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.

(20) Büchi, G.; Pickenhagen, W.; Wüest, H. *J. Org. Chem.* **1972**, *37*, 4192.

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

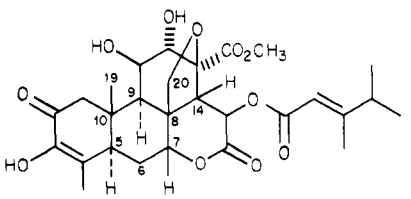
Dwight D. Weller* and Eugene P. Stirchak

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331

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



1

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

(1) Polonsky, J. *Fortschr. Chem. Org. Naturst.* **1973**, *30*, 101.

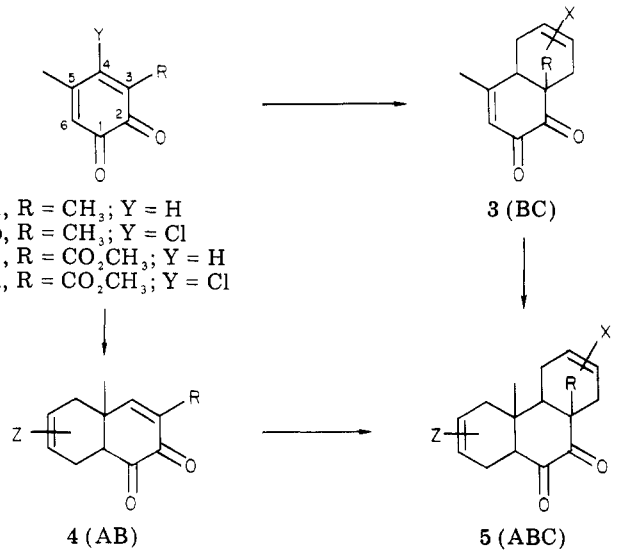
(2) (a) Cassady, J. M.; Suffness, M. In Antitumor Agents Based on Natural Product Models"; Academic Press: New York, 1980; p 201. (b) Pierre, A.; Robert-Gero, M.; Tempete, C.; Polonsky, J. *Biochem. Biophys. Acta* **1980**, *93*, 675. (c) Trager, W.; Polonsky, J. *Am. J. Trop. Med. Hyg.* **1981**, *30*, 531. (d) Odjo, A.; Priart, J.; Polonsky, J.; Roth, M. *C. R. Hebd. Seances Acad. Sci.* **1981**, *293*, 241.

(3) Sneden, A. T. "Advances in Medical Oncology, Research and Education"; Pergamon Press: Oxford and New York, 1979; Vol. 5, p 75.

(4) Kupchan, S. M.; Britton, R. W.; Lacadie, J. A.; Ziegler, M. F.; Sigel, C. W. *J. Org. Chem.* **1975**, *40*, 648.

0022-3263/83/1948-4873$01.50/0

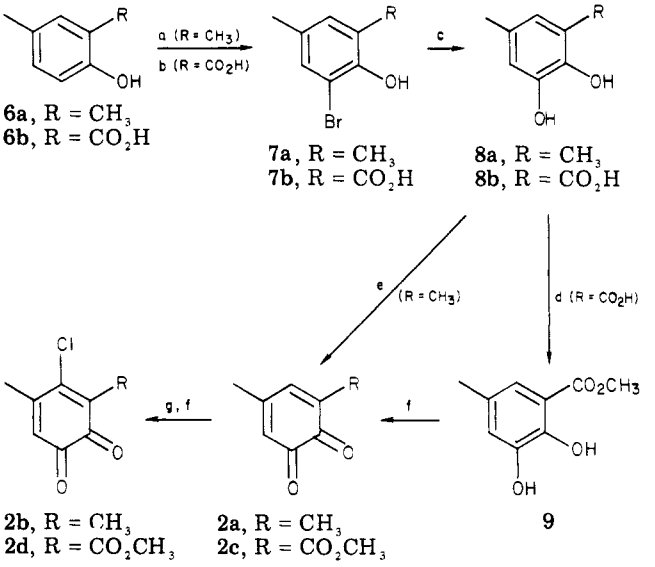
Scheme I



skeleton has received considerable attention due to the ability of this reaction to incorporate and control the stereochemistry of several centers at one time.[5-7] We envisioned that the ABC carbocyclic unit **5** of the picrasane might arise from an *o*-quinone which had been twice annulated via the Diels–Alder reaction (Scheme I). The C-3 and C-5 substitutents of the quinone will ultimately become C-19 and C-20 of the quassinoids. Further, the residual oxo groups of the quinone will become the C-7 oxygen substituent and, in the case of the 6-oxygenated quassinoids,[8] the C-6 hydroxyl group.

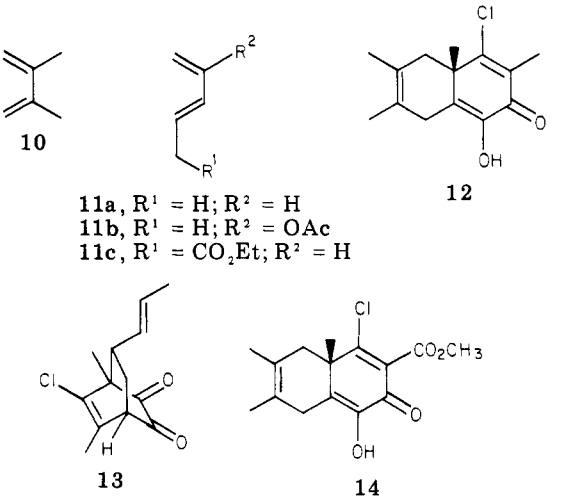
o-Quinones **2a–d** were chosen as model dienophiles for this study. During the pioneering work on the reaction of *o*-quinones with dienes, Ansell found that 3,5-disubstituted *o*-quinones undergo reaction primarily at the 3,4-olefin when the C-5 substituent is not an electron-withdrawing group.[9] Alternatively, 3,4,5-trisubstituted *o*-quinones were found to undergo reaction at the less hindered 5,6 site.[9] From these observations, **2a** and **2c** were expected to yield BC type cycloadducts **3**, while **2b** and **2d** would produce AB systems **4**. In the latter two quinones, we postulated the C-4 chloro group to be an easily introducible group, capable of directing addition to the 5,6-olefin and which could be readily removed via a reductive process later in the synthesis.[11] The need to direct cycloaddition to the 5,6-position of the quinones follows from the greater dieneophilicity of the α-methylcyclohexenone moiety of the AB system, vis-à-vis, the β-methylcyclohexenone of the BC system. This would favor an AB system as a substrate for the second annulation over a BC picrasane fragment. This report details attempts to achieve positional selectivity in the Diels–Alder reactions of *o*-quinones **2a–d**. Additionally, the stereochemistry of the cycloaddition reaction and the attempted epimerization of the initially formed cis-fused BC ring junction to the natural trans ring fusion have been studied for the products of **2c**.

Scheme II[a]



[a] a, NBS, DMF, 25 °C; b, Br_2, CH_3CO_2H, 60 °C; c, NaOH, H_2O, $CuSO_4$, reflux; d, CH_3OH, $BF_3{\cdot}OEt_2$, reflux; e, *o*-chloranil, Et_2O; f, Ag_2O, Et_2O, 25 °C; g, HCl, 2-propanol/benzene.

Chart I



The syntheses of *o*-quinones **2a–d** are shown in Scheme II. The known 3,5-dimethyl-*o*-benzoquinone **2a**[9] was prepared by a much improved process involving bromination of 2,4-dimethylphenol (**6a**) followed by copper-catalyzed displacement of the bromide by hydroxide[12] to give 3,5-dimethylcatechol (**8a**) in a 59% yield. Oxidation with *o*-cloranil gave *o*-quinone **2a**. Catechol **8b** was available in 60% yield by a similar sequence of reactions from 5-methylsalicylic acid[13] (**6b**). Esterification and oxidation using silver oxide gave **2c**. Chlorination of the

(5) (a) Grieco, P. A.; Ferrino, S.; Vidari, G. *J. Am. Chem. Soc.* **1982**, *102*, 7587. (b) Grieco, P. A.; Lis, R.; Ferrino, S.; Jaw, J. Y. *J. Org. Chem.* **1982**, *47*, 601. (c) See also Voyle, M.; Kyler, S. K.; Arseniyadis, S.; Dunlap, N. K.; Watt, D. S. *Ibid.* **1983**, *48*, 470.

(6) (a) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175. (b) Kraus, G. A.; Taschner, M. J.; Shimagaki, M. *Ibid.* **1982**, *47*, 4271.

(7) Stojanac, N.; Stojanac, Z.; White, P. S.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 3346.

(8) (a) Wani, M. C.; Taylor, H. L.; Thompson, J. B.; Wall, M. E. *J. Nat. Prod.* **1978**, *41*, 578. (b) Sieda, A. A.; Kinghorn, A. D.; Cordell, G. A.; Farnsworth, N. R. *Ibid.* **1978**, *41*, 584. (c) Wani, M. C.; Taylor, H. L.; Thompson, J. B.; Wall, M. E.; McPhail, M. T.; Onan, K. D. *Tetrahedron* **1979**, *35*, 17.

(9) (a) Ansell, M. F.; Bignold, A. J.; Gosden, A. F.; Leslie, V. J.; Murray, R. *J. Chem. Soc. C* **1971**, 1414. (b) Ansell, M. F.; Gosden, A. F.; Leslie, V. J.; Murray, R. A. *Ibid.* **1971**, 1401. (c) Ansell, M. F.; Leslie, V. J. *Ibid.* **1971**, 1423.

(10) Grieco[5a,b] has successfully utilized the Diels–Alder reaction of an AB type system in the syntheses of quassin and castelanolide.

(11) For an example of the reductive dechlorination of β-chloroenones see Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 636.

(12) (a) Klag, G.; Wunderlich, H.; Jung, G.; Linder, O. German Patent 2 237 808 (Cl. C 07c); *Chem. Abstr.* **1974**, *80*, 14732d. (b) Torii, S.; Tanaka, H.; Siroi, T.; Akada, M. *J. Org. Chem.* **1979**, *44*, 3305. (c) Banerjee, S. K.; Manolopoulo, M.; Pepper, J. M. *Can. J. Chem.* **1962**, *40*, 2175.

(13) Cameron, D.; Jerskey, H.; Baine, O. *J. Org. Chem.* **1950**, *15*, 233.

Table I. Diels-Alder Addition of Quinones 2a-d with Dienes

quinone	diene (mol %, h)[a]	products, %[b] 3,4	5,6	other	yield, %[c]
2a	10 (300, 14)	100[d]	0		77
	11a (320, 14)	88	12		67
	11b (320, 14)	84	16		70
2b	10 (290, 28)	0	100		27
	11a (300, 28)	0	12	88 (13)[e]	57
	11b (290, 120)	0	100		13
2c	10 (240, 124)	100	0		46
	11a (250, 3)	100	0		87
	11b (310, 14)	100	0		85
	11c (170, 14)	100	0		74
	21b (130, 14)	100	0		50
2d	10 (300, 14)	0	100		72
	11a (290, 14)	0	100		19
	11b (300, 14)	18	18;64		17

[a] Diene and quinone were mixed in dry chloroform and stirred in the dark for the indicated time. Workup by evaporation and chromatography gave products. See the supplemental experimental section for details. [b] Relative percent of product arising from Diels-Alder reaction of the quinones at the 3,4- or 5,6-positions. [c] Purified yield. [d] ^{1}H NMR of the crude reaction mixture showed the presence of 10% of the 5,6-adduct. [e] See text for structure.

simple *o*-quinones **2a,c** was achieved by treatment with anhydrous HCl in 2-propanol.[14] Reoxidation of the intermediate chlorocatechols with silver oxide provided **2b** and **2d** in 72% and 70% yield, respectively. The position of chlorine incorporation was indicated in both cases by the loss, in the ^{1}H NMR spectrum, of the more downfield C-4 proton signal. Although the quinones **2a–d** are routinely used for Diels–Alder reactions immediately, they can be stored at −78 °C for several days without decomposition.

The dienes chosen for study were **10** and **11a,b** (Chart I). Dimethylbutadiene (**10**) would serve as a basis for comparison of our results to those of Ansell in regards to the stability and reactivity of *o*-quinones **2a–d**. Piperylene **11a** and 2-acetoxypiperylene **11b**, when directed to attack the 5,6-olefin, would produce potentially useful precursors to the AB ring system. Attack of these dienes at the 3,4-olefin would provide data applicable to analogous dienes useful for constructing BC ring intermediates. The results of the reactions of *o*-quinones with the model dienes are shown in Table I. The ratio of isomers derived from attack at the 3,4- vs. the 5,6-olefin was determined by ^{1}H NMR spectroscopy.[15] No attempt was made to determine stereochemistry in these simple adducts. The results indicate that **2a** reacts preferentially and in good yield at the 3,4-position to give BC systems. *o*-Quinone **2c** gives attack exclusively at the 3,4-olefin and in excellent yield. It should be noted that large excesses of the diene were not required, in contrast to the results of Ansell.[9] This increases the attractiveness of the method, especially in cases where the diene component is not readily available.

As indicated in Table I, the reactions of the chloroquinones **2b** and **2d** were less successful. With dimethylbutadiene, *o*-quinone **2b** afforded a single isolable product in 27% yield. The presence of a hydroxyl group led to the assignment as the enolized 5,6-adduct **12**.[15] In contrast, the reaction of **2b** with piperylene produced two products in 7% and 50% yields. The minor product was shown to be the enolized 5,6-adduct.[15b] The structure of the major isomer was assigned as the bicyclo[2.2.2]octane derivative **13** and was rigorously proved by interpretation of the 360-MHz ^{1}H NMR spectrum.[15b,16,17] The bicyclooctane product arises from a Diels–Alder reaction in which the *o*-quinone **2b** serves as the diene component and **11a** as the dieneophile and accords with earlier observations by Ansell.[9c]

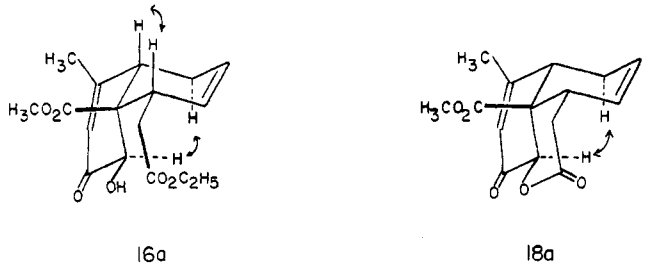


Figure 1. NOE relationships in **16a** and **18a**.

The Diels–Alder reactions of *o*-quinone **2d** at the 5,6-olefin were predicted to occur with greater facility than the corresponding reaction of **2b**. In this case, the C-3 carbomethoxy group was expected to increase the dieneophilicity of both the 3,4- and 5,6-enone systems. Although the accelerating effect of the ester group on the cycloaddition would be most strongly felt at the 3,4-position, the presence of the 4-chloro substituent should hinder attack at this site. Encouragingly, treatment of **2d** with dimethylbutadiene afforded a single adduct **14** in 72% yield. The adduct was readily identified as the enolized 5,6-addition product by its ^{1}H NMR spectrum.[15a] Unfortunately, reaction of **2d** with piperylene was less successful, giving many reaction products and only 19% of the 5,6-adduct. Furthermore, reaction of **2d** with 2-acetoxypiperylene was also poor, affording three recognizable cycloadducts in low yield, including some 3,4-adduct. Thus, although *o*-quinones **2b** and **2d** react preferentially at the 5,6-position during Diels–Alder reactions, the yields are typically low and side reactions are numerous. Attempted catalysis of the cycloaddition using Lewis acids led to rapid decomposition of the quinone.

The ease with which dienes may be added to *o*-quinone **2c** and the difficulty in the addition of dienes to the 5,6-position of chloroquinones **2b** and **2d** prompted a closer examination of the 3,4-addition approach. In order to more closely model the natural materials, ethyl 3,5-hexadienoate **11c** was reacted with **2c** to give **15a** in 80% yield. Diketone **15a** was converted into **16a** in 63% yield by reduction with lithium tri-*tert*-butoxyaluminum hydride followed by

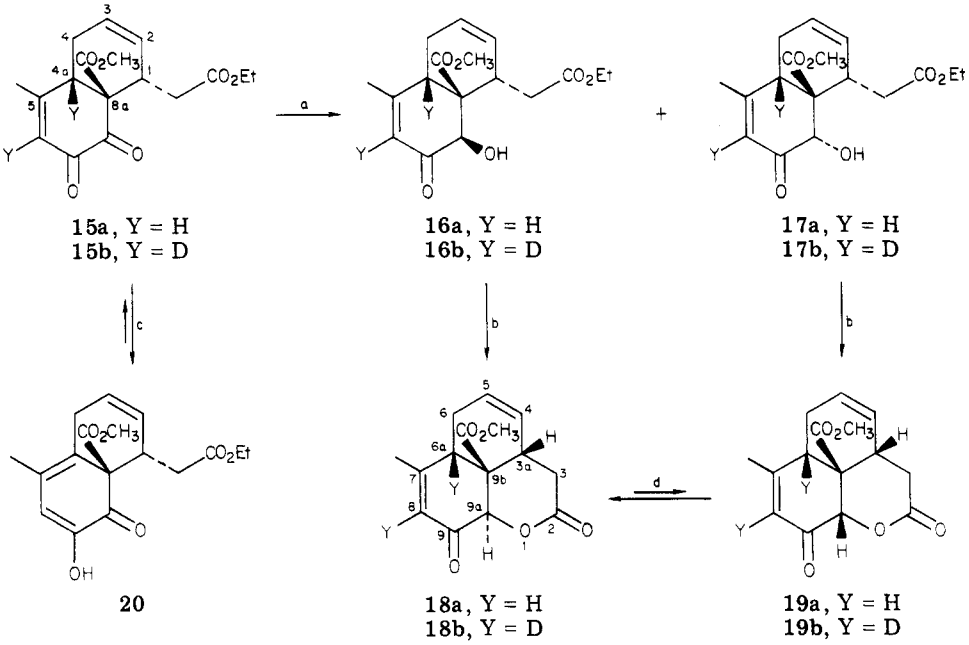
(14) Horner, L.; Burger, T. *Ann. Chem.* **1967**, *708*, 105.

(15) (a) In the 3,4-adducts of **2a** the β-methylcyclohexenone unit showed a vinylic methyl at ~2.1 ppm and the vinyl proton at ~6.2 ppm. The corresponding 5,6-adducts of **2a** showed a vinylic methyl at ~1.9 ppm and a vinyl proton at ~6.4 ppm consistent with the α-methylcyclohexenone unit. In the additions of **2b** and **2d**, 3,4-adducts were indicated by the presence of the intact β-methylcyclohexenone unit as for **2a**. The 5,6-adducts of **2b** and **2d** showed no vinyl protons and were additionally found to be enolic, as indicated by the presence of an exchangeable hydrogen in the 5–6 ppm region. (b) For spectral and analytical details of these adducts see the supplementary materials section.

(16) The position of addition of **2a** onto piperylene in **13** was clear from the appearance of the bridgehead proton as a triplet, J = 3 Hz, at ~3.36 ppm, indicating that the adjacent carbon of the ethane bridge was a methylene group. The stereochemistry of the adduct was assigned by consideration of the chemical shifts of the protons on the ethane bridge. The two methylene protons show widely different chemical shifts due to the location of one in the deshielding zone of the nearby carbon–carbon double bond[17] and appear at 2.44 ppm (ddd, J = 3, 10, 15 Hz) and at 1.70 ppm (m, obscured by the vinyl methyl absorption at δ 1.70). The methine proton on the bridge must be oriented toward the alkene bridge, due to its relatively downfield chemical shift (2.53 ppm, dt, J = 5, 10 Hz) and its large coupling (10 Hz) with the adjacent downfield methylene proton, which is consistent with the syn periplanar relationship between these two protons.

(17) (a) Roll, D. R.; Huitric, A. C. *J. Pharm. Sci.* **1965**, *54*, 1118. (b) Tori, K.; Takano, Y.; Kitahonoki, K. *Chem. Ber.* **1964**, *97*, 2798. (c) Tori, K.; Hamashima, Y.; Takamizawa, A. *Chem. Pharm. Bull.* **1964**, *12*, 924.

Scheme III[a]



15a, Y = H
15b, Y = D

16a, Y = H
16b, Y = D

17a, Y = H
17b, Y = D

20

18a, Y = H
18b, Y = D

19a, Y = H
19b, Y = D

[a] a, $NaBH_4$, EtOH, 25 °C; b, CF_3CO_2H; 25 °C; c, $KOBu^t$, THF, 25 °C; d, DBU, THF, 25 °C.

isomerization of the mixture of hydroxy ketones with sodium ethoxide in ethanol (Scheme III). Treatment of **16a** with trifluoroacetic acid gives the BCD quassinoid analogue **18a** in 82% yield. Similarly, alcohol **17a**, obtained from the reduction of **15a** prior to base isomerization, yielded lactone **19a** in 74%. The stereochemistry of these products was established by labeling experiments and ^1H NMR. Reaction of ethyl 3,5-hexadienoate with **2c**-*4,6-d*$_2$ and further treatment as in Scheme III produced **15b–19b** with no loss of scrambling of the label at the ring junction or the vinyl position.[18] This indicated that all these materials possess the BC cis ring fusion which was established in the Diels–Alder reaction. That the cycloaddition reaction proceeded with the expected endo stereochemistry was demonstrated by NOE experiments.[19] Although the chemical shifts of the H-6a and H-3a protons of the lactones and the corresponding H-1 and H-4a protons of **15a** and **17a** are too close to observe a meaningful NOE, the chemical shifts of these protons in **16a** are sufficiently separated. Here, a strong enhancement of H-4a was observed upon irradiation of H-1 (Figure 1). Thus the Diels–Alder reaction of **2c** proceeded with the endo orientation to give the correct quassinoid relative configuration at C-1 and C-8a in **15a**. The assignment of stereochemistry to C-8 of **16a** as shown was made on the basis of a strong NOE between H-8 and the psuedoaxial proton at C-4 (Figure 1). A similar effect was obtained for the lactone **18a**.

The isomerization of **15a** was attempted in order to prepare closer precursors to the quassin series and to determine the ability of this partial structure to adopt the natural quassinoid configuration. The necessary epimerization of the BC ring fusion from cis to trans has been a pivotal issue in previous approaches.[20,21] However, equilibration (DBU/tetrahydrofuran or DBU/methanol) of **15a** yielded only a 9/1 mixture of enol **20** and **15a**. Although the alcohol **17a** is rapidly converted into **16a** by brief treatment with base, prolonged treatment or vigorous conditions caused decomposition, possibly via a retro-aldol reaction.[6] The lactones **18a** and **19a** may be readily equilibrated to a 2/1 ratio of **18a**/**19a** with DBU in tetrahydrofuran but, again the instability of these materials prohibited the use of vigorous isomerization conditions.[18]

Since the lactone in **18a** and **19a** is very sensitive to nucleophilic attack, the ethers **26** and **27** were prepared as in Scheme IV.[22] These materials were readily separable by chromatography and characterized by decoupling and NOE experiments in the 360-MHz ^1H NMR, wherein they showed close analogy to the lactones **18a** and **19a**. Treatment of either ether with sodium methoxide in methanol rapidly produced a mixture of **26** and **27** (6/1). The use of methanol-*O*-*d*$_1$ for this isomerization lead to rapid incorporation of deuterium into C-9a and the vinyl methyl at C-7. After 72 h at 25 °C approximately 50% exchange was observed at C-8, however no exchange at C-6a was found. Again, heating in base led to decomposition of the system. It was thus not possible to isomerize the 3,4-addition products of **2c** (**15a**, **18a**, **19a**, **26**, **27**) into the desired trans-fused ring systems. In order to achieve this isomerization, it will be necessary to alter the con-

(18) Catechol acid **8b** was treated with 5% sulfuric acid-*d*$_2$ in deuterium oxide for 5 days to yield **19b** with greater than 98% deuterium at C-6 and 93% deuterium at C-4. Esterification with boron trifluoride and methanol-*O*-*d*$_1$, gave labeled **9**, which was converted as per usual into **18b** and **19b**. Treatment of this material with DBU in tetrahydrofuran at 65 °C caused no scrambling of the label. Further, no exchange at C-6a was observed with potassium *tert*-butoxide in *tert*-butyl alcohol/tetrahydrofuran.

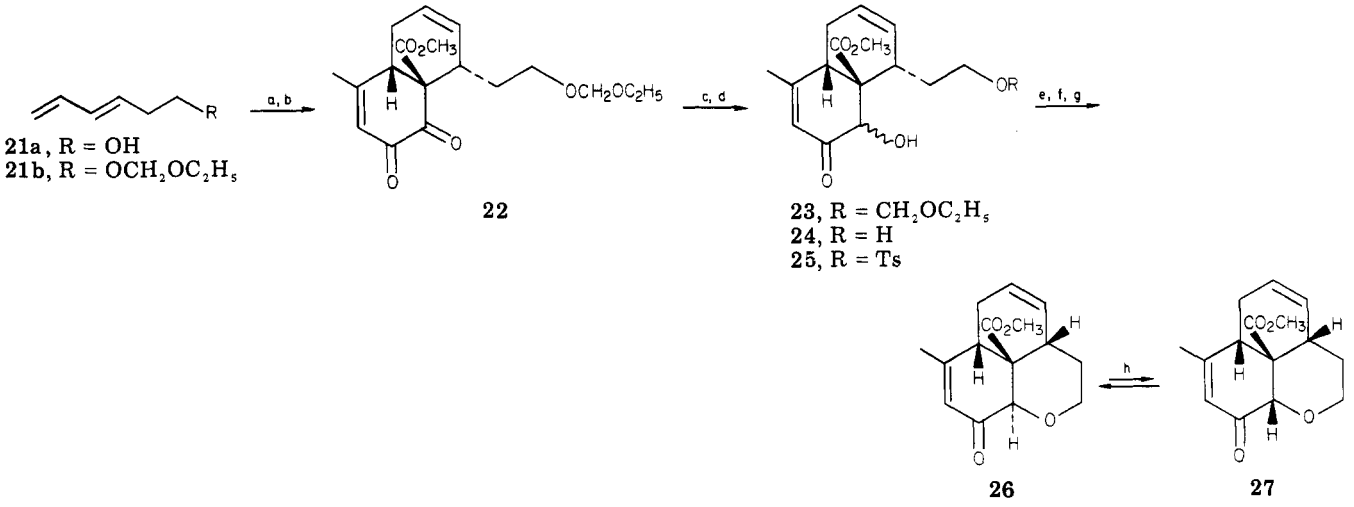
(19) Hall, L. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1980**, *102*, 5703.

(20) The approach of Grieco, utilized in the synthesis of quassin and castelanolide, employs as reactants a trans-fused AB picrasane fragment diene.[5] By thus fixing the stereochemistry of the dieneophile, the approach of the diene is directed to the α face of the dienophile. The required endo stereochemistry was observed, and the cis BC ring fusion was epimerized later in the synthesis to the more stable trans configuration. The configurations of C-9 and C-14 of the quassinoids are in the thermodynamically more stable forms, thus allowing these centers to be established late in a synthesis, provided that the stereochemistries of C-5, C-7, C-8, and C-10 have been fixed.[21] Kraus has constructed a BCE picrasane fragment via the Diels–Alder reaction of a *p*-quinone and a deconjugated sorbate derivative.[7] This annulation proceeded via the desired endo transition state, and the cis-fused ring system could be epimerized to the trans system at the bicyclic (BC) stage.

(21) (a) Valenta, Z.; Papadopoulos, S.; Podesva, C. *Tetrahedron* **1961**, *15*, 100. (b) Valenta, Z.; Gray, A. H.; Orr, D. E.; Papadopoulos, S.; Podesva, C. *Ibid.* **1962**, *18*, 1433.

(22) Sodium ethoxide in ethanol at 25 °C rapidly converts **18a** and **19a** into alcohol **16a**.

Scheme IV[a]



[a] a, NaH, $ClCH_2OC_2H_5$, DMF, 25 °C; b, 2c, $CHCl_3$, 25 °C; c, $LiAl(OBu^t)_3H$, Et_2O, 25 °C; d, NaOEt, EtOH, 25 °C; e, aq HCl, THF, 50 °C; f, tosyl chloride, pyridine, 0 °C; g, HMPA, 70 °C; h, $NaOCH_3$, CH_3OH, 25 °C.

formational preferences of the system, most probably by the manipulation of the C ring. The most useful variation would be the early formation of the E-ring ether bridge, which sets the C ring in the natural quassinoid conformation.

Experimental Section

Low-resolution mass spectrometry was performed on a Varian MAT CH-7 or a Finnigan 3500. Infrared spectra were recorded on Perkin-Elmer spectrophotometers, Model 727B and Model 137. Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. ^1H NMR analyses were performed on Varian spectrometers, Model FT-80, Model HA-100, or Model EM-360. High-resolution ^1H NMR spectra were obtained on a Nicolet 360-MHz instrument at the University of Oregon. Chemical shifts (δ) are reported as parts per million downfield from tetramethylsilane as internal standard. High resolution mass spectra were obtained on a CEC-103B mass spectrometer by Richard Wielesek at the University of Oregon Micro-Analytical Lab. Combustion analyses were performed by Richard Wielesek at the University of Oregon Micro-Analytical Lab and by MicAnal, Tucson, AZ.

6-Bromo-2,4-dimethylphenol (7a). To a solution of 30.0 g (0.25 mol) of the phenol **6a** in 125 mL of DMF, a solution of 43.8 g (0.25 mol) of NBS in 125 mL of DMF was added dropwise. The mixture was stirred for 1 day then poured into 1500 mL of H_2O. The aqueous solution was extracted with 5% benzene/hexane and the extracts were combined, washed with H_2O and brine, and dried ($MgSO_4$). The solvent was removed and the residue distilled (5.5 torr, 85–90 °C (lit.[23] 24 torr, 135–137 °C)) to afford 43.0 g (87%) of the bromophenol as an oil: MS, m/z 200 (M^+), 202 (M + 2), 121 (100); IR (thin film) 3550, 1485 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (1 H, s) 7.01 (1 H, s), 5.53 (1 H, OH), 2.41 (3 H, s), 2.38 (3 H, s).

3,5-Dimethyl-1,2-benzenediol (8a). A solution of 300 g (7.5 mol) of NaOH in 3000 mL of H_2O was stirred under reduced pressure (aspirator) for 1.5 h. Then, 2 g of $CuSO_4$ was added to the solution and stirring under reduced pressure was coninued for an additional 15 min. The aqueous solution was transferred by cannula to a 5-L flask containing 55.6 g (0.28 mol) of the bromophenol **7a**. The resulting solution was refluxed for 6 h, cooled, and acidified with HCl. The aqueous mixture was extracted with ether and the etheral extractions were combined, washed with brine, dried (Na_2SO_4), and evaporated to provide 28.09 g (73.5%) of a crude solid. Short path distillation (1 torr, 110 °C (lit.[9b] 12 torr, 134–136 °C)) and recrystalization (hexane/toluene) afforded pure **8a**: mp 69.5–71 °C [lit.[9b] mp 71 °C]; MS, m/z 138 (M^+, 100), 123; IR (KBr) 3470, 3300, 1610, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.67 (2 H, s), 2.37 (6 H, s).

3,5-Dimethyl-3,5-cyclohexadiene-1,2-dione (2a). As previously described by Ansell,[9b] 1.02 g (7.39 mmol) of catechol **8a** was treated with 1.95 g (7.96 mmol) of *o*-chloranil in 70 mL of ether and produced 0.97 g (96%) of the desired *o*-quinone **2a**: ^1H NMR ($CDCl_3$) δ 6.66 (1 H, br s), 6.15 (1 H, br s), 2.14 (3 H, d, J = 1 Hz), 1.99 (3 H, s).

2,3-Dihydroxy-5-methylbenzoic Acid (8b). By the procedure described above for the preparation of **8a**, 30.2 g (0.13 mol) of **7b**,[24] 252 g (6.3 mol) of NaOH, and 2 g of $CuSO_4$ in 3000 mL of H_2O gave 20.1 g (92%) of the crude dihydroxybenzoic acid, which was not purified but further reacted directly. Purification could be accomplished by sublimation (100 °C at 0.25 torr): mp 204–205 °C (lit.[25] mp 204 °C); MS, m/z 168 (M^+), 150 (100); IR (KBr) 3520, 3300–2400, 1670, 1620 cm^{-1}; ^1H NMR ($CDCl_3$ with trace Me_2SO-d_6) δ 7.34 (1 H, br s), 7.05 (1 H, d, J = 2 Hz), 2.40 (3 H, s).

2,3-Dihydroxy-5-methylbenzoic Acid, Methyl Ester (9). To a solution of 20.1 g (0.12 mol) of **8b** in 360 mL of MeOH was added 28.6 mL (0.238 mol) of BF_3·Et_2O and the resulting mixture heated at reflux for 4 h. Aqueous $NaHCO_3$ was added to the reaction mixture until the pH of the aqueous layer was 6, and then the mixture was further diluted with H_2O and extracted with ether. The combined ethereal extracts were washed with saturated brine, dried ($MgSO_4$) and evaporated to give 18.0 g (80%) of a crude solid which was recrystallized from 20% MeOH/H_2O to yield 17.0 g (75%) of the catechol ester **9**: mp 99–100 °C; MS, m/z 182 (M^+), 150 (100); IR (KBr) 3360, 1665, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.19 (1 H, s), 6.96 (1 H, s), 5.64 (2 H, s, OH), 3.96 (3 H, s), 2.28 (3 H, s).

Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.35; H, 5.41.

3-Methyl-5,6-dioxo-1,3-cyclohexadienecarboxylic Acid, Methyl Ester (2c). To a solution of 1.03 g (5.66 mmol) of catechol **9** in ether (75 mL) was added 6.06 g (26.1 mmol) of Ag_2O and 5.01 g of Na_2SO_4. The heterogeneous solution was vigorously stirred for 20 min and filtered and the solid Ag_2O washed extensively with ether. The combined ether solutions returned 0.87 g (85%) of the desired quinone **2c** as a red-green solid which was used immediately: MS, m/z 180 (M^+), 121 (100), 65, 39; IR (KBr) 1690, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.64 (1 H, d, J = 2 Hz), 6.44 (1 H, s), 3.90 (3 H, s), 2.29 (3 H, d, J = 2 Hz); calcd for $C_9H_8O_4$, M_r 180.042; found, M_r 180.043.

4-Chloro-3,5-dimethyl-1,2-benzenediol and 4-Chloro-3,5-dimethyl-3,5-cyclohexadiene-1,2-dione (2b). A solution of 1.64 g (1.21 mmol) of **2a** in 15 mL dry benzene was added to 150 mL of 0.3 M HCl in anhydrous 2-propanol. The resulting solution was vigorously stirred for 5 min, during which time the color of the solution changed from red to a light yellow. The volume of

(23) Orten, K. J. P.; Coates, E. J. *J. Chem. Soc.* **1907**, *91*, 35.

(24) Merchant, J. R.; Desai, V. V.; *J. Chem. Soc. C* **1968**, 499.

(25) *Beilstein*, **1927**, Band X, System No. 1106, No. 14.

the solution was reduced to 15 mL by evaporation and diluted with 100 mL of ether. The ethereal solution was washed with water and brine and then dried ($MgSO_4$). Removal of the solvent afforded 2.08 g (100%) of the crude chlorocatechol. The crude product was purified by column chromatography with silica gel (4% acetone/$CHCl_3$) which yielded 1.72 g (83%) of pure chlorocatechol: mp 83.5–84.5 °C; MS, m/z 172 (174) (M^+), 137 (100); IR (KBr) 3300 (br), 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.43 (1 H, s), 2.33 (3 H, s), 2.29 (3 H, s); calcd for $C_8H_9ClO_2$, M_r 172.029; found, M_r 172.028.

As was previously described for the preparation of carbomethoxy-*o*-quinine **2c**, 0.92 g (5.23 mmol) of the chlorocatechol was treated with 6.27 g (27.0 mmol) of Ag_2O and 6.00 g of Na_2SO_4 to produce 0.73 g (80%) of chloroquinone **2b** as red solid. The product was not purified and was used immediately: MS, m/z 170 (M^+), 172 (M + 2, 100), 174 (M + 4); IR (KBr) 1740, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.27 (1 H, br m), 2.29 (3 H, d, J = 1.5 Hz), 2.14 (3 H, s); calcd for $C_8H_7ClO_2$, M_r 170.013; found, M_r 170.013.

6-Chloro-2,3-dihydroxy-5-methylbenzoic Acid, Methyl Ester and 2-Chloro-3-methyl-5,6-dioxo-1,3-cyclohexadienecarboxylic Acid, Methyl Ester (2d). As previously described for the preparation of the chlorodimethylcatechol, 1.75 g (9.7 mmol) of quinone **2c** in 15 mL of benzene was added to 80 mL of 0.25 M HCl in 2-propanol and produced 2.10 g (100%) of a crude solid. Chromatography on silica gel with 5% acetone/$CHCl_3$ afforded 1.27 g (60%) of pure chlorocatechol: mp 75–77 °C; MS, m/z 216 (M^+) 218 (M + 2), 182 (100); IR (KBr) 3440, 1710, 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.99 (1 H, s), 4.03 (3 H, s), 2.31 (3 H, s); calcd for $C_9H_9ClO_4$, M_r 216.019; found, M_r 216.019.

As was previously described for the oxidation of **9**, 0.88 g (4.62 mmol) of the chlorocatechol was reacted with 5.27 g (22.7 mmol) of Ag_2O in the presence of 4.30 g of Na_2SO_4 and gave 0.76 (87%) of the desired chloroquinone **2d** which was not purified but used immediately: MS, m/z 214 (M^+), 216 (M + 2), 184, 134; IR (neat) 1770, 1740, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.44 (1 H, d, J = 2 Hz), 3.93 (3 H, s), 2.31 (3 H, d, J = 2 Hz); calcd for $C_9H_7ClO_4$, M_r 214.003; found, M_r 214.004.

8a-Carbomethoxy-7,8-dioxo-5-methyl-1,4,4a,8a-tetrahydronaphthalene-1-acetic Acid, Ethyl Ester (15a). To a solution of 1.89 g (10.5 mmol) of **2c** in 4 mL of $CHCl_3$ was added 2.53 g (18.1 mmol) of ethyl 3,5-hexadienoate.[26] The solution was stirred overnight in darkness. The solvent was removed and 0.92 g of excess diene was recovered by short-path distillation [80–100 °C (5 torr)]. The residue was flash chromatographed on silica (4% acetone/$CHCl_3$) and afforded 2.41 g (74%) of the adduct as a yellow solid. Recrystallization with toluene/hexane (1/2) gave mp 101–102.5 °C; UV (MeOH) λ_{max} 264 nm (ϵ 4600); MS, m/z 320 (M^+), 215 (100); IR ($CHCl_3$) 1735, 1685, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 6.14 (1 H, d, J = 1.8 Hz), 5.65 (2 H, m), 4.12 (2 H, dq, J = 6.8, 4.0 Hz), 3.70 (3 H, s), 3.27 (1 H, dd, J = 12.6, 6.5 Hz), 3.16 (1 H, m), 3.03 (1 H, dd, J = 17.0, 10.2 Hz), 2.70 (1 H, m), 2.56 (1 H, dd, J = 17.0, 4.3 Hz), 2.16 (3 H, d, J = 1.8 Hz), 1.75 (1 H, m), 1.24 (3 H, t, J = 6.8 Hz).

Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.32; H, 6.00.

8a-Carbomethoxy-8β-hydroxy-5-methyl-7(4*H*)-oxo-1,4a,8,8a-tetrahydronaphthalene-1-acetic Acid, Ethyl Ester (16a) and 8a-Carbomethoxy-8α-hydroxy-5-methyl-7(4*H*)-oxo-1,4a,8,8a-tetrahydronaphthalene-1-acetic Acid, Ethyl Ester (17a). At room temperature, 0.22 g (5.87 mmol) of $NaBH_4$ was added in six batches over 10–15 min to a solution of 5.09 g (15.9 mmol) of **15a** in 50 mL of THF and 25 mL of EtOH. The solution was stirred an additional 5 min, poured into dilute aqueous HOAc, and extracted with ether. After washing with aqueous $NaHCO_3$, H_2O, and brine and drying (Na_2SO_4), the solvent was removed to furnish 4.87 g (95%) of a semisolid which was flash chromatographed on silica gel (5% acetone/$CHCl_3$). The first fraction, 2.19 g (43%), contained unreacted **15a** and considerable amounts of reduced materials. The second fraction, 1.55 g (30%), contained both hydroxy ketones and a mixture of diols. The third fraction, 0.58 (11%), contained only a mixture of diols as an oil (total recovery, 4.32 g, 84%). The first two fractions were further chromatographed (SiO_2, 2% acetone/$CHCl_3$) on an LC 500 HPLC system. From an initial 3.91 g, 0.41 g of **15a**, 1.11 g of alcohol **16a**, and 1.30 g of alchol **17a** were recovered (total recovery from HPLC, 82%). Recrystallization from toluene/hexane afforded 0.97 g (19%) of the alcohol **16a**: R_f (5% acetone/$CHCl_3$) 0.36; mp 144–145 °C; MS, m/z 322 (M^+), 217 (100); IR ($CHCl_3$) 3530, 1725, 1680, 1620 cm^{-1}; ^1H NMR ($CHCl_3$, 360 MHz) δ 5.85 (2 H, q, J = 7.1 Hz), 3.66 (3 H, s), 3.49 (1 H, d, J = 5.7 Hz (–OH)), 3.37 (1 H, m), 3.06 (1 H, dd, J = 11.5, 7 Hz), 2.82 (1 H, dd, J = 17, 11 Hz), 2.68 (1 H, m), 2.54 (1 H, dd, J = 17, 4 Hz), 1.99 (3 H, d, J = 1.2 Hz), underlying 1.99 (1 H, m), 1.26 (3 H, t, J = 7.1 Hz); calcd for $C_{17}H_{22}O_6$, M_r 322.142; found, M_r 322.142.

17a: R_f (5% acetone/$CHCl_3$) 0.26; mp 143–144.5 °C (toluene/hexane); MS, m/z 322 (M^+), 171 (100); IR ($CHCl_3$) 3500, 1730, 1675, 1625 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 5.94 (1 H, s), 5.74 (2 H, m), 4.58 (1 H, s), 4.14 (2 H, q, J = 7.1 Hz), 3.72 (3 H, s), 3.43 (1 H, dd, J = 16, 11 Hz), 2.36 (2 H, m), 2.04 (3 H, s), 1.26 (3 H, t, J = 7.1 Hz); calcd for $C_{17}H_{22}O_6$, M_r 322.143; found, M_r 324.141.

Alternatively, a solution of $LiAl(OBu^t)_3H$ (80 mg, 0.314 mmol) in THF (1 mL) was added slowly to a solution of **15a** (78.5 mg, 0.245 mmol) in THF (1 mL). the reaction was stirred for 30 min, diluted with ether, poured into 0.5 N HCl, and extracted thoroughly with ether. The extracts were washed with H_2O and brine, dried, and then evaporated to afford 67.8 mg (86%) of a mixture of hydroxy ketones. The mixture was dissolved in ethanol (3 mL) and toluene (1 mL) and treated with NaOEt/ethanol (0.02 mL, 1.69 M). The solution was stirred for 2 h and worked up as usual to provide 49.7 mg (73%, 63% overall) of **16a**.

6,6aα-Dihydro-2,9(3*H*,9aα*H*)-dioxo-7-methylnaphthalene[1,8-*bc*]pyran-9bβ(3aα*H*)-carboxylic Acid, Methyl Ester (19a). A solution of 68.4 mg (0.21 mmoles) of **17a** in 1 mL of TFA was stirred 3 min and solvent was removed in vacuo. Chromatography of the residue by MPLC on silica (3% acetone/$CHCl_3$) furnished 43.2 mg (74%) of the desired lactone **19a**: R_f (5% acetone/$CHCl_3$) 0.29; mp 142–143 °C (toluene/hexane); MS, m/z 276 (M^+, 100); IR (KBr) 1750, 1730, 1680, 1625 cm^{-1}; ^1H NMR ($CHCl_3$, 360 MHz) δ 6.01 (2 H, br s), 5.63 (1 H, br d, J = 10 Hz), 5.17 (1 H, s), 3.78 (3 H, s), 3.23 (1 H, br s), 3.07 (1 H, dd, J = 10, 4 Hz), 2.99 (1 H, dd, J = 15, 6 Hz), 2.45 (1 H, dd, J = 15, 4 Hz), 2.36 (1 H, dt, J = 16, 5 Hz), 2.11 (3 H, s), underlying 2.11 (1 H, m).

Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.21; H, 5.82.

6,6aα-Dihydro-2,9(3*H*,9aβ*H*)-dioxo-7-methylnaphthalene[1,8-*bc*]pyran-9bβ(3aα*H*)-carboxylic Acid, Methyl Ester (18a). A solution of 66.7 mg (0.21 mmol) of alcohol **16a** in 1 mL of TFA was stirred 5 min and the solvent was removed in vacuo. Recrystallization of the residue using 40% toluene/hexane afforded 46.8 mg (82%) of lactone **18a**: R_f (5% acetone/$CHCl_3$) 0.15; mp 171–171.5 °C; MS, m/z 276 (M^+), 121 (100); IR (KBr) 1735, 1700, 1630 cm^{-1}; ^1H NMR ($CHCl_3$, 360 MHz) δ 5.98 (1 H, m), 5.84 (1 H, s), 5.68 (1 H, dd, J = 11, 2.5 Hz), 4.98 (1 H, s), 3.72 (3 H, s), 3.18 (1 H, dd, J = 11, 7 Hz), 3.10 (1 H, m), 2.74 (1 H, dd, J = 17, 8 Hz), underlying 2.74 (1 H, m), 2.57 (1 H, dd, J = 18, 3 Hz), 2.04 (3 H, s), underlying 2.04 (1 H, m).

Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.05; H, 5.74.

8a-Carbomethoxy-7-hydroxy-5-methyl-8(8a*H*)-oxo-1,4-dihydronaphthalene-1-acetic Acid, Ethyl Ester (20). To a solution of 196 mg (0.61 mmol) of **15a** in 3 mL of THF was added 0.19 mL (1.57 M, 0.30 mmol) of potassium *tert*-butoxide in *tert*-butyl alcohol. After 19 h, the solution was diluted with ether and poured into 2% aqueous $NaHCO_3$. The layers were separated and the aqueous solution was further extracted with ether. The combined etheral solutions were washed with brine, dried (Na_2SO_4), and evaporated to give 150 mg (76%) of a 9/1 mixture of **20**/**15a**. Chromatography on silica gel (5% acetone/$CHCl_3$) and recrystallization (25% toluene/hexane) gave **20**: mp 129–131 °C; UV (MeOH) λ_{max} 365 nm (ϵ 3200), (MeOH with 2 drops of 4 N aqueous NaOH) λ_{max} 410 (ϵ 3200); MS, m/z 320 (M^+), 187 (100); IR (neat) 3420, 1735, 1640 cm^{-1}; ^1H NMR ($CHCl_3$) δ 6.42 (1 H, s), 6.14–5.57 (2 H, m), 410 (2 H, q, J = 7 Hz), 3.66 (3 H, s), 1.98 (3 H, d, J = 1 Hz), 1.23 (3 H, t, J = 7 Hz); calcd for $C_{17}H_{20}O_6$, M_r 320.126; found, M_r 320.127.

(26) (a) Stevens, R. V.; Chirpeck, R. E.; Harrison, B. C.; Lai, J. *J. Am. Chem. Soc.* **1976**, *98*, 6317. (b) Paul, R.; Tchelotcheff, S. *C. R. Hebd. Seances Acad. Sci.* **1974**, *224*, 118.

Acknowledgment. We thank the N. L. Tartar Fund and the National Institutes of Health (RR07079) for support of this work and Dr. Charles Klopfenstein at the University of Oregon for acquisition of the 360-MHz ^1H NMR spectra.

Registry No. **2a**, 4370-49-4; **2b**, 87567-88-2; **2b** (diol), 87568-17-0; **2c**, 87567-89-3; **2d**, 87567-90-6; **2d** (diol), 87568-18-1; **6a**, 105-67-9; **6b**, 89-56-5; **7a**, 15191-36-3; **7b**, 17746-75-7; **8a**, 2785-75-3; **8b**, 6049-93-0; **9**, 87567-91-7; **10**, 513-81-5; **11a**, 2004-70-8; **11b**, 87567-92-8; **11c**, 74054-58-3; **12**, 87567-93-9; **13**, 87567-94-0; **14**, 87567-95-1; **15a**, 87567-96-2; **15b**, 87567-97-3; **16a**, 87567-98-4; **16b**, 87567-99-5; **17a**, 87637-78-3; **17b**, 87637-79-4; **18a**, 87568-00-1; **18b**, 87568-01-2; **19a**, 87637-80-7; **19b**, 87637-81-8; **20**, 87568-02-3; **21a**, 5747-07-9; **21b**, 87568-03-4; **22**, 87585-82-8; **23a**, 87568-04-5; **23b**, 87637-82-9; **24a**, 87568-05-6; **24b**, 87637-83-0; **25a**, 87568-06-7; **25b**, 87637-84-1; **26**, 87568-07-8; **27**, 87638-48-0; 4a,5,8,8a-tetrahydro-4,6,7,8a-tetramethylnaphthalene-1,2-dione, 32249-85-7; 4a,5,8,8a-tetrahydro-4,8,8a-trimethylnaphthalene-1,2-dione, 87568-08-9; 4a,5,8,8a-tetrahydro-3,4a,8-trimethylnaphthalene-1,2-dione, 87568-09-0; 6-acetoxy-4a,5,8,8a-tetrahydro-4,8,8a-trimethylnaphthalene-1,2-dione, 87568-10-3; 6-acetoxy-4a,5,8,8a-tetrahydro-3,4a,8-trimethylnaphthalene-1,2-dione, 87568-11-4; methyl 1,8a-dihydro-5,6-dioxo-2,3,8-trimethylnaphthalene-4a-(4*H*)-carboxylate, 87568-12-5; methyl 1,8a-dihydro-4,8-dimethyl-5,6-dioxonaphthalene-4a(4*H*)-carboxylate, 87568-13-6; methyl 2-acetoxy-1,8a-dihydro-4,8-dimethyl-5,6-dioxonaphthalene-4a(4*H*)-carboxylate, 87568-14-7; 4-chloro-5,8-dihydro-1-hydroxy-3,4a,8-trimethylnaphthalen-2(4a*H*)-one, 87568-15-8; 6-acetoxy-4-chloro-5,8-dihydro-1-hydroxy-3,4a,8-trimethylnaphthalen-2(4a*H*)-one, 87568-16-9; methyl 1-chloro-8,8a-dihydro-5,8a-dimethyl-4-hydroxy-3(5*H*)-oxonaphthalene-2-carboxylate, 87585-83-9; *o*-chloranil, 2435-53-2.

Supplementary Material Available: Analytical and spectral details of the Diels–Alder cycloaddition products of quinones **2a–d** with the model dienes, and the preparation of **22–27** (11 pages). Ordering information is given on any current masthead page.

A Pyrolytic Route to the Phthalide–Isoquinolines

Varadaraj Elango and Maurice Shamma*

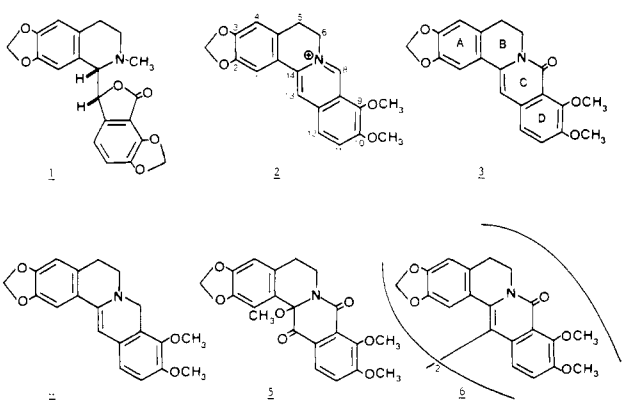
Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Received June 27, 1983

Pyrolysis of 8,13-dioxo-14-methoxycanadine (**5**) yields methyl keto ester **11** (35%), aromatic phthalide–isoquinoline **12** (15%), and (+)-chilenine (**13**, 7%). Methyl keto ester **11** can be reduced quantitatively to **12** with sodium borohydride. Catalytic reduction of **12** followed by N-methylation affords (±)-β-hydrastine (**18**) and (±)-α-hydrastine (**19**).

The phthalide–isoquinoline alkaloid (+)-bicuculline (**1**, Chart I) is a competitive antagonist of γ-aminobutyric acid (GABA), an important neurotransmitter in the mammalian nervous system.[1] The potential usefulness of (+)-bicuculline and other phthatlide–isoquinolines in this pharmacological area and the use of phthalide–isoquinolines as precursors in the synthesis of other isoquinoline alkaloids have prompted several investigations of new synthetic avenues for their preparation.[2]

Chart I



Specifically, we were interested in developing a simple and practical route to the phthalide–isoquinolines (±)-β-hydrastine (**18**) and (±)-α-hydrastine (**19**) starting with berberine (**2**), a common and inexpensive quaternary protoberberine alkaloid commercially available in ton quantities.

One of the "classical" reactions of berberine (**2**) is that it undergoes oxidation–reduction upon treatment with hydroxide base to supply in equal amounts oxyberberine (**3**) and the unstable dihydroberberine (**4**) which can readily be reoxidized to berberine.[3] It was also known that pyridinium chlorochromate oxidation of oxyberberine (**3**), followed by addition of methanol, supplied 8,13-dioxo-14-methoxycanadine (**5**).[4] Since **5** incorporates several of the structural features required for its transformation into a phthalide–isoquinoline, our efforts were focussed first

(1) Curtis, D. R.; Johnston, G. A. R. *Ergeb. Physiol., Biol. Chem. Exp. Pharmakol.* **1974**, *69*, 98. (b) DeFeudius, F. V.; Mandel, P., Eds. "Amino Acid Neurotransmitters"; Raven: New York, 1981. (c) Roberts. E.; Chase, T. N.; Towers, D. B., Eds "GABA in Nervous System Functions"; Raven: New York, 1976.

(2) (a) For the conversion of 8-methoxyberberine phenolbetaine to α- and β-hydrastine, see: Moniot, J. L.; Shamma, M. *J. Am. Chem. Soc.* **1976**, *98*, 6714; *J. Org. Chem.* **1979**, *44*, 4337. Moniot, J. L.; Hindenlang, D. M.; Shamma, M. *Ibid.* **1979**, *44*, 4343. (b) For the photochemical conversion of the nonnaturally occurring norcoralyne into an aromatic phthalide–isoquinoline, see: Imai, J.; Kondo, Y. *Heterocycles* **1977**, *6*, 959. Kondo, Y.; Imai, J.; Nozoe, S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 919. (c) For the conversion of the ophiocarpines into the hydrastines, see: Hanaoka, M.; Nagami, K.; Imanishi, T. *Chem. Pharm. Bull.* **1979**, *27*, 1947. (d) For the photolytic conversion of oxyberberine to β-hydrastine, see: Shamma, M.; Hindenlang, D. M.; Wu, T.-T.; Moniot, J. L. *Tetrahedron Lett.* **1977**, 4285. (e) For the transformation of 3-halophthalides into phthalide–isoquinolines, see: Slemon, C. E.; Hellwig, L. C.; Ruder, J.-P.; Hoskins, E. W.; MacLean, D. B. *Can. J. Chem.* **1981**, *59*, 3055. (f) For the utilization of Reissert intermediates, see: Kerekes, P.; Gaál, G.; Bognár, R.; Toro, T.; Costisella, B. *Acta Chim. Acad. Sci. Hung.* **1980**, *105*, 283. Hung, T. V.; Mooney, B. A.; Prager, R. H.; Ward, A. D. *Aust. J. Chem.* **1981**, *34*, 151. (g) For the formation of phthalide–isoquinolines by lithiation of alkoxyaromatics, see: Hung, T. V.; Mooney, B. A.; Prager, R. H.; Tippett, J. M. *Aust. J. Chem.* **1981**, *34*, 383. DeSilva, S. O.; Ahmad, I.; Snieckus, V. *Tetrahedron Lett.* **1978**, 5107. (h) For the use of electrochemical reduction, see Shono, T. *Yakugaku Zasshi* **1982**, *102*, 995. Shono, T.; Usui, Y.; Hamaguchi, H. *Tetrahedron Lett.* **1980**, *21*, 1351. (i) For the application of the Passerini reaction, see Falck, J. R.; Manna, S. *Ibid.* **1981**, *22*, 619. (j) For the condensation of isoquinolinium salts with phthalide anions, see Tippett, J. M.; Ward, A. D. *Aust. J. Chem.* **1981**, *34*, 1885.

(3) Perkin, W. H., Jr. *J. Chem. Soc.* **1918**, *113*, 722.

(4) Manikumar, G.; Shamma, M. *Heterocycles* **1980**, *14*, 827.

0022-3263/83/1948-4879$01.50/0