Synthesis of Novel Mercaptophenyl Carbocyclic *C*-Nucleoside Analogue Using Sequential [3,3]-Sigmatropic Rearrangement and Ring-closing Metathesis

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Novel mercaptophenyl carbocyclic *C*-nucleoside analogue was synthesized *via* a cyclopentenol intermediate **10**, which was prepared using a sequential [3,3]-sigmatropic rearrangement and ring-closing metathesis (RCM). Friedel-Crafts alkylation was then used to couple the thiophenol.

Key Words : Carbocyclic *C*-nucleoside, [3,3]-Sigmatropic rearrangement, Ring-closing metathesis, Friedel-Crafts alkylation

Introduction

Recently, aromatic *C*-nucleosides[1] for both information storage and retrieval of DNA were synthesized, which generally bind DNA quite nonselectively at almost any sequence. This has paved the way for the generation of new functional materials, a new genetic code, or novel antisense nucleotides.[2] The replacement of natural DNA bases with aromatic analogues can provide functions towards the expansion of the genetic alphabet and be used to align metal ions along a helical axis inside the duplex.[3]

Synthesis of natural carbocyclic and *C*-nucleoside analogues have been inspired by their interesting biological activities as well as their chemical and enzymatic stability.[4] *C*-nucleosides are a unique class of nucleosides in which the heterocyclic is connected to sugar moiety by a *C-C* bond instead of the *C-N* bond of natural nucleosides.[5] As a result, they are resistant to the chemical and enzymatic hydrolytic cleavage of the glycosidic bond.

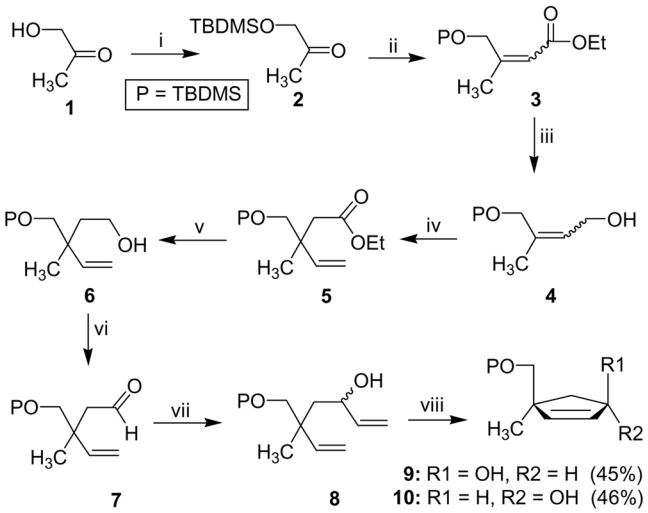
Therefore, as a part of our drug discovering program, a novel mercaptophenyl carbocyclic *C*-nucleoside analogue, which combine the properties of the enzyme resistant carbocyclic carbohydrate moiety[6] and the redox-active nucleosidic base, were synthesized using thiophenol. This paper reports the synthetic route employing a versatile reaction sequence ([3,3]-sigmatropic rearrangement, ring-closing metathesis, and Friedel-Crafts alkylation) from a simple acyclic starting material.

Results and Discussion

As shown in Scheme 1, the α,β-unsaturated ethylester **3** was synthesized from acetol **1** and reduced by DIBALH at –78 °C in CH_2Cl_2 to give the allylic alcohol **4**. The allylic alcohol was subjected to a [3,3]-sigmatropic rearrangement using triethylorthoacetate to produce the γ,δ-unsaturated ester **5**.[7] The ester derivative **5** was reduced to alcohol **6** by DIBALH, which was then oxidized to the aldehyde **7** using PCC. The slow addition of vinylmagnesium bromide to a solution of the aldehyde **7** in THF at –78 °C could furnish the divinyl intermediate **8**.

Using the divinyl **8**, the formation of five-membered carbocycle was examined. RCM[8] now stands as one of the most powerful tools for preparing medium to large ring systems through *C-C* bond formation. This powerful procedure was successfully adopted for the elaboration of our desired five member carbocyclic moiety. Therefore, the divinyl **8** was subjected to ring-closing metathesis conditions using the 2nd generation Grubbs' catalyst [$(Im)Cl_2PCy_3Ru$-CHPh] to afford the cyclopentenol **9** (45%) and **10** (46%), respectively.[9] The relative stereochemistry of the cyclopentenol products (**9** and **10**) was determined by employing the NOE experiment between the proximal hydrogen atoms. Upon the irradiation of C_1-H, a relatively strong NOE was observed at the methyl protons of compound **9** [C_4-H (0.7%)], but not at the methyl protons of compound **10** [C_4-H (0.2%)] (Figure 1).

To our surprise, the Friedel-Craft approach *via* electrophilic aromatic disulfide was applied successfully to the allylic position of the carbocyclic system, which is usually



Scheme 1. Synthesis of cyclopentenol intermediates. Reagents: i) TBDMSCI, CH_2Cl_2, imidazole; ii) Triethylphosphonoacetate, NaH, THF; iii) DIBALH, CH_2Cl_2, –20 °C; iv) Triethylorthoacetate, propionic acid, overnight, 130-135 °C; v) DIBALH, toluene, –78 °C; vi) PCC, 4MS, CH_2Cl_2; vii) CH_2=CHMgBr, THF, –78 °C; viii) Grubbs' catalyst II, CH_2Cl_2, reflux, overnight.

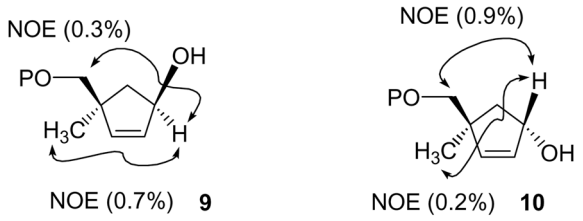


Figure 1. NOE comparisons of compound **9** and **10**.

employed in the furanose system.[10] The activation of the hydroxyl group of compound **10** to the acetoxy group **11** was made using acetic anhydride, which was coupled to phenyl disulfide in the condition of $SnCl_4$ as a Lewis acid to give the desired disulfide derivative **12**. The disulfide linkage of compound **12** was reduced successfully by $LiAlH_4$ to provide the thiophenol analogue **13**, and which was readily desilyated by a treatment with tetrabutylammonium fluoride (TBAF) to provide compound target aromatic *C*-nucleoside analogue **14**. Although the structure of compound synthesized analogue is quite different from the classical nucleosides, its antiviral activity was evaluated against a wide variety of DNA and RNA viruses [herpes simplex virus type 1 (HSV-1 strain KOS) and type-2, starin G], vaccinia virus, vesicular stomatitis virus, thymidine kinase-deficient (TK HSV-1 stain KOS), varicella-zoster virus (TK VZV stain Oka and TK strain 07/1), cytomegalovirus (stain AD-169 and Davis), Coxackie B4 virus]. However, this structure did not show any significant antiviral activity against several viruses.

The synthetic information obtained in the present study will be useful for the synthesis of novel aromatic C-nucleosides and their derivatives to clarify the mechanism of the disulfide base-pairing for base-to-base formation during the incorporation of synthetic aromatic *C*-nucleosides into DNA.

In summary, a synthetic procedure of novel non-classical nucleoside analogue was developed using sequential Johnson's Claisen rearrangement, ring-closing metathesis, and Friedel-Crafts alkylation. In our laboratory, this reiterative three-step sequences (*i.e.* [3,3]-sigmatropic rearrangement, ring-closing metathesis, and Friedel-Crafts reaction) have been widely used for the synthesis of a variety of non-classical aromatic nucleoside analogues and their phosphramidite derivatives.

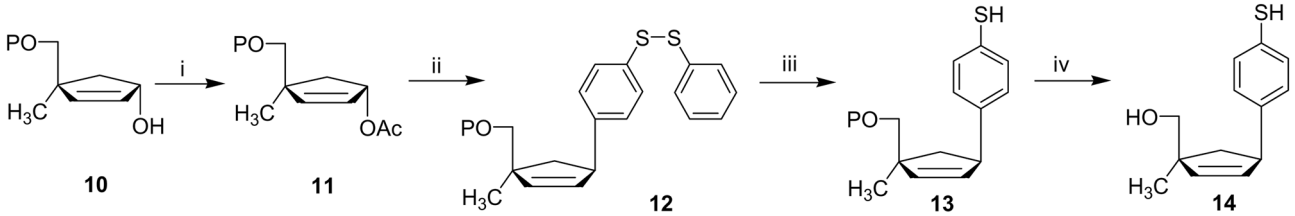
Experiments

The melting points were determined on a Mel-temp II laboratory device and were uncorrected. The NMR spectra were recorded on a Bruker 300 Fourier transform spectrometer; the chemical shifts are reported in parts per million (δ) and the signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublets). The UV spectra were obtained on a Beckman DU-7 spectrophotometer. The elemental analyses were performed using an Elemental Analyzer System (EA1112). The TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Unless stated otherwise, all the reactions were carried out in a N_2 atmosphere. Dry dichloromethane, benzene and pyridine were obtained by distillation from CaH_2. Dry THF was obtained by distillation from Na and benzophenone immediately before use.

2-(*t*-Butyldimethylsilyloxy)-acetone (2): TBDMSCl (44 g, 0.297 mol) was added slowly to a solution of acetol **1** (20 g, 0.27 mol) and imidazole (27 g, 0.405 mol) in CH_2Cl_2 (300 mL) at 0 °C, and stirred for 5 h at the same temperature. The solvent was evaporated under reduced pressure. The residue was extracted twice with diethyl ether and water. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give compound **2** (39.6 g, 78%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.05 (s, 2H), 2.07 (s, 3H), 0.84 (s, 9H), 0.07 (s, 6H).

(E) and (Z)-4-(*t*-Butyldimethylsilyloxy)-3-methyl-but-2-enoic acid ethyl ester (3): Triethyl phosphonoacetate (1.405 mL, 9.25 mmol) was added drop wise to a suspension of sodium hydride (60% in mineral oil, 0.37 g, 9.25 mmol) in distilled THF at 0 °C, and stirred constant at room temperature for 1 h. The ketone **2** (1.74 g, 9.25 mmol) was added to this mixture and stirred for 1 h. The solution was neutralized with AcOH, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give compound **3** (2.29 g, 96%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.99 (s, 1H), 4.17 (q, J = 6.9 Hz, 2H), 4.13 (s, 2H), 2.05, 1.96 (s, s, 3H), 1.22 (t, J = 6.7 Hz, 3H), 0.93, 0.90 (s, s, 9H), 0.09, 0.08 (s, s, 6H).

(*E*,*Z*)-4-(*t*-Butyldimethylsilyloxymethyl)-3-methyl-but-2-en-1-ol (4): DIBALH (53.9 mL, 1.0 M solution in hexane) was added slowly to a solution of compound **3** (6.64 g, 25.7 mmol) in CH_2Cl_2 (150 mL) at −20 °C, and stirred for 1 h at the same temperature. Methanol (53 mL) was then added to the resulting mixture. The mixture was stirred at room temperature for 3 h, and the resulting solid was filtered through a Celite pad. The filtrate was concentrated under



Scheme 2. Synthesis of mercaptophenyl carbocyclic *C*-nucleoside.

vacuum, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to give the allylic alcohol **4** (4.95 g, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.68 (br s, 1H), 4.21 (d, J = 6.6 Hz, 2H), 4.03 (s, 2H), 1.77, 1.64 (s, s, 3H), 0.91 (s, 9H), 0.07 (s, 6H).

(±)-3-(*t*-Butyldimethylsilyloxymethyl)-3-methyl-pent-4-enoic acid ethyl ester (5): Propionic acid (0.5 mL) was added to a solution of allylic alcohol **4** (6 g, 27.73 mmol) in tiethyl orthoacetate (110 mL), and the mixture was heated at 130-135 °C overnight with constant stirring under conditions suitable for the removal of ethanol by distillation. The excess triethyl orthoaceate was distilled off and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give compound **5** (6.59 g, 83%) as a colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.91 (d, J = 10.8 Hz, 1H), 5.89 (d, J = 11.4 Hz, 1H), 5.05 (d, J = 1.2 Hz, 1H), 5.02 (d, J = 7.5 Hz, 1H), 4.01 (q, J = 7.2 Hz, 2H), 3.46 (d, J = 9.3 Hz, 1H), 3.41 (d, J = 9.3 Hz, 1H), 2.40 (d, J = 3.3 Hz, 2H), 1.23 (t, J = 7.5 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.94, 143.11, 112.99, 69.91, 59.83, 41.33, 25.81, 22.60, 20.70, 18.20, 14.26, -5.58.

(±)-3-(*t*-Butyldimethylsilyloxymethyl)-3-methyl-pent-4-en-1-ol (6) DIBALH (33.98 mL, 1.0 M solution in hexane) was added slowly to a solution of compound **5** (7.5 g, 16.18 mmol) in CH_2Cl_2 (200 mL) at −20 °C, and stirred for 1 h. Methanol (34 mL) was then added to the resulting mixture. The mixture was stirred at room temperature for 2 h, and the resulting solid was filtered through a Celite pad. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:6) to give the alcohol **6** (3.56 g, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.89 (dd, J = 17.7, 11.4 Hz, 1H), 5.06 (dd, J = 4.5, 1.2 Hz, 1H), 5.02 (dd, J = 10.5, 0.9 Hz, 1H), 3.67 (dd, J = 11.7, 6.3 Hz, 1H), 3.46 (d, J = 9.6 Hz, 1H), 3.38 (d, J = 9.6 Hz, 1H), 1.69 (t, J = 5.7 Hz, 2H), 1.00 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.45, 112.80, 70.81, 59.34, 41.18, 25.84, 21.04, 18.29, −5.52; Anal calc for $C_{13}H_{28}O_2Si$: C, 63.87; H, 11.55. Found: C, 63.74; H, 11.61.

(±)-3-(*tert*-Butyl-dimethylsilyloxymethyl)-3-methyl-pent-4-enal (7): 4 Å molecular sieves (4.2 g) and PCC (3.87 g, 18.13 mmol) were added slowly to a solution of compound **6** (1.76 g, 7.2 mmol) in CH_2Cl_2 (100 mL) at 0 °C, and stirred overnight at rt. An excess of diethyl ether (200 mL) was then added to the mixture. The mixture was stirred vigorously for 2 h at the same temperature, and the resulting solid was filtered through a short silica gel column. The filtrate was concentrated under vacuum and purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give compound **7** (1.39 g, 80%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.75 (t, J = 3.3 Hz, 1H), 5.96 (d, J = 11.1 Hz, 1H), 5.90 (d, J = 10.8 Hz, 1H), 5.14 (d, J = 8.4 Hz, 1H), 5.11 (d, J = 16.2 Hz, 1H), 3.49 (d, J = 9.6 Hz, 1H), 3.40 (d, J = 9.3 Hz, 1H), 2.41 (t, J = 3.0 Hz, 2H), 1.12 (s, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.08, 142.61, 113.93, 70.53, 50.70, 41.60, 25.80, 21.30, −5.61.

(*rel*)-(3R and 3S,5S)-5-(*tert*-Butyl-dimethylsilyloxymethyl)-5-methyl-hepta-4-1,6-diene-3-ol (8): Vinylmagnesium bromide (9.8 mL, 1 M solution in THF) was added slowly to a solution of compound **7** (2.83 g, 8.89 mmol) in anhydrous THF at −78 °C and stirred for 2 h at the same temperature. The mixture was quenched with a saturated ammonium chloride solution (10 mL), and elevated to room temperature. The mixture was extracted with EtOAc and water, and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, and then filtered. The filtrate was concentrated under reduced pressure, and purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give a mixture of compound **8** (2.19 g, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.02-5.74 (m, 2H), 5.27-4.99 (m, 4H), 4.25 (br s, 1H), 3.56-3.40 (m, 2H), 1.70-1.56 (m, 2H), 1.08, 1.02 (s, s, 3H), 0.91 (s, 9H), 0.08 (s, 6H).

(*rel*)-(1*R*,4*S*)-4-(*tert*-Butyldimethylsilanyloxymethyl)-4-methyl-cyclopenten-2-ol (9); and (*rel*)-(1*S*,4*S*)-4-(*tert*-butyldimethylsilanyloxymethyl)-4-methyl-cyclopenten-2-ol (10): A 2nd generation Grubbs' catalyst (22 mg, 0.025 mmol) was added to a solution of compound **8** (935 mg, 3.46 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was refluxed overnight, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to give the cyclopentenol **9** (377 mg, 45%) and compound **10** (386 mg, 46%); compound **9**: Spectra for **9**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.81 (dd, J = 5.4, 2.1 Hz, 1H), 5.45 (d, J = 5.7 Hz, 1H), 4.50 (t, J = 7.8 Hz, 1H), 3.32 (s, 2H), 1.83 (dd, J = 14.1, 6.9 Hz, 1H), 1.67 (d, J = 14.1, 1H), 0.95 (s, 3H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.34, 133.89, 76.14, 69.35, 50.04, 45.20, 25.99, 23.32, 18.57, -5.52; ; Anal calc for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.32; H, 10.98. Spectra for **10**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.73 (m, 2H), 4.84 (t, J = 6.0 Hz, 1H), 3.32 (s, 2H), 2.29 (dd, J = 13.5, 7.5 Hz, 1H), 1.37 (dd, J = 13.5, 4.2 Hz, 1H), 1.11 (s, 3H), 0.87 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.50, 133.02, 77.61, 70.64, 50.94, 44.83, 25.83, 24.67, 18.23, −5.50; Anal calc for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.56; H, 10.76.

(*rel*)-(1*S*,4*S*)-1-Acetoxy-4-(*tert*-butyldimethylsilanyloxymethyl)-4-methyl-cyclopenten-2-ene (11): Acetic anhydride (1.64 g, 16.08 mmol) and dimethylaminopyridine (131 mg, 1.072 mmol) were added to a solution of compound **10** (2.6 g, 10.72 mmol) in anhydrous pyridine (15 mL) at 0 °C. The mixture was then stirred overnight at room temperature. A sat. $NaHCO_3$ (5 mL) solution was added to the mixture and concentrated under reduced pressure. The residue was extracted with EtOAc/water, and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, and then filtered. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give compound **11** (2.59 mg, 85%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.71 (m, 1H), 5.59 (m, 1H), 4.29 (dd, J = 12.6, 6.8 Hz, 1H), 3.36 (s, 2H), 2.23 (dd, J = 13.4, 7.4 Hz, 1H), 2.07 (s, 3H), 1.53 (dd, J = 13.4, 4.4 Hz, 1H), 1.10 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.78, 141.54, 133.32, 77.54, 75.34, 51.02, 44.65, 25.73, 24.43,

18.54, 17.14, −5.55; Anal calc for $C_{15}H_{28}O_3Si$: C, 63.33; H, 9.92. Found: C, 63.12; H, 10.09.

(*rel*)-(1*S*,4*S*)-*t*-Butyldimethyl-[1-methyl-4-(4-phenyldisulfanylphenyl)-cyclopent-2-enylmethoxy]-silane (12): Phenyldisulfide (2.13 g, 9.75 mmol) was added to a solution of compound **11** (1.85 g, 6.5 mmol) in CH_2Cl_2 (7 mL) at –15 °C. $SnCl_4$ (13 mL, 1 M in CH_2Cl_2) was then added slowly to the mixture at the same temperature. The mixture was stirred for 5 h at 0 °C and quenched by adding a saturated $NaHCO_3$ solution (25 mL) and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and filtered. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:50) to give compound **12** (2.33 g, 81%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37-7.18 (m, 9H), 5.71 (dd, J = 5.4, 2.1 Hz, 1H), 5.60 (dd, J = 5.1, 1.5 Hz, 1H), 4.29 (dd, J = 12.6, 4.8 Hz, 1H), 3.31 (d, J = 10.5 Hz, 2H), 2.36 (dd, J = 13.8, 8.4 Hz, 1H), 1.61 (dd, J = 13.8, 4.8 Hz, 1H), 1.13 (s, 3H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.29, 140.57, 140.21, 136.32, 133.56, 130.73, 129.36, 128.43, 126.62, 76.98, 74.32, 51.54, 43.48, 25.73, 24.43, 18.54, −5.55; Anal calc for $C_{25}H_{34}OS_2Si$: C, 67.82; H, 7.74; S, 14.48. Found: C, 67.99; H, 7.87; S, 14.31.

(*rel*)-(1*S*,4*S*)-1-[4-(*tert*-Butyldimethylsilanyloxymethyl)-4-methyl-cyclopent-2-enyl]-benzenethiol (13): To a solution of compound **12** (1.83 g, 4.14 mmol) in anhydrous THF (40 mL) was slowly added $LiAlH_4$ (786 mg, 20.7 mmol) at 0 °C. The mixture was stirred overnight at room temperature and quenched by adding 1 N H_2SO_4 (4.5 mL), and the stirred for a further 10 min. The mixture was extracted with CH_2Cl_2/H_2O, and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, and then filtered. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give compound **13** (429 mg, 31%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35-7.17 (m, 4H), 5.85 (dd, J = 5.7, 2.4 Hz, 1H), 5.73 (dd, J = 4.5, 2.4 Hz, 1H), 4.29 (m, 1H), 3.55 (d, J = 2.7 Hz, 1H), 3.40 (s, 1H), 3.29 (d, J = 10.5 Hz, 2H), 2.22 (m, 1H), 1.70 (m, 1H), 1.11 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.60, 135.28, 133.44, 131.04, 128.83, 126.62, 76.48, 75.07, 52.43, 44.43, 25.56, 24.21, 18.32, −5.58; Anal calc for $C_{19}H_{30}OSSi$: C, 68.20; H, 9.04; S, 9.58. Found: C, 68.36; H, 8.90; S, 9.45.

(*rel*)-(1*S*,4*S*)-1-[4-(Hydoxymethyl)-4-methyl-cyclopent-2-enyl]-benzenethiol (14): TBAF (2.14 mL, 1.0 M solution in THF) was added to a solution of compound **13** (480 mg, 1.43 mmol) in THF (15 mL) at 0 °C. The mixture was stirred for 5 h at rt and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 2:1) to give compound **14** (251 mg, 80%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55-7.19 (m, 4H), 5.89 (dd, J = 5.4, 2.1 Hz, 1H), 5.74 (dd, J = 5.7, 1.2 Hz, 1H), 4.32 (m, 1H), 3.62 (s, 2H), 3.38 (s, 1H), 2.28 (dd, J = 14.4, 8.4 Hz, 1H), 1.84 (dd, J = 14.4, 4.2 Hz, 1H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.38, 135.00, 133.84, 130.96, 128.85, 126.68, 69.48, 60.07, 51.43, 39.43, 24.52; Anal calc for $C_{13}H_{16}OS$: C, 70.87; H, 7.32; S, 14.55. Found: C, 70.77; H, 7.20; S, 14.68.

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