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Mycothiazole: Synthesis of the C8–C18 Subunit and Further Evidence of the (*Z*)-Δ^{14} Double Bond Configuration

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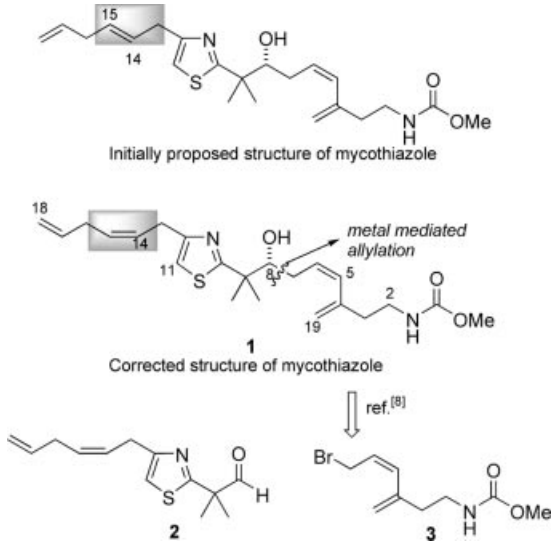
The synthesis of mycothiazole derivatives was undertaken in order to have further evidence of the C14–C15 double bond configuration. The recently revised (*Z*) configuration in the natural compound is consistent with the data found for our synthetic analogs.

Introduction

Mycothiazole (**1**) is a marine natural compound isolated by Crews et al. from the Vanuatuan sponge *Spongia mycofijiensis*[1] and is also found in the extracts of another marine sponge of the genus *Dactylospongia*.[2] Compound **1** shows antihelminthic activity in vitro, and it is being studied by the National Cancer Institute (NCI) in the Unites States because it exhibits selective toxicity against small cell lung cancer lines.[3] Its stereostructure was solved in 2000 by an asymmetric total synthesis,[4] even though some discrepancies −attributed to possible contamination of the isolated product− were found in the $[a]_D^{23}$ values between the synthetic and natural products. Another total synthesis of *rac*-mycothiazole was recently published by Cossy and coworkers and no mention was made of problems concerning the overall structure of mycothiazole.[5] An additional synthesis of simplified analogs was published in 2006 and discrepancies in the configuration of the C14–C15 double bond were not discussed.[6] Very recently Crews et al. revised the initially proposed (*E*) configuration to (*Z*) on the basis of NOE measurements and comparison with a new natural analog, mycothiazole-4,19-diol.[7]

During our attempt directed towards the total synthesis of **1** and analogs, we have synthesized two (*Z*)-Δ^{14}-configured intermediates which have provided additional corroboration of the new proposed structure of naturally derived mycothiazole.

As shown in Scheme 1, our retrosynthetic strategy for **1** is based in a convergent approach. We envisioned that a coupling reaction of a 1,4-dienethiazole, C8–C18 segment **2** and 1,3-diene system **3**,[8] would be furnished by a regio- and stereoselective metal mediated allylation.



Scheme 1. Retrosynthetic analysis of mycothiazole.

The development of this synthetic strategy prompted us to investigate different 1,4 diene systems with (*E*)- or (*Z*) geometry which can further confirm the proposed (*Z*) configuration of the C14 double bond of **1**.

Results and Discussion

In order to obtain the 1,4-diene with the (*Z*) configuration we considered two different approximations: a metal cross-coupling methodology and a Wittig-like approach. Firstly, silyl-protected amide **4a** was prepared with the use of standard procedures from methyl 3-hydroxy-2,2-dimethylpropanoate. Treatment of this compound with Lawesson's reagent[9] followed by Hantzsch's methodology[10] gave the thiazole in moderate yield (50%). By using an aprotic solvent such as THF, an intermediary 2-thiazoline was ob-

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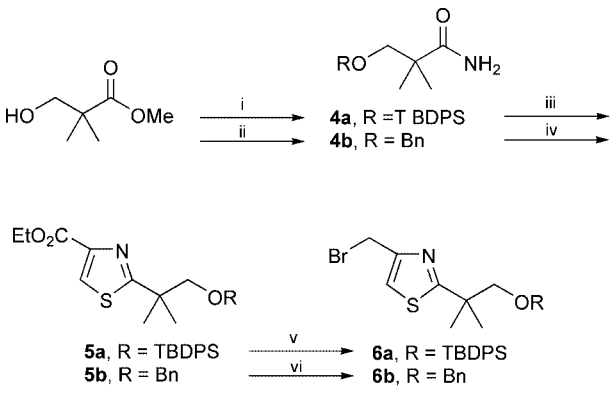
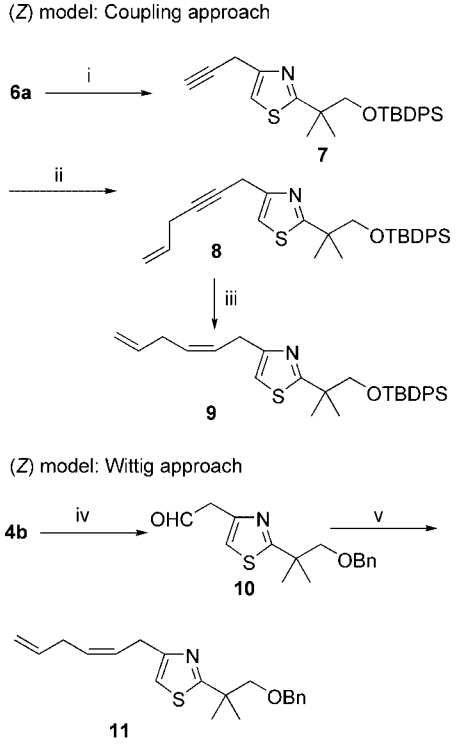
served by ^{1}H NMR spectroscopic analysis, which was then dehydrated with trifluoroacetic acid to afford thiazolic compound **5a** in almost quantitative yield (see Scheme 2). The resulting ester was fully reduced and later brominated to give thiazole **6a**. The bromide was then converted into terminal alkyne **7** through an indium/palladium assisted cross-coupling reaction developed by Sarandeses et al.[11] This alkyne was transformed into **8** by copper catalysis, and then hydrogenated under Lindlar′s conditions to diene **9** in a very moderate yield (26%, see Scheme 3).



Scheme 2. Synthesis of the thiazole core. Reagents and conditions: (i): 1. TBDPSCl, imidazole, DMF, 95%; 2. KOH, EtOH, 80%; 3. PCl_5, hexanes, then aq. NH_3, 85%. (ii): 1. BnBr, NaH, 70%; 2. KOH, EtOH, 95%; 3. PCl_5, hexanes, then aq. NH_3, 90%. (iii): 1. Lawesson, DCM, 90%; 2. $BrCH_2COCO_2Et$, Py, TFAA, THF, 95%. (iv): 1. Lawesson, DCM, 95%; 2. $BrCH_2COCO_2Et$, EtOH, Δ, 95%. (v): 1. DIBAL-H, Et_2O, –78 °C, 90%; 2. CBr_4, Ph_3P, THF, 95%. (vi): 1. DIBAL-H, DCM, –40 °C, 80%; 2. CBr_4, Ph_3P, THF, 80%.



Scheme 3. Synthesis of C8–C18 fragments of mycothiazole with a (*Z*)-Δ^{14} configuration. Reagents and conditions: (i): $InCl_3$, ≡MgBr, $Pd(dppf)Cl_2$, THF, 70%. (ii): CH_2=$CHCH_2Br$ EtMgBr, CuBr, THF, 80%. (iii): H_2; Lindlar, quinoline,THF/EtOH, 26%. (iv): 1. Lawesson, DCM, 95%; 2. $ClCH_2COCH_2CO_2Et$, EtOH, Δ, 95%; 3. DIBAL-H, PhMe, 95%. (v): CH_2=$CHCH_2CH_2PPh_3Br$, *n*BuLi, THF, 41%.

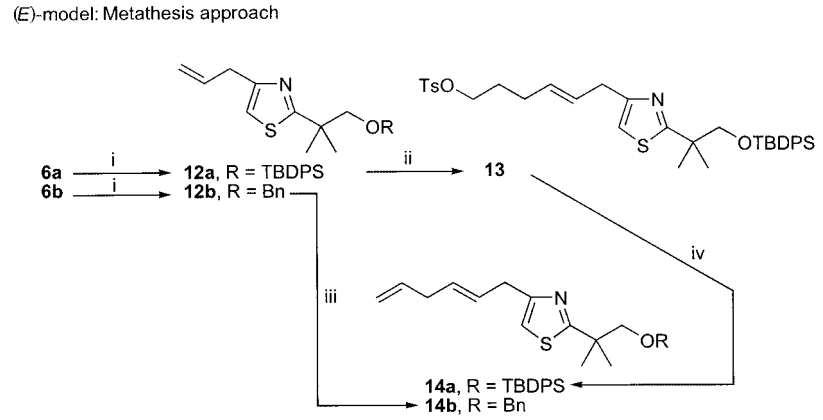
The second strategy to obtain (*Z*)-analog **11** involved the synthesis of the thiazole core from the thioamide of **4b** (previously synthesized in Scheme 2) and ethyl 4-chloro-3-oxobutyrate. The resulting ester was reduced with the use of DIBAL-H in toluene to afford aldehyde **10**, which was used for the key Wittig reaction with 3-butenyltriphenylphosphonium bromide. This reaction to (*Z*)-Δ^{14} alkene **11** resulted in low conversion (41%), which was likely a result of enolization of the aldehyde during formation of the double bond.

In additional effort to confirm the (*Z*) configuration of the C14 double bond, and to have more spectroscopic data for this type of system, we decided to obtain the same diene but with an (*E*) geometry. We envisioned an ene cross metathesis (CM) approach, where **6a** was converted into CM type III alkene **12a**[12] (no homodimerization) by using indium trichloride cross coupling chemistry.[11] This terminal alkene was metathesized with tosylated 5-pentenol, a CM type II alkene,[13] by using the second generation ruthenium alkylidine complex as a catalyst,[14] to give **13** in a 68% yield. The *E*/*Z* selectivity of the reaction was strongly dominated by the (*E*) isomer, with small amounts of the sterically less favored (*Z*) isomeric double bond.[15] β-elimination of the tosyl group in **13** gave desired product **14a** by using NaI and DBU in DME.

A more direct route to obtain a similar diene involved a cross metathesis process of **12b** and 1,4-pentadiene, a CM type I alkene (rapid homodimerization). Attempted metathesis reaction between these two alkenes in the presence of the Grubbs second generation catalyst at room temperature was unsuccessful (Scheme 4). However, the reaction heated at 40 °C with 7.8 equiv. of diene and in the presence of 8% loading of catalyst in dichloromethane proceeded with very poor conversion. After chromatographic removal of the ruthenium residues, we isolated unreacted alkene **12b**, homodimerization, and polymerization side products derived from the diene, and desired product **14b** in only 20% yield.

With both (*Z*) and (*E*) models in hand, edited *g*HSQC experiments were run to verify assignments for carbons and protons from C13 to C16 (see Figure 1). The highfield values observed for (*Z*) models **9** and **11** at C13 (δ_C = 29.8 ppm) and C16 (δ_C = 31.7 ppm) matched those reported for the natural product, whereas the same carbons resonated downfield in (*E*) compound **14a**. Clearly, the carbon chemical shifts for C13 and C16 in **9** and **11** showed a noteworthy steric compression effect, as one would expect.[16]

In conclusion, NMR studies confirmed the (*Z*) configuration of the Δ^{14} double bond of mycothiazole, as reported very recently by Crews and coworkers. Investigations directed at the total synthesis of **1** are underway in our research group.



Scheme 4. Synthesis of analogs of mycothiazole with a (*E*)-Δ^{14} configuration. Reagents and conditions: (i): $InCl_3$,CH_2=$CHMgBr$, $Pd(dppf)Cl_2$, THF, 80%; (ii): CH_2=$CHCH_2CH_2CH_2OTs$, Grubbs 2nd generation, catalyst, PhMe, 80 °C, 50%. (iii): CH_2=$CHCH_2CH$=CH_2, Grubbs 2nd generation, CH_2Cl_2, room temp., 20%. (iv): NaI, DBU, DME, 20%.

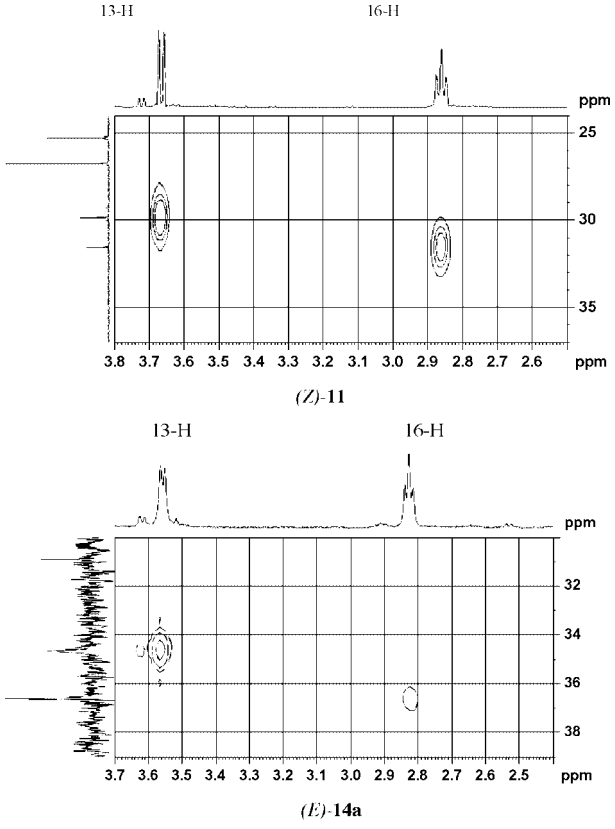


Figure 1. Edited *g*HSQC experiment of models **11** (in $CDCl_3$) and **14a** (in C_6D_6).

Experimental Section

General Methods: All reactions were conducted in oven (135 °C) or flame-dried glassware under an inert atmosphere of dry argon (Argon C50) with dry solvents under anhydrous conditions, unless otherwise noted. Solvents were dried by distillation from a suitable desiccating agent. Tetrahydrofuran, diethyl ether, toluene, and dimethylethyleneglycol were distilled from sodium/benzophenone. Dichloromethane, hexane, and acetonitrile were distilled from calcium hydride. Pyridine was distilled from potassium hydroxide. Starting materials and reagents were purchased from commercial suppliers and used without further purification except the following: hexanes and ethyl acetate used in chromatography were distilled prior to use. Reactions were monitored by thin layer chromatography (TLC) carried out on Merck silica gel plates (60 F_{254}) by using UV light as the visualizing agent and an ethanolic solution of phosphomolybdic acid or *p*-anisaldehyde/sulfuric acid/acetic acid and heat as developing agents. Flash chromatography was performed on silica gel Merck 60 (230–400 mesh) following Still conditions. ^{1}H NMR spectra were recorded with a Bruker AC 200F (200 MHz) and Bruker Avance 300 (300 MHz) and 500 (500 MHz). Chemical shifts are reported with the solvent as the internal standard ($CHCl_3$ δ = 7.26 ppm, C_6H_6 δ = 7.16 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br. = broad, m = multiplet or overlap of non-equivalent resonances), coupling constants (Hz), integration and assignment. ^{13}C NMR spectra were recorded with a Bruker AC 200F (50 MHz) and Bruker Avance 300 (75 MHz) and 500 (125 MHz) with complete proton decoupling. Chemical shifts are reported in ppm with the solvent as an internal reference ($CDCl_3$ δ = 77.16 ppm, C_6H_6 δ = 128.26 ppm). Data are reported as follows: chemical shift, multiplicity with respect to proton (deduced from DEPT experiments, s = quaternary C, d = CH, t = CH_2, q = CH_3), and assignment. LRESIMS or ApCIMS spectra were run with a Thermoquest Navigator spectrometer using MeOH as a solvent. HRESIMS were measured with a Bruker FTMS Apex or a Waters Q-TOF Premier spectrometer.

3-(*tert*-Butyldiphenylsilyloxy)-2,2-dimethylpropanamide (4a): To a stirred solution of methyl 2,2-dimethyl-3-hydroxypropionate (2 mL, 15.4 mmol) in anhydrous *N*,*N*-dimethylformamide (10 mL), cooled in a ice bath, imidazole (4.10 g, 59.6 mmol) and *tert*-butyldiphenylsilane chloride (5 mL, 18.8 mmol) were slowly added. The reaction mixture was stirred at 0 °C for 15 min and then warmed to room temperature. After 12 h, a 5% solution of hydrochloric acid (15 mL) was added, and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with water (50 mL) and a saturated aqueous solution of NaCl (50 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The yellow oil obtained was flash chromatographed (silica gel, 10% ethyl acetate in hexanes) to give methyl 3-(*tert*-butyldiphenylsilyloxy)-2,2-dimethylpropanoate as a colorless oil (5.4 g, 95%).^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.66 (m, 4 H, SiPh), 7.41 (m, 6 H, SiPh), 3.68 (s, 3 H, OCH_3), 3.66 (s, 2 H, 8-H), 1.21 (s, 6 H, 20-H and 21-H), 1.04 [s, 9 H, $SiC(CH_3)_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.0 (s, C-10), 135.7 (d, SiPh), 133.6 (s, SiPh), 129.7 (d, SiPh), 127.7 (d, SiPh), 70.9 (t, C-8), 51.7

(q, OCH_3), 45.1 (s, C-9), 26.8 [q, $SiC(CH_3)_3$], 22.2 (q, C-20 and C-21), 19.4 [s, $SiC(CH_3)_3$] ppm. (+)-LRESIMS: *m/z* (%) = 371 (3) $[M + H]^+$, 393 (100) $[M + Na]^+$, 409 (5) $[M + K]^+$.

To a stirred solution of methyl 3-(*tert*-butyldiphenylsilyloxy)-2,2-dimethylpropanoate (5.6 g, 15 mmol) in ethanol (50 mL), a 10% KOH ethanol solution (25 mL) was added. The reaction mixture was heated at reflux for 24 h and then poured into ice (200 mL). By the addition of a 10% solution of hydrochloric acid, the formation of a white solid was observed, until pH 3–4. The mixture was extracted with dichloromethane (3 × 300 mL), and the organic phase was dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was flash chromatographed (silica gel, 10% ethyl acetate in hexanes) to give 3-(*tert*-butyldiphenylsilyloxy)-2,2-dimethylpropanoic acid as a white solid (4.3 g, 80%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.67 (m, 4 H, SiPh), 7.41 (m, 6 H, SiPh), 3.67 (s, 2 H, 8-H), 1.24 (s, 6 H, 20-H and 21-H), 1.06 [s, 9 H, $SiC(CH_3)_3$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 183.0 (s, C-10), 135.7 (d, SiPh), 133.4 (s, SiPh), 129.8 (d, SiPh), 127.9 (d, SiPh), 70.6 (t, C-8), 44.9 (s, C-9), 26.9 [q, $SiC(CH_3)_3$], 22.0 (q, C-20 and C-21), 19.5 [s, $SiC(CH_3)_3$] ppm. (+)-LRESIMS: *m/z* (%) = 357 (4) $[M + H]^+$, 379 (100) $[M + Na]^+$, 395 (3) $[M + K]^+$. (+)-HRESIMS: calcd. for $C_{21}H_{29}O_3Si$ $[M + H]^+$ 357.1886; found 357.1896.

To a stirred suspension of 3-(*tert*-butyldiphenylsilyloxy)-2,2-dimethylpropanoic acid (2.5 g, 7.10 mmol) in anhydrous hexane (10 mL), cooled in an ice bath, was added phosphorus pentachloride (2.18 g, 9.94 mmol). The resultant suspension was stirred for 10 min at 0 °C and 1 h at room temperature. A 30% solution of ammonia (5 mL) was slowly added at 0 °C, and the reaction was stirred at this temperature for 3 h. Water (50 mL) was added, and the mixture was extracted with dichloromethane (3 × 50 mL). The organic phase was dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was flash chromatographed (silica gel, 30% ethyl acetate in hexanes) to give 3-(*tert*-butyldiphenylsilyloxy)-2,2-dimethylpropanamide (**4a**) as a white solid (2.1 g, 85%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.68 (m, 4 H, SiPh), 7.43 (m, 6 H, SiPh), 6.71 (br. s, 1 H, NH_2), 5.42 (br. s, 1 H, NH_2), 3.62 (s, 2 H, 8-H), 1.16 (s, 6 H, 20-H and 21-H), 1.09 [s, 9 H, $SiC(CH_3)_3$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 179.6 (s, C-10), 135.6 (d, SiPh), 132.6 (s, SiPh), 129.9 (d, SiPh), 127.8 (d, SiPh), 70.2 (t, C-8), 43.6 (s, C-9), 26.9 [q, $SiC(CH_3)_3$], 22.6 (q, C-20and C-21), 19.2 [s, $SiC(CH_3)_3$] ppm. (+)-LRESIMS: *m/z* (%) = 356 (25) $[M + H]^+$, 378 (100) $[M + Na]^+$, 394 (33) $[M + K]^+$. (+)-HRESIMS: calcd. for $C_{21}H_{30}NO_2Si$ $[M + H]^+$ 356.2046; found 356.2045.

3-(Benzyloxy)-2,2-dimethylpropanamide (4b): To a stirred suspension of 60% sodium hydride (NaH) in mineral oil (4.5 g, 111.2 mmol) in anhydrous tetrahydrofuran (40 mL), cooled in an ice bath, was added methyl 2,2-dimethyl-3-hydroxypropionate (4.8 mL, 37.0 mmol). The resultant suspension was stirred for 20 min at room temperature. Benzyl bromide (4.5 mL, 37 mmol) was slowly added at 0 °C, and the reaction was stirred at room temperature for 24 h. The reaction suspension was chilled in an ice bath, and the excess NaH was quenched with water (50 mL). The reaction mixture was extracted with ethyl acetate (3 × 50 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated. The residue was flash chromatographed (silica gel, 10% ethyl acetate in hexanes) to give methyl 3-(benzyloxy)-2,2-dimethylpropanoate as a colorless oil (5.6 g, 70%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.32 (m, 5 H, Ph), 4.54 (s, 2 H, CH_2Ph), 3.69 (s, 3 H, OCH_3), 3.47 (s, 2 H, 8-H), 1.23 (s, 6 H, 20-H and 21-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177 (s, C-10), 138.3 (s, Ph), 128.2 (d, Ph), 127.3 (d, Ph), 76.8 (t, C-8), 73.1 (t, CH_2Ph), 52.8 (q, OCH_3), 43.8 (s, C-9), 26.2 (q, C-20 and C-21) ppm. (+)-LRESIMS: *m/z* (%) = 223 (4) $[M + H]^+$, 245 (34) $[M + Na]^+$, 261 (8) $[M + K]^+$, 277 (100) $[M + Na + MeOH]^+$.

To a stirred solution of methyl 3-(benzyloxy)-2,2-dimethylpropanoate (4.6 g, 20.8 mmol) in ethanol (50 mL), a 10% KOH ethanol solution (20 mL) was added. The reaction mixture was heated at reflux for 24 h and then poured into ice (100 mL). By the addition of a 10% solution of hydrochloric acid, the formation of a white solid was observed, until pH 3–4. The mixture was extracted with dichloromethane (3 × 100 mL), and the organic phase was dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude material, 3-(benzyloxy)-2,2-dimethylpropanoic acid, was obtained as a white solid (4.1 g, 95%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 11.49 (br. s, 1 H, OH), 7.35 (m, 5 H, Ph), 4.59 (s, 2 H, CH_2Ph), 3.51 (s, 2 H, 8-H), 1.28 (s, 6 H, 20-H and 21-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 182.9 (s, C-10), 138.1 (s, Ph), 127.5 (d, Ph),127.4 (d, Ph), 76.5 (t, C-8), 73.3 (t, CH_2Ph), 43.5 (s, C-9), 22.3 (q, C-20 and C-21) ppm. (+)-LRESIMS: *m/z* (%) = 209 (12) $[M + H]^+$, 231 (100) $[M + Na]^+$, 263 (10) $[M + Na + MeOH]^+$. (+)-HRESIMS: calcd. for $C_{12}H_{17}O_3$ $[M + H]^+$ 209.1178; found: 209.1178.

To a stirred suspension of 3-(benzyloxy)-2,2-dimethylpropanoic acid (4.1 g, 19.7 mmol) in anhydrous hexane (60 mL), cooled in an ice bath, was added phosphorus pentachloride (4.8 g, 21.7 mmol). The resultant suspension was stirred for 10 min at 0 °C and 1 h at room temperature. A 30% solution of ammonia (12 mL) was slowly added at 0 °C, and the reaction was stirred at this temperature for 3 h. Water (200 mL) was added, and the mixture was extracted with dichloromethane (3 × 100 mL). The organic phase was dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude material, 3-(benzyloxy)-2,2-dimethylpropanamide (**4b**), was obtained as a white solid (3.7 g, 90%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.33 (m, 5 H, Ph), 6.65 (br. s, 1 H, NH_2), 5.95 (br. s, 1 H, NH_2), 4.56 (s, 2 H, CH_2Ph), 3.43 (s, 2 H, 8-H), 1.19 (s, 6 H, 20-H and 21-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 179.7 (s, C-10), 137.6 (s, Ph), 128.5 (d, Ph), 128.4 (d, Ph), 127.8 (d, Ph), 127.5 (d, Ph), 127.3 (d, Ph), 76.6 (t, C-8), 73.5 (t, CH_2Ph), 42.6 (s, C-9), 23.0 (q, C-20 and C-21) ppm. (+)-LRESIMS: *m/z* (%) = 208 (44) $[M + H]^+$, 230 (100) $[M + Na]^+$, 246 (21) $[M + K]^+$. (+)-HRESIMS: calcd. for $C_{12}H_{18}NO_2$ $[M + H]^+$ 208.1338; found 208.1341.

Ethyl 2-[2-(*tert*-Butyldiphenylsilyloxy)-1,1-dimethylethyl]thiazol-4-carboxylate (5a): To a stirred suspension of Lawesson′s reagent (0.36 g, 0.86 mmol) in anhydrous dichloromethane (6 mL) was added a solution of 3-(*tert*-butyldiphenylsilyloxy)-2,2-dimethylpropanamide (**4a**) (0.5 g, 1.42 mmol) in anhydrous dichloromethane (6 mL). The reaction mixture was stirred for 24 h. The solvent was evaporated under reduced pressure, and water/diethyl ether (1:1, 20 mL) was added to the residue. The aqueous phase was extracted with diethyl ether (3 × 10 mL), and the combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (50 mL) and a saturated aqueous solution of NaCl (50 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The yellow solid obtained was flash chromatographed (silica gel, 30% ethyl acetate in hexanes) to give 3-(*tert*-butyldiphenylsilyloxy)-2,2-dimethylpropanethioamide as a white solid (0.48 g, 90%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 8.5 (br. s, 1 H, NH_2), 7.65 (m, 4 H, SiPh), 7.43 (m, 6 H, SiPh), 3.62 (s, 2 H, 8-H), 1.3 (s, 6 H, 20-H and 21-H), 1.09 [s, 9 H, $SiC(CH_3)_3$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 217.2 (s, C-10), 135.7 (d, SiPh), 132.4 (s, SiPh), 130.2 (d, SiPh), 128.0 (d, SiPh), 71.6 (t, C-8), 48.3 (s, C-9), 27.1 [q, $SiC(CH_3)_3$], 25.9 (q, C-20 and C-21), 19.4 [s, $SiC(CH_3)_3$] ppm. (+)-LRESIMS: *m/z* (%) = 372(39) $[M + H]^+$, 394 (8) $[M + Na]^+$. (+)-HRESIMS: calcd. for $C_{21}H_{30}NOSSi$ $[M + H]^+$ 372.1817; found 372.1820.

To a stirred solution of 3-(*tert*-butyldiphenylsilyloxy)-2,2-dimethylpropanethioamide (0.05 g, 0.136 mmol) in anhydrous dimethylformamide (2.5 mL) was added ethyl bromopyruvate (0.05 mL, 0.358 mmol). The reaction mixture was stirred at room temperature for 2 h, and ethyl acetate (40 mL) was added to dilute. The organic phase was washed with water (3 × 40 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was flash chromatographed (silica gel, 10% ethyl acetate in hexanes) to give ethyl 2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]-4-hydroxy-4,5-dihydrothiazol-4-carboxylate as a colorless oil (0.066 g, 90%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.65 (m, 4 H, SiPh), 7.39 (m, 6 H, SiPh), 4.25 (dq, ^3J = 2.5, 7.1 Hz, 2 H, OCH_2CH_3), 3.82 (d, ^3J = 12.0 Hz, 1 H, 11-H), 3.34 (d, ^3J = 12.0 Hz, 1 H, 11′-H), 3.66 (s, 2 H, 8-H), 1.26 (m, 9 H, 20-H and 21-H and OCH_2CH_3), 1.05 [s, 9 H, $SiC(CH_3)_3$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 184.5 (s. C-10), 171.3 (s, C-13), 135.8 (d, SiPh), 133.6 (s, SiPh), 129.7 (d, SiPh), 127.7 (d, SiPh), 105.5 (s, C-12), 71.5 (t, C-12), 62.8 (t, CH_3CH_2O), 44.1 (s, C-9), 40.3 (t, C-11), 26.9 [q, $SiC(CH_3)_3$], 24.4 (t, C-20 and C-21), 19.5 [s, $SiC(CH_3)_3$], 14.1 (q, CH_3CH_2O) ppm. (+)-LRESIMS: *m*/*z* (%) = 486 (100) [M + H]$^+$, 508 (37) [M + Na]$^+$.

To a stirred solution of 3-(*tert*-butyldiphenylsilyloxy)-2,2-dimethylpropanethioamide (0.42 g, 1.12 mmol) in anhydrous tetrahydrofuran (25 mL) was added ethyl bromopyruvate (0.5 mL, 3.58 mmol). The reaction mixture was stirred at room temperature for 2 h and anhydrous pyridine (2 mL) and trifluoroacetic anhydride (0.25 mL, 1.75 mmol) were added. Dichloromethane (100 mL) was added to dilute. The organic phase was washed with saturated aqueous solution of $NaHCO_3$ (3 × 100 mL) and water (3 × 100 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was flash chromatographed (silica gel, 10% ethyl acetate in hexanes) to give ethyl 2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]thiazol-4-carboxylate (**5a**) as a colorless oil (0.495 g, 95%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 8.09 (s, 1 H, 11-H), 7.62 (m, 4 H, SiPh), 7.38 (m, 6 H, SiPh), 4.43 (q, ^3J = 7.1 Hz, 2 H, OCH_2CH_3), 3.82 (s, 2 H, 8-H), 1.52 (s, 6 H, 20-H and 21-H), 1.41 (t, ^3J = 7.1 Hz, 3 H, OCH_2CH_3), 1.05 [s, 9 H, $SiC(CH_3)_3$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.4 (s, C-10), 161.5 (s, C-13), 146.5 (s, C-12), 135.6 (d, SiPh), 133.1 (s, SiPh), 129.7 (d, SiPh), 127.6 (d, SiPh), 126.8 (d, 11-C), 72.4 (t, 8-C), 61.0 (t, CH_3CH_2O), 43.4 (s, 9-C), 26.8 [q, $SiC(CH_3)_3$], 25.4 (t, 20-C and 21-C), 19.5 [s, $SiC(CH_3)_3$], 14.4 (q, CH_3CH_2O) ppm. (+)-LRESIMS: *m*/*z* (%) = 468 (48) [M + H]$^+$, 490 (100) [M + Na]$^+$, 506 (5) [M + K]$^+$.

Ethyl 2-(2-Benzyloxy-1,1-dimethylethyl)thiazol-4-carboxylate (5b): To a stirred suspension of Lawesson's reagent (5.5 g, 13.3 mmol) in anhydrous dichloromethane (20 mL) was added a solution of 3-(benzyloxy)-2,2-dimethylpropanamide (**4b**) (2.5 g, 12.0 mmol) in anhydrous dichloromethane (20 mL). The reaction mixture was stirred for 24 h. The solvent was evaporated under reduced pressure, and water/diethyl ether (1:1, 60 mL) was added to the residue. The aqueous phase was extracted with diethyl ether (3 × 30 mL), and the combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (100 mL) and a saturated aqueous solution of NaCl (100 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The yellow solid obtained was flash chromatographed (silica gel, 30% ethyl acetate in hexanes) to give 3-benzyloxy-2,2-dimethylpropanethioamide as a white solid (2.5 g, 95%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 8.38 (br. s, 1 H, NH_2), 7.83 (br. s, 1 H, NH_2), 7.33 (m, 5 H, Ph), 4.57 (s, 2 H, CH_2Ph), 3.54 (s, 2 H, 8-H), 1.34 (s, 6 H, 20-H and 21-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 216.5 (s, C-10), 137.3 (s, Ph), 128.5 (d, Ph), 128.0 (d, Ph), 127.6 (d, Ph), 77.6 (t, C-8), 73.7 (t, CH_2Ph), 47.3 (s, C-9), 26.2 (q, C-20 and C-21) ppm. (+)-LRESIMS: *m*/*z* (%) = 224 (100) [M + H]$^+$, 246 (50) [M + Na]$^+$. (+)-HRESIMS: calcd. for $C_{12}H_{18}NOS$ [M + H]$^+$ 224.1109; found 224.1104.

To a stirred solution of 3-(benzyloxy)-2,2-dimethylpropanethioamide (1.0 g, 4.6 mmol) in ethanol (40 mL) was added ethyl bromopyruvate (1.0 mL, 7.2 mmol). The reaction mixture was heated at reflux for 24 h. The solvent was evaporated under reduced pressure, and a mixture of saturated aqueous solution of $NaHCO_3$/diethyl ether (1:1, 40 mL) was added to the residue. The aqueous phase was extracted with diethyl ether (3 × 20 mL), and the combined organic extracts were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was flash chromatographed (silica gel, 30% ethyl acetate in hexanes) to give ethyl 2-(2-benzyloxy-1,1-dimethylethyl)thiazol-4-carboxylate (**5b**) as a yellow oil (1.3 g, 95%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 8.05 (s, 1 H, 11-H), 7.31 (m, 5 H, Ph), 4.52 (s, 2 H, CH_2Ph), 4.39 (q, ^3J = 7.1 Hz, 2 H, OCH_2CH_3), 3.62 (s, 2 H, 8-H), 1.53 (s, 6 H, 20-H and 21-H), 1.39 (t, ^3J = 7.1 Hz, 3 H, OCH_2CH_3) ppm. (+)-LRESIMS: *m*/*z* (%) = 320 (100) [M + H]$^+$, 342 (77) [M + Na]$^+$.

4-Bromomethyl-2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]-thiazole (6a): To a stirred solution of ethyl 2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]thiazol-4-carboxylate (**5a**) (0.34 g, 0.72 mmol) in anhydrous diethyl ether (5 mL) at –78 °C, was slowly added DIBAL-H (1.6 mL, 1.6 mmol). After 1 h, the reaction was quenched with a 1 M aqueous solution of $KHSO_4$ (2 mL) and stirred for 1 h. The mixture was extracted with diethyl ether (3 × 5 mL), and the combined organic extracts were washed with a 1 M aqueous solution of $KHSO_4$ (3 × 5 mL), water (5 mL) and a saturated aqueous solution of NaCl (5 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was flash chromatographed (silica gel, 20% ethyl acetate in hexanes) to give 4-hydroxymethyl-2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]-thiazole as a white solid (0.28 g, 90%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.61 (m, 4 H, SiPh), 7.38 (m, 6 H, SiPh), 7.05 (t, ^3J = 0.9 Hz, 1 H, 11-H), 4.74 (d, ^3J = 4.6 Hz, 2 H, 13-H), 3.76 (s, 2 H, 8-H), 3.12 (t, ^3J = 4.6 Hz, 1 H, OH), 1.47 (s, 6 H, 20-H and 21-H), 1.03 [s, 9 H, $SiC(CH_3)_3$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.6 (s, C-10), 155.5 (s, C-12), 135.6 (d, SiPh), 133.1 (s, SiPh), 129.7 (d, SiPh), 127.6 (d, SiPh), 113.7 (d, C-11), 72.4 (t, C-8), 61.0 (t, C-13), 43.2 (s, C-9), 27.3 [q, $SiC(CH_3)_3$], 25.4 (q, C-20 and C-21), 19.5 [s, $SiC(CH_3)_3$] ppm. (+)-LRESIMS: *m*/*z* (%) = 426 (61) [M + H]$^+$, 448 (100) [M + Na]$^+$, 464 (24) [M + K]$^+$. (+)-HRESIMS: calcd. for $C_{24}H_{32}NO_2SiS$ [M + H]$^+$ 426.1923; found 426.1938.

To a stirred solution of 4-hydroxymethyl-2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]thiazole (0.34 g, 0.80 mmol) and carbon tetrabromide (0.58 g, 1.73 mmol) in anhydrous tetrahydrofuran (5 mL), cooled in an ice bath, was added a solution of triphenylphosphane (0.50 g, 1.88 mmol) in tetrahydrofuran (5 mL). The reaction was then warmed to room temperature. After 30 min, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (15 mL). The mixture was extracted with diethyl ether (3 × 10 mL), and the combined organic extracts were washed with water (30 mL) and a saturated aqueous solution of NaCl (30 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was flash chromatographed (silica gel, 5% ethyl acetate in hexanes) to give 4-bromomethyl-2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]thiazole (**6a**) as a colorless oil (0.37 g, 95%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.62 (m, 4 H, SiPh), 7.42 (m, 6 H, SiPh), 7.22 (s, 1 H, 11-H), 4.63 (d, 2 H, 13-H), 3.28 (s, 2 H, 8-H), 1.49 (s, 6 H, 20-H and 21-H), 1.03 [s, 9 H, $SiC(CH_3)_3$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.6 (s, C-10), 151.3 (s, C-12), 135.6

(d, SiPh), 133.1 (s, SiPh), 129.7 (d, SiPh), 127.6 (d, SiPh), 117 (d, C-11), 72.4 (t, C-8), 43.2 (s, C-9), 27.8 (t, C-13), 27 [q, $SiC(CH_3)$], 25.4 (q, C-20 and C-21), 19.5 [s, $SiC(CH_3)_3$] ppm. (+)-LRESIMS; *m/z* (%) = 488 (72) $[M + H, {}^{79}Br]^+$, 490 (74) $[M + H, {}^{81}Br]^+$, 510 (81) $[M + Na, {}^{79}Br]^+$, 512 (100) $[M + Na, {}^{81}Br]^+$.

4-Bromomethyl-2-(2-benzyloxy-1,1-dimethylethyl)thiazole (6b): To a stirred solution of ethyl 2-(2-benzyloxy-1,1-dimethylethyl)thiazol-4-carboxylate (**5b**) (1.4 g, 4.4 mmol) in anhydrous dichloromethane (20 mL) at –40 °C, was slowly added DIBAL-H (15 mL, 15 mmol). After 20 min, the addition of DIBAL-H (5 mL, 5 mmol) was repeated. The reaction was followed by TLC repeating additions of DIBAL-H until the end of the reaction. When the starting material had disappeared, the reaction was quenched with methanol and then poured into ice with a 10% solution of hydrochloric acid. After 15 min the mixture was extracted with diethyl ether (3 × 100 mL), and the organic phase was dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was flash chromatographed (silica gel, 20% ethyl acetate in hexanes) to give 4-hydroxymethyl-2-(2-benzyloxy-1,1-dimethylethyl)thiazole as a yellow oil (1.0 g, 80%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.32 (m, 5 H, Ph), 7.05 (s, 1 H, 11-H), 4.63 (d, ^3J = 5.6 Hz, 2 H, 13-H), 4.51 (s, 2 H, CH_2Ph), 3.63 (s, 2 H, 8-H), 3.15 (t, ^3J = 5.6 Hz, 1 H, OH), 1.47 (s, 6 H, 20-H and 21-H) ppm. LRESIMS; *m/z* (%) = 278 (26) $[M + H]^+$, 300 (100) $[M + Na]^+$, 316 (5) $[M + K]^+$.

To a stirred solution of 4-hydroxymethyl-2-(2-benzyloxy-1,1-dimethylethyl)thiazole (0.7 g, 2.5 mmol) and carbon tetrabromide (1.6 g, 4.7 mmol) in anhydrous tetrahydrofuran (10 mL), cooled in an ice bath, was added a solution of triphenylphosphane (1.4 g, 5.1 mmol) in tetrahydrofuran (10 mL). The reaction was then warmed to room temperature. After 24 h, the solvent was evaporated under reduced pressure, and the residue was flash chromatographed (silica gel, 20% ethyl acetate in hexanes) to give 4-bromomethyl-2-(2-benzyloxy-1,1-dimethylethyl)thiazole (**6b**) as a colorless oil (0.7 g, 80%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.31 (m, 5 H, Ph), 7.22 (s, 1 H, 11-H), 4.63 (s, 2 H, CH_2Ph), 4.53 (s, 2 H, 13-H), 3.62 (s, 2 H, 8-H), 1.42 (s, 6 H, 20-H and 21-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.5 (s, C-10), 151.3 (s, C-12), 138.4 (s, Ph), 128.3 (d, Ph), 127.3 (d, Ph), 117.3 (d, C-11), 78.8 (t, C-8), 73.3 (t, CH_2Ph), 42.2 (s, C-9), 27.6 (t, C-13), 25.9 (q, C-20 and C-21) ppm. (+)-LRESIMS: *m/z* (%) = 340 (69) $[M + H, {}^{79}Br]^+$, 342 (52) $[M + H, {}^{81}Br]^+$, 362 (100) $[M + Na, {}^{79}Br]^+$, 364 (89) $[M + Na, {}^{81}Br]^+$.

General Procedure for the Preparation of Indium Organometallics: A 25 mL round-bottomed flask furnished with a stirrer bar was charged with $InCl_3$ (0.37 mmol) and dried under vacuum with a heat gun. The mixture was cooled, a positive argon pressure was established, and dry THF (4 mL) was added. The resulting solution was cooled to –78 °C, and a solution of RLi or RMgBr (1.1 mmol, 1.0–1.8 M in hexanes, THF, or Et_2O) was slowly added (15–30 min). The mixture was stirred for 30 min, the cooling bath was removed, and the reaction mixture was warmed to room temperature.

2-[2-(*tert*-Butyldiphenylsilyloxy)-1,1-dimethylethyl]-4-prop-2-ynylthiazole (7): A solution of ethynylindium (0.27 mmol, ≈ 0.1 M) (prepared following the general procedure) was added to a mixture of 4-bromomethyl-2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]thiazole (**6a**) (0.10 g, 0.21 mmol) and palladium catalyst {[1,1′-bis(diphenylphosphanyl)ferrocenedichloropalladium(II)], complex with dichloromethane 1:1} (0.005 g, 0.006 mmol) in anhydrous tetrahydrofuran (3 mL). The resulting mixture was heated at reflux under an argon atmosphere until the starting material was consumed, and the reaction was then quenched by the addition of a few drops of methanol. The mixture was concentrated in vacuo and Et_2O (5 mL) was added. The organic phase was washed with aqueous HCl (10%, 5 mL), saturated aqueous $NaHCO_3$ (10 mL), and saturated aqueous NaCl (10 mL), dried, filtered, and concentrated in vacuo. The residue was flash chromatographed (silica gel, 10% ethyl acetate in hexanes) to give 2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]-4-prop-2-ynylthiazole (**7**) as a yellow oil (0.063 g, 70%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.60 (m, 4 H, SiPh), 7.38 (m, 6 H, SiPh), 7.16 (t, ^3J = 1.2 Hz, 1 H, 11-H), 3.76 (br. s, 4 H, 13-H and 8-H), 2.23 (t, ^3J = 2.7 Hz, 1 H, 15-H), 1.47 (s, 6 H, 20-H and 21-H), 1.04 [s, 9 H, $SiC(CH_3)_3$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.2 (s, C-10), 150.5 (s, C-12), 135.6 (d, SiPh), 133.1 (s, SiPh), 129.7 (d, SiPh), 127.6 (d, SiPh), 113.5 (d, C-11), 80.8 (s, C-14), 72.4 (t, C-8), 70.5 (d, C-15), 43.2 (s, C-9), 27.3 [q, $SiC(CH_3)_3$], 25.4 (q, C-20 and C-21), 22.2 (t, C-13), 19.5 [s, $SiC(CH_3)_3$] ppm. (+)-LRESIMS: *m/z* (%) = 434(62) $[M + H]^+$, 456 (100) $[M + Na]^+$.

2-[2-(*tert*-Butyldiphenylsilyloxy)-1,1-dimethylethyl]-4-hex-5-en-2-ynylthiazole (8): To a stirred solution of 2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]-4-prop-2-ynylthiazole (**7**) (0.179 g, 0.413 mmol) in anhydrous tetrahydrofuran (1.5 mL), ethylmagnesium bromide (0.2 mL, 0.60 mmol) was slowly added. The reaction mixture was then heated for 1 h at reflux and cooled to 20 °C. A tiny amount of copper(I) bromide was then added in one portion, and the mixture was stirred for 15 min. Allyl bromide (0.12 mL,1.37 mmol) were added dropwise, and the temperature was raised again to reflux. After 1 h, the reaction mixture was cooled and hydrolyzed with a saturated aqueous solution of NH_4Cl (3 mL). The water layer was extracted with diethyl ether (3 × 2 mL), and the extracts were dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was flash chromatographed (silica gel, 2% diethyl ether in hexanes) to give 2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]-4-hex-5-en-2-ynylthiazole (**8**) as a colorless oil (0.157 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.58 (m, 4 H, SiPh), 7.40 (m, 6 H, SiPh), 7.13 (t, ^3J = 1.2 Hz, 1 H, 11-H), 5.88 (tdd, ^3J = 5.2, 10.3, 16.8 Hz, 1 H, 17-H), 5.39 (ddd, ^3J = 1.8, 3.5, 16.9 Hz, 1 H, 18-H), 5.14 (ddd, ^3J = 1.7, 3.4, 10.0 Hz, 1 H, 18′-H), 3.77–3.75 (m, 4 H, 13-H and 8-H), 3.04 (tt, ^3J = 2.1, 4.2 Hz, 2 H, 16-H), 1.46 (s, 6 H, 20-H and 21-H), 1.02 [s, 9 H, $SiC(CH_3)_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.2 (s, C-10), 152.1 (s, C-12), 135.8 (d, SiPh), 133.6 (s, SiPh), 133.1 (d, C-17), 129.7 (d, SiPh), 127.7 (d, SiPh), 116.1 (t, C-18), 113.4 (d, C-11),79.2 (s, C-15), 79.1 (s, C-14), 72.8 (t, C-8), 43.2 (s, C-9), 26.9 [q, $SiC(CH_3)$], 25.5 (q, C-20 and C-21), 23.3 (t, C-16), 22.3 (t, C-13), 19.5 [s, $SiC(CH_3)_3$] ppm. (+)-HRESIMS: calcd. for $C_{29}H_{36}NOSSi$ $[M + H]^+$ 474.2287; found 474.2260.

(*Z*)-2-[2-(*tert*-Butyldiphenylsilyloxy)-1,1-dimethylethyl]-4-(hexa-2,5-dienyl)thiazole (9): To a stirred solution of 2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]-4-hex-5-en-2-ynylthiazole (**8**) (0.035 g, 0.074 mmol) in ethanol/tetrahydrofuran (1:1, 0.75 mL) was added Lindlar′s catalyst (0.004 g). Quinoline (0.01 mL, 0.081 mmol) was also added. The reaction flask was evacuated, purged with hydrogen three times, and then stirred under a hydrogen atmosphere for 14 h. The reaction was filtered through celite with ethyl acetate and the solvent evaporated under reduced pressure. The residue was flash chromatographed (silica gel, 1% diethyl ether in hexanes) to give (*Z*)-2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]-4-(hexa-2,5-dienyl)thiazole (**9**) as colorless oil (0.009 g, 26%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.58 (m, 4 H, SiPh), 7.38 (m, 6 H, SiPh), 6.76 (t, ^3J = 1.1 Hz, 1 H, 11-H), 5.92–5.57 (m, 3 H, 14-H, 15-H and 17-H), 5.06 (qd, ^3J = 1.8, 17.2 Hz, 1 H, 18-H), 4.99 (ddd, ^3J = 1.6, 3.3, 10.2 Hz, 1 H, 18′-H), 3.74 (s, 2 H, 8-H), 3.56 (d, ^3J = 7.2 Hz, 2 H, 13-H), 2.89 (ddd, ^3J = 1.5, 6.3, 7.2 Hz, 2 H, 16-H), 1.45 (s, 6 H, 20-H and 21-H), 1.00 [s, 9 H, $SiC(CH_3)_3$] ppm.

^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.71 (m, 4 H, SiPh), 7.22 (m, 6 H, SiPh), 6.45 (t, ^3J = 0.9 Hz, 1 H, 11-H), 5.84–5.48 (m, 3 H, 14-H, 15-H, and 17-H), 5.03 (qd, ^3J = 1.8, 17.2 Hz, 1 H, 18-H), 4.96 (ddd, ^3J = 1.6, 3.4, 10.0 Hz, 1 H, 18′-H), 3.88 (s, 2 H, 8-H), 3.55 (d, ^3J = 7.3 Hz, 2 H, 13-H), 2.74 (ddd, ^3J = 1.4, 6.2, 7.4 Hz, 2 H, 16-H), 1.43 (s, 6 H, 20-H and 21-H), 1.13 [s, 9 H, $SiC(CH_3)_3$] ppm. ^{1}H NMR (500 MHz, C_6D_6, 25 °C): δ = 7.70 (m, 4 H, SiPh), 7.22 (m, 6 H, SiPh), 6.45 (t, ^3J = 1.2 Hz, 1 H, 11-H), 5.82–5.50 (m, 3 H, 14-H, 15-H, and 17-H), 5.03 (ddd, ^3J = 1.7, 3.5, 17.2 Hz, 1 H, 18-H), 4.95 (ddd, ^3J = 1.7, 3.2, 10.3 Hz, 1 H, 18′-H), 3.88 (s, 2 H, 8-H), 3.55 (d, ^3J = 7.3 Hz, 2 H, 13-H), 2.75 (t, ^3J = 6.7 Hz, 2 H, 16-H), 1.43 (s, 6 H, 20-H and 21-H), 1.13 [s, 9 H, $SiC(CH_3)_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.7 (s, C-10), 155.1 (s, C-12), 136.8 (d, C-17), 135.8 (d, SiPh), 133.7 (s, SiPh), 129.7 (d, SiPh), 128.8 (d, C-15), 127.7 (d, SiPh), 127.3 (d, C-14), 115.1 (t, C-18), 112.1 (d, C-11), 72.9 (t, C-8), 43.1 (s, C-9), 31.7 (t, C-16), 29.8 (t, C-13), 26.9 [q, $SiC(CH_3)_3$], 25.5 (q, C-20 and C-21), 19.5 [s, $SiC(CH_3)_3$] ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 177.6 (s, 10-C), 155.7 (s, C-12), 137.1 (d, C-17), 136.3 (d, SiPh), 134.2 (s, SiPh), 130.2 (d, SiPh), 128.8 (d, C-15), 128.3 (d, SiPh), 128.1 (d, C-14), 115.2 (t, C-18), 112.5 (d, C-11), 73.4 (t, C-8), 43.5 (s, C-9), 32.0 (t, C-16), 30.3 (t, C-13), 27.3 [q, $SiC(CH_3)_3$], 25.7 (q, C-20 and C-21), 19.8 [s, $SiC(CH_3)_3$] ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 177.6 (s, C-10), 155.7 (s, C-12), 137.1 (d, C-17), 136.3 (d, SiPh), 134.2 (s, SiPh), 130.2 (d, SiPh), 128.8 (d, C-15), 128.3 (d, SiPh), 128.1 (d, C-14), 115.2 (t, C-18), 112.5 (d, C-11), 73.4 (t, C-8), 43.5 (s, C-9), 32.0 (t, C-16), 30.3 (t, C-13), 27.3 [q, $SiC(CH_3)_3$], 25.8 (q, C-20 and C-21), 19.8 [s, $SiC(CH_3)_3$] ppm. (+)-HRESIMS: calcd. for $C_{29}H_{38}NOSSi$ $[M + H]^+$ 476.2443; found 476.2441.

2-(2-Benzyloxy-1,1-dimethylethyl)thiazol-4-ethanal (10): To a stirred solution of 3-(benzyloxy)-2,2-dimethylpropanethioamide (2.8 g, 12.4 mmol) in ethanol (35 mL) was added ethyl 4-chloro-3-oxo-butyrate (2.4 mL, 17.4 mmol). The reaction mixture was heated at reflux for 24 h. The solvent was evaporated under reduced pressure and a saturated aqueous solution of $NaHCO_3$/diethyl ether (1:1, 50 mL) was added to the residue. The aqueous phase was extracted with diethyl ether (3 × 25 mL), and the combined organic extracts were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was flash chromatographed (silica gel, 30% ethyl acetate in hexanes) to give ethyl 2-(2-benzyloxy-1,1-dimethylethyl)thiazol-4-acetate as a brown oil (3.7 g, 95%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.32 (m, 5 H, Ph), 7.05 (s, 1 H, 11-H), 4.52 (s, 2 H, CH_2Ph), 4.23 (q, 2 H, OCH_2CH_3), 3.82 (s, 2 H, 13-H), 3.62 (s, 2 H, 8-H), 1.43 (s, 6 H, 20-H and 21-H), 1.22 (t, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 177.1 (s, C-10), 170.2 (s, C-14), 148.3 (s, C-12), 139.2 (s, Ph), 128.5 (d, Ph), 127.6 (d, Ph), 115.3 (d, C-11), 79.4 (t, C-8), 73.4 (t, *C*H_2Ph), 61.2 (t, O*C*H_2CH$_3$), 42.2 (s, C-9), 38.1 (t, C-13), 26 (q, C-20 and C-21), 14.0 (q, OCH$_2$*C*H$_3$) ppm.

To a stirred solution of ethyl 2-(2-benzyloxy-1,1-dimethylethyl)-thiazol-4-acetate (1 g, 3.0 mmol) in anhydrous toluene (20 mL) at –80 °C was slowly added DIBAL-H (3.6 mL, 3.6 mmol). The internal temperature was maintained at –78 °C. After 20 min, the addition of DIBAL-H (1.2 mL, 0.9 mmol) was repeated. The reaction was followed by TLC. When the starting material was not observed, the reaction was quenched with methanol and then poured into ice with a 10% solution of hydrochloric acid. After 15 min, the mixture was extracted with ethyl acetate (3 × 100 mL), and the organic phase was dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was flash chromatographed (silica gel, 20% ethyl acetate in hexanes) to give 2-(2-benzyloxy-1,1-dimethylethyl)-thiazol-4-ethanal (**10**) as a yellow oil (0.8 g, 95%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 9.83 (t, 1 H, 14-H), 7.32 (m, 5 H, Ph), 7.02 (s, 1 H, 11-H), 4.52 (s, 2 H, CH_2Ph), 3.82 (d, 2 H, 13-H), 3.62 (s, 2 H, 8-H), 1.45 (s, 6 H, 20-H and 21-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 199.2 (s, C-14), 178.2 (s, C-10), 147.4 (s, C-12), 138.3 (s, Ph), 128.5 (d, Ph), 127.6 (d, Ph), 115.4 (d, C-11), 79.3 (t, C-8), 73.2 (t, CH_2Ph), 46.2 (t, C-13), 42.3 (s, C-9), 26 (q, C-20 and C-21) ppm.

2-(2-Benzyloxy-1,1-dimethylethyl)-4-(2*Z*)-hexa-2,5-dienylthiazole (11): To a stirred suspension of 3-butenyltriphenylphosphonium bromide (0.058 g, 0.15 mmol), in anhydrous tetrahydrofuran, a solution of butyllithium in hexanes (0.1 mL, 0.15 mmol) was slowly added. After 10 min, a solution of 2-(2-benzyloxy-1,1-dimethylethyl)thiazol-4-ethanal (**10**) (0.041 g, 0.15 mmol) in tetrahydrofuran (1 mL) was added. The reaction was followed by TLC. When the starting material was no longer observed, water (10 mL) was added to the reaction. The mixture was extracted with diethyl ether (3 × 5 mL), and the combined organic extracts were washed with saturated aqueous solution of NaCl (3 × 20 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was flash chromatographed (silica gel, 5% ethyl acetate in hexanes) to give 2-(2-benzyloxy-1,1-dimethylethyl)-4-(2*Z*)-hexa-2,5-dienylthiazole (**11**) as a yellow oil (0.020 g, 41%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.33 (m, 5 H, Ph), 6.75 (t, 1 H, 11-H), 5.72 (m, 1 H, 17-H), 5.75 (m, 1 H, 14-H), 5.62 (m, 1 H, 15-H), 5.05 (m, 1 H, 18-H), 4.54 (s, 2 H, CH_2Ph), 3.63 (s, 2 H, 8-H), 3.56 (d, 1 H, 13-H), 2.89 (t, 1 H, 16-H), 1.35 (s, 6 H, 20-H and 21-H) ppm.

4-Allyl-2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]thiazole (12a): A solution of trivinylindium (1.2 mmol, ≈ 0.1 M) (prepared following the general procedure) was added to a mixture of 4-bromomethyl-2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]thiazole (**6a**) (0.5 g, 1.02 mmol) and palladium catalyst {[1,1′-bis(diphenylphosphanyl)ferrocenedichloropalladium(II)], complex with dichloromethane 1:1} (0.029 g, 0.036 mmol) in anhydrous tetrahydrofuran (5 mL) heated at reflux. The resulting mixture was heated at reflux under an argon atmosphere until the starting material was consumed, and the reaction was then quenched by the addition of a few drops of methanol. The mixture was concentrated in vacuo and Et_2O (10 mL) was added. The organic phase was washed with aqueous HCl (10%, 10 mL), saturated aqueous $NaHCO_3$ (30 mL), and saturated aqueous NaCl (30 mL), dried, filtered, and concentrated in vacuo. The residue was flash chromatographed (silica gel, 10% ethyl acetate in hexanes) to give 4-allyl-2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]thiazole (**12a**) as a yellowish oil (0.36 g, 80%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.60 (m, 4 H, SiPh), 7.38 (m, 6 H, SiPh), 6.80 (t, ^3J = 0.9 Hz, 1 H, 11-H), 6.09 (tdd, ^3J = 6.7, 10.1, 16.9 Hz, 1 H, 14-H), 5.16 (m, 2 H, 15-H), 3.77 (s, 2 H, 8-H), 3.57 (ddd, ^3J = 1.3, 2.4, 6.7 Hz, 2 H, 13-H), 1.47 (s, 6 H, 20-H and 21-H), 1.02 [s, 9 H, $SiC(CH_3)_3$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 177.7 (s, C-10), 154.8 (s, C-12), 135.8 (d, SiPh), 135.7 (d, C-14), 133.7 (s, SiPh), 129.7 (d, SiPh), 127.7 (d, SiPh), 116.7 (t, C-15), 112.5 (d, C-11), 72.9 (t, C-8), 43.1 (s, C-9), 36.3 (t, C-13), 26.9 [q, $SiC(CH_3)_3$], 25.6 (q, C-20and C-21), 19.5 [s, $SiC(CH_3)_3$] ppm. (+)-LRESIMS: *m*/*z* (%) = 436 (61) $[M + H]^+$, 458 (100) $[M + Na]^+$, 474 (8) $[M + K]^+$.

4-Allyl-2-(2-benzyloxy-1,1-dimethylethyl)thiazole (12b): A solution of trivinylindium (2 mmol, ≈ 0.1 M) (prepared following the general procedure) was added to a mixture of 4-bromomethyl-2-(2-benzyloxy-1,1-dimethylethyl)thiazole (**6b**) (0.7 g, 2 mmol) and palladium catalyst {[1,1′-bis(diphenylphosphanyl)ferrocenedichloropalladium(II)], complex with dichloromethane 1:1} (0.032 g, 0.04 mmol) in anhydrous tetrahydrofuran (7 mL) heated at reflux. The resulting mixture was heated at reflux under an argon atmosphere until the starting material was consumed, and the reaction

was then quenched by the addition of a few drops of methanol. The mixture was concentrated in vacuo and Et_2O (10 mL) was added. The organic phase was washed with aqueous HCl (10%, 15 mL), saturated aqueous $NaHCO_3$ (15 mL), and saturated aqueous NaCl (15 mL), dried, filtered, and concentrated in vacuo. The residue was flash chromatographed (silica gel, 10% ethyl acetate in hexanes) to give 4-allyl-2-(2-benzyloxy-1,1-dimethylethyl)thiazole (**12b**) as a colorless oil (0.45 g, 80%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.31 (m, 5 H, Ph), 6.79 (t, ^3J = 0.9 Hz, 1 H, 11-H), 6.08 (m, 1 H, 14-H), 5.18 (qd, $^3J_{H,H}$ = 1.7, 4.3 Hz, 1 H, 15-H), 5.11 (t, ^3J = 1.3 Hz, 1 H, 15′-H), 4.52 (s, 2 H, CH_2Ph), 3.62 (s, 2 H, 8-H), 3.56 (ddd, ^3J = 1.3, 2.4, 6.8 Hz, 2 H, 13-H), 1.47 (s, 6 H, 20-H and 21-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 177.5 (s, C-10), 154.5 (s, C-12), 138.5 (s, Ph), 135.4 (d, C-14), 128.2 (d, Ph), 127.3 (d, Ph), 116.5 (t, C-15), 112.5 (d, C-11), 79.0 (t, C-8), 73.2 (t, CH_2Ph), 41.9 (s, C-9), 36.0 (t, C-13), 25.9 (q, C-20 and C-21) ppm. (+)-LRESIMS: *m*/*z* (%) = 288 (65) $[M + H]^+$, 310 (100) $[M + Na]^+$.

6{2-[2-(*tert*-Butyldiphenylsilyloxy)-1,1-dimethylethyl]thiazol-4-yl}hex-4-enyl-4-methylbenzenesulfonate (13): To a stirred solution of tricyclohexylphosphane[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium(IV) dichloride (Grubbs′ ruthenium catalyst) (4.7 mg, 0.0055 mmol) in anhydrous toluene (0.250 mL), was slowly added a solution of 4-allyl-2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]thiazole (**12a**) (0.033 g, 0.076 mmol) and 4-octene-1,8-ditosylate (0.063 g, 0.139 mmol) in toluene (0.5 mL). The reaction mixture was heated at 80 °C for 18 h, and the reaction was then quenched by the addition of a few drops of methanol. The reaction mixture was suspended into silica gel and flash chromatographed (silica gel, 8% diethyl ether in hexanes) to give 6{2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]thiazol-4-yl}hex-4-enyl-4-methylbenzenesulfonate (**13**) as a mixture *Z*/*E* isomers (1:7) as a colorless oil (0.024 g, 50%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.79 (m, 2 H, Ts), 7.57 (m, 4 H, SiPh), 7.41 (m, 2 H, Ts), 7.34 (m, 6 H, SiPh), 6.71 (s, 1 H, 11-H), 5.63 (ttd, ^3J = 1.1, 6.7, 14.9 Hz, 1 H, 14-H), 5.45 (m, 1 H, 15-H), 4.04 (t, ^3J = 6.3 Hz, 2 H, 18-H), 3.74 (s, 2 H, 8-H), 3.43 (d, ^3J = 6.7 Hz, 2 H, 13-H), 2.43 (s, 3 H, Ts), 2.08 (q, ^3J = 6.9 Hz, 2 H, 17-H), 1.73 (td, ^3J = 6.5, 13.4 Hz, 2 H, 16-H), 1.45 (s, 6 H, 20-H and 21-H), 1.00 [s, 9 H, $SiC(CH_3)_3$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.7 (s, C-10), 155.2 (s, C-12), 144.8 (s, Ts), 135.8 (d, SiPh), 133.6 (s, Ts), 133.4 (s, SiPh), 130.4 (t, C-15), 129.9 (d, Ts), 129.7 (d, SiPh), 128.6 (d, C-14), 128.0 (d, Ts), 127.7 (d, SiPh), 112.3 (d, C-11), 72.9 (t, C-8), 69.9 (t, C-18), 43.1 (s, C-9), 34.9 (t, C-13), 28.6 (q, C-16), 28.3 (q, C-17), 26.9 [q, $SiC(CH_3)_3$], 25.6 (q, C-20 and C-21), 21.7 (q, Ts), 19.5 [s, $SiC(CH_3)_3$] ppm. (+)-HRESIMS: calcd. for $C_{36}H_{46}NO_4S_2Si$ $[M + H]^+$ 648.2638; found 648.2699.

(*E*)-2-[2-(*tert*-Butyldiphenylsilyloxy)-1,1-dimethylethyl]-4-(hexa-2,5-dienyl)thiazole (14a): To a stirred solution of 6{2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]thiazol-4-yl}hex-4-enyl-4-methylbenzenesulfonate (**13**) (0.023 g, 0.035 mmol) and sodium iodide (0.016 g, 0.107 mmol) in anhydrous dimethylethylenglycol (0.35 mL), 1,8-diazabicylo[5.4.0]-undec-7-ene (0.01 mL, 0.065 mmol) was added. The reaction mixture was heated at reflux. After 2 h, the reaction was diluted with diethyl ether (2 mL) and water (2 mL) was also added. The aqueous phase was extracted with diethyl ether (3 × 2 mL), and the combined organic extracts were washed with a saturated aqueous solution of NaCl (5 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was flash chromatographed (silica gel, 2% diethyl ether in hexanes) to give (*E*)-2-[2-(*tert*-butyldiphenylsilyloxy)-1,1-dimethylethyl]-4-(hexa-2,5-dienyl)thiazole (**14a**) as a colorless oil (0.0034 g, 20%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.57 (m, 4 H, SiPh), 7.41 (m, 2 H, SiPh), 7.34 (m, 4 H, SiPh), 6.77 (s, 1 H, 11-H), 5.84 (ttd, ^3J = 6.4, 10.1, 16.6 Hz, 1 H, 17-H), 5.70 (ttd, ^3J = 1.2, 6.6, 14.6 Hz, 1 H, 14-H), 5.59 (m, 1 H, 15-H), 5.05 (ddd, ^3J = 1.7, 3.4, 17.2 Hz, 1 H, 18-H), 5.00 (ddd, ^3J = 1.3, 3.0, 10.0 Hz, 1 H, 18′-H), 3.75 (s, 2 H, 8-H), 3.53 (d, ^3J = 6.6 Hz, 2 H, 13-H), 2.80 (ddt, ^3J = 1.0, 2.5, 6.4 Hz, 2 H, 16-H), 1.46 (s, 6 H, 20-H and 21-H), 1.00 [s, 9 H, $SiC(CH_3)_3$] ppm. ^{1}H NMR (500 MHz, C_6D_6, 25 °C): δ = 7.70 (m, SiPh), 7.22 (m, SiPh), 6.44 (d, ^3J = 0.9 Hz, 1 H, 11-H), 5.80–5.45 (m, 3 H, 14-H, 15-H and 17-H), 5.02 (m, 1 H, 18-H), 4.97 (m, 1 H, 18′-H), 3.88 (s, 2 H, 8-H), 3.51 (d, ^3J = 6.6 Hz, 2 H, 13-H), 2.66 (t, ^3J = 6.3 Hz, 2 H, 13-H), 1.13 (s, 6 H, 20-H and 21-H), 0.42 [s, 9 H, $SiC(CH_3)_3$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.1 (d, C-17), 135.8 (d, SiPh), 133.6 (s, SiPh), 129.7 (d, SiPh), 127.7 (d, SiPh), 115.3 (t, C-18), 112.5 (d, C-11), 72.8 (t, C-8), 43.2 (s, C-9), 36.8 (t, C-16), 34.8 (t, C-13), 26.9 [q, $SiC(CH_3)_3$], 25.6 (q, C-20 and C-21), 19.5 [s, $SiC(CH_3)_3$] ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 177.5 (s, C-10), 156.1 (s, C-12), 137.4, 136.3, 134.2, 130.2, 129.0, 115.5 (t, C-18), 112.7 (d, C-11), 73.4 (t, C-8), 43.6 (s, C-9), 35.7 (t, C-13), 32.6 (t, C-16), 27.3 [q, $SiC(CH_3)_3$], 25.8 (q, C-20 and C-21), 19.8 [s, $SiC(CH_3)_3$] ppm. (+)-HRESIMS: calcd. for $C_{29}H_{38}NOSSi$ $[M + H]^+$ 476.2443; found 476.2455.

2-(2-Benzyloxy-1,1-dimethylethyl)-4-(2*E*)-hexa-2,5-dienylthiazole (14b): In a sealed tube was placed tricyclohexylphosphane[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium(IV) dichloride (Grubbs′ ruthenium catalyst) (6.5 mg, 0.0076 mmol) and was added a mixture of a 0.7 M solution of 1,4-pentadiene in anhydrous dichloromethane (1 mL, 0.70 mmol) and 4-allyl-2-(2-benzyloxy-1,1-dimethylethyl)thiazole (**12b**) (0.026 g, 0.09 mmol). The tube was sealed under an argon atmosphere and heated to 40 °C. After 24 h, the solvent was evaporated under reduced pressure and the catalyst was separated by flash chromatography (silica gel, 50% diethyl ether in hexanes) to give a mixture of starting material and 2-(2-benzyloxy-1,1-dimethylethyl)-4-(2*E*)-hexa-2,5-dienylthiazole (**14b**). The yield of the reaction was calculated using the integration of the 11-H and 16-H ^{1}H NMR signals. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.30 (m, Ph), 6.76 (t, ^3J = 0.9 Hz, 11-H), 5.93–5.43 (m, 14-H, 15-H, and 17-H), 5.06–4.96 (m, 18-H and 18′-H), 4.52 (s, CH_2Ph), 3.61 (s, 8-H), 3.51 (d, ^3J = 6.6 Hz, 13-H), 2.81 (t, ^3J = 6.3 Hz, 16-H), 1.47 (s, 20-H and 21-H) ppm. (+)-HRESIMS: calcd. for $C_{20}H_{26}NOS$ $[M + H]^+$ 328.1735; found 328.1735.

Supporting Information (see footnote on the first page of this article): ^{1}H NMR, ^{13}C NMR, and mass spectra for all synthetic compounds.

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