Synthesis of Ardisinol II

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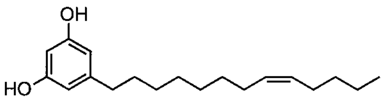
Abstract: The first and also a concise synthesis of ardisinol II by two routes in excellent yields are described.

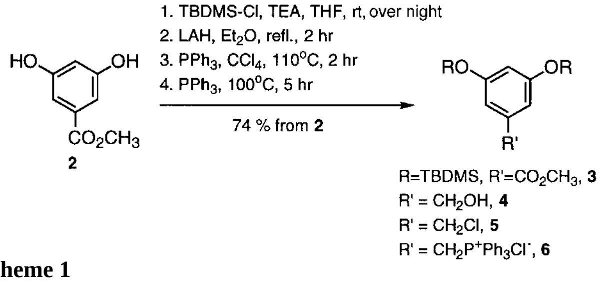
Key words: resorcinol derivatives, Wittig reaction, Würtz coupling, antitubercular agent, ardisinol II

Ardisinol II is the active principle isolated from *Ardisia japonic* (Hornsted) Blume (Myrsinaceae),[1] the Chinese medicinal herb, which has been used for treatment of lung tuberculosis and asthma in folk medicine.[2] The compound inhibits the growth of *Mycobacterium tuberculosis* in vitro. In tests with 201 patients, the compound was 81.5% effective.[3] Its structure was elucidated as (*Z*)-5-(8'-tridecenyl)resorcinol **(1)**.[1] Due to its safety and effectivity, further studies aimed at development of these new amorphous resorcinol derivatives as antitubercular agents were carried out in China, Japan, UK and USA.[4] In this paper we describe the first and also a concise synthesis of ardisinol II **(1)** by two different routes in high overall yields. This second approach for convergent synthesis of ardisinol II via Würtz-type cross-coupling established an efficient strategy for construction of the amorphous resorcinol derivatives and other structurally related substances such as cadol[4] in excellent yield.



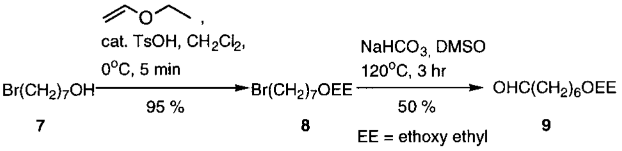
Ardisinol II 1

Commercially available, methyl 3,5-dihydroxybenzoate **(2)** was protected[5] with *tert*-butyldimethylsilyl chloride in the presence of triethylamine in anhydrous THF to give the bis(silyl) ether **3** in 100% yield (Scheme 1). Reduction of **3** with $LiAlH_4$ in anhydrous diethyl ether afforded the corresponding alcohol **4** in almost 100% yield. The alcohol **4** was converted efficiently into the benzyl chloride **5**[6] under triphenylphosphine and carbon tetrachloride conditions[6] in 87% yield. The benzyl chloride **5** reacted with triphenylphosphine to generate the phosphonium chloride[7] **6** in 85% yield.



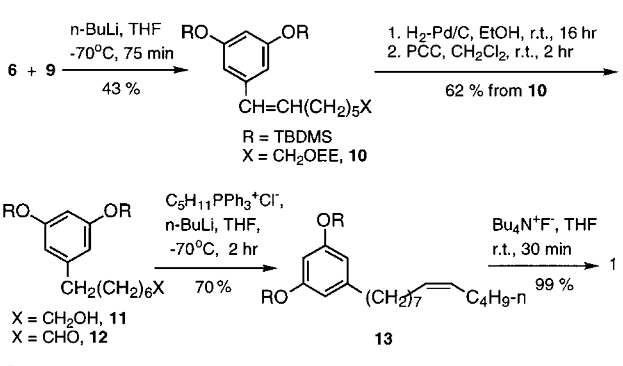
Scheme 1

Synthesis of the side chain part was achieved by the transformations presented in Scheme 2 from commercially available, 7-bromoheptan-1-ol **(7)**. Protection[5] of **7** with ethyl vinyl ether in the presence of a catalytic amount of TsOH in anhydrous CH_2Cl_2 provided the ethoxy ethyl (EE) ether **8** in 95% yield, which was converted successively into the aldehyde **9** by Kornblum oxidation with $DMSO/NaHCO_3$ in 50% yield.[8]



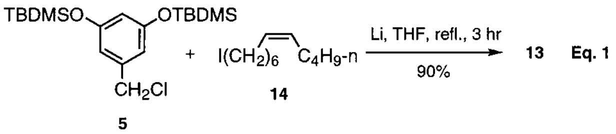
Scheme 2

The coupling (Scheme 3) of the phosphonium salt **6** with the aldehyde **9** was carried out by the Wittig reaction to form the olefin **10**[9] in 43% yield. Catalytic hydrogenation[10] of the olefin **10** with palladium-charcoal in ethanol and deprotection of the EE group of compound **10** under the hydrogenation conditions gave the hydrogenation and deprotection product **11** in 77% yield. This was converted into the aldehyde **12** in 80% yield by treatment with pyridinium chlorochromate (PCC) in anhydrous CH_2Cl_2.[11] Conversion of **12** to the *cis*-enriched olefin **13** (*Z*/*E*, 85:15, $AgNO_3/SiO_2$ column, hexane/Et_2O, 20:1)[12] was achieved by the Wittig reaction at –70°C in 70% yield. Finally, deprotection[5] of the silyl ether **13** with tetrabutylammonium fluoride afforded the final product **1** in 99% yield.

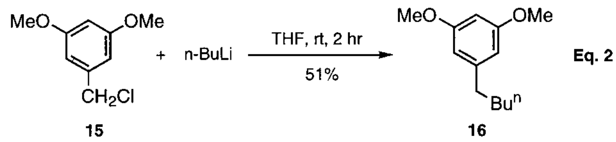


Scheme 3

A second project focused on exploring a facile route to provide a large amount of the target compound which was assayed for pharmacological activity. The conceived approach to ardisinol II **(1)** has been centered around the key step, coupling between the aromatic part **5** and the side chain part such as (*Z*)-1-iodododec-7-ene **(14)** via Würtz-type cross-coupling reaction in good yield of 90% (Scheme 4). The organolithium reagent generated in situ from iodide **14** reacted preferentially with benzyl chloride **5**, which is more reactive than **14** as an alkyl halide, and that a high yield of coupling product **13** was attained. Although the Würtz-type cross-coupling reaction is normally of less synthetic value in total synthesis of natural products due to dimerization, in this case the desired cross-coupling reaction takes precedence over dimerization probably through the organolithium as an intermediate, according to the model study shown below (Scheme 5).

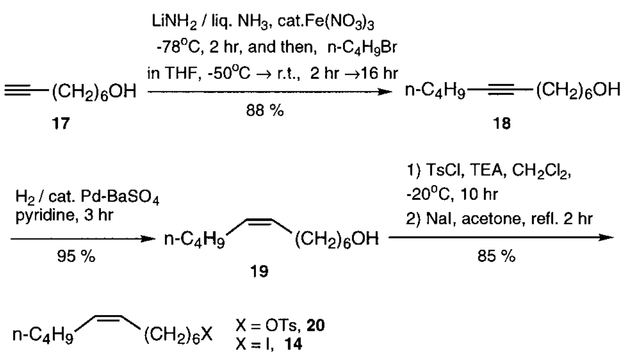


Scheme 4



Scheme 5

Synthesis of the side chain part was achieved by the transformations presented in Scheme 6 from oct-7-yn-1-ol **(17)**. Thus, **17** was treated with $LiNH_2$ in liq. NH_3 to form the corresponding lithium alkynide in the presence of $Fe(NO_3)_3$ as a catalyst,[13] and then reacted with BuBr to afford dodec-7-yn-1-ol **(18)**[13] in 88% yield. The semihydrogenation of **18** was carried out in pyridine by using 10% palladium on barium sulfate as a catalyst to yield only the *cis*-isomer of dodec-7-en-1-ol **(19)**[14] (GC analysis) in 95% yield. The (*Z*)-dodec-7-en-1-ol **(19)** was converted into the corresponding tosylate **20** by treatment with TsCl and Et_3N in CH_2Cl_2 in 94% yield. Furthermore, the tosylate **20** was reacted with NaI in acetone at reflux to give (*Z*)-1-iodododec-7-ene **(14)** in 91% yield (Scheme 6). After Würtz-type cross-coupling between the aromatic part **5** and the side chain part of **14**, the corresponding silyl ether **13** was obtained as described before (Scheme 4).



Scheme 6

In summary, the first total synthesis of ardisinol II **(1)** was realized in 14% overall yield in the first route via 9 steps through conventional Wittig strategy. In the second convergent approach the excellent yield of 64% via 5 steps has been attained by utilizing Würtz-type cross-coupling as the key reaction. All the spectra were identical to the natural product. All the new compounds were characterized by spectroscopic measurements.

Melting points are uncorrected. ^1H NMR spectra were obtained on a JEOL PS-100 or a Bruker AM 400 NMR spectrometer. IR spectra were recorded on a Perkin-Elmer 599B Spectrometer. Mass spectra were recorded on a Varian MAT-711 Spectrometer. All air-sensitive reactions were run under argon atmosphere, and anhydrous reagents were added through using oven-dried syringes.

Methyl 3,5-Bis(*tert*-butyldimethylsilyloxy)benzoate (3):

To a solution of *tert* -butyldimethylsilyl chloride (4.97 g, 33 mmol) in THF (15 mL) was added a solution of **2** (2.52 g, 15 mmol) and Et_3N (6.7 mL, 45 mmol) in THF (20 mL) at r.t. The mixture was stirred overnight, diluted with THF, then filtered and extracted with Et_2O. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed (hexane/Et_2O, 20:1) to give **3** as an oil (6.0 g, ≈100%).

^1H NMR (100 MHz, CCl_4): $\delta = 6.96$ (s, 2 H, ArH), 6.34 (s, 1 H, ArH), 3.80 (s, 3 H, CO_2CH_3), 0.96 [s, 18 H, 2 $SiC(CH_3)_3$], 0.16 [s, 12 H, 2 $Si(CH_3)_2$].

IR (film): $\nu = 2950$, 2930, 2860, 1730, 1590, 1450, 1340, 1170, 930, 830, 770 cm^{-1}.

MS: *m*/*z* = 396 (M^+), 339.

Anal. Calcd. for $C_{20}H_{36}O_4Si_2$: C, 60.56; H, 9.15. Found: C, 60.43; H, 9.04.

3,5-Bis(*tert*-butyldimethylsilyloxy)benzyl Alcohol (4):

To a solution of $LiAlH_4$ (0.7 g, 18.4 mmol) in Et_2O (50 mL) was added silyl ether **3** in Et_2O (50 mL) at r.t. The mixture was stirred for 2 h and quenched with H_2O. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed (hexane/Et_2O, 3:1) to give the alcohol **4** as an oil (5.58 g, ≈100%).

^1H NMR (100 MHz, CCl_4): $\delta = 6.28$ (s, 2 H, ArH), 6.06 (s, 1 H, ArH), 4.20 (s, 2 H, $ArCH_2$), 1.56 (br, 1 H, OH), 0.94 [s, 18 H, 2 $SiC(CH_3)_3$], 0.12 [s, 12 H, 2 $Si(CH_3)_2$].

IR (film): $\nu = 3340$ (br), 2950, 2930, 2860, 1590, 1450, 1330, 1165, 930, 830, 770 cm^{-1}.

MS: *m*/*z* = 368 (M^+), 311, 293.

Anal. Calcd. for $C_{19}H_{36}O_3Si_2$: C, 61.90; H, 9.84. Found: C, 61.88; H, 9.76

3,5-Bis(*tert*-butyldimethylsilyloxy)benzyl Chloride (5):

A mixture of **4** (110 mg, 0.3 mmol), PPh_3 (170 mg, 0.64 mmol) and CCl_4 (excess) was heated in a sealed tube at 110 °C for 2 h. The mixture was evaporated and chromatographed (hexane/Et_2O, 20:1) to give chloride **5** as an oil (100 mg, 87%).

^1H NMR (100 MHz, CCl_4): $\delta = 6.26$ (s, 2 H, ArH), 6.00 (s, 1 H, ArH), 4.26 (s, 2 H, $ArCH_2$), 0.88 [s, 18 H, 2 $SiC(CH_3)_3$], 0.08 8s, 12 H, 2 $Si(CH_3)_2$].

IR (film): $\nu = 2950$, 2930, 2860, 1590, 1450, 1340, 1260, 1170, 1060, 930, 830, 770 cm^{-1}.

MS: *m*/*z* = 387 (M^++1), 386 (M^+), 330, 329, 287.

Anal. Calcd. for $C_{19}H_{35}ClO_2Si_2$: C, 58.95; H, 9.11. Found: C, 58.77 H, 9.08

3,5-Bis(*tert*-butyldimethylsilyloxy)benzyltriphenylphosphonium

Chloride (6):

A mixture of **5** (90 mg, 0.23 mmol) and PPh_3 (65 mg, 0.25 mmol) was heated to melting state and then to 100 °C for 5 h. The mixture was cooled to r.t. and washed with Et_2O (5 mL) to give salt **6** (130 mg, 86%); mp 229–233 °C.

^{1}H NMR (100 MHz, TFA): δ = 7.51 [m, 15 H, $P(C_6H_5)_3$], 6.48 (s, 1 H, ArH), 6.18 (s, 2 H, ArH), 4.36 (s, 1 H, Ar*CH*PPh_3Cl), 4.22 (s, 1 H, Ar*CH*PPh_3Cl), 0.8 [s, 18 H, 2 $SiC(CH_3)_3$], 0.0 [s, 12 H, 2 $Si(CH_3)_2$].

IR (film): ν = 3400 (br), 3100, 2950, 2930, 2860, 2760, 1590, 1470, 1460, 1450, 1440, 1335, 1250, 1160, 1025, 830, 770 cm^{-1}.

MS: *m/z* = 613, 612, 555.

Anal. Calcd. for $C_{37}H_{50}ClO_2PSi_2$: C, 68.43; H, 7.76. Found: C, 68.50 H, 7.81

7-(1-Ethoxyethoxy)heptanal (9):

To a solution of **7** (100 mg, 0.55 mmol) and TsOH (10 mg) in CH_2Cl_2 (2 mL) was added ethyl vinyl ether (42 mg, 0.58 mmol) at 0 °C. The mixture was stirred for 10 min, diluted with Et_2O (20 mL) and then washed with 5% aq $NaHCO_3$ solution to pH 8. The organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed (hexane/Et_2O, 20:1) to give 1-bromo-7-(ethoxyethyl)heptane **(8)** as an oil (140 mg, 95%).

^{1}H NMR (100 MHz, CCl_4): δ = 4.48 (q, 1 H, *J* = 6 Hz, OCH), 3.25 (m, 6 H, $BrCH_2$, OCH_2, OCH_2), 1.72 (m, 2 H), 1.38 (m, 6 H), 1.02–1.20 (m, 8 H).

A solution of **8** (267 mg, 1 mmol) and $NaHCO_3$ (100 mg, 1 mmol) in DMSO (5 mL) was heated at 120 °C for 3 h. To this mixture was added NaI (15 mg) and ether (10 mL) at r.t. The mixture was washed with a solution of hexane/Et_2O (1:1, 30mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed (hexane/Et_2O, 2:1) to give aldehyde **9** as an oil (100 mg, 50%).

^{1}H NMR (100 MHz, CCl_4): δ = 9.64 (s, 1 H, CHO), 4.50 (q, 1 H, *J* = 6 Hz, OCH), 3.10–3.54 (m, 4 H, 2 OCH_2), 2.30 (t, 2 H, *J* = 7 Hz, C*H*$_2$CHO), 1.36 (m, 6 H), 1.02–1.18 (m, 8 H).

IR (film): ν = 2950, 1720, 1250, 1025 cm^{-1}.

MS: *m/z* = 202 (M^+), 173, 156, 109.

Anal. Calcd. for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.12 H, 10.79

1-[3,5-Bis(*tert*-butyldimethylsilyloxy)phenyl]-8-(1-ethoxyethoxy)oct-1-ene (10):

To a suspension of **6** (2.5 g, 4.47 mmol) in THF (8 mL) was added BuLi (3.4 mL, 1.39 M, 4.73 mmol) at r.t. The mixture was stirred for 75 min and then cooled to –70 °C. To this solution was added aldehyde **9** (880 mg, 4.36 mmol) in THF (3 mL) at that temperature and then the mixture was stirred overnight at r.t. The solution was diluted with Et_2O (200 mL), washed with H_2O, brine, dried (Na_2SO_4) and evaporated. The residue was chromatographed (hexane/Et_2O, 12.5:1) to give the olefin triether **10** as an oil (1 g, 43%).

^{1}H NMR (100 MHz, CCl_4): δ = 6.00–6.20 (m, 5 H, ArH, CH=CH), 4.48 (q, 1 H, *J* = 6 Hz, OCH), 3.20–3.40 (m, 4 H, 2 OCH_2), 2.10 (m, 2 H), 1.00–1.40 (m, 14 H) 0.94 [s, 18 H, 2 $SiC(CH_3)_3$], 0.12 [s, 12 H, $Si(CH_3)_2$].

IR (film): ν = 2950, 2930, 2860, 1590, 1470, 1250, 1060, 1030, 830, 770 cm^{-1}.

MS: *m/z* = 537 (M^++1), 536 (M^+), 522, 507, 490, 464, 448, 443, 407, 389, 377, 366, 352.

Anal. Calcd. for $C_{30}H_{56}O_4Si_2$: C, 67.11; H, 10.51. Found: C, 67.12; H, 10.60

8-(3,5-Bis(*tert*-butyldimethylsilyloxy)phenyl)octan-1-ol (11)

A solution of **10** (60 mg, 0.11 mmol) and Pd/C (70 mg, 5%) in EtOH (2 mL) was hydrogenated for 16 h under 1 atm at r.t. The mixture was filtered and the filtrate concentrated. The residue was chromatographed (hexane/Et_2O, 2:1) to give the disilyl ether alcohol **11** as an oil (40 mg, 77%).

^{1}H NMR (100 MHz, CCl_4): δ = 6.12 (s, 2 H, ArH), 6.00 (s, 1 H, ArH), 3.50 (t, 2 H, *J* = 7 Hz, C*H*$_2$OH), 2.40 (t, 2 H, *J* = 7.5 Hz, ArC*H*$_2$), 1.16–1.60 (m, 13 H), 1.00 [s, 18 H, $SiC(CH_3)_3$], 0.16 [s, 12 H, $Si(CH_3)_2$].

IR (film): ν = 3350 (br), 2950, 2930, 2860, 1590, 1470, 1250, 1160, 1020, 830, 770 cm^{-1}.

MS: *m/z* = 409, 352, 311, 239.

Anal. Calcd. for $C_{26}H_{50}O_3Si_2$: C, 66.89; H, 10.80. Found: C, 66.73; H, 10.58

8-(3,5-Bis(*tert*-butyldimethylsilyloxy)phenyl)octan-1-al (12):

To a mixture of PCC (57 mg, 0.28 mmol) in CH_2Cl_2 (1 mL) was added **11** (80 mg, 0.17 mmol) in CH_2Cl_2 (1 mL) at r.t. The mixture was stirred for 2 h, then diluted with a solution of hexane/Et_2O (2:1) and filtered through a silica gel column, and concentrated. The residue was chromatographed (hexane/Et_2O, 4:1) to give the aldehyde **12** as an oil (70 mg, 80%).

^{1}H NMR (100 MHz, CCl_4): δ = 9.60 (s, 1 H, CHO), 6.06 (s, 2 H, ArH), 5.92 (s, 1 H, ArH), 2.34 (m, 4 H), 1.20–1.60 (m, 10 H), 0.92 [s, 18 H, $SiC(CH_3)_3$], 0.12 [s, 12 H, $Si(CH_3)_2$].

IR (film): ν = 2950, 2930, 2860, 1730, 1590, 1470, 1250, 1165, 830, 770 cm^{-1}.

MS: *m/z* = 464 (M^+), 449, 435, 407, 379, 365, 351.

Anal. Calcd. for $C_{26}H_{48}O_3Si_2$: C, 67.18; H, 10.41. Found: C, 67.03; H, 10.40

(*Z*)-5-(8'-Tridecenyl)resorcinol Disilyl Ether (13):

To a solution of $C_5H_{11}P^+Ph_3Br^-$ (80 mg, 0.19 mmol) in THF (1 mL) was added BuLi (0.14 mL, 1.39 M, 0.19 mmol) at –20 °C. The mixture was stirred for 2 h and then cooled to –70 °C. To this solution was added aldehyde **12** (70 mg, 0.15 mmol) in THF (1 mL) at –70 °C. The mixture was stirred at –70 °C for 2 h and diluted with Et_2O. The Et_2O layer was washed with H_2O and brine. The organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed on $AgNO_3/SiO_2$ (hexane/Et_2O, 20:1) to give *Z*-**13** (47 mg, 60%) and *E*-**13** (8 mg, 10%).

^{1}H NMR (100 MHz, CCl_4): δ = 6.00 (2 H, s, ArH), 5.84 (1 H, s, ArH), 5.21 (2 H, t, *J* = 5 Hz, CH=CH), 2.26 (2 H, t, *J* = 7.5 Hz, ArC*H*$_2$), 1.80 (4 H, m, CH_2C=CCH_2), 1.10–1.17 [17 H, m, $(CH_2)_7$, CH_3] 0.80 [18 H, s, $SiC(CH_3)_3$], 0.00 [12 H, s, $Si(CH_3)_2$].

IR (film): ν = 2960, 2930, 2860, 1590, 1475, 1465,1450, 1260, 1250, 1165, 835, 770 cm^{-1}.

MS: *m/z* = 518 (M^+), 461, 447, 433,419, 405, 391, 377.

Anal. Calcd. for $C_{31}H_{58}O_2Si_2$: C, 71.75; H, 11.26. Found: C, 71.89; H, 11.40

(*Z*)-5-(8'-Tridecenyl)resorcinol (1):

To a solution of **13** (130 mg, 0.25 mmol) in THF (1 mL) was added Bu_4NF (250 mg, 0.79 mmol) in THF (1 mL) at r.t. The mixture was stirred for 0.5 h and concentrated. The residue was chromatographed (benzene/EtOAc, 15:1) to give **1** as an oil (73 mg, ≈100%).

^{1}H NMR (100 MHz, CCl_4): δ = 6.08 (br, 1 H, OH), 6.08 (s, 2 H, ArH), 6.00 (s, 1 H, ArH), 5.21 (t, 2 H, *J* = 5 Hz, CH=CH) 2.06 (t, 2 H, ArC*H*$_2$), 1.90 (m, 4 H, CH_2C=CCH_2), 1.20 [m, 14 H, $(CH_2)_7$] 0.82 (t, 3 H, *J* = 7 Hz, CH_3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.23 (d, 2 H, *J* = 2 Hz, ArH), 6.16 (s, 1 H, ArH), 5.68 (br, 1 H, OH), 5.35 (m, 2 H, *J* = 5, 10Hz, CH=CH), 2.44 (t, 2 H, *J* = 7.5 Hz, $ArCH_2$), 1.98(m, 4 H, CH_2C=CCH_2), 1.30 (m, 14 H, $(CH_2)_7$], 0.88 (t, 3 H, *J* = 7 Hz, CH_3).

IR (film): ν = 3350 (br), 2950, 2930, 2860, 1630, 1600, 1470, 1340, 1305, 1260, 1155, 1000, 840, 790, 700 cm^{-1}.

UV (MeOH): λ_{max} = 208, 275, 280 nm.

MS: *m/z* = 290 (M^+), 247, 233, 208, 205, 194, 191, 177, 163, 149, 137, 124 (100), 111.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.50; H, 10.41

Dodec-7-yn-1-ol (18):

To a solution of $Fe(NO_3)_3$ (200 mg, 0.83 mmol) in liquid NH_3

(250 mL) was added lithium (1.8 g, 260 mmol) at –78 °C. The mixture was stirred for 1 h and warmed to –50 °C. To this solution was added oct-7-yn-1-ol (**17**;12 g, 95 mmol) at –50 °C. After 2 h, BuBr (16 mL, 150 mmol) in THF (50 mL) was added. The mixture was stirred for 2 h at –50 °C, then stirred overnight at r.t. The mixture was diluted with benzene (300 mL) and H_2O (50 mL). The organic layers were separated and washed with aq 0.5 N HCl and H_2O. The aqueous layer was extracted with benzene and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was chromatographed (hexane/Et_2O, 2:1) to give **18** as an oil (15.14 g, 88%).

^{1}H NMR (100 MHz, CCl_4): $\delta = 3.48$ (t, 2 H, $J = 7$ Hz, CH_2OH), 2.04 (m, 4 H), 1.36 (m, 12 H), 0.86 (t, 3 H, $J = 7$ Hz, CH_3).

IR (film): $\nu = 3330$, 2940, 2840, 2260, 1440, 1070, 720 cm^{-1}.

MS: m/z = 181 (M^+–1), 165, 123, 109, 95, 81, 69, 67.

Anal. Calcd. for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.21; H, 12.39

(*Z*)-Dodec-7-en-1-ol (19):

A mixture of **18** (2 g, 11 mmol), pyridine (50 mL) and Pd/$BaSO_4$ catalyst (200 mg, 10%) was hydrogenated for 3 h. The mixture was filtered and concentrated. The residue was chramatographed (hexane/Et_2O, 1:1) to give **19** as an oil (1.92 g, 95%).

^{1}H NMR (100 MHz, CCl_4): $\delta = 5.20$ (t, 2 H, $J = 5$ Hz, CH=CH), 3.44 (t, 2 H, $J = 7$ Hz, CH_2OH), 2.70 (br, 1 H, OH), 1.94 (m, 4 H), 1.30 (m, 12 H), 0.86 (t, 3 H, $J = 7$ Hz, CH_3).

IR (film): $\nu = 3330$, 1665, 1470, 1060, 700 cm^{-1}.

MS: m/z = 184 (M^+), 167, 166, 125, 111, 97, 83, 71, 69.

Anal. Calcd. for $C_{12}H_{24}O$: C, 78.20; H, 13.12. Found: C, 78.09; H, 13.00

(*Z*)-1-Iodododec-7-ene (14):

To a solution of **19** (1 g, 5.4 mmol) and Et_3N (1.7 mL, 12.2 mmol) in CH_2Cl_2 (10 mL) was added TsCl (1.74 g, 9.1 mmol) in CH_2Cl_2 (10 mL) at –20 °C. The mixture was stirred overnight, and quenched with aq satd $NaHCO_3$ solution (10 mL) and extracted with Et_2O (3 × 20 mL). The extract was dried (Na_2SO_4) and concentrated and the residue chromatographed (hexane/Et_2O, 4:1) to give the tosylate **20** (1.75 g, 94%).

^{1}H NMR (100 MHz, $CDCl_3$): $\delta = 7.80$ (d, 2 H, ArH), 7.30 (d, 2 H, ArH), 5.30 (t, 2 H, J =5Hz, CH=CH), 3.98 (t, 2 H, CH_2OTs), 2.40 (s, 3 H), 1.90 (m, 4 H), 1.60 (m, 2 H), 1.26 (m, 10 H), 0.82 (t, 3 H, CH_3).

A solution of **20** (1.75 g, 5.1 mmol), NaI (2 g, 13 mmol) and acetone (25 mL) was refluxed for 2 h and concentrated. The mixture was diluted with Et_2O and washed with aq 0.23 N $Na_2S_2O_3$ solution and the aqueous layer was extracted with Et_2O. The combined layers were dried (Na_2SO_4) and concentrated. The residue was chromatographed (hexane) to give **14** as an oil (1.39 g, 91%).

^{1}H NMR (100 MHz, CCl_4): $\delta = 5.18$ (t, 2 H, $J = 5$ Hz, CH=CH), 3.0 (t, 2 H, $J = 7$ Hz, CH_2I), 1.10–1.20 (m, 16 H), 0.80 (t, 3 H, $J = 7$ Hz, CH_3).

IR (film): $\nu = 2950$, 2930, 2865, 1630, 1470, 1340, 1305, 1155, 1000, 840, 700 cm^{-1}.

MS: m/z = 294 (M^+), 167, 125, 111, 97.

Anal. Calcd. for $C_{12}H_{23}I$: C, 48.99; H, 7.88. Found: C, 48.80; H, 7.71

Cross-Coupling Between 3,5-bis(*tert*-butyldimethylsilyloxy)benzyl Chloride (5) and (Z)-1-Iodododec-7-ene (14):

To a solution of **5** (100 mg, 0.25 mmol) and (*Z*)-1-iodododec-7-ene (**14**; 90 mg, 0.30 mmol) in THF (1.5 mL) was added fresh lithium (5 mg, 0.71 mmol). The mixture was refluxed for 3 h until metallic lithium was consumed. The mixture was diluted with Et_2O (50 mL), washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed (hexane/Et_2O, 10:1) to give the silyl-protected ardisinol II **(13)** (120 mg, 90%). Its spectral data were identical with the previous sample reported above.

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