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Enantioselective synthesis of the individual stereoisomers of a brassinolide mimetic

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Abstract—The syntheses of all four stereoisomers of a nonsteroidal mimetic of the phytohormone brassinolide are reported. These are: (+)-(6*S*,7*R*,6′*S*,7′*R*)-, (−)-(6*R*,7*S*,6′*R*,7′*S*)-, (+)-(6*S*,7*R*,6′*R*,7′*S*)-, and (−)-(6*R*,7*S*,6′*S*,7′*R*)-1-[1-(4,6,7-trihydroxy-5,6,7,8-tetrahydronaphthyl)]-2-[1′-(6′,7′-dihydroxy-5′,6′,7′,8′-tetrahydronaphthyl)]ethyne.

1. Introduction

Brassinolide **1** is a phytohormone that was first isolated from *Brassica napus* pollen in 1979 by Grove et al.,[1] who elucidated its structure and reported that **1** displayed biological activity at doses as low as 1 ng per individual plant when applied exogenously to certain plant species. Since then, a variety of other naturally-occurring brassinosteroids have been discovered, although **1** is generally considered to be the most potent member of this family. Brassinolide and its congeners have been reported to increase the yields of numerous commercially important crops, as well as to improve their resistance to stress caused by temperature extremes, drought, and salinity.[2–4] Extensive studies have been directed toward the natural occurrence, biosynthesis, metabolism, molecular biology, physiological effects, and potential practical applications of these compounds.[2–4] Although several synthetic approaches to **1** and other brassinosteroids have made these compounds available,[5–7] the high cost of synthetic brassinosteroids and their very low natural abundance in plants have created formidable obstacles to their large-scale preparation and commercial exploitation. The discovery of more strongly bioactive synthetic derivatives,[8] as well as the synergy of brassinosteroids with less expensive auxins such as indole-3-acetic acid (IAA) and naphthaleneacetic acid (NAA),[9–11] have lowered the threshold of detectable activity to ca. 1 pg/plant. While these advances mitigate the high cost of brassinosteroids, commercial applications nevertheless remain very limited.

Structure–activity relationships (SAR) of brassinosteroids have been investigated by several groups[12–17] and considerable insight has been gained into the structural requirements of highly bioactive brassinosteroids. As part of such studies, we have prepared several dozen modified analogues[12] and subjected them to the rice leaf lamina inclination bioassay,[9] a technique that provides a rapid and highly sensitive method for comparing the bioactivities of various brassinosteroid structures. Based on the results of SAR studies, we recently designed a series of nonsteroidal mimetics of **1** that contain subunits bearing key functional groups mimicking those of **1**. The subunits are joined by rigid linkers of appropriate length, thereby generating structures that allow superimposition of the key substituents upon their counterparts in the minimum energy conformation of **1**.[18] In addition to the diol groups, the presence of a polar functionality on the B-ring is necessary for bioactivity.[19] Although the lactone moiety of **1** is optimal for this purpose, bioactivity is also observed in brassinosteroids containing other polar groups, including C-6 alcohols and ketones.[19,20] The relatively simple structures of the mimetics facilitates their synthesis, thus potentially lowering their cost compared to that of natural brassinosteroids. Among the first series of mimetic structures that were synthesized and subjected to the rice leaf lamina bioassay, two compounds, **2** and **3**, displayed significant bioactivity when coapplied with IAA. They comprise the first nonsteroidal mimetics of brassinolide.[18]

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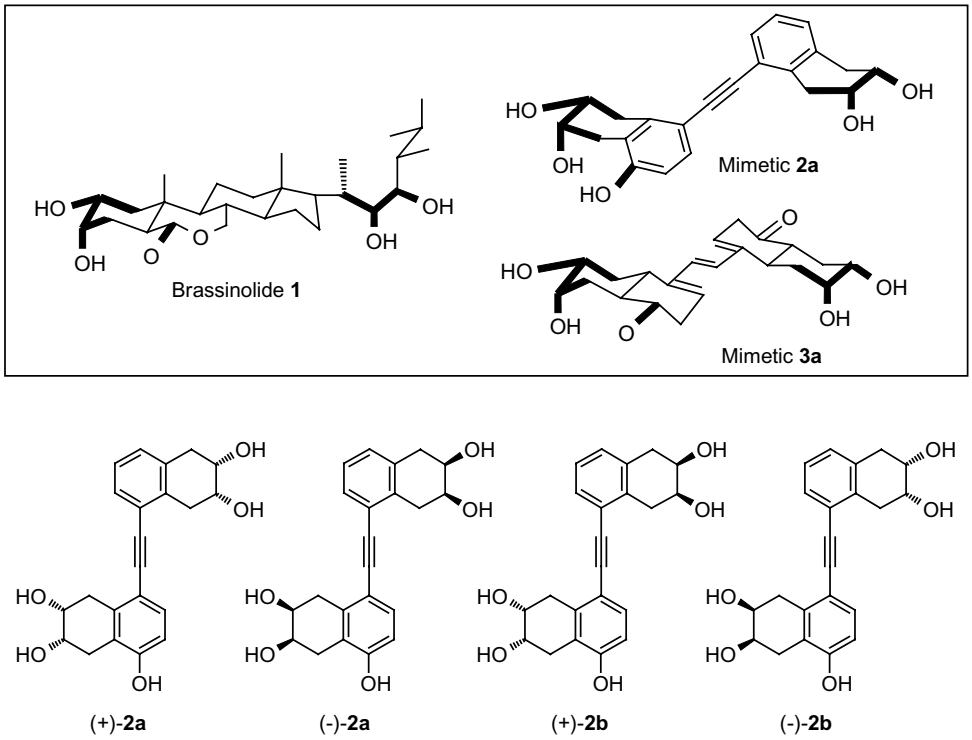
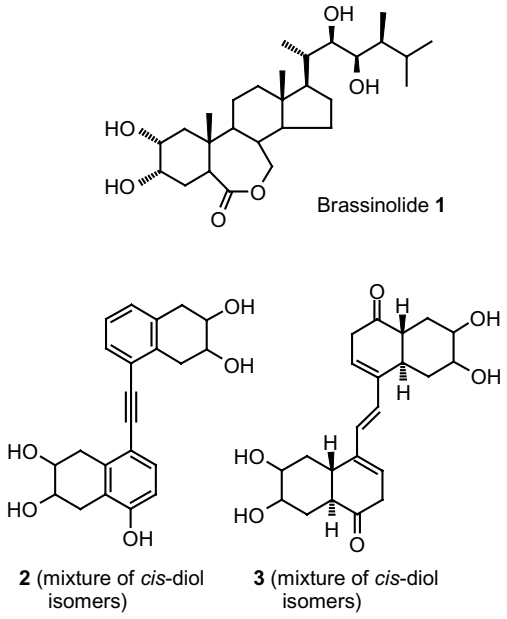


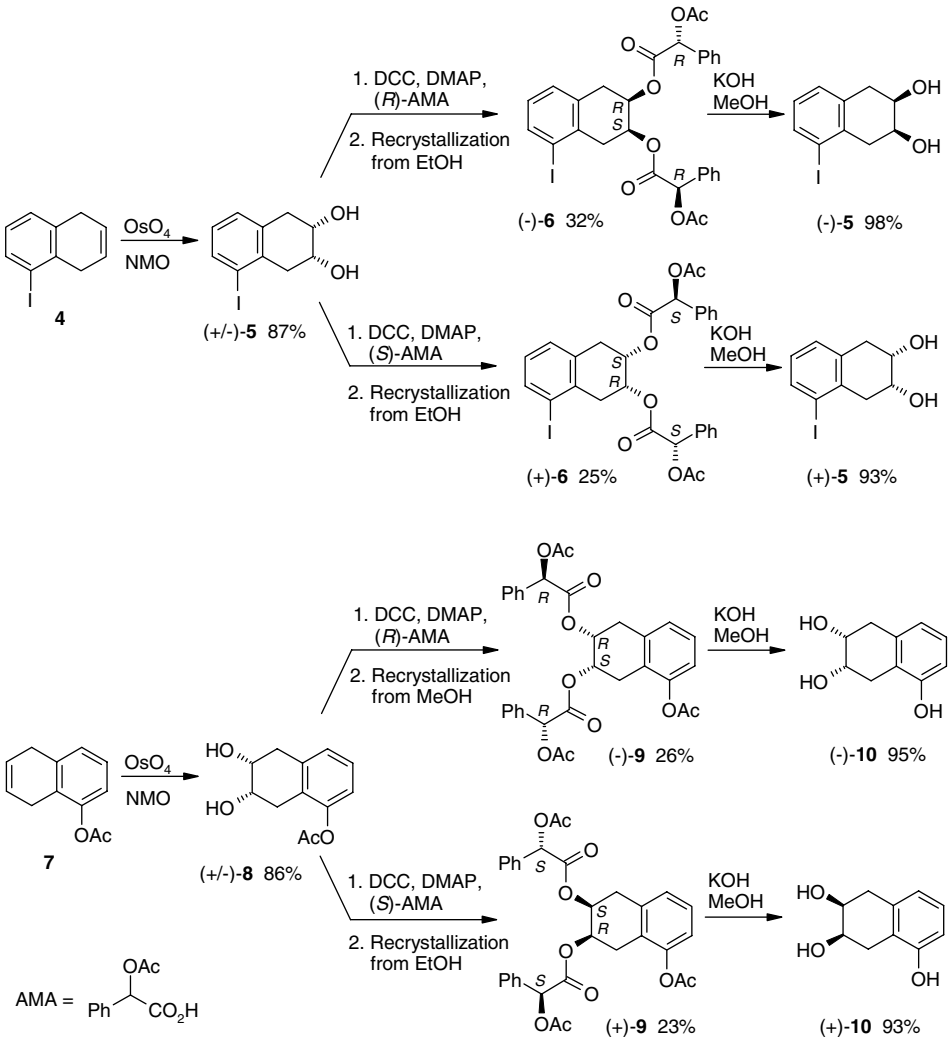
Figure 1. Stereoisomers of mimetic **2** and the superimposability of key groups (shown in bold) of mimetics **2a** and **3a** with those of brassinolide **1**.

Figure 1 shows the respective stereoisomers of two such mimetics **2a** and **3a**, where close superimposition of the two vicinal diol moieties is possible with those of **1**. Moreover, the phenolic hydroxyl or ketone groups of **2a** and **3a**, respectively, superimpose upon the lactone moiety of **1**. However, both **2** and **3** were originally obtained and assayed as mixtures of inseparable stereoisomers. Since individual stereoisomers often have strikingly different biological properties, we considered it of importance to synthesize and assay each stereoisomer separately. Herein we report the diastereo- and enantioselective preparation of all four stereoisomers of mimetic **2** (two diastereomers **2a** and **2b**, each consisting of a pair of enantiomers).



2. Results and discussion

Subunits **5** and **8**, containing the key vicinal *cis*-diol moieties, were first prepared from iodide **4**[21] and acetate **7**,[22] respectively, by Sharpless asymmetric dihydroxylation.[23] Unfortunately, enantioselectivity was too low for the purpose at hand. Thus, the asymmetric dihydroxylation of **4** with AD-mix-α and AD-mix-β (as purchased from the Aldrich Chemical Co.) afforded enantiomeric excesses (ee's) of 74% for (−)-**5** and 70% for (+)-**5**, respectively. The similar treatment of **7** with AD-mix-α and AD-mix-β provided ee's of 50% for (−)-**8** and 58% for (+)-**8**, respectively. The racemic diols **5**[18] and **8**[24] were therefore obtained by nonasymmetric osmium tetroxide-catalyzed dihydroxylation and resolved via their diesters **6** and **9**, prepared with (*R*)- and (*S*)-(*O*)-acetylmandelic acid (AMA),[25] as shown in Scheme 1. In each case, the less soluble mandelate diastereomer was subjected to repeated recrystallization until NMR analysis revealed the absence of the more soluble diastereomer. The absolute configurations of the diol carbinol stereocenters of mandelates (−)-**6** and (−)-**9** were established by X-ray crystallography with their ORTEP diagrams shown in Figures 2 and 3, respectively. Crystallographic data (excluding structure factors) for structures (−)-**6** and (−)-**9** herein have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 225578 and



Scheme 1.

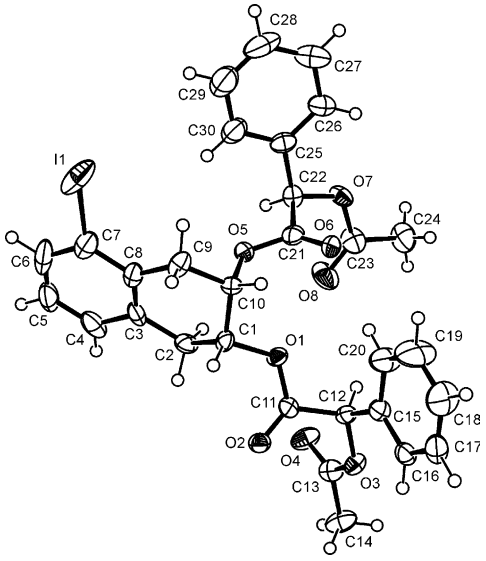


Figure 2. ORTEP diagram of (−)-**6**.

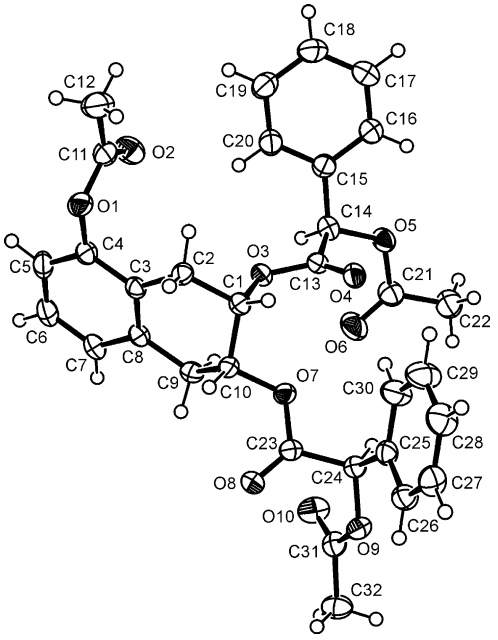
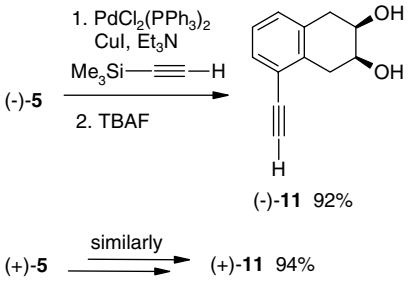


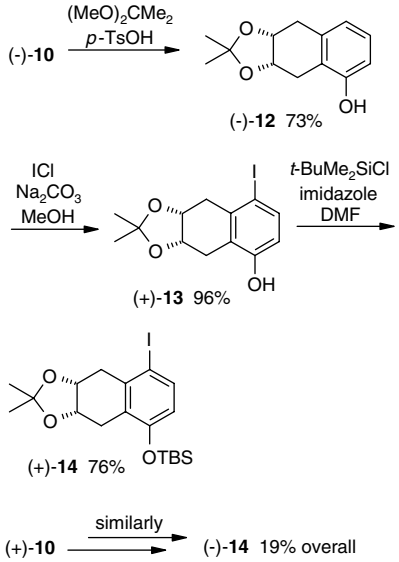
Figure 3. ORTEP diagram of (−)-**9**.

CCDC 225577, respectively. The enantioenriched diols **5** and **8**, obtained via asymmetric dihydroxylation, could also be used similarly in the preparation of esters **6** and **9**, respectively. Saponification of the ester groups of resolved **6** and **9** then afforded the pure enantiomers of the required diol **5** and triol **10**.

With the pure enantiomers of the subunits in hand, we proceeded to couple them with the required acetylenic linker to afford the respective stereoisomers (+)-**2a**, (−)-**2a**, (+)-**2b**, and (−)-**2b**. Thus, iodides (−)-**5** and (+)-**5** were converted to the corresponding acetylenes (−)-**11** and (+)-**11**, respectively, by means of Sonogashira reactions[26–28] (Scheme 2), while (−)-**10** and (+)-**10** were protected and iodinated with iodine monochloride[29] as shown in Scheme 3. A second Sonogashira coupling of each possible combination of (+)- and (−)-**11** with (+)- and (−)-**14**, followed by deprotection, then afforded the desired products **2a**–**d** (Scheme 4).

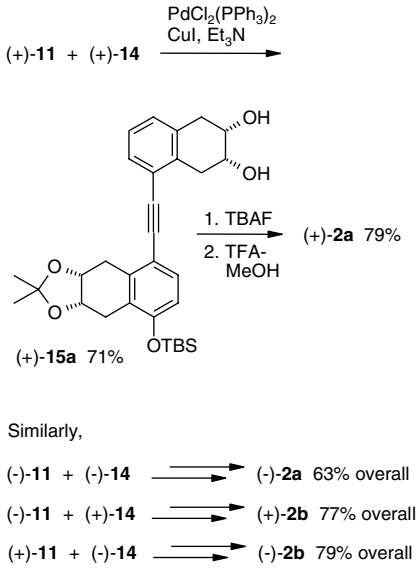


Scheme 2.



Scheme 3.

Preliminary bioassay results using the rice leaf lamina inclination assay of **2a**–**d** indicated that bioactivity was not confined to any single stereoisomer. Thus, three of the mimetics (+)-**2a**, (+)-**2b**, and (−)-**2b**, when coapplied with IAA, showed modest, but variable promotive effects on leaf lamina bending, but only at higher dose



Scheme 4.

levels. The mimetics were also examined (through co-application) with regard to their effects on the bending activity induced by brassinolide and IAA. Surprisingly, when applied at a dose equal to, or higher than the dose of brassinolide, the mimetics displayed the ability either to enhance synergistically the activity of coapplied brassinolide or to function as antagonists of brassinolide's promotive activity, depending on both the dose of brassinolide and of the mimetic. A more detailed investigation of this unexpectedly complex biological behavior of the individual stereoisomers, is currently in progress.

3. Experimental

3.1. General

NMR spectra were recorded in $CDCl_3$, with residual chloroform as the standard, unless otherwise noted. Mass spectra were obtained using EI at 70 eV. An A. H. Thomas hot-stage apparatus was used to measure melting points, which are uncorrected. Optical rotations were determined on a Rudolph Autopol IV polarimeter at 22 °C.

3.2. (−)-(6*R*,7*S*)-6,7-Bis[(*R*)-*O*-acetylmandeloxy]-1-iodo-5,6,7,8-tetrahydronaphthalene (−)-6

The racemic diol **5**[18] (816 mg, 2.81 mmol), 4-dimethylaminopyridine (34 mg, 10 mol%), and (*R*)-*O*-acetylmandelic acid[25] (1.15 g, 5.92 mmol) were stirred in dichloromethane (40 mL). The resulting slurry was cooled in an ice/water bath and dicyclohexylcarbodiimide (1.22 g, 5.91 mmol) in dichloromethane (15 mL) added dropwise over 1 h. The reaction mixture was allowed to reach ambient temperature while stirring overnight. It was filtered, washed with Na_2CO_3 solution, brine, dried over $MgSO_4$, and evaporated in vacuo to leave a colorless solid foam. Multiple recrystallizations

(absolute ethanol) furnished 580 mg (32%) of diester (−)-**6** as white needles: $[\alpha]_D = -100$ (*c* 1.0, CH_3OH); mp 113–115 °C; IR (film) 1749, 1230, 1056 cm^{-1}; ^1H NMR (200 MHz) δ 7.69 (d, $J = 8.7$ Hz, 1H), 7.45–7.28 (m, 10H), 7.08 (d, $J = 8.7$ Hz, 1H), 6.87 (t, $J = 8.6$ Hz, 1H), 5.86 (s, 1H), 5.77 (s, 1H), 5.37–5.21 (m, 2H), 3.19–3.11 (m, 2H), 2.87–2.58 (m, 2H), 2.18 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (50 MHz) δ 170.2, 169.8, 168.0, 167.8, 137.4, 134.5, 133.8, 133.4, 129.2, 129.1, 128.7, 128.6, 128.0, 127.4, 127.3, 101.7, 74.4, 74.3, 70.6, 70.1, 38.1, 32.0, 20.5, 20.3; MS, *m*/*z* (relative intensity, %) 388 (5), 254 (6), 203 (9), 178 (6), 128 (100), 89 (64). Anal. Calcd for $C_{30}H_{27}IO_8$: C, 56.09%; H, 4.24%. Found: C, 56.12%; H, 3.98%.

3.3. (+)-(6*S*,7*R*)-6,7-Bis[(*S*)-*O*-acetylmandeloxy]-1-iodo-5,6,7,8-tetrahydronaphthalene (+)-6

Racemic **5** was treated with (*S*)-*O*-acetylmandelic acid[25] as in the preceding procedure to afford, after multiple recrystallizations, 25% of diester (+)-**6** as white needles: $[\alpha]_D = +99.8$ (*c* 1.0, CH_3OH); mp 113–115 °C; IR (film) 1748, 1228, 1053 cm^{-1}; ^1H NMR (200 MHz) δ 7.69 (d, $J = 8.7$ Hz, 1H), 7.45–7.28 (m, 10H), 7.08 (d, $J = 8.7$ Hz, 1H), 6.87 (t, $J = 8.6$ Hz, 1H), 5.86 (s, 1H), 5.77 (s, 1H), 5.37–5.21 (m, 2H), 3.19–3.11 (m, 2H), 2.87–2.58 (m, 2H), 2.18 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (50 MHz) δ 170.2, 169.8, 168.0, 167.8, 137.4, 134.4, 133.7, 133.4, 129.1, 129.0, 128.8, 128.7, 128.0, 127.4, 127.2, 101.7, 74.4, 74.3, 70.6, 70.1, 38.1, 32.0, 20.5, 20.3; MS, *m*/*z* (relative intensity, %) 388 (16), 254 (20), 203 (29), 178 (17), 128 (100), 89 (46). Anal. Calcd for $C_{30}H_{27}IO_8$: C, 56.09%; H, 4.24%. Found: C, 56.14%; H, 3.94%.

3.4. (−)-(6*R*,7*S*)-1-Iodo-5,6,7,8-tetrahydro-6,7-naphthalenediol (−)-5

Potassium hydroxide (1.64 g, 29.2 mmol) was added to a slurry of ester (−)-**6** (2.35 g, 3.66 mmol) in methanol (45 mL). The mixture was stirred for 2 h and the resulting homogeneous solution evaporated in vacuo. The residue was taken up in $NaHCO_3$ solution and extracted several times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, evaporated in vacuo, and subjected to flash chromatography (elution with 80% ethyl acetate–hexanes) to give 1.04 g (98%) of diol (−)-**5** as a white solid: $[\alpha]_D = -37.3$ (*c* 1.0, CH_3OH); mp 138–140 °C (lit.[18] mp for (±)-**5**: 139–141 °C). The ^1H NMR spectrum was identical to that of (±)-**5**.

3.5. (+)-(6*S*,7*R*)-1-Iodo-5,6,7,8-tetrahydro-6,7-naphthalenediol (+)-5

The saponification of (+)-**6** was carried out as in the preceding procedure to afford 93% of diol (+)-**5** as a white solid: $[\alpha]_D = +40.2$ (*c* 0.93, CH_3OH); mp 138–140 °C (lit.[18] mp for (±)-**5**: 139–141 °C). The ^1H NMR spectrum was identical to that of (±)-**5**.

3.6. (±)-(*cis*)-1-Acetoxy-5,6,7,8-tetrahydro-6,7-naphthalenediol 8

Osmium tetroxide (156 μL of a 0.39 M solution in *tert*-butanol, 0.061 mmol), *N*-methylmorpholine *N*-oxide (1.57 g, 13.4 mmol), and water (220 μL, 12.2 mmol) were added to a solution of 5,8-dihydro-1-naphthyl acetate **7**[18] (2.29 g, 12.2 mmol) in acetone (75 mL). The solution was stirred for 18 h, after which sodium thiosulfate (250 mg) and Florisil (500 mg) were added and stirring then continued for a further 3 h. The mixture was filtered through Celite, the filtrate evaporated in vacuo, and the residue subjected to flash chromatography (elution with 50% ethyl acetate–hexanes) to give 2.33 g (86%) of diol (±)-**8**;[24] mp 144–145 °C (from acetone–benzene); IR (Nujol) 3339, 1744, 1077, 1050 cm^{-1}; ^1H NMR (200 MHz) (CD_3OD) δ 7.15 (t, $J = 8.4$ Hz, 1H), 7.00 (d, $J = 8.2$ Hz, 1H), 6.84 (d, $J = 8.2$ Hz, 1H), 4.03 (m, 2H), 3.11–2.63 (m, 4H), 2.30 (s, 3H); ^{13}C NMR (50 MHz) (CD_3OD) δ 173.4, 153.1, 139.7, 130.3, 130.2, 130.1, 123.0, 72.4, 72.1, 37.8, 32.4, 23.2; MS, *m*/*z* (relative intensity, %) 222 (M^+, 5), 204 (6), 180 (43), 162 (100), 133 (24), 120 (38). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85%; H, 6.35%. Found: C, 64.71%; H, 6.12%.

3.7. (−)-(6*R*,7*S*)-1-Acetoxy-6,7-bis[(*R*)-*O*-acetylmandeloxy]-5,6,7, 8-tetrahydronaphthalene (−)-9

Diol (±)-**8** (2.73 g, 12.3 mmol), 4-dimethylaminopyridine (150 mg, 1.23 mmol), and (*R*)-*O*-acetylmandelic acid[25] (5.01 g, 25.8 mmol) were dissolved in dichloromethane (125 mL) and the resulting slurry was cooled in an ice/water bath. Dicyclohexylcarbodiimide (5.32 g, 25.8 mmol) in dichloromethane (65 mL) was added dropwise over 1 h. The reaction mixture was stirred overnight at ambient temperature. The resulting slurry was filtered, the filtrate washed with Na_2CO_3 solution and brine, dried over $MgSO_4$, and evaporated in vacuo to leave a colorless solid foam. Multiple recrystallizations (from methanol) furnished 1.81 g (26%) of triester (−)-**9** as white needles; $[\alpha]_D = -92.1$ (*c* 1.0, acetone); mp 142–144 °C; IR (film) 1749, 1230, 1209, 1056, 1028 cm^{-1}; ^1H NMR (200 MHz) δ 7.41–7.30 (m, 10H), 7.19 (t, $J = 8.2$ Hz, 1H), 6.98 (d, $J = 8.1$ Hz, 1H), 6.91 (d, $J = 8.1$ Hz, 1H), 5.84 (s, 1H), 5.75 (s, 1H), 5.31 (m, 2H), 3.18 (m, 2H), 2.65 (m, 2H), 2.27 (s, 3H), 2.16 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (50 MHz) δ 170.3, 169.9, 168.7, 168.0, 167.8, 148.9, 133.9, 133.5, 133.4, 129.1, 128.9, 128.7, 128.6, 127.4, 127.3, 127.2, 126.5, 124.4, 119.9, 74.5, 70.0, 69.6, 31.3, 26.3, 20.7, 20.5, 20.2; MS, *m*/*z* (relative intensity, %) 575 (M^+, <1), 320 (7), 186 (14), 145 (100), 115 (91). Anal. Calcd for $C_{32}H_{30}O_{10}$: C, 66.89%; H, 5.26%. Found: C, 66.95%; H, 5.09%.

3.8. (+)-(6*S*,7*R*)-1-Acetoxy-6,7-bis[(*S*)-*O*-acetylmandeloxy]-5,6,7,8-tetrahydronaphthalene (+)-9

Racemic **8** was treated with (*S*)-*O*-acetylmandelic acid[25] as in the preceding procedure to afford, after multiple recrystallizations from methanol, 23% of triester (+)-**9** as white needles: $[\alpha]_D = +94.7$ (*c* 1.0, acetone); mp

142–144 °C; IR (film) 1745, 1235, 1206, 1053, 1029 cm^{-1}; ^1H NMR (200 MHz) δ 7.41–7.30 (m, 10H), 7.19 (t, $J = 8.2$ Hz, 1H), 6.98 (d, $J = 8.1$ Hz, 1H), 6.91 (d, $J = 8.1$ Hz, 1H), 5.84 (s, 1H), 5.75 (s, 1H), 5.31 (m, 2H), 3.18 (m, 2H), 2.65 (m, 2H), 2.27 (s, 3H), 2.16 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (50 MHz) δ 170.2, 169.9, 168.6, 168.0, 167.8, 149.0, 133.9, 133.5, 133.5, 129.1, 128.8, 128.7, 128.6, 127.5, 127.4, 127.2, 126.5, 124.4, 119.9, 74.5, 70.0, 69.6, 31.3, 26.3, 20.7, 20.5, 20.2; MS, *m/z* (relative intensity, %) 575 (M^+, <1), 145 (100), 115 (67). Anal. Calcd for $C_{32}H_{30}O_{10}$: C, 66.89%; H, 5.26%. Found: C, 66.59%; H, 5.07%.

3.9. (−)-(6*R*,7*S*)-5,6,7,8-Tetrahydro-1,6,7-naphthalenetriol (−)-10

Potassium hydroxide (2.71 g, 48.3 mmol) was added to a slurry of ester (−)-**9** (4.89 g, 8.51 mmol) in methanol (100 mL). The mixture was stirred for 2 h and the homogeneous solution concentrated in vacuo. The residue was taken up in ethyl acetate and washed several times with brine, which was back-extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, and evaporated in vacuo to give a crude residue that afforded 1.46 g (95%) of white crystals (from ethanol–water) of triol (−)-**10**: $[\alpha]_D = -20.2$ (*c* 0.46, acetone); mp 184–186 °C (lit.[30] mp for (±)-**10**: 188–188.5 °C); ^1H NMR (200 MHz) (acetone-d_6–D_2O) δ 6.85 (t, $J = 7.8$ Hz, 1H), 6.57 (d, $J = 7.9$ Hz, 1H), 6.51 (d, $J = 7.6$ Hz, 1H), 4.06–3.91 (m, 2H), 2.95–2.61 (m, 4H).

3.10. (+)-(6*S*,7*R*)-5,6,7,8-Tetrahydro-1,6,7-naphthalenetriol (+)-10

The saponification of (+)-**9** was carried out as in the preceding procedure to afford 93% of triol (+)-**10** as a white solid: $[\alpha]_D = +18.9$ (*c* 0.38, acetone); mp 184–186 °C (lit.[30] mp for (±)-**10**: 188–188.5 °C). The ^1H NMR spectrum was identical to that of (−)-**10**.

3.11. (−)-(6*R*,7*S*)-1-Ethynyl-5,6,7,8-tetrahydro-6,7-naphthalenediol (−)-11

Diol (−)-**5** (1.04 g, 3.60 mmol), dichlorobis(triphenylphosine)palladium(II) (63 mg, 2.5 mol %), and copper(I) iodide (34 mg, 5 mol %) were placed in an oven dried flask, which was then purged with argon. Benzene (105 mL), triethylamine (25 mL), and trimethylsilylacetylene (710 μL, 5.04 mmol) were added via syringe. Stirring was continued overnight and the reaction quenched with brine and extracted several times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. The residue was taken up in THF (50 mL), chilled to 0 °C, and treated with tetrabutylammonium fluoride (4.3 mL of a 1.0 M solution in THF, 4.3 mmol). The mixture was stirred for 2 h, after which NH_4Cl solution was added, followed by extraction several times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, evaporated in vacuo, and subjected to flash chromatography (elution with 55% ethyl acetate–hexanes) to yield 624 mg (92%) of acetylene (−)-**11**: $[\alpha]_D = -49.2$ (*c* 0.84, CH_3OH); mp 134–137 °C (lit.[18] mp for (±)-**11**: 133–136 °C). The ^1H NMR spectrum was identical to that of (±)-**11**.[18]

3.12. (+)-(6*S*,7*R*)-1-Ethynyl-5,6,7,8-tetrahydro-6,7-naphthalenediol (+)-11

Diol (+)-**5** was treated similarly to afford 94% of acetylene (+)-**11**: $[\alpha]_D = +47.6$ (*c* 0.72, CH_3OH); mp 134–136 °C (lit.[18] mp for (±)-**11**: 133–136 °C). The ^1H NMR spectrum was identical to that of (±)-**11**.[18]

3.13. (−)-(6*R*,7*S*)-6,7-(Isopropylidenedioxy)-5,6,7,8-tetrahydro-1-naphthol (−)-12

p-Toluenesulfonic acid (41.5 mg, 10 mol %) was added to a slurry of triol (−)-**10** (392 mg, 2.18 mmol) and 2,2-dimethoxypropane (1.61 mL, 13.1 mmol). The mixture was stirred for 2 h at ambient temperature, at which time the homogeneous solution was diluted with dichloromethane, washed with $NaHCO_3$ solution and brine, dried over Na_2SO_4, and evaporated in vacuo to give an off-white solid. The crude residue was subjected to flash chromatography (elution with 20% ethyl acetate–hexanes) to give 352 mg (73%) of (−)-**12** as a white solid: $[\alpha]_D = -22.8$ (*c* 0.64, $CHCl_3$); mp 112–114 °C; ^1H NMR (200 MHz) δ 7.04 (t, $J = 7.7$ Hz, 1H), 6.79 (d, $J = 7.4$ Hz, 1H), 6.69 (d, $J = 8.0$ Hz, 1H), 4.63 (m, 2H), 3.17–2.58 (m, 4H), 1.35 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (50 MHz) δ 152.8, 137.2, 126.8, 121.1, 121.0, 113.5, 108.0, 74.1, 73.9, 34.3, 26.3, 26.1, 24.4. The NMR spectra were identical to those of (±)-**12**.[18]

3.14. (+)-(6*R*,7*S*)-4-Iodo-6,7-(isopropylidenedioxy)-5,6,7,8-tetrahydro-1-naphthol (+)-13

A slurry of (−)-**12** (1.75 g, 7.94 mmol), Na_2CO_3 (8.42 g, 79.4 mmol), and methanol (100 mL) was cooled to 0 °C. Iodine monochloride (1.35 g, 8.31 mmol) was added over 45 min and the slurry stirred at ambient temperature for 3 h, at which time the reaction was filtered and evaporated in vacuo to give 2.64 g (96%) of (+)-**13**, which was used directly in the next step. A portion was subjected to flash chromatography (elution with 20% ethyl acetate–hexanes) to afford (+)-**13** as a white solid: $[\alpha]_D = +23.4$ (*c* 0.44, CH_3OH); mp 173–175 °C (lit.[18] mp for (±)-**13**: 172–175 °C); ^1H NMR (200 MHz) δ 7.56 (d, $J = 8.5$ Hz, 1H), 6.49 (d, $J = 8.5$ Hz 1H), 4.88 (s, 1H), 4.66–4.55 (m, 2H), 3.26–3.10 (m, 2H), 2.83–2.52 (m, 2H), 1.33 (s, 3H), 1.15 (s, 3H). The ^1H NMR spectrum was identical to that of (±)-**13**.[18]

3.15. (+)-(6*R*,7*S*)-1-*tert*-Butyldimethylsilyloxy-4-iodo-6,7-(isopropylidenedioxy)-5,6,7,8-tetrahydronaphthalene (+)-14

Imidazole (2.26 g, 33.3 mmol), *tert*-butyldimethylsilyl chloride (2.52 g, 16.7 mmol), and (+)-**13** (2.64 g,

7.63 mmol) were stirred overnight in DMF (42 mL). The mixture was diluted with water and extracted several times with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by flash chromatography (elution with 2% ethyl acetate–hexanes) to give 2.67 g (76%) of silyl ether (+)-**14**: $[\alpha]_D = +22.3$ (*c* 0.75, acetone); mp 71–73 °C (lit.[18] mp for (±)-**14**: 72–73 °C); ^{1}H NMR (200 MHz) δ 7.53 (d, $J = 8.6$ Hz, 1H), 6.49 (d, $J = 8.6$ Hz, 1H), 4.59–4.45 (m, 2H); 3.16–2.67 (m, 4H), 1.32 (s, 3H), 1.20 (s, 3H), 1.04 (s, 9 H) 0.21 (s, 6 H). The ^{1}H NMR spectrum was identical to that of (±)-**14**.[18]

3.16. (−)-(6*S*,7*R*)-1-*tert*-Butyldimethylsilyloxy-4-iodo-6,7-(isopropylidenedioxy)-5,6,7,8-tetrahydronaphthalene (−)-14

The same procedure was used to prepare (−)-**14** from (+)-**10** as was employed for the preparation of (+)-**14** from (−)-**10** with an overall yield of 19%. The intermediates and product had the following specific rotations: (+)-**12**: $[\alpha]_D = +25.6$ (*c* 0.59, $CHCl_3$); (−)-**13**: $[\alpha]_D = -24.8$ (*c* 0.77, CH_3OH); (−)-**14**: $[\alpha]_D = -20.6$ (*c* 0.95, acetone). The ^{1}H NMR spectra of these products were identical to those of their enantiomers.

3.17. (+)-(6*S*,7*R*,6′*S*,7′*R*)-1-{1-[4-(*tert*-Butyldimethylsilyloxy)-6,7-(isopropylidenedioxy)-5,6,7,8-tetrahydronaphthyl]}-2-[1′-(6′,7′-dihydroxy-5′,6′,7′,8′-tetrahydronaphthyl)]ethyne (+)-15a

Acetylene (+)-**11** (219 mg, 1.16 mmol), iodide (+)-**14** (562 mg, 1.22 mmol), dichlorobis(triphenylphosphine)palladium(II) (41 mg, 5 mol%), and copper(I) iodide (22 mg, 10 mol%) were placed in an oven dried 100 mL round bottom flask and purged with argon. Benzene (46 mL) and triethylamine (11 mL) were added by syringe. The reaction was stirred overnight, quenched with brine, and extracted several times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, evaporated in vacuo, and flash chromatographed (elution with 50–100% ethyl acetate–hexanes) to give 430 mg (71%) of acetylene (+)-**15a** as a solid foam: $[\alpha]_D = +93.3$ (*c* 0.94, $CHCl_3$); ^{1}H NMR (200 MHz) δ 7.41–7.27 (m, 2H), 7.18–7.02 (m, 2H), 6.71 (d, $J = 8.4$ Hz, 1H), 4.63–4.46 (m, 2H), 4.23–4.11 (m, 2H), 3.30–2.73 (m, 8 H), 2.48 (br s, 2H), 1.34 (s, 3H), 1.25 (s, 3H) 1.03 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (50 MHz) δ 153.2, 138.9, 134.9, 133.4, 130.5, 129.6, 128.9, 126.3, 125.8, 123.4, 117.2, 115.4, 108.2, 93.1, 90.1, 74.0, 73.7, 69.1, 68.8, 34.4, 33.6, 32.4, 27.0, 26.5, 25.8, 24.4, 18.3, −4.1, −4.2.

3.18. (+)-(6*S*,7*R*,6′*S*,7′*R*)-1-[1-(4,6,7-Trihydroxy-5,6,7,8-tetrahydronaphthyl)]-2-[1′-(6′,7′-dihydroxy-5′,6′,7′,8′-tetrahydronaphthyl)]ethyne (+)-2a and its isomers (−)-2a, (+)-2b, and (−)-2b

Acetylene (+)-**15a** (430 mg, 0.826 mmol) was dissolved in THF (20 mL) containing tetrabutylammonium fluoride (1.0 mL of a 1.0 M solution in THF, 1.0 mmol). After 2 h, the reaction was quenched with NH_4Cl solution and extracted several times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated in vacuo to leave a crude residue that was used immediately in the next step. Hence, TFA (5 mL) was added to a solution of the crude product in methanol (85 mL). The solution was refluxed for 2 h, after which the methanol and TFA were removed in vacuo and flash chromatographed (10% methanol–ethyl acetate) to afford 238 mg (79%) of the desired mimetic (+)-**2a** as a white solid: $[\alpha]_D = +93.5$ (*c* 0.20, CH_3OH); mp 258–274 °C ^{1}H NMR (200 MHz) δ 7.30 (m, 1H), 7.21 (d, $J = 8.2$ Hz, 1H), 7.09 (m, 2H), 6.62 (d, $J = 8.2$ Hz, 1H), 4.14–4.04 (m, 4H), 3.17 (m, 4H), 2.99 (m, 2H), 2.87 (m, 2H); ^{13}C NMR (50 MHz) δ 154.9, 136.4, 134.4, 133.2, 130.0, 128.7, 128.0, 125.0, 123.1, 120.5, 113.2, 111.3, 92.7, 89.8, 68.3, 68.2, 68.1, 67.8, 33.7, 32.9, 32.8, 28.2; MS, *m*/*z* (relative intensity, %) 366 (M^+, 23), 348 (26), 330 (62); HRMS calculated for $C_{22}H_{22}O_5$: 366.1467. Found: 366.1483. Products (−)-**2a**, (+)-**2b**, and (−)-**2b** were prepared similarly from the corresponding isomers of **11** and **14** in the overall yields shown in Scheme 4. Their specific rotations and exact masses were: (−)-**2a**: $[\alpha]_D = -92.3$ (*c* 0.38, CH_3OH), HRMS 366.1448; (+)-**2b**: $[\alpha]_D = +4.2$ (*c* 0.10, CH_3OH), HRMS 366.1459, and (−)-**2b**: $[\alpha]_D = -4.3$ (*c* 0.30, CH_3OH), HRMS 366.1455.

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