Design, Synthesis, and Bioactivity of the First Nonsteroidal Mimetics of Brassinolide

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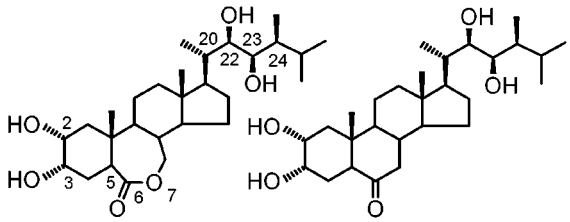
Ten novel compounds, each consisting of two subunits and a linker, were designed with the aid of molecular modeling to resemble the natural steroidal phytohormone brassinolide. The mimetics were synthesized and subjected to the rice leaf lamina inclination bioassay to test for brassinosteroid activity. Most of the mimetics displayed very weak or no bioactivity, but two were strongly active when coapplied with the auxin indole-3-acetic acid (IAA), which synergizes the activity of brassinosteroids. Thus, 1-(4,6α,7α-trihydroxy-5,6,7,8-tetrahydronaphthyl)-2-(6α′,7α′-dihydroxy-5′,6′,7′,8′-tetrahydronaphthyl)ethyne (**4**) and (*E*)-1,2-bis[*trans*-(4aα,8a*β*)-4-oxo-6α,7α-dihydroxy-4a,5,6,7,8,8a-hexahydro-(3*H*)-naphthyl]ethylene (**11**) showed exceptional activity at doses as low as 0.01 ng and 0.001 ng/plant, respectively. These compounds are the first biologically active nonsteroidal brassinolide mimetics.

Introduction

Brassinolide (**1**) is a powerful plant hormone that was first isolated in 1979 by Grove and co-workers.[1] It manifests biological activity on a wide range of plant species when applied exogenously, in some cases at doses as low as 1 ng/individual plant.[2−4] Although **1** and related brassinosteroids such as castasterone (**2**) (Chart 1) are found widespread throughout the plant kingdom, natural sources of brassinosteroids are an impractical source of these compounds because of their very low concentrations (typically ppb to ppt). While several syntheses of **1** and its analogues have been reported,[5−7] they are lengthy, expensive, and provide relatively small amounts of the products. Despite the poor availability of brassinosteroids, a great deal of effort has been expended on investigations of their chemistry, biological properties, field applications, and molecular biology.[2−4] The discovery of simpler, more easily available compounds capable of mimicing the biological activity of natural brassinosteroids would thus be of considerable interest. We now report the design, preparation, and bioactivity of the first nonsteroidal brassinolide mimetics.

Chart 1. Structures of Brassinosteroids 1 and 2



Brassinolide (**1**) Castasterone (**2**)

Results and Discussion

Recent structure−activity studies of brassinosteroids have revealed that, inter alia, the vicinal diol groups and the configurations of their stereocenters are of importance in maintaining strong bioactivity,[8−10] which is presumably mediated by highly selective binding to one or more putative brassinosteroid receptors that initiates signal transduction and ultimately gene expression.[11] The 5α-configuration is required for optimum activity,[12] but the B-ring tolerates considerable variation, providing that the presence of a polar functional group, which does not have to be a lactone, is maintained.[13] Thus, based on existing structure−activity information, we endeavored

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[‡] Department of Biological Sciences.

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(2) *Brassinosteroids: Chemistry, Bioactivity and Applications*; Cutler, H. G.; Yokota, T.; Adam, G., Eds., ACS Symposium Series 474, American Chemical Society: Washington, D. C., 1991.
(3) *Brassinosteroids: Steroidal Plant Hormones*; Sakurai, A.; Yokota, T.; Clouse, S. D., Eds., Springer-Verlag: Tokyo, 1999.
(4) Khripach, V. A.; Zhabinskii, V. N.; de Groot, A. E. *Brassinosteroids: A New Class of Plant Hormones*; Academic Press: San Diego, 1999.
(5) For a review of earlier synthetic work, see: Back, T. G. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed., Elsevier: Amsterdam, 1995; Vol. 16, pp 321−364.
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(8) Adam, G.; Porzel, A.; Schmidt, J.; Schneider, B.; Voigt, B. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed., Elsevier: Amsterdam, 1996; Vol. 18, pp 495−549.
(9) Brosa, C. In *Biochemistry and Function of Sterols*; Parish, E. J.; Nes, W. D., Ed., CRC Press: Boca Raton, FL, 1997; pp 201−220.
(10) Yokota, T.; Mori, K. In *Molecular Structure and Biological Activity of Steroids*; Bohl, M.; Duax, W. L., Eds., CRC Press: Boca Raton, FL, 1992; pp. 317−340.
(11) Clouse, S. D.; Feldmann, K. A. In *Brassinosteroids: Steroidal Plant Hormones*; Sakurai, A.; Yokota, T.; Clouse, S. D., Eds., Springer-Verlag: Tokyo, 1999; Ch. 8.
(12) Seto, H.; Fujioka, S.; Koshino, H.; Suenaga, T.; Yoshida, S.; Watanabe, T.; Takatsuto, S. *Phytochemistry* **1999**, *52*, 815.
(13) Baron, D. L.; Luo, W.; Janzen, L.; Pharis, R. P.; Back, T. G. *Phytochemistry* **1998**, *49*, 1849.

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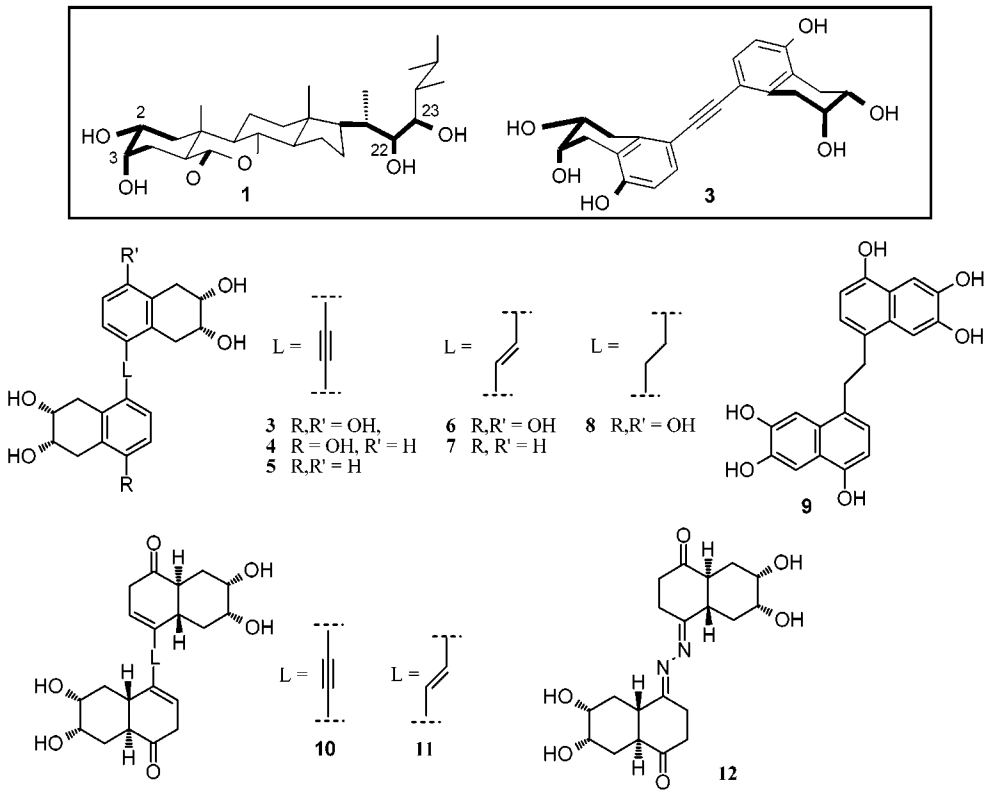
Chart 2. Conformations of Brassinolide (1) and Mimetic 3 and Structures of Mimetics 3−12



to design nonsteroidal analogues consisting of two rigid subunits containing vicinal diol groups, joined by an appropriate linker, that would permit close superimposition of individual hydroxyl groups upon those of brassinolide (**1**). A gauche relationship between the hydroxyl groups of each vicinal pair and an additional hydroxyl or keto group in the B-ring to satisfy the requirement for a polar functionality were also deemed necessary. A prototype brassinosteroid mimetic (**3**) is shown in Chart 2, with key structural features highlighted. Compounds **4**−**12** were the other structures chosen as potential mimetics, or were included for purposes of comparison.

A series of bicyclic subunits containing the key diol groups, and generally an additional hydroxyl or keto group to mimic the polar B-ring functionality of natural brassinosteroids such as **1** or **2**, were linked by means of acetylene, *trans*-alkene, -CH_2CH_2- or azine linkers (Chart 2). This afforded structures that superimposed relatively closely with **1**. For greater ease of synthesis, all of the mimetics except **4** were assembled from two identical subunits, thereby including a redundant hydroxyl or carbonyl group in the upper subunit of the coupled product. Since the subunits of the coupled products, except those of **9**, were racemic, the products were formed as inseparable mixtures of diastereomers, arising from pairs of matched and mismatched subunits.[14] Although the C=N bonds of azine **12** can generate *E* and *Z* isomers, we assume that the product consists chiefly or exclusively of the less sterically crowded *E*,*E*-isomer. For convenience, only the stereoisomers that most closely resemble **1** are shown in Chart 2 and were the subjects of molecular modeling studies (vide infra). The unseparated mixtures of isomers were used in subsequent bioassays.

The relative spatial orientation of the alcohol moieties of brassinolide is illustrated in Chart 2, where the conformation was determined by an initial MM2 minimization, followed by a Monte Carlo search to locate the global minimum energy conformation, and finally by ab initio (STO 3G basis set) refinement.[15] Other molecular modeling studies of brassinosteroids have also been reported recently[16−19] and an X-ray crystal structure of brassinolide was determined by its discoverers.[1] The minimum energy conformation of brassinolide was then used as a starting point for the rational design of the various nonsteroidal analogues. The modeling of several of the mimetic structures showed excellent overlap of the

(14) While it is recognized that the bioactivity of the individual stereoisomers of the mimetics may differ, our strategy was to first synthesize and screen the mimetics as mixtures of (±) and meso isomers in order to identify those mixtures containing any active components. In the future, we intend to resynthesize the subunits of active mimetics in an enantioselective manner and thus procure individual stereoisomers of the active mimetics for further biological evaluation.

(15) Molecular modeling was performed on an IBM RS/6000 Model 250 Power PC. Initial MM2 molecular mechanics and Monte Carlo searches were performed with MacroModel Version 4.5 (W. C. Still, Columbia University). The resulting structures were imported into Spartan Version 4.1.1 (Wave function Inc.) and further refined by ab initio calculations with the STO 3G basis set for **1**, or by semiempirical calculations using the AM1 basis set for the mimetics. For a further description of molecular mechanics with MM2, see: (a) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177, American Chemical Society: Washington, D. C., 1982. (b) Bowen, J. P.; Allinger, N. L. *Rev. Comput. Chem.* **1991**, *2*, 81. For a further description of STO 3G and other ab initio methods, see: (c) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986; Chapter 4. For the AM1 method, see: Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

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(18) McMorris, T. C.; Patil, P. A.; Chavez, R. G.; Baker, M. E.; Clouse, S. D. *Phytochemistry* **1994**, *36*, 585.

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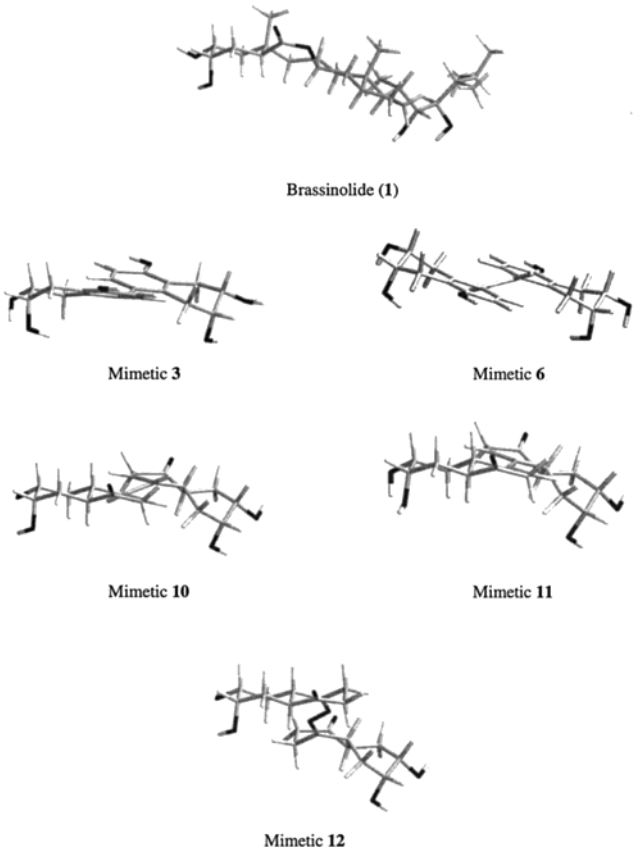
Chart 3. Molecular Modeling of Brassinolide (1) and Mimetics 3, 6, and 10−12



key hydroxyl groups with the vicinal diol functionalities of brassinolide. The inclusion of phenolic hydroxyl groups in the subunits of **3**, **4**, **6**, **8**, and **9**, instead of ketone or lactone carbonyl groups as found in castasterone (**2**) and brassinolide (**1**), respectively, was validated by the observation that reduction of the 6-keto group of castasterone afforded a pair of C-6 alcohol epimers that were both significantly bioactive.[20] Compounds **5** and **7**, where both subunits lack polar functions at this position, and compound **9**, where the hydroxyl groups of the diol units are coplanar instead of gauche, were included for comparison.

Molecular modeling of representative structures **3** (identical skeleton to **4** and **5**), **6** (identical skeleton to **7**), **10**, **11**, and **12** was performed similarly and compared with that of brassinolide (**1**). To obtain optimum superimposition of the hydroxyl groups of the acetylene-linked mimetics **3** and **10** with the hydroxyl groups of brassinolide, it was necessary to constrain key dihedral angles about the linear acetylene linker to match those in brassinolide. Geometry optimization and semiempirical (AM1) energy minimization of the constrained structures indicated that their energies were 6.5 and 0.6 kJ/mol, respectively, higher than those of their respective global energy minima.[15] The constrained conformations are therefore readily accessible at room temperature through normal conformational interchange. Graphical depictions of the structures of representative mimetics **3**, **6**, and **10**−**12**, as well as of brassinolide (**1**), are shown in Chart 3.

(20) (a) Sung, G. C. Y.; Janzen, L.; Pharis, R. P.;Back, T. G. *Phytochemistry* **2000**, *55*, 121. (b) Fujioka, S.; Noguchi, T.; Takatsuto, S.; Yoshida, S. *Phytochemistry* **1998**, *49*, 1841.

Table 1. Interatomic Distances (Å Units) between Diol Oxygen Atoms in 1 and Mimetics 3, 6, 10, 11, and 12

	compound					
atom	**1**	**3**	**6**	**10**	**11**	**12**
O2−O3	2.81	2.82	2.83	2.66	2.74	2.78
O22−O23	2.67	2.84	2.83	2.77	2.78	2.75
O2−O22	11.36	9.92	10.87	9.29	10.98	11.18
O2−O23	13.77	11.90	12.56	11.46	12.62	12.17
O3−O22	10.94	10.38	10.96	9.90	11.11	11.41
O3−O23	13.49	12.61	13.12	12.25	13.20	12.58

Interatomic distances between the oxygen atoms of the vicinal diol moieties of brassinolide and the mimetics are presented in Table 1 and provide a quantitative measure of how well the mimetics resemble the structure of **1**. Compounds **8** and **9**, containing CH_2CH_2 linkers, have numerous local minimum energy conformations and are not included in Table 1.

On this basis, the data in Table 1 indicate that compounds **6** and **11** show the greatest structural similarity to **1**. It is important to note that the calculated conformations of brassinolide, as well as those of the mimetics, may be substantially different in the aqueous environment of biological systems where hydrogen-bonding with water may significantly affect their structures. Notwithstanding this limitation, molecular modeling provides a convenient means by which a first generation of potential mimetics can be evaluated and refined.

The synthesis of mimetics **3**−**5** is shown in Scheme 1. Tetrahydonaphthalene **13** was obtained from α-naphthol by a literature procedure.[21] Iodination in the *para* position was effected with chloramine T and sodium iodide to afford **14**.[22] Sonogashira coupling[23] of **14** with trimethylsilylacetylene produced **15**. The iodide **16** was then prepared from α-naphthylamine as reported previously.[24] Dihydroxylation and Sonogashira coupling then provided acetylene **18**. Similar coupling of iodide **14** with acetylene **15** and deprotection afforded the bisphenol **3** as a mixture of the corresponding meso and (±) isomers, while the coupling of the silyl ether **20** with **18**, followed by removal of protecting groups, produced the monophenol **4** as two diastereomeric (±) pairs. Finally, the coupling of **17** and **18** afforded the mimetic **5**, lacking phenolic hydroxyl groups, as a mixture of a meso compound and a (±) pair.

Mimetics **6**−**8** were prepared as shown in Scheme 2. Iodide **20** was subjected to Stille coupling[25] with *trans*-bis(tri-*n*-butylstannyl)ethylene,[26] to afford **22** in one step, but in low yield. Deprotection provided **6** as a mixture of a *meso* compound and a (±) pair. Hydrogenation and deprotection of **22** produced **8** in the form of a similar mixture of stereoisomers. Product **7**, which is devoid of

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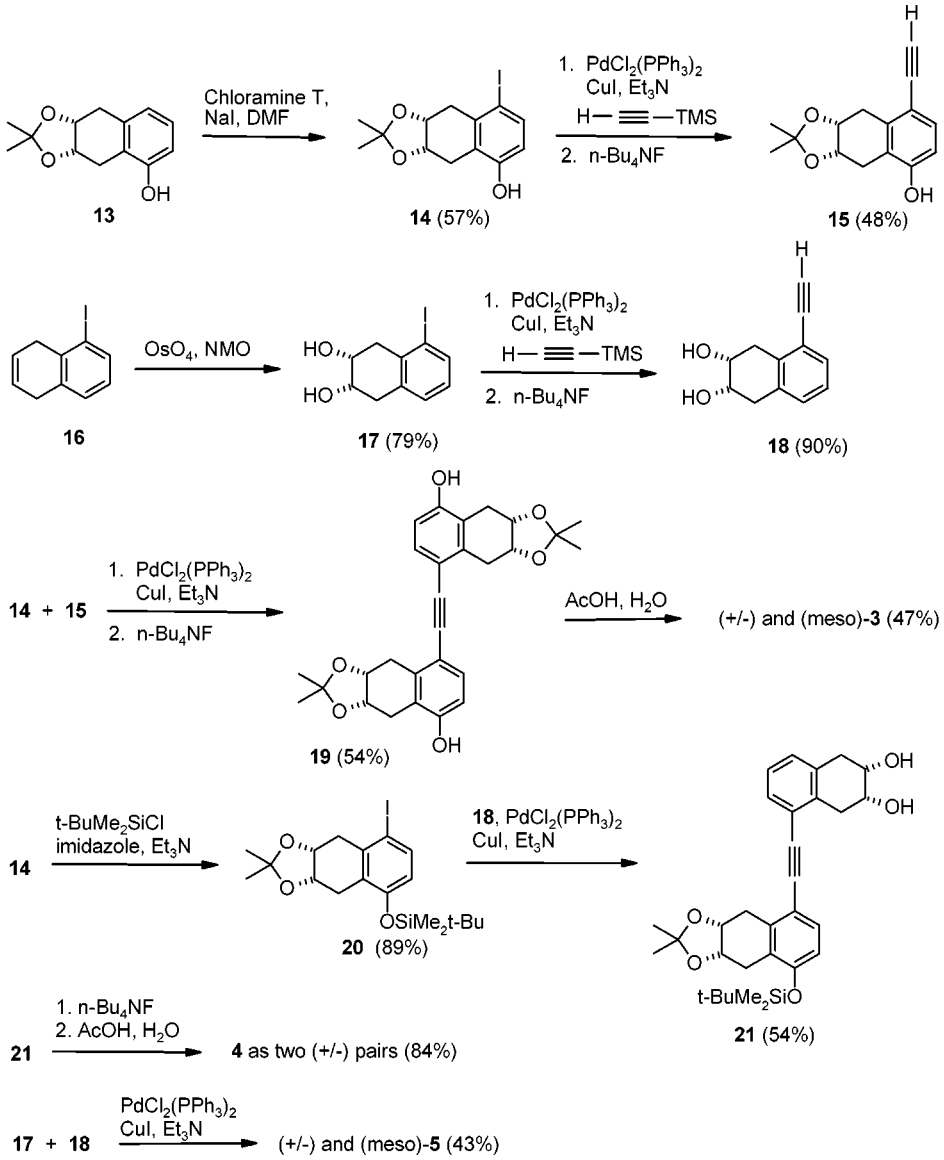
(25) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, 1995; pp 228−239.

(26) Renaldo, A. F.; Labadie, J. W.; Stille, J. K. *Org. Synth.* **1988**, *67*, 86.

Scheme 1



phenolic hydroxyl groups, was similarly prepared from **17** and *trans*-bis(tri-*n*-butylstannyl)ethylene.

The naphthalene-based mimetic **9** was obtained as outlined in Scheme 3. The diene **23** was prepared from tartaric acid by literature procedures.[27] Its Diels−Alder cycloaddition with benzoquinone and spontaneous air oxidation provided **24**, which was hydrogenated to the corresponding 1,4-dihydroxynaphthalene, followed by silylation of one phenolic hydroxyl group and conversion of the other to its triflate. Stille coupling of the resulting triflate **25** with *trans*-bis(tri-*n*-butylstannyl)ethylene afforded **26**. Direct deprotection of the six phenolic groups of the latter resulted in a product that was easily oxidized by air, thereby obviating its potential utility as a brassinosteroid mimetic. However, hydrogenation of the *trans*-ethylene linker prior to deprotection afforded the stable product **9**.

The mimetics **10**−**12**, which are based on the *trans*-decalone subunit, were prepared from **27**, in turn derived from the Diels−Alder cycloaddition of benzoquinone and 1,3-butadiene[28] (see Scheme 4). Monoprotection of **27** to **28** was accompanied by extensive epimerization to the more stable *trans*-decalone isomer. The mixture was subjected to *cis*-dihydroxylation to afford **29** as an inseparable mixture of *trans*-fused α,α- and *β*,*β*-diol isomers, along with the α,α-diol **30**, obtained as the sole product from the *cis*-fused system, and easily separable from **29**. Further ketalization of **29** produced separable acetonide epimers **31** and **32**. Moreover, similar ketalization of **30**, followed by quantitative base-catalyzed epimerization via the corresponding enolate, provided additional **32** (total yield: 56%). The assignment of the relative stereochemistry of the two acetonides, **31** and **32**, was based on NMR data, including DEPT, COSY, HMQC, and HMBC experiments. Stereoisomer **32** was then converted to the corresponding enol triflate **33**, followed by Stille coupling with either bis(tri-*n*-butylstannyl)acetylene[29] or *trans*-bis(tri-*n*-butylstannyl)ethylene[26] and deprotection, to afford the desired products

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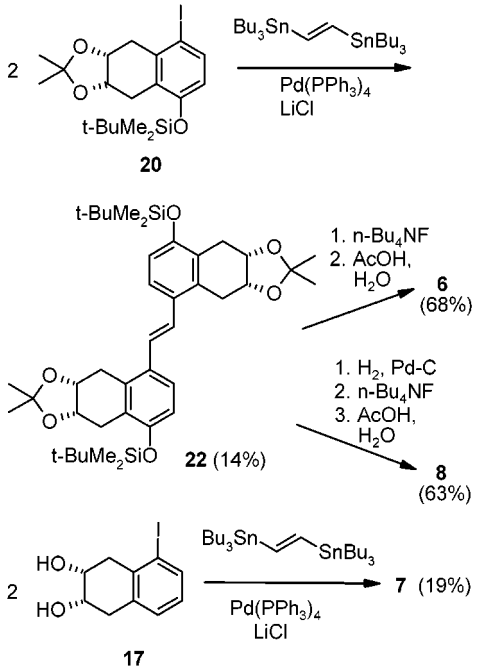
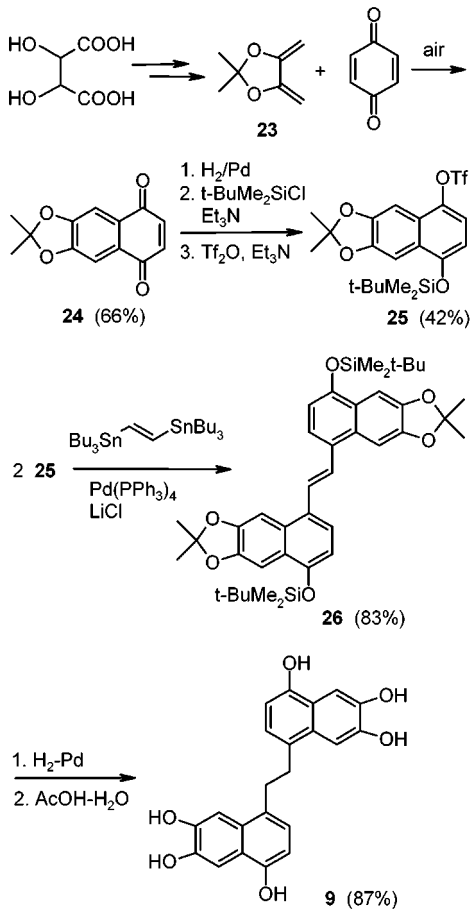
Scheme 2



Scheme 3



10 and **11**, respectively, each obtained as a mixture of *meso*- and (±)-stereoisomers. Finally, *cis*-dihydroxylation of the *trans*-fused decalone **36** provided diol **37**.[30] The latter was treated with only 0.25 equiv of hydrazine to minimize polymerization and afforded the corresponding azine **12** as a mixture of stereoisomers in 56% yield based on hydrazine (Scheme 5). Attempts to prepare **12** from the monoketone **32** and hydrazine failed because of decomposition during attempts at removal of the ketal protecting groups.

Compounds **3**−**12**, along with **1** for comparison, were then subjected to the rice leaf lamina inclination bioassay,[31] a rapid, highly sensitive, and convenient means for detecting and measuring brassinosteroid bioactivity (Figures 1−3). The assay is based on the downward movement response (angle) of the rice seedlings' second leaf lamina from a nearly upright ca. 160° in untreated control plants to angles of less than 90° when a highly active brassinosteroid is applied. A plot of leaf lamina angle vs the logarithm of the dose in nanograms therefore provides a convenient and quantitative indication of bioactivity. Moreover, brassinosteroids show synergy with auxins, such as indole-3-acetic acid (IAA), in this bioassay.[31,32] For example, the coapplication of IAA with brassinolide lowers the threshold of detectable activity of **1** from ca. 1 ng to between 0.1 and 0.01 ng.[13,33] The bioassays of **3**−**12** were therefore run both in the presence and absence of 1000 ng of added IAA. Initially, IAA and the mimetics were applied in 0.5 μL microdrops in 95% ethanol. The results for compounds that were active under these conditions are provided in Figure 1; data for inactive compounds are not shown. As expected, compounds **5** and **7**, which lack a polar functional group corresponding to the B-ring lactone moiety of **1**, proved completely inactive at all dosage levels, with or without IAA application. Similarly, compounds **8** and **9**, containing a saturated linker, displayed no bioactivity, perhaps in part because of excessive conformational mobility that impedes binding to the putative brassinosteroid receptor. Mimetics **3** and **4**, where an acetylenic linker joins subunits containing at least one phenolic group to satisfy the need for a polar B-ring function, showed statistically significant biological activity, but only when coapplied with IAA in 95% ethanol, and only at high doses. Mimetic **6**, which contains identical subunits to **3**, but employs a *trans*-ethylene linker, yielded a similar response. The *trans*-decalone-based mimetics **10** and **12**, possessing acetylenic and azine linkers, respectively, were devoid of brassinosteroid activity at all doses even with the coapplication of IAA. However, mimetic **11** showed somewhat better biological activity when it was coapplied with IAA in ethanol microdrops. Since mimetic **11** is poorly soluble in ethanol, we repeated the bioassay using dimethyl sulfoxide (DMSO), but with no improvement in bioactivity (data not shown). We then tested **11** in a 2.5:8:89.5 (v/v/v) mixture of the formulating agent Atlas G-1086,[34] DMSO, and water. In the Atlas solution, **11** alone was inactive across a wide range of doses (Figure

(29) (a) Luijten, J. G. A.; Van Der Kerk, G. J. M. *Rec. Trav. Chim. Pays-Bas* **1964**, *83*, 295−300. (b) Luijten, J. G. A.; Janssen, M. J.; Van Der Kerk, G. J. M. *Rec. Trav. Chim. Pays-Bas* **1962**, *81*, 202−205.

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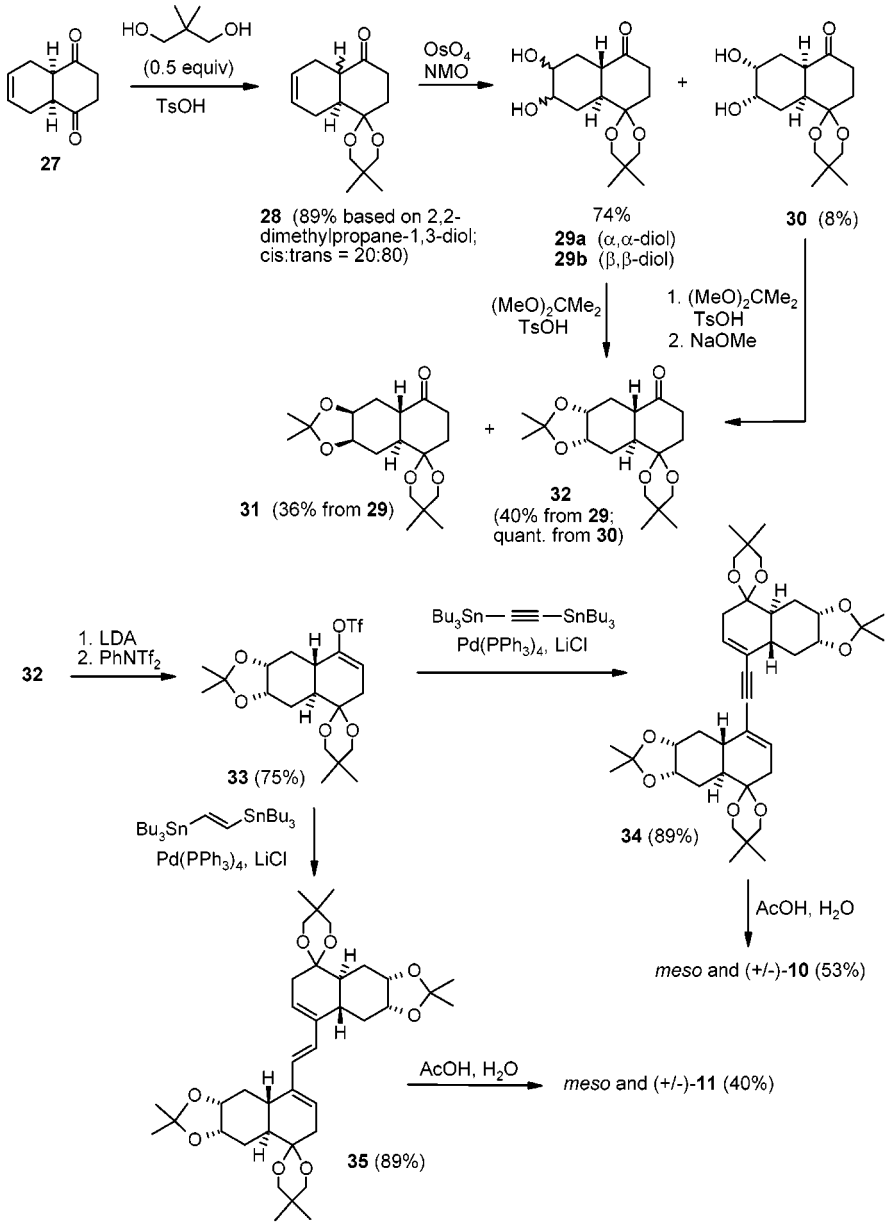
(32) (a) Mandava, N. B. *Annu. Rev. Plant Physiol. Plant Mol. Biol.* **1988**, *39*, 23. (b) Sasse, J. M. In *Brassinosteroids: Chemistry, Bioactivity and Applications*; Cutler, H. G.; Yokota, T.; Adam, G., Eds., ACS Symposium Series 474, American Chemical Society: Washington, D. C., 1991; pp 158−166.

(33) Back, T. G.; Janzen, L.; Nakajima, S. K., Pharis, R. P. *J. Org. Chem.* **1999**, *64*, 5494.

(34) Atlas G-1086 (polyoxyethylene sorbitol hexaoleate) is a proprietary formulation of ICI Americas Inc., a subsidiary of Imperial Chemical Industries PLC.

Scheme 4



3, top curve). However, when **11** was tested in the Atlas solution with 1000 ng/plant of IAA, the rice leaf lamina bending response increased dramatically, especially at the lower doses of **11**, with a strong bending response even at the lowest dose of 0.001 ng of **11** (Figure 2). Mimetics **4** and **6** were then tested in Atlas in a similar manner, but only the bioactivity of **4** increased significantly (compare Figures 2 and 1). We also observed that higher doses of mimetics **4** and **11** (100 to 10000 ng/plant in Atlas solution) gave an appreciably diminished bioactivity (see Figure 2), suggesting the possibility that the 1000 ng dose of IAA might be suboptimal at the higher doses of **4** and **11**. Since Fujioka et al.[20b] recently reported that the coapplication of 5000 ng of IAA was more effective than 1000 ng in increasing the response of rice plants to brassinosteroids in the leaf lamina bioassay, we reexamined the biological activity of **11** in the presence of 1000, 5000, 7500, and 10000 ng of IAA. Indeed, the effect of **11** was appreciably enhanced when it was applied in the Atlas solution after the IAA dose (in 95% ethanol) was increased from 1000 to 5000 ng (Figure 3). However, doses of IAA higher than 5000 ng proved supraoptimal and/or toxic (data not shown).

The bending response within the population of rice also differs between brassinolide and mimetics **4** and **11**. At a near-optimal dose of brassinolide and 1000 ng of IAA (Figure 2), the distribution of individual plants within the tested population, with respect to angle response, is typically Gaussian (bell-shaped). However, for mimetics **4** or **11** coapplied with 1000 ng of IAA, individual plants within the population are relatively evenly distributed across a wide range of leaf lamina bending angles**.** Moreover, when mimetic **11** is coapplied with 5000 ng of IAA, the population distribution of responding plants approaches Gaussian at near maximal responses. Thus, the mimetics not only have an absolute requirement for IAA, but increased levels of IAA (i.e., the more effective 5000 ng dose) yield a population response to **11** that more closely mimics the response seen with brassinolide and IAA.

In conclusion, we report the first nonsteroidal mimetics of brassinolide that possess brassinosteroid-like biological

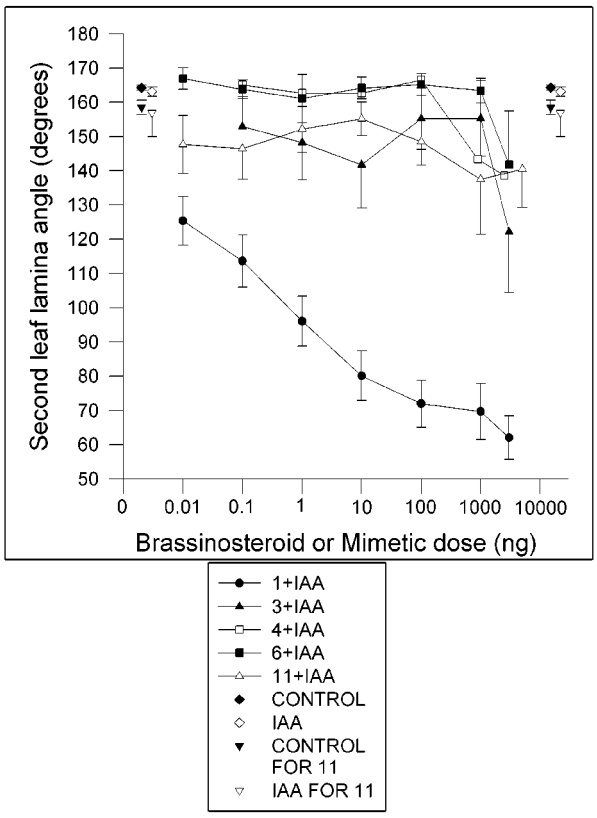
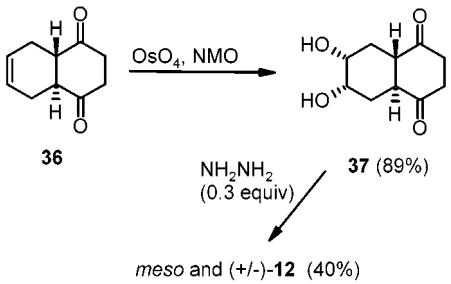


Figure 1. Bioassay of mimetic **3**, **4**, **6**, and **11** vs **1** as the standard in the presence of 1000 ng of IAA. All compounds were applied in 95% ethanol. Error bars represent 95% confidence limits.

Scheme 5



activity in the rice leaf lamina bioassay. Two mimetics (**3** and **6**) showed low, but statistically significant bioactivity, when applied at relatively high doses, but only when coapplied with IAA. In contrast, mimetic **11**, which has a structure that is closely superimposable upon that of **1**, when coapplied with IAA in a 2.5% aqueous solution of Atlas, proved highly active across a broad range of doses (Figures 2 and 3). Mimetic **4**, while showing a poorer structural resemblance to brassinolide than **11**, was, however, similar to **11** in bioactivity when applied in the Atlas solution with IAA. Our results therefore indicate that it is possible to prepare biologically active nonsteroidal analogues of brassinolide consisting of a relatively rigid scaffolding (except for possible free rotation about some of the linkers) that holds key functional groups in the required spatial orientation to mimic the structure and geometry of **1** and related brassinosteroids.

Experimental Section

NMR signals from diastereomeric products generally coincided and could not be resolved, except where otherwise noted.

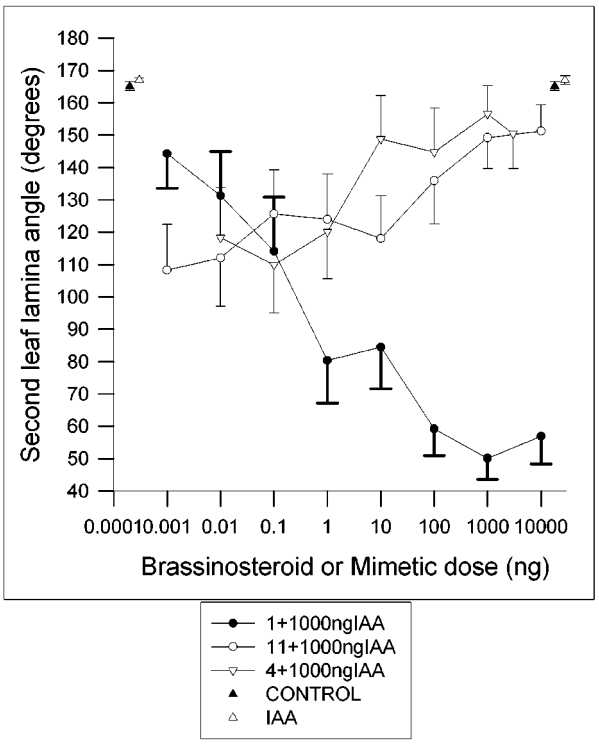


Figure 2. Bioassay of mimetics **4** and **11** vs **1** as the standard, applied in 2.5% aqueous Atlas in the presence of 1000 ng of IAA. Error bars represent 95% confidence limits and are shown in bold for **1** to distinguish them from those of **4** and **11**.

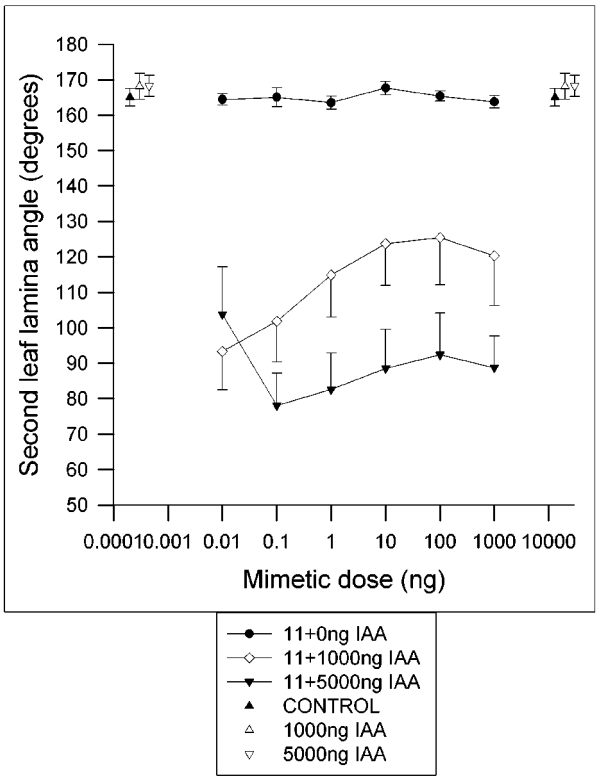


Figure 3. Bioassay of mimetic **11** applied in 2.5% aqueous Atlas in the presence of 0, 1000, and 5000 ng of IAA. Error bars represent 95% confidence limits.

^{1}H NMR integrations are based on one subunit for symmetrical products. Where ^{13}C NMR signals are listed as C, CH, CH_2, or CH_3, the assignments were made on the basis of DEPT

experiments. Chromatography was performed on flash grade silica gel unless indicated otherwise.

(±)-4-Iodo-6α,7α-(isopropylidenedioxy)-5,6,7,8-tetrahydro-1-naphthol (14). Alcohol **13**[22] (0.99 g, 4.50 mmol) was dissolved in 10 mL of DMF. Subsequent addition of sodium iodide (808 mg, 5.40 mmol) and chloroamine-T trihydrate (1.52 g, 5.40 mmol) resulted in a murky, yellowish-green solution, which was stirred for 2.75 h at room temperature. The mixture was diluted with water, acidified with 10% HCl solution, and extracted several times with ether. The combined ether layers were washed with 5% $NaHSO_3$ and NaCl solutions, dried ($MgSO_4$), evaporated in vacuo, and purified by chromatography (elution with 5% ethyl acetate−hexanes) to afford 892 mg (57%) of iodide **14**: mp 172−175 °C (from methylene chloride−hexanes); IR (KBr) 3249, 1591, 1188, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$−CD_3OD) δ 7.54 (d, J = 8.5 Hz, 1 H), 6.48 (d, J = 8.5 Hz, 1 H), 5.32 (s, 1 H, OH), 4.63−4.61 (m, 2 H), 3.18 (m, 2 H), 2.74 (m, 1 H), 2.56 (m, 1 H), 1.33 (s, 3 H), 1.14 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$−CD_3OD) δ 154.4 (C), 139.2 (C), 136.5 (CH), 123.7 (C), 115.6 (CH), 108.1 (C), 87.8 (C), 74.2 (CH), 73.9 (CH), 38.7 (CH_2), 26.7 (CH_2), 26.0 (CH_3), 24.2 (CH_3); mass spectrum, *m*/*z* (relative intensity, %) 346 (M^+, 25), 331 (34), 288 (37), 144 (67), 43 (100). Anal. calcd for $C_{13}H_{15}IO_3$: C, 45.11; H, 4.37. Found: C, 45.18; H, 4.46.

(±)-4-Ethynyl-6α,7α-(isopropylidenedioxy)-5,6,7,8-tetrahydro-1-naphthol (15). Iodophenol **14** (500 mg, 1.44 mmol) was dissolved in 7 mL of dry 1,4-dioxane and 7 mL of dry triethylamine. Dichlorobis(triphenylphosphine)palladium(II) (10 mg, 1 mol %), copper(I) iodide (5.5 mg, 2 mol %), and (trimethylsilyl)acetylene (407 μL, 2.88 mmol) were added, and the mixture was stirred at 70 °C for 24 h. The mixture was diluted with ethyl acetate, and the aqueous layer was acidified with 10% HCl solution and extracted with ethyl acetate. The combined organic layers were washed with $NaHCO_3$ and NaCl solutions, dried (Na_2SO_4), and evaporated. The crude coupled material was dissolved in 20 mL of THF, tetra-*n*-butylammonium fluoride (2.0 mL of a 1.0 M solution in THF, 2.0 mmol) was added, and the mixture was stirred at room temperature for 3 h. The reaction was concentrated in vacuo, diluted with ethyl acetate, washed with NaCl solution, dried (Na_2SO_4), concentrated in vacuo, and the residue was purified by chromatography (elution with 30% ethyl acetate−hexanes) to furnish 168 mg (48%) of **15**: mp 152−156 °C (from acetonitrile); IR (KBr) 3260, 2437, 1590, 1160, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.6 Hz, 1 H), 6.63 (d, J = 8.3 Hz, 1 H), 5.18 (s, 1 H, OH), 4.65−4.63 (m, 2 H), 3.32 (dd, J = 15.3, 3.6 Hz, 1 H), 3.17 (s, 1 H), 3.11 (dd, J = 16.6, 3.4 Hz, 1 H), 2.77 (dd, J = 15.1, 3.4 Hz, 1 H), 2.57 (dd, J = 15.2, 3.4 Hz, 1 H), 1.33 (s, 3 H), 1.15 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$−CD_3OD) δ 154.4 (C), 140.0 (C), 131.3 (CH), 121.8 (C), 113.3 (CH), 112.9 (C), 108.0 (C), 82.4 (C), 78.7 (CH), 76.7 (CH), 73.9 (CH), 31.7 (CH_2), 26.2 (CH_3), 26.0 (CH_2), 24.3 (CH_3); mass spectrum, *m*/*z* (relative intensity, %) 244 (M^+, 52), 229 (58), 186 (90), 169 (80), 43 (100). Exact mass calcd for $C_{15}H_{16}O_3$: 244.1099. Found: 244.1094.

(±)-5-Iodo-1,2,3,4-tetrahydro-2α,3α-naphthalenediol (17). Osmium tetroxide (1.7 mL of a 0.39 M solution in *tert*-butyl alcohol, 0.66 mmol) and 4-methylmorpholine *N*-oxide (1.61 g, 13.8 mmol) were added to a solution of 5-iodo-1,4-dihydronaphthalene[24] (**16**) (3.35 g, 13.1 mmol). The mixture was stirred for 2.5 h at room temperature. Florisil (1 g) and solid sodium thiosulfate (714 mg) were added, and the stirring was continued for 2 h before the solid was removed by filtration. The filtrate was evaporated in vacuo, and the residue was chromatographed (elution with 40% ethyl acetate−hexanes) to afford 3.00 g (79%) of diol **17**: mp 139−141 °C (from chloroform); IR (KBr) 3333, 1555, 1175, 1068, 1051, 773 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.71 (d, J = 7.7 Hz, 1 H), 7.10 (d, J = 7.5 Hz, 1 H), 6.84 (t, J = 7.7 Hz, 1 H), 4.10 (m, 2 H), 3.01 (m, 4 H), 2.08 (br s, 2 H, 2 OH); ^{13}C NMR (50 MHz, $CDCl_3$−CD_3OD) δ 136.9 (CH), 136.0 (C), 135.2 (C), 129.2 (CH), 127.6 (CH), 102.2 (C), 69.4 (CH), 68.7 (CH), 40.7 (CH_2), 34.5 (CH_2); mass spectrum, *m*/*z* (relative intensity, %) 290 (M^+, 45), 272 (60), 232 (50), 145 (100), 115 (96), 91 (31), 77 (64). Anal. Calcd for $C_{10}H_{11}IO_2$: C, 41.40; H, 3.82. Found: C, 41.43; H, 3.81.

(±)-1-Ethynyl-5,6,7,8-tetrahydro-6α,7α-naphthalenediol (18). Dichlorobis(triphenylphosphine)palladium(II) (242 mg, 5 mol %) and copper(I) iodide (33 mg, 2.5 mol %) were added to a solution of iodide **17** (2.00 g, 6.89 mmol) in 65 mL of dry 1,4-dioxane and 65 mL of dry triethylamine. Subsequently, (trimethylsilyl)acetylene (1.46 mL, 10.3 mmol) was added, and the mixture was refluxed for 8 h, at which time a further 1.5 equiv of (trimethylsilyl)acetylene (1.46 mL, 10.3 mmol), 2.5 mol % of dichlorobis(triphenylphosphine)palladium(II) (121 mg), and 2.5 mol % of copper(I) iodide (33 mg) were added. The mixture was refluxed for 16 h before water was added. The mixture was acidified with 10% HCl solution and extracted with ethyl acetate. The combined organic layers were washed with NaCl solution, dried (Na_2SO_4), and evaporated in vacuo. The residue was dissolved in 100 mL of THF and was cooled to 0 °C, followed by the addition of tetra-*n*-butylammonium fluoride (7.6 mL of a 1.0 M solution in THF, 7.6 mmol). The reaction was stirred for 5 h at room temperature, NH_4Cl solution was added, and the mixture was extracted several times with ethyl acetate. The combined organic layers were washed with NaCl solution, dried (Na_2SO_4), concentrated under vacuum, and chromatographed (elution with 50% ethyl acetate−hexanes) to give 1.17 g (90%) of acetylene **18**: mp 133−136 °C (from methanol−water); IR (KBr) 3360, 1579, 1054, 1007, 976 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 1 H), 7.12 (m, 2 H), 4.74 (br s, 2 H, OH), 4.18 (m, 2 H), 3.32 (s, 1 H), 3.22 (dd, J = 17.7, 5.3 Hz, 1 H), 3.12 (dd, J = 17.7, 6.5 Hz, 1 H), 3.03 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8 (C), 133.6 (C), 130.3 (CH), 129.5 (CH), 125.6 (CH), 121.7 (C), 81.8 (C), 81.7 (CH), 68.7 (CH), 68.6 (CH), 48.8 (CH_2), 34.0 (CH_2); mass spectrum, *m*/*z* (relative intensity, %) 188 (M^+, 11), 170 ($M^+ - H_2O$, 100), 128 (88), 115 (43). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.47; H, 6.58.

(±)-1,2-Bis[4-hydroxy-6α,7α-(isopropylidenedioxy)-5,6,7,8-tetrahydronaphthyl]ethyne (19) and Its Meso Isomer. Iodide **14** (235 mg, 0.680 mmol) and acetylene **15** (166 mg, 0.680 mmol) were dissolved in 5 mL of dry 1,4-dioxane and 5 mL of dry triethylamine. To this mixture were added dichlorobis(triphenylphosphine)palladium(II) (4.7 mg, 1 mol %) and copper(I) iodide (2.5 mg, 2 mol %). The reaction mixture was refluxed for 18 h, acidified with 10% HCl solution, and extracted several times with ethyl acetate. The combined extracts were washed with $NaHCO_3$ and NaCl solutions, dried (Na_2SO_4), evaporated in vacuo, and chromatographed (elution with 5−20% ethyl acetate−hexanes) to afford 168 mg (54%) of the coupled product **19**, which consisted of (±)- and *meso*-diastereomers that could not be separated. Compound **19** was recrystallized from ethyl acetate−hexanes: mp 268−272 °C; IR (KBr) 3340, 1589, 1159, 1047, 817 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.24 (d, J = 8.3 Hz, 1 H), 6.77 (d, J = 8.4 Hz, 1 H,), 4.62 (m, 2 H), 3.33 (ddd, J = 15.2, 9.2, 3.7 Hz, 1 H), 3.13 (ddd, J = 15.2, 7.3, 3.7 Hz, 1 H), 2.84 (dt, J = 15.1, 4.7, Hz, 1 H), 2.59 (ddd, J = 15.3, 8.6, 4.2 Hz, 1 H); the following signals are from resolved acetonide methyl groups of the two diastereomers: 1.26 (s, 1.5 H), 1.25 (s, 1.5 H), 1.06 (s, 1.5 H), 1.04 (s, 1.5 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 155.4 (C), 139.9 (C), 139.8 (C), 131.1 (CH), 123.2 (C), 115.5 (C), 115.4 (C), 114.0 (CH), 108.3 (C), 108.2 (C), 90.9 (C), 74.8 (CH), 74.6 (CH), 32.8 (CH_2), 32.7 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 26.6 (CH_3), 24.7 (CH_3); mass spectrum, *m*/*z* (relative intensity, %) 462 (M^+, 1), 185 (7), 142 (100), 100 (44). Exact mass calcd for $C_{28}H_{30}O_6$: 462.2042. Found: 462.2050.

(±)-1,2-Bis[4,6α,7α-trihydroxy-5,6,7,8-tetrahydronaphthyl]ethyne (3) and Its Meso Isomer. The bisacetonide **19** (257 mg, 0.556 mmol) was stirred in 10 mL of 80% acetic acid solution at 60 °C for 1 h, and then the acetic acid was removed in vacuo. The residue was purified by chromatography (elution with 5% ethanol−chloroform) to furnish 101 mg (47%) of **3** as an inseparable mixture of (±)- and *meso*-diastereomers: mp 280−283 °C (from methanol−water); IR (KBr) 3390, 1582, 1062, 812 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.16 (d, J =

8.3 Hz, 1 H), 6.60 (d, J = 8.3 Hz, 1 H), 4.08 (m, 2 H), 3.14 (d, J = 5.5 Hz, 2 H), 2.87 (d, J = 5.6 Hz, 2 H); ^{13}C NMR (100 MHz, CD_3OD) δ 156.7 (C), 138.2 (C), 131.5 ($CH_,$), 122.6 (C), 115.9 (C), 113.1 (CH), 92.3 (C), 70.3 (CH), 69.9 (CH), 35.0 (CH_2), 30.2 (CH_2); mass spectrum, m/z (relative intensity, %) 382 (M^+, 2), 99 (11), 69 (11), 40 (100). Anal. Calcd for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80. Found: C, 68.79; H, 6.03.

(±)-1-*tert*-Butyldimethylsilyloxy-4-iodo-6α,7α-(isopropylidenedioxy)-5,6,7,8-tetrahydronaphthalene (20). Phenol **14** (667 mg, 1.92 mmol), *tert*-butyldimethylsilyl chloride (578 mg, 3.84 mmol), and imidazole (522 mg, 7.68 mmol) were stirred in 10 mL of dry DMF for 18 h at room temperature, water was added, and the reaction mixture was extracted several times with ethyl acetate. The combined organic layers were washed with 10% HCl solution and $NaHCO_3$ and NaCl solutions, dried (Na_2SO_4), and evaporated to dryness under vacuum. The crude product was purified by chromatography (elution with 2% ethyl acetate−hexanes) to give 777 mg (89%) of silyl ether **20**: mp 72−73 °C (from hexanes−methanol); IR (KBr) 1568, 1164, 1055, 1035, 846 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.6 Hz, 1 H), 6.50 (d, J = 8.6 Hz, 1 H), 4.52 (m, 2 H), 3.08 (dd, J = 15.0, 4.7 Hz, 1 H), 3.01 (dd, J = 15.0, 4.5 Hz, 1 H), 2.88 (dd, J = 15.0, 4.1 Hz, 1 H), 2.72 (dd, J = 15.0, 4.0 Hz, 1 H), 1.32 (s, 3 H), 1.19 (s, 3 H,), 1.02 (s, 9 H), 0.21 (s, 3 H) 0.20 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.5 (C), 139.9 (C), 136.6 (CH), 128.2 (C), 119.4 (CH), 108.2 (C), 90.2 (C), 74.3 (CH), 74.0 (CH), 39.2 (CH_2), 27.9 (CH_2), 26.5 (CH_3), 25.8 (CH_3), 24.5 (CH_3), 18.3 (C), −4.1 (CH_3), −4.2 (CH_3); mass spectrum, m/z (relative intensity, %) 460 (M^+, 100), 445 (19), 345 (79), 218 (37), 73 (52). Anal. Calcd for $C_{19}H_{29}IO_3Si$: C, 49.56; H, 6.35. Found: C, 49.13; H, 5.99.

(±)-1-[6α,7α-(Isopropylidenedioxy)-4-*tert*-butyldimethylsilyloxy-5,6,7,8-tetrahydronaphthyl]-2-[6α′,7α′-dihydroxy-5′,6′,7′,8′-tetrahydronaphthyl]ethyne (21) As Two (±) Pairs. Dichlorobis(triphenylphosphine)palladium(II) (31 mg, 5 mol %) and copper(I) iodide (4 mg, 2.5 mol %) were added to a solution of iodide **20** (403 mg, 0.87 mmol) and acetylene **18** (165 mg, 0.87 mmol) in 12 mL of a 1:1 mixture of dry 1,4-dioxane and triethylamine. The mixture was refluxed for 21 h, diluted with water, acidified with 10% HCl, and extracted with ethyl acetate. The combined ethyl acetate layers were washed with NaCl solution, dried (Na_2SO_4), evaporated in vacuo, and chromatographed (elution with 50−100% ethyl acetate−hexanes) to yield 247 mg (54%) of **21** as a solid foam. The inseparable mixture of two (±) pairs had: IR (film) 3328, 1583, 1052, 1005 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 7.4 Hz, 1 H), 7.31 (d, J = 8.3 Hz, 1 H), 7.12 (t, J = 7.6 Hz, 1 H), 7.06 (d, J = 7.6 Hz, 1 H), 6.71 (d, J = 8.4 Hz, 1 H), 4.54 (m, 2 H), 4.17 (m, 2 H), 3.34−3.14 (m, 3 H), 3.10−2.92 (m, 4 H), 2.80 (ddd, J = 15.0, 13.0, 4.5 Hz, 1 H), 2.43 (br s, 1 H, OH), 2.30 (br s, 1 H, OH), 1.34 (s, 3 H), 1.25 (s, 3 H), 1.03 (s, 9 H), 0.24 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4 (C), 139.1 (C), 134.8 (C), 133.2 (C), 130.6 (CH), 130.5 (CH), 129.9 (CH), 129.7 (CH), 128.9 (CH), 126.4 (C), 126.0 (CH), 123.6 (C), 117.3 (CH), 115.5 (CH), 108.3 (C), 93.3 (C), 90.1 (C), 74.1 (CH), 74.0 (CH), 73.8 (CH), 69.2 (CH), 69.0 (CH), 68.9 (CH), 34.5 (CH_2), 33.7 (CH_2), 32.5 (CH_2), 29.7 (CH_2), 27.2 (CH_2), 27.1 (CH_2), 26.7 (CH_3), 26.6 (CH_3), 25.8 (CH_3), 24.5 (CH_3), 18.3 (C), −4.1 (CH_3), −4.2 (CH_3).; mass spectrum, m/z (relative intensity, %) 520 (M^+, 68), 502 (32), 484 (13), 73 (100). Exact mass calcd for $C_{31}H_{40}O_5Si$: 520.2645. Found: 520.2615.

(±)-1-(4,6α,7α-Trihydroxy-5,6,7,8-tetrahydronaphthyl)-2-(6α′,7α′-dihydroxy-5′,6′,7′,8′-tetrahydronaphthyl)-ethyne (4) As Two (±) Pairs. Silyl ether **21** (200 mg, 0.38 mmol) was dissolved in 15 mL of THF and cooled to 0 °C, and tetra-*n*-butylammonium fluoride (420 μL of a 1 M solution in THF, 0.42 mmol) was added. After 2 h, NH_4Cl solution was added, and the reaction mixture was extracted several times with ethyl acetate. The extracts were washed with NaCl solution, dried (Na_2SO_4), evaporated under reduced pressure, and chromatographed (elution with 100% ethyl acetate) to furnish 143 mg (92%) of the corresponding phenol, which was used directly in the next step.

The above phenol (143 mg, 0.352 mmol) was stirred in 5 mL of 80% acetic acid solution for 45 min at room temperature. The solvent was removed in vacuo, and the solid residue was repeatedly dissolved in methanol and evaporated under reduced pressure to remove the final traces of acetic acid. This afforded 117 mg (91%) of **4**, obtained as an inseparable mixture of two (±) pairs. It was further purified by recrystallization from methanol: mp 278−281 °C; IR (KBr) 3360, 1580, 1073 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.30 (d, J = 7.2 Hz, 1 H), 7.21 (d, J = 8.2 Hz, 1 H), 7.09 (m, 2 H), 6.62 (d, J = 8.2 Hz, 1 H), 4.14−4.07 (m, 4 H), 3.17 (m, 4 H), 2.99 (m, 2 H), 2.87 (m, 2 H); ^{13}C NMR (100 MHz, CD_3OD) δ 154.9 (C), 136.4 (C), 134.4 (C), 133.2 (C), 130.0 (CH), 128.7 (CH), 128.0 (CH), 125.0 (CH), 123.1 (C), 120.5 (C), 113.2 (C), 111.3 (CH), 92.7 (C), 89.8 (C), 68.3 (CH), 68.2 (CH), 68.1 (CH), 67.8 (CH), 33.7 (CH_2), 32.9 (CH_2), 32.8 (CH_2), 28.2 (CH_2); mass spectrum, m/z (relative intensity, %) 366 (M^+, 39), 348 (7), 330 (14), 83 (32), 40 (100). Exact mass calcd for $C_{22}H_{22}O_5$: 366.1467. Found: 366.1450.

(±)-1,2-Bis[6α,7α-dihydroxy-5,6,7,8-tetrahydronaphthyl]ethyne (5) and Its Meso Isomer. Iodide **17** (242 mg, 0.83 mmol) and acetylene **18** (157 mg, 0.83 mmol) were dissolved in 6 mL of dry 1,4-dioxane and 6 mL of dry triethylamine. Dichlorobis(triphenylphosphine)palladium(II) (29 mg, 5 mol %) and copper(I) iodide (4 mg, 2.5 mol %) were added, and the reaction was refluxed for 24 h. The mixture was diluted with water and filtered, and the filtrate was evaporated under reduced pressure. Chromatography with 5−10% methanol-chloroform gave 125 mg (43%) of **5** as a tan powder consisting of an inseparable mixture of (±)- and *meso*-diastereomers: IR (KBr) 3341, 1582, 1206, 1174, 1080 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.35 (dd, J = 7.2, 1.8 Hz, 1 H), 7.13 (m, 2 H), 4.12 (ddd, J = 6.8, 5.3, 1.8 Hz, 1H), 4.08 (ddd, J = 6.4, 5.1, 2.0 Hz, 1 H), 3.26−3.14 (m, 2 H), 3.06−2.95 (m, 2 H); ^{13}C NMR (100 MHz, CD_3OD) δ 137.0 (C), 135.8 (C), 130.9 (CH), 130.6 (CH), 127.1 (CH), 124.6 (C), 93.9 (C), 70.3 (CH), 70.1 (CH), 35.7 (CH_2), 35.0 (CH_2); mass spectrum, m/z (relative intensity, %) 350 (M^+, 100), 314 (60), 296 (26), 215 (27). Exact mass calcd for $C_{22}H_{22}O_4$: 350.1518. Found: 350.1502.

***(E)*-(±)-1,2-Bis[6α,7α-(Isopropylidenedioxy)-4-*tert*-butyldimethylsilyloxy-5,6,7,8-tetrahydronaphthyl]ethene (22) and Its Meso Isomer.** The iodide **20** (1.489 g, 3.23 mmol was dissolved in dry dioxane (3 mL). *E*-1,2-Bis(tri-*n*-butylstannyl)ethylene (985 mg, 1.62 mmol) was added in 1 mL of dry dioxane, followed by tetrakis(triphenylphosphine)palladium-(0) (198 mg, 0.16 mmol, 5 mol %), lithium chloride (413 mg, 9.7 mmol), and 2,6-di-*tert*-butyl-4-methylphenol (a few crystals) in 20 mL of dry dioxane. A further portion of dry dioxane (10 mL) was added, and the resulting solution was refluxed under nitrogen for 4 days. Several additional portions (total 2.5 mol %) of tetrakis(triphenylphosphine)palladium(0) were added during this time. The reaction mixture was cooled to room temperature, diluted with ether (200 mL), and washed five times with 5% ammonium hydroxide solution. The aqueous layers were extracted three times with ether, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was chromatographed (elution with 0−5% ethyl acetate−hexanes) to afford 153 mg (14%) of **22** as a clear colorless oil: IR (neat): 1593, 1486, 1277, 1163, 1037 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.6 Hz, 1 H), 7.13 (s, 1 H), 6.73 (d, J = 8.5 Hz, 1 H), 4.49 (m, 2 H), 2.96 (m, 4 H), 1.34 (s, 3 H), 1.27 (s, 3 H), 1.05 (s, 9 H,), 0.25 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6 (C), 135.0 (C), 130.1 (C), 126.8 (CH), 126.2 (C), 124.7 (CH), 117.6 (CH), 108.4 (C), 74.5 (CH), 74.0 (CH), 30.5 (CH_2), 27.5 (CH_2), 26.9 (CH_3), 26.1 (CH_3), 24.8 (CH_3), 18.5 (C), −3.8 (CH_3), −3.9 (CH_3); mass spectrum, m/z (relative intensity, %) 692 (M^+, <1), 635 (1), 277 (44), 73 (100). Exact mass calcd for $C_{40}H_{60}O_6Si_2$: 692.3929. Found: 692.3943.

***(E)*-(±)-1,2-Bis[4,6α,7α-trihydroxy-5,6,7,8-tetrahydronaphthyl]ethene (6) and Its Meso Isomer.** Compound **22** (204 mg, 0.295 mmol) was dissolved in dry THF (22 mL) at 0 °C and tetra-*n*-butylammonium fluoride in THF (1 M, 0.6 mL, 0.6 mmol) was added under argon, and the solution was stirred for 10 min. Saturated NH_4Cl solution was added, and the mixture was stirred for an additional 10 min. It was then extracted four times with ethyl acetate, and the organic layers were combined and washed with brine, dried ($MgSO_4$), filtered,

and concentrated in vacuo to afford a white solid. The crude product was chromatographed (elution 0−80% ethyl acetate in hexanes) to give 122 mg (89%) of the corresponding bisphenol; mp 233−238 °C; IR (KBr) 3344, 1592, 1377, 1281, 1156, 1048 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 1 H), 7.37 (d, J = 8.6 Hz, 1 H), 7.06 (s, 1 H), 6.70 (d, J = 8.5 Hz, 1 H), 4.50 (m, 2 H), 3.00 (m, 1 H), 2.92 (m, 1 H), 2.70 (m, 1 H), 2.55 (m, 1 H), 1.22 (s, 3 H), 1.03 (s, 3 H); ^{13}C (100 MHz, DMSO-d_6) δ 153.6 (C), 134.4 (C), 127.2 (C), 124.6 (CH), 123.7 (CH), 121.3 (C), 113.1 (CH), 106.9 (C), 73.5 (CH), 72.9 (CH), 29.0 (CH_2), 26.4 (CH_3), 25.7 (CH_2), 24.3 (CH_3); mass spectrum, *m*/*z* (relative intensity, %) 464 (M^+, 5), 406 (29), 348 (100),. Exact mass calcd for $C_{28}H_{32}O_6$: 464.2199. Found: 464.2205.

The above product (109 mg, 0.228 mmol) was stirred in 5 mL of 80% acetic acid for 1 h at 60 °C. The solvent was evaporated in vacuo to afford a yellow solid that was triturated with 3 mL of 50% methanol−chloroform, filtered, and dried to afford **6** (68 mg, 76%) as a white crystalline solid; mp >310 °C; IR (KBr) 3329, 1587, 1458, 1282, 1067 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1 H), 7.25 (d, J = 8.4 Hz, 1 H), 6.90 (s, 1 H), 6.63 (d, J = 8.3 Hz, 1 H), 4.54 (dd, J = 13.0, 3.3 Hz, 2 H), 3.86 (m, 2 H), 2.82 (m, 2 H), 2.66 (d, J = 5.2 Hz, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.4 (C), 133.2 (C), 127.5 (C), 124.8 (CH), 123.3 (CH), 121.3 (C), 112.0 (CH), 68.1 (CH), 67.4 (CH), 32.4 (CH_2), 29.4 (CH_2).

(*E*)-(±)-1,2-Bis[6α,7α-dihydroxy-5,6,7,8-tetrahydronaphthyl]ethene (7) and Its Meso Isomer. The iodide **17** (217 mg, 0.748 mmol) and *E*-1,2-bis(tri-*n*-butylstannyl)ethylene (235 mg, 0.374 mmol) were dissolved in 2 mL of dry dioxane. A solution of lithium chloride (100 mg, 2.38 mmol), tetrakis-(triphenylphosphine)palladium(0) (50 mg, 0.043 mmol), and 2,6-di-*tert*-butyl-4-methylphenol (a few crystals) in 4 mL of dry dioxane was added. The mixture was refluxed under nitrogen for 48 h. After 24 h, another portion of 100 mg of tetrakis-(triphenylphosphine)palladium(0) was added. The reaction mixture was then diluted with water (10 mL) and 10 mL of 10% 2-propanol−chloroform. The aqueous layer was extracted repeatedly with 10% 2-propanol−chloroform, and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford a white solid. The crude product was chromatographed (elution 0−15% methanol-chloroform) to afford 27 mg (19%) of **7** as white crystals; mp 260−263 °C (from methanol); IR (KBr) 3344, 1676, 1456, 1057 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.44 (d, J = 7.9 Hz, 1 H), 7.17 (s, 1 H), 7.13 (t, J = 7.7 Hz, 1 H), 7.00 (d, J = 7.7, 1 H), 4.65 (d, J = 3.8 Hz, 1 H), 4.62 (d, J = 4.5 Hz, 1 H), 3.91 (m, 2 H), 2.89 (m, 4 H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 136.2 (C), 134.8 (C), 132.3 (C), 128.4 (CH), 127.7 (CH), 125.7 (CH), 123.1 (CH), 68.1 (CH), 67.7 (CH), 34.9 (CH_2), 32.4 (CH_2); mass spectrum, *m*/*z* (relative intensity, %) 352 (M^+, 59), 221 (67), 115 (79), 60 (100), 43 (67). Exact mass calcd for $C_{22}H_{24}O_4$: 352.1675. Found: 352.1671.

(±)-1,2-Bis[4,6α,7α-trihydroxy-5,6,7,8-tetrahydronaphthyl]ethane (8) and Its Meso Isomer. Compound **22** (152 mg, 0.219 mmol) was dissolved in 8 mL of ethyl acetate. Palladium on charcoal (2.4 mg of 10%) was added, and the mixture was stirred vigorously at room temperature under 1 atm of hydrogen (balloon) overnight. The mixture was filtered through Celite and concentrated in vacuo to afford the reduced product (144 mg, 95%) as a clear, colorless oil: IR (neat) 1596, 1486, 1268, 1057, 841 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.81 (dd, J = 8.4, 5.1 Hz, 1 H), 6.60 (dd, J = 8.3, 2.2 Hz, 1 H), 4.34 (m, 2 H), 3.04−2.71 (m, 6 H), 1.33 (s, 3 H), 1.28 (s, 3 H), 1.02 (s, 9 H), 0.20 (s, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 151.3 (C), 135.2 (C), 132.3 (C), 128.0 (CH), 126.1 (C), 117.0 (CH), 108.4 (C), 74.5 (CH), 74.1 (CH), 34.8 (CH_2), 30.6 (CH_2), 27.6 (CH_2), 26.9 (CH_3), 26.1 (CH_3), 24.7 (CH_3), 18.5 (C), −3.9 (CH_3), −3.9 (CH_3); mass spectrum, *m*/*z* (relative intensity, %) 694 (M^+, <1), 561 (10), 347 (100). Exact mass calcd for $C_{40}H_{62}O_6Si_2$: 694.4085. Found 694.4069.

The above product (318 mg, 0.457 mmol) was dissolved in 35 mL of dry THF at 0 °C. Tetra-*n*-butylammonium fluoride (1 mL of a 1 M solution in THF, 1 mmol) was added, and the reaction mixture was stirred at 0 °C for 10 min. Saturated ammonium chloride solution was added, and the mixture was stirred for 15 min. The mixture was then extracted four times with ethyl acetate, and the organic layers were combined and washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude material was chromatographed (elution with 0−80% ethyl acetate−hexanes) to afford 184 mg (86%) of the desilylated product; mp 210−215 °C: IR (KBr) 3332, 1596, 1495, 1283, 1209, 1159, 1046 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.92 (d, J = 3.7 Hz, 1 H), 6.73 (dd, J = 8.2, 1.3 Hz, 1 H), 6.55 (d, J = 8.2 Hz, 1 H), 4.43 (s, 2 H), 2.90−2.50 (m, 6 H), 1.22 (s, 3 H), 1.03 (s, 3 H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 152.3 (C), 134.4 (C), 129.6 (C), 127.1 (CH), 121.3 (C), 112.5 (CH), 106.9 (C), 73.5 (CH), 73.0 (CH), 34.4 (CH_2), 29.4 (CH_2), 26.4 (CH_3), 25.9 (CH_2), 24.4 (CH_3); mass spectrum, *m*/*z* (relative intensity, %) 466 (M^+, 1), 233 (29), 175 (81), 128 (100). Exact mass calcd for $C_{28}H_{34}O_6$: 466.2355. Found: 466.2387.

The diacetonide (110 mg, 0.235 mmol) was stirred in 6 mL of 80% acetic acid at 60 °C for 2 h. The solvent was evaporated in vacuo to afford a pale yellow solid. The crude product was triturated with 5 mL of 50% chloroform−methanol solution to afford 70 mg (77%) of **8** as a white crystalline solid; mp >315 °C: IR (KBr) 3298, 1589, 1458, 1283, 1062 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1 H), 6.80 (d, J = 8.1 Hz, 1 H), 6.55 (d, J = 8.1 Hz, 1 H), 4.51 (m, 2 H), 3.85 (s, 2 H), 2.76 (m, 2 H), 2.66 (m, 2 H), 2.54 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.0 (C), 133.3 (C), 130.0 (C), 126.1 (CH), 121.3 (C), 111.4 (CH), 68.2 (CH), 67.5 (CH), 33.2 (CH_2), 31.7 (CH_2), 29.6 (CH_2).

6,7-Isopropylidenedioxy-1,4-naphthoquinone (24). A mixture of diene **23**[27c] (1.030 g, 8.2 mmol), benzoquinone (2.65 g, 24.5 mmol), 2,6-di-*tert*-butyl-4-methylphenol (57 mg), and benzene (10 mL) was heated in a sealed vessel under argon at 75−85 °C. The mixture was concentrated, exposed to air, and chromatographed (elution with 20% dichloromethane−hexanes) to give 1.25 g (66%) of **24**: mp 195−198 °C (sealed capillary; dec; from ethyl acetate); ^1H NMR (200 MHz, $CDCl_3$) δ 7.35 (s, 2 H), 6.84 (s, 2 H), 1.73 (s, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 184.0, 152.1, 138.0, 128.7, 120.7, 105.7, 25.9; mass spectrum, *m*/*z* (relative intensity, %) 230 (M^+, 100), 216 (24), 190 (51), 162 (23). Anal. Calcd for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38. Found: C, 67.45; H, 4.69.

1-*tert*-Butyldimethylsilyloxy-6,7-isopropylidenedioxy-4-trifloxynaphthalene (25). A mixture of quinone **24** (517 mg, 2.25 mmol) and 10% Pd−C (9 mg) in ethyl acetate was stirred under hydrogen (balloon) for 2 h. The mixture was filtered, and the filtrate was evaporated in vacuo. The resulting crude naphthol was dissolved in 20 mL of dry dichloromethane containing triethylamine (0.476 mL, 3.44 mmol) and *tert*-butyldimethylsilyl chloride (371 mg, 2.47 mmol) was added. The solution was stirred under argon for 16 h and was then evaporated and chromatographed (elution with 10% ethyl acetate−hexanes) to give 430 mg (55%) of the corresponding monosilyl ether.

The above product (430 mg, 1.24 mmol), triethylamine (0.257 mL, 1.85 mmol), and triflic anhydride (0.224 mL, 1.36 mmol) were stirred in 10 mL of dry dichloromethane for 30 min. The mixture was poured into water and extracted with with several portions of dichloromethane. The combined extracts were dried (Na_2SO_4), evaporated, and chromatographed (elution with 5% ethyl acetate−hexanes) to give 455 mg (42% overall yield from **24**) of **25** as an oil: IR: 1720, 1602, 1465, 1202, 1134 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.43 (s, 1 H), 7.21 (s, 1 H), 7.16 (d, J = 8.5 Hz, 1 H), 6.68 (d, J = 8.5 Hz, 1 H), 1.77 (s, 6 H), 1.11 (s, 9 H), 0.32 (s, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.8, 149.5, 148.4, 139.0, 125.5, 124.7, 119.0, 118.7 (q, J = 320 Hz), 116.1, 109.8, 99.5, 97.3, 26.0, 25.8, 18.4, −4.3; mass spectrum, *m*/*z* (relative intensity, %) 478 (M^+, 34), 347 (31), 346 (54), 345 (78), 73 (100). Exact mass calcd for $C_{20}H_{25}F_3O_6SSi$: 478.1093. Found: 478.1129.

(*E*)-1,2-Bis[4-*tert*-butyldimethylsilyloxy-6,7-(isopropylidenedioxy)naphthyl]ethene (26). A mixture of triflate **25** (452 mg, 0.95 mmol), (*E*)-1,2-bis(tri-*n*-butylstannyl)ethylene (287 mg, 0.47 mmol), $Pd(PPh)_4$ (109 mg, 0.094 mmol), and LiCl (120 mg, 2.8 mmol) in dry dioxane (10 mL) was refluxed under argon for 4 days. After cooling, the mixture was diluted with hexanes and filtered. The filtrate was evaporated and chromatographed (elution with 1% ethyl acetate−hexanes) to give

298 mg of crude **26** containing ca. 10% of starting material **25**. Further purification by preparative TLC (silica gel, 2% ethyl acetate−hexanes) afforded 83% of pure **26** as an oil: IR: 1715, 1595, 1451, 1360, 1223, 1014, 960 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$) δ 7.51 (s, 1 H), 7.48 (d, J = 8.0 Hz, 1 H), 7.45 (s, 1 H), 7.40 (s, 1 H), 6.78 (d, J = 8.0 Hz, 1 H), 1.74 (s, 6 H), 1.11 (s, 9 H), 0.32 (s, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.8, 148.3, 147.1, 129.8, 128.1, 127.3, 124.3, 122.3, 118.0, 111.4, 100.4, 99.4, 26.0, 25.9, 18.5, −4.1; mass spectrum, *m*/*z* (relative intensity, %) 684 (M^+, <1), 627 (12), 570 (16), 569 (23), 285 (23), 73 (100). Exact mass calcd for $C_{40}H_{52}O_6Si_2$: 684.3303. Found: 684.3354.

1,2-Bis(4,6,7-trihydroxynaphthyl)ethane (9). Compound **26** (50 mg, 0.073 mmol) and 10% Pd−C (12 mg) were stirred in ethyl acetate for 12 h under hydrogen (balloon). The mixture was filtered and evaporated to give 48 mg (96%) of the protected derivative of **9**. This was refluxed in 15 mL of 80% acetic acid for 12 h. The solution was evaporated, and the residue was chromatographed (elution with 50% ethyl acetate−hexanes, followed by 30% methanol−chloroform) to give 24 mg (91%) of naphthol **9** as an oil: IR: 3320, 1616, 1592, 1448, 1238, 1144 cm^{-1};^{1}H NMR (200 MHz, acetone-d_6) δ 7.61 (s, 1 H), 7.43 (s, 1 H), 6.95 (d, J = 7.5 Hz, 1 H), 6.59 (d, J = 7.5 Hz, 1 H), 3.13 (s, 2 H); ^{13}C NMR (200 MHz, acetone-d_6) δ 151.0, 146.8, 145.3, 129.5, 128.1, 123.9, 121.4, 106.9, 106.1, 105.9, 34.6; mass spectrum, *m*/*z* (relative intensity, %) 378 (M^+, 1.7), 189 (39), 188 (100), 160 (95), 114 (71). Exact mass calcd for $C_{22}H_{18}O_6$: 378.1103. Found: 378.1135.

(±)-4,4-(2,2-Dimethylpropylenedioxy)-2,3,4,4a,5,8,8a-hexahydro-1-naphthalenone (28). 2,2-Dimethyl-1,3-propanediol (3.20 g, 30.8 mmol) and *p*-toluenesulfonic acid (117 mg, 0.615 mmol) were added to a solution of (*cis*-4a,8a)-2,3,-4a,5,8,8a-hexahydro-1,4-naphthalenedione[28] (**27**) (10.1 g, 61.5 mmol) in 100 mL of benzene. The mixture was refluxed for 4 h in a flask equipped with a Dean−Stark trap. The mixture was diluted with benzene, washed with $NaHCO_3$ solution, dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (elution with 8% ethyl acetate−hexanes) to provide two fractions. The first contained 6.82 g (89%, based on 2,2-dimethyl-1,3-propanediol as the limiting reagent) of a mixture of *cis* and *trans* isomers of **28** in the ratio of 20:80 with: IR (KBr) 1710, 1126, 1110, 757 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.64 (m, 2 H,), 3.76 (d, J = 10.9 Hz, 1 H), 3.65 (d, J = 11.1 Hz, 1 H), 3.50−3.35 (m, 2 H), 3.07 (ddd, J = 13.8, 5.4, 3.0 Hz, 1 H), 2.66−2.15 (m, 7 H), 1.95 (ddd, J = 12.7, 10.4, 5.4 Hz, 1 H), 1.50 (ddd, J = 14.0, 14.0, 4.4 Hz, 1 H), 1.24 (s, 2.4 H, from *trans*-**28**), 1.06 (s, 0.6 H, from *cis*-**28**), 0.98 (s, 0.6 H, from *cis*-**28**), 0.78 (s, 2.4 H, from *trans*-**28**); mass spectrum, *m*/*z* (relative intensity, %) 250 (M^+, 77), 193 (69), 107 (43), 79 (74), 69 (100). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.66; H, 8.80.

Further elution recovered 48% of partly epimerized starting material **27**.

(±)-*trans*-(4aα,8a*β*)-4,4-(2,2-Dimethylpropylenedioxy)-6-α,7α-dihydroxy-2,3,4,4a,5,6,7,8,8a-octahydro-1-naphthalenone (29a) and Its *trans*-(4aα,8a*β*)-6*β*,7*β* (29b) and *cis*-(4aα,-8aα)-6α,7α (30) Isomers. The 20:80 mixture of *cis*- and *trans*-**28** (3.60 g, 14.4 mmol) was dissolved in acetone and cooled to 0 °C. Osmium tetroxide (1.84 mL of a 0.39 M solution in *tert*-butyl alcohol), 4-methylmorpholine *N*-oxide (1.79 g, 15.3 mmol), and water (700 μL, 39 mmol) were added, and the mixture was stirred for 4 h before Florisil (5 g) and sodium thiosulfate (1 g) were added. The mixture was stirred overnight, filtered through Celite, evaporated in vacuo, and chromatographed (elution with 25−50% ethyl acetate−hexanes) to give 3.02 g (74%) of a mixture of the *trans* ring-fused isomers **29a** and **29b** as a white powder and 0.34 g (8%) of the *cis* ring-fused isomer **30** as a white powder. The less polar *trans* isomers **29a** and **29b** had: IR (KBr) 3381, 1713, 1101, 1022 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.07 (br s, 1 H), 3.77−3.57 (m, 3 H), 3.47−3.35 (m, 2 H), 3.10−2.97 (m, 1 H), 2.52−2.25 (m, 3 H), 2.19−1.93 (m, 3 H), 1.83−1.41 (m, 3 H), 1.21 (s, 3 H), 0.77 (s, 3 H); mass spectrum, *m*/*z* (relative intensity, %) 284 (M^+, 8) 227 (100), 141 (56). Exact mass calcd for $C_{15}H_{24}O_5$: 284.1624. Found: 284.1609.

The more polar fraction contained the *cis* ring-fused isomer **30**: mp 137−138 °C (from ether); IR (KBr) 3457, 1714, 1118, 1110 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 (br s, 1 H), 3.87−3.85 (m, 1 H), 3.70 (d, J = 11.4 Hz, 1 H), 3.55 (d, J = 11.4 Hz, 1 H), 3.49 (dd, J = 11.4, 1.0 Hz, 1 H), 3.43 (dd, J = 11.4, 1.0 Hz, 1 H), 3.13−3.10 (m, 1 H), 2.89 (s, 1 H), 2.59−2.50 (m, 2 H), 2.44 (s, 1 H) 2.33−2.17 (m, 3 H), 2.01−1.96 (m, 1 H), 1.85 (ddd, J = 14.1, 14.1, 5.1 Hz, 1 H), 1.55 (ddd, J = 12.1, 12.1, 5.0 Hz, 1 H), 1.17−1.09 (m, 1 H), 1.06 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.6 (C), 97.7 (C), 70.1 (CH_2), 70.2 (CH_2), 68.7 (CH), 67.5 (CH), 44.9 (CH), 37.0 (CH_2), 34.0 (CH), 30.2 (C), 29.8 (CH_2), 29.3 (CH_2), 26.9 (CH_2), 22.8 (CH_3), 22.5 (CH_3); mass spectrum, *m*/*z* (relative intensity, %) 284 (M^+, 3) 227 (9), 141 (100). Exact mass calcd for $C_{15}H_{24}O_5$: 284.1624. Found: 284.1618.

(±)-*trans*-(4aα,8a*β*)-4,4-(2,2-Dimethylpropylenedioxy)-6α,7α-(isopropylidenedioxy)-2,3,4,4a,5,6,7,8,8a-octahydro-1-naphthalenone (32) and Its 6*β*,7*β* Isomer (31). The mixture of diols **29a** and **29b** (3.9 g, 14 mmol), 2,2-dimethoxypropane (3.4 mL, 28 mmol), and *p*-toluenesulfonic acid (130 mg, 0.68 mmol) were refluxed in 200 mL of dichloromethane for 2 h. The reaction mixture was washed with $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography (elution with 5−10% ethyl acetate−hexanes) to give 1.8 g (40%) of isomer **32** and 1.6 g (36%) of isomer **31**. Ketone **32**: mp 169−171 °C (from chloroform−hexanes); IR (KBr) 1710, 1218, 1098, 1055 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (br s, 1 H), 4.01 (ddd, J = 10.3, 5.1, 5.1 Hz, 1 H), 3.72 (d, J = 11.3 Hz, 1 H), 3.70 (d, J = 11.3 Hz, 1 H), 3.43 (d, J = 11.3 Hz, 1 H), 3.37 (dd, J = 11.3, 1.4 Hz, 1 H), 3.02 (ddd, J = 14.1, 5.1, 2.4 Hz, 1 H), 2.57 (br d, J = 13.0, 1 H), 2.42 (ddd, J = 14.5, 14.5, 5.6, 1 H), 2.33 (m, 1 H), 2.30−2.21 (m, 2 H), 2.08−1.97 (m, 2 H), 1.52−1.43 (m, 1 H), 1.46 (s, 3 H), 1.36 (m), 1.32 (s, 3 H), 1.20 (s, 3 H), 0.76 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1 (C), 108.6 (C), 96.8 (C), 74.4 (CH), 73.5 (CH), 71.0 (CH_2), 70.2 (CH_2), 45.5 (CH), 45.0 (CH), 37.4 (CH_2), 30.4 (C), 29.3 (CH_2), 29.0 (CH_3), 26.9 (CH_3), 26.6 (CH_2), 26.1 (CH_2), 23.6 (CH_3), 22.5 (CH_3); mass spectrum, *m*/*z* (relative intensity, %) 324 (M^+, 35), 309 (56), 267 (91), 209 (11), 209 (37), 141 (100). Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.27; H, 8.33.

The more polar isomer **31**: mp 131−132 °C (from chloroform−hexanes); IR (KBr) 1713, 1114, 1093, 1042 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (ddd, J = 4.2, 4.2, 1.9 Hz, 1 H), 4.01 (ddd, J = 10.5, 6.5, 4.6 Hz, 1 H), 3.72 (d, J = 11.3 Hz, 1 H), 3.65 (d, J = 11.3 Hz, 1 H), 3.44 (dd, J = 11.3, 2.6 Hz, 1 H), 3.36 (dd, J = 11.3, 2.6 Hz, 1 H), 3.03 (ddd, J = 14.1, 5.6, 2.8 Hz, 1 H), 2.63 (ddd, J = 12.2, 12.2, 4.0 Hz, 1 H), 2.49−2.40 (m, 2 H), 2.32−2.24 (m, 2 H), 1.73 (ddd, J = 12.7, 12.7, 10.7 Hz, 1 H), 1.66 (ddd, J = 16.0, 12.2, 3.9 Hz, 1 H), 1.54−1.47 (m, 1 H), 1.51 (s, 3 H), 1.40 (ddd, J = 14.4, 14.4, 4.2 Hz, 1 H), 1.32 (s, 3 H), 1.20 (s, 3 H), 0.74 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9 (C), 108.6 (C), 96.5 (C), 74.8 (CH), 72.9 (CH), 71.0 (CH_2), 70.2 (CH_2), 48.1 (CH), 43.2 (CH), 37.5 (CH_2), 30.4 (C), 29.1 (CH_3), 28.5 (CH_2), 26.8 (2 CH_2), 26.3 (CH_3), 23.5 (CH_3), 21.7 (CH_3); mass spectrum, *m*/*z* (relative intensity, %) 324 (M^+, 2), 309 (19), 267 (100), 209 (11), 141 (86), 69 (80). Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.40; H, 9.11.

The *cis* ring-fused isomer **30**, prepared as indicated above, was dissolved in 1 mL of methanol. To this solution, sodium methoxide (2 mL of a 0.13 M solution in methanol) was added and the mixture was refluxed for 2 h. It was then diluted with ethyl acetate, washed with $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated in vacuo to give a quantitative yield of the epimerized acetonide **32** with properties identical to those of the preceding sample.

(±)-*trans*-(4aα,8a*β*)-4,4-(2,2-Dimethylpropylenedioxy)-6α,7α-(isopropylidenedioxy)-1-trifloxy-4a,5,6,7,8,8a-hexahydro-(3*H*)-naphthalene (33). Ketone **32** (2.27 g, 7.00 mmol) in 35 mL of dry THF was added dropwise to a solution of LDA (85 mL of a 0.12 M solution in THF, 9.88 mmol) at −78 °C, and stirring was continued for 3 h. *N*-Phenyltrifluoromethanesulfonimide (3.75 g, 10.5 mmol) in 30 mL of dry THF was slowly added, and the mixture was allowed to warm to

room-temperature overnight. The reaction was quenched with water and the THF was removed on the rotary evaporator. The aqueous solution was extracted several times with hexanes, and the combined extracts were washed with NaCl solution, dried ($MgSO_4$), and evaporated in vacuo. The crude product was subjected to Kugelrohr distillation, 80 °C at 0.1 Torr, to remove the last traces of the triflating agent. The distillation residue contained 2.4 g (75%) of triflate **33** as a white solid: mp 132−133 °C (dec) (from hexanes); IR (KBr) 1142, 1076, 1027, 910 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.64−5.58 (m, 1 H), 4.32 (m, 1 H), 4.14−4.03 (m, 1 H), 3.66 (d, J = 11.5 Hz, 2 H), 3.37 (d, J = 11.6 Hz, 2 H), 3.31−3.21 (m, 1 H), 2.58 (d, J = 13.2 Hz, 1 H), 2.33−2.21 (m, 2 H), 2.13−1.89 (m, 3 H), 1.48 (s, 3 H), 1.35 (s, 3 H), 1.34−1.26 (m, 1 H), 1.17 (s, 3 H), 0.74 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7 (C), 118.5 (q, J = 320 Hz, CF_3) 114.7 (CH), 108.4 (C), 95.4 (C), 73.7 (CH), 73.3 (CH), 70.5 (CH_2), 70.3 (CH_2), 43.0 (CH), 36.7 (CH), 31.8 (CH_2), 30.0 (C), 28.6 (CH_3), 27.3 (CH_2), 26.4 (CH_3), 24.8 (CH_2), 22.9 (CH_3), 22.1 (CH_3); mass spectrum, *m/z* (relative intensity, %) 441 (M^+ − 15, 15), 323 (76), 265 (100). Anal. Calcd for $C_{19}H_{27}F_3O_7S$: C, 50.00; H, 5.96. Found: C, 50.01; H, 5.75.

(±)-1,2-Bis[*trans*-(4aα,8a*β*)-4,4-(2,2-dimethylpropylenedioxy)-6α,7α-(isopropylidenedioxy)-4a,5,6,7,8,8a-hexahydro-(3*H*)-naphthyl]ethyne (34) and Its Meso Isomer. A solution of triflate **33** (218 mg, 0.478 mmol) and bis(tri-*n*-butylstannyl)acetylene (144 mg, 0.238 mmol) in 6 mL of dry THF was added to a slurry of lithium chloride (61 mg, 1.4 mmol) and tetrakis(triphenylphosphine)palladium(0) (28 mg, 5 mol %) in 2 mL of THF. The mixture was refluxed for 12 h and was extracted several times with ether. The combined ether layers were washed twice with NaCl solution and dried ($MgSO_4$), and the solvent was evaporated. The crude product was chromatographed (elution with 7.5% ethyl acetate−hexanes) to afford 135 mg (89%) of an inseparable mixture of (±)- and *meso*-**34**: mp 295−296 °C (dec) (from ethyl acetate); IR (KBr) 1151, 1133, 1120, 1110, 1096, 1048, 1021 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.94 (m, 1 H), 4.32 (br s, 1 H), 4.11 (m, 1 H), 3.68 (d, J = 11.3 Hz, 1 H), 3.63 (d, J = 11.6 Hz, 1 H), 3.33 (d, J = 11.6 Hz, 2 H), 3.22 (m, 1 H), 2.59 (d, J = 13.9 Hz, 1 H), 2.46 (m, 1 H), 2.05−1.99 (m, 2 H), 1.84 (m, 2 H), 1.48 (s, 3 H), 1.35 (s, 3 H), 1.29−1.27 (m, 1 H), 1.18 (s, 3 H), 0.73 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.6 (CH), 124.3 (C), 108.1 (C), 96.2 (C), 88.9 (C), 74.7 (CH), 73.8 (CH), 70.2 (CH_2), 70.1 (CH_2), 42.0 (CH), 37.3 (CH), 34.9 (CH_2), 30.0 (C), 29.3 (CH_2), 28.6 (CH_3), 26.6 (CH_3), 24.9 (CH_2), 23.0 (CH_3), 22.1 (CH_3); mass spectrum, *m/z* (relative intensity, %) 638 (M^+, 38), 580 (3), 552 (3), 267 (24), 83 (100). Anal. Calcd for $C_{38}H_{54}O_8$: C, 71.44; H, 8.52. Found: C, 71.12; H, 8.36.

(±)-1,2-Bis[*trans*-(4aα,8a*β*)-4-oxo-6α,7α-dihydroxy-4a,5,6,7,8,8a-hexahydro-(3*H*)-naphthyl]ethyne (10) and Its Meso Isomer. Acetylene **34** (100 mg, 0.156 mmol) was stirred in 50 mL of 80% acetic acid for 18 h. The acetic acid was then removed by distillation at 0.1 Torr, while the temperature of the still pot was kept below 30 °C. The remaining yellow powder was washed several times with benzene to remove 2,2-dimethyl-1,3-propanediol. The residue contained 32 mg (53%) of **10** as a mixture of (±) and meso isomers: mp >300 °C; IR (KBr) 3376, 1708, 1667, 1004 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.13 (dd, J = 6.5, 3.8 Hz, 1 H), 4.54 (d, J = 5.8 Hz, 1 H), 4.34 (d, J = 2.8 Hz, 1 H), 3.80 (br s, 1 H), 3.40−3.38 (m, 1 H), 3.25−3.19 (m, 1 H), 2.79 (d, J = 22.7 Hz, 1 H), 2.59−2.51 (m, 1 H), 2.29−2.23 (m, 1 H), 2.03 (ddd, J = 12.1, 3.7, 3.7 Hz, 1 H), 1.89 (ddd, J = 14.2, 3.4, 3.4 Hz, 1 H), 1.62 (dd, J = 24.3, 12.1 Hz, 1 H), 1.35 (dd, J = 13.1, 13.1 Hz, 1 H); ^{13}C NMR (100 MHz,DMSO-d_6) δ 208.7 (C), 131.7 (CH), 124.3 (C), 88.7 (C), 70.1 (CH), 67.4 (CH), 44.8 (CH), 40.5 (CH_2), 39.9 (CH), 33.3 (CH_2), 29.9 (CH_2). Since compound **10** was insufficiently volatile to provide a satisfactory electron impact mass spectrum, it was converted to the corresponding hexaacetate by treatment with acetic anhydride in pyridine in the presence of a catalytic amount of 4-(dimethylamino)-pyridine for 5 h. The hexaacetate: ^1H NMR (200 MHz, $CDCl_3$) δ 6.33 (dd, J = 6.1, 2.8 Hz, 1 H), 5.85 (dd, J = 6.2, 2.7 Hz, 1 H), 5.36 (br s, 1 H), 4.92−4.81 (m, 1 H), 2.83−2.73 (m, 1 H), 2.52−2.20 (m, 3 H), 2.18 (s, 3 H), 2.10 (s, 3 H), 2.04 (s, 3 H), 2.02−1.82 (m, 1 H), 1.77−1.59 (m, 2 H); mass spectrum, *m/z* (relative intensity, %) 638 (M^+, 0.6), 596 (1), 554 (3), 43 (100). Exact mass calcd for $C_{34}H_{38}O_{12}$: 638.2363. Found: 638.2330.

(±)-(*E*)-1,2-Bis[*trans*-(4aα,8a*β*)-4,4-(2,2-dimethylpropylenedioxy)-6α,7α-(isopropylidenedioxy)-4a,5,6,7,8,8a-hexahydro-(3*H*)-naphthyl]ethene (35) and Its Meso Isomer. Triflate **33** (136 mg, 0.300 mmol) was converted into the coupled product **35** by the same procedure used in the preparation of **34**, except that (*E*)-1,2-bis(tri-*n*-butylstannyl)-ethylene was used instead of bis(tri-*n*-butylstannyl)acetylene. Chromatography (elution with 7.5% ethyl acetate−hexanes) provided 85 mg (89%) of **35** as an inseparable mixture of (±)- and *meso*-**35**: mp 312−315 °C (dec) (from ethyl acetate−hexanes); IR (KBr) 1150, 1131, 1117, 1093, 1072, 1047, 972 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 (s, 0.5 H, one diastereomer), 5.91 (s, 0.5 H, other diastereomer), 5.55 (dd, J = 16.1, 6.1 Hz, 1 H), 4.35 (br s, 1 H), 4.11 (m, 1 H), 3.69 (d, J = 11.3 Hz, 1 H), 3.62 (d, J = 11.6 Hz, 0.5 H, one diastereomer), 3.58 (d, J = 11.6 Hz, 0.5 H, other diastereomer), 3.36−3.28 (m, 2 H), 3.19 (dd, J = 18.2, 6.3 Hz, 1 H), 2.68−2.57 (m, 1 H), 2.37 (m, 1 H), 2.18−2.08 (m, 1 H), 2.01 (d, J = 18.3 Hz, 1 H), 1.94−1.84 (m, 2 H), 1.46 (s, 3 H), 1.34 (s, 3 H), 1.30−1.20 (m, 1 H), 1.17 (s, 3 H), 0.73 (s, 1.5 H, one diastereomer), 0.72 (s, 1.5 H, other diastereomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5 (CH), 138.4 (CH), 128.0 (CH), 127.8 (C), 122.3 (C), 122.2 (C), 108.0 (C), 96.5 (C), 74.9 (CH), 73.8 (CH), 70.3 (CH_2), 70.2 (CH_2), 42.9 (CH), 36.6 (CH), 36.4 (CH), 35.5 (CH_2), 35.4 (CH_2), 30.0 (C), 29.7 (C), 29.0 (CH_2), 28.6 (CH_3), 26.6 (CH_3), 26.5 (CH_3), 25.4 (CH_2), 23.0 (CH_3), 22.1 (CH_3); mass spectrum, *m/z* (relative intensity, %) 640 (M^+, 14), 267 (10), 141 (10), 83 (100). Exact mass calcd for $C_{38}H_{56}O_8$: 640.3975. Found: 640.3978.

(*E*)-1,2-Bis[*trans*-(4aα,8a*β*)-4-oxo-6α,7α-dihydroxy-4a,5,6,7,8,8a-hexahydro-(3*H*)-naphthyl]ethylene (11) and Its Meso Isomer. Compound **35** (100 mg, 0.156 mmol) was deprotected by stirring for 14 h in 50 mL of 80% acetic acid solution. The acetic acid was removed by distillation under high vacuum with the temperature of the still pot never exceeding 30 °C. The yellow residue was triturated with chloroform to remove 2,2-dimethyl-1,3-propanediol. The residue contained 24 mg (40%) of **11** as a mixture of (±)- and meso-isomers: mp >300 °C; IR (KBr) 3386, 1706, 1658, 1072, 1010 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.25 (m, 1 H), 5.81 (m, 1 H), 4.49 (d, J = 5.7 Hz, 1 H), 4.31 (d, J = 3.1 Hz, 1 H), 3.80 (br s, 1 H), 3.42−3.39 (m, 1 H), 3.23−3.12 (m, 1 H), 2.73−2.68 (m, 1 H), 2.63−2.57 (m, 1 H), 2.35 (m, 1 H), 1.98 (m, 1 H), 1.88 (m, 1 H), 1.56−1.45 (m, 1 H), 1.41−1.34 (m, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 210.8 (C), 139.8 (CH), 131.7 (CH), 121.8 (C), 71.3 (CH), 63.3 (CH), 45.7 (CH), 42.0 (CH), 41.4 (CH_2), 34.3 (CH_2), 31.0 (CH_2). Compound **11** was insufficiently volatile to provide a satisfactory electron impact mass spectrum and therefore was converted into its corresponding diacetonide by treatment with 2,2-dimethoxypropane and *p*-toluenesulfonic acid in methylene chloride for 2 h: ^1H NMR (200 MHz, $CDCl_3$) δ 6.21−6.05 (m, 1 H), 5.91−5.71 (m, 1 H), 4.43−4.27 (m, 1 H), 4.24−4.01 (m, 1 H), 3.32−3.08 (m, 1 H), 2.97−2.61 (m, 2 H), 2.57−2.14 (m, 4 H), 1.95−1.80 (m, 1 H), 1.51 (s, 3 H), 1.37 (s, 3 H); *m/z* (relative intensity, %) 468 (M^+, 3), 466 (11), 464 (14), 59 (49), 43 (100). Exact mass calcd for $C_{28}H_{36}O_6$: 468.2511. Found: 468.2483.

(±)-*trans*-(4aα,8a*β*)-6α,7α-dihydroxy-2,3,4a,5,6,7,8a-octahydro-1,4-naphthalenedione (37). A solution of naphthalenedione **36**[30] (1.12 g, 6.82 mmol), osmium tetroxide (870 μL of a 0.39 M solution in *tert*-butyl alcohol, 0.34 mmol), 4-methylmorpholine *N*-oxide (840 mg, 7.17 mmol), and water (0.25 mL, 14 mmol) was stirred for 3 h. Florisil (2.5 g) and sodium thiosulfate (0.5 g) were added, and the mixture was stirred for a further 1 h. The solid material was removed by filtration, the solvent was evaporated in vacuo, and the crude product was purified by chromatography (elution with 70−100% ethyl acetate−hexanes) to afford 1.2 g (89%) of diol **37** as a solid foam: IR (KBr) 3442, 1709, 1156, 1061, 1008 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6−CD_3OD) δ 4.03−3.88 (m, 1 H), 3.55 (d, J = 12.0, 4.6, 2.7 Hz, 1 H), 2.88−2.45 (6 H), 2.25 (dt, J = 14.4, 3.8 Hz, 1 H), 2.05 (dt, J = 8.2, 3.8, Hz, 1 H), 1.72 (m, 1 H), 1.50 (ddd, J = 14.2, 11.9, 2.3 Hz, 1 H); ^{13}C NMR (50 MHz,

$CD_3COCD_3-CD_3OD$) δ 210.8 (C), 209.6 (C), 71.2 (CH), 68.8 (CH), 47.9 (CH), 43.5 (CH), 37.3 (CH_2), 37.2 (CH_2), 32.1 (CH_2), 28.9 (CH_2); mass spectrum, *m*/*z* (relative intensity, %) 198 (M^+, 11), 180 (53), 151 (55), 95 (85), 81 (100). Exact mass calcd for $C_{10}H_{14}O_4$: 198.0892. Found: 198.0881.

6,7-Dihydroxy-2,3,4a,5,6,7,8,8a-octahydro-4-oxo-naphthalenone Azine (12) (Mixture of Isomers). A solution of diketone **37** (112 mg, 0.57 mmol) and hydrazine (8 μL of 55%, 0.1 mmol) was refluxed in 5 mL of *n*-butanol for 3 h before the *n*-butanol was removed by Kugelrohr distillation at 50 °C at 0.1 Torr. The crude product was purified by chromatography (elution with 5−15% methanol−chloroform) to give 71 mg (63%) of recovered starting material and 31 mg (40% based on hydrazine) of a mixture of azine stereoisomers **12** as a white powder. The mixture had: mp >300 °C; IR (KBr) 3428, 1710, 1634 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 4.61−4.18 (m, 2 H,), 3.79 (br s, 1 H), 3.50−3.36 (m, 1 H), 2.95−2.54 (m, 3 H), 2.44−2.11 (m, 3 H), 2.09−1.26 (m 4 H); due to the complexity of the carbon spectrum only the distinguishing signals are listed: ^{13}C NMR (50 MHz, $CDCl_3-CD_3OD$) δ 211.8−210.3 (m, C═O), 163.5−162.4 (m, C═N), 70.5−70.2 (m, C-6 or C-7), 67.7−66.9 (m, C-6 or C-7); mass spectrum, *m*/*z* (relative intensity, %) 392 (M^+, 4), 310 (5), 249 (5), 36 (100). Exact mass calcd for $C_{20}H_{28}N_2O_6$: 392.1947. Found: 392.1942.

Bioassays. Brassinolide (**1**) and each of the mimetics **3**−**12** were tested for biological activity by means of the rice leaf lamina assay, using a dwarf cv., Tan-ginbozu, as described by Takeno and Pharis.[31] The compounds were dissolved in 95% ethanol or in a 2.5:8:89.5 (v/v/v) mixture of Atlas G-1086, DMSO, and water and applied as 0.5 μL microdrops to the rice plants 48 h after planting the germinated seeds on 0.8% water agar. At high doses, several rounds of application of the 0.5 μL microdrops were required to attain the desired dose per plant. Where IAA was a cotreatment, it was similarly applied ca.. 2 h prior to the application of **1** or **3**−**12**. The resultant leaf lamina angle was measured 60−65 h later. For an individual bioassay, each data point is the mean of the leaf angles from ca. 36 plants for doses up to 100 ng and from ca. 24 plants for the 1000 and 10000 ng doses. Parallel applications of ethanol alone or 2.5% aqueous Atlas solution alone (controls) and IAA alone (1000 ng) were also carried out (see Figures 1−3). In all of the figures, error bars represent 95% confidence limits.

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Supporting Information Available: ^1H- and ^{13}C NMR spectra of compounds **3**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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