Hindered Rotation in Arylnaphthalene Lignans

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Many arylnaphthalene lignans show biological activity and although few of them contain stereogenic centers, they may nevertheless be chiral if there is hindered rotation about the aryl−naphthalene bond. A relatively high barrier to rotation may give rise to separable rotational enantiomers (atropisomers) which might have quite different pharmacological properties. In order to investigate this possibility we have synthesized the natural products justicidin A, justicidin B, retro-helioxanthin, retro-justicidin B, and helioxanthin as well as four other arylnaphthalenes lignan analogs. We have studied the aryl−naphthalene rotational barrier in these compounds by dynamic NMR and HPLC and find barriers to rotation ranging from 16.9 to 21.5 kcal/mol. This translates to half-lives for individual atropisomers of less than 10 min at room temperature. The experimentally found barriers are compared to those obtained from molecular orbital calculations.

Introduction

The term atropisomerism was introduced by Kuhn to describe molecules that are chiral and exist in enantiomeric forms solely due to hindered rotation about carbon−carbon single bonds.[1] The term was originally applied to optical isomers of biphenyls, many of which are known, although other compounds exhibit this same type of isomerism.

In our studies of lignan natural products we discovered anomalies in the NMR spectra of some arylnaphthalene lignans which indicated that these compounds suffered hindered rotation about the phenyl−naphthalene bond.[2] This raised the possibility that arylnaphthalene lignans, many of which show biological activity, might exist as separable enantiomers (atropisomers) that exhibit different biological activity. Pharmacological activity which depends on atropisomeric form is known for other natural products such as (−)-ancistrocladine and (−)-gossypol.[3,4]

Although hindered rotation and atropisomerism have been studied in some 1-substituted naphthalenes (sulfoxides, amines, ketones, and imines[5]) there are relatively few studies of atropisomerism in 1-phenylnaphthalenes. To our knowledge there have been no dynamic NMR studies of such compounds and few reports of stable atropisomers. A recent paper on the synthesis of (−)-*O*-methylancistrocladine reports an improved synthesis of the stable atropisomer of aldehyde **1** via an asymmetric biaryl coupling.[4] Fukushi *et al.* also used an asymmetric biaryl coupling to produce **2**, a compound useful for the determination of the absolute configurations of secondary alcohols.[6] Selective reaction of enantiotopic substituent groups in symmetric phenylnaphthalenes has also been used to prepare stable atropisomers of compounds having the general structure **3**.[7]

With respect to less stable atropisomers, House *et al.* studied hindered rotation in 5,8-diarylnaphthalenes by dynamic NMR and found that the barrier to rotation for 1,8-diphenylnaphthalene-3′-dimethylcarbinol was 16 kcal/mol.[8] In earlier work, Hall *et al.* were able to resolve and measure half-lives for 1-phenylnaphthalene-2′-carboxylic acid and 1-phenylnaphthalene-2′,8-dicarboxylic acid and found them to be between 2 and 15 min at room temperature in water.[9] In an even earlier paper, Gilchrist *et al.* concluded, on the basis of shielding effects in NMR, that there was hindered rotation in the lignan derivative tetradehydrootobain, **4** (Scheme 1), although neither the height of the barrier nor the lifetime of individual enantiomers was assessed.[10]

In our own work we noted that phenylnaphthalenes **5** and **6** (Scheme 2) showed a doubling of peaks for some NMR transitions.[2] For instance, in compound **5** the 2′ and 3′ carbons appeared at a different chemical shift than the 6′ and 5′ carbons in the ^{13}C NMR spectrum. This meant that the rotation of the phenyl group was slow enough on the NMR time scale to make C-2′ (C-3′) diastereotopic with respect to C-6′ (C-5′). Similarly in compound **6**, a doubling of many lines was observed. In this case the hindered rotation of the unsymmetrical phenyl group gave rise to a new element of asymmetry and the existence of two different diastereomers whose lifetimes were long enough that the individual isomers could be observed in the NMR spectrum. A search of the literature revealed that many similar anomalies in the NMR spectra of arylnaphthalene lignans have been observed and recorded but, except for one case,[11] no correlation to hindered rotation was made.[12]

[⊗] Abstract published in *Advance ACS Abstracts,* April 1, 1996.

(1) Kuhn, R. Molekulare Asymmetrie. In *Stereochimie,* Freudenberg, H., Ed., Franz Deutike: Leipzig-Wien, 1933; pp 803−824.

(2) Charlton, J. L.; Chee, Gaiklean; McColeman, H. *Can. J. Chem.* **1995**, *73*, 1454.

(3) For a review on biaryl compounds and their synthesis see Bringmann, G.; Walter, R.; Wirich, R. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 977.

(4) Leighton, B. N.; Rizzacasa, M. A. *J. Org. Chem.* **1995**, *60*, 5702.

(5) Casarini, D.; Foresti, E., Gasparrini, F.; Lunazzi, L.; Macciantelli, D.; Misiti, D. Villani, C. *J. Org. Chem.* **1993**, *58*, 5674.

(6) Fukushi, Y.; Yajima, C.; Mizutami, J. *Tetrahedron Lett.* **1995**, *35*, 599.

(7) Hayashi, T.; Niizuma, S.; Kanikawa, T.; Suzuki, N.; Uozumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9101.

(8) House, H. O.; Campbell, W. J.; Gall, M. *J. Org. Chem.* **1970**, *35*, 1815.

(9) Hall, D. M.; Ridgwell, S.; Turner, E. E. *J. Chem. Soc.* **1954**, 2498.

(10) Gilchrist, I.; Hodges, R.; Porte, A. L. *J. Chem. Soc.* **1962**, 1980.

(11) Trujillo, J. M.; Jorge R., E.; Navarro, E.; Boada, J. *Phytochemistry* **1990**, *29*, 2991; NMR of **1** (J_1 in reference), methylenedioxy protons reported as a double doublet; NMR of **2** (J_2 in reference) indicated that it exists as a mixture of rotameric diastereomers.

(12) (a) Pelter, A.; Ward, R. S.; Satyanarayana, P.; Collins, P. *Tetrahedron Lett.* **1982**, *23*, 571. NMR of **7a** (retro-justicidin B), methylenedioxy protons reported as a multiplet. (b) Holmes, T. L.; Stevenson, R. *J. Chem. Soc.* **1971**, 2091; NMR of retro-helioxanthin (**XIV** in reference), methylenedioxy protons reported as double doublets. (c) Okigawa, M.; Maeda, T.; Kawano, N. *Tetrahedron* **1970**, 4301; NMR of justicidin A and B (**I** and **II** in reference), methylenedioxy protons reported as quartets.

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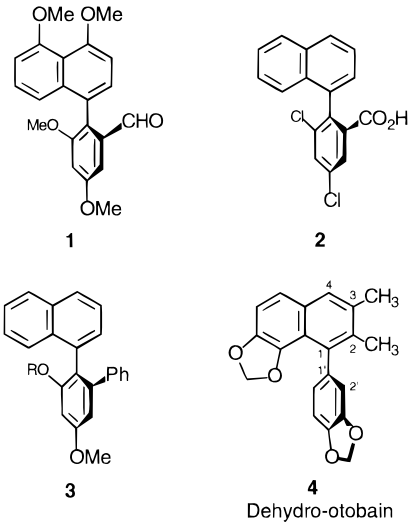
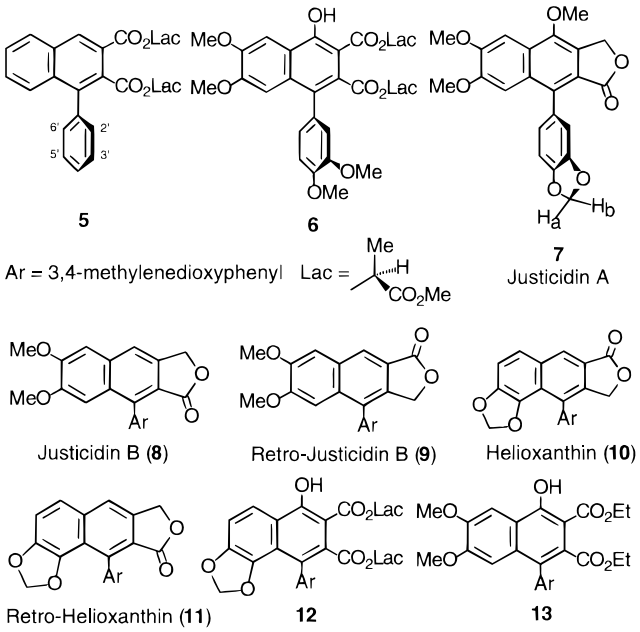
Scheme 1



Scheme 2



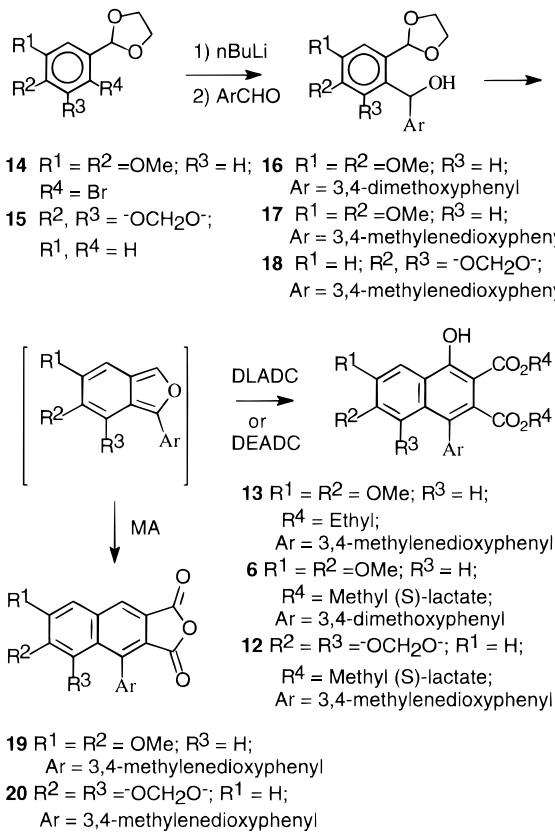
To test the hypothesis that hindered rotation in arylnaphthalene lignans may give rise to isolable atropisomers we have synthesized the natural products justicidin A (**7**), justicidin B (**8**), retro-justicidin B (**9**), helioxanthin- (**10**), and retro-helioxanthin (**11**) as well as the lignan analogs **5, 6, 12,** and **13** (Scheme 2). All of the compounds **5-13** were analyzed by variable temperature NMR to determine the barrier to rotation about the phenyl–naphthalene bond. In one case (compound **6**) the barrier was also estimated by separating the diastereomers by HPLC and measuring the rate of re-equilibration to a mixture of diastereomers.

Results and Discussion

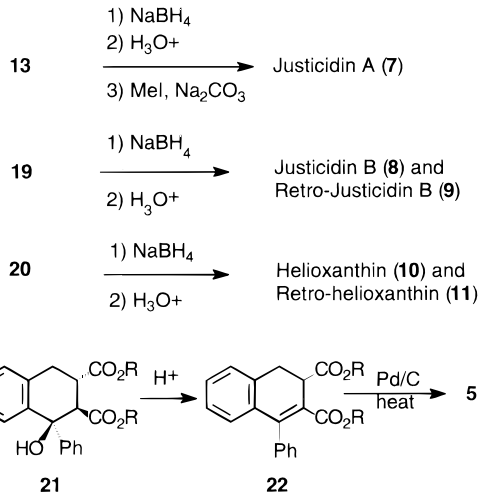
The lignans and lignan analogs **5-13** were synthesized as shown in Schemes 3 and 4. The hydroxy acetals **16**–**18** were all prepared using a published method,[13] and due to their instability they were not isolated, but were converted directly to the transient isobenzofurans by heating in the presence of acetic acid. The isobenzofurans were trapped *in situ* by either diethyl acetylenedicarboxylate (DEADC), the acetylenedicarboxylate of methyl (*S*)-lactate (DLADC),[2] or maleic anhydride (MA). Diethyl ester **13** was reduced, lactonized, and methylated to give justicidin A (**7**). The anhydrides **19** and **20** were not characterized but were converted directly to the mixture of lactones **8** and **9**, and, **10** and **11**, respectively, by reducing with sodium borohydride followed by treatment with acid. Compound **5** was synthesized by dehydration of the known cycloadduct **21** to give dihydronaphthalene **22,** which in turn was dehydrogenated to **5** (Scheme 4).

Compounds **5-13** were studied by NMR as a function of temperature. Table 1 indicates the solvents used, the temperature range over which spectra were recorded, and the signals monitored.

Scheme 3



Scheme 4



(13) Keay, B. A.; Plauman, H. P. Rajapaksa, D.; Rodrigo, R. *Can. J. Chem.* **1983**, *61*, 1987.

Table 1. Solvent, Temperature Range, and Peaks Analyzed for DNMR Study

cpd	solv[a]	temp, K	exchanging signals
5	D	300−383	129.82 (CH), 130.16 (CH) C_2' and C_6'
6	D	300−353	no broadening or coalescence
7	T	300−363	5.27 (d, 1H, J = 1.48), 5.42 (d, 1H, J = 1.48) $-OCH_2O-$
8	T	300−363	5.26 (d, 1H, J = 1.49), 5.40 (d, 1H, J = 1.49) $-OCH_2O-$
9	D	300−353	5.26 (d, 1H, J = 14.8), 5.36 (d, 1H, J = 14.8) lactone CH_2
10	D	300−358	6.06 (s, 1H, J = 0.49), 6.11 (s, 1H, J = 0.49) phenyl $-OCH_2O-$
11	D	300−338	5.91 (s, 1H), 5.93 (s, 1H) naphthyl $-OCH_2O-$
12	D	300−378	1.01 (d, 3H, J = 6.81), 1.06 (d, 3H, J = 6.81) lactyl C-CH_3
13	D	300−353	no broadening or coalescence

[a] D = DMSO-d_6, T = toluene-d_8.

In each compound slow rotation at the lowest temperature gave rise to signals from individual diastereotopic protons/carbons (or from individual diastereomers for compounds **6** and **12**). As mentioned previously, at the slow rotation limit, the 2′ and 3′ carbons in compound **5** are diastereotopic to the 6′ and 5′ carbons and appear at a different chemical shift in the ^{13}C NMR spectrum. Compounds **6** and **12** show a doubling of signals for all protons since slow rotation in these compounds gives rise to two diastereomers, each with their own spectrum. In compounds **7-11** all of the methylene groups (on both the methylenedioxy and lactone groups) give rise to AB patterns, rather than singlets, since the two protons are diastereotopic when rotation is slow. Similar AB patterns are observed for the methylenedioxy protons in compound **13**. As the temperature increases, the rotation of the pendant aryl ring exchanges the diastereotopic protons (or the diastereomers for compounds **6** and **12**), and the signals mentioned above broaden and begin to coalesce. The experimental spectra were recorded at increasing temperatures and the experimental spectra simulated using the computer program DNMR3.[14a] Required input parameters for this program are the chemical shifts of the signals being simulated, coupling constants (to other nuclei), the transverse relaxation time, the populations of the exchanging species, the rate constant for exchange, and the experimental spectral data. The input parameters (other than the experimental spectral data) were manually adjusted until the simulated spectra visually matched the experimental spectra. As an example, the observed and simulated spectra for compound **12** are given in Figure 1, and the input parameters for DNMR3 are given in Table 2. In this compound slow rotation of the pendant aryl ring gives rise to diastereomeric atropisomers. At low temperature the NMR spectrum of **12** exhibits four separate doublets for the lactyl methyls, and as the temperature increases, these four doublets slowly collapse and ultimately would form two doublets (although this limit was not reached in the present study).

(14) (a) Marat, K. Xsim, copyright 1995, a computer program incorporating DNMR3, Kleiser, D. A.; Binsch, G. *DNMR3 - A computer program for the calculation of complex exchange-broadened NMR spectra (a modified version for spin systems exhibiting magnetic equivalence or symmetry*), QCPE program 165, 1970. (b) The standard deviations in the calculated enthalpies and entropies of activation shown in Table 3, produced by linear regression analysis of the rate constants (Eyring plots), should be interpreted cautiously since the number of data points in each plot was small and the temperature range over which data was collected was also relatively small.

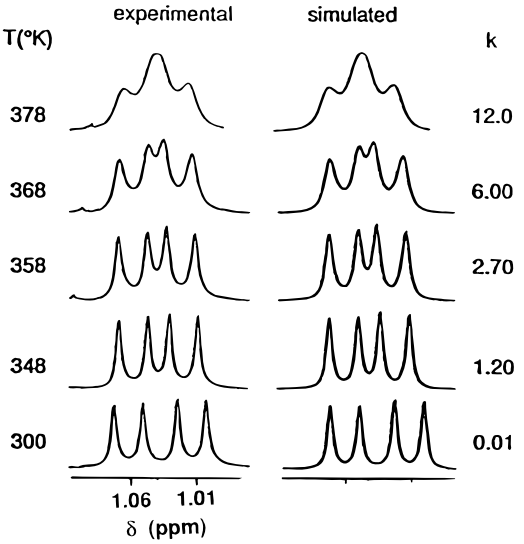


Figure 1. ^1H DNMR spectra of lignan analog **12** (lactylmethyl region).

Table 2. Exchange Rate Constants (k), Free Energies of Activation for Exchange ($\Delta G^{\ddagger}$), Chemical Shifts of Exchanging Signals (δ), Coupling Constants (J), and Transverse Relaxation Time T_2, as a Function of Temperature for Compound 12

temp, K	k s^{-1}	$\Delta G^{\ddagger}$,[a] kcal/mol	δ,[b] ppm	J,[c] Hz	T_2,[d] s
300	0.01	20.31	1.06, 1.01	6.81	0.20
348	1.20	20.35	1.11, 1.07	6.81	0.23
358	2.70	20.37	1.12, 1.09	6.81	0.24
368	6.00	20.38	1.13, 1.10	6.81	0.24
378	12.0	20.43	1.14, 1.11	6.81	0.24

[a] Calculated from $\Delta G^{\ddagger} = RT[23.760 + \ln(T/k)]$, where $R = 1.983 \times 10^{-3}$ kcal/mol/K. [b] Chemical shifts for the exchanging lactyl methyl groups. [c] Coupling constants to the neighboring methine hydrogen were constant for both signals. [d] Transverse relaxation times measured from a reference signal.

The experimental exchange rate constants (k) were plotted as a function of temperature (T) for compounds **5** and **7**−**12** using the Eyring equation

$$\ln(k/T) = -\Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R + \ln(k_B/h)$$

in order to determine the enthalpies and entropies of activation ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, see Table 3[14b]) for the rotational barrier in each molecule (k_B is the Boltzman constant, h is Planck's constant, and R is the universal gas constant). The Eyring plot of the experimental exchange rate constants for compound **12** is given in Figure 2.

For comparison purposes the free energy of activation $\Delta G^{\ddagger}$, and halflife τ for exchange were calculated for each molecule at 23 °C from

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$$

$$k = (k_B T/h)e^{-\Delta G^{\ddagger}/RT} \qquad \tau = 1/k$$

The thermodynamic and rate parameters are given in Table 3.

The NMR spectra of compounds **6** and **13** were invariant with temperature, indicating that the rate of rotation of the pendant aryl group was too slow in these com-

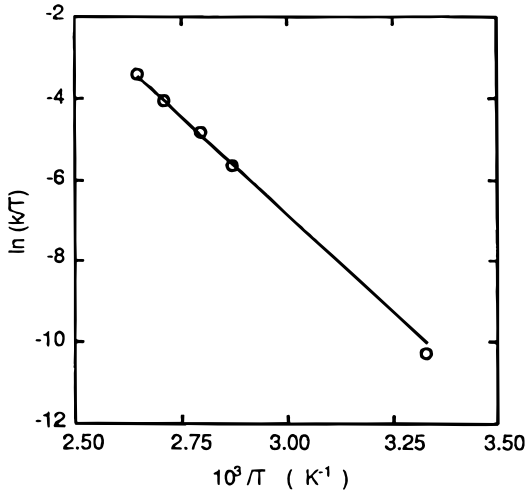


Figure 2. Eyring plot of exchange rate constants from analysis of DNMR spectra of **12**.

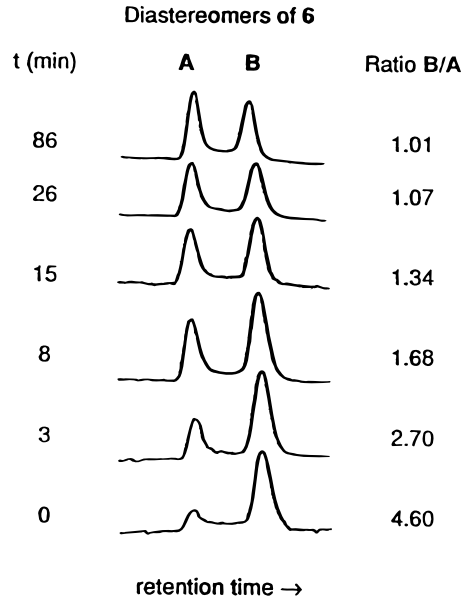


Figure 3. HPLC analysis of the atropisomeric equilibration of lignan analog **6** at 23 °C.

pounds to measure by dynamic NMR effects. Since compound **6** would exist as a mixture of diastereomers if rotation were very slow, an attempt was made to analyze this compound by HPLC on an achiral reverse phase column. Analysis at room temperature gave two poorly resolved peaks, but lowering the temperature of the column to 4 °C allowed for almost baseline separation. The slower running peak was collected and after storing at 23 °C for various times ranging from 0 to 86 min, was reinjected (see Figure 3).

In this way a very crude estimate of the rate constant for return to the original equilibrium mixture could be calculated. The free energy of activation for the rotation of the aryl group in compound **6** at 23 °C is also given in Table 3.

An attempt was made to use molecular orbital methods to determine if calculations could provide a reliable indication of the relative barriers to rotation in arylnaphthalenes. The computer program Spartan[15] was used at

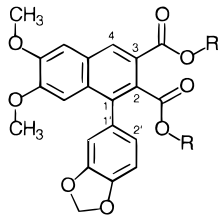
(15) Spartan, HP Version 3.1.4 Starbase. Copyright Wavefunction Inc., 18401 Von Karman, Suite 370, Irvine, CA 92715.

Table 3. Rate and Thermodynamic Parameters for Hindered Rotation in Arylnaphthalenes

cpd	$\Delta H^{\ddagger}$,[a] kcal/mol	$\Delta S^{\ddagger}$,[a] cal/mol/K	$\Delta G^{\ddagger}_{23}$,[b] kcal/mol	$\Delta H^{\ddagger}_{calcd}$,[c] kcal/mol	τ, s
5	18.7(0.7)	-3.6(1.9)	19.8	–	42.5
6	–	–	21.4	14.6	894
7	18.3(0.4)	−0.6(1.1)	18.5	13.4	4.8
8	19.3(1.0)	2.8(2.8)	18.5	13.6	4.8
9	17.0(0.5)	0.1(2.8)	16.9	11.9	0.3
10	16.9(0.4)	−3.7(1.2)	18.0	11.9	2.1
11	18.8(0.4)	4.4(1.1)	17.5	13.3	0.9
12	19.0(0.3)	-3.8(0.7)	20.1	14.5	70.2
13	–	–	–	15.2	–

[a] From Eyring plots of exchange rate constants. Numbers in parentheses are standard deviations in this variable. [b] Calculated using $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$. [c] From AM1 calculations.[15]

Scheme 5



the AM1 level with geometry optimization to determine the energy difference between the relaxed molecule and the molecule with the dihedral angle 2−1−1′−2′ (for numbering see Scheme 5) fixed at 0°. All calculations were performed starting with the arylnaphthalene carbon skeleton in one plane and substituents oriented as shown in Scheme 5. The computed rotational barriers are given in Table 3.

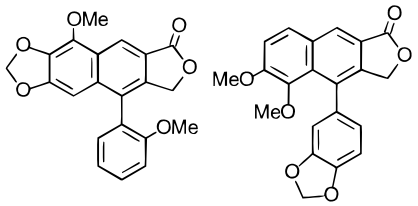
The major conclusion to be drawn from the dynamic NMR measurements is that all of the arylnaphthalene lignans and analogs studied have a rotational barrier too small for individual atropisomers to be isolated at room temperature. Ester groups at the 2 position present a higher barrier than the 2,3-lactones of either orientation, and a 7,8-methylenedioxy ring decreases the barrier relative to a hydrogen at position 8, presumably because of ring strain. Notably, the dihydronaphthalene **22** showed no hindered rotation at all in its NMR spectrum, in contrast to the fully aromatized compound **5**. It seems reasonable to conclude that hindered rotation will also not be observed in natural lignans having a 3,4-dihydronaphthalene structure.

MO calculations at the AM1 level are relatively unsophisticated and it was not surprising that the calculated barriers to rotation were far removed from the experimentally measured values. MO calculations at the *ab initio* level would have been preferred but the computational time required was excessive at that level. Nevertheless the calculations do show that AM1 computations can predict *relative* barriers to rotation and they should be useful for calculating relative barriers to rotation in related compounds. In this respect, we have calculated the barriers in a lignan, **23**,[16] a lignan analog, **24**[11] (Scheme 6), and compound **1** (Scheme 1), in order to assess the effect of a methoxy group at the 8 position, as well as substituents at the 2′ and 6′ positions.

These compounds had calculated barriers of 16.3, 11.9, and 29.1 kcal/mol respectively. The 29.1 kcal/mol barrier for **1** is consistent with the fact that it is known to form stable atropisomers.[4] Comparing the calculated 11.9

(16) MacRae, W. D.; Towers, G. H. *Phytochemistry* **1984**, *24*, 1207.

Scheme 6



Prostalidin B (**23**) **24**

kcal/mol barrier for **24** with those in Table 3 would indicate that the 8-methoxy substituent alone is insufficient to give rise to stable atropisomers. The calculated barrier for prostalidin B (**23**) is higher than any of the calculated barriers found in Table 3 and may indicate the possibility of it forming stable atropisomers at room temperature. Investigation of this compound and others is ongoing.

Experimental Section

General Methods. The general experimental procedures and instrumentation have been described previously.[17] The instrument used to perform the dynamic NMR studies was a Bruker AM 300 FT spectrometer. Temperature was referenced to the known temperature dependent spectra of methanol (at low temperature) and ethylene glycol (at high temperature) and was accurate to ±1 °C.

Hydroxyacetals 16 and 17. 2-Bromo-5,6-dimethoxybenzaldehyde (1.32 g, 5.40 mmol), ethylene glycol (0.493 g, 7.95 mmol), and *p*-TsOH·5H_2O (90 mg) were refluxed in benzene (75 mL) under a Dean−Stark trap. After water ceased to distill (ca. 3 h), the solution was reduced to 10 mL by evaporation, cooled to room temperature, and then filtered through a short column of anhydrous silica gel, eluting with 50% EtOAc/hexanes (ca. 50 mL). Evaporation of the solvents gave a solid (1.56 g, 100% yield) which was very susceptible to hydrolysis. The crude acetal, **14,** was redissolved in dry THF (40 mL) under nitrogen, and cooled to −78 °C, and n-BuLi (2.45 M in hexanes, 2.30 mL, 5.6 mmol) was added dropwise over 5 min. The mixture was stirred for another 15 min, followed by the dropwise addition of 3,4-dimethoxybenzaldehyde (0.85 g, 5.11 mmol) or 3,4-(methylenedioxy)benzaldehyde (0.77 g, 5.11 mmol), in THF (10 mL). After stirring for 30 min, the solution was gradually warmed to room temperature and was stirred for another 2.5 h, followed by the addition of H_2O (30 mL). The resulting mixture was extracted with Et_2O (3 × 30 mL), dried ($MgSO_4$), and concentrated to give a colorless solid (1.90 g and 1.80 g, respectively, 100% and 98%) which turned green upon standing at room temperature. These crude products were not further purified or characterized, but were used immediately in the following Diels−Alder reactions.

Hydroxyacetal 18. The general procedure for preparation of this compound has been published by Rodrigo.[13] The ethylene glycol acetal of 3,4-dimethoxybenzaldehyde was prepared as described above for acetal **14,** by treating 3,4-dimethoxybenzaldehyde (0.81 g, 5.4 mmol) with ethylene glycol and *p*-TsOH in benzene. The unstable crude acetal **15** was immediately dissolved in dry THF (40 mL), followed by dropwise addition of n-BuLi (2.45 M in hexanes, 2.30 mL, 5.6 mmol) under nitrogen. The mixture was stirred for 15 min and then at ice temperature for 20 min. The mixture was again cooled to −78 °C, followed by dropwise addition of 3,4-(methylenedioxy)benzaldehyde (0.77 g, 5.11 mmol) in THF (10 mL). The resulting orange solution was stirred at that temperature for 20 min and then at room temperature for 1.5 h. The workup procedure was similar to that described for the preparation of hydroxyacetals **16** and **17**, and the brown-green residue (1.75 g, 94%) isolated was also employed in the following reactions without further purification or characterization.

(17) Maddaford, S. P.; Charlton, J. L. *J. Org. Chem.* **1993**, *58*, 4132−4138.

General Procedure for the Synthesis of Arylnaphthalenes. Glacial acetic acid was added to a mixture of hydroxyacetal **16**, **17**, or **18** and dienophile in a minimum amount of solvent and the temperature of the mixture quickly brought up to 140 °C. The mixture was heated for 1−20 h, depending on the type of dienophile used. The cooled mixture was diluted with CH_2Cl_2 (10 mL), washed with 5% sodium bicarbonate solution (3 × 10 mL), dried ($MgSO_4$), and concentrated under vacuum.

Lignan Analogue 6. Acetal **16** (0.16 g, 0.41 mmol), DLADC (0.10 g, 0.35 mmol),[2] CH_2Cl_2 (0.3 mL), and acetic acid (0.2 mL) were heated at 140 °C for 1 h and worked up as above. Chromatography of the crude product using 25-35% EtOAc/hexanes afforded a colorless solid (0.18 g, 85%): mp 69−72 °C, identical to that previously reported.[2]

Lignan Analogue 13. Acetal **17** (0.247 g, 0.69 mmol), DEADC (0.119 g, 0.70 mmol), CH_2Cl_2 (0.3 mL), and acetic acid (0.2 mL) were heated at 140 °C for 1 h. After work-up as above, the crude product was recrystallized from CH_2Cl_2/hexanes to afford a colorless solid (0.28 g, 80%): mp 152−153 °C; IR (CH_2Cl_2) 3303 (OH), 1730, 1658 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.95 (t, 3H, J = 7.09), 1.26 (t, 3H, J = 7.09), 3.65 (s, 3H), 3.93 (s, 3H), 3.95 (q, 2H, J = 7.09), 4.34 (q, 2H, J = 7.09), 6.09 (AB, 2H, $\Delta\delta$ = 10.17), 6.68 (dd, 1H, J = 7.9, 1.63), 6.72 (s, 1H), 6.78 (d, 1H, J = 1.52), 7.00 (d, 1H, J = 7.91), 7.64 (s, 1H), 11.95 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.8 (CH_3), 13.9 (CH_3), 55.8 (CH_3) 56.1 (CH_3), 60.8 (CH_2), 61.9 (CH_2), 101.0 (CH_2), 101.1 (C), 102.8 (CH), 105.7 (CH), 107.9 (CH), 111.4 (CH), 119.8 (C), 124.3 (CH), 127.4 (C), 129.0 (C), 130.6 (C), 132.2 (C), 147.0 (C), 147.2 (C), 149.6 (C), 152.3 (C), 159.6 (C), 168.7 (CO), 170.2 (CO); mass spectrum m/z (relative intensity) 468 (M^+, 23), 422 (19), 394 (88), 149 (75); HRMS calcd for $C_{25}H_{24}O_9$ 468.1420, found 468.1409.

Anhydride 19. Acetal **17** (0.30 g, 0.83 mmol), maleic anhydride (83 mg, 0.85 mmol), acetic anhydride (0.3 mL), CH_2Cl_2 (0.3 mL), and glacial acetic acid (0.2 mL) were heated at 140 °C for 20 h and worked up as above to give a yellow oily solid (0.35 g) which was used directly in the next reduction reaction without purification. ^1H NMR ($CDCl_3$) δ 3.86 (s, 3H), 4.09 (s, 3H), 6.10 (AB, 2H, $\Delta\delta$ = 10.69, J = 1.36), 6.86 (m, 1H), 6.88 (s, 1H), 7.00 (dd, 1H, J = 7.71, 0.58), 7.21 (s, 1H), 7.36 (s, 1H), 8.33 (s, 1H).

Lignan Analogue 12. Acetal **18** (0.500 g, 1.45 mmol), DLADC (0.411 g, 1.44 mmol), CH_2Cl_2 (0.5 mL) and acetic acid (0.6 mL) were heated at 140 °C for 1.5 h. The foamy brown solid obtained after workup was recrystallized from methanol to afford light yellow crystals (0.72 g, 88%): mp 150−151 °C; $[\alpha]^{20}_D$ +34.1° (c 0.47, $CHCl_3$); IR (CH_2Cl_2) 3370 (OH), 1746, 1660 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.01 (d, 3H, J = 6.81), 1.06 (d, 3H, J = 6.81), 1.45 (d, 3H, J = 6.98), 1.46 (d, 3H, J = 6.98), 3.59 (s, 6H), 3.69 (s, 3H), 3.70 (s, 3H), 4.99 (q, 2H, J = 6.89), 5.35 (q, 1H, J = 6.98), 5.37 (q, 1H, J = 6.98), 5.91−6.07 (m, 8H), 6.62−6.89 (m, 6H), 7.46 (d, 2H, J = 8.82), 8.08 (d, 2H, J = 8.82), 11.78 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 16.4 (CH_3), 16.5 (CH_3), 16.8 (CH_3), 17.1 (CH_3), 52.2 (2 × CH_3), 52.5 (2 × CH_3), 69.5 (CH), 69.6 (CH), 70.2 (2 × CH), 99.6 (C), 99.7 (C), 100.9 (2 × CH_2), 101.6 (2 × CH_2), 107.0 (2 × CH), 110.7 (3 × CH), 111.6 (CH), 111.8 (CH), 119.8 (CH), 120.9 (2 × C), 121.6$_7$ (C), 121.7$_4$ (C), 124.3 (CH), 124.5 (CH), 125.0 (C), 125.1 (C), 129.8$_8$ (C), 129.9$_0$ (C), 130.8 (2 × C), 130.9 (2 × C), 142.5$_6$ (C), 142.6$_0$ (C), 146.4 (2 × C), 147.0 (2 × C), 148.8 (2 × C), 161.9 (CO), 162.0 (CO), 166.7$_8$ (CO), 166.8$_0$ (CO), 168.8$_3$ (CO), 168.9 (CO), 170.2 (CO), 170.4 (CO); mass spectrum m/z (relative intensity) 568 (M^+, 10), 464 (10), 378 (91), 306 (17); HRMS calcd for $C_{28}H_{24}O_{13}$ 568.1216, found 568.1241.

Anhydride 20. Acetal **18** (0.50 g, 1.45 mmol), maleic anhydride (0.142 g, 1.45 mmol), acetic anhydride (0.5 mL), CH_2Cl_2 (0.5 mL), and acetic acid (0.2 mL) were heated at 140 °C for 24 h. A yellow solid (0.44 g, 85%) was obtained after workup and was used in the next reaction without further purification. ^1H NMR ($CDCl_3$) δ 6.00 (AB, 2H, $\Delta\delta$ = 6.26, J = 1.24), 6.07 (AB, 2H, $\Delta\delta$ = 10.55, J = 1.36), 6.82 (m, 1H), 6.84 (s, 1H), 6.89 (dd, 1H, J = 7.46, 0.9), 7.44 (d, 1H, J = 8.56), 7.75 (d, 1H, J = 8.56), 8.43 (s, 1H).

Justicidin A (7). This compound was synthesized by methylation of diphyllin (4-*O*-demethyljusticidn A). Diphyllin

was prepared using a modification of a procedure published by Sammes *et. al.*[18] Analog **13** (0.10 g, 0.20 mmol), $NaBH_4$ (38 mg, 1 mmol), and *i*-PrOH (20 mL) were refluxed under nitrogen for 24 h. 10% HCl (ca. 6 mL) was added cautiously, and the mixture was stirred for 1 h, followed by extraction with ether. The solution was concentrated to give a yellow solid which was then recrystallized from EtOH to afford pure diphyllin (46 mg, 60%): mp 284−286 °C (lit.,[12c] 284−287 °C); ^{1}H NMR (acetone-d_6) δ 3.72 (s, 3H), 4.00 (s, 3H), 5.37 (s, 2H), 6.08 (AB, 2H, $\Delta\delta$ = 3.65, J = 0.95), 6.80 (dd, 1H, J = 7.82, 1.64), 6.84 (d, 1H, J = 1.49), 6.96 (d, 1H, J = 7.97), 7.09 (s, 1H), 7.70 (s, 1H), identical to that previously reported.[12c] Diphyllin (17 mg, 0.04 mmol), DMSO (10 mL), MeI (0.1 mL, 1.6 mmol), and anhyd K_2CO_3 (0.1 g, 1.4 mmol) were refluxed for 20 min. The mixture was acidified to pH 1-2 with 10% HCl (ca. 4 mL), extracted with benzene (3 × 10 mL), concentrated, and chromatographed (20−50% EtOAc/hexanes) to give a light yellow solid collected in the first eluted fraction (15 mg, 95%): mp 262−263 °C (lit.,[12c] 261−263 °C); ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 4.07 (s, 3H), 4.13 (s, 3H), 5.54 (s, 2H), 6.07 (AB, 2H, $\Delta\delta$ = 13.42, J = 1.40), 6.79 (dd, 1H, J = 7.82, 1.65), 6.82 (d, 1H, J = 1.43), 6.95 (d, 1H, J = 7.70), 7.06 (s, 1H), 7.54 (s, 1H).

General Procedure for the Preparation of Justicidin B (8), Retro-justicidin B (9), Helioxanthin (10), and Retro-helioxanthin (11). A modified literature procedure was used.[19] The appropriate anhydride **19** or **20**, $NaBH_4$, and THF were stirred at room temperature for 40 min. The mixture was worked up as in the procedure described for the preparation of justicidin A (diphyllin preparation). The crude product was chromatographed with 33% EtOAc/hexanes to give the first (major) and the second (minor) fractions which contained the lactones resulting from the reduction at the more and the less hindered carbonyl atoms, respectively.

Justicidin B (8) and Retro-justicidin B (9). Anhydride **19** (72 mg, 0.18 mmol), $NaBH_4$ (20 mg, 0.53 mmol), and THF (10 mL) were treated as above. The ^{1}H NMR spectrum of the crude product indicated a ratio of 3:2 of retro-justicidin B to justicidin B. The first eluted fraction contained retro-justicidin B (**9**) as a colorless solid (35 mg, 51%): mp 214−216 °C (lit.,[12a] 218−220 °C); ^{1}H NMR (DMSO-d_6) δ 3.74 (s, 3H), 3.93 (s, 3H), 5.33 (AB, 2H, $\Delta\delta$ = 30.29, J = 14.8), 6.14 (AB, 2H, $\Delta\delta$ = 9.69), 6.97 (dd, 1H, J = 7.97, 1.64), 7.11 (m, 3H), 7.68 (s, 1H), 8.38 (s, 1H).

The second eluted fraction contained justicidin B (**8**), which was isolated as a colorless solid (18 mg, 26%): mp 234−237 °C (lit.,[12c] 235−238 °C); ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 4.05 (s, 3H), 5.37 (AB, 2H, $\Delta\delta$ = 0.93, $J \approx$ 14), 6.07 (AB, 2H, $\Delta\delta$ = 12.48, J = 1.46), 6.79 (dd, 1H, J = 7.80, 1.48), 6.85 (s, 1H), 6.96 (d, 1H, J = 7.82), 7.10 (s, 1H), 7.18 (s, 1H), 7.69 (s, 1H), identical to that previously reported.[12c]

Helioxanthin (10) and Retro-helioxanthin (11). Anhydride **20** (60 mg, 1.6 mmol), $NaBH_4$ (20 mg, 0.53 mmol), and THF (10 mL) were treated as described in the general procedure. The ^{1}H NMR spectrum showed the presence of helioxanthin and retro-helioxanthin in a ratio of 10:1. The first collected chromatography fraction was helioxanthin (**10**), a light yellow solid (43 mg, 77%): mp 239−242 °C (lit.,[12b] 243−244 °C); ^{1}H NMR (DMSO-d_6) δ 5.29 (s, 2H), 6.00 (AB, 2H, $\Delta\delta$ = 5.75, J = 0.67), 6.09 (AB, 2H, $\Delta\delta$ = 14.54, J = 0.49), 6.89 (dd, 1H, J = 7.95, 1.61), 6.97 (d, 1H, J = 7.94), 7.01 (d, 1H, J = 1.52), 7.50 (d, 1H, J = 8.66), 7.94 (d, 1H, J = 8.78), 8.28 (s, 1H).

The second eluted fraction afforded a bright orange residue (4.8 mg, 8%) which was identified as retro-helioxanthin (**11**): mp 262−266 °C (lit.[12b] 264−268 °C); ^{1}H NMR (DMSO-d_6) δ 5.43 (s, 2H), 5.92 (AB, 2H, $\Delta\delta$ = 4.28), 6.08 (AB, 2H, $\Delta\delta$ = 4.76), 6.74 (dd, 1H, J = 7.88, 1.63), 6.88 (d, 1H, J = 1.56), 6.90 (d, 1H, J = 7.95), 7.53 (d, 1H, J = 8.64), 7.72 (d, 1H, J = 8.74), 8.08 (s, 1H).[12b]

Lignan Analogue 5. The cycloadduct formed from α-phenylbenzocyclobutenol and the fumarate of methyl (*S*)-lactate[17] (0.201 g, 0.43 mmol) was refluxed with *p*-TsOH (30 mg) in benzene (10 mL) for 2 h. The reaction mixture was concentrated in vacuo and chromatographed (EtOAc/hexanes) on silica gel to give a yellow residue (0.15 g, 79%). $[\alpha]^{20}_D$ +42.2 (*c* 0.018, $CHCl_3$); IR ($CHCl_3$) 1671 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (d, 3H, J = 7.03), 1.44 (d, 3H, J = 7.07), 3.39 (m, 2H), 3.61 (s, 3H), 3.66 (s, 3H), 4.00 (dd, 1H, J = 4.63, 6.59), 4.81 (q, 1H, J = 7.03), 5.08 (q, 1H, J = 7.07), 6.75 (d, 1H, J = 7.67), 7.08 (m, 1H), 7.24 (m, 4H), 7.37 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 16.2 (CH_3), 16.9 (CH_3), 31.3 (CH_2), 41.0 (CH), 52.0$_9$ (CH_3), 52.1$_4$ (CH_3), 68.6 (CH), 68.8 (CH), 123.3 (C), 126.8 (CH), 127.4 (CH), 127.8$_0$ (CH), 127.8$_4$ (3 × CH), 128.8 (2 × CH), 129.5 (CH), 134.4 (C), 134.6 (C), 138.9 (C), 149.3 (C), 167.2 (CO), 170.9$_0$ (CO), 170.9$_5$ (CO), 171.9 (CO); mass spectrum *m*/*z* (relative intensity) 466 (M^+, 0.4), 334 (10), 274 (15), 231 (39); HRMS calcd for $C_{26}H_{26}O_8$ 466.1628, found 466.1657. A mixture of the dihydrophenylnaphthalene **22** (0.120 g, 0.25 mmol) and Pd/C (0.30 g) in xylenes (10 mL) was refluxed vigorously for 40 h. The mixture was filtered through a short column of silica gel washing with hexanes. The product was then eluted with EtOAc and concentrated to give a pale yellow oil (0.100 g, 90%) with properties identical to those previously reported.[2]

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of all compounds (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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