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Novel stereoselective syntheses of (2*E*,4*E*)-4-(4,4-dimethylpent-2-ynylidene)-N^1,N^5-dimethyl-N^1,N^5-bis(naphthalen-1-ylmethyl)pent-2-ene-1,5-diamine

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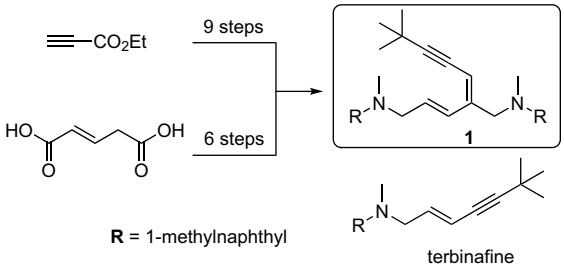
ABSTRACT

We report two different synthetic approaches for the stereoselective synthesis of (2*E*,4*E*)-4-(4,4-dimethylpent-2-ynylidene)-N^1,N^5-dimethyl-N^1,N^5-bis(naphthalen-1-ylmethyl)pent-2-ene-1,5-diamine **1**, an important impurity-reference standard for the chemical characterization of terbinafine. The diamine **1** was obtained in only six steps with a good overall yield starting from commercially available glutaconic acid.

1. Introduction

Pharmaceutical impurities consist of reaction by-products generated during the synthesis of active pharmaceutical ingredients (APIs) and degradation products formed during the formulation manufacturing process and/or the storage of the APIs. The presence of these unwanted chemicals, also referred to as 'related substances', even in small amounts may influence the efficacy and safety of the pharmaceutical products. Indeed, the presence of such impurities and their levels in the drug products are indicative of the product quality and can imply a risk to patient safety.

Impurity profiling (i.e., the identity as well as the quantity of the impurity in the pharmaceuticals) is now receiving important critical attention from regulatory authorities: limits of impurities present in the APIs and formulations are incorporated to different pharmacopoeias. Moreover, the International Conference of Harmonization (ICH) has formulated a workable guideline regarding the control of impurities.[1] Although these impurities are usually present at very low levels, it is imperative to characterize their identities in order to make proactive decisions with respect to optimization of synthesis routes and formulation development and ultimately to design a control strategy for manufacturing process. For this reason, there is a significant demand for impurity-reference standards along with and the API-reference standards for both regulatory authorities and pharmaceutical companies. The work reported here was directed toward the development of two feasible new synthetic routes to (2*E*,4*E*)-4-(4,4-dimethylpent-2-ynylidene)-N^1,N^5-dimethyl-N^1,N^5-bis(naphthalen-1-ylmethyl)pent-2-ene-1,5-diamine **1**[2] (Scheme 1) intended as impurity-reference standard for the chemical characterization of terbinafine, an orally and topically active antifungal agent.[3]



Scheme 1.

2. Results and discussion

Construction of the dienyne system poses a number of synthetic challenges, the most arduous of which is apparently the stereoselective formation of the *E*-configured trisubstituted double bond. This stereochemical issue could be obviated starting from the easily accessible (*Z*)-ethyl 2,3-dibromoprop-2-enoate **2**,[4] which has been shown to undergo two successive coupling reactions to afford in a highly stereoselective manner 2,3-disubstituted (*Z*)-propenoates.[5]

Two consecutive Sonogashira couplings with 3,3-dimethylbut-1-yne and propargyl alcohol, according to the retrosynthetic pathway summarized in Scheme 2, should deliver the whole carbon framework to which two molecules of *N*-methyl-1-(naphthalen-1-yl)methanamine could be simultaneously attached by a substitution reaction. The use of propargyl alcohol as a coupling agent should play

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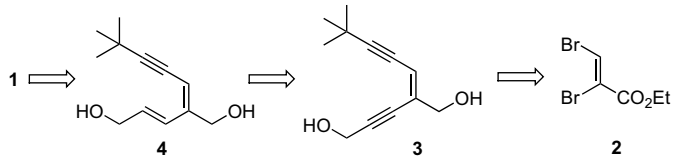


Scheme 2. Retrosynthetic analysis of compound **1**.

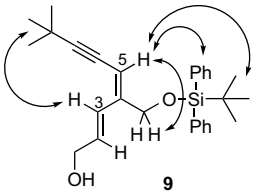


Figure 1. Selected NOEs exhibited by compound **9**.

a dual role, allowing the chemo- and stereoselective reduction of the propargylic triple bond to an *E*-configured alkene by the action of sodium bis(2-methoxyethoxy)aluminum dihydride (Red-Al®).[6]

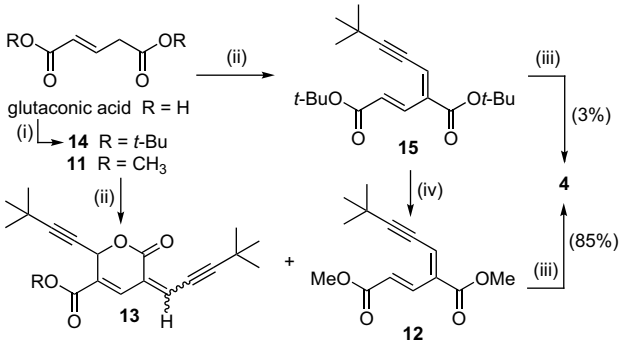
The starting (*Z*)-ethyl 2,3-dibromoprop-2-enoate **2**, readily available by bromination of ethyl propiolate,[4] was coupled with 3,3-dimethylbut-1-yne employing the Pd-modified version of the Castro–Stephens reaction[7] to give the enyne **5** in 64% yield (Scheme 3). Reduction of the ester with DIBALH followed by protection of the resultant alcohol as a *tert*-butyldiphenyl silyl ether afforded the (*Z*)-vinyl bromide **7** in 31% yield over two steps. Attempts to couple **7** with propargyl alcohol by applying the same experimental conditions as in the first Sonogashira reaction met with failure. Several reaction variables were investigated including palladium and copper source, catalyst loading, solvent, and base. As a result, the choice of base proved to have the most significant influence on the product formation. The use of piperidine,[8] all other experimental conditions being unchanged, led to the desired endiyne **8** in 79% isolated yield. Stereoselective reduction of the triple bond adjacent to the hydroxy group with Red-Al® afforded in moderate yields the dienyne **9**.

The *E* configuration of the newly created double bond was confirmed by the 16.3 Hz coupling constant correlating the two relevant hydrogen atoms. The NOESY spectrum of dienyne **9** proved the *E* configuration of the trisubstituted double bond. Relevant NOE correlations are indicated by curved arrows in Figure 1.

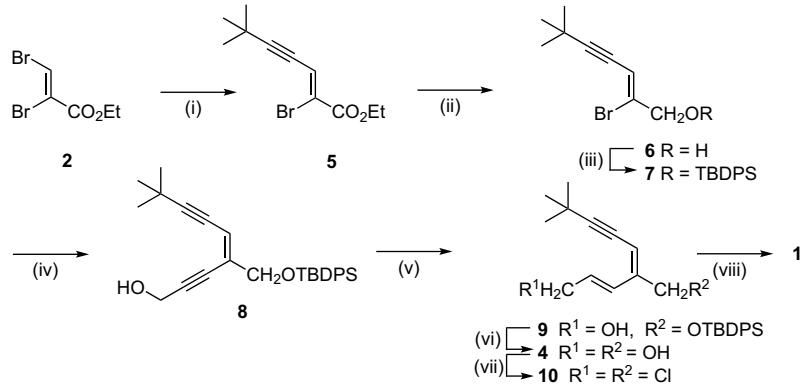
Removal of the silyl ether protecting group of **9** by reaction with TBAF afforded the diol **4** in 75% yield. Mesylation under standard conditions gave a mixture of three products corresponding to the dichloro compound and an about equimolar mixture of the two monomesyl-monochloro derivatives. In order to make easier the purification procedure, the reaction was carried out in the presence of TBAC, thus maximizing the formation of the dichloro derivative **10**, that could be isolated in 80% yield. Nucleophilic substitution with excess *N*-methyl-1-(naphthalen-1-yl)methanamine in DMF gave the final product **1** in 90% yield. Although the above synthetic scheme was shown to be successful within the limits of its purpose, that is the preparation of a small amount of **1** as a reference standard, the length of the synthetic sequence (nine linear steps), the use of expensive Pd catalysts in two steps, and the modest overall yield could strongly limit its attractiveness, particularly in industrial laboratories. As a consequence, it seemed to us more useful to design a new synthetic approach to **1** rather than embark on the usually tedious optimization of each single step of the previous synthesis.

Focusing our attention on the key intermediate diol **4**, we reasoned that its whole carbon skeleton could be assembled through an aldol condensation between the enolate of a dialkyl pent-2-enedioate (glutaconate) and 4,4-dimethylpent-2-ynal (Scheme 4). Dehydration of the resulting propargylic alcohol and reduction of both ester groups should afford the target diol **4**. The most critical aspect of this simplified sequence is the stereochemical outcome of the elimination step leading to the trisubstituted double bond. However, Lewin and Carrol reported that a trisubstituted double bond with the desired *E* configuration could be directly formed by the base-promoted condensation of dimethyl β-methylglutaconate and a conjugated aldehyde.[9] In practice, reaction at −78 °C of the lithium enolate of commercial dimethyl glutaconate **11** with 4,4-dimethylpent-2-ynal[10] followed by warming to 0 °C to drive the reaction to completion gave directly the dienyne **12** albeit in isolated yields not higher than 43% (Scheme 4).

Several attempts to further improve yields by varying the base, temperature, and quenching agents were to no avail. We were able



Scheme 4. Reagents: (i) BOC_2O, DMAP, *t*-BuOH (74%); (ii) (*t*-Bu)C≡CCHO, LDA, THF, −78 °C (85%); (iii) DIBALH, $PhCH_3$, −78 °C (85%); (iv) MeOH, H_2SO_4, 80 °C (95%).



Scheme 3. Reagents: (i) (*t*-Bu)C≡CH, $Pd(PPh_3)_4$, CuI, (*i*-Pr)$_2$NH, DMF (64%); (ii) DIBALH, DCM, −78 °C (64%); (iii) *tert*-butylchlorodiphenylsilane, Et_3N, DMAP, DCM (57%); (iv) CH≡CCH_2OH, $Pd(PPh_3)_4$, CuI, piperidine, DMF (79%); (v) Red-Al®, THF, −30 °C (26%); (vi) TBAF, THF (75%); (vii) MsCl, TBAC, Et_3N, DCM (80%); (viii) *N*-methyl-1-(naphthalen-1-yl)-methanamine, DMF (90%).

to isolate in pure form a major side product (20% yield) identified as the lactone **13**. Although our data do not speak directly to the order of events governing this overall transformation, an obvious sequence could be the δ-lactonization of the β-alkoxy ester derived by an initial aldol reaction followed by deprotonation of the unsaturated lactone, α-addition of a second aldehyde molecule onto the resulting dienolate, and final E1cB elimination to give **13**.

Spectroscopic data (^{1}H and ^{13}C NMR, see S14 and S15 in Supplementary data) indicated that **13** was formed as a single diastereoisomer, but the configuration of the trisubstituted exocyclic double bond was not assigned as the NOESY spectrum did not give unambiguous results. The use of sterically more demanding ester functions could prevent the aforementioned δ-lactonization from being a competitive pathway.

Thus, when the di-*tert*-butylester **14** was substituted for the former dimethyl ester **11**, the aldol condensation yields improved to 85% under similar experimental conditions, affording compound **15**. However the preparation of the unknown di-*tert*-butyl glutaconate **14** from the corresponding acid was not trivial. After several attempts[11] we eventually found that reaction of glutaconic acid with di-*tert*-butyl dicarbonate in *t*-BuOH with catalytic DMAP[12] afforded the corresponding di-*tert*-butylester in an acceptable 74% yield. Unfortunately, the following reduction of diester **15** with DIBALH gave only trace amounts of the desired diol **4**, even under forcing reaction conditions. The use of other reducing agents gave no better results. This poor reactivity toward hydride reagents can be ascribed to the steric hindrance of the bulky *tert*-butyl group since the correponding dimethyl ester **12** was shown to undergo smooth DIBALH reduction to the diol **4** in 85% yield. A somewhat awkward, but high yielding, circumvention was therefore inevitable. Transesterification of the di-*tert*-butylester **15** with sulfuric acid in methanol gave the corresponding dimethyl ester in 95% yield, pure enough to carry on the next reduction step without any chromatographic purification. The diol **4**, obtained as detailed above, was identical in all respects to that prepared following the first synthetic sequence.

3. Conclusion

In summary, two different syntheses of **1** were developed having in common the intermediate diol **4**, which could be prepared in 50% yield and only four steps starting from glutaconic acid. The key step is an aldol condensation followed by in situ stereoselective E1cB elimination. The alternative approach starting from ethyl propargylate, based on two consecutive Sonogashira couplings, required three more synthetic steps and gave an overall lower yield.

Experiments are underway to study the scope of the aldol addition–elimination process in order to develop a general methodology for the stereoselective synthesis of various highly substituted (*E*,*E*) 1,3-diene-4-yne systems.

4. Experimental section

4.1. General experimental details

Common reagents and materials were purchased from commercial sources and purified by recrystallization or distillation. Solvents were purified according to the guidelines in Purification of Laboratory Chemicals.[13] Diisopropylamine, diisopropylethylamine, and triethylamine were distilled from CaH_2 prior to use. Yields were calculated for compounds purified by flash chromatography and judged homogeneous by thin-layer chromatography, NMR, and mass spectrometry. Thin-layer chromatography was performed on Merck Kieselgel 60 F_{254} plates eluting with solvents indicated, visualized by a 254 nm UV lamp, and stained with aqueous ceric molybdate solution or iodine and a solution of 4,4′-methylenebis-*N*,*N*-dimethylaniline, ninhydrin, and KI in an aqueous ethanolic solution of AcOH. Flash chromatography was performed on Merck Kieselgel 60 (230–400 mesh). Nuclear magnetic resonance spectra were acquired at 400 MHz for ^{1}H and 100 MHz for ^{13}C. The abbreviatons s, d, t, q, br s, and m stand for the resonance multiplicities singlet, doublet, triplet, quartet, broad singlet, and multiplet, respectively. In the peak listing of ^{13}C spectra abbreviations s and t refer to zero and two protons attached to the carbons, as determined by DEPT-135 experiments. Glassware for all reactions was oven-dried at 110 °C and cooled in a desiccator, or flame-dried and cooled under a stream of nitrogen or argon prior to use. Liquid reagents and solvents were introduced by oven-dried syringes through septa-sealed flasks under an inert atmosphere.

4.2. (*Z*)-Ethyl 2-bromo-6,6-dimethylhept-2-en-4-ynoate (5)

A solution of (*Z*)-ethyl 2,3-dibromoprop-2-enoate (2.00 g, 7.75 mmol) in dry DMF (6 mL) was alternatively evacuated and flushed with nitrogen. The flask was cooled in ice and tetrakis-(triphenylphosphine) palladium (0.073 g, 0.063 mmol) and cuprous iodide (0.098 g, 0.52 mmol) were added in sequence. The reaction mixture was allowed to warm to room temperature and a solution of 3,3-dimethylbut-1-yne (1.34 mL, 10.86 mmol) and diisopropylamine (1.5 mL, 10.86 mmol) in DMF (2 mL) was added. The color turned from green to orange-red. After 2 h stirring, additional tetrakis(triphenylphosphine) palladium (0.073 g, 0.063 mmol) and cuprous iodide (0.098 g, 0.52 mmol) were added. When TLC analysis (hexane/ethyl acetate 97:3, double run) indicated consumption of the starting dibromide, the reaction mixture was poured into a saturated $NaHCO_3$ solution and the mixture extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo to give a brown oil. Flash chromatography with hexane/diethyl ether (98:2) afforded 1.29 g of **5** as a brown oil (64%). R_f 0.34 (hexane/diethyl ether 98:2). IR (neat, cm^{-1}) 1727, 2193, 2226. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 9H), 1.35 (t, J=7.1 Hz, 3H), 4.31 (q, J=7.1 Hz, 2H), 7.30 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 29.3 (s), 30.8, 63.0 (t), 77.1 (s), 116.0 (s), 123.1 (s), 125.5, 162.7 (s). MS (EI) m/z (% rel intensity)=258.0 (13.9) [M$^+$, ^{79}Br], 260.0 (13.9) [M$^+$, ^{81}Br], 229.0 (32.6) [M$^+$, ^{79}Br], 231.0 (32.6) [M$^+$, ^{81}Br], 149.0 (61.2) [M$^+$], 91.0 (100) [M$^+$]. Anal. Calcd for $C_{11}H_{15}BrO_2$: C, 50.98; H, 5.83. Found: C, 50.96; H, 5.81.

4.3. (*Z*)-2-Bromo-6,6-dimethylhept-2-en-4-yn-1-ol (6)

To a solution of the bromo ester **5** (1.00 g, 3.86 mmol) in dry toluene (19 mL) maintained at −78 °C under nitrogen was added dropwise a 1 M CH_2Cl_2 solution of DIBALH (8.5 mL). When TLC analysis (hexane/ethyl acetate 8:2) indicated consumption of the starting ester, typically 1 h, the reaction mixture was allowed to warm to 0 °C and quenched by addition of a water solution (10 mL) of tartaric acid (0.30 g). The aqueous layer was extracted with a 1:1 mixture of hexane/ethyl acetate and the combined organic phases were dried over Na_2SO_4, filtered, and evaporated in vacuo to give a yellow oil. Purification by flash chromatography (hexane/ethyl acetate 82:18) gave pure **6** as a yellow oil (0.538 g, 64%). R_f 0.34 (hexane/ethyl acetate 82:18). IR (neat, cm^{-1}) 1007, 1617, 2208, 2233, 3318. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 9H), 1.85–2.08 (br s, 1H, exchanges with D_2O), 4.33 (s, 2H), 6.25 (t, J=1.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.8 (s), 31.2, 68.1 (t), 76.1 (s), 106.2 (s), 111.9, 135.3 (s). MS (EI) m/z (% rel intensity)=216.0 (16.5) [M$^+$, ^{79}Br], 218.0 (16.5) [M$^+$, ^{81}Br], 201.0 (9.9) [M$^+$, ^{79}Br], 203.0 (9.9) [M$^+$, ^{81}Br], 137.0 (21.5) [M$^+$], 122.0 (100) [M$^+$], 91.0 (64.5) [M$^+$]. Anal. Calcd for $C_9H_{13}BrO$: C, 49.79; H, 6.04. Found: C, 49.83; H, 6.06.

4.4. (*Z*)-(2-Bromo-6,6-dimethylhept-2-en-4-ynyloxy)(*tert*-butyl) diphenylsilane (7)

To an ice cooled solution of the alcohol **6** (0.40 g, 1.84 mmol) in dichloromethane (13 mL) containing distilled triethylamine (1.29 mL, 9.2 mmol) and DMAP (0.07 g, 0.57 mmol) under nitrogen was added dropwise *tert*-butylchlorodiphenylsilane (0.556 mL, 2.21 mmol) dissolved in 5 mL of the same solvent. The mixture was allowed to warm to room temperature and, after 2 h, an additional portion of *tert*-butylchlorodiphenylsilane (0.282 mL, 1.10 mmol) was added. After 4 h the reaction mixture was quenched by addition of water (13 mL). The aqueous layer was extracted with a 1:1 mixture of hexane/ethyl acetate and the combined organic phases were dried over Na_2SO_4, filtered, and evaporated in vacuo to give a pale yellow oil. Purification by column chromatography (gradient elution from 100% hexane to hexane/ethyl acetate 99:1) gave pure **7** as a colorless oil (0.477 g, 57%). R_f 0.34 (hexane/ethyl acetate 99:1). IR (neat, cm^{-1}) 1105, 1624, 2198, 2225. ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.32 (s, 9H), 4.32 (d, J=1.8 Hz, 2H), 6.47 (t, J=1.8 Hz, 1H), 7.38–7.50 (m, 6H), 7.65–7.70 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7 (s), 27.2, 28.8 (s), 31.3, 68.4 (t), 76.3 (s), 105.6 (s), 109.9, 128.3, 130.4, 133.1 (s), 134.4 (s), 135.9. MS (EI) m/z (% rel intensity)=454.1 (1.5) [M^+, ^{79}Br], 456.1 (1.5) [M^+, ^{81}Br], 397.0 (14.2) [M^+, ^{79}Br], 399.0 (14.2) [M^+, ^{81}Br], 91.0 (100) [M^+]. Anal. Calcd for $C_{25}H_{31}BrOSi$: C, 65.92; H, 6.86. Found: C, 65.84; H, 6.84.

4.5. (*E*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-8,8-dimethylnona-4-en-2,6-diyn-1-ol (8)

A solution of the vinyl bromide **7** (0.35 g, 0.77 mmol) in dry DMF (1.5 mL) was alternatively evacuated and flushed with nitrogen. The flask was cooled in ice and propargyl alcohol (0.054 mL, 0.92 mmol), tetrakis(triphenylphosphine) palladium (0.045 g, 0.039 mmol), cuprous iodide (0.029 g, 0.154 mmol), and piperidine (0.152 mL, 1.54 mmol) were added in sequence. The reaction mixture was allowed to warm to room temperature and after 4 h under stirring a second aliquot of propargyl alcohol (0.022 mL, 0.385 mmol), tetrakis(triphenylphosphine) palladium (0.045 g, 0.039 mmol), and cuprous iodide (0.029 g, 0.154 mmol) were added. After 24 h, the same amount of reagents as the second aliquot were added and the reaction mixture was stirred for further 12 h. The reaction was quenched by treatment with a saturated $NaHCO_3$ aqueous solution (7 mL). The aqueous layer was extracted with ethyl acetate (3×10 mL) and the combined organic phases were washed with water, dried over Na_2SO_4, and evaporated to give a brown oil. Purification by flash chromatography (hexane/ethyl acetate 85:15) afforded pure **8** as a brown oil (0.261 g, 79%). R_f 0.36 (hexane/ethyl acetate 85:15). IR (neat, cm^{-1}) 1105, 2196, 2220, 3335. ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.33 (s, 9H), 1.45–1.54 (br s, 1H, exchanges with D_2O), 4.24 (d, J=2.0 Hz, 2H), 4.43 (s, 2H), 6.24 (t, J=2.0, 1H), 7.37–7.50 (m, 6H), 7.64–7.70 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7 (s), 27.2, 28.2 (s), 31.4, 52.0 (t), 65.5 (t), 77.2 (s), 82.9 (s), 94.7 (s), 106.5 (s), 114.8, 128.2, 130.3, 132.2 (s), 133.4 (s), 135.9. MS (ESI) m/z=431.6 [M+H]$^+$, 453.6 [M+Na]$^+$. Anal. Calcd for $C_{28}H_{34}O_2Si$: C, 78.09; H, 7.96. Found: C, 78.12; H, 7.98.

4.6. (2*E*,4*E*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-8,8-dimethylnona-2,4-dien-6-yn-1-ol (9)

A solution of the propargyl alcohol **8** (0.207 g, 0.48 mmol) in dry THF (5 mL) under nitrogen was cooled to −30 °C and treated with a 65 wt% solution in toluene of sodium bis(2-methoxyethoxy)-aluminum dihydride (0.230 mL, 0.77 mmol). After 1 h, the reaction mixture was allowed to warm to room temperature and stirring continued for additional 30 min. Saturated NH_4Cl (8 mL) was cautiously added and the aqueous layer extracted with Et_2O. The organic phases were combined, dried with Na_2SO_4, and evaporated giving a pale yellow oil. Purification by flash chromatography (hexane/ethyl acetate 8:2) afforded 0.053 g (26%) of the allyl alcohol **9** as a colorless oil. R_f 0.34 (hexane/ethyl acetate 8:2). IR (neat, cm^{-1}) 1105, 2198, 2217, 3326. ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.34 (s, 9H), 1.37–1.68 (br s, 1H, exchanges with D_2O), 4.21 (d, J=5.8 Hz, 2H), 4.41 (d, J=1.6 Hz, 2H), 5.78 (td, J=5.9, 16.3 Hz, 1H), 6.00 (s, 1H), 6.84 (d, J=16.3 Hz, 1H), 7.38–7.47 (m, 6H), 7.66–7.72 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7 (s), 27.2, 28.8 (s), 31.5, 63.6 (t), 64.5 (t), 76.6 (s), 106.7 (s), 108.5, 127.7, 128.2, 129.6, 130.2, 133.6 (s), 135.9, 144.9 (s). MS (ESI) m/z=433.7 [M+H]$^+$, 455.7 [M+Na]$^+$. Anal. Calcd for $C_{28}H_{36}O_2Si$: C, 77.73; H, 8.39. Found: C, 77.85; H, 8.42.

4.7. (2*E*,4*E*)-4-(4,4-Dimethylpent-2-ynylidene)pent-2-ene-1,5-diol (4)

1. By deprotection of the silyl ether **9**: an ice cooled solution of **9** (0.080 g, 0.185 mmol) in THF (2 mL) under nitrogen was treated with 1 M solution of TBAF (1.12 mL, 1.12 mmol) in THF. After 1 h, the solution was allowed to warm to room temperature and the solvent removed at reduced pressure. The residue was treated again with the same TBAF solution (1.12 mL, 1.12 mmol) and reacted for 3 h, after which time saturated NH_4Cl (3 mL) was added and the aqueous phase extracted with a 1:1 mixture of hexane/ethyl acetate. The combined organic layers were dried (Na_2SO_4) and evaporated to give a pale yellow solid. Purification by flash chromatography (hexane/ethyl acetate 35:65) afforded the diol **4** as a white solid; mp=67–68 °C (0.027 g, 75%). R_f 0.36 (hexane/ethyl acetate 35:65), 0.44 (hexane/ethyl acetate 3:7). IR (neat, cm^{-1}) 1051, 2208, 2218, 3255. ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 9H), 1.57–1.68 (br s, 2H, exchanges with D_2O), 4.31 (d, J=5.6 Hz, 2H), 4.36 (s, 2H), 5.73 (s, 1H), 6.11 (td, J=5.7, 16.2 Hz, 1H), 6.83 (d, J=16.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.8 (s), 31.4, 63.6 (t), 64.2 (t), 76.2 (s), 107.2 (s), 110.4, 127.6, 131.2, 145.4 (s). MS (ESI) m/z=195.3 [M+H]$^+$, 217.3 [M+Na]$^+$. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.20; H, 9.35.

2. By hydrolysis of the dimethyl ester **12**: to a solution of the dimethyl ester **12** (0.400 g, 1.60 mmol) in dry toluene (6.4 mL) maintained at −78 °C under nitrogen was added dropwise 1 M *n*-hexane solution of DIBALH (6.4 mL). When TLC analysis (hexane/ethyl acetate 8:2) indicated consumption of the starting ester, typically 1.5 h, the reaction mixture was allowed to warm to 0 °C and then quenched by addition of a water solution (5 mL) of tartaric acid (0.160 g). The aqueous layer was extracted with three portions of a 1:1 mixture of hexane/ethyl acetate and the combined organic phases were dried over Na_2SO_4, filtered, and evaporated in vacuo to give a pale yellow solid. Purification by flash chromatography (hexane/ethyl acetate, 35:65) gave pure **4** as a white solid (0.265 g, 85%). Physical and spectroscopic data were identical to those of the product obtained by the previous synthetic sequence.

4.8. (2*E*,4*E*)-Dimethyl 4-(4,4-dimethylpent-2-ynylidene)pent-2-enedioate (12)

1. By aldol condensation: a THF solution (2 mL) of the dimethyl ester **11** (0.201 g, 1.27 mmol) was added dropwise at −78 °C to a 0.2 M solution of LDA (1.27 mmol) in THF, prepared from equimolar amounts of diisopropylamine and 1.6 M *n*-butyllithium in hexane. After stirring for 30 min, a solution of 4,4-dimethylpent-2-ynal (0.154 g, 1.40 mmol) in dry THF (1 mL) was added dropwise and stirring at −78 °C was continued for 1 h. The reaction was allowed to warm to 0 °C and then quenched by the addition of wet silica gel (2.0 g). The suspension was filtered by suction washing thoroughly with dichloromethane, ethyl acetate, and methanol. Evaporation of the solvents gave a brown oil that was purified by flash chromatography (hexane/ethyl acetate 9:1) to afford pure **12**

(0.137 g, 43%) as a pale yellow oil. 2. By transesterification: a solution of the di-*tert*-butylester **14** (0.1 g, 0.30 mmol) in dry MeOH (10 mL) was treated with a catalytic amount of 96% H_2SO_4 and the reaction mixture was heated at 80 °C for 28 h. The solvent was removed under vacuum and the residue taken up with ethyl acetate, washed with a saturated solution of $NaHCO_3$ and the aqueous phase extracted with ethyl acetate. The combined organic layers were dried with Na_2SO_4 and evaporated to give 0.071 g (95%) of the dimethyl ester **12**. R_f 0.36 (hexane/ethyl acetate 9:1), 0.70 (hexane/ethyl acetate 7:3). IR (neat, cm^{-1}) 1717, 2189, 2207. ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 9H), 3.80 (s, 3H), 3.83 (s, 3H), 6.90 (s, 1H), 6.92 (d, J=16.0 Hz, 1H), 7.77 (d, J=16.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.4 (s), 30.8, 52.1, 52.7, 76.9 (s), 119.4 (s), 123.6, 127.1, 134.8 (s), 137.2, 166.1 (s), 168.1 (s). MS (ESI) m/z=251.3 $[M+H]^+$, 273.3 $[M+Na]^+$. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.22; H, 7.27.

4.9. (*E*)-Di-*tert*-butyl pent-2-enedioate (14)

To a solution of (*E*)-pent-2-enedioic acid (0.200 g, 1.54 mmol) in dry *t*-BuOH (4 mL) under nitrogen, di-*tert*-butyl dicarbonate (0.672 mg, 3.08 mmol) and DMAP (0.056 g, 0.456 mmol) were added sequentially at room temperature. When TLC analysis (hexane/ethyl acetate 8:2) indicated consumption of di-*tert*-butyl dicarbonate (R_f 0.65), typically 3 h, two more equivalents of the above reagent were added and stirring was continued for 2 h. The reddish mixture was evaporated under vacuum and the residue flash chromatographed (hexane/ethyl acetate 85:15) to afford 0.272 g of the di-*tert*-butylester **14** (74%) as colorless oil. R_f 0.60 (hexane/ethyl acetate 85:15). IR (neat, cm^{-1}) 1655, 1713, 1732. ^1H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.49 (s, 9H), 3.13 (dd, J=1.5, 7.2 Hz, 2H), 5.83 (td, J=1.5, 15.6 Hz, 1H), 6.89 (td, J=7.2, 15.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 28.5, 39.0 (t), 80.8 (s), 81.8 (s), 126.5, 139.4, 165.6 (s), 169.7 (s). MS (ESI) m/z=243.3 $[M+H]^+$, 265.3 $[M+Na]^+$. Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.62; H, 9.17.

4.10. (2*E*,4*E*)-Di-*tert*-butyl 4-(4,4-dimethylpent-2-ynylidene)pent-2-enedioate (15)

A THF solution (1.5 mL) of di-*tert*-buthylester **14** (0.208 g, 0.86 mmol) was added dropwise at −78 °C to a 0.2 M solution of LDA (1.03 mmol), prepared from equimolar amounts of diisopropylamine and 1.6 M *n*-butyllithium in hexane. After stirring for 30 min, a solution of 4,4-dimethylpent-2-ynal (0.104 g, 0.95 mmol) in dry THF (0.6 mL) was added dropwise and stirring at −78 °C was continued for 1 h. The reaction mixture was allowed to warm to 0 °C and then quenched by the addition of wet silica gel (2.0 g). The suspension was filtered by suction washing abundantly with dichloromethane, ethyl acetate, and methanol. Evaporation of the solvents gave a pale yellow solid that was purified by flash chromatography (hexane/ethyl acetate 9:1) to afford pure **15** (0.242 g, 85%) as a white solid, mp=97–98 °C. R_f 0.70 (hexane/ethyl acetate 9:1). IR (neat, cm^{-1}) 1617, 1710, 2194, 2210. ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 9H), 1.52 (s, 9H), 1.53 (s, 9H), 6.78 (s, 1H), 6.82 (d, J=16.2 Hz, 1H), 7.62 (d, J=16.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 28.6, 29.3 (s), 30.9, 77.0 (s), 80.6 (s), 82.2 (s), 117.8 (s), 125.2, 125.9, 136.1, 136.8 (s), 165.0 (s), 166.9 (s). MS (ESI) m/z=335.4 $[M+H]^+$, 357.4 $[M+Na]^+$. Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.83; H, 9.03.

4.11. (2*E*,4*E*)-1-Chloro-4-(chloromethyl)-8,8-dimethylnona-2,4-dien-6-yne (10)

To an ice cooled solution of the diol **4** (0.256 g, 1.32 mmol) in CH_2Cl_2 (6.6 mL) under nitrogen were added distilled triethylamine (0.46 mL, 3.30 mmol), freshly distilled methanesulfonyl chloride (0.225 mL, 2.90 mmol), and solid TBAC (0.734 g, 2.64 mmol). After 1.5 h stirring, the reaction mixture was allowed to warm to room temperature. Stirring was continued for 2 h, after which time the reaction mixture was quenched by addition of water (4.8 mL). The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4, filtered, and evaporated in vacuo to give a pale yellow oil. The residue was flash chromatographed (100% hexane) to afford the dichloride **10** as a colorless oil (0.244 g, 80%). R_f 0.30 (100% hexane). IR (neat, cm^{-1}) 1686, 2198, 2218. ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 9H), 4.22–4.27 (m, 4H), 5.80 (s, 1H), 6.15 (td, J=7.0, 15.9 Hz, 1H), 6.83 (d, J=15.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.9 (s), 31.2, 44.9 (t), 45.7 (t), 75.8 (s), 109.6 (s), 115.5, 128.5, 129.4, 141.6 (s). MS (EI) m/z=195.0, 197.0 (1:3) $[M^+-Cl]$, 159 $[M^+-Cl-HCl]$. Anal. Calcd for $C_{12}H_{16}Cl_2$: C, 62.35; H, 6.98. Found: C, 62.18; H, 6.96.

4.12. (2*E*,4*E*)-4-(4,4-Dimethylpent-2-ynylidene)-N^1,N^5-dimethyl-N^1,N^5-bis(naphthalen-1-ylmethyl)pent-2-ene-1,5-diamine (1)

A solution of the dichloride **10** (0.125 g, 0.54 mmol) and *N*-methyl-1-(naphthalen-1-yl)methanamine (0.370 g, 2.16 mmol) in freshly distilled DMF (1.5 mL) was stirred under nitrogen for 24 h and then diluted with saturated aqueous $NaHCO_3$ (15 mL). The crude mixture was extracted with three portions of ethyl acetate. The combined organic layers were washed with water, dried (Na_2SO_4), and evaporated to give a brownish oil. Purification by flash chromatography afforded 0.243 g (90%) of the final product **1**. R_f 0.36 (hexane/ethyl acetate 89:11). IR (neat, cm^{-1}) 2194, 2211. ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 9H), 2.19 (s, 3H), 2.20 (s, 3H), 3.17 (d, J=6.9 Hz, 2H), 3.23 (s, 2H), 3.85 (s, 2H), 3.90 (s, 2H), 5.67 (s, 1H), 6.12 (td, J=6.7, 15.8 Hz, 1H), 6.80 (d, J=15.9 Hz, 1H), 7.33–7.53 (m, 8H), 7.70–7.90 (m, 4H), 8.22–8.31 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.8 (s), 31.6, 42.9, 43.1, 60.6 (t), 61.1 (t, 2C), 61.3 (t), 77.0 (s), 106.0 (s), 110.8, 125.2, 125.3, 125.6 (2C), 126.0 (2C), 126.2, 126.3, 127.8, 127.9, 128.3, 128.4, 128.8, 128.9, 130.4, 130.9, 132.9 (s), 133.0 (s), 134.3 (s), 134.4 (s), 135.3 (s), 135.4 (s), 144.8 (s). MS (ESI) m/z=501.7 $[M+H]^+$, 523.7 $[M+Na]^+$. Anal. Calcd for $C_{36}H_{40}N_2$: C, 86.35; H, 8.05. Found: C, 86.54; H, 8.08.

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Supplementary data

NOESY spectra of compound **9** and copy of $^1H/^{13}C$ NMR spectra for products **1**, **4**–**10**, and **12**–**15**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.04.095.

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