J = 14.5 and 10.2 Hz, 1 H, the other of 4-CH_2), 5.63 (dd, J = 10.2 and 7.5 Hz, 1 H, 5-H), and 6.90-8.51 (m, 9 H, Ph and Ar); ^{13}C NMR ($CDCl_3$) δ 61.76 (t, 4-C), 80.67 (d, 5-C), 119.65, 122.76 (each d), 127.40 (s), 128.16, 128.28, 131.33, 136.80, 149.36 (each d), 160.10 (s), and 163.51 (s, 2-C); MS, *m/e* (relative intensity) 224 (M^+, 21), 117 (38), 105 (94), 77 (100), and 51 (50); HRMS calcd for $C_{14}H_{12}N_2O$ 224.0949, found 224.0947.

59: yellow oil; IR (neat) 1670 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.92 (t, 3 H, $(CH_2)_3CH_3$), 1.18-1.86 (m, 4 H, $CH_2(CH_2)_2Me$), 2.35 (t, 2 H, $CH_2(CH_2)_2Me$), 3.83 (dd, J = 14.1 and 7.8 Hz, 1 H, one of 4-CH_2), 4.22 (dd, J = 14.1 and 9.9 Hz, 1 H, the other of 4-CH_2), 5.44 (dd, J = 9.9 and 7.8 Hz, 1 H, 5-H), and 7.00-8.53 (m, 4 H, Ar); ^{13}C NMR ($CDCl_3$) δ 13.23 (q, $(CH_2)_3CH_3$), 21.87 (t, $(CH_2)_2CH_2Me$), 27.29 (t, CH_2CH_2Et), 27.54 (t, $CH_2(CH_2)_2Me$), 60.74, (t, 4-C), 80.03 (d, 5-C), 119.48, 122.61, 136.66, 149.22 (each d), 160.01 (s), and 167.62 (s, 2-C); MS, *m/e* (relative intensity) 204 (M^+, 8), 162 (16), 147 (50), 119 (65), 78 (40), 55 (50), and 40 (100); HRMS calcd for $C_{12}H_{16}N_2O$ 204.1262, found 204.1271.

Registry No. **1**, 90606-25-0; **2**, 90606-26-1; **3**, 18293-48-6; **4**, 101402-19-1; **5**, 101402-20-4; **6**, 101402-21-5; **7**, 101402-22-6; **8**, 101402-23-7; **8'**, 101402-56-6; **9**, 101402-24-8; **10**, 101402-25-9; **11**, 101402-26-0; **12**, 101402-27-1; **13**, 101402-28-2; **14**, 101402-29-3; **15**, 101402-30-6; **16**, 101402-31-7; **17**, 930-88-1; **18**, 624-49-7; **19**, 624-48-6; **20**, 764-42-1; **21**, 96-33-3; **22**, 78-94-4; **23**, 101402-32-8; **24**, 101402-33-9; **25**, 101402-34-0; **26**, 101402-35-1; **27**, 101402-36-2; **28**, 101402-37-3; **29**, 101402-38-4; **30**, 101402-39-5; **31**, 101402-40-8; **32**, 41413-77-8; **33**, 101402-41-9; **34**, 101402-42-0; **35**, 101402-43-1; **36**, 101402-44-2; **37**, 101402-45-3; **38**, 762-42-5; **39**, 1087-09-8; **40**, 69640-27-3; **41**, 101402-46-4; **42**, 101402-47-5; **43**, 101402-48-6; **44**, 101402-49-7; **45**, 101402-50-0; **46**, 100-52-7; **47**, 104-87-0; **48**, 98-01-1; **49**, 98-03-3; **50**, 1121-60-4; **51**, 22020-69-5; **52**, 66614-71-9; **53**, 14225-46-8; **54**, 101402-51-1; **55**, 101402-52-2; **56**, 101402-53-3; **57**, 101402-54-4; **58**, 92148-78-2; **59**, 101402-55-5; PhLi, 591-51-5; MeMgI, 917-64-6; EtLi, 811-49-4; BuLi, 109-72-8; $LiCH_2COOEt$, 56267-15-3; $NaCH(COOMe)_2$, 18424-76-5; CH_2=CHLi, 917-57-7.

Reactions of Enamines of Cyclic Ketones with Methyl Propiolate. Reinvestigation and Application in a Tandem Ring Expansion with Four C Atoms

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Enamines of cyclic ketones **1** with ring sizes ranging from seven to twelve react with methyl propiolate via (2 + 2) cycloaddition and subsequent *conrotatory* ring opening of the cyclobutene moiety in **2**. The resulting *cis,trans*-cycloalkadienes **3** rearrange further via a thermal [1,5] hydrogen shift to the corresponding *cis,cis*-cycloalkadienes **4**. The structures previously described in the literature of several of these cycloalkadienes are shown to be incorrect. For a representative *cis,trans*-cycloalkadiene (**3g**, R = H) and a *cis,cis*-cycloalkadiene (**5a**, R = H) the structures were proven by single-crystal X-ray analysis. The reactive "enamine" moiety in **4** allows a tandem ring-expansion reaction of enamines of cyclic ketones with four C atoms. Reaction of **4** with a second electron-deficient acetylenic ester gives the *cis,cis,trans*-cycloalkatrienes **6**.

Reactions of enamines of cyclic ketones with acetylenic esters in an apolar solvent[2,3] have often been employed for ring enlargement with two C atoms.[4] Examples include the synthesis of medium-sized heterocycles[5-11] and of natural products such as muscone,[12,13] steganone,[14] and velleral.[15] This ring expansion involves a (2 + 2) cyclo-

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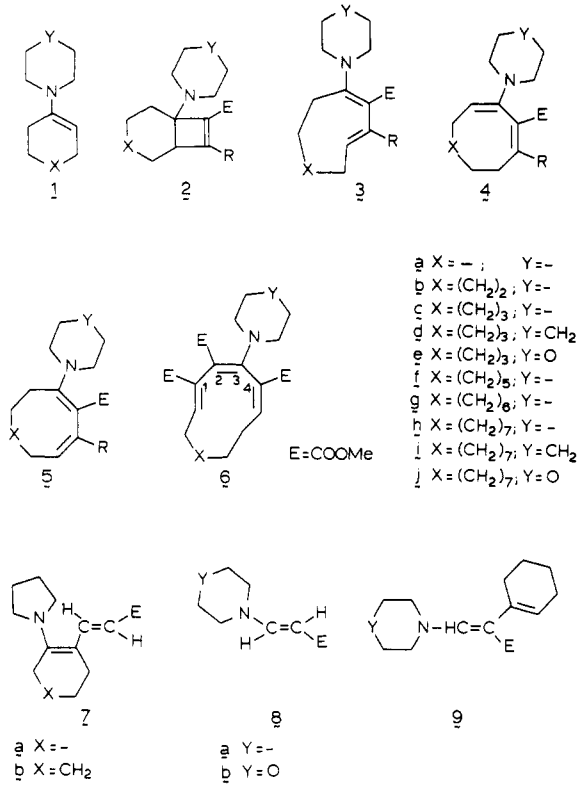
0022-3263/86/1951-2004$01.50/0

Chart I



addition followed by thermal rearrangement of the fused cyclobutenes formed. With regard to the stereochemistry of the ring-expanded products, it has been generally accepted[16] that the ring opening of the cis-fused 3-aminocyclobutenes occurs in a disrotatory mode which would be a forbidden process according to Woodward and Hoffmann.[17] However, according to Epiotis[18] the presence of strongly polarizing groups at the termini of the π-electron system will lower the activation energy for the "disallowed" disrotatory process. As a consequence also the disrotatory conversion of (di)methyl 1-(dialkylamino)bicyclo[*n*.2.0]-alkene-(ψ,)ω-(di)carboxylates (**2**, R = E or H) would be a facile thermal reaction.

Previously we have reported on the stereochemistry of the ring-enlargement products obtained from the reaction of enamines of cyclic ketones with dimethyl acetylenedicarboxylate (DMAD) as the acetylenic ester.[19] We have demonstrated that the initial ring-opening products, which are formed at room temperature, have the cis,trans configuration as in **3** (R = E). This means that opening of the annulated cyclobutene moiety occurs in the symmetry-allowed *conrotatory* fashion. Thermally, the *cis,trans*-cycloalkadienes **3** (R = E) isomerize via a [1,5] sigmatropic hydrogen shift to the *cis,cis*-cycloalkadienes **4** (R = E).

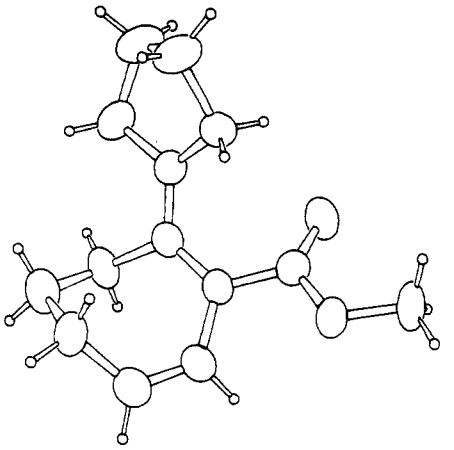


Figure 1. Ortep view of *cis,cis*-cycloheptadiene **5a** (R = H).

The *cis,cis*-cycloalkadienes **5** (R = E) which previously had been regarded as the reaction products of enamines of cyclic ketones with DMAD in apolar solvents are probably formed via two consecutive [1,5] hydrogen shifts, with the *cis,cis*-cycloalkadienes **4** (R = E) as intermediates. For the dimethyl dihydro-6-(1-pyrrolidinyl)-2*H*-thiocin-4,5-dicarboxylates **3**, **4**, and **5** (R = E, X = S, Y = –), the structures unequivocally have been proven by single-crystal X-ray analysis.[19] More recently Andersen et al.[20] have also reported such a conrotatory opening of the cyclobutene moiety.

When we compared these results with the literature[13,21-25] on reactions of enamines of cyclic ketones and (m)ethyl propiolate as the acetylenic ester, we concluded that the information available on the stereochemistry of the ring-expanded products is unreliable. Since the appropriate proof is lacking, in some cases structures are obviously only correct by accident.

In addition we were interested in the possibility of a tandem ring-enlargement reaction using this chemistry as a [1,5] hydrogen shift in the initial ring-expanded product can generate a compound with a reactivity comparable to the starting enamine. In such reactions methyl propiolate has the advantage over DMAD in producing less substituted products.

Results[26]

Reactions of Enamines of Cyclic Ketones and Methyl Propiolate in Apolar Solvents. Huebner et al.[21] and Brannock et al.[22] have reported the reactions of enamines of cyclopentanone with (m)ethyl propiolate. At temperatures below 35 °C the (2 + 2) cycloadducts **2** (R = H, X = –) were the isolated products which on standing at room temperature or on heating rearranged to the cycloheptadienes **5** (R = H, X = –), for which no proof of stereochemistry has been presented. We have repeated

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(26) These results have partly been the subject of a preliminary communication. See: Vos, G. J. M.; Reinhoudt, D. N.; Benders, P. H.; Harkema, S.; van Hummel, G. J. *J. Chem. Soc., Chem. Commun.* **1985**, 661.

these reactions with 1-(1-cyclopenten-1-yl)pyrrolidine (**1a**) as the substrate and could largely reproduce these results. In the ^{1}H NMR spectra of a solution of the (2 + 2) cycloadduct **2a** (R = H) in deuteriochloroform recorded at different time intervals at ambient temperature we observed in addition to the signals which can be attributed to **5a** (R = H) and to methyl (*E*)-3-[2-(1-pyrrolidinyl)-1-cyclopenten-1-yl]-2-propenoate (**7a**)[27] as described by Brannock et al.,[22] two doublets one at δ 4.32 and the other one at δ 7.45 (J = 13 Hz), which we assigned to methyl (*E*)-3-(1-pyrrolidinyl)-2-propenoate (**8a**).[28] Spectra of authentic samples of **5a** (R = H), **7a**, and **8a** served for identification.[29] During the reactions of enamines and methyl propiolate the formation of compounds **8**, which had previously escaped detection, turned out to be a major problem in the purification of the ring-expanded products (vide infra). It cannot be ruled out that also in these reactions products **8** are formed from the intermediate (2 + 2) cycloadducts. For the ring-expanded product **5a** (R = H) we could confirm the cis,cis geometry of the 1,3-diene moiety primarily on comparison of the coupling constant of 10.0 Hz (cf. lit.[21] 10.1 Hz) for the doublet of the vinylic proton with the value of $\geq$15 Hz in the *cis,trans*-cycloalkadienes **3** (R = H, X $\geq$ $(CH_2)_2$) (vide infra).[32] A single-crystal X-ray analysis provided definite proof of structure (Figure 1). The bond lengths for the double bonds are 1.396 (2) and 1.334 (2) Å. The endocyclic torsion angles for the double bonds are −20.3° and 4.0°.

Brannock et al.[22] have reported that the reactions of enamines of cyclohexanone with methyl propiolate in an apolar solvent do not afford either bicyclooctene derivatives **2** (R = H, X = CH_2) or the corresponding cyclooctadienes but methyl 2-(1-cyclohexen-1-yl)-3-(dialkylamino)-2-propenoates **9**.[33] Therefore we did not study these reactions.[34]

From the reaction of 1-(1-cyclohepten-1-yl)pyrrolidine (**1b**) and methyl propiolate in diethyl ether at room temperature Brannock et al.[22] have isolated the product of ring enlargement, for which the structural formula of the *cis,trans*-cyclononadiene **3b** (R = H) has been drawn. As no evidence has been presented for this stereochemistry and in view of the structure given for the corresponding cyclodecadiene derivative (viz. **5c** (R = H), vide infra),[23] we assume that this assignment is only correct by accident. On repeating the reaction we have obtained support for the structure **3b** (R = H) from the large coupling constant of 15.1 Hz for the doublet of the vinylic proton at C-9 in the ^{1}H NMR spectrum. Furthermore the absorption for the vinylic proton at C-8 is shielded for 0.32 ppm (lit.[22] 0.37 ppm) compared with the absorption for the proton at C-6 in the *cis,cis*-cycloheptadiene derivative **5a** (R = H). Clearly, the shielding is not as large as in compounds **3**, where R = E, because of the absence of the methoxycarbonyl function at the adjacent C-atom.[19] We also observed that compound **3b** (R = H) is quite unstable and rearranges in the solid state on standing overnight at room temperature[22] as well as in solution. For the oily product Brannock et al.[22] have presented the structure of methyl 2-(1-pyrrolidinyl)-*trans,cis*-2,9-cyclononadiene-1-carboxylate. However, by comparison of the absorptions of the vinylic protons at δ 4.28 (lit.[22] 4.17) and at δ 7.04 (lit.[22] 6.95) with those of the vinylic protons in compounds **4** (R = E) (δ 4.05–5.04)[19] and **5** (R = E) (δ 6.65–6.88),[19] respectively, it is obvious to us that this product has the cis,cis geometry as in **4b** (R = H). Further support for this stereochemistry has been obtained from the product of reaction with DMAD (vide infra).

The Eastman Kodak group[22] has also dealt with the products of reaction of 1-(1-cycloocten-1-yl)pyrrolidine (**1c**) with methyl propiolate. In a study describing the preparation of cyclodecanone from cyclooctanone,[23] two of them have presented the *cis,cis*-cyclodecadiene structure **5c** (R = H) for the solid ring-expanded product which was obtained at room temperature. However, on the basis of similar arguments as used in the case of the initial ring-expansion product from **1b**, viz. the coupling constant of 14.9 Hz measured by us for the doublet of the proton at C-10 in the ^{1}H NMR spectrum and the shielding of the proton at C-9 for 0.47 ppm as compared with the corresponding proton in the *cis,cis*-cycloheptadiene derivative **5a** (R = H), we propose the cis,trans structure **3c** (R = H). We could confirm that on standing at room temperature an oil is formed from this compound. In analogy to the corresponding isomerization product from the reaction of 1-(1-cyclohepten-1-yl)pyrrolidine (**1b**), Brannock et al.[22] have ascribed the methyl 2-(1-pyrrolidinyl)-*trans,cis*-2,10-cyclodecadiene-1-carboxylate structure to this product. However, similar reasons as in the case of **1b** (vide supra) prompt us to assign the cis,cis structure **4c** (R = H).

The *cis,trans*-cyclononadiene **3b** (R = H) and the corresponding cyclodecadiene derivative **3c** (R = H) are solid products which easily can be isolated with sufficient purity from the reaction of methyl propiolate with **1b** and **1c**, respectively. The ^{1}H NMR spectrum of the residue of the ethereal mother liquor of the reaction of **1c** with methyl propiolate shows in addition to the signals of **3c** (R = H) two doublets at δ 4.36 and at δ 7.49 (J = 13 Hz), respectively, which can be assigned to **8a**.[28,30] The formation of this type of compounds proved to be a serious problem when oily products arise as was the case in the reactions of 1-(1-cycloocten-1-yl)piperidine (**1d**) and of 4-(1-cycloocten-1-yl)morpholine (**1e**) with methyl propiolate in an apolar solvent at room temperature. Using chromatography, we did not succeed in obtaining **3d** (R = H) and **3e** (R = H) as pure compounds. From the latter reaction we could isolate methyl (*E*)-3-(4-morpholinyl)-2-propenoate (**8b**)[36] as a pure solid which was fully characterized.

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(29) Previously it has been reported that **2a** (R = H) in a protic polar solvent such as methanol after 45 h at room temperature was converted for 84% into a 2:1 mixture of **7a** and **8a**.[30]

(30) Visser, G. W. Ph.D. Thesis, Twente University of Technology, Enschede (The Netherlands), 1982. Erroneously, in a preliminary communication the mixture mentioned in ref 29 was ascribed the composition of the *E* and *Z* isomers (2:1) of the Michael adduct of **1a** to methyl propiolate.[31]

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(32) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: Oxford, 1969; p 301.

(33) On the basis of the isolated products of hydrolysis the formation of an abnormal reaction product of the same type next to the ring-expanded product in the reaction of 1-(1-cyclohexen-1-yl)pyrrolidine and methyl tetrolate in DMF is very likely.[12]

(34) It has been mentioned that 1-(1-cyclohexen-1-yl)pyrrolidine reacted with methyl propiolate in methanol as a solvent to afford a 4:1 mixture of the *E* and *Z* isomers of the Michael adduct.[35] However, in view of the coupling constants reported (viz. J = 15 and 13 Hz, respectively) this may not be correct. Presumably, a mixture of **7b** and **8a** has been formed as can be concluded from comparison of the ^{1}H NMR spectral data with those of **7a**,[27] (isolated) **7b**,[30] and independently prepared **8a**.[28,30]

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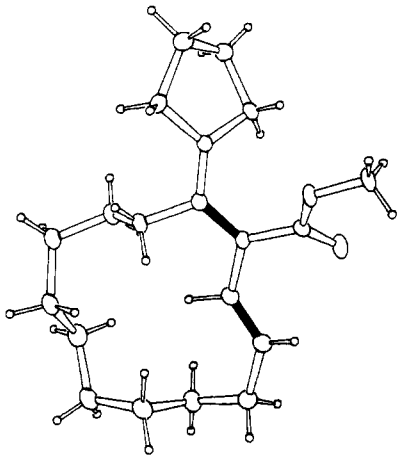

Figure 2. Ortep view of *cis,trans*-cyclotridecadiene **3g** (R = H).

We were able to minimize the formation of the methyl (*E*)-3-(dialkylamino)-2-propenoates **8** by carrying out the reactions at higher temperatures. Refluxing the reaction mixture of **1d** and methyl propiolate for 2 h in hexane gave the *cis,trans*-cyclodecadiene **3d** (R = H) as an unstable oil (contaminated with some **4d** (R = H)), which after refluxing for 2 h in toluene gave the *cis,cis*-cyclodecadiene **4d** (R = H) likewise as an oil. The enamine **1e** was converted quantitatively into the *cis,cis*-cyclodecadiene **4e** (R = H) by reaction with methyl propiolate in refluxing hexane for 3 days; a 66% yield was obtained after refluxing in toluene for 6 h.

We also have reacted the pyrrolidinyl enamine of cyclodecanone (**1f**) with methyl propiolate. After 2 h reaction in refluxing hexane the *cis,trans*-cyclododecadiene **3f** (R = H) was obtained as an unstable oil, which rearranged after 2 h reflux in toluene to the *cis,cis*-cyclododecadiene **4f** (R = H).

Parham and Sperley[24] have reported the corresponding reaction of 1-(1-cycloundecen-1-yl)pyrrolidine (**1g**). They performed the reaction in diethyl ether at room temperature and isolated a solid which was recrystallized from heptane. A methyl 2-(1-pyrrolidinyl)-*cis,trans*-1,12-cyclotridecadiene-1-carboxylate structure was presented for this unstable product. However, the chemical shifts as well as the multiplicity of some peaks mentioned for this initial ring-enlargement product [e.g., δ 6.68 (dd, J = 8 and 14 Hz) and δ 3.46 (d, J = 14 Hz) for the vinylic protons] differ substantially from those found by us for compounds **3** (R = H, X $\geq$ $(CH_2)_2$). On repeating this experiment we have recrystallized the crude solid reaction product from diethyl ether at −20 °C. The NMR spectroscopic data of this compound were similar to those observed for other *cis,trans*-cycloalkadienes **3** (R = H, X $\geq$ $(CH_2)_2$). Finally, a single-crystal X-ray analysis proved the structure to be the *cis,trans*-cyclotridecadiene **3g** (R = H) (Figure 2). Bond lengths and endocyclic torsion angles for the double bonds are 1.381 (2) and 1.332 (2) Å, and 15.6° and 179.3°, respectively. We could confirm that **3g** (R = H) was unstable; in solution isomerization to **4g** (R = H) took place at room temperature and faster in refluxing hexane.

From the reaction of 1-(1-cyclododecen-1-yl)pyrrolidine (**1h**) and methyl propiolate in refluxing hexane Brannock et al.[22,23] have obtained the initial ring-enlargement product without assigning the stereochemistry. For the reaction product from **1h** and ethyl propiolate Stork and coworkers[13] have presented the ethyl 2-(1-pyrrolidinyl)-*cis,trans*-2,14-cyclotetradecadiene-1-carboxylate[13a] as well as the ethyl 2-(1-pyrrolidinyl)-*trans,trans*-2,14-cyclotetradecadiene-1-carboxylate[13b] structure. Russian authors[25] have reported the reaction of 4-(1-cyclododecen-1-yl)morpholine (**1j**) and ethyl propiolate. They performed the reaction in pentane at 95–100 °C and obtained ethyl 2-(4-morpholinyl)-1,13-cyclotetradecadiene-1-carboxylate as the product. From the abstract the cis,cis stereochemistry as in **5j** (R = H) has to be concluded. On carrying out the reaction of **1h** and methyl propiolate in refluxing hexane for 2 h we always obtained a (inseparable) mixture of the *cis,trans*- and *cis,cis*-cyclotetradecadiene **3h** (R = H) and **4h** (R = H), in which the former predominates. This mixture could not be converted into **4h** (R = H) exclusively, either by prolonged refluxing in hexane or by refluxing in toluene. At room temperature, however, in diethyl ether as a solvent the "exclusive" formation of the initial ring-enlargement product **3h** (R = H) together with **8a** takes place, as can be concluded from a ^{1}H NMR spectrum recorded after removal of the solvent. Refluxing the residue in hexane for 2 h similarly afforded a mixture of **3h** (R = H) and **4h** (R = H). In contrast to **1h** reaction of the enamine **1i** with methyl propiolate in refluxing toluene for 18 h afforded almost exclusively the *cis,cis*-cyclotetradecadiene **4i** (R = H). The morpholinyl enamine **1j** could be converted into the *cis,trans*-cyclotetradecadiene **3j** (R = H) and into a mixture of **3j** (R = H) and **4j** (R = H) in which the *cis,cis*-cyclotetradecadiene **4j** (R = H) predominates by reaction with methyl propiolate in refluxing toluene for 2.5 h and 23 h, respectively.

Application of the *cis,cis*-Cycloalkadienes 4 (R = H, X $\geq$ $(CH_2)_2$) in a Tandem Ring Expansion with Four C Atoms. From the former part of this paper we may conclude that the two-carbon ring expansion by reaction of enamines of cyclic ketones containing seven or more C atoms with methyl propiolate in an apolar solvent ultimately affords the *cis,cis*-cycloalkadienes **4** (R = H, X $\geq$ $(CH_2)_2$). As in the latter compounds likewise an "enamine" type of double bond (δ_{H_3} 4.01–4.57) is present, we wanted to investigate the possibility of a second two-carbon ring enlargement by reacting them with an acetylenic ester.

Reaction of the *cis,cis*-cyclononadiene **4b** (R = H) with an equivalent amount of DMAD in diethyl ether at room temperature for 1 h gave after column chromatography an oil. The mass spectrum provided evidence for a 1:1 addition product. From the ^{13}C NMR spectrum we concluded the presence of nine sp^2-hybridized carbon atoms including three carbonyl C atoms. The region of the olefinic protons in the ^{1}H NMR spectrum revealed the presence of two doublets of doublets, one at δ 5.91 and one at δ 6.74. On the basis of the absorptions for the vinylic hydrogens in compounds **3** (R = E) (δ 5.40–6.06) and **5** (R = E) (δ 6.65–6.88), respectively, the former doublet can be attributed to a H atom at a trans, the latter one to a H atom at a cis double bond. Therefore we concluded that the reaction product was trimethyl 3-(1-pyrrolidinyl)-*cis,cis,trans*-2,4,11-cycloundecatriene-1,2,4-tricarboxylate (**6b**).

The *cis,cis*-cyclodecadienes **4c–e** (R = H) could be converted similarly into the *cis,cis,trans*-cyclododecatrienes **6c–e** by reaction with DMAD in diethyl ether at room temperature. All three compounds showed in the ^{1}H NMR spectrum two diagnostic doublets of doublets at δ 6.00–6.01 and at δ 6.86–6.94, respectively. The morpholinyl derivative **6e** was obtained as a solid. An X-ray structure determination definitely proved the cis,cis,trans stereochemistry of the 1,3,5-hexatriene moiety.[26]

In the case of the cyclododecadiene derivative **4f** (R = H) the crude product from **1f** and methyl propiolate was used in the reaction with DMAD and in the case of the cyclotetradecadiene derivative the mixture of the *cis,trans*- and *cis,cis*-cyclotetradecadiene **3h** (R = H) and **4h** (R =

H) (vide supra). Both the cyclotetradecatriene **6f** and the cyclohexadecatriene **6h** could be obtained, although not in a pure state. Prior to the latter experiment we had confirmed that in principle it is also possible to start with a *cis,trans*-cycloalkadiene **3** (R = H, X ≥ $(CH_2)_2$). With the cyclodecadiene derivative **3c** (R = H), which can easily be obtained in a pure form, as the substrate a quantitative yield of **6c** was obtained after a 1-week reaction with DMAD in diethyl ether at room temperature.

Discussion

As mentioned in the introduction, this work was initiated by the—in some respects surprising—results of our previous study of the reactions of enamines of cyclic ketones and DMAD in an apolar solvent.[19] As in that study we have assumed that the (2 + 2) cycloadducts all have the cis stereochemistry. A trans fusion of a five- or six-membered ring to a cyclobutene ring can be ruled out on the basis of the steric strain involved. As with DMAD in the case of larger rings compounds **2** (R = H) cannot be isolated.[22] According to Clark and Untch[37] the more stable bicyclic (2 + 2) cycloadducts of silyl enol ethers and ethyl propiolate all have the cis stereochemistry and (*Z*)-((*tert*-butyldimethylsilyl)oxy)cyclododecene even fails to give a cycloadduct whereas the *E* isomer reacts to the cis cycloadduct.

Therefore, assuming the cis stereochemistry of the (2 + 2) cycloadducts we could demonstrate that these 1-(dialkylamino)-*cis*-bicyclo[*n*.2.0]alkenes **2** (R = H) undergo a *conrotatory* ring opening for $n \geq 7$. This mode of reaction, which also has been observed in the reactions with DMAD,[19] is in agreement with the principle of conservation of orbital symmetry in electrocyclic reactions.[17] The outward rotation of the dialkylamino group nicely fits in with the results of Kirmse and Houk[38] who recently have established that the preference for substituents at C-3 and C-4 of the cyclobutene moiety to rotate outwardly, rather than inwardly, increases as the π-donor nature of the substituent increases. In addition, steric factors may also play a role. Our findings offer new evidence against the generally accepted statement that ring opening in compounds in which a ring with eight or less atoms is cis annulated to a cyclobutene ring must occur by way of the symmetry-forbidden disrotatory mode[16,39] or by homolytic[40] or heterolytic[41] pathways all having a higher activation energy. Ring opening of 3-aminocyclobutenes to which a 5-, 7-, 8-, or 12-membered ring is cis-annulated by a concerted disrotatory fashion has theoretically been forwarded on the basis of qualitative configuration interaction analysis of an asymmetrically substituted cyclobutene.[18] The ring opening of the intermediate methyl 1-(dialkylamino)bicyclo[*n*.2.0]alkene-ω-carboxylates (**2**, R = H) occurs at a much faster rate as compared with the unsubstituted derivatives.[41-46] This is in agreement with the theoretical work of Epiotis.[18] Carpenter,[47] however, has predicted that substitution at the cyclobutene moiety decreases the rate of the conrotatory ring opening and increases the rate of the disrotatory one. The presence of an electron-donating substituent at the bridgehead position and of an electron-withdrawing group at the neighboring sp^2-hybridized C atom may be essential. If their positions are interchanged as in the 1-nitro-ω-(dialkylamino)bicyclo[*n*.2.0]alkenes, thermally "stable" compounds are obtained.[48]

The *cis,trans*-cycloalkadienes **3** (R = H, X ≥ $(CH_2)_2$) which are formed as the initial ring-enlargement products smoothly isomerize to the *cis,cis*-cycloalkadienes **4** (R = H, X ≥ $(CH_2)_2$). This conversion which similarly has been observed in the reactions with DMAD[19] can be interpreted as a [1,5] sigmatropic hydrogen shift.[49]

The [1,5] hydrogen shift regenerates an "enamine" type of double bond and we were able to react them again with an acetylenic ester, especially with DMAD. The formation of the *cis,cis,trans*-cycloalkatrienes **6b–f** and **6h** can be explained by a (2 + 2) cycloaddition of DMAD to the C-2–C-3 double bond of the *cis,cis*-cycloalkadienes **4b–f** (R = H) and **4h** (R = H) followed by a symmetry-allowed conrotatory opening of the annulated cyclobutene ring. Here again the dialkylamino group rotates outwardly in agreement with the work published by Kirmse and Houk[38] (vide supra). Indirectly we did prove in this manner the stereochemistry of the *cis,cis*-cycloalkadienes **4** (R = H, X ≥ $(CH_2)_2$), since otherwise only an (unlikely) (2 + 2) cycloaddition to a *trans,cis*-cycloalkadiene followed by a symmetry-forbidden disrotatory ring opening would give rise to the isolated products **6**.

The sequence of reactions, viz. (2 + 2) cycloaddition, electrocyclic ring opening, [1,5] hydrogen shift, followed again by the first two steps, enables a tandem ring expansion with four C atoms. Starting from the enamines the yields of **6b–f** and **6h** amount to 33–74%. Hitherto, starting from enamines of cyclic ketones and acetylenic esters ring enlargement with four C atoms was only possible in a multistep reaction sequence via the ketone with two C atoms more than the starting material.[22,23]

Experimental Section

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ^1H NMR spectra ($CDCl_3$) were recorded with a Bruker WP-80 spectrometer and ^{13}C NMR spectra ($CDCl_3$) with a Nicolet MT 200 spectrometer (Me_4Si as an internal standard). Mass spectra were obtained with a Varian MAT 311A spectrometer. Elemental analyses were carried out by E. Hoogendam of the Laboratory of Chemical Analysis of the Twente University of Technology.

When no other directions are given reactions were carried out under a nitrogen atmosphere. Petroleum ether refers to the fraction with bp 60–80 °C unless stated otherwise. Diethyl ether was dried by distillation from lithium aluminum hydride, hexane by distillation from lithium, and toluene by distillation from diphosphorous pentoxide. All solvents were stored over 4-Å molecular sieves under a nitrogen atmosphere.

1-(1-Cyclopenten-1-yl)pyrrolidine (**1a**) was prepared as described in the literature.[50] The other enamines were prepared according to the method of Carlson et al.[51] by reaction of the ketone and the appropriate secondary amine in the presence of titanium tetrachloride in petroleum ether as a solvent.

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Methyl 2-(1-Pyrrolidinyl)-*cis*,*cis*-1,6-cycloheptadiene-1-carboxylate (5a, R = H). A solution of **2a** (R = H)[22] (7.7 g, 35 mmol) in 125 mL of toluene was refluxed for 1 h. After trituration of the residue with petroleum ether and subsequent recrystallization pure **5a** (R = H) was obtained: yield 35%; mp 115–119 °C (petroleum ether) (lit.[22] mp 117–119 °C); ^{1}H NMR δ 6.47 (d, J = 10.0 Hz, 1 H, H-7), 5.75 (dt, J = 6.7 and 10.0 Hz, 1 H, H-6), 3.67 (s, 3 H, OCH_3), 3.6–3.2 (m, 4 H, NCH_2), 2.6–1.6 (m, 10 H, CH_2); ^{13}C NMR δ 165.7 and 165.4 (s, C=O and C-2), 131.8 (d, C-7), 124.3 (d, C-6), 96.8 (s, C-1), 51.9 (t, NCH_2), 50.6 (q, OCH_3); mass spectrum, m/e 221.139 (M^+, calcd for $C_{13}H_{19}NO_2$, 221.142).

Methyl 2-(1-Pyrrolidinyl)-*cis*,*trans*-1,8-cyclononadiene-1-carboxylate (3b, R = H). Essentially, the reaction of **1b** with methyl propiolate was carried out as described by Brannock et al.:[22] mp 64–65 °C; ^{1}H NMR δ 6.26 (d, J = 15.1 Hz, 1 H, H-9), 5.43 (ddd, J = 6.6, 7.9 and 14.8 Hz, 1 H, H-8), 3.63 (s, 3 H, OCH_3) [it was not possible to record ^{13}C NMR spectra of pure **3b** (R = H) because of fast isomerization to **4b** (R = H)]; mass spectrum, m/e 249.170 (M^+, calcd for $C_{15}H_{23}NO_2$, 249.173).

Methyl 2-(1-Pyrrolidinyl)-*cis*,*cis*-2,9-cyclononadiene-1-carboxylate (4b, R = H). From 3b (R = H). Stirring a solution of **3b** (R = H) (0.25 g, 1.0 mmol) in methanol (5 mL) for 2 h and allowing the temperature to rise from 0 to 20 °C afforded after removal of the solvent **4b** (R = H) as an oil[22] in a quantitative yield.

From 1b and Methyl Propiolate. To a solution of **1b** (1.65 g, 10.0 mmol) in 50 mL of refluxing toluene was added methyl propiolate (0.84 g, 10.0 mmol) rapidly. The reaction mixture was refluxed for 2 h. After removal of the solvent at reduced pressure the remaining oil was purified by column chromatography (basic alumina (IV), ethyl acetate) to give pure **4b** (R = H): yield 100%; oil;[22] ^{1}H NMR δ 7.04 (t, J = 8.7 Hz, 1 H, H-9), 4.28 (dd, J = 6.8 and 9.3 Hz, 1 H, H-3), 3.75 (s, 3 H, OCH_3), 3.2–2.8 (m, 4 H, NCH_2); ^{13}C NMR δ 166.9 (s, C=O), 147.0 (d, C-9), 140.6 (s, C-2), 131.0 (s, C-1), 98.9 (d, C-3), 51.9 (q, OCH_3), 47.9 (t, NCH_2); mass spectrum, m/e 249.173 (M^+, calcd for $C_{15}H_{23}NO_2$, 249.173).

Methyl 2-(1-Pyrrolidinyl)-*cis*,*trans*-1,9-cyclodecadiene-1-carboxylate (3c, R = H). This compound was prepared according to the procedure given by Brannock et al.:[22,23] mp 101–103 °C (lit.[22] mp 102–105 °C); ^{1}H NMR δ 6.12 (d, J = 14.9 Hz, 1 H, H-10), 5.28 (dt, J = 7.5 and 14.9 Hz, 1 H, H-9), 3.64 (s, 3 H, OCH_3), 3.7–3.3 (m, 4 H, NCH_2), 2.5–1.1 (m, 16 H, CH_2); ^{13}C NMR δ 165.4 and 164.2 (s, C=O and C-2), 138.1 (d, C-10), 128.4 (d, C-9), 96.6 (s, C-1), 51.8 (t, NCH_2), 50.5 (q, OCH_3); mass spectrum, m/e 263.189 (M^+, calcd for $C_{16}H_{25}NO_2$, 263.189).

Methyl 2-(1-Pyrrolidinyl)-*cis*,*cis*-2,10-cyclodecadiene-1-carboxylate (4c, R = H). Upon standing of a ^{1}H NMR sample of **3c** (R = H) at room temperature for ca. 145 h, quantitative isomerization had taken place to **4c** (R = H). In refluxing toluene this isomerization was complete within 2 h: oil;[22] ^{1}H NMR δ 6.89 (dd, J = 4.5 and 12.3 Hz, 1 H, H-10), 4.01 (t, J = 8.0 Hz, 1 H, H-3), 3.75 (s, 3 H, OCH_3), 3.2–2.8 (m, 4 H, NCH_2), 2.2–0.7 (m, 16 H, CH_2); ^{13}C NMR δ 167.1 (s, C=O), 147.1 (d, C-10), 140.9 (s, C-2), 132.5 (s, C-1), 97.8 (d, C-3), 52.0 (q, OCH_3), 48.0 (t, NCH_2); mass spectrum, m/e 263.188 (M^+, calcd for $C_{16}H_{25}NO_2$, 263.189).

Methyl 2-(1-Piperidinyl)-*cis*,*trans*-1,9-cyclodecadiene-1-carboxylate (3d, R = H). To a solution of **1d** (0.97 g, 5.0 mmol) in 25 mL of refluxing hexane was added methyl propiolate (0.42 g, 5.0 mmol) rapidly. The mixture was refluxed for 2 h. Removal of the solvent at reduced pressure gave **3d** (R = H) containing some **4d** (R = H) as an unstable oil: ^{1}H NMR δ 6.15 (d, J = 15.1 Hz, 1 H, H-10), 5.28 (dt, J = 7.5 and 15.0 Hz, 1 H, H-9), 3.63 (s, 3 H, OCH_3), 3.5–3.1 (m, 4 H, NCH_2).

Methyl 2-(1-Piperidinyl)-*cis*,*cis*-2,10-cyclodecadiene-1-carboxylate (4d, R = H). A solution of the crude **3d** (R = H) in toluene was refluxed for 2 h. After removal of the solvent under reduced pressure the residue was purified by column chromatography (basic alumina (IV), ethyl acetate) to afford **4d** (R = H) as an oil: yield 92%; ^{1}H NMR δ 6.91 (dd, J = 4.4 and 12.2 Hz, 1 H, H-10), 4.39 (t, J = 7.9 Hz, 1 H, H-3), 3.74 (s, 3 H, OCH_3), 3.0–2.6 (m, 4 H, NCH_2); ^{13}C NMR δ 167.4 (s, C=O), 147.9 (d, C-10), 144.5 (s, C-2), 132.5 (s, C-1), 103.7 (d, C-3), 51.9 (q, OCH_3), 49.1 (t, NCH_2); mass spectrum, m/e 277.206 (M^+, calcd for $C_{17}H_{27}NO_2$, 277.204).

Methyl 2-(4-Morpholinyl)-*cis*,*cis*-2,10-cyclodecadiene-1-carboxylate (4e, R = H). Methyl propiolate (2.52 g, 30.0 mmol) was added rapidly to a solution of **1e** (5.85 g, 30.0 mmol) in 50 mL of boiling toluene. After refluxing for 6 h, the solvent was removed under reduced pressure and the residue purified by column chromatography (basic alumina (IV), chloroform) to afford **4e** (R = H) as an oil: yield 66%; ^{1}H NMR δ 6.95 (dd, J = 4.5 and 12.3 Hz, 1 H, H-10), 4.44 (t, J = 8.1 Hz, 1 H, H-3), 3.74 (s, 3 H, OCH_3), 3.9–3.5 (m, 4 H, OCH_2), 3.0–2.7 (m, 4 H, NCH_2); ^{13}C NMR δ 167.1 (s, C=O), 148.6 (d, C-10), 143.7 (s, C-2), 131.5 (s, C-1), 104.7 (d, C-3), 67.0 (t, OCH_2), 52.0 (q, OCH_3), 48.6 (t, NCH_2); mass spectrum, m/e 279.183 (M^+, calcd for $C_{16}H_{25}NO_3$, 279.183).

Reaction of 1e with Methyl Propiolate. Isolation of Methyl (*E*)-3-(4-Morpholinyl)-2-propenoate (8b). Methyl propiolate (0.40 g, 4.8 mmol) was added dropwise to a solution of **1e** (0.92 g, 4.7 mmol) in 10 mL of hexane in a carefully dried apparatus in an argon atmosphere. After stirring for 96 h at room temperature a solid and an oil had separated. The solvent was removed (T < 25 °C) and the residue extracted with petroleum ether. After removal of the solvent the resulting semisolid residue was triturated with petroleum ether (bp 40–60 °C). Column chromatography (silica gel, chloroform) followed by recrystallization afforded the analytically pure compound: mp 72–74 °C (chloroform) (lit.[36a] mp 76–78 °C, lit.[36b,c] mp 69.5–70.5 °C); ^{1}H NMR δ 7.36 (d, J = 13.4 Hz, 1 H, H-3), 4.69 (d, J = 13.2 Hz, 1 H, H-2), 3.67 (s, 3 H, OCH_3), 3.9–3.5 (m, 4 H, OCH_2), 3.4–3.1 (m, 4 H, NCH_2); ^{13}C NMR δ 169.7 (s, C=O), 151.8 (d, C-3), 85.9 (d, C-2), 66.2 (t, OCH_2), 50.6 (q, OCH_3), 48.7 (t, NCH_2); mass spectrum, m/e 171.089 (M^+, calcd, 171.090).

Anal. Calcd for $C_8H_{13}NO_3$ (M_r 171.198): C, 56.13; H, 7.65; N, 8.18. Found: C, 55.98; H, 7.87; N, 7.95.

Methyl 2-(1-pyrrolidinyl)-*cis*,*trans*-1,11-cyclododecadiene-1-carboxylate (3f, R = H) containing some **4f** (R = H) was obtained as an unstable oil in the same manner as described for **3d** (R = H): ^{1}H NMR δ 6.14 (d, J = 15.6 Hz, 1 H, H-12), 5.52 (dt, J = 6.6 and 15.6 Hz, 1 H, H-11), 3.65 (s, 3 H, OCH_3), 3.5–3.2 (m, 4 H, NCH_2).

Methyl 2-(1-Pyrrolidinyl)-*cis*,*cis*-2,12-cyclododecadiene-1-carboxylate (4f, R = H). A solution of the above mixture in 25 mL of toluene was refluxed for 2 h to give after removal of the solvent **4f** (R = H) containing some **3f** (R = H), which could not be purified by chromatography because of decomposition: ^{1}H NMR δ 6.93 (dd, J = 3.8 and 10.9 Hz, 1 H, H-12), 4.08 (dd, J = 3.8 and 9.9 Hz, 1 H, H-3), 3.73 (s, 3 H, OCH_3), 3.1–2.7 (m, 4 H, NCH_2).

Methyl 2-(1-Pyrrolidinyl)-*cis*,*trans*-1,12-cyclotridecadiene-1-carboxylate (3g, R = H). The reaction of **1g** (3.0 g, 13.6 mmol in 10 mL of diethyl ether) with methyl propiolate (1.14 g, 13.6 mmol) was essentially performed as described by Parham and Sperley.[24] Removal of the solvent at reduced pressure at room temperature afforded an oil, which solidified on cooling at −20 °C: mp 73–78 °C[52] (diethyl ether, −20 °C) (lit.[24] mp 81–83 °C); ^{1}H NMR δ 6.13 (d, J = 15.6 Hz, 1 H, H-13), 5.33 (dt, J = 6.4 and 15.6 Hz, 1 H, H-12), 3.67 (s, 3 H, OCH_3), 3.5–3.1 (m, 4 H, NCH_2); ^{13}C NMR δ 167.7 (s, C=O), 159.0 (s, C-2), 130.5 (d, C-13), 127.6 (d, C-12), 97.3 (s, C-1), 50.9 (q and t, OCH_3 and NCH_2); mass spectrum, m/e 305.235 (M^+, calcd for $C_{19}H_{31}NO_2$, 305.236).

Methyl 2-(1-Pyrrolidinyl)-*cis*,*cis*-2,13-cyclotridecadiene-1-carboxylate (4g, R = H). This compound was obtained although not exclusively by refluxing a solution of **3g** (R = H) (0.50 g, 1.64 mmol) in hexane (10 mL) for 2.5 h and removal of the solvent. The residual oil could not be purified by chromatography: ^{1}H NMR δ 6.86 (dd, J = 3.2 and 10.7 Hz, 1 H, H-13), 4.02 (dd, J = 4.5 and 8.2 Hz, 1 H, H-3), 3.75 (s, 3 H, OCH_3), 3.1–2.7 (m, 4 H, NCH_2); ^{13}C NMR δ 167.1 (s, C=O), 147.7 (d, C-13), 139.9 (s, C-2), 131.5 (s, C-1), 100.2 (d, C-3), 51.9 (q, OCH_3), 47.9 (t, NCH_2); mass spectrum, m/e 305.237 (M^+, calcd for $C_{19}H_{31}NO_2$, 305.236).

Mixture of Methyl 2-(1-Pyrrolidinyl)-*cis*,*trans*-1,13-cyclotetradecadiene-1-carboxylate (3h, R = H) and Methyl 2-(1-Pyrrolidinyl)-*cis*,*cis*-2,14-cyclotetradecadiene-1-carboxylate (4h, R = H). The reaction of **1h** (1.18 g, 5.0 mmol) with methyl propiolate (0.42 g, 5.0 mmol) was performed as de-

(52) The depression of the melting point as compared with the reported one[24] is probably caused by isomerization of **3g** (R = H) to **4g** (R = H).

scribed for the preparation of **3d** (R = H).[56] The oily residue which resulted after removal of the solvent consisted of **3h** (R = H) and **4h** (R = H) with the former predominating. Neither prolonged refluxing in hexane nor refluxing in toluene for 2 h and once again for 15.5 h did result in the exclusive formation of **4h** (R = H).

3h (R = H): ^{1}H NMR δ 6.18 (d, J = 15.6 Hz, 1 H, H-14), 5.26 (dt, J = 6.8 and 15.4 Hz, 1 H, H-13), 3.67 (s, 3 H, OCH_3), 3.4–3.1 (m, 4 H, NCH_2); ^{13}C NMR δ 169.0 (s, C=O), 157.3 (s, C-2), 128.0 (d, C-14), 126.9 (d, C-13), 97.8 (s, C-1), 50.9 (q, OCH_3), 50.6 (t, NCH_2); mass spectrum, m/e 319.250 (M^+, calcd for $C_{20}H_{33}NO_2$, 319.251).

4h (R = H): ^{1}H NMR δ 6.91 (dd, J = 3.9 and 11.0 Hz, 1 H, H-14), 4.18 (dd, J = 4.4 and 9.5 Hz, 1 H, H-3), 3.72 (s, 3 H, OCH_3), 3.1–2.8 (m, 4 H, NCH_2).

Methyl 2-(1-Piperidinyl)-*cis*,*cis*-2,14-cyclotetradecadiene-1-carboxylate (4i, R = H). To a solution of the enamine **1i** (1.25 g, 5.0 mmol) in 25 mL of warm (80 °C) toluene was added methyl propiolate (0.42 g, 5.0 mmol) rapidly. The reaction mixture was refluxed for 18 h. Removal of the solvent at reduced pressure afforded a yellow oil, which could not be purified by chromatography: ^{1}H NMR δ 6.91 (dd, J = 3.7 and 11.0 Hz, 1 H, H-14), 4.51 (dd, J = 4.8 and 9.2 Hz, H-3), 3.72 (s, 3 H, OCH_3); ^{13}C NMR δ 167.9 (s, C=O), 147.9 (d, C-14), 143.2 (s, C-2), 130.3 (s, C-1), 106.9 (d, C-3), 51.8 (q, OCH_3), 49.4 (t, NCH_2); mass spectrum, m/e 333.267 (M^+, calcd for $C_{21}H_{35}NO_2$, 333.267).

Methyl 2-(4-Morpholinyl)-*cis*,*trans*-1,13-cyclotetradecadiene-1-carboxylate (3j, R = H). This compound was obtained although not in pure state by performing the reaction of **1j** with methyl propiolate as described in the preparation of **4i** (R = H) for only a 2.5-h reaction. No attempts were made at further purification: yellow oil; ^{1}H NMR δ 6.16 (d, J = 15.9 Hz, 1 H, H-14), 5.44 (dt, J = 6.7 and 15.8 Hz, 1 H, H-13), 3.75 (s, 3 H, OCH_3), 3.9–3.5 (m, 4 H, OCH_2); ^{13}C NMR δ 169.6 (s, C=O), 153.7 (s, C-2), 129.0 (d, C-14), 125.9 (d, C-13), 114.4 (s, C-1), 67.4 (t, OCH_2), 51.2 (q, OCH_3), 50.5 (t, NCH_2); mass spectrum, m/e 335.246 (M^+, calcd for $C_{20}H_{33}NO_3$, 335.246).

Methyl 2-(4-Morpholinyl)-*cis*,*cis*-2,14-cyclotetradecadiene-1-carboxylate (4j, R = H). This compound, contaminated with some **3j** (R = H), was obtained in a similar way as **4i** (R = H) after a 23-h reaction. Attempts to purify the mixture by column chromatography failed: light-brown oil; ^{1}H NMR δ 6.96 (dd, J = 3.7 and 11.0 Hz, 1 H, H-14), 4.57 (dd, J = 4.5 and 9.6 Hz, 1 H, H-3), 3.73 (s, 3 H, OCH_3), 3.9–3.5 (m, 4 H, OCH_2); ^{13}C NMR δ 167.4 (s, C=O), 148.2 (d, C-14), 142.2 (s, C-2), 129.3 (s, C-1), 107.5 (d, C-3), 66.9 (t, OCH_2), 51.8 (q, OCH_3), 48.9 (t, NCH_2); mass spectrum, m/e 335.247 (M^+, calcd for $C_{20}H_{33}NO_3$, 335.246).

General Procedure for the Reaction of *cis*,*cis*-Cycloalkadienes 4 (R = H, X ≥ $(CH_2)_2$) with DMAD. Preparation of 6b–f and 6h. DMAD (0.71 g, 5.0 mmol) was added dropwise to a solution of **4b–f** (R = H) (5.0 mmol) in 25 mL of diethyl ether at room temperature. For the preparation of **6h** a mixture of **3h** (R = H) and **4h** (R = H) was used. After the reaction was complete, the solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel, ethyl acetate (**6b–e**, **6h**) or ethyl acetate/chloroform, 1:1, **6f**).

Trimethyl 3-(1-pyrrolidinyl)-*cis*,*cis*,*trans*-2,4,11-cycloundecatriene-1,2,4-tricarboxylate (6b): reaction time 1 h; yield 40%; oil; ^{1}H NMR δ 6.74 (dd, J = 5.4 and 7.8 Hz, 1 H, H-5), 5.91 (dd, J = 3.7 and 11.5 Hz, 1 H, H-11), 3.73, 3.61 and 3.59 (s, 9 H, OCH_3); ^{13}C NMR δ 167.6, 165.2 and 164.8 (s, C=O), 153.6 (s, C-3), 149.2 and 147.6 (d, C-5 and C-11), 129.6 (s, C-1 and C-4), 96.4 (s, C-2); mass spectrum, m/e 391.202 (M^+, calcd for $C_{21}H_{29}NO_6$, 391.200).

Trimethyl 3-(1-pyrrolidinyl)-*cis*,*cis*,*trans*-2,4,12-cyclododecatriene-1,2,4-tricarboxylate (6c): reaction time 2 h; yield 100%; oil; ^{1}H NMR δ 6.86 (dd, J = 4.4 and 9.3 Hz, 1 H, H-5), 6.00 (dd, J = 4.3 and 8.9 Hz, 1 H, H-12), 3.72, 3.63 and 3.60 (s, 9 H, OCH_3); ^{13}C NMR δ 167.9, 166.2 and 165.8 (s, C=O), 152.1 (s, C-3), 149.5 and 147.0 (d, C-5 and C-12), 130.1 and 130.0 (s, C-1 and C-4), 98.4 (s, C-2); mass spectrum, m/e 405.220 (M^+, calcd for $C_{22}H_{31}NO_6$, 405.215).

Trimethyl 3-(1-piperidinyl)-*cis*,*cis*,*trans*-2,4,12-cyclododecatriene-1,2,4-tricarboxylate (6d): reaction time 2 h; yield 80%; oil; ^{1}H NMR δ 6.89 (dd, J = 4.6 and 9.3 Hz, 1 H, H-5), 6.01 (dd, J = 4.9 and 8.1 Hz, 1 H, H-12), 3.70, 3.64 and 3.60 (s, 9 H, OCH_3); ^{13}C NMR δ 167.6, 166.7 and 166.5 (s, C=O), 155.0 (s, C-3), 150.9 and 146.8 (d, C-5 and C-12), 130.8 and 130.5 (s, C-1 and C-4), 101.3 (s, C-2); mass spectrum, m/e 419.237 (M^+, calcd for $C_{23}H_{33}NO_6$, 419.231).

Trimethyl 3-(4-morpholinyl)-*cis*,*cis*,*trans*-2,4,12-cyclododecatriene-1,2,4-tricarboxylate (6e): reaction time 2 days; yield 50%; mp 90–91.5 °C (diisopropyl ether); ^{1}H NMR δ 6.94 (dd, J = 4.4 and 9.5 Hz, 1 H, H-5), 6.01 (dd, J = 4.6 and 8.6 Hz, 1 H, H-12), 3.72, 3.67 and 3.61 (s, 13 H, OCH_3 and OCH_2); ^{13}C NMR δ 167.3, 167.1 and 166.2 (s, C=O), 153.6 (s, C-3), 151.6 and 147.1 (d, C-5 and C-12), 130.0 and 129.9 (s, C-1 and C-4), 103.4 (s, C-2), 66.7 (t, OCH_2); mass spectrum, m/e 421.209 (M^+, calcd, 421.210).

Anal. Calcd for $C_{22}H_{31}NO_7$ (M_r 421.495): C, 62.69; H, 7.41; N, 3.32. Found: C, 62.59; H, 7.77; N, 3.58.

Trimethyl 3-(1-pyrrolidinyl)-*cis*,*cis*,*trans*-2,4,14-cyclotetradecadiene-1,2,4-tricarboxylate (6f): reaction time 2 h; yield 42%; oil; ^{1}H NMR δ 6.83 (dd, J = 6.2 and 10.6 Hz, 1 H, H-5), 5.83 (dd, J = 4.6 and 10.5 Hz, 1 H, H-14), 3.82, 3.68 and 3.50 (s, 9 H, OCH_3); ^{13}C NMR δ 169.1, 168.1 and 165.9 (s, C=O), 153.4 (s, C-3), 145.8 and 141.6 (d, C-5 and C-14), 133.3 and 128.2 (s, C-1 and C-4), 100.8 (s, C-2); mass spectrum, m/e 433.242 (M^+, calcd for $C_{24}H_{35}NO_6$, 433.246).

Trimethyl 3-(1-pyrrolidinyl)-*cis*,*cis*,*trans*-2,4,16-cyclohexadecadiene-1,2,4-tricarboxylate (6h): reaction time 2 h; yield 42%; oil; ^{1}H NMR δ 6.80 (t, J = 7.8 Hz, 1 H, H-5), 5.84 (dd, J = 6.8 and 8.3 Hz, 1 H, H-16), 3.81, 3.69 and 3.51 (s, 9 H, OCH_3); ^{13}C NMR δ 168.9, 168.2 and 165.9 (s, C=O), 153.9 (s, C-3), 144.5 and 142.4 (d, C-5 and C-16), 132.6 and 130.1 (s, C-1 and C-4), 101.2 (s, C-2); mass spectrum, m/e 461.275 (M^+, calcd for $C_{26}H_{39}NO_6$, 461.278).

X-ray Diffraction. The crystal structures of **5a** (R = H), **3g** (R = H), and **6e** have been determined by X-ray diffraction with the following experimental conditions:

5a (R = H): monoclinic; $P2_1/n$; a = 14.740 (6), b = 8.903 (4), and c = 9.313 (4) Å; β = 102.03 (3)°; Z = 4; d_c = 1.23 g·cm^{-3}; Enraf-Nonius CAD4-diffractometer; Mo Kα radiation (0.7107 Å); graphite monochromator; T = 293 (2) K; ω–2θ scan mode; scan speed (ω) varying between 1 and 5° min^{-1}; $2\theta_{max}$ 55°; scan width (ω) (0.9 + 0.34 tan ω)°; number of reflexions measured 2738; number of reflexions used in refinements ($I > 3\sigma(I)$) 2117; number of parameters refined 222; R = 3.5%; R_w = 5.2%.

3g (R = H): triclinic; P$\bar{1}$; a = 10.620 (1), b = 9.767 (1), and c = 9.419 (1) Å; α = 115.62 (2)°, β = 104.84 (2)°, γ = 72.28 (3)°; Z = 2; d_c = 1.22 g·cm^{-3}; Philips PW 1100 diffractometer; Mo Kα radiation; graphite monochromator; T = 173 (2) K; ω–2θ scan mode; scan speed (ω) 6° min^{-1}; $2\theta_{max}$ 60°; scan width (ω) 1.5°; number of reflexions measured 3870; number of reflexions used in refinements ($I > 3\sigma(I)$) 2926; number of parameters refined 324; R = 3.7%; R_w = 4.5%.

6e: Crystallographic details are reported elsewhere.[26]

Structure solution and refinement using Multan[53] were done with the Enraf-Nonius VAXSDP package.[54] Hydrogen atoms were found from difference Fourier syntheses. Parameters refined in the last cycles were scale factor, extinction parameter, positional parameters of all atoms, thermal parameters (isotropic for H atoms, anisotropic for others). The drawings were made with Ortep.[55]

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(56) **Note added in proof**: Performing the reaction according to the *Organic Syntheses*[23] procedure (viz. refluxing the reaction mixture of **1h** and methyl propiolate for exactly 1 h) exclusively yields **3h** (R = H) as a solid.[22]

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Registry No. **1b**, 14092-11-6; **1d**, 101471-70-9; **1e**, 101471-72-1; **1f**, 52919-64-9; **1g**, 101471-74-3; **1h**, 35595-58-5; **1i**, 101471-78-7; **1j**, 101471-80-1; **2a** (R = H), 82483-74-7; **3b** (R = H), 101493-68-9; **3c** (R = H), 101471-69-6; **3d** (R = H), 101471-71-0; **3f** (R = H), 101493-69-0; **3g** (R = H), 101471-75-4; **3h** (R = H), 101471-77-6; **3j** (R = H), 101471-81-2; **4b** (R = H), 98712-11-9; **4c** (R = H), 98728-15-5; **4d** (R = H), 98712-12-0; **4e** (R = H), 98712-09-5; **4f** (R = H), 98712-13-1; **4g** (R = H), 101471-76-5; **4h** (R = H), 98712-14-2; **4i** (R = H), 101471-79-8; **4j** (R = H), 101471-82-3; **5a** (R = H), 92196-97-9; **6b**, 98712-16-4; **6c**, 98712-17-5; **6d**, 99015-75-5; **6e**, 98712-10-8; **6f**, 98712-18-6; **6h**, 98712-19-7; **8b**, 101471-73-2; DMAD, 762-42-5; $HC{\equiv}CCO_2CH_3$, 922-67-8.

Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond distances, and bond angles for **5a** (R = H) and **3g** (R = H) (15 pages). Ordering information is given on any current masthead page.

Cycloaddition Routes to Azaanthraquinone Derivatives.[1] 1. Use of Azadienophiles

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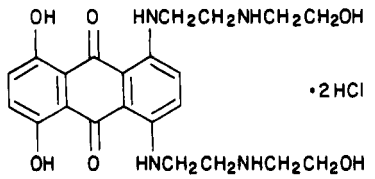
The mono- and diazanaphthoquinones underwent facile cycloaddition with cyclic and alicyclic dienes, and in the majority of these cycloadditions the initial 1:1-cycloadducts or their tautomers and intermediate products formed in the oxidation procedure leading to the final azaanthraquinones were isolated. Quinoline-5,8-dione and 1-methoxy-1,3-cyclohexadiene gave the 8-methoxy isomer in an essentially regiospecific cycloaddition; isoquinoline-5,8-dione, however, gave both the 5- and 8-methoxy isomers in a 2.8:1 ratio. These structural assignments were verified by alternative syntheses of the possible isomers using heteroatom-directed lithiation procedures.

Mitoxantrone (1) and related anthraquinones are of special interest in cancer chemotherapy, with mitoxantrone now undergoing clinical trials.[2] Mitoxantrone has been shown to be an intercalant[3] and, on the basis of a theoretical model[4] for intercalation, it was predicted that azaanthraquinone analogues of 1 would be very effective intercalants, and their study as potential antitumor agents is thus of considerable interest.[5] We now describe cycloaddition routes to a variety of azaanthraquinones, which establish the regiochemistry of the cycloadditions with asymmetric dienes and characterize the discrete intermediates involved in the overall reaction pathway.



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Several azaanthraquinones[6] have been described in the literature, and the synthetic routes employed have usually involved the classical Friedel–Crafts approach,[6g] introduction of the 9,10-carbonyl functions by oxidation of the corresponding hydrocarbon,[6h] or cycloaddition of an azanaphthoquinone with an appropriate diene.[6b-f] The present study establishes the Diels–Alder approach as a versatile method for introduction of substituents into the final azaanthraquinone.

Cycloadditions with Cyclic Dienes. These are expected to occur with formation of a 1:1-cycloadduct, followed by tautomerization and ready oxidation to yield a bridged ring system which can undergo thermal elimination of ethylene leading to the azaanthraquinone. Quinoline-5,8-dione (**2a**) underwent ready reaction with 1,3-cyclohexadiene (**3**: R = H) in boiling benzene over 24 h. The initial 1:1-cycloadduct separated from the cooled reaction mixture as its quinol tautomer **4a** (R = R^1 = H) (75%), and oxidation of **4a** (R = R^1 = H) with Ag_2O in DME gave the bridged-adduct 6,9-dihydro-6,9-ethanobenzo[*g*]quinoline-5,10-dione (**5a**: R = R^1 = H). The

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