residue was purified by flash chromatography (silica, CH_2Cl_2/CH_3OH, 0–1%) to yield the title compound as a yellow crystalline solid (49.8 mg, 0.10 mmol, 100%), mp 215–220 °C dec. No diiodination product was ever found when this procedure was used. However, from the reaction of deoxymethoxatin triester with excess I_2O_5 in refluxing DMF a compound was isolated that on the basis of MS, is presumably the diiodo compound.

^1H NMR ($CDCl_3$) δ 12.78 (1 H, br s), 8.87 (1 H, s), 8.03 (1 H, d, J = 9.0 Hz), 7.90 (1 H, d, J = 9.0 Hz), 4.48 (2 H, q, J = 7.0 Hz), 4.17 (3 H, s), 4.10 (3 H, s), 1.50 (3 H, t, J = 7.0 Hz); IR (KBr) 3350, 3050, 1725 cm^{-1}; MS, m/e 483 (M + 1, 21), 482 (100), 378 (38); absolute mass, calcd for $C_{18}H_{15}N_2O_6I$ 481.998, found 481.998.

Reduction of Deoxymethoxatin Triester 10. Method A. Zn/CF_3COOH. To a stirred solution of deoxymethoxatin triester **10** (36 mg, 0.10 mmol) in 4 mL of CF_3COOH was added a liberal excess of Zn powder. Stirring was continued for 35 min, after which the reaction mixture was evaporated without external heating. CH_2Cl_2 and aqueous $NaHCO_3$ were added, and the liquids were decanted from the remaining zinc, which was thereafter washed twice with CH_2Cl_2. The layers were separated; the aqueous layers were extracted once with CH_2Cl_2, and the combined organic layers were washed with H_2O and brine. After the solution was dried over Na_2SO_4, it was evaporated. The residue was subjected to preparative TLC (silica, CH_2Cl_2/acetone, 5%) to yield two fractions.

High-R_f compound: 9 mg (0.024 mmol, 24%) of a white crystalline solid, mp 164–167 °C (CH_2Cl_2/hexane), which was identified as *trans*-6,7,8,9-tetrahydrodeoxymethoxatin triester **15**; ^1H NMR ($CDCl_3$) δ 9.16 (1 H, br s), 7.41 (1 H, d, J = 8.8 Hz), 7.12 (1 H, d, J = 2.0 Hz), 6.56 (1 H, d, J = 8.8 Hz), 4.75 (1 H, br s), 4.53 (1 H, dd, J = 12.3 Hz, J = 2.5 Hz), 4.38 (2 H, q, J = 7.1 Hz), 4.02 (1 H, dd, J = 5.8 Hz, J = 1.5 Hz), 3.86 (3 H, s), 3.76 (3 H, s), 2.75 (1 H, ddd, J = 13.1 Hz, J = 2.5 Hz, J = 1.5 Hz), 1.85 (1 H ddd, J = 13.1 Hz, J = 12.2 Hz, J = 5.8 Hz), 1.42 (3 H, t, J = 7.0 Hz); IR (KBr) 3400, 3290, 2940, 1730, 1705, 1685 cm^{-1}; MS, m/e 360 (100), 301 (38), 241 (39), 195 (82); absolute mass, calcd for $C_{18}H_{20}N_2O_6$ 360.132, found 360.133.

Low-R_f compound: 21 mg (0.058 mmol, 58%) of a white crystalline solid, mp 99–100 °C, which was identified as *cis*-6,7,8,9-tetrahydrodeoxymethoxatin triester **15**; ^1H NMR ($CDCl_3$) δ 9.00 (1 H, br s), 7.41 (1 H, d, J = 9.2 Hz), 7.11 (1 H, d, J = 2.0 Hz), 6.55 (1 H, d, J = 9.2 Hz), 4.56 (1 H, br s), 4.37 (2 H, q, J = 7.0 Hz), 4.11 (2 H, two almost identical, superimposed dd, J = 5.5 Hz, J = 1.0 Hz, for both protons), 2.65 (2 H, two almost identical superimposed ddd, J = 14.5 Hz, J = 7.0 Hz, J = 5.5 Hz for both protons) 1.40 (3 H, t, J = 7.0 Hz); IR (KBr) 3390, 2930, 1720, 1670 cm^{-1}; MS, m/e 360 (100), 301 (36), 241 (34), 195 (70); absolute mass, calcd for $C_{18}H_{20}N_2O_6$ 360.132, found 360.132.

Method B. H_2/PtO_2, CF_3COOH. Deoxymethoxatin triester **10** (36 mg, 0.1 mmol) was dissolved in 0.8 mL of CF_3COOH. A small amount of PtO_2 was added and the solution was hydrogenated at normal pressure during 72 h. The solution was evaporated and the residue partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted once with CH_2Cl_2. The combined CH_2Cl_2 solutions were washed with H_2O and brine, dried on Na_2SO_4, and evaporated. The residue was purified on TLC as before to yield 27 mg (0.075 mmol, 75%) of the cis and 2 mg (0.006 mmol, 6%) of the trans tetrahydro compound **15**.

Acknowledgment. In addition to gifts of samples[31] we are grateful to Waters Associates for large-scale HPLC, to Prof. R. H. Abeles for interest and valuable discussion, to Dr. W. D. Weringa and A. Kiewiet, University of Groningen, The Netherlands, for 200-MHz NMR spectra and absolute mass spectra, and to the National Cancer Institute (National Institutes of Health) for partial financial support (Grant CA-23496).

Registry No. **1**, 72909-34-3; **2**, 73030-04-3; **4b**, 80721-35-3; **5a**, 7126-57-0; **6**, 95912-16-6; **7**, 95912-17-7; **8a**, 80721-36-4; **8a** (dibromide), 95912-26-8; **8b**, 80721-37-5; **8b** (ylide), 95912-18-8; (*E*)-**9**, 80721-38-6; (*Z*)-**9**, 80721-39-7; **10**, 80721-40-0; **12a**, 95912-19-9; **12b**, 95912-20-2; **12c**, 95912-21-3; **12d**, 95912-22-4; **13** (Y = Z = I), 95912-27-9; **13a**, 80721-41-1; **13c**, 80721-43-3; **13d**, 95912-23-5; **13e**, 95912-24-6; **14**, 80721-42-2; *cis*-**15**, 95912-25-7; *trans*-**15**, 95935-33-4; **16a**, 80721-44-4; **16b**, 80721-47-7; **17**, 80721-45-5; **18**, 80721-46-6; 2,4,6-trimethylpyridine, 108-75-8.

Stereospecific Intramolecular Diels–Alder Reaction of an *o*-Quinone Methide

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An *o*-quinone methide generated by the thermal dehydration of a functionalized 2-hydroxybenzyl alcohol was found to undergo the intramolecular Diels–Alder reaction. The presence of a remote chiral center on the dienophile resulted in complete sterocontrol during the transition state for cycloaddition. The synthesis of cyclized products **13** and **18** possessing the ring system and absolute configuration of naturally ocurring cannabinols is described.

In recent years there has been a great deal of interest in the intramolecular Diels–Alder reaction.[1] This interest stems from the fact that the intramolecular Diels–Alder reaction is both regioselective and stereospecific. As a consequence of its intramolecularity, this reaction may be employed to assemble complex polycyclic molecular structures in a single step. The use of *o*-quinodimethane derivatives as eneophilic partners in the intramolecular Diels–Alder reaction is well established.[2] We became interested in the chemistry of *o*-quinone methide in connection with another study in progress in our laboratories. We sought to determine whether a suitably functionalized *o*-quinone methide would participate as a diene in the intramolecular Diels–Alder reaction. Specifically, we were interested in the generation of substituted *o*-quinone methides by the thermal dehydration of *o*-hydroxybenzyl alcohol derivatives.

The intermolecular Diels–Alder cycloaddition of *o*-quinone methide has been known for some time.[3] Since

(1) For a review on the subject, see: Oppolzer, W. *Angew. Chem., Intl. Ed. Engl.* **1977**, *16*, 10

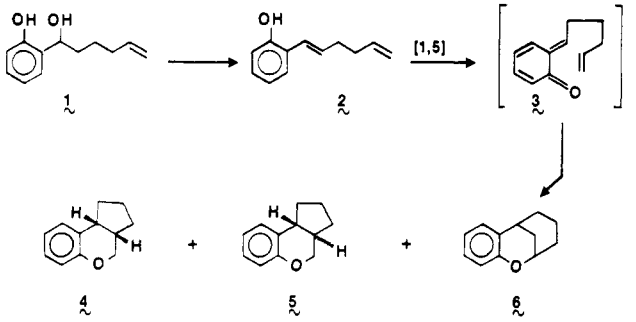
(2) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1982**, *104*, 7609–7622 and references therein.

(3) Chapman, O. L.; Engel, M. R.; Springer, J. P.; Clardy, J. C. *J. Am. Chem. Soc.* **1971**, *93*, 6696–6698.

0022-3263/85/1950-1695$01.50/0

the quinone methide is an inverse electron demand diene, most of the dienophiles employed have been electron rich. Dienophiles such as ketene acetals and vinyl ethers readily participate in the [4 + 2] cycloaddition with *o*-quinone methide. The cycloaddition of *o*-quinone methide with olefins substituted with mildly electron-releasing (alkyl) or electron-accepting substituents does not occur as readily.[4]

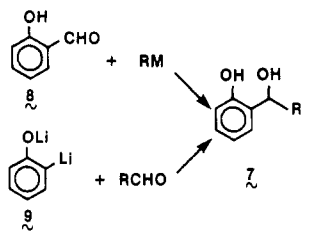
The intramolecular Diels–Alder reaction of an *o*-quinone methide, generated by the oxidation of a substituted *o*-allyl phenol, was employed for the biomimetric synthesis of carpanone.[3] The thermal dehydration of an *o*-hydroxybenzyl alcohol, followed by intramolecular Diels–Alder cycloaddition has been reported by two groups. Schmid[4] and co-workers reported that thermolysis of **1** at 147 °C resulted in dehydration to the styrene derivative **2**.



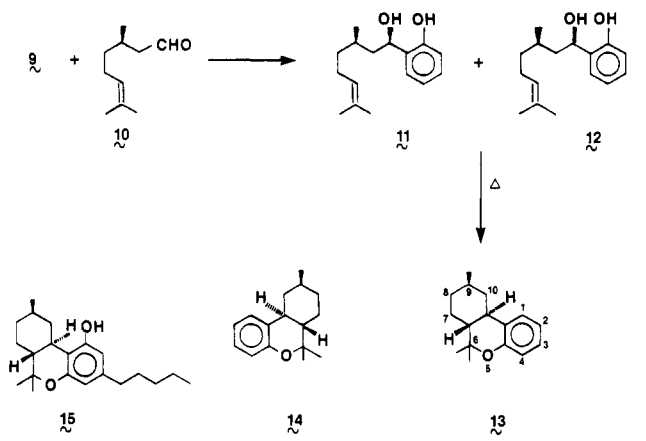
Prolonged heating of **2** at 270 °C produced the cycloadducts **3**, **4**, and **5** in a combined yield of 69%. It was postulated that a [1,5] hydrogen shift had occurred to generate *o*-quinone methide **3**, followed by a [4 + 2] cycloaddition to produce the observed products. Boeckelheide and Mao[5] reported that pyrolysis of **1** at 600 °C in a flow system gave the cyclized product **5** in 12% yield. Herein we report the details of our study on the regio- and stereospecific cycloaddition of *o*-quinone methides generated by the thermal dehydration of 2-hydroxybenzyl alcohol derivatives.

Results and Discussion

We chose to prepare the α-hydroxybenzyl alcohol precursors **7**, from the dianion **9** and an aldehyde, rather than



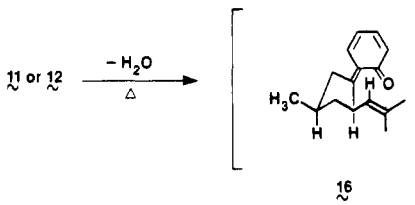
the condensation of salicylaldehyde (**8**) and an organometallic reagent. Treatment of *o*-bromophenol in ether at 0 °C with 2 equiv of *n*-butyllithium provided lithium *o*-lithiophenoxide (**9**) in excellent yield.[7] Reaction of the dilithium salt **9** with (*R*)-citronellal (**10**) in ether at −20 °C followed by protonation with NH_4Cl gave a 1:1 mixture of **11** and **12**. While **11** and **12** could be separated by silica gel chromatography, we found that the mixture could be used directly in the next step without separation. Heating



an *o*-dichlorobenzene solution of **11** and **12** to 180 °C for 0.25 h resulted in the formation of the cycloadduct **13** in 95% yield. The structure of **13** was based on its spectral properties.

The 300-MHz proton NMR spectrum of **13** contained a doublet at δ 0.96 (J = 6.6 Hz), for the C-9 methyl and singlets at δ 1.12 and 1.37 for the 6α and 6β methyls, respectively. The trans ring juncture was confirmed by the appearance of H-10a as a triplet of doublets ($J_{10a,6a}$ = $J_{10a,10\beta}$ = 10.5 Hz at δ 2.43 and H-10α as a broad doublet ($J_{10\alpha,10\beta}$ = 11.5 Hz) at 2.37. The multiplicity and the magnitude of the coupling constants was very similar to the reported value for the hexahydrocannabinol (**15**).[8] The absence of the C-1 hydroxyl in **13** resulted in a greater than 0.5-ppm upfield shift of the 10α proton as compared to **15**.[9] The proton-decoupled carbon-13 NMR of **13** showed the presence of 16 carbons, and the APT[10] and off-resonance decoupled spectra were consistent[11] with the assigned structure. The optical isomer **14** was also prepared by the aforementioned process starting with (*S*)-citronellal; its spectral properties were identical with those of **13**.

The stereospecificity of the cyclization of **11** and **12** and their optical isomers deserved comment. The cycloadduct **13** was obtained by thermal dehydration of both pure **11** and **12** as well as a 1:1 mixture of **11** and **12**. The *o*-quinone methide **16** formed by dehydration of **11** or **12** rapidly

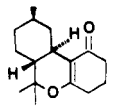


cycloadds to the remote olefin. A pseudoequatorial conformation adopted by the C-9 methyl in the chair-like transition state accounts for the observed stereospecificity. Since the ring fusion produced during the intramolecular Diels–Alder was trans, the exo transition state during cycloaddition must have been more energetically favorable than the endo transition state. A preference for the exo transition state was observed during the intramolecular cycloaddition of a substituted *o*-quinodimethane.[12] Tietze

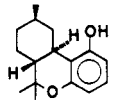
(4) Hug, R.; Hansen, H. J.; Schmid, H. *Helv. Chim. Acta* **1972**, *55*, 1675–1691.
(5) Boeckelheide, V.; Mao, Y. L. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1732–1734.
(6) Gilman, H.; Arntzen, C. E.; Webb, F. J. *J. Org. Chem.* **1945**, *10*, 374.
(7) Talley, J. J.; Evans, I. A. *J. Org. Chem.* **1984**, *49*, 5267–5269.
(8) Archer, R. A.; Boyd, D. B.; Demarco, P. V.; Tyminski, I. J.; Allinger, N. L. *J. Am. Chem. Soc.* **1970**, *92*, 5200–5206.
(9) The close proximity of the 10α-H to the C-1 hydroxyl is responsible for the downfield shift of this proton in a number of cannabinol derivatives, see: Fahrenholtz, K. E.; Lurie, M.; Kierstead, R. W. *J. Am. Chem. Soc.* **1976**, *89*, 5934–5941.
(10) Pratt, S. L.; Shoolery, J. N. *J. Magn. Reson.* **1982**, *46*, 535–539.
(11) The carbon-13 NMR of **13** was similar to hexahydrocannabinol, see: Hawkins, B. L.; Roberts, J. D. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 1027–1029.

reported the same stereospecificity during the preparation of **17** by intramolecular Diels–Alder reaction.[13]

We next turned our attention to the preparation of the known **18**,[14] a close relative of hexahydrocannabinol (**15**).



17



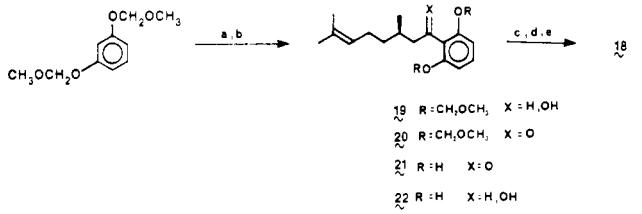
18

Regiospecific ortho-metalation of 1,3-bis(o-methoxymethyl)resorcinol with an equivalent of n-butyllithium[15] followed by condensation with (*R*)-citronellal gave a 1:1 mixture of diastereomers **19** in 67% yield after chromatography on silica gel (Scheme I). The plan was then to remove the methoxymethyl protecting groups to produce the hydroxyphenol **22**. Attempted removal of the protecting groups with a number of acidic and basic reagents resulted in the formation of numerous products. The problem was circumvented by oxidation of the mixture of diastereomers with Collins reagent. The ketone **20** was isolated in 83% yield after purification by silica gel chromatography. The structure of **20** was based on 300-MHz proton NMR analysis. The allylic methyls were observed at δ 1.60 (br s) and 1.64 (br s), and the methyl at C-9 was observed at δ 0.97 (d, J = 6 Hz). A pair of multiplets at δ 1.25 and 1.41 were assigned to the diastereotropic protons at C-10. The allylic methylene at C-11 displayed a multiplet at δ 2.00. The methylene protons at C-8 appeared as a pair of doublet of doublets at δ 2.61 and 2.80 (J = 8.1 Hz, J = 16.9 Hz) and (J = 5.2 Hz, J = 16.9 Hz), respectively. Irradiation of the C-9 methine located at δ 2.17 resulted in collapse of the C-8 protons into two doublets and the C-9 methyl to a singlet, indicating that the geminal coupling was 16.9 Hz. The methoxymethyl groups showed singlets at δ 3.44 (6 H) and 5.10 (4 H); the latter signal partially obscured the vinyl multiplet at δ 5.14. The aromatic protons were observed as a 2-H doublet at δ 6.79 (J = 8.4 Hz) and a 1-H triplet at δ 7.20 (J = 8.4 Hz). The 16-Line carbon-13 NMR was consistent with the assigned structure.

The cleavage of the methoxymethyl protecting groups was readily effected by treatment of **20** in boiling anhydrous methanol containing a catalytic amount of p-toluenesulfonic acid. The hydroxyphenol **21** was obtained in 91% yield after silica gel chromatography. The proton NMR of **21** was very similar to the spectrum obtained from **20**. The proton-decoupled carbon-13 NMR of **21** showed 14 lines and the off-resonance spectrum was consistent with the assigned structure. The infrared spectrum of **21** showed a strong OH band at 3340 cm^{-1} and a carbonyl stretching frequency at 1630 cm^{-1}.

Reduction of **21** with sodium borohydride in methanol at 0 °C produced the very acid-sensitive alcohols **22** in 95% yield. The presence of four allylic methyl resonances of approximately equal intensity in the proton NMR indicated that a 1:1 mixture of diastereomers had been formed. The absence of a carbonyl absorption in the infrared spectrum demonstrated that the desired alcohols had been produced. Allowing the neat oil or the chloroform solution

Scheme I[a]



[a] (a) n-BuLi, Et_2O, 25 °C, (*R*)-citronellal (b) $CrO_3 \cdot 2Py/CH_2Cl_2$, 25 °C, 2 h. (c) Anhydrous MeOH, Δ, p-TsOH. (d) $NaBH_4$·MeOH, 0 °C. (e) Δ or CF_3COOH.

to stand at room temperature resulted in the formation of cyclized product **18**. It was found that the optimum procedure for the preparation of **18** was to add several microliters of trifluoroacetic acid to a chloroform solution of **22** at room temperature. After neutralization of the trifluoroacetic acid and purification by recrystallization from n-hexane, the known **18**, mp 56–58 °C, was obtained in 87% yield. The proton NMR spectrum of **18** was identical with that reported by Tietze.[14] The very characteristic triplet of doublets at δ 2.48 for H-10a (J = 10.5 Hz) and broad doublet at δ 3.06 for H-10α (J = 12 Hz) confirmed that the desired cycloadduct had been obtained.

Conclusion. The intramolecular Diels–Alder reaction of suitably functionalized 2-hydroxybenzyl alcohols proceeds with excellent regio- and stereospecificity. The presence of a chiral center on the alkyl side chain resulted in a high degree of stereocontrol during the cycloaddition reaction. Starting with (*R*)-citronellal produced cyclized products with the ring system and absolute configuration of the cannabinol family of compounds.

Experimental Section

Melting points were determined on a Thomas Hooever apparatus and are uncorrected. Infrared spectra were recorded on a Beckman Microlab MX-250 instrument as neat liquids or chloroform solutions; absorbance positions are reported in reciprocal centimeters, cm^{-1}. Proton magnetic resonance spectra were recorded on Varian EM-390 (90 MHz) and Varian XL-300 (300 MHz) spectrometers, as solutions in deuteriochloroform. Chemical shifts are reported in ppm relative to tetramethylsilane as internal standard; observed coupling constants are in hertz. High-resolution mass spectra were recorded on a MAT instrument. Medium-pressure liquid chromatography was performed on silica gel, 0.032–0.063 mm, ICN, in Michael-Miller columns. Components were detected at 280 nm by a ISCO Model UA-5 UV detector. Thin-layer chromatography (TLC) was carried out with Whatman glass plates (0.25 mm) with silica gel. Tetrahydrofuran and ether were distilled from sodium benzophenone ketyl immediately prior to use. Dichloromethane and chloroform were distilled from P_2O_5 and stored over activated 3-Å molecular sieves.

2-((1*S*,3*R*)-1-Hydroxy-3,7-dimethyloct-7-enyl)phenol and 2-((1*R*,3*R*)-1-Hydroxy-3,7-dimethyloct-7-enyl)phenol (11 and 12). To a solution of n-butyllithium (75 mL, 0.116 mol, 1.55 M in hexane) in ether (50 mL) cooled to 0 °C was added o-bromophenol (10.0 g, 0.058 mol). After 2 h of stirring at room temperature, the solution was cooled to 0 °C, and (*R*)-citronellal (8.91 g, 0.0578 mol) in ether (20 mL) was added dropwise over a period of 30 min. The solution was stirred at 0 °C for 2 h and then quenched by the dropwise addition of concentrated ammonium chloride. The phases were separated and the aqueous phase was extracted with ether. The combined ethereal layer was washed with sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, and filtered, and the solution was concentrated to give a slightly yellow oil, 14.30 g. The oil was purified by flash chromatography on silica gel using 5:1 hexane/ethyl acetate as an eluant to give 13.55 g, 94%, of a mixture of desired diastereomers: R_f 0.63 and 0.59 (3:1 hexane/ethyl acetate); ^1H NMR (90 MHz) δ 0.92 (d, 3 H, J = 6 Hz), 1.30 (m, 3 H), 1.57 (s, 3 H), 1.63 (s, 3 H), 1.93 (m, 3 H), 2.33 (m, 1 H), 3.57 (br s, 1 H, exchanges

(12) Funk, r. L.; Vollhard, K. C. P. *J. Am. Chem. Soc.* **1977**, *99*, 5483–5484.

(13) Teitze, L. F.; Kiedrowski, G. V.; Harms, K.; Clegg, W.; Sheldrick, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 134–135. See also: Tietze, L. F.; Kiedrowski, G. V. *Tetrahedron Lett.* **1981**, *22*, 219–222.

(14) Tietze et al. (Tietze, L. F.; Kiedrowski, G. V.; Berger, B. *Tetrahedron Lett.* **1982**, *23*, 51–54) report mp 58 °C for **18**.

(15) Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Link, J. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 6885–6888.

with D_2O), 4.83 (m, 1 H), 5.10 (m, 1 H), 5.65 (br s, 1 H, exchanges with D_2O), 6.70–7.23 (m, 4 H); ^{13}C NMR (200 MHz) one diastereomer 17.63 (q), 20.12 (q), 25.25 (t), 25.69 (q), 28.90 (d), 37.55 (t), 44.42 (t), 73.74 (d), 117.00 (d), 119.81 (s), 124.75 (d), 126.94 (d), 127.12 (d), 128.29 (s), 128.61 (d), 155.27 ppm (s); IR (neat liquid) 3361, 2916, 2855, 1605, 1486, 1451, 1381, 1370, 1300, 1275, 1251, 1144, 749 cm^{-1}; mass spectrum, no parent ion seen by EI, M – H_2O at m/e 230.

(6a*R*,9*R*,10a*R*)-6,6,9-Trimethyl-1-hydroxy-6a,7,8,9,10,10a-hexahydro-6*H*-dibenzo[*b*,*d*]pyran (13). A solution of the benzyl alcohol mixture **11** and **12** (8.0 g, 0.032 mol) in 150 mL of *o*-dichlorobenzene was heated to reflux (180 °C) for 0.25 h under nitrogen. The solution was cooled to room temperature, and the solution was passed through a plug of glass wool to remove most of the water generated, then further dried over anhydrous magnesium sulfate, and filtered, and the solution was concentrated to give an oil. The crude product was purified by flash chromatography on silica gel using 15:1 hexane/ethyl acetate as an eluant to give 6.52 g, 88%, of colorless oil: R_f 0.75 (10:1 hexane/ethyl acetate); ^1H NMR (300 MHz) δ 0.96 (d, 3 H, J = 6 Hz), 0.80–1.67 (m, 6 H), 1.12 (s, 3 H), 1.37 (s, 3 H), 1.82 (m, 1 H), 2.37 (dm, 1 H, J = 11.5 Hz), 2.43 (td, 1 H, J = 10.5 Hz, J = 3 Hz), 6.80 (dd, 1 H, J = 8.1 Hz, J = 1.1 Hz), 6.84 (ddd, 1 H, J = 7.6 Hz, J = 7.5 Hz, J = 1.1 Hz), 7.08 (ddm, 1 H, J = 7.5 Hz, J = 8.1 Hz), 7.23 (br d, 1 H, J = 7.7 Hz); ^{13}C NMR (200 MHz) 20.07 (q), 22.50 (q), 27.52 (t), 27.93 (q), 32.37 (d), 34.72 (t), 35.45 (d), 39.46 (t), 46.71 (d), 77.12 (s), 116.96 (d), 119.40 (d), 125.30 (s), 125.82 (d), 127.08 (d), 153.11 ppm (s); IR (neat liquid) 2919, 2855, 1579, 1484, 1382, 1369, 1300, 1253, 1216, 1143, 956 cm^{-1}; mass spectrum calcd for $C_{16}H_{22}O$ 230.1671, found 230.1674.

2-((1*S*,3*S*)-1-Hydroxy-3,7-dimethyloct-7-enyl)phenol and 2-((1*R*,3*S*)-1-Hydroxy-3,7-dimethyloct-7-enyl)phenol. Reaction of lithium *o*-lithiophenoxide with (*S*)-citronellal gave a 1:1 mixture of diastereomers in 90% yield: R_f 0.63 and 0.59 (3:1 hexane/ethyl acetate); ^1H NMR (90 MHz) δ 0.92 (d, 3 H, J = 6 Hz), 1.30 (m, 3 H), 1.57 (s, 3 H), 1.63 (s, 3 H), 1.93 (m, 3 H), 2.33 (m, 1 H), 3.57 (br s, 1 H, exchanges with D_2O), 4.83 (m, 1 H), 5.10 (m, 1 H), 5.65 (br s, 1 H, exchanges with D_2O), 6.70–7.23 (m, 4 H); ^{13}C NMR (200 MHz) (one diastereomer) 19.14 (q), 20.12 (q), 25.44 (t), 25.69 (q), 29.20 (d), 36.64 (t), 44.26 (t), 73.38 (d), 117.00 (d), 119.81 (s), 124.75 (d), 126.94 (d), 127.12 (d), 128.61 (d), 131.22 (s), 155.27 ppm (s); IR (neat liquid) 3360, 2915, 2850, 1605, 1487, 1450, 1380, 1370, 1300, 1275, 1250, 1144, 750 cm^{-1}; mass spectrum, no parent ion observed, M – H_2O at m/e 230.

(6a*S*,9*S*,10a*S*)-6,6,9-Trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-dibenzo[*b*,*d*]pyran (14). Thermolysis of 2-((1*S*,3*S*)-1-hydroxy-3,7-dimethyloct-7-enyl)phenol and 2-((1*R*,3*S*)-3,7-dimethyloct-7-enyl)phenol in *o*-dichlorobenzene gave **14** in 92% yield: R_f 0.75 (10:1 hexane/ethyl acetate); ^1H NMR (90 MHz) δ 0.96 (d, 3 H, J = 6 Hz), 0.80–1.67 (m, 6 H), 1.12 (s, 3 H), 1.37 (s, 3 H), 1.82 (m, 1 H), 2.37 (dm, 1 H, J = 10.5 Hz), 2.43 (td, 1 H, J = 3 Hz, J = 10.5 Hz), 6.80 (dd, 1 H, J = 8.1 Hz, J = 1.1 Hz), 6.84 (ddd, 1 H, J = 7.7 Hz, J = 7.5 Hz, J = 1.1 Hz), 7.08 (ddm, 1 H, J = 7.5 Hz, J = 8.1 Hz), 7.23 (br d, 1 H, J = 7.7 Hz); ^{13}C NMR (200 MHz) 20.12 (q), 22.60 (q), 27.62 (q), 28.00 (d), 32.44 (t), 34.84 (t), 35.56 (d), 39.57 (t), 46.83 (d), 76.94 (s), 117.09 (d), 125.17 (s), 125.81 (d), 127.14 (d), 153.21 ppm (s); IR (neat liquid) 2968, 2928, 2857, 1486, 1451, 1300, 1253, 1215, 1143, 748 cm^{-1}; mass spectrum calcd for $C_{16}H_{22}O$ 230.1670, found 230.1673.

2-((1*R*,3*R*)-1-Hydroxy-3,7-dimethyloct-7-enyl)bis(*O*-methoxymethyl)resorcinol and 2-((1*S*,3*R*)-1-Hydroxy-3,7-dimethyloct-7-enyl)bis(*O*-methoxymethyl)resorcinol (19). To a stirred solution of *n*-butyllithium in hexane (30 mL, 1.3 M, 39 mmol) in 50 mL of anhydrous ether cooled to −15 °C was added 1,3-bis(*O*-methoxymethyl)resorcinol (7.722 g, 39 mmol). After warming to room temperature and stirring for an additional 6 h, (*R*)-citronellal (6.006 g, 39 mmol) was added, and the solution was stirred for an additional 1 h. The solution was quenched by the addition of saturated ammonium chloride. The ethereal phase was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude oil (12.728 g) was purified by medium-pressure liquid chromatography using hexane/ethyl acetate as eluant to give 9.12 g, 66%, of a 1:1 mixture of diastereomers: R_f 0.68 and 0.73 (3:1 hexane/ethyl acetate); ^1H NMR (90 MHz) δ 1.00 (d, 3 H, J = 6 Hz), 1.33 (m, 2 H), 1.54 (s, 3 H), 1.64 (s, 3 H), 1.88 (m, 5 H), 3.38 (s, 7 H, 6 H after exchange with D_2O), 5.10 (m, 1 H), 5.18 (m, 1 H), 6.76 (d, 2 H, J = 6 Hz), 7.13 (t, 1 H, J = 6 Hz); ^{13}C NMR (200 MHz) 17.59 (q), 20.38 (q), 25.29 (t), 25.67 (q), 29.78 (d), 36.98 (t), 45.12 (t), 56.20 (q), 66.44 (d), 94.64 (t), 108.24 (d), 121.84 (s), 124.98 (d), 128.22 (d), 130.84 (s), 155.53 ppm (s); IR (neat liquid) 3557, 2912, 1594, 1466, 1439, 1256, 1152, 1091, 1040 cm^{-1}; mass spectrum calcd for $C_{20}H_{32}O_5$ 352.2250, found 352.2251.

2-((3*R*)-3,7-Dimethyl-1-oxooct-7-enyl)bis(*O*-methoxymethyl)resorcinol (20). To a solution of dipyridine chromium(VI) oxide (20.04 g, 87 mmol) in 250 mL of dry dichloromethane was added a solution of the alcohols (5.11 g 14.5 mmol) in 20 mL of dichloromethane. The solution was stirred at room temperature for 3 h and then decanted from precipitated chromium salts. The chromium salts were washed with dichloromethane; the combined dichloromethane solution was washed with dilute hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave 4.22 g, 83%, of pure ketone: R_f 0.58 (3:1 hexane/ethyl acetone); ^1H NMR (300 MHz) δ 1.00 (d, 3 H, J = 6.6 Hz), 1.25 (m, 1 H), 1.41 (m, 1 H), 1.57 (s, 3 H), 1.67 (s, 3 H), 2.00 (m, 2 H), 2.17 (m, 1 H), 2.61 (dd, 1 H, J = 8.1 Hz, J = 16.9 Hz), 2.80 (dd, 1 H, J = 5.2 Hz, J = 16.9 Hz), 3.44 (s, 6 H), 5.10 (m, 1 H), 5.14 (s, 4 H), 6.79 (d, 2 H, J = 8.4 Hz), 7.20 (t, 1 H, J = 8.4 Hz); ^{13}C NMR (200 MHz) 17.63 (q), 19.86 (q), 25.54 (t), 25.71 (q), 28.50 (d), 37.09 (t), 52.35 (t), 56.20 (q), 94.59 (q), 108.29 (d), 122.97 (s), 124.62 (d), 130.34 (d), 131.20 (s), 154.19 (s), 204.16 ppm (s); IR (neat liquid) 2950, 2912, 1760, 1595, 1464, 1249, 1096, 1041, 922 cm^{-1}; mass spectrum calcd for $C_{20}H_{30}O_5$ 350.2093, Found 350.2094.

2-((3*R*)-3,7-Dimethyl-1-oxooct-7-enyl)resorcinol (21). A solution of the bis(*o*-methoxymethyl) ketone (3.812 g, 10.9 mmol) in 150 mL of anhydrous methanol containing *p*-toluenesulfonic acid (16 mg, 0.092) was heated to reflux for 12 h. The solution was poured into water and then extracted with ether. The ether layer was washed with saturated sodium bicarbonate and saturated sodium chloride and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave 2.681 g of material that was contaminated with some monoprotected material (R_f 0.74 on silica gel with 3:1 hexane/ethyl acetate). The product was purified by medium-pressure liquid chromatography using hexane/ethyl acetate as eluant to give 2.601 g, 91%, of pure dihydroxy ketone; R_f 0.50 (3:1 hexane/ethyl acetate); ^1H NMR (300 MHz) δ 0.97 (d, 3 H, J = 6.6 Hz), 1.28 (m, 1 H), 1.40 (m, 1 H), 1.59 (s, 3 H), 1.67 (s, 3 H), 2.02 (m, 2 H), 2.17 (m, 1 H), 2.93 (dd, 1 H, J = 8.0 Hz, J = 16.1 Hz), 3.20 (dd, 1 H, J = 5.4 Hz, J = 16.1 Hz), 5.10 (t, 1 H, J = 1.3 Hz), 6.14 (d, 2 H, J = 8.2 Hz), 7.23 (t, 1 H, J = 8.2 Hz); ^{13}C NMR (200 Hz) 17.64 (q), 19.93 (q), 25.61 (t), 25.68 (q), 29.61 (d), 37.33 (t), 52.04 (t), 108.48 (d), 110.55 (s), 124.63 (d), 131.36 (s), 135.88 (d), 161.30 (s), 208.24 ppm (s); IR (neat liquid) 3337, 2954, 2913, 1626, 1593, 1449, 1232, 1040 cm^{-1}; mass spectrum calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1567.

2-((1*S*,3*R*)-1-Hydroxy-3,7-dimethyloct-7-enyl)resorcinol and 2-((1*R*,3*R*)-1-Hydroxy-3,7-dimethyloct-7-enyl)resorcinol (22). To a stirred solution of the dihydroxy ketone (2.103 g, 8.03 mmol) in 20 mL of anhydrous methanol cooled to 0 °C was added sodium borohydride (0.400 g, 10.6 mmol). The solution was stirred at the temperature for a period of 20 min and then diluted with water. The aqueous phase was extracted with ether, the ether solution was washed with brine, dried over anhydrous magnesium sulfate, and filtered, and the solvent was evaporated. The crude oil was purified by medium-pressure liquid chromatography on silica gel using 3:1 hexane/ethyl acetate as eluant to provide 2.005 g, 94%, of unstable oil which was used directly in the next step. Upon standing, the mixture of alcohols rapidly was converted into the cyclized material: R_f 0.22 (3:1 hexane/ethyl acetate); ^1H NMR (90 MHz) δ 0.97 (d, 3 H, J = 6 Hz), 1.33 (m, 3 H), 1.60 (s, 3 H), 1.67 (s, 3 H), 1.97 (m, 3 H), 2.83 (m, 1 H), 3.52 (br s, 1 H, exchanges with D_2O), 5.13 (br t, 1 H, J = 6 Hz), 5.50 (m, 1 H), 6.40 (d, 2 H, J = 7.5 Hz), 7.00 (t, 1 H, J = 7.5 Hz), 7.10 (br s, 2 H, exchanges with D_2O); IR ($CHCl_3$ solution) 3583, 3340, 2913, 2852, 1601, 1459, 1286, 1000 cm^{-1}; mass spectrum, only M – H_2O was observed.

(6a*R*,9*R*,10a*R*)-6,6,9-Trimethyl-1-hydroxy-6a,7,8,9,10,10a-hexahydro-6*H*-dibenzo[*b*,*d*]pyran (18). To a stirred solution of the phenol alcohol (520 mg, 1.97 mmol) under nitrogen in 50 mL of chloroform was added 0.05 mL of trifluoroacetic acid (0.074 mmol). The solution was stirred at room temperature for a period

of 3 h, and then the reaction mixture was poured into saturated aqueous sodium bicarbonate, the phases were separated, and the aqueous phase was extracted with chloroform. The combined chloroform layer was dried over anhydrous magnesium sulfate and filtered and the solution was concentrated to give an off-white solid that was further purified by medium-pressure liquid chromatography on silica gel using hexane/ethyl acetate as eluant to give 423 mg, 87%, of pure product: mp 56–58 °C; R_f 0.31 (3:1 hexane/ethyl acetate); ^{1}H NMR (90 MHz) δ 0.93 (d, 3 H, J = 6 Hz), 1.05 (s, 3 H), 1.35 (s, 3 H), 0.5–1.95 (m, 7 H), 2.48 (td, 1 H, J = 10.5 Hz, J = 2.5 Hz), 3.06 (dm, 1 H, J = 12 Hz), 4.73 (s, 1 H, exchanges with D_2O), 6.18 (dd, 1 H, J = 8 Hz, J = 1.5 Hz), 6.35 (dd, 1 H, J = 8 Hz, J = 1.5 Hz), 6.88 (t, 1 H, J = 8 Hz); ^{13}C NMR (200 MHz) 18.94 (q), 22.58 (q), 27.70 (q), 28.08 (d), 32.98 (t), 35.52 (t), 35.59 (d), 38.84 (t), 49.15 (d), 77.22 (s), 107.26 (d), 110.29 (d), 113.14 (s), 127.19 (d), 155.04 (s), 155.31 ppm (s); IR ($CHCl_3$) 3352, 2966, 1615, 1588, 1450, 1220, 1020 cm^{-1}; mass spectrum calcd for $C_{16}H_{22}O_2$ 246.1620, found 246.1610.

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Registry No. **9**, 55274-02-7; (*R*)-**10**, 2385-77-5; (*S*)-**10**, 5949-05-3; (1*R*,3*R*)-**11**, 95891-86-4; (1*S*,3*S*)-**11**, 95891-96-6; (1*S*,3*R*)-**12**, 95891-87-5; (1*R*,3*S*)-**12**, 95891-97-7; **13**, 95891-88-6; **14**, 95891-89-7; **18**, 81710-25-0; (1*R*,3*R*)-**19**, 95891-90-0; (1*S*,3*R*)-**19**, 95891-91-1; **20**, 95891-92-2; **21**, 95891-93-3; (1*R*,3*R*)-**22**, 95891-94-4; (1*S*,3*R*)-**22**, 95891-95-5; bis(*O*-methoxymethyl)resorcinol, 3688-89-9.

Catalyzed Oxidative Nitration of Nitronate Salts[1]

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Nitronate salts are converted to *gem*-dinitro compounds with nitrite ion and persulfate, in the presence of a catalytic amount of ferricyanide. The use of cyanide or sulfinate salts in place of nitrile gave *gem*-cyanonitro compounds and α-nitro sulfones, respectively.

A convenient laboratory procedure for the conversion of primary and secondary nitroalkanes to *gem*-dinitro compounds is the oxidative nitration reaction of Kaplan and Shechter.[2] In this reaction a nitronate salt is oxidized with silver nitrate in the presence of nitrite ion. A drawback of the reaction is the expense of the silver nitrate reagent.

$$R_1R_2C{=}NO_2^- \xrightarrow[AgNO_3]{NaNO_2} R_1R_2C(NO_2)_2$$

More recently, Mataoz, Piotrowska, and Urbanski[3] reported that potassium ferricyanide can be used in place of the silver salt with secondary nitro compounds. Subsequently, Kornblum et al.[4] found conditions that were also applicable to primary as well as secondary nitroalkanes and applied the reaction to many examples. The quantities of reagents used, however, make the method unattractive for large scale preparations.[5] The applicability of the reaction in the presence of other functional groups was not reported. We had a need for 2,2-dinitro alcohols, and attempts to apply these conditions to the preparation of 2,2-dinitropropanol and 2,2-dinitropropanediol resulted in only trace yields.

Another mild oxidant that acts on nitronate ions is persulfate ion, which has a much lower equivalent weight than ferricyanide. However, the reaction of persulfate with the salt of 2-nitropropane in the presence of nitrite ion was reported to result only in dimerization to give 2,3-dimethyl-2,3-dinitrobutane.[3] It is known, however, that persulfate oxidizes ferrous to ferric ion,[6] so it appeared conceivable that persulfate could be used as the oxidant for obtaining *gem*-dinitro compounds in the presence of a catalytic amount of ferricyanide. The reduced iron salt resulting from the nitration would be continually reoxidized.

This combination was found to be effective for the oxidative nitration of nitro compounds with a variety of functional groups. Examples are summarized in Table I.

The reactions were generally conducted at 25–35 °C in aqueous solution with ether, tetrahydrofuran, or methylene chloride as an organic cosolvent, and ice-bath cooling was used to control the initial exotherm. Optimum yields were obtained with the use of 4–5 mol of sodium nitrite per mol of nitro compound, and yields were 10–20% lower with 1–2 mol of nitrite. Stoichiometric amounts of sodium persulfate and catalytic amounts of potassium ferricyanide (0.1–0.2 equiv) were used.

2,2-Dinitropropane,[3] 1,1-dinitrocyclohexane,[3,4] 1,1-dinitrocyclopentane,[4] and 2,2-dimethyl-5,5-dinitro-1,3-dioxane[3] were reported previously with ferricyanide as the oxidant. Products listed in Table I that were previously prepared by the oxidative nitration with silver nitrate are 2,2-dinitropropane,[2] 1,1-dinitrocyclohexane,[2] 1,1-dinitroethane,[2] 1,1-dinitrobutane,[9] 4,4-dinitro-1-butene,[7] 3,3-dinitrooxetane,[8] 2,2-dinitropropanol,[2] and 2,2-dinitropropanediol.[1,9] Other syntheses of 2,2-dinitropropyl methyl ether[10] and 2,2-dimethyl-5,5-dinitro-1,3-dioxane[11]

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