Intramolecular Diels-Alder Reactions. XI. Modal Selectivity in the Syntheses of Some Parent Cyclolignan Lactones (1)

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$Ph(C_2)CH_2Cl$ and $Ph(C_2)'CO_2Na$ [where (C_2) = -C≡C- or *trans*-CH=CH-, $(C_2)'$ = -C≡C- or *cis*-CH=CH-] reacted in refluxing dimethylformamide to yield unsaturated esters $Ph(C_2)'CO_2$-$CH_2(C_2)Ph$ and/or their intramolecular Diels-Alder cyclization products (cyclolignan lactones). It was found that modal selectivity for cyclization in DMF sometimes varies from that found previously with acetic anhydride as solvent. Two new parent tetrahydrocyclolignan lactones were synthesized.

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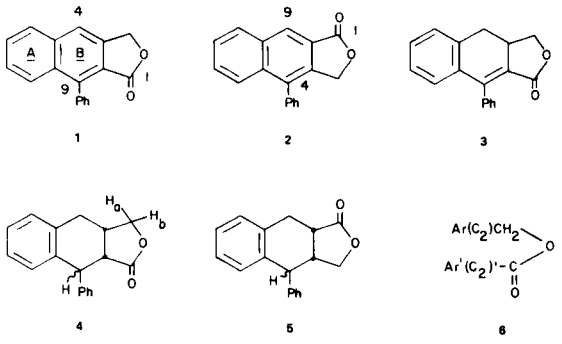
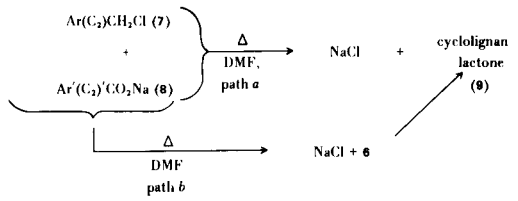
Cyclolignan lactones are natural products which occur in two major skeletal series, 9- and 4-phenylnaphtho-[2,3-*c*]furan-1(3*H*)ones, (**1**) and (**2**), respectively. Within these series ring *B* may be aromatic (as in **1** and **2**) or hydroaromatic (as in dihydro compound **3** and the tetrahydro compounds **4** and **5**). As a rational synthetic route to these parent structures and their ring-substituted derivatives we visualized a Diels-Alder condensation between an unsaturated alcohol moiety $Ar(C_2)CH_2OH$ and an unsaturated acid moiety $Ar'(C_2)'CO_2H$, where (C_2) and



$(C_2)'$ are variously *cis*-CH=CH-, *trans*-CH=CH-, or -C≡C- units. Two approaches have been developed, namely the thermal cyclization (usually in refluxing acetic anhydride) of the preformed ester **6**, *i.e.*, an intramolecular Diels-Alder reaction (4-9), and the *in situ* reaction of an unsaturated chloride **7** (formed from the alcohol) with the sodium salt **8** of the unsaturated acid in refluxing dimethylformamide (DMF) (10). Two plausible, significantly different

Scheme 1

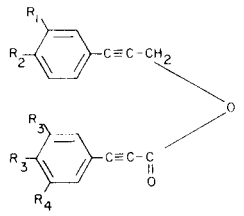


mechanistic pathways are envisioned for the transformation in DMF (Scheme 1). Path *b* is a two-step sequence, wherein the unsaturated ester **6** forms as an intermediate and subsequently cyclizes to the cyclolignan lactone **9**. It was the only pathway considered in an earlier investigation (10), wherein three cases of the type (C_2) = *trans*-CH=CH-, $(C_2)'$ = -C≡C- gave comparable yields of parent compound **3** and two of its ring-substituted derivatives by either the acetic anhydride or the DMF methods. Path *a*, on the other hand, would not involve intermediate **6**. It would occur either by initial [4 + 2] intermolecular cycloaddition of **7** and **8**, followed by lactone formation; or (as seems more likely) it would be a concerted intermolecular process, wherein cycloaddition and lactone formation take place in a single step.

As noted in two other papers (11,12) Diels-Alder formation of products in cyclolignan lactone series **1** results from mode 1 cyclization [believed to involve interaction between the highest occupied molecular orbital (HOMO) of the 4π-electron system in the $Ar(C_2)$ portion (electron donor) and the lowest unoccupied molecular orbital (LUMO) of the 2π-electron system in the $(C_2)'$ unit

(electron acceptor)] and formation of products in series **2** results from mode 2 cyclization [from interaction between the HOMO of the 4π-electron system in the $Ar'(C_2)'$ portion and the LUMO of the 2π-electron system in the (C_2) unit]. In the present paper we consider the modal selectivities and reaction mechanisms which prevail in the syntheses of some parent cyclolignan lactones (Ar = Ar' = Ph) by the DMF method.

Refluxing an equimolar mixture of sodium phenylpropiolate and phenylpropargyl chloride in DMF gave a mixture of **2** (15% yield) and **1** (6% yield). The predominance of **2** in the condensation-cyclization product from DMF (mode 2:mode 1 = 2.5:1) contrasts with isolation of **1** only (39%) from refluxing phenylpropargyl phenylpropiolate (**10a**) in acetic anhydride (6). However, mode 2 cyclization is preferred (2.7:1 and 1.2:1) in cases **10b** and **10c**, where the phenyl groups bear methoxy or methylenedioxy substituents (5). A mixture of **1** and **2** has also been reported (13) from reduction of 1-phenylnaphthalene-2,3-



a: R_1 R_2 R_3 R_4 H
b: R_1 R_2 R_3 MeO; R_4 H
c: R_1R_2 OCH_2O; R_3 R_4 MeO

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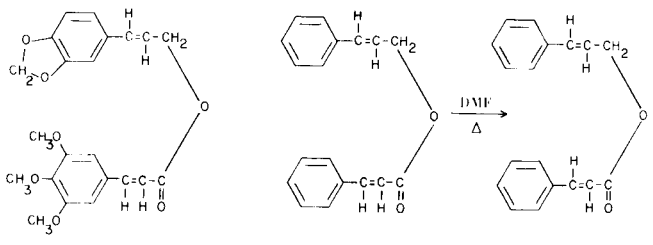
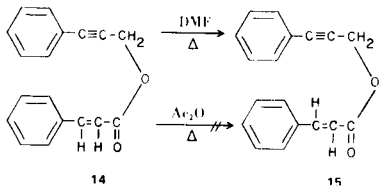
dicarboxylic acid anhydride with zinc and sulfuric acid in acetic acid or with lithium aluminum hydride in tetrahydrofuran.

Refluxing sodium *cis*-cinnamate with *trans*-cinnamyl chloride in DMF for 35 hours produced a 31% yield of crystalline **5**. Its structure was assigned on the basis of its infrared spectrum (*cis*-lactone) (14) and its oxidation to **2**. Stereochemistry at C-4 was not established (15). However, this cyclization in mode 2 again contrasts with previous



11 12 13



14 15

results from the Diels-Alder condensation in mode 1 (20% yield) of ester **11** in acetic anhydride.

The extended reaction period used in the synthesis of **5** was chosen on the basis of reaction sampling as a function of time. After 5 hours of reaction time the mixture consisted mainly (> 95%) of the isomeric open-chain esters *trans*-cinnamyl *cis*-cinnamate (**12**) and *trans*-cinnamyl *trans*-cinnamate (**13**). After 30 hours of refluxing there appeared to be 35-50 mole % of lactone **5** present, while **12** plus **13** still comprised 50% of the mixture. In a separate run it was noted that preformed **13** (16) does not cyclize in DMF over an extended period of refluxing (17). Thus, it is now apparent that path *b* (with **12** as an intermediate) prevails and that neither path *a* nor the transformation **12→13→5** occurs. On this basis we ascribe the difference in modal selectivity in Diels-Alder cyclizations of **11** and **12** either to ring substituent effects or solvent effects (or both) on the HOMO and LUMO energy levels of the alcoholic and acidic moieties of ester **12**.

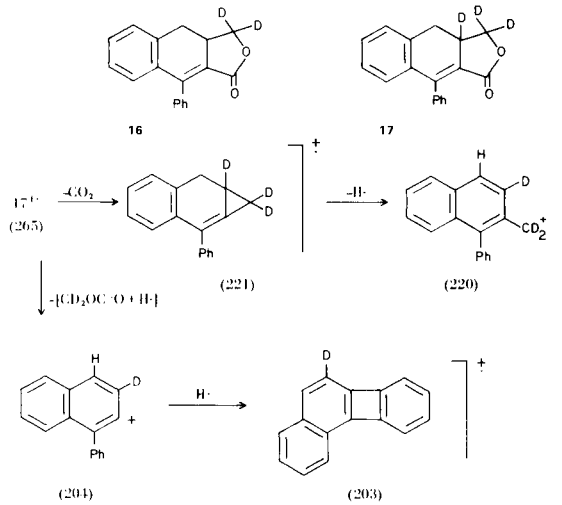
The reaction of sodium *cis*-cinnamate with phenylpropargyl chloride in refluxing DMF was followed in the aforementioned manner. After 5 hours there were approximately equimolar amounts of **14** and **15** present. After 27 hours only **15** remained; no lactone product was found. To see if acetic anhydride would effect cyclization of **14** this compound was synthesized in DMF (40 minutes reaction time), transferred to acetic anhydride, and refluxed for 24 hours. Neither cyclization of **14** nor isomerization to **15** occurred. The failure of **15** to cyclize in acetic anhydride was noted previously (6). Hence, it is now apparent that **13-15** do not undergo intramolecular Diels-Alder reaction in either refluxing acetic anhydride or DMF (6).

As a synthetic route to tetrahydrocyclolignan lactone **4** we conducted electrochemical reduction of dihydro compound **3** in anhydrous acetonitrile-tetraethylammonium bromide-hydrogen bromide at constant cathode potential (10) to give crystalline *cis*-lactone **4** [stereochemistry at C-9 undetermined (18)] in 60% yield [overall yield of 31% from phenylpropiolic acid] (19).

The mass spectra of **4** and **5** are of interest since they show significant fragmentation peaks at m/e 204 and 205 (presumably 1-phenylnaphthalene molecular ion and its protonated species) and at 178 and 179 (ascribed to anthracene molecular ion and its protonated species). Loss of the elements of formyloxy radical is observed in both cases to give a peak at m/e 219. Surprisingly, **4** also gives an abundant fragment at m/e 190, which corresponds to the loss of $C_3H_6O_2$ from the molecular ion.

For comparative purposes mass spectra were also obtained on dihydrocyclolignan lactone **3** and its dideuterio and trideuterio derivatives **16** and **17** (6). Common, principal fragmentation patterns for these three compounds

Scheme 2



are shown in Scheme 2 (for **17**, as an example).

EXPERIMENTAL (20)

9- and 4-Phenylnaphtho[2,3-c]furan-1(3*H*)ones, (**1**) and (**2**), Respectively.

A mixture of 2.26 g. of phenylpropargyl chloride (21) and 2.52 g. of anhydrous sodium phenylpropiolate (equimolar amounts) (10) in 30 ml. of anhydrous dimethylformamide was refluxed (nitrogen atmosphere) for 5 hours. The cooled, brown reaction mixture was filtered to remove precipitated sodium chloride and evaporated *in vacuo*. A chloroform extract of the residue was washed with water, dried, and evaporated. The residue was crystallized from ethanol and then evaporatively distilled at 130° (0.6 mm.) to yield 0.8 g. (21%) of white solid, m.p. 130-144°, which consisted of a mixture of **2** and **1** in a molar ratio of 2.5:1, as determined by pmr analysis [comparative integrations of peaks at δ 8.59 (H-9 of **2**) (5), 5.48 (2 H-3 of **1**) (6), and 5.32 ppm (2 H-3 of **2**) (22)]. Thin layer chromatography of the mixture (with silica gel G; plus hexane-ethyl acetate, 2.7:1 by volume) showed two faintly purple fluorescent spots in ultraviolet light (23) at R_f values of 0.4 for **1** and 0.7 for **2**. The slower moving spot was indistinguishable from that caused by an authentic sample of **1** (6). The components were separated by thick layer chromatography (silica gel 60F-254, 2 mm. thickness, E. Merck) and extracted into chloroform. The yellow solid from the leading zone was recrystallized from ethanol and methanol to give white needles of **2**, m.p. 152-154°; ir (chloroform): 1760 cm^{-1} (γ-lactone); uv (95% ethanol): max 241 nm (log ε 4.65), 291 (3.72), 301 (3.74), 331 shoulder (3.41), 3.42 (3.49); pmr (deuteriochloroform): δ 5.32 (s, 2, methylene group), 7.2-8.3 (m, phenyl group plus H-5 to H-8), 8.59 ppm (s, 1, H-9); mass spectrum, m/e (relative abundance): 260 (49, M^+), 231 (100, $[M - CHO]^+$), 205 metastable peak (260→231), 203 (35), 202 (53, $[M - CH_2OC{=}O]^+$), 101 (35); reported (13) m.p. 164.5-165.5° plus closely similar spectral data.

Anal. Calcd. for $C_{18}H_{12}O_2$: C, 83.1; H, 4.7. Found: C, 82.9; H, 4.7.

From the other zone of the thick layer chromatogram was obtained crystalline **1**, identical in pmr spectrum with an authentic sample (6).

Sodium *cis*-Cinnamate.

Freshly prepared and washed ethyl *cis*-cinnamate (24) was refluxed for 30 minutes with an equimolar quantity of sodium hydroxide in 80% ethanol. Evaporation of the solvent *in vacuo* left anhydrous sodium *cis*-cinnamate as a white solid (95% yield); pmr (deuterium oxide, with sodium 3-trimethylsilylpropane-1-sulfonate as reference) δ 6.23 and 6.69 (2d, 1 each, J_{AB} = 13 Hz, *cis*-vinylene group), 7.3-7.9 ppm (m, 5, phenyl ring); unchanged on storage in a brown bottle in the dark for a period of weeks.

Reaction of Phenylpropargyl Chloride and Sodium *cis*-Cinnamate in DMF.

A mixture of equimolar amounts of phenylpropargyl chloride (21) and sodium *cis*-cinnamate in DMF was refluxed for 5 hours. A sample of the mixture was removed, diluted with water, and extracted with chloroform. The organic layer was evaporated to leave a liquid which was dissolved in deuteriochloroform. The pmr spectrum showed no evidence for the presence of unreacted phenylpropargyl chloride (δ 4.36, s, methylene), but did indicate the presence of both phenylpropargyl *cis*-cinnamate (**14**) and phenylpropargyl *trans*-cinnamate (**15**) in *ca.* equal amounts [δ 4.98 and 5.07 (2s, 2 methylene groups), 6.01 and 7.01 (2d, J = 13 Hz, *cis*-vinylene), 6.52 and *ca.* 7.83 ppm (2d, J = 16 Hz, *trans*-vinylene)]. At the end of 27 hours of refluxing the remaining reaction mixture was processed in the same way. Only **15** was present as based on direct comparison of infrared (in carbon tetrachloride) and pmr spectra with those of an authentic sample (16). There was no clear evidence for the presence of a lactone product.

In a second run the reactants were first refluxed in DMF for 40 minutes. The solvent was evaporated and the residue was dissolved in acetic anhydride. Refluxing this latter solution for 24 hours and then work-up in analogous fashion showed spectral evidence for the presence of **14**, but none for **15** or a lactone product.

cis(3a,9a)-4-Phenyl-3a,4,9,9a-tetrahydronaphtho[2,3-c]furan-1(3*H*)one (**5**).

A mixture of 7.7 g. of *trans*-cinnamyl chloride and 8.7 g. of sodium *cis*-cinnamate (equimolar amounts) in 40 ml. of anhydrous dimethylformamide was refluxed (nitrogen atmosphere) for 35 hours. The suspension of brown solid in the refrigerated reaction mixture was decanted (from the compacted sodium chloride precipitate) and filtered. Collected solid was recrystallized from ethanol and methanol to give 4.2 g. (31%) of **5** as white leaflets, m.p. 143.5-144°; ir (chloroform): 1765 cm^{-1} (*cis*-lactone) (14); pmr (deuteriochloroform): δ 7.8-6.9 (m, 5 aromatic H), 6.9-6.7 (m, 1 aromatic H, H-8?), 4.7-3.7 (m, 3H), 3.7-2.8 ppm (m, 4H); mass spectrum, m/e (relative abundance): 265 (20), 264 (100, M^+), 219 (35, $[M\text{-}HCO_2\cdot]^+$), 205 (24), 204 (22), 180 (39), 179 (95), 178 (88), 165 (28), 129 (37), 128 (35), 115 (24), 91 (39), 51 (20).

Anal. Calcd. for $C_{18}H_{16}O_2$: Mol. wt. 264.115. Found (25): Mol. wt. 264.112.

Samples of the above reaction mixture were withdrawn at periods of 5 and 30 hours and analyzed in the manner used for the previous mixture; pmr δ 4.90, 4.78, and 4.68 (3s, methylene groups for *trans,cis* ester **12**, *trans,trans* ester **13** (16), and an unidentified product [polymer?], respectively), 7.01 and 6.01 (2d, J = 13 Hz, *cis*-vinylene), 7.83 and 6.54 (2d, J = 16 Hz, *trans*-vinylene), and 4.7-3.0 ppm (complex, lactone aliphatic protons). The earlier sample contained > 60 mole % of **12**, < 40% of **13**, probably no residual *trans*-cinnamyl chloride, and < 5% of lactone

and *ca.* 5% of the unidentified compound.

Conversion of **5** into **2**.

Following a published procedure for another compound (26), a mixture of 95.8 mg. of **5**, 192 mg. of *N*-bromosuccinimide, 5 mg. of benzoyl peroxide, and 30 ml. of dry carbon tetrachloride was refluxed for 35 minutes, during which time the solution became red and then colorless. The filtrate from the hot solution was evaporated and the residue was chromatographed on a thick-layer plate as in the separation of **1** and **2** (but with hexane:ethyl acetate = 4:1). Two zones were found. From the slower moving zone was isolated 73 mg. (77%) of **2**, m.p. 151-153°, identified by spectral comparison with the previous sample. The other zone gave a product which was not identified (but was not **1**).

cis(3a,9a)-9-Phenyl-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1-(3*H*)one (**4**).

To the catholyte of the electrochemical apparatus previously described (10) was added (over a period of one hour) a solution of 0.48 g. (1.8 mmoles) of lactone **3** in 30 ml. of anhydrous acetonitrile containing 4.2 mmoles of anhydrous hydrogen bromide. The cathode potential was maintained at -2.10 V (vs. SCE) during this addition and for 20 minutes longer. Electrolysis was stopped and combined solutions from both anode and cathode compartments were processed in the previous manner to yield an organic residue. Crystallization from methanol gave 0.291 g. (60%) of crude lactone **4**, m.p. 109-118°. Several recrystallizations from the same solvent yielded needles of **4**, m.p. 119-120°; ir (chloroform): 1765 cm^{-1} (*cis* lactone); pmr (deuteriochloroform): δ 7.5-6.7 (m, 9 aromatic H), 4.50 (d, 1, J = 3 Hz, H-9), 4.34 and 3.86 (2 overlapping d of d, 2 total, AB portion of an ABX system, J_{AB} = 9.2 Hz, $|J_{AX} + J_{BX}|$ = 4.4 Hz, H_a and H_b), 3.37 (d of d, 1, J = 3 and 9.5 Hz, H-9a), 3.2-2.2 (m, 3, H-3a and 2 H-4) (27); mass spectrum, m/e (relative abundance): 264 (100, M^+), 236 (45), 219 (35, $[M\text{-}HCO_2\cdot]^+$), 206 (21), 205 (45), 204 (53), 203 (29), 190 (94), 179 (32), 178 (29).

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.8; H, 6.1. Found: C, 81.8; H, 6.2.

Miscellaneous Mass Spectra.

For **3**: 263 (21), 262 (100, M^+), 232 (22), 231 (50, $[M\text{-}(CH_2O + H\cdot)]^+$), 218 (44), 217 (67, $[M\text{-}HCO_2\cdot]^+$), 215 (35), 204 (27), 203 (76), 202 (79), 101 (23).

For **16**: 265 (22), 264 (100, M^+), 231 (35, $[M\text{-}(CD_2O + H\cdot)]^+$), 220 (39), 219 (63, $[M\text{-}HCO_2\cdot]^+$), 217 (22), 204 (29), 203 (71), 202 (49), 101 (21).

For **17**: 266 (21), 265 (100, M^+), 264 (23), 221 (35), 220 (64, $[M\text{-}HCO_2\cdot]^+$), 219 (33), 218 (25), 205 (32), 204 (72), 203 (63), 202 (28).

REFERENCES AND NOTES

(1) For Paper X in this series, see reference 12; for Paper IX, see reference 11.

(2) NSF Undergraduate Research Participant, summer, 1975; Research Assistant, 1975-1976.

(3) Research and Teaching Assistant, 1968-1971; NDEA Fellow, 1971-1972.

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(15) It is expected to be *trans* to C-3a if a concerted intramolecular Diels-Alder reaction is involved.

(16) L. H. Klemm, K. W. Gopinath, G. C. Karaboyas, G. L. Capp, and D. H. Lee, *Tetrahedron*, **20**, 871 (1964).

(17) Experiment conducted by Gary Carpenter.

(18) It is expected to be *trans* to C-9a, *cf.* reference 10.

(19) At this time neither a dihydrocyclolignan lactone of series **2** nor a *trans*-lactone of either series has been obtained *via* our Diels-Alder procedures.

(20) Elemental analyses were performed by Dr. Susan Rottschaefer, University of Oregon. Infra-red spectra were obtained by means of a Beckman IR-7 spectrophotometer; pmr spectra, by means of a Varian Associates T-60, HA-100, or XL-100 spectrometer with tetramethylsilane as internal reference; ultraviolet spectra, by means of a Cary 15 instrument; and mass spectra at 70 eV by means of a CEC model 21-110 instrument. Only mass spectral peaks of relative abundance ≥ 20% are reported.

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