

73.35 (s, d*, $^3J_{PC} = 6.5$ Hz), 76.01 (d), [96.97 and 97.06] (d), [121.04 and 121.11] (d), 141.24 ppm (s); IR (KBr) 1226, 1059, 1032 cm^{-1} . Anal. Calcd for $\text{C}_{30}\text{H}_{51}\text{N}_2\text{O}_5\text{P}$: C, 65.43; H, 9.34; N, 5.09. Found: C, 65.19; H, 9.22; N, 5.28.

Reductive Epoxide-Ring Opening of Phosphorodiamidate Derivatives. Ethylamine (30 mL) was dried by passing through a chamber of NaOH and condensed under N_2 at -78°C . Lithium wire (45 mg, 6.77 mmol, cut into small pieces and flattened with a hammer) was then added to ethylamine with magnetic stirring over a period of 10 min. When virtually all of the lithium had dissolved (ca. 20 min), a solution of the steroidal phosphorodiamidate (0.125 g, 0.227 mmol) in 5 mL of dry THF was added to the dark blue solution dropwise through a syringe over a period of 2 min and then the dry ice/2-propanol bath was replaced with an ice-water bath, and the solution was allowed to warm to 0°C . After 60 min at 0°C , water (10 mL) was added, and the reaction mixture was allowed to warm to rt and was kept under continued stirring until most of the ethylamine had evaporated. The remaining aqueous solution was extracted with ethyl acetate (3×35 mL), and the combined organic solutions were washed with brine (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate, gradient elution) provided exclusively the (*Z*)-allylic alcohol **9**^{3a,d,6} as a crystalline white solid: mp 144–146 $^\circ\text{C}$ (lit.¹ oil) (74 mg, 81% from the 20*R*-isomer; 68 mg, 75% from the 20*S*-isomer; and 70 mg, 77% from a 3:1 mixture of 20*R* and 20*S* stereoisomers).

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1,6- and 1,8-Addition Reactions of Organocuprates to Michael Acceptors: NMR-Spectroscopic Observation of the Intermediates and Conclusions about the Reaction Mechanism

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The 1,4-addition of organocuprates to enones and enoates is one of the most important C–C bond-forming processes in organic chemistry.¹ This is due to the usually very high reactivity which allows broad applications of this reaction; furthermore, the importance of this process is enhanced by the use of diastereoselective² as well as en-

antioselective variants³ (using cuprates with chiral ligands). In contrast to the large number of applications of addition reactions of organocuprates, the understanding of the reaction mechanisms is poor; the knowledge of the mechanistic picture is prerequisite, however, for the fine-tuning of a reaction, e.g., for choosing chiral ligands suitable for enantioselective addition reactions.

The mechanism of the 1,4-addition reaction of cuprates to enones and enoates has been investigated using NMR spectroscopy.⁴ It was found that at low temperature attack of the cuprate at the C–C double bond of the Michael acceptor **1** gives rise to the formation of the π -complex **2** which is characterized by the bond between a copper atom and the π -system of the double bond and the interaction of a lithium atom with the carbonyl oxygen atom.⁵ Upon warming, the spectra of the lithium enolate **5** were obtained; intermediates formed during the transformation of **2** to **5** could not be detected by NMR spectroscopy. It has been postulated that this transformation proceeds via organocopper compound **3**; herein, the copper atom has the unstable oxidation state +3, and rapid reductive elimination of RCu should give the enolate **5**.⁴ This mechanism has been challenged by Berlan et al. who proposed the formation of species **4** by 1,2-addition of the cuprate across the C–C double bond; reductive elimination of RCu should again yield enolate **5**.⁶ In both cases it is assumed that the formation of the enolate **5** occurs by *intramolecular* addition of the cuprate bound in the π -complex;⁷ this assumption is also the basis for the mechanistic rationalizations of diastereoselective² and enantioselective³ cuprate additions. In this paper, it is shown that the 1,6- and 1,8-additions of organocuprates to Michael acceptors are also occurring via π -complexes of type **2**; in these cases, the formation of the addition products might proceed by *intermolecular* attack of a second cuprate at these π -complexes.

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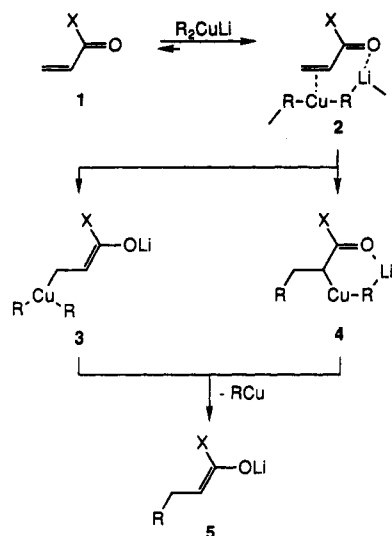
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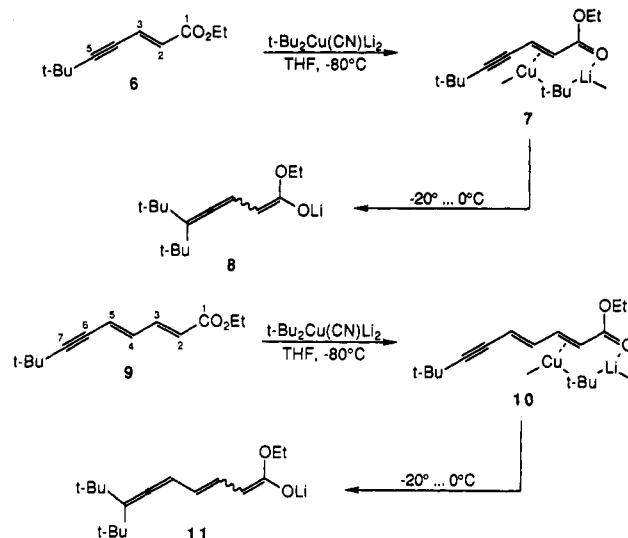
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The 1,6-addition of cuprates to 2-en-4-ynoates⁸ and the 1,8-addition to 2,4-dien-6-ynoates⁹ allow a versatile access to allenyl enolates with complex substitution patterns. From the mechanistic point of view it seems interesting whether in analogy to the 1,4-addition a π -complex of type 2 is formed or whether a different kind of interaction between the Michael acceptor and the cuprate occurs. A hint is obtained from semiempirical MNDO calculations: the LUMO coefficients of a 2-en-4-ynoate are considerably larger at the C-C double bond than at the triple bond;¹⁰ therefore, a soft nucleophile like a cuprate should preferably attack at the double bond.^{11,12} In order to examine this prediction by NMR spectroscopy, a suitable combination of cuprate, Michael acceptor, and solvent had to be found. With diethyl ether as solvent the 1,6-addition of cuprates to acceptor-substituted enynes occurs so rapidly that it is impossible to detect the intermediates of the reaction by NMR spectroscopy. In contrast, no reaction between lithium dimethylcuprate ($\text{Me}_2\text{CuLi}\cdot\text{LiI}$) and 2-en-4-ynoates takes place in tetrahydrofuran, and the NMR spectra show the unchanged set of signals for the Michael acceptor, i.e., no π -complex is formed. If lithium di-*tert*-butylcyanocuprate ($t\text{-Bu}_2\text{Cu}(\text{CN})\text{Li}_2$) in THF is used, however, the reaction is so slow that the intermediates can be observed by NMR spectroscopy.

If the enynoate 6 is added to a cold (-80°C) solution of $t\text{-Bu}_2\text{Cu}(\text{CN})\text{Li}_2$ in THF a brilliant orange-red solution is formed, giving the ^{13}C -NMR spectrum shown in Figure 1, 2nd row (cf. Experimental Section). In this spectrum all signals are doubled, a behavior that is very common in NMR spectra of cuprates;^{4,13} a possible reason could be the formation of geometric isomers of dimeric or of larger



complexes.¹³⁻¹⁵ The coordination of a copper atom with the π -system of the C-C double bond of 6 causes strong high-field shifts for the resonances of this bond (C-2: $\Delta\delta = -80.2/-80.9$ ppm, C-3: $\Delta\delta = -64.4/-65.4$ ppm); the assignment of the resonances for C-2 and C-3 was made by comparison with the chemical shifts of the π -complexes observed in 1,4-addition reactions.^{4d} In contrast, one signal of the triple bond is shifted slightly to high field and the other to low field. Smaller, but also very characteristic is the low-field shift of the carbonyl resonance ($\Delta\delta = +6.9/+8.1$ ppm) which is due to the interaction of the carbonyl oxygen atom with a lithium atom of the cuprate. Thus, in analogy to the 1,4-addition of cuprates to enones and enoates and in accordance with the frontier orbital interactions mentioned above, the π -complex 7⁵ is formed. The spectra of this π -complex remain unchanged up to -20°C ; between -20 and 0°C the 1,6-addition takes place, and the solution becomes virtually colorless. The ^{13}C -NMR spectrum (Figure 1, row 3) now shows the presence of the allenyl enolate 8¹⁶ with the typical low-field signal for the central carbon atom of the allenyl moiety ($\delta = 201.3$). As in the case of the 1,4-addition of cuprates to enones and enoates no intermediates formed during the reaction of 7 to 8 could be detected by NMR spectroscopy.

The mechanism of the 1,8-addition of cuprates to 2,4-dien-6-ynoates was examined using the same methods. In this case, the MNDO LUMO coefficients of the Michael acceptor do not allow a prediction of the regioselectivity of the cuprate attack since similar values for the two C-C double bonds are obtained.¹⁷ Due to the larger system of multiple bonds of the Michael acceptor, it is not possible to assign all signals in the ^{13}C -NMR spectrum of the π -

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(12) This argument also holds if the complexation of the copper atom is preceded by interaction of a lithium atom with the carbonyl oxygen atom: a model for this situation, protonated methyl 2-penten-4-ynoate, also gives larger LUMO coefficients at the C-C double bond than at the triple bond (+0.64 (C-1), +0.14 (C-2), -0.56 (C-3), 0.00 (C-4), +0.29 (C-5)).¹⁰

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(14) The structure and aggregation state of the cuprate bound in a π -complex cannot be determined by NMR spectroscopy; however, the nonlinear enantioselectivity observed recently by Tanaka et al.^{3m} and Rossiter et al.³ⁿ in 1,4-addition reactions of cuprates with chiral ligands seems to indicate that in π -complexes (as in free cuprates¹) dimeric cuprate clusters are involved.

(15) The doubling of the NMR resonances of cuprates derived from copper(I) iodide has been ascribed to the formation of LiI -complexed and LiI -free cuprate species;^{13c,d} however, it does not seem appropriate to use this explanation for the cyanocuprates used in this work since it is generally accepted that in these reagents the cyanide is bound completely in the cuprate complex.^{1c}

(16) ^{13}C -NMR spectra of the allenyl enolate obtained by 1,6-addition of $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2$ to 3-ethynyl-2-methyl-2-cyclopentenone: Cheng, M.; Hulce, M. *J. Org. Chem.* 1990, 55, 964-975.

(17) LUMO coefficients of methyl 2,4-heptadien-6-ynoate:¹⁰ -0.23 (C-1), -0.46 (C-2), +0.46 (C-3), +0.37 (C-4), -0.48 (C-5), -0.13 (C-6), +0.28 (C-7); LUMO coefficients of protonated methyl 2,4-heptadien-6-ynoate:^{10,12} +0.59 (C-1), +0.10 (C-2), -0.56 (C-3), -0.01 (C-4), +0.40 (C-5), -0.01 (C-6), -0.20 (C-7).

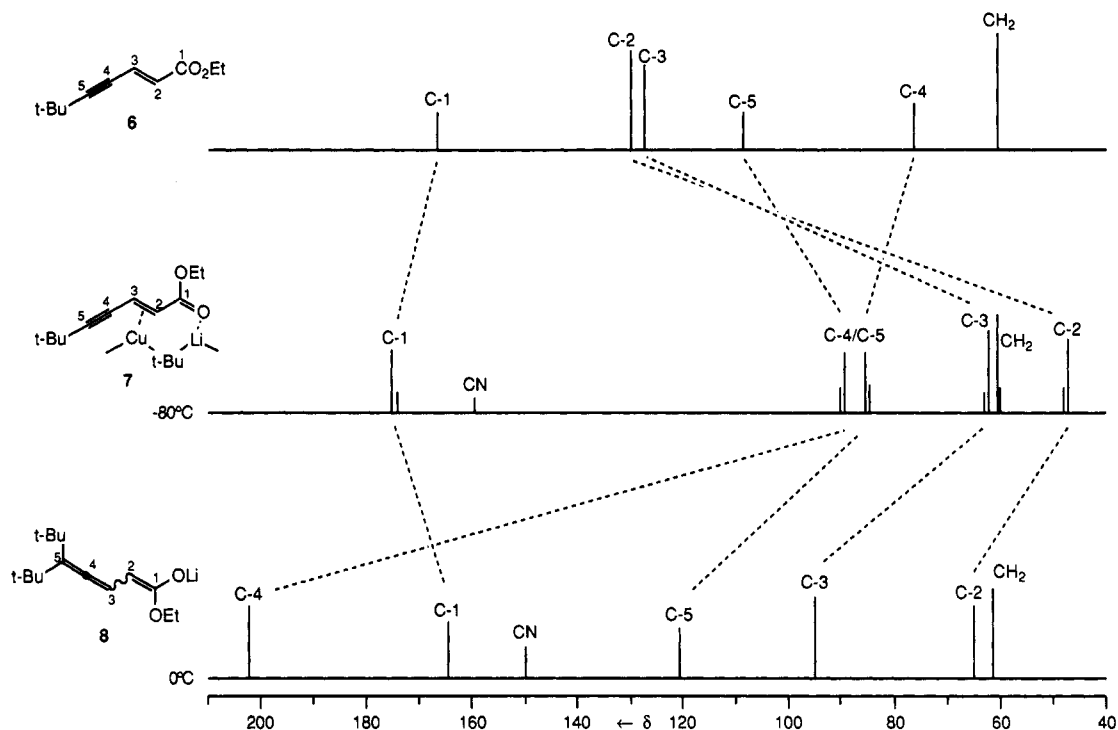


Figure 1. ^{13}C -NMR spectra of enynoate **6** (first row, CDCl_3 as solvent and internal standard ($\delta = 77.05$)), of π -complex **7** (second row, THF as solvent and internal standard ($\delta = 26.5$), -80°C), and of allenyl enolate **8** (third row, THF as solvent and internal standard ($\delta = 26.5$), -20°C).

complex formed by treatment of the dienyne **9** with lithium di-*tert*-butylcuprate in THF at -80°C (cf. Experimental Section); nevertheless, the high-field shifts of the signals for C-2 ($\Delta\delta = -62.2/-62.4$ ppm) and C-3 ($\Delta\delta = -72.6/-73.1$ ppm) as well as the low-field shift of the carbonyl resonance ($\Delta\delta = +5.3/+6.3$ ppm) provide unambiguous proof for the formation of the π -complex 10^5 of the cuprate at the double bond adjacent to the ester group, again existing as two species. The assignment of the resonance of C-3 was confirmed using a dienyne **9** labeled with a deuterium atom at this position; due to the missing intensity-enhancing NOE effect, the signals at $\delta = 70.3/70.8$ are no longer observed. As before, the 1,8-addition takes place upon warming of the solution between -20 and 0°C , giving rise to the formation of the vinylic allenyl enolate **11**; again, it is not possible to detect any intermediates during the formation of **11** from **10** by NMR spectroscopy.

In summary, it is found that the 1,4-, 1,6-, and 1,8-addition of cuprates to Michael acceptors proceed via analogous intermediates, i.e., π -complexes of the cuprate at the double bond adjacent to the carbonyl function. What are the factors that control the regiochemistry of these complexes? Whereas for the 1,4- and 1,6-addition the regioselectivity of the π -complexation is in accordance with frontier orbital interactions between the cuprate and the Michael acceptor, this explanation is not sufficient to account for the result of the 1,8-addition; in this case, according to the LUMO coefficients an attack of the cuprate at the C-4/C-5 double bond should be possible. The fact that the π -complex is formed exclusively at the double bond adjacent to the ester function indicates the importance of the interaction between a lithium atom of the cuprate cluster and the carbonyl oxygen atom. This interaction seems also to be crucial for the formation of the conjugate addition product; this conclusion can be drawn from the results obtained with 2-en-4-ynenitriles as Michael acceptors. These do not undergo 1,6-addition reactions with cuprates,^{8a} though they also form π -com-

plexes of type **7** (see Experimental Section). In these π -complexes the lithium-oxygen interaction is replaced by a lithium-nitrogen interaction, and the latter is obviously not sufficient to activate the Michael acceptor for the formation of the 1,6-addition product.

The fundamental difference between the 1,4-addition on one hand and the 1,6- and 1,8-addition on the other hand is of course that in the first case the sites of π -complexation and of nucleophilic attack are equal whereas in the latter cases they are different. There are two possible explanations for the formation of the addition products **8** and **11** from the π -complexes **7** and **10**: (i) inter- or intramolecular rearrangement of the π -complex to a different intermediate, e.g., a π -complex of the cuprate at the triple bond, and (ii) intermolecular attack of a second cuprate at the triple bond of the π -complex with simultaneous rearrangement of the π -system and decomplexation of the first π -bonded cuprate. An experimental decision between these two mechanisms has to await kinetic studies of the 1,6- and 1,8-addition reactions.⁷ For two reasons the latter pathway, i.e., the intermolecular reaction of the π -complex with a second cuprate, appears to be more likely, however. Firstly, in view of the importance of the lithium-oxygen interaction for the feasibility of the conjugate addition reaction (see above), it seems unlikely that the formation of the 1,6- and 1,8-addition products takes place under removal of this interaction. Secondly, it has been found experimentally that factors which are impeding the formation of π -complex **7**, i.e., steric congestion at the C-C double bond of 2-en-4-ynoates, also hamper the formation of the 1,6-addition product.^{8b} Thus, it seems reasonable to include the possibility of an intermolecular pathway in the planning and interpretation of conjugate cuprate addition reactions.

Experimental Section

General Information. See ref 8a.

Preparation of the NMR Samples. In a two-necked round-bottom flask with attached 5-mm NMR tube a suspension

of 89.6 mg (1.0 mmol) of copper(I) cyanide in 2 mL of THF was cooled to -30°C , and 1.2 mL of *t*-BuLi (2.0 mmol, 1.7 M solution in pentane) was added dropwise. The mixture was stirred at -30°C for 30 min, then cooled to -80°C , and a solution of 0.9 mmol of the Michael acceptor (6: 162.2 mg; 9: 185.7 mg) in 1 mL of THF was added dropwise. The red solution was stirred for 15 min at -80°C and then ca. 3 mL was removed with a syringe, followed by addition of 0.2 mL of THF- d_6 . The remaining solution was degassed by three freeze-pump-thaw cycles; during thawing the temperature was kept below -80°C . The solution was transferred into the precooled (-80°C) NMR tube which was sealed off under vacuum. By the same procedure, a NMR sample of the π -complex of 6,6-dimethyl-2-hepten-4-ynenitrile (119.9 mg, 0.9 mmol) with $\text{Me}_2\text{CuLi}\cdot\text{LiI}$ (from 190.4 mg = 1.0 mmol copper(I) iodide and 1.3 mL (2.0 mmol) of MeLi (1.5 M solution in diethyl ether)) was prepared with diethyl ether as solvent.

^{13}C -NMR data, obtained with a Bruker WM-300 spectrometer at 75.5 MHz.

6 (CDCl_3 as solvent and internal standard ($\delta = 77.05$)): δ 14.2 (+, $\text{CO}_2\text{CH}_2\text{CH}_3$), 28.3 (x, C-6), 30.6 (+, $\text{C}(\text{CH}_3)_3$), 60.5 (-, CO_2CH_2), 76.5 (x, C-4), 108.4 (x, C-5), 126.1 (x, C-3), 129.1 (x, C-2), 166.1 (x, C-1).

7 (THF as solvent and internal standard ($\delta = 26.5$), -80°C): δ 48.2/48.9 (+, C-2), 59.3/59.6 (-, CO_2CH_2), 60.7/61.7 (+, C-3), 84.7/84.9 (x, C-4/C-5), 89.3/89.5 (x, C-4/C-5), 159.2 (x, CN), 173.0/174.2 (x, C-1).

8 (THF as solvent and internal standard ($\delta = 26.5$), -20°C): δ 61.7 (-, CO_2CH_2), 64.1 (+, C-2), 94.9 (+, C-3), 120.4 (x, C-5), 149.5 (x, CN), 164.2 (x, C-1), 201.3 (x, C-4).

9 (CDCl_3 as solvent and internal standard ($\delta = 77.05$)): δ 14.3 (+, $\text{CO}_2\text{CH}_2\text{CH}_3$), 28.3 (x, C-8), 30.8 (+, $\text{C}(\text{CH}_3)_3$), 60.4 (-, CO_2CH_2), 78.0 (x, C-6), 105.9 (x, C-7), 120.4 (+, C-5), 122.0 (+, C-2), 137.4 (+, C-4), 143.4 (+, C-3), 166.7 (x, C-1).

10 (THF as solvent and internal standard ($\delta = 26.5$), -80°C): δ 58.6/59.6 (-, CO_2CH_2), 59.6/59.8 (+, C-2), 70.3/70.8 (+, C-3), 81.2/81.3 (x, C-6), 93.9/94.0 (x, C-7), 172.0/173.0 (x, C-1).

11 (THF as solvent and internal standard ($\delta = 26.5$), -20°C): δ 59.8/60.1 (-, CO_2CH_2), 78.5 (+, C-2), 95.1 (+, C-3/C-5), 103.4 (+, C-3/C-5), 116.7 (x, C-7), 129.5 (+, C-4), 171.8/173.0 (x, C-1), 204.1 (x, C-6).

6,6-Dimethyl-2-hepten-4-ynenitrile (CDCl_3 as solvent and internal standard ($\delta = 77.05$)): δ 28.4 (x, C-6), 30.3 (+, $\text{C}(\text{CH}_3)_3$), 75.9 (x, C-4), 107.2 (+, C-2), 111.0 (x, C-5), 117.2 (x, C-1), 131.9 (+, C-3).

π -Complex of 6,6-dimethyl-2-hepten-4-ynenitrile with $\text{Me}_2\text{CuLi}\cdot\text{LiI}$ (Et_2O as solvent and internal standard ($\delta = 14.6$), -50°C): δ 25.6 (+, C-2), 28.5 (x, C-6), 31.8 (+, $\text{C}(\text{CH}_3)_3$), 40.5 (+, C-3), 82.6 (x, C-4/C-5), 89.3 (x, C-4/C-5), 128.7 (x, C-1).

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Abnormal Weiss-Cook Condensation of *cis*-6-Cyclodecene-1,2-dione with Dimethyl 1,3-Acetonedicarboxylate. The Consequences of Ring Strain Release

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The 2-fold condensation of dimethyl 1,3-acetonedicarboxylate (2) with α -dicarbonyl compounds, the Cook-Weiss reaction, has served very well as a vehicle for the rapid assembly of heavily functionalized diquinane frameworks under relatively mild conditions.² The ex-

(1) Author to whom inquiries concerning the X-ray crystallographic analysis should be addressed.

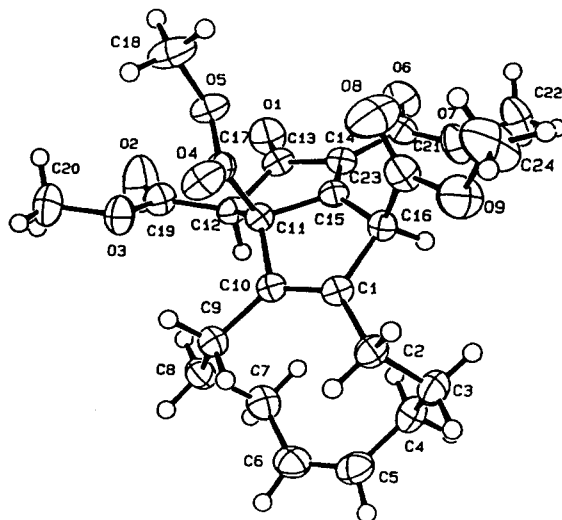
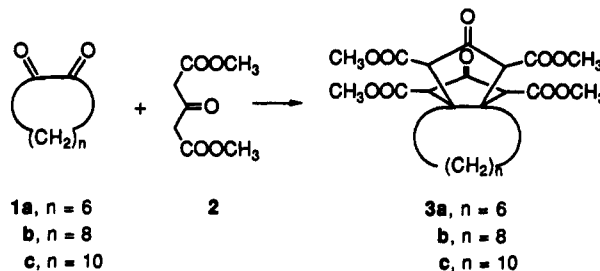


Figure 1. ORTEP diagram of 8. The non-hydrogen atoms are represented by 50% probability thermal ellipsoids. The hydrogen atoms are drawn with an artificial radius.

tensive carbon-carbon bond construction that materializes has been formulated in terms of a sequence of aldol, Michael, and β -elimination reactions.³ Aliphatic 1,2-dicarbonyl compounds enter effectively into this condensation; alicyclic analogues have proven more variable in their response. Thus, while [*n*.3.3]propellanes 3a and 3c are formed in good yield (>80%) under modestly acidic or basic conditions,⁴ cyclodecane-1,2-dione (1b) has been reported to give 3b inefficiently (30%) and only when strong basic catalysis is applied.⁵



One might question whether the last observation is an indicator of a possible interrelationship between ring size and relative ease of cyclopentannulation. Certainly, the value of *n* is crucial to smooth operation of the Cook-Weiss process.

Our laboratory has been engaged in the synthesis of 1,5-biscyclooctatetraenophanes.⁶ For the [2₂] derivative, early use is made of the conversion of 4 to 5 at pH 5.6.⁷ The yield of this conversion peaks at 86%. In a more recent extension of this chemistry, *cis*-6-cyclodecene-1,2-dione (6)⁸ failed to undergo detectable cyclocondensation

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