temperature, 4.30 g (9.5 mmol) of crown ether alcohol **22** dissolved in 50 mL of THF was added dropwise during 1 h. The reaction mixture was stirred for 1 h and 3.10 g (12.3 mmol) of 2-bromodecanoic acid dissolved in 50 mL of THF was added dropwise over a 3-h period. The reaction mixture was stirred for 62 h at room temperature and the THF was evaporated in vacuo. Water was carefully added to the residue to destroy unconsumed NaH and then more water (200 mL total) was added. The resulting alkaline aqueous solution was acidified to pH 2 with 6 N HCl and extracted with CH_2Cl_2 (4 × 100 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to afford 7.0 g of brown oil. Purification by column chromatography on silica gel eluting with acetone as eluent to remove impurities and then with MeOH provided 2.6 g of crude product as a yellow solid which was contaminated with 2-bromodecanoic acid. The yellow solid was dissolved in 100 mL of $CHCl_3$ and washed with 0.02 N NaOH (4 × 100 mL) and then with 100 mL of 0.1 N HCl. The $CHCl_3$ layer was dried over $MgSO_4$ and evaporated in vacuo to afford 2.30 g (38%) of **9** as a very viscous oil: IR (neat) 3450–3000 (COOH), 1745 and 1715 (sh) (C=O); ^1H NMR ($CDCl_3$) 0.6–2.1 (m, 17), 3.5–4.6 (m, 22), 6.90 (s, 8), 9.45 (br s, 1). Anal. Calcd for $C_{33}H_{48}O_{10}$: C, 65.54; H, 8.00. Found: C, 65.55; H, 7.89.

2-(*sym*-Dicyclohexano-16-crown-5-oxy)decanoic Acid (14). NaH (8.0 g, 167mmol) was washed with *n*-pentane under nitrogen to remove the protecting mineral oil. THF (80 mL) was added and after the mixture had been stirred for 0.5 h at room temperature, 12.0 g (33.5 mmol) of crown ether alcohol **23** dissolved in 50 mL of THF was added dropwise during 1.5 h. The reaction mixture was stirred for 1 h and 12.04 g (47.9 mmol) of 2-bromodecanoic acid dissolved in 100 mL of THF was added during a 2 h period. After the reaction mixture had been stirred for 10 h, a second portion of 2-bromodecanoic acid (3.1 g, 12.3 mmol) was added and stirring was continued for another 15 h. Water was carefully added to destroy the unconsumed NaH and the THF was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 and acidified with 4 M HCl. The separated CH_2Cl_2 layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was loaded onto a column of basic alumina (Brockman Activity 1). Unreacted 2-bromodecanoic acid and **23** were removed by elution with Et_2O and THF, respectively. Compound **14** was eluted with MeOH which contained 3% concentrated HCl (by volume). The methanolic eluent was evaporated in vacuo and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated to yield 7.20 g (41%) of **14** as an oil: IR (neat) 3500–3000 (COOH), 1753 (C=O), 1107 (COC); ^1H NMR ($CDCl_3$), 0.7–2.8 (m, 33), 3.1–4.9 (m, 18), 8.2 (br s, 1). Anal. Calcd for $C_{29}H_{52}O_8$: C, 65.88; H, 9.91. Found: C, 65.73; H, 9.88.

Registry No. **7**, 87598-60-5; **8**, 87598-61-6; **9**, 87598-62-7; **10**, 87598-63-8; **11**, 87598-64-9; **12**, 87598-65-0; **13**, 87598-66-1; **14**, 87598-67-2; **15**, 42397-72-8; **17**, 68822-97-9; **18**, 68822-98-0; **18** tetrahydropyranyl derivative, 87598-68-3; **19**, 78328-81-1; **20**, 78328-78-6; **21**, 78328-79-7; **22**, 87655-07-0; **23**, 87598-69-4; **24**, 81633-82-1; **25**, 87598-70-7; **26**, 87598-71-8; **27**, 87598-72-9; **28**, 87598-73-0; **29**, 87598-74-1; **31**, 37860-51-8; catechol, 120-80-9; 1,3-dibromopropane, 109-64-8; 1,2-bis(2-chloroethoxy)ethane, 112-26-5; tetraethyl glycol, 112-60-7; catechol mono-2-tetrahydropyranyl ether, 21645-25-0; cesium hydroxide, 21351-79-1; epichlorohydrin, 106-89-8; bromoacetic acid, 79-08-3; methyl bromoacetate, 96-32-2; 2-bromodecanoic acid, 2623-95-2; 1-bromobutane, 109-65-9; 1-bromooctane, 111-83-1; 1-bromotetradecane, 112-71-0.

Inverse Electron Demand Diels–Alder Reactions of 4,6-Dimethyl-2-oxo-2*H*-pyran-5-carboxylic Acid Esters and Morpholino Enamines: Regiospecific Preparation of 3- or 4-Substituted-2,6-dimethylbenzoates[1]

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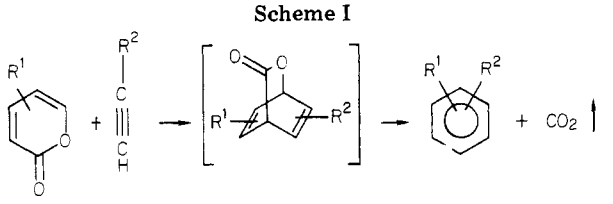
Received April 20, 1983

Previously, α-pyrones have been used as dienes in cycloaddition reactions with enamines to form adducts that, upon elimination of carbon dioxide via a cycloreversion reaction and concomitant aromatization through amine elimination, provided substituted aryl derivatives; however, the regioselectivity of this reaction was not determined. We report that the Diels–Alder reaction of methyl or ethyl 4,6-dimethyl-2-oxo-2*H*-pyran-5-carboxylate with morpholino enamines is regiospecific. By proper choice of enamine either of the isomeric 2,6-dimethylbenzoates may be obtained as a single product. In several cases a single regioisomeric dihydrobenzoate, which results from elimination of carbon dioxide from the initial cycloadduct, was isolated and characterized.

Introduction

The discovery in these laboratories that pyrethroid esters derived from cyclopropane and closely related carboxylic acids coupled with substituted biphenyl-3-methanols were highly effective insecticides[2] prompted us to investigate regiospecific synthesis routes to highly substituted benzyl alcohols, including biphenylmethanols, that would be practical in terms of allowing the preparation of the alcohols in sufficient yield and purity to make the derived esters commercially attractive.

Scheme I



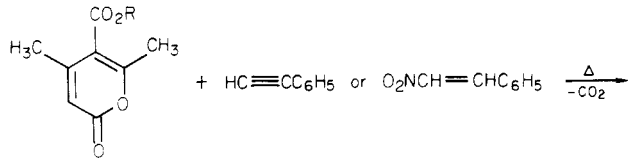
Conceptually, we were intrigued by earlier investigations of α-pyrones being used as dienes in cycloaddition reactions with alkynes[3] to form adducts which, upon elimina-

(1) Presented in part at the 185th National Meeting of the American Chemical Society, Seattle, WA, March, 1983; American Chemical Society: Washington, D.C.

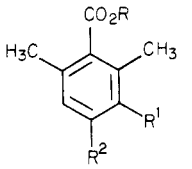
(2) (a) Plummer, E. L. U.S. Patent 4 130 657 to FMC Corporation, Dec 19, 1978. (b) Plummer, E. L. U.S. Patent 4 214 004 to FMC Corporation, July 22, 1980. (c) Engel, J. F. U.S. Patent 4 238 505 to FMC Corporation, Dec 9, 1980. (d) Plummer, E. L.; Pincus, D. S. *J. Agric. Food Chem.* **1981**, *19*, 1118. (e) Plummer, E. L. U.S. Patent 4 329 518 to FMC Corporation, May 11, 1982. (f) Engel, J. F.; Plummer, E. L.; Stewart, R. R.; Van Saun, W. A.; Montogomery, R. E.; Cruickshank, P. A.; Harnish, W. N.; Nethery, A. A. and Crosby, G. A. In "IUPAC Pesticide Chemistry"; J. Miyamoto et al., Eds.; Pergamon Press: New York, 1983; pp 101–106. (g) Cardis, A. B. U.S. Patent 4 375 476 to FMC Corporation, March 1, 1983.

0022-3263/83/1948-4869$01.50/0

Scheme II



2a, R = C_2H_5
b, R = CH_3

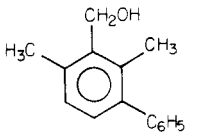


3a, $R^1 = C_6H_5$; $R^2 = H$
b, $R^1 = H$; $R^2 = C_6H_5$

tion of carbon dioxide via a cycloreversion reaction and concomitant aromatization, provided aryl derivatives (Scheme I).

Results and Discussion

Since an early target in our program was 2,4-dimethyl-[1,1'-biphenyl]-3-methanol (1), the readily available



1

methyl or ethyl[4] ester of 4,6-dimethyl-2-oxo-2*H*-pyran-5-carboxylate (2) afforded both the correct substitution pattern in the diene, provided regioselectivity could be attained, and a convenient starting material for our initial investigations. Reduction of the ester moiety in the derived benzoates with lithium aluminum hydride would provide the desired alcohol.

Scheme II summarizes the results obtained by combining the pyrone **2a** with an equal molar amount of phenylacetylene and heating at the boiling point of the mixture. Although a certain degree of regioselectivity was observed, as determined by spectral analysis (NMR), the undesired regioisomeric product predominated (4:1 ratio of **3b**:**3a**). These results are in agreement with the work of Stille and co-workers[5] who observed a similar distribution of regioisomers in the reaction of phenylacetylene with 4,6-diphenyl-2-pyrone.

Recently, Danishefsky and co-workers have shown that methyl β-nitroacrylate behaves as a methyl propiolate equivalent.[6] Since the nitro group controls the regiochemistry of the cycloaddition and is subsequently eliminated, a net inversion of regiochemistry is realized. With this in mind, we examined the cycloaddition reaction of pyrone **2a** with β-nitrostyrene; however, a mixture of **3a** and **3b** was obtained in a ratio similar to that already observed with phenylacetylene.

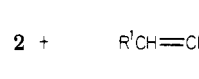
Because pyrones **2** are electron-deficient dienes, it was thought that a Diels-Alder reaction with inverse electron demand would be more facile.[7] The reaction of α-pyrones with enamines was particularly intriguing since control of the regiochemistry by the proper choice of enamine should be possible (Scheme III). Indeed, the reaction of α-pyrones with electron-rich olefins, such as ketene acetals,[8,9] ynamines,[10] and enamines,[11] has been investigated to a limited extent. Although the reaction of enamines and α-pyrones has been briefly investigated, the regiochemistry of the reaction has not been examined.

We report that the Diels-Alder reaction of pyrones **2** with enamines **4** is regiospecific and by the proper choice of enamine, only a single isomeric benzoate is obtained. The regiocontrol is illustrated by the reaction of pyrone **2a** with the morpholino enamines of phenylacetaldehyde (**4a**) or acetophenone (**4b**) to give **3a** and **3b**, respectively. That only a single isomer is formed is clear from the NMR spectra of the crude reaction mixtures.

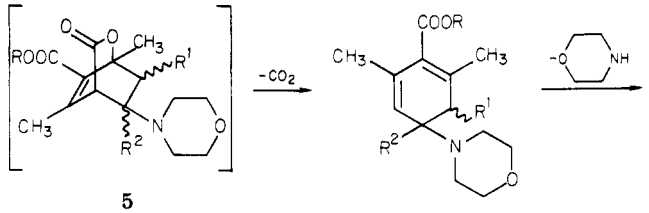
Since it has been reported that pyrrolidine enamines react with 1,2,4-triazine in higher yields than the corresponding morpholine enamine,[12] the reaction of pyrone **2a** with the pyrrolidine enamine of acetophenone was examined. This reaction, however, gave mostly a tarry residue with very little of the desired product.

The morpholino enamines of cyclopentanone (**4c**) and cyclohexanone (**4d**) were also investigated. The reaction conditions of morpholinocyclopentene (**4c**) and pyrone **2b**

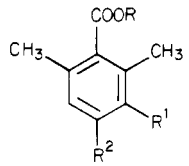
Scheme III



4a, $R^1 = C_6H_5$; $R^2 = H$
b, $R^1 = H$; $R^2 = C_6H_5$
c, $R^1, R^2 = (CH_2)_3$
d, $R^1, R^2 = (CH_2)_4$
e, $R^1 = CH_3$; $R^2 = H$
f, $R^1 = (CH_3)_2CH$; $R^2 = H$



5 6



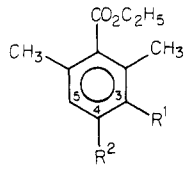
3a, R = C_2H_5; $R^1 = C_6H_5$; $R^2 = H$
b, R = C_2H_5; $R^1 = H$; $R^2 = C_6H_5$
c, R = CH_3; $R^1, R^2 = (CH_2)_3$
d, R = CH_3; $R^1, R^2 = (CH_2)_4$
e, R = C_2H_5; $R^1 = CH_3$; $R^2 = H$
f, R = C_2H_5; $R^1 = (CH_3)_2CH$; $R^2 = H$

(3) Salomon, R. G.; Burns, J. R.; Dominic, W. J. *J. Org. Chem.* **1976**, *41*, 2918.
(4) Ethyl isodehydracetate is prepared by the acid-catalysed condensation/cyclization of ethyl acetoacetate ("Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 549) or may be purchased from Aldrich Chemical Co.
(5) Reed, J. A.; Shilling, C. L., Jr.; Tarvin, R. C.; Rettig, T. A.; Stille, J. K. *J. Org. Chem.* **1969**, *34*, 2188.
(6) Danishefsky, S.; Prisbylla, M. P.; Hiner, S. *J. Am. Chem. Soc.* **1978**, *100*, 2918.
(7) Shusherina, N. P. *Russ. Chem. Rev. (Engl. Transl.)* **1974**, *43*, 851.
(8) Boger, D.; Mullican, M. D. *Tetrahedron Lett.* **1982**, *23*, 4551, 4555, and references cited therein. Boger, D.; Patel, M.; Mulligan, M. D. *Ibid.* **1982**, *23*, 4559.
(9) Behringer, H.; Heckmaier, P. *Chem. Ber.* **1969**, *102*, 2835.
(10) Bryson, T. A.; Donelson, D. M. *J. Org. Chem.* **1977**, *42*, 2930. Ireland, R. E.; McGarvey, G. J.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B.; Thaisrivongs, S. *J. Am. Chem. Soc.* **1980**, *102*, 6178.
(11) Märkl, G.; Fuchs, R. *Tetrahedron Lett.* **1972**, 4695.
(12) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1981**, *46*, 2179.

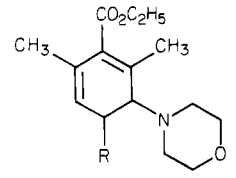
were somewhat milder (140 °C) than the reaction of morpholinocyclohexene (**4d**) and **2b** (200 °C).[13]

The reaction of pyrone **2a** with the more reactive enamines **4e** and **4f** was next examined. Upon heating a mixture of pyrone **2a** and enamine **4e** at reflux in toluene, carbon dioxide was evolved. However, upon solvent removal and examination of the residue by ^{1}H NMR spectroscopy, it became evident that the desired benzoate **3e** was not present. Instead, the major component appeared to still contain morpholine, which suggested the possibility of the dihydrobenzoate **6e**. In fact, dihydrobenzoate **6e** could be isolated in 35% yield from the crude reaction mixture by a sequence involving aqueous acid extraction, basification, ether extraction, and finally silica gel column chromatography. Similarly, dihydrobenzoate **6f** was obtained in 50% yield from the reaction of pyrone **2a** and enamine **4f** in refluxing toluene. To the best of our knowledge, **6e** and **6f** are the first examples of dihydrobenzoates isolated from the cycloaddition reaction of pyrones and enamines (or electron-rich olefins).[14]

It should be noted that there was no sign of a regioisomeric dihydrobenzoate in either case upon examination of both the crude reaction mixture or the aqueous acid soluble fraction by ^{1}H NMR spectroscopy. The structures of dihydrobenzoates **6e** and **6f** were confirmed by a combination of chemical and spectral methods. Both **6e** and **6f** afforded the benzoates **3e** and **3f**, respectively, upon thermolysis.



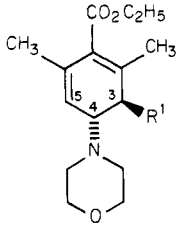
3e, $R^1 = CH_3$; $R^2 = H$
f, $R^1 = (CH_3)_2CH$; $R^2 = H$
g, $R^1 = H$; $R^2 = CH_3$
h, $R^1 = H$; $R^2 = (CH_3)_2CH$



9g, R = CH_3
h, R = $(CH_3)_2CH$

The appearance of AB quartets for the aromatic protons H_4 and H_5 in the ^{1}H NMR spectra of **3e** and **3f** rules out the regioisomeric, symmetrically substituted benzoates **3g** and **3h**, which would be expected to show only a singlet for the aromatic protons H_3 and H_5. These results eliminate the regioisomeric dihydrobenzoates **9g** and **9h** as the dihydrobenzoates obtained from these cycloadditions.

The ^{13}C NMR spectra of **6e** and **6f** exhibit olefinic resonances at δ 116.4 (d), 127.2 (s), 131.4 (s), and 141.7 (s) for **6e** and at δ 118.8 (d), 129.3 (s), 131.3 (s), and 137.8 (s) for **6f**. The ^{1}H NMR spectra of **6e** and **6f** are also quite



6e, $R^1 = CH_3$
f, $R^1 = (CH_3)_2CH$

informative. Both compounds exhibit broad olefinic (H_5) doublets at ca. δ 5.35 and broad doublets (H_4) at δ 2.86 (for **6e**) and δ 3.08 (for **6f**) with $J_{4,5}$ = 6.0 Hz. Irradiation of the H_5 doublet at δ 5.35 caused the H_4 doublets at δ 2.86 and 3.08 to collapse to broad singlets. This implies that there is no appreciable coupling between H_3 and H_4 (i.e., $J_{3,4} < 1$ Hz). Considering the *E*-configuration of the enamine starting materials **4e** and **4f**,[15] it appears reasonable to assume that the dihydrobenzoates **6e** and **6f** have trans stereochemistry. Examination of Dreiding models of **6e** and **6f** reveals that if both R^1 and the morpholine substituents are quasiequatorial, then the H_4C-CH_3 dihedral angle approaches 180°. A large $J_{3,4}$ coupling constant would be anticipated for a dihedral angle close to 180°,[16] which is obviously not the case (i.e., $J_{3,4} < 1$ Hz). Additionally, the H_5C-CH_4 dihedral angle approaches 90° when both R^1 and the morpholine substituent are quasiequatorial. A neglible coupling constant would be expected for such a dihedral angle. This is not consistent with the observed $J_{4,5}$ coupling constants (i.e., $J_{4,5}$ = 6.0 Hz). Consequently, the observed ^{1}H NMR spectral data for **6e** and **6f** appear to be most consistent for a trans configuration with an extensive population of the conformation in which the R^1 and morpholine substituents are quasiaxial.[17]

In conclusion, we have demonstrated that the Diels–Alder reaction of the methyl or ethyl ester of 4,6-dimethyl-2-oxo-2*H*-pyran-5-carboxylate with enamines is regiospecific and by the proper choice of enamine only a single isomeric benzoate is obtained. An extension of this study to other pyrones is the subject of further investigation.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer Model 735B infrared spectrophotometer. ^{1}H NMR spectra were obtained on a Varian T-60, FT-80A, or XL-100 spectrometer. ^{13}C NMR spectra were recorded on a Varian FT-80A spectrometer operating at 20.0 MHz. Microanalyses were performed at FMC Corporation, Princeton, NJ. Preparative chromatographies were performed on EM silica gel 60 (70–230 mesh) and EM neutral alumina, E. Merck Co.

Cycloaddition Reaction of 4-(2-Phenylethenyl)morpholine (4a) and Ethyl 4,6-Dimethyl-2-oxo-2*H*-pyran-5-carboxylate (2a). Phenylacetaldehyde (31.2 g, 26.0 mmol) and morpholine (23.0 g, 26.0 mmol) were combined under a dry nitrogen atmosphere in dry toluene (350 mL). The mixture was heated under reflux and water was removed with a Dean–Stark trap to provide a solution of 4-(2-phenylethenyl)morpholine (**4a**).[18] Ethyl 4,6-dimethyl-2-oxo-2*H*-pyran-5-carboxylate (49.1 g, 25.0 mmol) was added to the enamine solution over a period of 45 min and then the toluene was removed by distillation to leave a dark brown residue. During the distillation the residue was heated to 200 °C. Chromatography of this material over silica gel eluting with 1:1 methylene chloride–heptane afforded a fraction (35.6 g) that was further purified by vacuum distillation. The fractions collected between 110 and 141 °C (0.10–0.15 mm Hg) were homogeneous and were combined to provide ethyl 2,4-dimethyl-[1,1′-biphenyl]-3-carboxylate (**3a**), 28.3 g (45%), as a yellow oil: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.37 (t, *J* = 7.0 Hz, 3 H), 2.20 (s, 3 H), 2.33 (s, 3 H), 4.37 (q, *J* = 7.0 Hz, 2 H), 6.87–7.40 (br m, 7

(13) In addition to the expected product **3d** the corresponding morpholino amide **8**, which was independently synthesized from the carboxylic acid **7**, was obtained.

(14) It should be noted that Behringer and Heckmaier have reported the isolation of the primary cycloadducts from the reaction of coumalates and ketene acetals.[9]

(15) Sauer, J.; Prahl, H. *Chem. Ber.* **1969**, *102*, 1917.

(16) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Oxford, 1969; p 288 and references cited therein.

(17) The two cis conformations can be likewise ruled out upon examination of Dreiding models and consideration of the observed $J_{3,4}$ and $J_{4,5}$ coupling constants. The preferred conformation can be rationalized by relief of $A^{(1,2)}$ strain of CH_3/R^1 and by relief of gauche morpholine/R^1 interactions. See: Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

(18) Schreiber, W. L.; Vock, M.; Hall, J. B.; Shuster, E. J.; Quin, A. D. U.S. Patent 3 922 237 to International Flavors and Fragances Inc., Nov 25, 1975.

H). Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.53; H, 7.04.

This ester was reduced with lithium aluminum hydride (ether) to provide 2,4-dimethyl-[1,1'-biphenyl]-3-methanol (1): mp 77-79°C, ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.78 (s, 1H); 2.25 (s, 3H); 2.40 (s, 3H); 4.76 (s, 2H); 7.00–7.50 (m, 7H). Anal. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.64; H, 7.54.

Cycloaddition Reaction of 4-(1-Phenylethenyl)morpholine (4b) and Ethyl 4,6-Dimethyl-2-oxo-2*H*-pyran-5-carboxylate (2a). A mixture of ethyl 4,6-dimethyl-2-oxo-2*H*-pyran-5-carboxylate (4.73 g, 25 mmol) and 4-(1-phenylethenyl)morpholine (4.90 g, 25 mmol) was heated under nitrogen. The evolution of carbon dioxide began slowly at 110 °C. The temperature was raised to ca. 145 °C and heated for 6 h. The cooled reaction mixture was dissolved in ether (100 mL) and washed successively with 10% aqueous hydrochloric acid (2 × 50 mL) and brine (50 mL). The dried (magnesium sulfate) ethereal layer was evaporated at reduced pressure to give a brown oil. Kugelrohr distillation of the oil gave 3.5 g (55%) of product which crystallized on standing. Recrystallization from petroleum ether gave 3.2 g (50%) of pure product (**3b**): mp 40–42 °C, IR (melt) 2980, 1730, 1280, 1120, 1080, 770, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.37 (t, J = 7.3 Hz, 3 H), 2.40 (s, 6 H), 4.43 (q, J = 7.3 Hz, 2 H), 7.3–7.7 (m, 7 H). Anal. Calcd for $C_{17}H_{12}O_2$: C, 80.28; H, 7.13. Found: C, 80.50; H, 7.11.

Cycloaddition Reaction of 4-(1-Cyclopentenyl)morpholine (4c) and Methyl 4,6-Dimethyl-2-oxo-2*H*-pyran-5-carboxylate (2b). A mixture of 4-(1-cyclopentenyl)morpholine (8.4 g, 55 mmol) and methyl 4,6-dimethyl-2-oxo-2*H*-pyran-5-carboxylate (9.1 g, 50 mmol) was heated under nitrogen. The evolution of carbon dioxide began at ca. 130 °C. The reaction mixture was heated at 150 °C for 1 h. The cooled reaction mixture was dissolved in ether (200 mL) was washed successively with 10% aqueous hydrochloric acid (100 mL) and brine (100 mL). The dried (magnesium sulfate) ethereal layer was evaporated at reduced pressure to give an oil which crystallized on standing. Recrystallization (petroleum ether) yielded 6.4 g (63%) of pure product (**3c**): mp 39–41 °C; IR (melt) 2940, 1720, 1440, 1260, 1140, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 2.00 (pent, J = 7 Hz, 2 H), 2.20 (s, 3 H), 2.23 (s, 3 H), 2.77 (br t, J = 7 Hz, 2 H), 2.87 (br t, J = 7 Hz, 2 H), 3.88 (s, 3 H), 6.90 (br s, 1 H). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.30; H, 7.98.

Cycloaddition Reaction of 4-(1-Cyclohexenyl)morpholine (4d) and Methyl 4,6-Dimethyl-2-oxo-2*H*-pyran-5-carboxylate (2b). A mixture of 4-(1-cyclohexenyl)morpholine (9.2 g, 55 mmol) and methyl 4,6-dimethyl-2-oxo-2*H*-pyran-5-carboxylate (9.1 g, 50 mmol) was heated under nitrogen. The evolution of carbon dioxide began at ca. 150 °C. The reaction was heated to 200 °C for 5 h. Workup as above gave a brown oil containing two major spots by TLC. The oil was placed on a plug of silica gel (100 g). Elution with hexane (500 mL), 9:1 hexane–acetone (500 mL), 4:1 hexane–acetone (1 L), and finally 1:1 hexane–acetone gave 7.1 g of impure ester **3e** and 4.2 g of impure amide **8**. The ester fraction was distilled bulb-to-bulb to give 4.5 g (41%) of pure product (**3e**): IR (neat) 2920, 2850, 1720, 1440, 1270, 1150, and 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.6–1.9 (m, 4 H), 2.13 (s, 3 H), 2.23 (s, 3 H), 2.4–2.8 (m, 4 H), 3.90 (s, 3 H), 6.83 (bd s, 1 H). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.80; H, 8.27.

The impure amide **8** was placed on 100 g of alumina and eluted with 95:5 hexane–acetone and then 9:1 hexane–acetone. The resulting oil crystallized on standing. Recrystallization from petroleum ether–isopropyl ether yielded 3.0 g (22%) of amide **8** which was identical to the authentic sample prepared below.

1,3-Dimethyl-5,6,7,8-tetrahydronaphthalene-2-carboxylic Acid (7). The reaction was done by a slight modification of the Bartlett–Johnson procedure.[19] Hexamethylphosphoramide (100 mL) was degassed and 5.9 g (75 mmol) of 1-propanethiol was added. To this solution was slowly added 1 equiv (42 mL of a 1.8 M ethereal solution) of methyllithium. To the resulting slurry was added methyl 1,3-dimethyl-5,6,7,8-tetrahydronaphthalene-2-carboxylate (3.20 g, 14.7 mmol) dissolved in 25 mL of hexamethylphosphoramide. After stirring for 0.5 h, the reaction mixture was poured into 10% aqueous hydrochloric acid (200 mL) and extracted with ether (250 mL). The product was precipitated by the addition of 15% sodium hydroxide solution (100 mL). The precipitate was filtered and washed several times with ether. The aqueous layer was extracted with ether (2 × 100 mL). The precipitate and aqueous base layer were acidified, combined, and extracted with ether (200 mL). The dried (magnesium sulfate) ethereal layer was evaporated at reduced pressure to give a crystalline product. Recrystallization (petroleum ether–ether) yielded 2.6 g (87%) of pure **7**: mp 144–146 °C; IR ($CHCl_3$) 3000, 2920, 1690, 1300 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.6–1.9 (m, 4 H), 2.27 (s, 3 H), 2.37 (s, 3 H), 2.4–2.8 (m, 4 H), 6.83 (br s, 1 H), 12.0 (s, 1 H). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.49; H, 7.95.

1,3-Dimethyl-5,6,7,8-tetrahydronaphthalene-2-carboxylic Acid Morpholide (8). To a solution of 1,3-dimethyl-5,6,7,8-tetrahydronaphthalenecarboxylic acid (1.1 g, 5.4 mmol) and 0.1 mL of *N,N*-dimethylformamide in 10 mL of dry ether oxalyl chloride (2.0 g, 15 mmol) was slowly added. After stirring for 1 h, the solvent and excess oxalyl chloride were removed at reduced pressure. The crude acid chloride was dissolved in 25 mL of dry ether and 1.7 g (20 mmol) of morpholine was added. After stirring for 1 h, the reaction mixture was poured into 10% aqueous hydrochloric acid (50 mL) and ether (100 mL). The organic phase was washed with brine. The dried (magnesium sulfate) ethereal layer was evaporated at reduced pressure to give 1.5 g of a thick glass. Trituration (petroleum ether) and recrystallization (petroleum ether–isopropyl ether) yielded 1.1 g (75%) of pure product **8**: mp 91–92 °C; IR ($CDCl_3$) 2900, 1730, 1430, 1280, 1255, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.7–1.9 (m, 4 H), 2.10 (s, 3 H), 2.18 (s, 3 H), 2.5–2.8 (m, 4 H), 3.2 (m, 2 H), 3.6 (m, 2 H), 3.8 (m, 4 H) 6.81 (br s, 1 H). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.58; H, 8.30; N, 4.92.

Cycloaddition Reaction of 4-(1-Propenyl)morpholine (4e) and Ethyl 4,6-Dimethyl-2-oxo-2*H*-pyran-5-carboxylate (2a). A solution of 4-(1-propenyl)morpholine (9.09 g × 56%, 40.0 mmol) and ethyl 4,6-dimethyl-2-oxo-2*H*-pyran-5-carboxylate (4.17 g × 94%, 20.0 mmol) in toluene (30 mL) was heated at reflux with stirring for 4 h. (Evolution of carbon dioxide was monitored by a gas bubbler.) Upon cooling, the reaction mixture was diluted with ether (30 mL) and extracted with 10% aqueous hydrochloric acid (2 × 60 mL). The combined aqueous acidic extracts were then washed with ether (60 mL), basified with 20% aqueous sodium hydroxide (with external cooling), and extracted with ether (2 × 60 mL). The combined ethereal extracts were in turn washed with brine (60 mL). The dried (magnesium sulfate) ethereal layer was then evaporated at reduced pressure to give an orange oil (3.50 g). Chromatography of this material over silica gel eluting with a 50% ether–hexane mixture afforded ethyl *trans*-4-(4-morpholino)-2,3,6-trimethyl-3,4-dihydrobenzoate (**6e**) as a yellow oil (1.95 g, 35%): IR (neat) 2930, 1715, 1450, 1245, 1115, 1095, 1070, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 0.99 (d, J = 7.5 Hz, 3 H), 1.32 (t, J = 7.0 Hz, 3 H), 1.83 (br t, 3 H), 1.88 (s, 3 H), 2.09–2.40 (m, 3 H), 2.45–2.71 (m, 2 H), 2.86 (br d, J = 6.0 Hz, 1 H, collapses to br s upon irradiation of d at 5.36), 3.63 (t, J = 4.5 Hz, 4 H), 4.25 (q, J = 7.0 Hz, 2 H), 5.36 (br d, J = 6.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 14.3 (q), 18.1 (q), 18.9 (q), 19.8 (q), 34.7 (d), 48.2 (t), 60.3 (t), 63.6 (d), 67.3 (t), 116.4 (d), 127.2 (s), 131.4 (s), 141.7 (s), 168.9 (s). Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C 68.51; H, 8.71; N, 5.25.

Preparation of Ethyl 2,3,6-Trimethylbenzoate (3e). Ethyl *trans*-4-(4-morpholino)-2,3,6-trimethyl-3,4-dihydrobenzoate (3.41 g, 12.2 mmol) was heated at 220 °C (sand bath temperature) with stirring for 2 h. (The morpholine was collected in a Dean–Stark trap as it distilled from the reaction mixture.) Upon cooling, the reaction mixture was dissolved in ether (50 mL) and washed successfully with 10% aqueous hydrochloric acid (2 × 50 mL) and brine (50 mL). The dried (magnesium sulfate) ethereal layer was evaporated at reduced pressure to give a brown liquid (2.07 g). Chromatography of this material over silica gel eluting with a 1% acetone–hexane mixture afforded ethyl 2,3,6-trimethylbenzoate (**3e**) as a light yellow liquid (1.90 g, 81%): IR (neat) 2960, 1720, 1280, 1245, 1180, 1160, 1060, 825 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.37 (t, J = 7 Hz, 3 H), 2.18 (s, 3 H), 2.25 (br s, 6 H), 4.39 (q, J = 7 Hz, 2 H), 6.90 (d, J = 8 Hz, 1 H), 7.08 (d, J = 8 Hz, 1 H). These spectral data agree with the spectral data reported for **3e**

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which was prepared by an alternate route by Büchi and coworkers.[20] Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 74.88; H, 8.15.

Cycloaddition Reaction of 4-(3-Methyl-1-butenyl)morpholine (4f) and Ethyl 4,6-Dimethyl-2-oxo-2*H*-pyran-5-carboxylate (2a). A solution of 4-(3-methyl-1-butenyl)morpholine (6.21 g, 40.0 mmol) and ethyl 4,6-dimethyl-2-oxo-2*H*-pyran-5-carboxylate (4.17 g × 94%, 20.0 mmol) in toluene (30 mL) was heated at reflux with stirring for 24 h. (Evolution of carbon dioxide was monitored by a gas bubbler.) Upon cooling, the reaction mixture was diluted with ether (30 mL) and extracted with 10% aqueous hydrochloric acid (2 × 60 mL). The combined aqueous acidic extracts were then washed with ether (60 mL), basified with 20% aqueous sodium hydroxide (with external cooling), and extracted with ether (2 × 60 mL). The combined ethereal extracts were in turn washed with brine (60 mL). The dried (magnesium sulfate) ethereal layer was then evaporated at reduced pressure to give a brown oil (3.94 g). Chromatography of this material over silica gel eluting with a 50% ether–hexane mixture afforded ethyl *trans*-2,6-dimethyl-3-(1-methylethyl)-4-(4-morpholino)-3,4-dihydrobenzoate (**6f**) as a yellow-brown oil (3.07 g, 50%): IR (neat) 2940, 1725, 1445, 1365, 1285, 1235, 1115, 1065, 995 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 0.76 (d, J = 7.0 Hz, 3 H), 0.98 (d, J = 7.0 Hz, 3 H), 1.32 (t, J = 7.0 Hz, 3 H), 1.79 (br t, 3 H), 1.89, (s, 3 H), 1.97–2.09 (m, 1 H), 2.11–2.37 (m, 3 H), 2.46–2.76 (m, 2 H), 3.08 (br d, J = 6.0 Hz, 1 H, collapses to br s upon irradiation of d at 5.34), 3.65 (t, J = 4.5 Hz, 4 H), 4.25 (q, J = 7.0 Hz, 2 H), 5.34 (br d, J = 6.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 20.0 MHz) δ 14.3 (q), 18.2 (q), 19.6 (q), 19.9 (q), 20.3 (q), 30.2 (d), 45.1 (d), 47.9 (t), 57.5 (d), 60.2 (t), 67.3 (t), 118.8 (d), 129.3 (s), 131.3 (s), 137.8 (s), 169.0 (s). Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.45; H, 9.80; N, 4.59. When this reaction was repeated in refluxing *p*-xylene on the same scale and for the same length of time, a 24% yield of ethyl *trans*-2,6-dimethyl-3-(1-methylethyl)-4-(4-morpholino)-3,4-dihydrobenzoate (**6f**) was obtained. In addition, a 41% yield of ethyl 2,6-dimethyl-3-(1-methylethyl)benzoate (**3f**) was isolated from the hydrochloric acid insoluble fraction.

Preparation of Ethyl 2,6-Dimethyl-3-(1-methylethyl)benzoate (3f). Ethyl *trans*-2,6-dimethyl-3-(1-methylethyl)-4-(4-morpholino)-3,4-dihydrobenzoate (3.44 g, 11.2 mmol) was heated at 205 °C (sand bath temperature) with stirring for 2 h. (The morpholine was collected in a Dean–Stark trap as it distilled from the reaction mixture.) Upon cooling, the reaction mixture was dissolved in ether (50 mL) and washed successively with 10% aqueous hydrochloric acid (2 × 50 mL) and brine (50 mL). The dried (magnesium sulfate) ethereal layer was evaporated at reduced pressure to give a yellow-brown liquid (2.12 g). Chromatography of this material over silica gel eluting with a 1% acetone/hexane mixture afforded ethyl 2,6-dimethyl-3-(1-methylethyl)benzoate (**3f**) as a light yellow liquid (1.99 g, 81%): IR (neat) 2950, 1725, 1270, 1235, 1120, 1025, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.20 (d, J = 7 Hz, 6 H), 1.38 (t, J = 7 Hz, 3 H), 2.25 (s, 6 H), 3.15 (sept, J = 7 Hz, 1 H), 4.41 (q, J = 7 Hz, 2 H), 7.01 (d, J = 8 Hz, 1 H), 7.21 (d, J = 8 Hz, 1 H). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.38; H, 8.93.

Acknowledgment. We thank Colleen L. Roberts for her technical assitance and acknowledge the support of Drs. Philip A. Cruickshank and Ronald E. Montgomery during the investigatory stages of this work and the encouragement of Dr. Guy A. Crosby during the preparation of the manuscript.

Registry No. **2a**, 3385-34-0; **2b**, 41264-06-6; **3a**, 87555-72-4; **3b**, 87555-73-5; **3c**, 87555-74-6; **3d**, 87555-75-7; **3e**, 36596-66-4; **3f**, 86246-79-9; **4a**, 36838-59-2; **4b**, 7196-01-2; **4c**, 936-52-7; **4d**, 670-80-4; **4e**, 20521-59-9; **4f**, 53828-74-3; **6e**, 87555-76-8; **6f**, 87555-77-9; **7**, 87555-79-1; **8**, 87555-80-4; methyl 1,3-dimethyl-5,6,7,8-tetrahydronaphthalene-2-carboxylate, 87555-78-0.

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Quassinoid Synthesis via *o*-Quinone Diels–Alder Reactions

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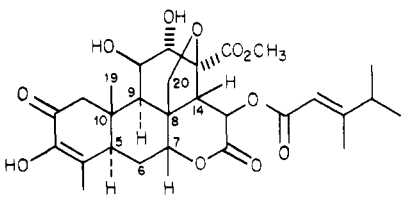
Received April 26, 1983

The reaction of 3,5-disubstituted *o*-quinones (**2a**, **2c**) and 4-chloro-3,5-disubstituted *o*-quinones (**2b**, **2d**) with simple dienes was investigated as a potential route to the quassinoid skeleton. Quinones **2a** and **2c** reacted in high yield at the 3,4-position with only a small excess of diene. Attempted equilibration of the cis-fused cycloadducts to the trans-fused system failed due to the intervention of a stable enol form, as in **20**. Compound **2c** with ethyl 3,5-hexadienoate gave **15a**, which upon reduction and lactonization provided BCD-ring tricyclic quassinoid analogues **18a** and **19a**. Again isomerization to the BC trans-fused system was not possible. The chloroquinones showed some preference for Diels–Alder reaction at the 5,6-position, but the additions were characterized generally by low yields, side reactions, and lessened stereoselectivity.

The discovery of strong biological activity in the extracts of the bark, roots, and leaves of plants and trees belonging to the Simaroubaceae family has led to the isolation and identification of a large number of related compounds known as quassinoids.[1] The range of biological activity of this class of compounds includes antiviral, antimalarial, and antifeedent, but the greatest attention has been focused on their potent antineoplastic actvity.[2,3] Bruceantin (1)[4] has shown activity against several tumor lines both



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in vitro and in vivo and has progressed to clinical trials at the National Cancer Institute.[3] The use of the Diels–Alder cycloaddition for the construction of the picrasane

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