of PtO_2 and 20 mL of anhydrous ethanol. The flask was placed on the hydrogenation apparatus and the catalyst reduced for 20 h. During the first 15 min the finely dispersed catalyst coagulated to form larger particles. After extended reduction the fine dispersion again appeared.

To the reduced catalyst was added 5 mL of 4.2×10^{-3} M optically active binaphthyl ($[\alpha]^{23}_{589}$ +145°) in ethanol. Stirring was started, and the $t = 0$ and subsequent samples were removed by withdrawing 1-mL aliquots of the reaction suspension with a syringe fitted with an 18-gauge needle. The samples were then quickly filtered through a Swinny syringe filter and analyzed for optical activity. Kinetic data were treated as for the carbon-catalyzed reactions.[5]

For study of the effect of platinum concentration on the reaction rate, one of two methods was used. In one case a kinetic run was begun as above, but after about 1 half-life the stirring was stopped and the catalyst allowed to settle to the bottom of the flask. Some of the supernatant (typically one-third) was removed and the stirring started again at the new platinum concentration.

In the second method a kinetic run was also started as above and followed for times between 1 and 2 half-lives. After that time the stirring was stopped, and a fresh volume of optically active binaphthyl solution, of the same molarity as the reaction solution, was added. The reaction was started again at the new platinum concentration.

Both methods required a careful determination of the volume of samples removed in order to ascertain the change in solution volume when the supernatant was removed or more solution added. Both methods gave the same results; i.e., the rate did not change with a change in catalyst concentration.

The dependence of rate on binaphthyl concentration was determined by using a variation on the first method. After removal of some of the supernatant an equivalent volume of a higher concentration binaphthyl solution was added and the stirring restarted. In this way the binaphthyl concentration but not the catalyst concentration was changed.

Air used for poisoning was first filtered through $CaSO_4$ and then injected into the reaction solution over a period of 20 s. Cyclohexene (Matheson Coleman and Bell) was purified by being washed three times with equivalent volumes of saturated $NaHSO_3$ and three times with distilled H_2O, dried over $MgSO_4$, and then distilled under argon from CaH_2 (bp 82.5 °C uncor). Cyclohexane (Fisher, ACS certified) was purified by being shaken four times with an equivalent volume of 1:1 H_2SO_4 and HNO_3, washed to neutrality with saturated $NaHCO_3$, washed with distilled H_2O, dried over $MgSO_4$, and then distilled (bp 79.8 °C uncor). Both cyclohexene and cyclohexane was added to the stirred reaction suspension by slow injection over a period of 20 s.

Unsuccessful efforts were made to produce consistently separate batches of catalyst with the same or even similar activity. The ethanol, initially used as supplied, was dried and distilled. All glassware was cleaned with chromic acid, concentrated alcoholic potassium hydroxide, and acetone and dried in an oven. The hydrogenation apparatus was also cleaned. The hydrogen, in addition to being deoxygenated and dried, was passed through a liquid nitrogen trap to remove possible hydrocarbon contaminants. None of these cleanup procedures had a significant effect on increasing or reproducing catalyst activity. Platinum oxide which was years old would still produce an active catalyst, so variation of the platinum oxide did not appear to be the problem. Different methods of stirring were also tried with no success in improving catalysis. Running the catalyst through several oxidation-reduction cycles with hydrogen peroxide as the oxidant (and hydrogen as the reductant) did not improve the catalysis. Such unproductive efforts limited and finally prevented any expansion of the work at this time.

Acknowledgment. This work was supported by grants from the Natural Sciences and Engineering Research Council of Canada.

Registry No. 1,1'-Binaphthyl, 604-53-5; platinum, 7440-06-4.

Toward the Total Synthesis of Quassin

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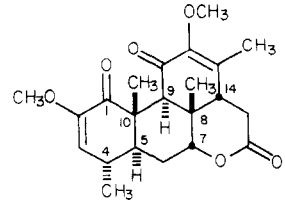
An approach to the synthesis of the diterpenoid quassin, 1, is given, centering around an intramolecular Diels-Alder reaction of the bis(orthoquinone) 2.

The structure of the diterpenoid quassin, 1, was elucidated by Valenta[2] and co-workers in 1961, culminating a study started in 1935 by Clark[3] on the isolates of quassia wood.[4] More recently work on quassin has been involved with its synthesis and in 1980 Grieco[5] and his collaborators published a total synthesis of *dl*-quassin. This paper is to report on our efforts toward the goal of the total synthesis of quassin.



1

There are seven asymmetric centers in quassin. Three of these centers, C(4), C(9), and C(14), are at epimerizable carbons. Quassin may be subjected to conditions (sodium methylsulfinylmethide in dimethyl sulfoxide) that would allow epimerization of these centers and is recovered unchanged. Thus, in devising a synthetic scheme only the

(1) This work was abstracted from the Ph.D. dissertations of D. E. Lee and L. F. Courtney. A preliminary report of this work was given at the 181st National Meeting of the American Chemical Society, Atlanta, GA, March 1981.

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

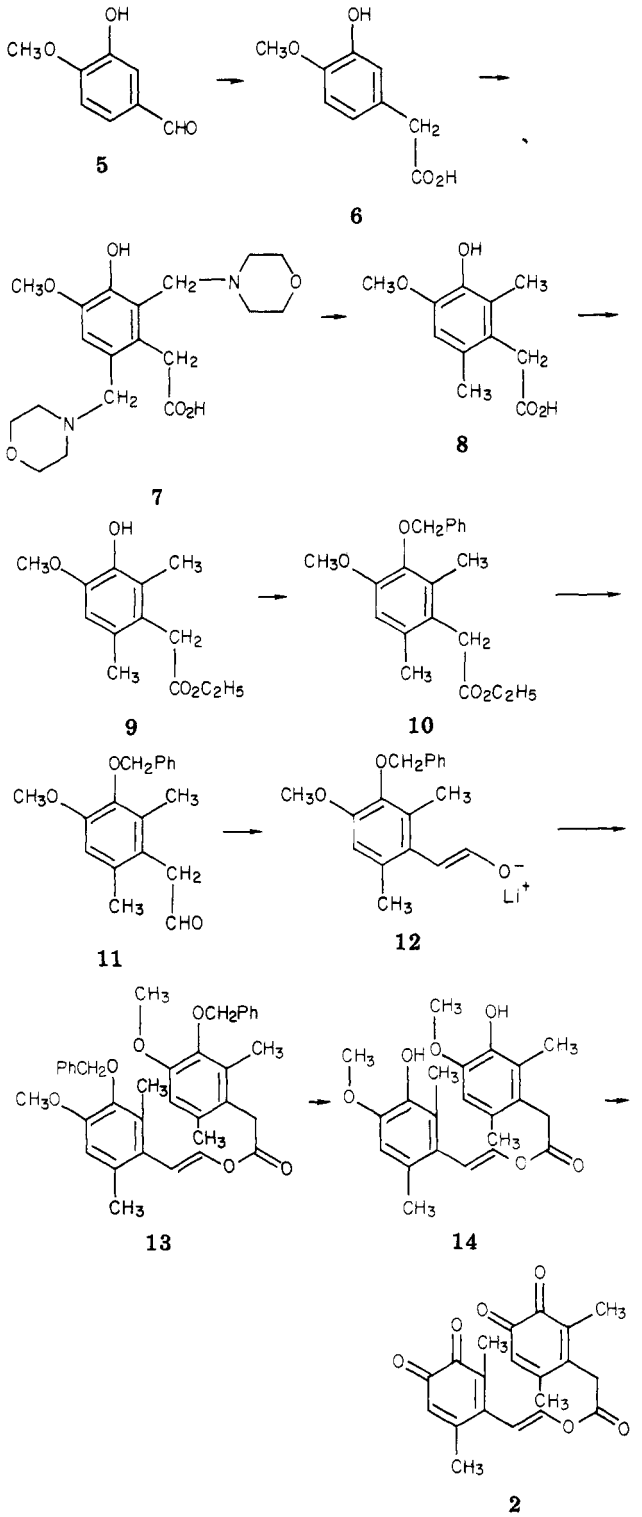
(3) Clark, E. P. *J. Am. Chem. Soc.* **1937**, *59*, 927, 2511.

(4) For a review, see Polonsky, J. *J. Fortschr. Chem. Org. Naturst.* **1973**, *30*, 101.

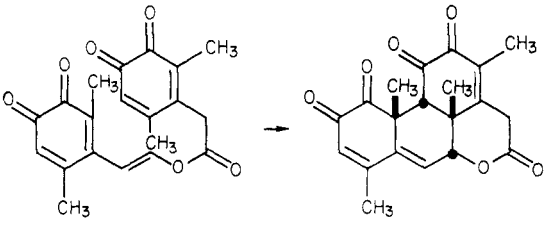
(5) Grieco, P. A.; Ferrino, S.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7587. In this paper there is referenced many earlier synthetic efforts.

0022-3263/82/1947-0610$01.25/0

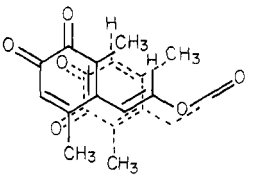
Scheme I



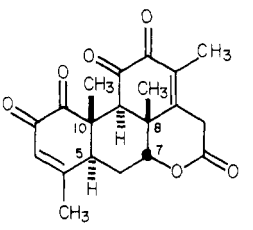
stereochemistry at the four centers C(5), C(7), C(8) and C(10) must be of prime concern, for the other centers could be eventually isomerized to the desired relative configurations. In the Grieco synthesis an intermolecular Diels–Alder reaction was used to establish the appropriate chirality at C(8) and C(10) with the desired stereochemistry at C(5) being built into the dienophile used and that at C(7) developed subsequently by the appropriate reduction of a carbonyl group. Our approach is centered about the intramolecular Diels–Alder reaction of the bis(orthoquinone) **2** to **3**. The Alder–Stein[6] rules of endo addition



(transition-state **2A**) would lead us to expect the desired stereochemistry at C(7), C(8), and C(10) to be generated.



Epimerization at C(9), followed by reduction of the 5,6 double bond (from the less hindered underside) would then provide **4** in which the proper stereochemistry at the four key centers, C(5), C(7), C(8), and C(10), obtains. The conversion of **4** to quassin would then involve precedented steps of reduction and methylation.

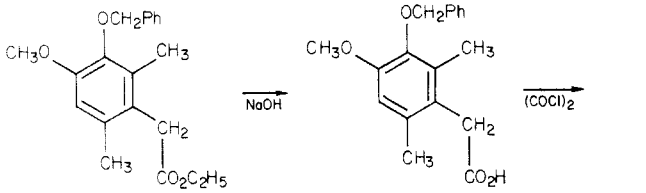


The initial goal of our approach, and the subject of this report, was the synthesis of the bis(orthoquinone) **2**. This substance has all of the carbons and functionality of quassin and lacks only two C to C bonds which would be established by the intramolecular Diels–Alder reaction. The synthetic plan for **2** is given in Scheme I.

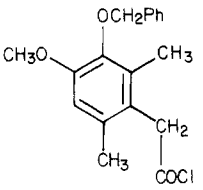
The conversion of isovanillin, **5**, to the phenylacetic acid **6** was accomplished according to the procedure of Grewe[7] as modified by Brossi.[8] It involved cyanohydrin formation followed by reductive hydrolysis. Mannich base **7** was generated with CH_2O, KOH, and morpholine in ethanol. The hydrogenolysis of **7** to **8** proved difficult and required 10% Pd/C in ethanol with acid catalysis at 125 °C and 2500 psi of hydrogen. The crude hydrogenolysis product was esterified to afford the phenolic ester **9** in 80% overall yield from **6**. Benzylation of **9** with K_2CO_3 and benzyl bromide gave **10** (91% yield), which was reduced with diisobutylaluminum hydride to the aldehyde **11** (98% yield). Our plan was to use aldehyde **11** as the source of enolate **12** and acylate this enolate with the acid chloride **15**. Compound **15** was prepared from intermediate **10** which had also served as the precursor of aldehyde **11**. Enolate **12** was generated with lithium 2,2,6,6-tetramethylpiperidide at 0 °C. It was found that equilibration of the *E* and *Z* enolates was effected at room temperature and that the equilibrium was strongly toward the *E* isomer.

(6) Alder, K.; Stein, G. *Angew. Chem.* **1937**, *50*, 510.

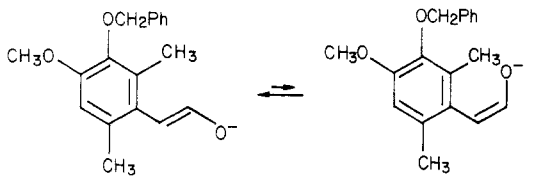
(7) Grewe, R.; Fischer, H. *Chem. Ber.* **1963**, *96*, 1520.
(8) Rice, K. C.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 592.
(9) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227.



10 17



15



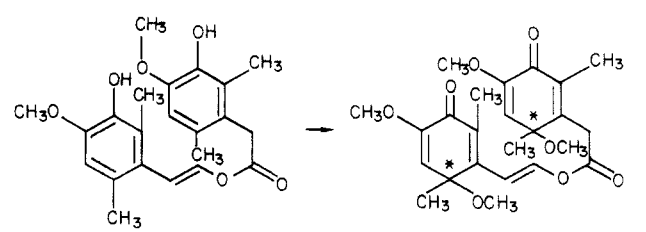
Thus, when the enolate was acylated at 0 °C, a mixture of the *E* and *Z* enol esters (from NMR spectral analysis) were obtained. This mixture could be separated by medium-pressure liquid chromatography. However, if the acylation was carried out at room temperature, only the *E* isomer, **13**, was formed and could be isolated in 54% yield.

The cleavage of the benzyl ethers in **13** with trimethylsilyl iodide was then studied. Initially the yields in this reaction were quite poor. It was found that purified trimethylsilyl iodide was required, for the hydrogen iodide impurity that normally accompanies trimethylsilyl iodide rapidly added to the enol ester double bond. This purification was accomplished by distilling the trimethylsilyl iodide over calcium hydride onto copper just before its use.

In addition to the purification of the cleavage reagent, we developed a modification of the usual workup procedure. The debenzylation was quenched with triethylamine, to remove the benzyl iodide formed in the course of the reaction, and after a water wash to separate the ammonium salts, the trimethyl silyl ethers were hydrolyzed to **14** by warming in methanol. By this procedure the cleavage of **13** to **14** could be realized in 80% yield.

The oxidation of **14** to **2** provided us with a signficant challenge. Many oxidants were tried, including sodium periodate, tetra-*n*-butylammonium periodate, potassium ferricyanide, vanadium oxytrichloride, and ferric chloride. For the most part, only unrecognizable products were produced.

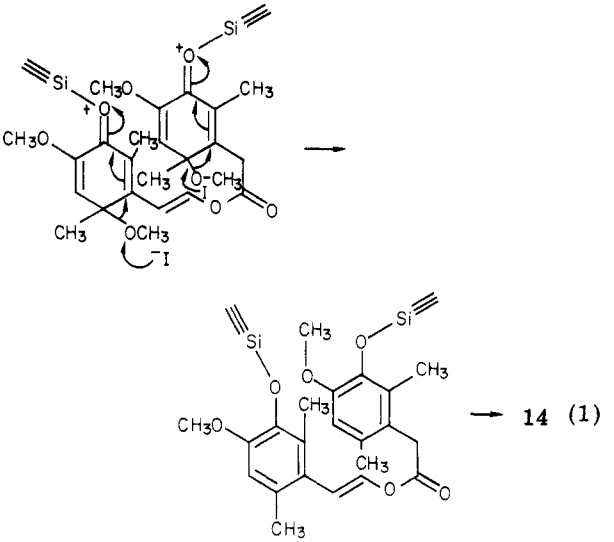
Thallium nitrate in methanol was successful in generating a product with the phenolic rings oxidized to the proper oxidation state; namely, compound **16**. In this



14 16

transformation two asymmetric centers are introduced into the molecule (starred). Compound **16** was isolated in 94% yield of chromatographed material which was homogeneous to thin-layer chromatography. Its NMR spectrum exhibited no spurious resonances in the *C*-methyl or *O*-methyl regions. However, it resisted attempts at crystallization and is most likely a mixture of diastereoisomers.

Efforts to hydrolytically convert **16** to the desired bis(*o*-quinone) **2** led to gross mixtures that could not be characterized. It became apparent that the enol ester was sensitive to usual hydrolysis conditions. Treatment of **16** with trimethylsilyl iodide returned phenol **14**, presumably via reaction 1.



14 (1)

The desired conversion of **14** to **2** was finally realized by using a procedure developed by Rapoport[9] using silver(II) oxide. Thus, when **14** was treated with AgO in tetrahydrofuran mixed with 6 N nitric acid (!) the bis(orthoquinone) **2** was produced and isolated as a red glass. The NMR and infrared spectra of **2** nicely establish its structure. A broad singlet at 2.07 ppm (6 H) represents the two methyls adjacent to the quinone carbonyls. Two closely spaced doublets (2.12 and 2.20 ppm, 3 H each) represent the two methyls β to the quinone carbonyls, each showing a 1–3 coupling with their respective vinyl quinone hydrogens. A broad singlet at 3.70 ppm (2 H) is due to the methylene adjacent to the enol ester carbonyl. A doublet centered at 5.94 ppm is the enol ester olefinic proton adjacent to the quinone ring. It shows coupling (13.5 Hz) with the other enol ester olefinic proton (centered at 7.46 ppm) and with one of the quinone methyls. A broad singlet at 6.25 ppm (2 H) represents the two quinone vinyl protons.

With **2** in hand we initiated a study of effecting the intramolecular Diels–Alder reaction that would form the final two carbon to carbon bonds needed for the constitution of the quassin ring system. Our results have been disappointing, with the usual conditions (Lewis acid catalyzed and uncatalyzed) for bringing about Diels–Alder cyclizations being ineffective in this instance. We attribute our difficulty to the deactivation of the diene moiety of **2** by the strong electron withdrawing substituents and will report subsequently on the consequences of modifying this part of the molecule to relieve this constraint.

Experimental Section

Melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were taken on a Varian EM 390 (90 MHz) or a Varian EM 360 (60 MHz). Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane, which was used as the internal standard. Coupling constants (J) are reported in hertz (Hz).

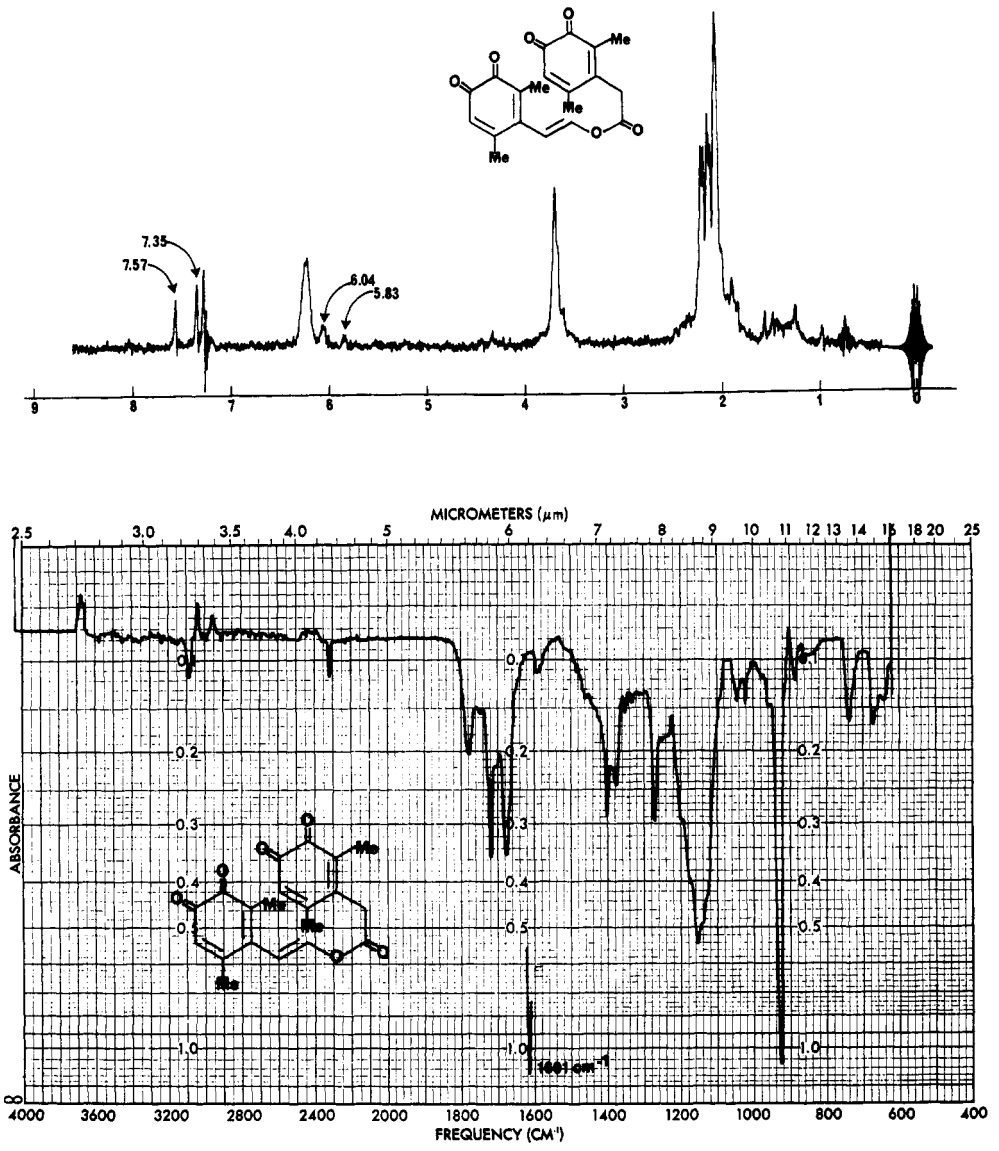


Figure 1.

Infrared spectra were taken on a PE 257, a PE 467, or a PE 727B spectrometer and are reported in reciprocal centimeters (cm^{-1}). Polystyrene film was used to calibrate spectra at 1601 cm^{-1}. Mass spectra were taken on a Finnigan 4000 GC/MS. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA.

Bis(morpholino) Mannich Base (7).[10] To a dry flask was added 3.26 g (110 mmol) of paraformaldehyde and a catalytic amount of potassium hydroxide in 28 mL of absolute ethanol. The flask was purged with nitrogen and cooled to 0 °C. Morpholine (9.54 g, 110 mmol) was added dropwise followed by the addition of 10.0 g (54.8 mmol) of **6** all at once after which the reaction was stirred at reflux for 12 h. The solvent was removed in vacuo to afford 21.07 g (100%) of **7** as a white foam: NMR (60 MHz, $(CD_3)_2CO$) δ 2.68 (m, 8 H), 3.51–4.02 (m, 12 H), 3.94 (s, 3 H), 4.09 (s, 2 H), 6.78 (s, 1 H); IR (KBr) 3040, 3005, 2898, 1735, 1600, 1500, 1485, 1465, 1412, 1361, 1342, 1320, 1275, 1127, 1012, 960, 920, 880 cm^{-1}.

Phenylacetic Ester 9.[11] Compound **7** (21.07 g, 60 mmol) 1.0 g of 10% Pd/C, 16 mL (192 mmol) of concentrated hydrochloric acid, and 400 mL of absolute ethanol were added to the glass liner of an Amico super-pressure reaction vessel. The reaction was hydrogenated, with shaking, at 2500 psi of hydrogen and 125 °C for 8 h. The catalyst was removed by filtration and the solvent was removed in vacuo. To this residue was added 150 mL of absolute ethanol and 3.0 mL of concentrated sulfuric acid. The reaction mixture was stirred at reflux under a nitrogen atmosphere for 6 h. The solvent was removed in vacuo and the residue diluted with ether. This solution was then washed with 10% bicarbonate and brine and dried over sodium sulfate. Evaporation of the solvent under reduced pressure provided 10.97 g of crude ester which was chromatographed on silica gel with ether/hexanes as the eluent to give 10.52 g (80% from **6**) of **9** as a colorless solid: mp 50.5–52.0 °C; NMR (90 MHz, $CDCl_3$) δ 1.22 (t, 3 H, J = 7 Hz), 2.18 (s, 3 H), 2.24 (s, 3 H), 3.60 (s, 2 H), 3.80 (s, 3 H), 4.45 (q, 2 H, J = 7 Hz), 5.66 (s, 1 H), 6.59 (s, 1 H); IR (KBr) 3495, 3250, 2950, 1704, 1607, 1512, 1472, 1352, 1338, 1290, 1190, 1108, 1022, 980, 920, 825 cm^{-1}; mass spectrum, m/e 238 (M^+, 23.91), 239 (M + 1, 3.51), 240 (M + 2, 0.22), 165 (M − 73, 100). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.48; H, 7.65.

[Methoxy(benzyloxy)phenyl]acetic Ester 10. Compound **9** (5.91 g, 24.8 mmol) and 17.0 g (123 mmol) of potassium carbonate in 100 mL of acetone saturated with potassium carbonate were stirred at reflux under a nitrogen atmosphere for 30 min. Benzyl bromide (6.0 mL, 49.6 mmol) was added all at once and the reaction was stirred at reflux for an additional 14 h. The solvent was removed in vacuo, and the residue diluted with water and extracted 3 times with ether. The combined extracts were washed with brine and dried over sodium sulfate. Evaporation of the solvent under reduced pressure and removal of the excess benzyl bromide under a high vacuum provided 7.46 g of crude benzyl ether derivative. Chromatography on silica gel with ether/hexanes as the eluent gave 7.38 g (91%) of pure **10** as a colorless solid: mp 43.0–44.0 °C; NMR (60 MHz, $CDCl_3$) δ 1.20 (t, 3 H, J = 7.0

(10) This procedure is essentially that given by Boschetti, E.; Molko, D.; Aknin, J.; Fontaine, L.; Grand, M. *Chim. Ther.* **1966**, *7*, 403; *Chem. Abstr.* **1967**, *66*, 94873.

(11) Previc, E. P. U.S. Patent 3461.72, 1969.

Hz), 2.20 (s, 3 H), 2.29 (s, 3 H), 3.58 (s, 2 H), 3.78 (s, 3 H), 4.10 (q, 2 H, J = 7.0 Hz), 4.90 (s, 2 H), 6.64 (s, 1 H), 7.39 (m, 5 H); IR ($CHCl_3$) 2950, 1730, 1595, 1485, 1460, 1450, 1340, 1320, 1275, 1225, 1150, 1110, 1075, 1020, 980, 900, 825 cm^{-1}; mass spectrum, m/e 328 (M^+, 13.10), 329 (M + 1, 2.33), 237 (M - 91, 14.30), 91 (M - 237, 100.00). Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.13; H, 7.38. Found: C, 72.87; H, 7.45.

[Methoxy(benzyloxy)phenyl]acetaldehyde 11.[12] Compound **10** (5.00 g, 15.0 mmol) was dissolved in 50 mL of dry ether and the flask was purged with nitrogen and cooled to -78 °C. A 22.50-mL sample (22.5 mmol) of 1 M diisobutylaluminum hydride in hexanes was added to the solution dropwise and the mixture was stirred at -78 °C over 30 min. The reaction was quenched with saturated ammonium chloride and the mixture allowed to warm slowly to room temperature. This was diluted with ether and washed with 10% hydrochloric acid, 10% sodium hydroxide, and water. Each aqueous wash was back-extracted with ether. The combined extracts were washed with brine and dried over sodium sulfate. Evaporation of the solvent under reduced pressure provided 4.30 g of the crude aldehyde. Chromatography on silica gel with ether/hexanes as the eluent afforded 4.20 g (98%) of pure **11** as a colorless solid: mp 32.0–33.0 °C; NMR (60 MHz, $CDCl_3$) δ 2.18 (s, 3 H), 2.37 (s, 3 H), 3.68 (d, 2 H, J = 3 Hz), 3.89 (s, 3 H), 4.95 (s, 2 H), 6.73 (s, 1 H), 7.43 (m, 5 H), 9.65 (t, 1 H, J = 3 Hz); IR ($CHCl_3$) 2960, 2750, 1720, 1685, 1600, 1490, 1470, 1455, 1380, 1330, 1290, 1225, 1115, 1085, 1010, 985, 850 cm^{-1}; mass spectrum, m/e 284 (M^+, 47.63), 285 (M + 1, 9.04), 286 (M + 2, 0.79), 193 (M - 91, 52.62. Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.02; H, 7.10. Found: C, 75.98; H, 7.14.

[Methoxy(benzyloxy)phenyl]acetic Acid 17. Phenylacetic (5.67 g, 17.3 mmol) ester **10** and 34.6 g (86.5 mmol) of sodium hydroxide in 100 mL of a 50/50 mixture of methanol/water were stirred at room temperature for 12 h. The solvent was removed in vacuo, and the residue was diluted with water and washed with two portions of methylene chloride. The alkaline aqueous phase was made acidic with dilute hydrochloric acid and extracted 3 times with methylene chloride. The combined extracts were washed with brine and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave 5.22 g (100%) of pure **17** as a colorless solid: mp 130.5–132.0 °C; NMR (60 MHz, $CDCl_3$) δ 2.24 (s, 3 H), 2.33 (s, 3 H), 3.62 (s, 2 H), 3.83 (s, 3 H), 4.92 (s, 2 H), 6.66 (s, 1 H), 7.40 (m, 5 H); IR ($CHCl_3$) 3050, 3000, 1715, 1610, 1495, 1475, 1340, 1230, 1130 cm^{-1}; mass spectrum, m/e 300 (M^+, 6.71), 301 (M + 1, 1.24), 209 (M - 91, 24.77), 91 (M - 209, 100.00). Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.97; H, 6.72. Found: C, 71.90; H, 6.74.

[Methoxy(benzyloxy)phenyl]acetyl Chloride 15.[13] Phenylacetic acid **17** (243 mg, 0.81 mmol) was dissolved in 10 mL of dry benzene and the flask was purged with nitrogen. Oxalyl chloride (85 μL, 0.97 mmol) was added all at once and the mixture stirred at room temperature for 14 h. The solvent, excess oxalyl chloride, and byproducts were removed in vacuo to provide 258 mg (100%) of **15** as a yellow oil. The acid chloride is not purified further but used immediately to prepare enol ester **13**: NMR (90 MHz, $CDCl_3$) δ 2.12 (s, 3 H), 2.27 (s, 3 H), 3.84 (s, 3 H), 4.08 (s, 2 H), 4.91 (s, 2 H), 6.64 (s, 1 H), 7.38 (m, 5 H); IR (neat 2950, 1800, 1492, 1465, 1460, 1380, 1335, 1285, 1230, 1195, 1120, 1085, 970, 955, 845, 800 cm^{-1}; mass spectrum, m/e 318 (M^+, 24.47), 319 (M + 1, 6.07), 320 (M + 2, 10.80), 321 (M + 3, 2.10), 255 (M - 63, 31.15), 227 (M - 91, 29.43).

Dimethoxy Bis(benzyloxy) Enol Ester 13. Lithium tetramethylpiperidide was prepared as follows. To a dry flask containing a trace of 2,2'-bipyridyl as an indicator was added 5 mL of dry tetrahydrofuran. The flask was purged with argon and cooled to 0 °C. 2,2,6,6-Tetramethylpiperidine (410 μL, 2.44 mmol) was added followed by the dropwise addition of 1.6 mL (2.44 mmol) of 1.5 M n-butyllithium in hexanes. The reaction mixture was warmed to room temperature and stirred for 15 min to afford 2.44 mmol of lithium tetramethylpiperidide.

To a cooled solution (0 °C) of lithium tetramethylpiperidide in THF was added 630 mg (2.22 mmol) of **11** in THF dropwise. After the addition was complete the reaction mixture was warmed to room temperature and stirred for 45 min still under an atmosphere of argon. Compound **15** (1.06 g, 3.33 mmol) was then added to the flask all at once and the reaction mixture was stirred at reflux for 3 h. The solvent was removed in vacuo and the residue diluted with ethyl acetate. This solution was washed with 10% hydrochloric acid and water, and the aqueous phases were back-extracted with ethyl acetate. The combined extracts were washed with brine and dried over sodium sulfate. Evaporation of the solvent under reduced pressure provided 1.10 g of crude trans (E) enol ester. The crude oil was filtered through silica gel with ether/hexanes as the eluent and recrystallized from ether/hexanes to give 680 mg (54%) of **13** as a colorless solid: mp 122.0–123.0 °C; NMR (90 MHz, $CDCl_3$) δ 2.17 (s, 3 H), 2.24 (s, 3 H), 2.30 (s, 3 H), 2.36 (s, 3 H), 3.74 (s, 2 H), 3.86 (s, 6 H), 4.95 (s, 4 H), 6.24 (d, 1 H, J = 13.5 Hz), 6.68 (s, 2 H), 7.37 (m, 11 H); IR ($CHCl_3$) 3045, 2970, 1750, 1670, 1610, 1495, 1475, 1465, 1450, 1390, 1335, 1230, 1155, 1125, 1080, 1000, 950, 855 cm^{-1}. Anal. Calcd for $C_{36}H_{38}O_6$: C, 76.29; H, 6.77. Found: C, 76.20; H, 6.81. The cis (Z) enol ester exhibited essentially the same NMR spectrum with one of the enol ester vinyl protons at 5.68 (d, 1 H, J = 6 Hz) in place of the 6.24 (d, 1 H, J = 13.5 Hz) resonance in the trans (E) isomer.

Dimethoxy Dihydroxy Enol Ester 14. Compound **13** (500 mg, 0.9 mmol) was dissolved in 5 mL of dry acetonitrile and the flask was purged with argon. Trimethylsilyl iodide[14] (282 μL, 2.0 mmol) was added to the flask and the reaction mixture stirred at 35–40 °C for 1 h. Triethylamine (500 μL, 3.6 mmol) was added and the reaction mixture stirred for an additional 1 hour at 35–40 °C. The solution was diluted with ethyl acetate and washed with two portions of 2% hydrochloric acid which were back-extracted with ethyl acetate. The combined extracts were washed with brine and dried over sodium sulfate. The solvent was removed to afford the silyl ether. The silyl ether was then hydrolyzed by taking it up in 5 mL of absolute methanol and warming this solution to reflux for a few minutes or until a precipitate formed in the bottom of the flask (product). The methanol was removed in vacuo, the residue taken up in ethyl acetate/hexanes, and the solution filtered through silica gel. The solvent was concentrated to initiate crystallization, providing 278 mg (80%) of **14** as a colorless solid: mp 181.0–181.5 °C; NMR (90 MHz, $CDCl_3$) δ 2.22 (s, 3 H), 2.27 (s, 3 H), 2.30 (s, 3 H), 2.37 (s, 3 H), 3.79 (s, 2 H), 3.90 (s, 6 H), 5.63 (s, 1 H), 5.66 (s, 1 H), 6.34 (d, 1 H, J = 13.5 Hz), 6.60 (s, 1 H), 6.65 (s, 1 H), 7.29 (d, 1 H, J = 13.5 Hz); IR ($CHCl_3$) 3580, 3070, 3000, 2900, 1750, 1665, 1630, 1500, 1475, 1455, 1310, 1260, 1200, 1150, 1130, 1010, 950, 855 cm^{-1}. Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.37; H, 6.79. Found: C, 68.38; H, 6.79.

Thallium Nitrate Oxidation to 16.[15] A flask containing 100 mg (0.26 mmol) of **14**, 2 mL of dry THF, and 7 mL of absolute methanol was purged with argon and cooled to 0 °C. Thallium trinitrate trihydrate (230 mg, 0.52 mmol) in methanol was added and the reaction mixture was stirred at room temperature for 15 min. The reaction was then filtered through silica gel with methylene chloride as the eluent to remove the thallium salts. This solution was washed with water and the aqueous layer back-extracted with methylene chloride. The combined extracts were washed with brine and dried over sodium sulfate. Evaporation of the solvent under reduced pressure provided 111 mg of crude **16**. Column chromatography through silica gel with ethyl acetate/hexanes as the eluent provided 107 mg (94%) of **16** as a yellow glass. In some of the preparations crystalline product was obtained from benzene/hexanes. However, this material had a broad melting point range. **16**: NMR (90 MHz, $CDCl_3$) δ 1.45 (s, 3 H), 1.54 (s, 3 H), 1.97 (s, 3 H), 2.08 (s, 3 H), 3.04 (s, 3 H), 3.08 (s, 3 H), 3.61 (d, 2 H, J = 6 Hz), 3.61 (s, 6 H), 5.68 (s, 2 H), 6.41 (d, 1 H, J = 13.5 Hz), 8.21 (d, 1 H, J = 13.5 Hz); IR ($CHCl_3$) 3050, 2980, 1765, 1660, 1635, 1470, 1390, 1360, 1230, 1140, 1080, 1040, 995, 875 cm^{-1}. Anal. Calcd for $C_{24}H_{30}O_8$: C, 64.55; H, 6.81. Found: C, 64.59; H, 6.81.

Bis(o-quinone) Enol Ester 2.[9] To a flask containing 100 mg (0.26 mmol) of **14** and 256 mg (2.1 mmol) of silver(II) oxide in 10 mL of dry THF, purged with argon and cooled to 0 °C, was

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Table I

solvent	temp, °C	catalysts[a]
THF	30–150	Et_2AlCl
benzene	80–150	$AlCl_3$
toluene	111	$BF_3 \cdot Et_2O$
xylenes	140	$TiCl_4$
methanol	65	$SnCl_4$
chloroform	61	

[a] The Lewis acid catalysts were used in a variety of solvents at room temperature or lower.

added 518 μL (3.1 mmol) of 6 N HNO_3 all at once with stirring. The reaction mixture was warmed to room temperature and stirred for 5 min. The red mixture was diluted with cold water and extracted 3 times with chloroform. The combined extracts were washed with brine and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave a "quantitative" yield of **2** free of starting material and byproducts according to its NMR spectrum. Significant decomposition of this material occurs within 24 h. NMR (60 MHz, $CDCl_3$) δ 2.07 (bs, 6 H), 2.12 (d, 3 H, J = 2.0 Hz), 2.20 (d, 3 H, J = 2.0 Hz) 3.70 (bs, 2 H), 5.94 (d, 1 H, J = 13.5 Hz), 6.25 (bs, 2 H), 7.46 (d, 1 H, J = 13.5 Hz); IR ($CHCl_3$) 3070, 1765, 1695, 1665, 1385, 1365, 1260, 1155, 925 cm^{-1}.

Trimethylsilyl Iodide Reaction with 16. This reaction was done in an NMR tube by dissolving 45 mg (0.01 mmol) of **16** in about 0.35 mL of $CDCl_3$. The tube was purged with argon and cooled to −78 °C, and 571 μL (0.404 mmol) of TMSI was added. The tube was allowed to warm to room temperature and the reaction followed in an NMR spectrometer. After 50 min the spectrum was identical with the spectrum of the bis(trimethylsilyl ether) of **14**, which was obtained in the cleavage of **13** by TMSI.

Diels–Alder Studies with 2. Table I lists the solvents, temperatures, and catalysts that have been tried. In each case the products formed under the reaction conditions listed in Table I were gross mixtures and could not be characterized. Usually polymeric precipitates were formed.

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Synthesis of 4,4,5,5-Tetradehydro and *cis*-4,5-Didehydro Prostacyclin Analogues

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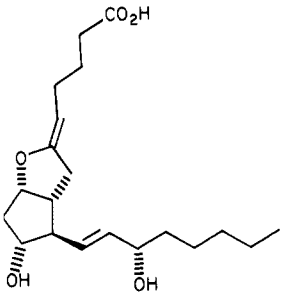
The synthesis of 4,4,5,5-tetradehydro and *cis*-4,5-didehydro prostacyclin analogues is described. The separation of the 6α and 6β isomers has been easily achieved at an early stage of the synthesis. The configuration of the 6α and 6β isomers has been determined by conversion of those isomers into 13,14-dihydro-6α-PGI_1 and 6β-13,14-dihydro-6β-PGI_1, respectively, via catalytic hydrogenation and correlation of the TLC mobilities of these isomers with authentic 13,14-dihydro-6α-PGI_1 and 13,14-dihydro-6β-PGI_1.

Introduction

It is well established that prostacyclin (PGI_2, 1) is both a potent inhibitor of platelet aggregation and a powerful vasodilator.[1] However, its inherent instability has attracted interest in the search for more stable analogues which will either mimic or split the biological profile of natural prostacyclin. One of the most logical variations has been to stabilize the enol ether functionality of the molecule. This objective has been achieved by converting the enol ether into the corresponding cyclic ether (PGI_1, **13b**)[2] or by shifting the double bond from C_{5-6} to C_{4-5} (*trans*-4,5-didehydro-PGI_1, **2**).[3] We report herein the straightforward synthesis of the 4,4,5,5-tetradehydro-PGI_1 analogues, **9a** and **9b**, and the *cis*-4,5-didehydro-PGI_1 analogues, **12a** and **12b**.

Results and Discussion

Since the *cis*-4,5-didehydro-PGI_1 analogues, **12a** and **12b**, could in theory be easily obtained from the partial hydrogenation of the corresponding 4,4,5,5-tetradehydro-PGI_1 analogues, **9a** and **9b**, the logical choice for the initial target



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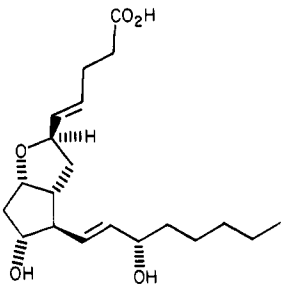

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for the synthesis was the acetylenic analogues. From our previous synthetic work on 4,5-acetylenic prostaglandins[4] we were aware that the intermediate yne-one **4a** was easily obtainable in one step from the Corey lactone **3**. We decided, therefore, to approach the synthesis via this intermediate. The key problems in this approach involved the following: (a) separation of the C-6 epimers, (b) cyclization of the diols **5a** and **5b**, and (c) determination of the configuration at C-6.

As is shown in Scheme I the Corey lactone **3** was reacted with 1.5 equiv of [4-[(dimethyl-*tert*-butylsilyl)oxy]pentynyl]lithium at room temperature for 1 h to give 86% of pure yne-one **4a** after chromatographic purification.[4] The appearance of a strong IR band at 1680 cm^{-1} indicated that the equilibrium favored the conjugated yne-one rather than the cyclic lactol. Sodium borohydride reduction of yne-one

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