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Transmissive Olefination Route to Putative "Morinol I" Lignans

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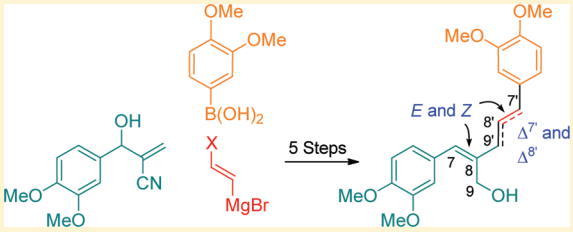
Supporting Information

ABSTRACT: A series of morinol-type lignans were rapidly assembled using a Grignard-based transmissive olefination. In combination with palladium-catalyzed arylations, the strategy provides stereoselective access to (7*Z*,7′*E*), (7*E*,7′*E*), and (7*E*,7′*Z*) morinol diastereomers and the (7*Z*,8′*E*) and (7*E*,8′*E*) conjugated analogues. Critical for the *E*/*Z* stereoselectivity is a new, general method for converting alkenenitriles to alkenemethanols that circumvents the enal *E*/*Z* isomerization commonly encountered during conventional *i*-Bu_2AlH reduction.



Alkenenitrile pharmacophores are embedded within an array of pharmaceuticals[1] and natural products[2] (Figure 1). In many instances, the nitrile plays a key role in receptor

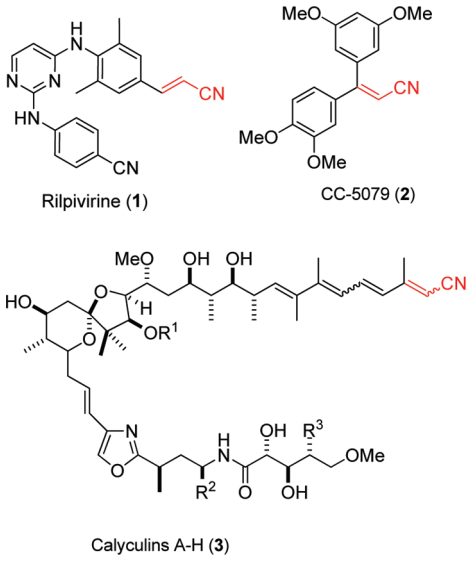
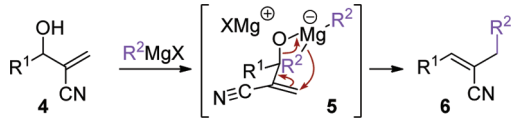


Figure 1. Bioactive alkenenitriles.

binding as with the potent anti-HIV agent[3] rilpivirine (**1**) where the nitrile groups interact deep within the binding pocket.[4] Consistent with the key role of the nitrile group, (*E*/*Z*)-alkenenitrile diastereomers often exhibit significantly different potencies as exemplified by the antitumor agent **2**.[5] A similar interplay of substitution and *E*/*Z* geometry influences the antitumor activity[6] of calyculins A−H (**3**), unusual (*E*)- and (*Z*)-tetraenenitriles from the marine sponges *Discodermia calyx* and *Lamellomorpha strongylata*.[2]

Selective access to diastereomeric (*E*)- and (*Z*)-alkenenitriles is challenging.[7] In addressing this challenge, a stereoselective synthesis of (*Z*)-alkenenitriles **6** was developed that hinges on an intramolecular transmissive olefination through a highly ordered transition structure (Scheme 1).[8] Addition of excess Grignard reagent to Baylis−Hilman-derived[9] hydroxyalkeneni-

Scheme 1. Transmissive Olefination Route to (*Z*)-Alkenenitriles



triles **4** triggers a displacement that selectively affords (*Z*)-alkenenitriles **6**. Mechanistic probes are consistent with a concerted reorganization through the magnesiate **5** in which the slender[10] nitrile group preferentially eclipses the carbinol substituent R^1.

Rapid access to (*Z*)-alkenenitriles from three readily available components, an aldehyde, acrylonitrile, and a Grignard reagent, appeared ideal for synthesizing and unraveling the structural ambiguity of the neolignan morinol I. Morinol I is one of a series of neolignans[11] (Figure 2, **8**−**19**) that were isolated during a bioactivity guided isolation of extracts from the roots of the traditional Chinese medicinal herb *Morina chinensis*.[12] Among morinol metabolites, the proposed structure **7** for morinol I is unique in having a skipped diene. All morinols, except morinol I, formally have water added to the C7−C8 bond. The related neolignan galanganal (**15**), isolated from the Zingiberaceae plant *Alpinia galangal*, has the same olefin position as **7** but the opposite C7 alkene geometry.[13]

Intriguingly, the HMBC and NOESY correlations reported for morinol I are not consistent with the skipped diene structure **7** but require a conjugated C7−C8 C9′−C8′ diene. Adding to the structural ambiguity is the secure structural identification of morinols A−D, through synthesis,[14] which *do* contain a C7′−C8′ olefin. Unfortunately, neither a sample nor

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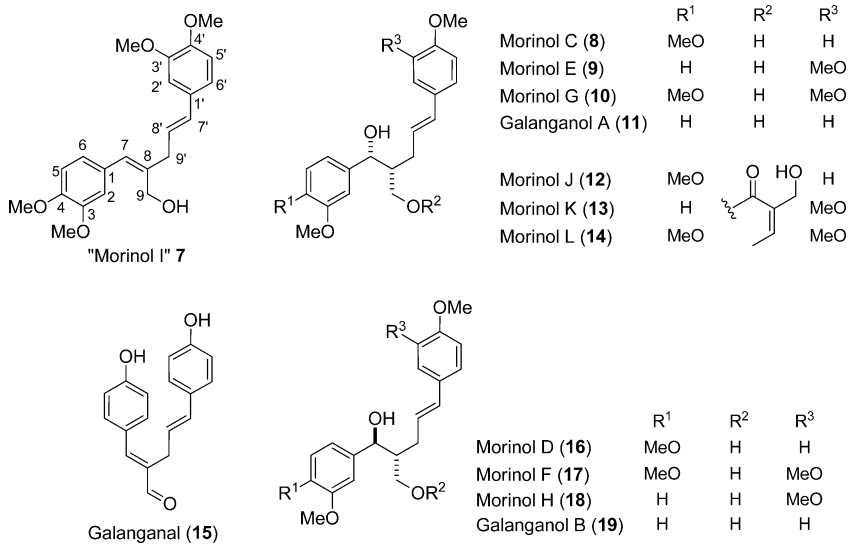
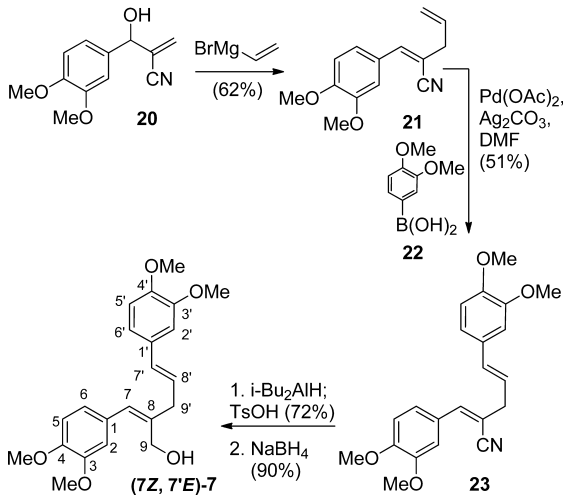


Figure 2. Representative morinol-type lignans.

spectral data of morinol I are available, leaving synthesis as the most promising method for determining the correct structure.[15]

The putative structure **7** of morinol I was rapidly assembled through a five-step sequence featuring a transmissive olefination (Scheme 2).[8] Addition of excess vinylmagnesium bromide to

Scheme 2. Transmissive Olefination Route to "Morinol I"

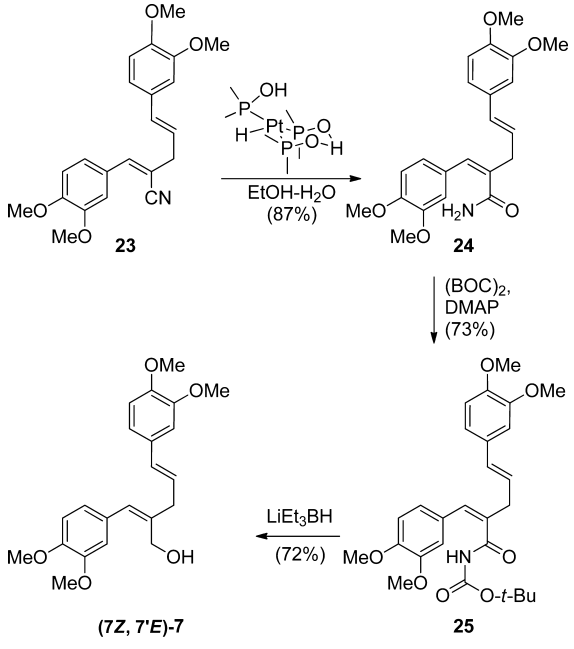


the veratraldehyde-derived nitrile **20**[9,16] afforded the (*Z*)-alkenenitrile **21** that was subjected to a palladium-catalyzed arylation[14a] with (3,4-dimethoxyphenyl)boronic acid (**22**) to provide **23**. Conventional *i*-Bu_2AlH reduction[17] of nitrile **23**, imine hydrolysis, and aldehyde reduction was irreproducible[18] and gave varying ratios of lignan (7*Z*,7′*E*)-**7** and the diastereomer (7*E*,7′*E*)-**7**. Neither (7*Z*,7′*E*)-**7** nor (7*E*,7′*E*)-**7** exhibit spectral data matching that of the natural product, although the NMR chemical shifts, such as the ^1H NMR shift for H7, appeared more consistent with the *Z*-configuration of the C7 olefin.

Using the transmissive olefination strategy to prepare (*Z*)-C7 lignans corresponding to that of morinol I requires a reproducible, stereoselective alkenenitrile to alkenol conversion. The stereoselective reduction of alkenenitriles to allylic alcohols is challenging because olefin isomerization can occur during the *i*-Bu_2AlH reduction–hydrolysis sequence,[19] in reversed nitrile hydrolysis–reduction sequences,[20] and through isomerization of the resulting enal.[21]

After some exploratory forays,[22] a stereoselective hydrolysis, acylation, reduction sequence was developed (Scheme 3). The

Scheme 3. Stereoselective Alkenenitrile to Hydroxymethyl Conversion



sequence exploits the facile platinum-catalyzed hydrolysis of nitriles[23] (**23** → **24**) and the selective reduction of imides.[24] Despite a lack of precedent for the reduction of *alkene*amides,[25] a brief survey of reducing agents and solvent identified $LiBH_4$ in THF as effective for reducing imide **25** to (7*Z*,7′*E*)-alkenol **7** without any trace of the 7*E*-diastereomer.[26]

Having developed a robust method for controlling the stereochemistry of the C7 olefin, (7*Z*,7′*Z*)-**7** was targeted because the data reported for morinol I suggested either the geometry or position of the (7′*Z*)-olefin was incorrect (Scheme

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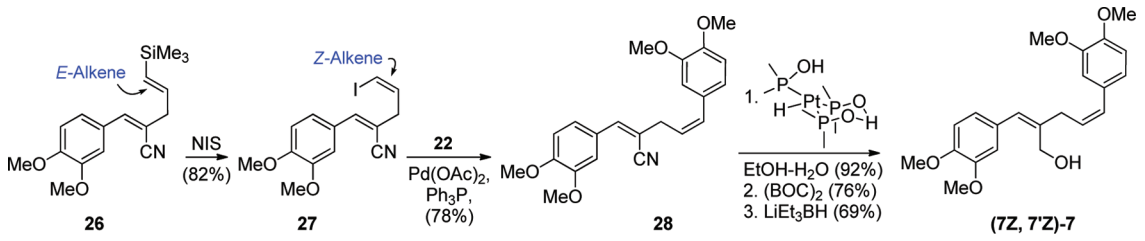
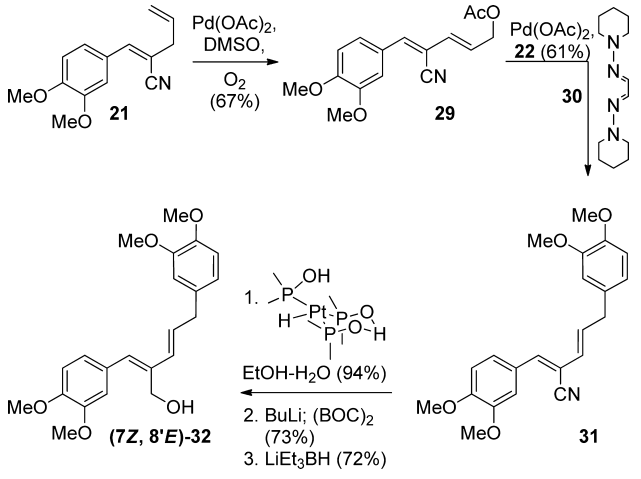
Scheme 4. Invertive Trimethylsilyl Iodine Route to (7Z,7′Z)-7



4). Key to the synthesis of (7Z,7′Z)-7 was the serendipitous discovery[27] that the trimethylsilylalkene **26**, obtained through the transmissive olefination of **20** with trimethylsilylvinylmagnesium bromide (52%),[28] underwent an efficient trimethylsilyl iodine interchange with inversion of stereochemistry. Treating vinylsilane **26** with *N*-iodosuccinimide in 1:1 dichloromethane/hexafluoroisopropanol[29] afforded the (*Z*)-iodide **27**[30] that was subjected to palladium-catalyzed coupling[31] with (3,4-dimethoxyphenyl)boronic acid (**22**) to afford **28** with retention of configuration. Subjecting **28** to the three-step hydrolysis, acylation, and reduction efficiently provided (7Z,7′Z)-7 with no erosion of olefin configuration.

Although morinol analogue (7Z,7′Z)-7 did not exhibit spectral data corresponding to that of the target, during the palladium-catalyzed coupling of **27**, traces of a conjugated dienenitrile were generated which exhibited a ^{1}H NMR methylene signal very similar to that reported for morinol I (δ 3.47 and 3.55, respectively). Attempts to isomerize the dienes (7Z,7′Z)-**28** and (7Z,7′Z)-7 proved fruitless, inspiring a new strategy based on the oxidative acetylation[32] of **21**. Using the "original" oxidative acetylation protocol,[32b] nitrile **21** was smoothly transformed into (7Z,8′E)-**29** (Scheme 5). Palladium-

Scheme 5. Transmissive Olefination Route to the Conjugated Morinol Analogue 32



catalyzed arylation of **29** with (3,4-dimethoxyphenyl)boronic acid (**22**) to afford (7Z,8′E)-dienenitrile **31** proceeded best by employing the hydrazine ligand **30**.[33] A slight modification of the hydrolysis, imide formation, and reduction was required because the conventional Boc-anhydride/DMAP procedure afforded the bis-Boc-acylimidodicarbonate.[34] Deprotonating the intermediate amide with BuLi and adding Boc anhydride afforded the requisite imide that was reduced without incident to the (7Z,8′E)-alcohol **32**. As a point of comparison, the sequential *i*-Bu$_2$AlH reduction, imine hydrolysis, and NaBH$_4$ reduction of nitrile **31** gave a 1:1 mixture of (7Z,8′E)-**32** and (7E,8′E)-**32**. Although (7Z,8′E)-**32** exhibited several ^{1}H NMR resonances similar to that of morinol, significant spectral differences are evident.

Graphing the ^{1}H and ^{13}C chemical shift differences between morinol I and the lignan diastereomers (7Z,7′E)-7, (7E,7′E)-7, (7E,7′Z)-7, (7Z,8′E)-**32**, and (7E,8′E)-**32** highlights the regions having the greatest discrepancy (Figure 3). Large differences in

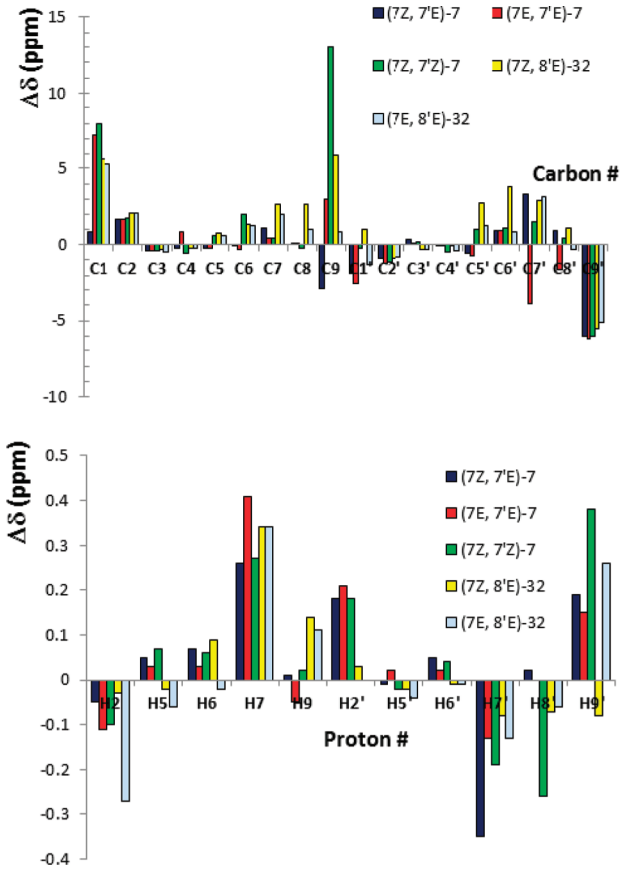


Figure 3. ^{13}C (top) and ^{1}H NMR (bottom) $\Delta\delta$ for morinol analogues.[35]

the ^{13}C chemical shift exist for C9 and C9′ in the pentadiene fragment and for C1 of the aromatic ring.[35] The ^{1}H chemical shift values for the aromatic protons are quite similar, whereas H7, H7′, and H9′ show pronounced differences relative to those reported for morinol I.[35] The lack of clear chemical shift correlations of regions within the synthetic lignans compared to values reported for morinol I leave the exact identity of the natural product in doubt.

Morinol-type lignans are readily assembled through sequential transmissive olefinations and palladium-catalyzed

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couplings. The sequence generates diaryl pentadienes with excellent control over the *E*/*Z* geometry and features a new strategy for converting (*Z*)-dienenitriles into (*Z*)-allylic alcohols. In contrast to the conventional *i*-Bu_2AlH reduction, imine hydrolysis, $NaBH_4$ reduction of alkenenitriles, the platinum-catalyzed hydrolysis, imide formation, and reduction smoothly generate allylic alcohols without any observable isomerization. The versatility of the transmissive olefination and the new reduction strategy is illustrated in the synthesis of five morinol-type lignans in the quest to determine the structure of the elusive natural product morinol I.

EXPERIMENTAL SECTION

(2*Z*,4*E*)-2-(3,4-Dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-4-enamide (24). Solid Parkins[23] catalyst [bis(dimethylphosphinous acid-$_k$P)dimethylphosphinyl-$_k$P-hydridoplatinum(II)] (0.5 mg, 0.0075 mmol) was added to an ethanol/water solution (1:1, 20 mL) of **23** (54.8 mg, 0.15 mmol), and then the reaction mixture was heated to reflux. After 15 h, the solution was cooled, the solvent was evaporated, and then the residue was purified by radial chromatography (70% EtOAc in hexanes) to afford 50.0 mg (87%) of the amide **24** as a white solid: mp 108−109 °C; IR (solid) 3416, 3338, 2935, 1672, 1518 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.31 (d, J = 7.2 Hz, 2H), 3.86 (s, 3H), 3.88 (s, 6H), 3.91 (s, 3H), 5.42 (s, 2H), 6.14 (dt, J = 16.0, 7.2 Hz, 1H), 6.47 (d, J = 16.0 Hz, 1H), 6.57 (s, 1H), 6.82 (dd, J = 8.4, 2.0 Hz, 2H), 6.90−6.97 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.8, 55.9, 56.0, 108.7, 111.0, 111.1, 111.3, 119.3, 121.3, 124.3, 128.3, 130.2, 130.3, 132.3, 135.3, 148.7, 148.9, 149.0, 172.1 ppm; HRMS for $C_{22}H_{25}NO_5$ [M + Na^+] calcd 406.1631, found 406.1619.

***tert*-Butyl-(2*Z*,4*E*)-2-(3,4-dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-4-enoylcarbamate (25).** Solid di-*tert*-butyldicarbonate (43.4 mg, 0.20 mmol) and 4-dimethylaminopyridine (1.2 mg, 0.01 mmol) were added to a rt, CH_2Cl_2 solution (5 mL) of **24** (40 mg, 0.10 mmol). After 20 h, the reaction mixture was poured into dichloromethane (10 mL), the phases were separated, and the organic phase was combined and then washed sequentially with 1 M HCl (10 mL) and water (10 mL). The solvent was evaporated, and the residue was then purified by radial chromatography (30% EtOAc in hexanes) to afford 35.3 mg (73%) of imide **25** as a light yellow oil: IR (neat) 2979, 1777, 1601 cm^{-1}, ^1H NMR ($CDCl_3$, 500 MHz) δ 1.43 (s, 9H), 3.31 (d, J = 7.2 Hz, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 6.22 (dt, J = 11.6, 7.2 Hz, 1H), 6.51 (d, J = 11.6 Hz, 1H), 6.51 (s, 1H), 6.80−7.02 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.8, 38.4, 55.8, 55.9, 84.6, 108.7, 110.8, 111.0, 111.1, 119.4, 124.0, 128.1, 130.5, 130.7, 132.7, 133.5, 148.6, 148.7, 149.0, 149.3, 170.7 ppm; HRMS for $C_{27}H_{33}NO_7$ [M + H^+] calcd 484.2336, found 484.2325.

(2*Z*,4*E*)-2-(3,4-Dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-4-en-1-ol (7*Z*,7′*E*)-7. A THF solution (0.13 mL) of lithium triethylborohydride (0.13 mmol, 1 M) was added to a rt, THF solution (5 mL) of **25** (30 mg, 0.06 mmol). After 2 h, an aqueous solution (10 mL) of 30% H_2O_2 was added. After 30 min, the aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic phase was washed with brine, dried (Na_2SO_4), concentrated, and purified by radial chromatography (30% EtOAc in hexanes) to afford 16.0 mg (72%) of alcohol (7*Z*,7′*E*)-**7** as a light yellow oil: IR (neat) 3520, 2935, 1598 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.59 (br s, 1H), 3.20 (d, J = 7.1 Hz, 2H), 3.88 (s, 6H), 3.89 (s, 3H), 3.91 (s, 3H), 4.34 (s, 2H), 6.20 (dt, J_1 = 15.8 Hz, J_2 = 7.1 Hz, 1H), 6.47 (d, J = 15.8 Hz, 1H), 6.50 (s, 1H), 6.84 (d, J = 8.3 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 6.89 (s, 1H), 6.95 (dd, J_1 = 8.1 Hz, J_2 = 2.0, 1H), 6.98 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.5, 55.8, 55.9, 55.9, 61.3, 108.6, 110.9, 111.1, 112.0, 119.1, 121.2, 126.0, 129.4, 129.8, 130.4, 131.7, 138.5, 148.1, 148.5, 148.6, 149.0 ppm; HRMS for $C_{22}H_{26}O_5$ [M + Na^+] calcd 393.1678, found 393.1696.

(2*Z*,4*E*)-2-(3,4-Dimethoxybenzylidene)-5-(trimethylsilyl)-pent-4-enenitrile (26). Neat 1,2-dibromoethane (0.01 mL, 0.07 mmol) was added to a suspension of Mg (22.4 mg, 0.89 mmol) in cold (0 °C) THF (0.8 mL). Neat (*E*)-(2-(trimethylsilyl)vinyl)bromide (0.09 mL, 0.69 mmol) was added dropwise, and after 1 h at 0 °C, the THF solution of the resulting Grignard reagent was added to a −20 °C THF solution (3 mL) of 2-((3,4-dimethoxyphenyl)(hydroxy)methyl) acrylonitrile **20**[9,16] (50 mg, 0.23 mmol). After 3 h, the reaction mixture was poured into aqueous, saturated NH_4Cl (2 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic phase was washed with brine, dried (Na_2SO_4), concentrated, and purified by radial chromatography (15% EtOAc in hexanes) to afford 36.8 mg (52%) of nitrile **26** as a light yellow oil: IR (neat) 2954, 2206, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ −0.01 (s, 9H), 3.16 (d, J = 6.6 Hz, 2H), 3.92 (s, 3H), 3.94 (s, 3H), 5.88 (d, J = 18.0 Hz, 1H), 6.04 (dt, J = 18.0, 6.6 Hz, 1H), 6.84 (s, 1H), 6.87 (d, J = 7.8 Hz, 1H), 7.19 (dd, J = 7.8, 1.8 Hz, 1H), 7.56 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −1.32, 42.7, 55.9, 106.2, 110.1, 110.7, 119.4, 123.3, 126.6, 134.7, 140.3, 143.9, 148.8, 150.5 ppm; HRMS for $C_{17}H_{23}NO_2Si$ [M + H^+] calcd 302.1577, found 302.1563.

(2*Z*,4*Z*)-2-(3,4-Dimethoxybenzylidene)-5-iodopent-4-enenitrile (27). Solid *N*-iodosuccinimide (146.3 mg, 0.65 mmol) was added to a 0 °C 1,1,1,3,3,3-hexafluoroisopropanol and dichloromethane (1:1) solution (1.6 mL) of **26** (130 mg, 0.43 mmol). After 10 min, the reaction mixture was poured into an aqueous, saturated NH_4Cl solution (2 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic phase was washed with brine, dried (Na_2SO_4), concentrated, and purified by radial chromatography (15% EtOAc in hexanes) to afford 125 mg (82%) of nitrile **27** as a light yellow oil: IR (neat) 2934, 2206, 1597 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.26 (d, J = 6.6 Hz, 2H), 3.93 (s, 3H), 3.94 (s, 3H), 6.39 (dt, J = 7.6, 7.6 Hz, 1H), 6.57 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.95 (s, 1H), 7.21 (dd, J = 8.4, 2.4 Hz, 1H), 7.52 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.8, 55.9 (2), 86.6, 104.0, 110.2, 110.7, 119.2, 123.4, 126.3, 135.6, 144.3, 148.8, 150.7 ppm; HRMS for $C_{14}H_{14}NO_2I$ [M + Na^+] calcd 377.9967, found 377.9944.

(2*Z*,4*Z*)-2-(3,4-Dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-4-enenitrile (28). Solid (3,4-dimethoxyphenyl)boronic acid (87.8 mg, 0.46 mmol), palladium acetate (14.0 mg, 0.06 mmol), and triphenyl phosphine (32.5 mg, 0.12 mmol) were added to a rt, THF solution (8 mL) of **27** (100.0 mg, 0.31 mmol). After 12 h, the reaction mixture was poured into water (2 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic phase was washed with brine, dried (Na_2SO_4), concentrated, and purified by radial chromatography (30% EtOAc in hexanes) to afford 88.3 mg (78%) of nitrile **28** as a light yellow oil: IR (neat) 2931, 2206 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.39 (d, J = 7.8 Hz, 2H), 3.89 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 5.72 (dt, J = 11.4, 7.2 Hz, 1H), 6.67 (d, J = 11.4 Hz, 1H), 6.83 (s, 1H), 6.85−6.89 (m, 3H), 6.91 (s, 1H), 7.19 (dd, J = 8.4, 1.8 Hz, 1H), 7.53 (d, J = 1.8 Hz, 1H); NOESY correlations between δ 5.72 and 6.67 established the *Z*-configuration of the disubstituted olefin; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.7, 55.9 (2), 106.8, 110.3, 110.8, 111.0, 111.9, 119.5, 121.1, 123.2, 124.9, 126.6, 129.3, 132.5, 143.6, 148.3, 148.7, 149.0, 150.7 ppm; HRMS for $C_{22}H_{23}NO_4$ [M + Na^+] calcd 388.1525, found 388.1512.

(2*Z*,4*Z*)-2-(3,4-Dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-4-enamide (i). Solid Parkins[23] catalyst [bis(dimethylphosphinous acid-$_k$P)dimethylphosphinyl-$_k$P-hydridoplatinum(II)] (0.6 mg, 0.01 mmol) was added to an ethanol/water solution (1:1, 20 mL) of **28** (80 mg, 0.22 mmol), and then the reaction was heated to reflux. After 15 h, the solvent was evaporated and the residue was purified by radial chromatography (70% EtOAc in hexanes) to afford 95.1 mg (92%) of amide **i** as a white solid: mp 101−102 °C; IR (solid) 3411, 3339, 2934, 2836, 1677, 1601 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.48 (d, J = 7.6 Hz, 2H), 3.88 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 5.43 (s, 2H), 5.75 (dt, J = 11.6, 7.6 Hz, 1H), 6.59 (s, 1H), 6.61 (d, J = 11.6 Hz, 1H), 6.80−7.00 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.1, 55.9 (2), 111.0, 111.3, 111.9, 121.2 (2), 126.3, 128.3, 129.8 (2), 131.4, 135.2, 148.1, 148.7, 148.8, 172.3 ppm; HRMS for $C_{22}H_{25}NO_5$ [M + Na^+] calcd 406.1631, found 406.1618.

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***tert*-Butyl-((2*Z*,4*Z*)-2-(3,4-dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-4-enoyl)carbamate (ii).** Solid di-*tert*-butyl dicarbonate (136.8 mg, 0.63 mmol) and 4-dimethylaminopyridine (2.9 mg, 0.02 mmol) were added to a CH_2Cl_2, rt, solution (5 mL) of **i** (90 mg, 0.24 mmol). After 20 h, the reaction mixture was poured into dichloromethane (10 mL) and washed sequentially with 1 M HCl (10 mL) and water (10 mL). The solvent was evaporated, and the residue was then purified by radial chromatography (30% EtOAc in hexanes) to afford 88.3 mg (76%) of imide **ii** as a light yellow oil: IR (neat) 3296, 2930, 1766, 1686 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.38 (s, 9H), 3.45 (d, J = 7.8 Hz, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 5.73 (dt, J = 11.4, 7.2 Hz, 1H), 6.61 (d, J = 6.0 Hz, 1H), 6.62 (d, J = 6.0 Hz, 1H), 6.80–6.92 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.8, 33.6, 55.8, 55.9 (2), 82.7, 110.7, 110.8, 110.9, 111.6, 121.2, 125.6, 127.8, 129.6, 131.8, 134.6, 148.1, 148.6, 148.8, 149.0, 149.1 ppm; HRMS for $C_{27}H_{33}NO_7$ [M + Na^+] calcd 506.2155, found 506.2155.

(1*Z*,4*Z*)-1,5-Bis(3,4-dimethoxyphenyl)penta-1,4-dien-2-ol (7*Z*,7′*Z*)-7. A THF solution (0.34 mL) of lithium triethylborohydride (0.34 mmol, 1 M) was added to a rt, THF solution (5 mL) of **ii** (80 mg, 0.17 mmol). After 2 h, an aqueous 30% solution (10 mL) of H_2O_2 was added. After 30 min, the aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic phase was washed with brine, dried (Na_2SO_4), concentrated, and purified by radial chromatography (30% EtOAc in hexanes) to afford 43.4 mg (69%) of alcohol (7*Z*,7′*Z*)-**7** as a light yellow oil: IR (neat) 3517, 2925, 1514 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.28 (s, 1H), 3.36 (d, J = 7.6 Hz, 2H), 3.88 (s, 6H), 3.89 (s, 3H), 3.91 (s, 3H), 4.35 (s, 2H), 5.82 (dt, J_1 = 11.6 Hz, J_2 = 7.6 Hz, 1H), 6.51(s, 1H), 6.66 (d, J = 11.6 Hz, 1H), 6.86 (d, J = 7.2 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 6.89 (s, 1H), 6.86 (d, J = 7.2 Hz, 1H), 6.93 (s, 1H), 6.94 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 34.7, 55.9 (3), 77.2, 110.9, 111.9, 112.0, 121.1, 121.2, 128.0, 129.0, 130.0, 131.0, 138.7, 148.0 ppm; HRMS for $C_{22}H_{26}O_5$ [M + Na^+] calcd 393.1678, found 393.1691.

(2*E*,4*Z*)-4-Cyano-5-(3,4-dimethoxyphenyl)penta-2,4-dien-1-yl Acetate (29). Solid 1,4-benzoquinone (37.7 mg, 0.35 mmol), palladium acetate (4.0 mg, 0.02 mmol), and 4 Å MS were added to a DMSO/AcOH solution (1:1, 5 mL) of **21** (40 mg, 0.17 mmol). The reaction was maintained at 40 °C under an air atmosphere using an air-filled balloon to maintain a slight positive pressure. After 72 h, the reaction mixture was poured into EtOAc (10 mL), the phases were separated, and the organic phase was washed with water (3 × 5 mL), dried (Na_2SO_4), concentrated, and purified by radial chromatography (20% EtOAc in hexanes) to afford 203 mg (67%) of nitrile **29** as a light yellow oil: IR (neat) 2254 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.14 (s, 3H), 3.95 (s, 3H), 3.96 (s, 3H), 4.74 (d, J = 6.0 Hz, 2H), 6.25 (dt, J = 15.8 Hz, 6.0 Hz, 1H), 6.41 (d, J = 15.8 Hz, 1H), 6.74 (s, 1H), 6.91 (d, J = 8.6 Hz, 1H), 7.01 (s, 1H), 7.27 (dd, J = 8.6 Hz, 2.2 Hz, 1H) 7.63 (d, J = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 21.0, 56.0, 63.8, 107.0, 110.6, 110.9, 116.2, 116.8, 124.5, 126.4, 127.0, 130.8, 144.4, 149.1, 151.4, 170.7 ppm; HRMS for $C_{16}H_{17}NO_4K$ [M + K^+] calcd 326.0789, found 326.0820.

(2*Z*,3*E*)-2-(3,4-Dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-3-enenitrile (31). Solid (3,4-dimethoxyphenyl)boronic acid (115 mg, 0.63 mmol) was added to a rt DMF (1.5 mL) and H_2O (0.5 mL) solution of **29** (150 mg, 0.522 mmol), K_2CO_3 (144 mg, 1.044 mmol), $Pd(OAc)_2$ (2.33 mg, 0.01 mmol), and ligand (*N*,*N*′*E*,*N*,*N*′*E*)-*N*,*N*′-(ethane-1,2-diylidene)bis-(piperidin-1-amine)[33] (2.31 mg, 0.01 mmol). After 1 h, the mixture was diluted with EtOAc and H_2O (10 mL, 1:1). The organic layer was separated, the aqueous phase was extracted with EtOAc (2 × 10 mL), and the combined organic phase was washed with brine, dried (Na_2SO_4), concentrated, and purified by radial chromatography (30% EtOAc in hexanes) to afford 116 mg (61%) of **31** as a white solid (mp 102–104 °C): IR 1025, 1144, 1265, 1514, 1554, 1627, 2214, 2836, 2934 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.49 (d, J = 7.0 Hz, 2H), 3.88 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 6.10 (d, J = 15.3 Hz, 1H), 6.38 (dt, J = 15.3, 6.8 Hz, 1H), 6.72–6.77 (m, 2H), 6.83–6.89 (m, 3H), 7.22 (dd, J = 8.4, 2.3 Hz, 1H), 7.58 (d, J = 2.3 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 400 MHz) δ 38.4, 55.9, 56.0, 108.1, 110.5, 110.9, 111.4, 112.0, 117.2, 120.7, 123.9, 126.8, 128.4, 131.6, 133.9, 142.2, 147.7, 149.0, 150.9 ppm; HRMS for $C_{22}H_{23}NO_4$ [M + Na^+] calcd 388.1519, found 388.1521.

(2*Z*,4*E*)-2-(3,4-Dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-4-enamide (iii). Solid Parkins[23] catalyst (bis(dimethylphosphinous acid-$_k$P)dimethylphosphinyl-$_k$P-hydridoplatinum(II)) (4.5 mg, 0.5 mol %, 0.01 mmol) was added to an ethanol–water (1:1, 20 mL) solution of **31** (75 mg, 0.21 mmol), and then the reaction was heated to reflux. After 15 h, the solvent was evaporated and the residue was purified by radial chromatography (70% EtOAc in hexanes) to afford 74 mg (94%) of the amide **iii** as a white solid: mp 144–146 °C; IR 3412, 3338, 1677 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.45 (d, J = 4.8 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 3.88 (s, 6H), 5.56 (br, s, 1H), 5.60 (br, s, 1H), 6.08–6.14 (m, 2H), 6.39 (s, 2H), 6.72–6.75 (m, 2H), 6.80–6.82 (m, 2H), 6.99–7.04 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 400 MHz) δ 38.8, 55.8, 55.9, 56.0, 111.0, 111.2, 111.3, 112.1, 120.7, 121.8, 128.1, 129.5, 130.2, 132.1, 135.0, 147.5, 148.8, 148.9, 149.1, 171.5 ppm; HRMS for $C_{22}H_{25}NO_5$ [M + Na^+] calcd 406.1625, found 406.1632.

***tert*-Butyl-((2*Z*,3*E*)-2-(3,4-dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-3-enoyl)carbamate (iv).** A cyclohexane solution of BuLi (2.0 M, 0.156 mmol) was added dropwise to a −78 °C THF (3 mL) solution of **iii** (60 mg, 0.156 mmol). After 1 h, a THF (1.0 mL) solution of di-*tert*-butyl dicarbonate (34 mg, 0.156 mmol) was added, and the reaction mixture was then allowed to warm slowly to room temperature. After 16 h, saturated, aqueous ammonium chloride (3 mL) was added followed by H_2O (5 mL). The organic layer was separated, the aqueous phase was extracted with EtOAc (2 × 10 mL), and the combined organic phase was washed with brine, dried (Na_2SO_4), concentrated, and purified by radial chromatography (50% EtOAc in hexanes) to afford 52 mg (68%) of **iv** as a pale yellow gummy liquid: IR 3280, 2934, 1767, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39 (s, 9H), 3.44 (d, J = 5.8 Hz, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 5.94–6.0 (m, 1H), 6.13 (d, J = 15.6 Hz, 1H), 6.44 (s, 1H), 6.71–6.74 (m, 2H), 6.79–6.82 (m, 2H), 6.90–6.93 (m, 2H), 7.30 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 400 MHz) δ 27.8, 38.8, 55.83, 55.89, 55.92, 55.98, 56.0, 82.9, 110.7, 111.1, 111.3, 112.1, 120.7, 132.0, 134.3, 136.0, 147.6, 148.9, 149.1, 149.3 ppm; HRMS for $C_{27}H_{33}NO_7Na$ [M + Na^+] calcd 506.2149, found 506.2142.

(2*Z*,3*E*)-2-(3,4-Dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-3-en-1-ol (7*Z*,9′*E*)-32. A THF solution (5 mL) of lithium triethylborohydride (0.17 mL, 0.17 mmol) was added to a 0 °C THF solution (3 mL) of **iv** (40 mg, 0.083 mmol), and then the solution was allowed to warm slowly to rt. After 2 h, an aqueous 30% solution of H_2O_2 (6 mL) was added. After 30 min, the aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic phase was washed with brine, dried (Na_2SO_4), concentrated, and purified by radial chromatography (30% EtOAc in hexanes) to afford 19 mg (62%) of (7*Z*,9′*E*)-**32** as a light yellow oil: IR 1023, 1138, 1232, 1258, 1511, 1593, 1709, 2835, 2932, 3510 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.47 (d, J = 6.5 Hz, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 4.47 (br, d, 2H), 6.11 (dt, J_1 = 15.8 Hz, J_2 = 6.5 Hz, 1H), 6.20 (d, J = 15.8 Hz, 1H), 6.58 (s, 1H), 6.74 (d, J = 2.0 Hz, 1H), 6.77 (dd, J_1 = 8.0 Hz, J_2 = 2.0, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.97 (dd, J_1 = 8.3 Hz, J_2 = 2.0 Hz, 1H), 7.00 (d, J = 2.0 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 400 MHz) δ 39.1, 55.87, 55.90, 55.92, 55.98, 58.3, 111.0, 111.3, 112.0, 112.2, 120.5, 121.7, 129.1, 129.6, 132.7, 133.1, 133.3, 136.4, 147.5, 148.5, 148.7, 149.0 ppm; HMBC correlation of the ^1H NMR hydroxymethyl signal at δ 3.47 with the olefinic ^{13}C signals at δ 133.3 and 136.4 confirms that the olefins are conjugated; HRMS for $C_{22}H_{26}O_5Na$ [M + Na^+] calcd 393.1672, found 393.1697.

(2*E*,3*E*)-2-(3,4-Dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-3-en-1-ol (7*Z*,9′*E*)-32 and (7*E*,9′*E*)-32. A cyclohexane solution of diisobutylaluminum hydride (1.0 M, 0.58 mmol) was added dropwise to a −78 °C toluene (4 mL) solution of **31** (100 mg, 0.274 mmol). The cooling bath was removed and the reaction allowed to slowly warm to rt. After 3 h, the reaction mixture was cooled to −78 °C and ethanol (1 mL) and aqueous acetic acid (50%, 1 mL) were added sequentially. After 15 min, the solution was

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allowed to warm to rt, the organic layer was separated, the aqueous phase was extracted with EtOAc (2 × 10 mL), and the combined organic phase was washed with water, aqueous $NaHCO_3$, and brine and then dried (Na_2SO_4) and concentrated to give the corresponding aldehyde (96 mg). The crude aldehyde (96 mg) was dissolved in methanol (7 mg, 0.30 mmol) at room temperature, and solid $NaBH_4$ was then added portionwise. After 15 min, saturated aqueous ammonium chloride (2 mL) was added, followed by water. The crude mixture was extracted with EtOAc (2 × 10 mL), NS the combined organic phase was washed with brine, dried (Na_2SO_4), concentrated, and purified by radial chromatography (35% EtOAc in hexanes) to afford 57 mg (56%) of a 1:1 mixture of alcohols (7*Z*,9′*E*)-**32** and (7*E*, 9′*E*)-**32** as a pale yellow oily liquid. For (7*E*,9′*E*)-**32**: IR 3504, 2933, 1592 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.42 (d, J = 6.9 Hz, 2H), 3.86 (s, 9H), 3.90 (s, 3H), 4.44 (br d, J = 2.8 Hz, 2H), 6.12 (dt, J_1 = 16.2 Hz, J_2 = 6.9 Hz, 1H), 6.56 (d, J = 16.2 Hz, 1H), 6.58 (s, 1H), 6.71 (s, 1H), 6.73 (d, J = 8.5, 1H), 6.82 (d, J = 8.5, 1H), 6.84 (d, J = 8.6 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 6.86 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 400 MHz) δ 39.4, 55.8, 55.9, 55.9, 56.0, 110.86, 111.3, 111.9, 112.6, 120.4, 122.2, 126.9, 128.2, 129.7, 131.3, 132.6, 136.1, 147.5, 148.2, 149.0 ppm; HRMS for $C_{22}H_{26}O_5Na$ [M + Na^+] calcD 393.1672, found 393.1704.

■ ASSOCIATED CONTENT

Supporting Information

^1H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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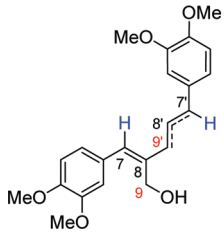

	H7	H7'	C9	C9'
"Morinol I"	6.24	3.55	64.2	127.2
(7*Z*, 7′*E*)-**7**	6.50	3.20	61.3	121.2
(7*E*, 7′*E*)-**7**	6.65	3.42	67.2	121.0
(7*Z*, 7′*Z*)-**7**	6.51	3.36	77.2	121.2
(7*Z*, 9′*E*)-**32**	6.58	3.47	58.3	121.7
(7*E*, 9′*E*)-**32**	6.58	3.42	65.4	122.1

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