Preparation of 9,13-di*cis* double bonds locked retinoids

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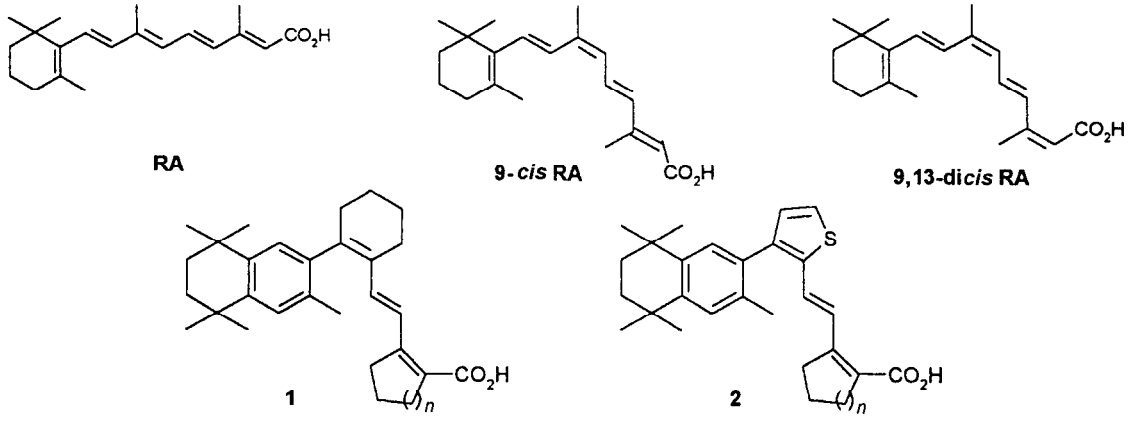
Synthesis of two retionids in which the 9, 13-di*cis* double bonds were locked in cycloalkene or thiophene was described. The key steps were the Wittig olefination of phosphonium salt 3 and 23 with aldehyde 14, followed by carbonylation of vinyl bromide 17 and 24 with carbon monoxide in the presence of $Pd(PPh_3)_4$.

Keywords Retinoid, Wittig olefination, palladium(0)-catalyzed carbonylation

Introduction

Retinoids are natural and synthetic analogs of Vitamin A. Because of their far ranging biological effects, retinoids have found clinical application in dermatology, oncology and show promise in other diverse therapeutic areas including arthritis, dyslipidemias, and the prevention of HIV-induced lymphopenia. Cumulative evidence has indicated that retinoids may exert their functions by regulating gene expression mediated by two classes of nuclear receptors: the retinoic acid receptor family (RAR)[1] and the retinoid X receptor family (RXR).[2] The physiological hormones for the RAR and RXR are proposed to be all-*trans*-retinoic acid (RA) and 9-*cis*-retinoic acid (9-*cis* RA) respectively. However, 9-*cis* RA can bind to and transcriptionally activate the RAR as well.[3] Unfortunately, use of the retinoids is associated with a number of significant side effects and therefore widespread clinical use of retinoids is severely limited. In view of the related, but clearly distinct, nature of these receptors, ligands which are selective for the RAR or RXR family would provide the capacity for independent control of the physiologic processes mediated by the RAR or RXR and further offer the possibility of improved therapeutic indices and reduced toxicity.[4] Recently, identification of 9,13-di*cis*-retinoic acid as a major plasma metabolite of 9-*cis* RA has been reported.[5] In order to investigate the function of 9,13-di*cis* RA and to obtain the selective substances for RXR or RAR receptor, we were interested in designing and preparing types **1** and **2** compounds in which the 9-*cis* and 13-*cis* double bonds are locked.[6]

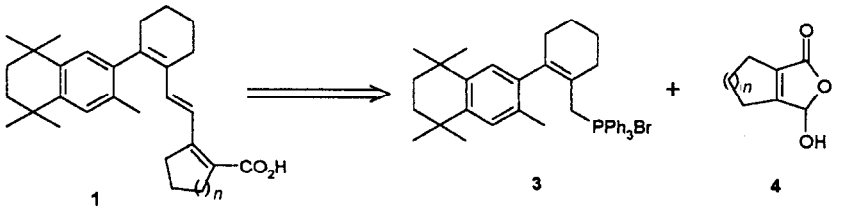


Received April 19, 1999; accepted June 7, 1999.
Project supported by the National Natural Science Foundation of China (No. 29702010).

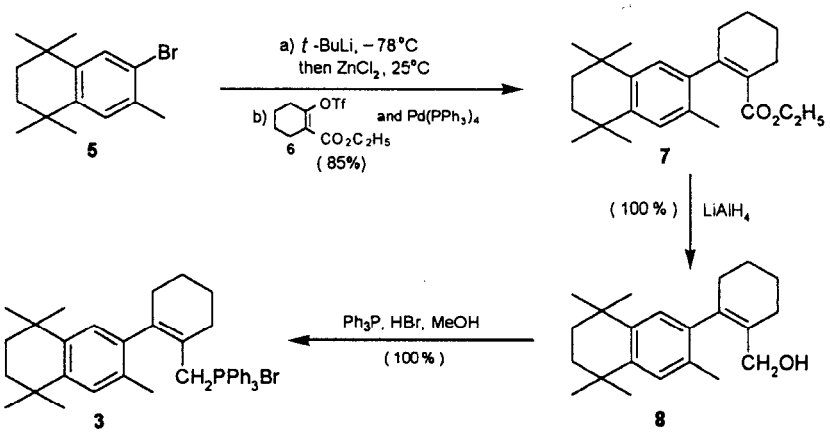
Results and discussion

Our initial synthetic plan was based on the Wittig reaction of phosphonium salts **3** and **4** (Scheme 1). Bromide **5** (Scheme 2), prepared in 85% yield by reaction of *o*-bromotoluene with 2, 5-dichloro-2, 5-dimethylhexane in the presence of aluminum chloride,[7] was used as the starting material for the synthesis of **3**. Bromide **5** was treated with *tert* - butyl lithium at - 78℃, followed by zinc chloride at room temperature to give the organozinc compound, which was in turn reacted with ethyl 2-(trifluoromethylsulfonyloxy)-1-cyclohexene-1-carboxylate **6**[8] under palladium catalysis[9] to give ester **7** in 85% yield. Lithium aluminum hydride reduction of the ester **7** to the alcohol **8**, followed by reaction with triphenylphosphine hydrogen bromide in dried methanol afforded the phosphonium salt **3** quantitatively.

Scheme 1



Scheme 2

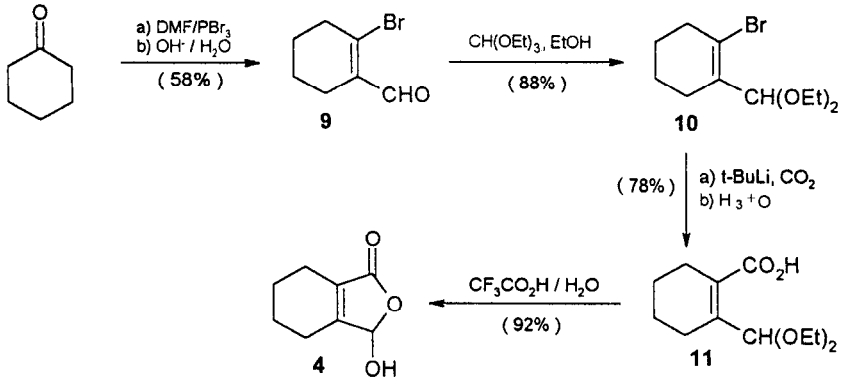


The syntheis of **4** ($n = 2$) began with cyclohexanone (Scheme 3). Treatment of cyclohexanone with dimethylformamide and phosphorus tribromide and subsequent neutralization gave aldehyde **9**,[10] which was protected with triethyl orthoformate to furnish the bromide **10**. Reaction of **10** with *tert*-butyl lithium at - 78℃ and subsequent carbonylation with carbon dioxide gave acid **11** in 78% yield. Treatment of **11** with 10% of trifluoroacetic acid in water provided the desired **4** in 92% yield.

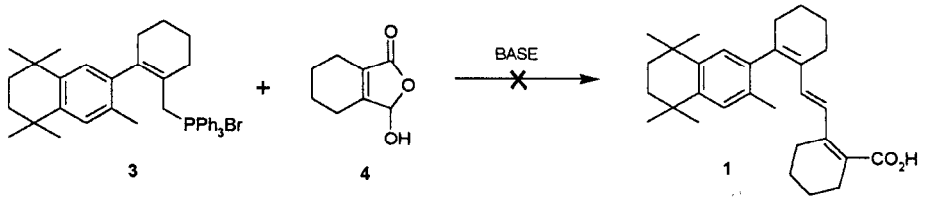
With the phosphonium salts **3** and **4** in hand, we proceeded to synthesize the target molecule **1**. However, the Wittig olefination of **3** and **4** did not occur in the presence of a number of bases, including NaH, *n*-BuLi, *t*-BuOK and KOH (Scheme 4).

Due to our lack of success in synthesis of **1** by retrosynthetic analysis outlined in Scheme 1, a new route was designed. Our new synthetic route was attempted by hydrolysis of the cyano group of compound **12** (Scheme 5). **12** could arise from a Wittig olefination between phosphonium salt **3** and aldehyde **13**.

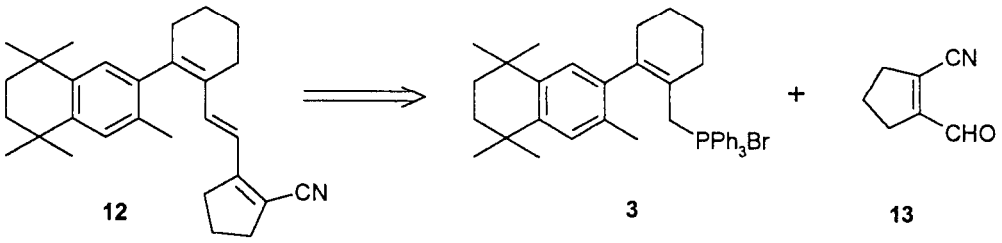
Scheme 3



Scheme 4



Scheme 5

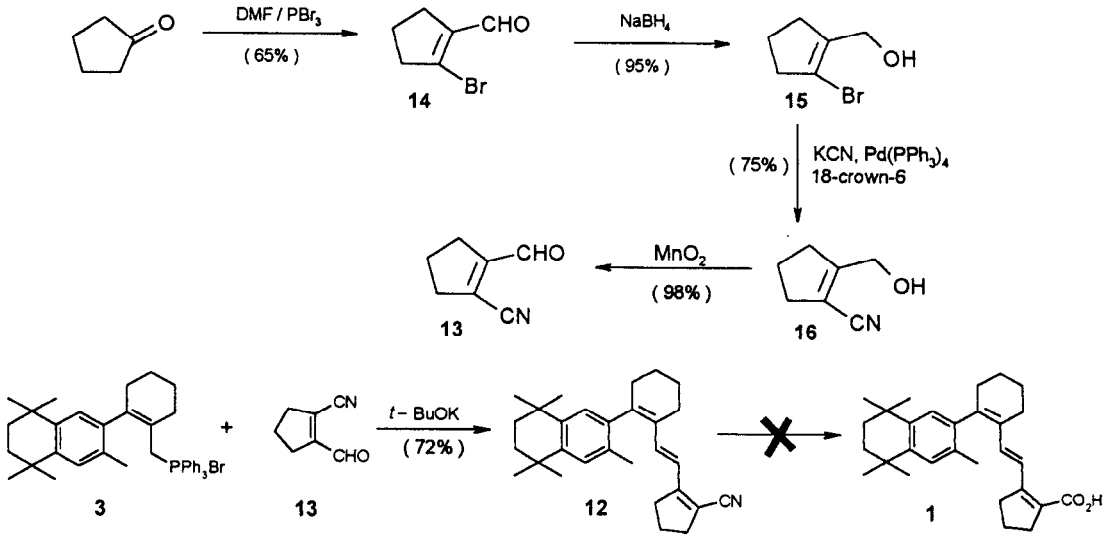


The starting material for the synthesis of **13**, which was outlined in Scheme 6, is cyclopentanone. Treatment of cyclopentanone with dimethylformamide and phosphorus tribromide in anhydrous chloroform gave **14**[10] which is an unstable compound and is easily changed to black bar. Immediate reduction of **14** with sodium borohydride afforded **15** that can be kept for several months at room temperature. Treatment of **15** with two molar equivalent of potassium cyanide in the presence of catalytic amount of palladium(0) complex and crown ether resulted in formation of **16**.[11] Then oxidation of **16** with activated manganese dioxide afforded **13** in high yield. Wittig olefination of the phosphonium salt **3** with aldehyde **13** in the presence of potassium *tert*-butoxide provided the single *trans*-isomer **12** in 72% yield. But the hydrolysis of compound **12** to target molecule **1** failed under a number of reaction conditions.

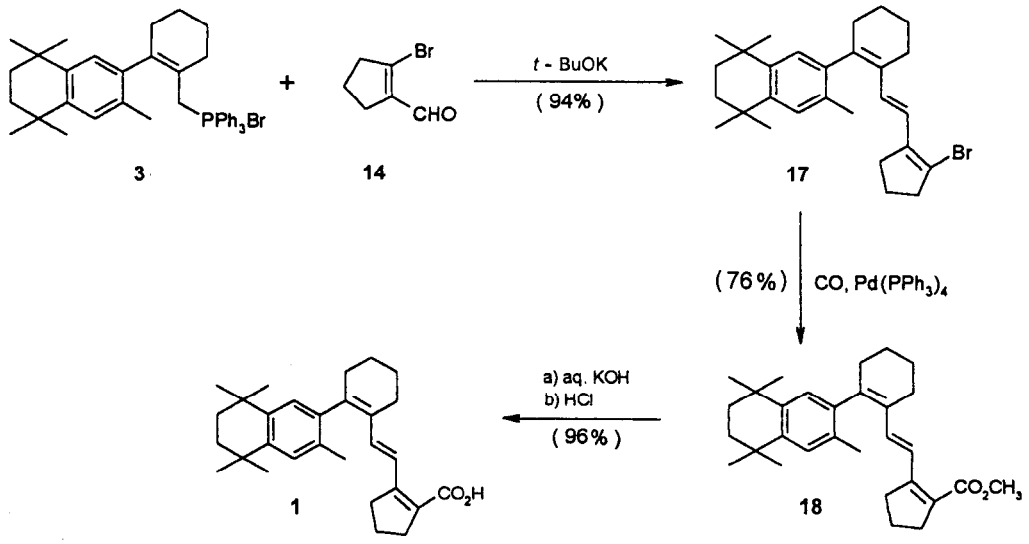
Finally, we were delighted to find a successful route to prepare compound **1** (Scheme 7). Wittig olefination of phosphonium salt **3** with 2-bromocyclopentene-1-ylaldehyde **14** in dried dichloromethane in the presence of potassium *tert*-butoxide gave the single *trans* isomer vinyl bromide **17** in 94% yield. The *trans* isomer was determined by the coupling constant of two vinyl protons

($J_{H,H}$ = 16.0 Hz). Carbonylation of the unstable vinyl bromide **17** with carbon monoxide in DMF under palladium(0) catalysis[12] at 85℃ afforded methyl carboxylate **18** in 76% yield. The ester **18** was cleanly saponified to the 9,13-di*cis*-blocked acid **1**.

Scheme 6



Scheme 7

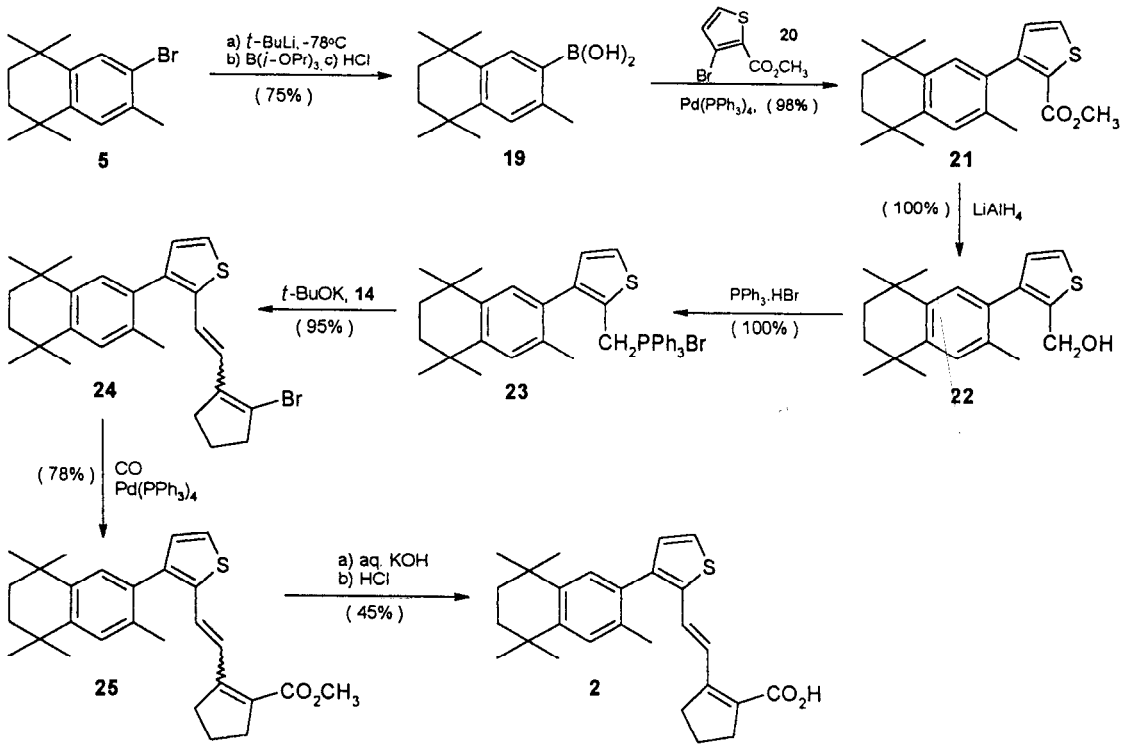


We then turned our attention to the synthesis of **2** (Scheme 8). Our initial approach to the key intermediate **21** by the cross-coupling of the corresponding organozinc compound of aryl bromide **5** with methyl 3-bromo-2-thiophenecarboxylate **20**[13] under palladium(0) or nickel(0) catalysis[14] failed and the compound **20** was recovered. Therefore, an alternative route was adopted for preparation of **21**. Aryl bromide **5** was reacted with *tert*-butyllithium, followed by the addition of triisopropylborate and then hydrolysis to a boronic acid **19** in 75% yield. The Suzuki cross-coupling[15] of boronic acid **19** with **20** in the presence of $Pd(PPh_3)_4$ gave the ester **21**

in 98% yield. Then the methodology used in Scheme 2 and Scheme 7 was extended to the preparation of **2**. Thus, in an analogous manner, phosphonium salt **23** was prepared from **21**. However, Wittig-olefination of phosphonium salt **23** with **14** afforded the mixture of vinyl bromide **24** in a ratio of *trans* : *cis* of 8 : 5 (as determined by ^{1}H NMR). The mixed vinyl bromide **24** could not be separated by column chromatography and used directly in carbonylation. The mixed ester **25** was hydrolyzed to give a solid which after recrystallization from absolute ethyl alcohol to afford the desired acid **2**.

The successful approach described herein, enabled us to synthesize a number of analogues related to **1** and **2**. The structure-activity relationship of these derivatives and their ability to transactivate RAR or RXR selectively are undergoing.

Scheme 8



Experimental

Melting points were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer with tetramethylsilane as the internal standard. The mass spectra were recorded on a Finnigan-MAT-8430 mass spectrometer using EI ionization at 70 eV. IR spectra were recorded as KBr discs on a Shimadzu IR-440 Spectrometer.

2-Bromo-3, 5, 5, 8, 8-pentamethyl-5, 6, 7, 8-tetrahydronapththalene (**5**)

A solution of 2,5-dichloro-2,5-dimethylhexane (0.43 mol) in dried dichloromethane (200 mL) was added dropwise to a mixture of 2-bromotoluene (50 mL, 0.43 mol) and anhydrous aluminum chloride (5.0 g) in dried dichloromethane (50 mL). Then the reaction mixture was stirred at room temperature for 30 min. 3 M HCl (60 mL) was slowly added to the mixture. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, evaporated to give a solid. Recrystallization of the solids from methanol gave **5** (90.0 g, 75%) as white solid. δ_H($CDCl_3$): 1.24(s, 6H), 1.27 (s, 6H), 1.64(s, 4H), 2.33(s, 3H), 7.13(s, 1H), 7.41(s, 1H). ν_{max}(cm^{-1}): 2957, 2856, 1499, 1481, 1386, 1361, 1301, 1190, 1078, 1020, 1003, 965, 921, 884, 838, 705, 676.

4, 5, 6, 7-*Tetrahydro*-3-*hydroxy*-1-(3*H*)-*isobenzofuranone* (**4**)

Phosphorus tribromide (68.0 g, 0.25 mol) was added dropwise to a solution of DMF (22.0 g, 0.3 mol) in $CHCl_3$ (80 mL) at 0℃ and the mixture was stirred for 20 min. Then a solution of cyclohexanone (9.8 g, 0.1 mol) in $CHCl_3$ (20 mL) was added. After stirring at room temperature for 15 h, the mixture was evaporated *in vacuo* and the residue was decomposed with ice (200 g). Then the mixture was immediately neutralized with solid $NaHCO_3$ and ether (150 mL) was added. The organic layer was separated, washed with water and brine, dried over Na_2SO_4. After removal of the solvents, the residue was distilled under reduced pressure to give **9** (10.9 g, 58%). A mixture of **9** (3.8 g, 20 mmol), ethyl orthoformate (4.5 g, 30 mmol) and anhydrous ethanol (10 mL) was stirred at room temperature for 20 h. After evaporation of ethanol *in vacuo*, the residue was distilled under reduced pressure to give **10** (4.4 g, 84%) as colorless oil. A mixture containing *tert*-butyllithium (15 mL, 25 mmol, 1.7 M in pentane) in dry THF (30 mL) was treated with **10** (5.2 g, 20 mmol) in dry THF (10 mL) under argon at −78℃ over a 10 min period. After 1 h, then carbon dioxide was bubbled through the reaction mixture for 30 min and the resultant solution stirred at −78℃ for 2 h under 1 atmosphere of carbon dioxide (balloon placed over the reflux condenser), whereupon the cooling bath was removed, and after an additional 30 min the reaction was quenched with 20 % aq AcOH. The usual extractive work-up (Et_2O) followed by drying with Na_2SO_4 gave **11** (3.1 g, 78%) after distillation for the removal of the less polar side products. A mixture of **11** (1.96 g, 10 mmol) and 10% aq. CF_3CO_2H (10 mL) was refluxed for 3 h. At this period, about 5 mL liquid was distilled. The resulting mixture was evaporated under reduced pressure to give **4** (1.4g, 92%) as a white solid. mp 64—66℃. δ_H($CDCl_3$): 1.50—1.90(m, 4H), 2.00—2.51(m, 4H), 4.84(br, 1H), 5.98(s, 1H). δ_C($CDCl_3$): 19.78, 21.40, 21.41, 22.49, 98.59, 129.54, 160.83, 172.40. *m/z* (%): 155(M^+ + H, 27), 137(34), 126(39), 108(48), 79(100).

Ethyl 2-(5,6,7,8-*tetrahydro*-3,5,5,8,8-*pentamethyl*-2-*naphthalenyl*)-1-*cyclohexene*-1-*carboxylate* (**7**)

A stirred solution of aryl bromide **5** (4.2 g, 15 mmol) in 40 mL anhydrous THF was added a solution of *tert*-butyllithium (18 mL, 30 mmol, 1.7 M in pentane) at −78℃ under argon. After stirrig at −78℃ for 1 h, it was warmed to room temperature and stirred for 1 h. A solution of zinc chloride (30 mL, 15 mmol, 0.5 M in THF) was added to the reaction mixture. The resulting mixture was stirred at room temperature for 1 h. A solution of triflate **6** (3.0 g, 10 mmol) and $Pd(PPh_3)_4$(0.8 g, 0.68 mmol) in THF (5mL) was added. The reaction mixture was refluxed for 3 h. After cooling to room temperature, 30 mL of 3 M HCl and 50 mL of ether were added. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, evaporated and purified by flash column chromatography (10% ether—90% hexane) to give **7** (3.0 g, 85%) as white solid. mp 62—63℃. δ_H($CDCl_3$): 0.62 (t, J = 7.0 Hz, 3H), 1.20(s, 3H), 1.22(s, 3H), 1.23(s, 3H), 1.28(s, 3H), 1.64(s, 4H), 1.73—1.76(m, 4H), 2.12(s, 3H), 2.12—2.28(m, 2H), 2.40—2.52 (m, 2H), 3.75(q, J = 7.0 Hz, 2H), 6.81(s, 1H), 7.01(s, 1H). ν_{max}(cm^{-1}): 2950, 2857, 1700, 1497, 1436, 1389, 1360, 1284, 1250, 1167, 1134, 1054, 1035, 894, 878, 824, 748, 721, 697. *m/z* (%): 355(M^+ + H, 85.0), 339(18.5), 309(100.0), 263 (11.0), 185(15.0). Anal. $C_{24}H_{34}O_2$. Calcd: C, 81.31; H, 9.67. Found: C, 81.47; H, 9.43.

2-(5, 6, 7, 8-*Tetrahydro*-3, 5, 5, 8, 8-*pentamethyl*-2-*naphthalenyl*)-1-*cyclohexene*-1-*methylenetriphenylphosphonium bromide* (**3**)

A solution of **7** (1.0 g, 3.2 mmol) in 15 mL dry ether was added dropwise to a stirred solution of lithium aluminum hydride (10 mL, 1.0 M solution in ether) at 0℃. The reaction mixture was stirred at room temperature for 15 min. The excess of LAH was destroyed by the addition of moist ether and water and the mixture was extracted with ether. The extracts were washed with brine, dried over Na_2SO_4 and evaporated to give oil which was dissolved in methanol (30 mL). To this solution was added Ph_3P·HBr (1.1 g, 3.2 mmol) and the mixture was stirred at room temperature for 17 h. Evaporation of methanol gave a crude phosphonium salt which was washed with ether. The phosphonium salt **3** was a white solid, and readily hygroscopic.

2-*Cyanocyclopentene*-1-*ylaldehyde* (**13**)

$NaBH_4$ (0.74 g, 20 mmol) was added to a solution of **14** (7.2 g, 40 mmol, the procedure for the preparation of **14** was similar to that of **9**) in dry methanol (30 mL) at 0℃. After stirring for 30 min, the reaction mixture was poured into ice water (50 mL) and extracted with ether (3 × 40 mL). The combined organics were washed with water and brine, dried over Na_2SO_4, evaporated and purified by flash column chromatography (10% ether—90% hexane) to give **15** (6.8 g, 94%) as colorless oil. A mixture of **15** (1.77 g, 10 mmol), potassium cyanide (1.3 g, 20 mmol), $Pd(PPh_3)_4$ (0.6 g, 0.5 mmol) and 18-crown-6 (50mg) in dry toluene (10 mL) was stirred at 90℃ for 1 h. Then the reaction mixture was poured into water (50 mL) and ether (60 mL). The organic layer was separated, evaporated and purified by flash column chromatography (20% ethyl acetate-80% hexane) to give **16** (0.92 g, 75%) as colorless oil. A mixture of **16** (0.25 g, 2 mmol), activated MnO_2(10 mmol) and anhydrous dichloromethane (30 mL) was stirred at room temperature for 6 h under nitrogen. Then the reaction mixture was diluted with dichloromethane (50 mL) and filtered. The inorganic solid was washed with dichloromethane. The combined filtrates were evaporated *in vacuo* to give **13** which was used in next reaction without further purification.

2-[[2-(5,6,7,8-*Tetrahydro*-3,5,5,8,8-*pentamethyl*-2-*naphthalenyl*)-1-*cyclohexenyl*]-1-*ethenyl*]-1-*cyclopentnylnitrile* (**12**)

A mixture of potassium *t*-butoxide (0.2 g, 1.78 mmol), **3** (1.0 g, 1.65 mmol) and dry dichloromethane (30 mL) was stirred at 0℃ for 30 min. Then a solution of **13** (0.18 g, 1.5 mmol) in dry dichloromethane (5 mL) was added and the resulting mixture was stirred at 0℃ for 4 h. The reaction mixture was poured into water (30 mL) and extracted with ether (2 × 50 mL). The combined organics were washed with water and brine, dried over Na_2SO_4, evaporated and purified by flash column chromatography (2% ether—98% hexane) to give **12** (0.42 g, 72%) as a yellow solid. δ_H($CDCl_3$): 1.21(s, 3H), 1.25(s, 3H), 1.27(s, 3H), 1.28(s, 3H), 1.67(s, 4H), 1.76—1.88(m, 6H), 2.07(s, 3H), 2.12—2.37(m, 6H), 2.57—2.62(m, 3H), 6.20(d, J = 16.0 Hz, 1H), 6.56(d, J = 16.0 Hz, 1H), 6.86(s, 1H), 7.06(s, 1H). δ_C ($CDCl_3$): 19.14, 22.47, 22.67, 22.90, 23.48, 25.00, 31.88, 32.08, 33.20, 34.01, 34.52, 35.36, 107.45, 117.48, 118.52, 126.63, 127.75, 130.60, 132.04, 135.93, 139.22, 142.07, 143.46, 145.33, 159.35. ν_{max} (cm^{-1}): 2960, 2860, 2208R, 1606, 1458, 1363, 965, 911, 734. *m/z* (%): 399(M^+, 100), 384(86), 328(20), 278 (20), 111(40). HRMS Calcd. for $C_{29}H_{37}N$: 399.2907. Found: 399.2888.

2-[[2-(5,6,7,8-*Tetrahydro*-3,5,5,8,8-*pentamethyl*-2-*naphthalenyl*)1-*cyclohexenyl*]-1-*ethenyl*]-1-*cyclopentenyl-carboxylic acid* (**1**)

A mixture of potassium *t*-butoxide (0.27 g, 2.4 mmol), **3** (1.28 g, 2.0 mmol) and dry dichloromethane (40 mL) was stirred at 0℃ for 30 min. Then a solution of **14** (0.35 g, 2.0 mmol) in dry dichloromethane (5 mL) was added and the resulting mixture was stirred at 0℃ for 4 h. The reaction mixture was poured into water (30 mL) and extracted with ether (2 × 60 mL). The combined organics were washed with water and brine, dried over Na_2SO_4, evaporated and purified by flash column chromatography (2% ether—98% hexane) to give **17** (0.84 g, 93%) as a colorless oil. Carbon monoxide was bubbled through a solution of **17** (0.68 g, 1.5 mmol), $Pd(PPh_3)_4$ (0.17 g, 0.15 mmol), triethylamine (0.42 mL, 3 mmol), LiCl (64 mg, 1.5 mmol) and dry methanol (2.7 mL, 60 mmol) in anhydrous DMF (10 mL) for 20 min. The mixture was heated at 85℃ for 15 h under 1 atmosphere of carbon monoxide (balloon placed over the reflux condenser). Diethyl ether (20 mL) was added to the cooled solution. The mixture was filtered through a pad of celite, and the pad rinsed with diethyl ether (2 × 10 mL). The combined filtrates were washed with water until neutral, dried over Na_2SO_4, evaporated and purified by flash column chromatography (10% ether—90% hexane) to give **18** (0.49 g, 76 %). Compound **18** (0.22 g, 0.5 mmol) was dissolved in 10 mL of methanol, while 1.2 g of KOH dissolved in 5 mL of water was added. The mixture was refluxed for 4 h. After cooling to 0℃, 2M HCl was added until the pH was 2, then 10 mL water and 25 mL ethyl acetate were added, The organic layer was separated, washed with water and

brine, dried over Na_2SO_4, and evaporated to give **1** (0.2 g, 96%). mp 264—264.5℃. δ_H($CDCl_3$): 1.22(s, 3H), 1.25(s, 3H), 1.26(s, 3H), 1.28(s, 3H), 1.72(s, 4H), 1.73—1.79(m, 6H), 2.08(s, 3H), 2.33—2.40(m, 6H), 2.67(t, J = 7.0 Hz, 2H), 6.27(d, J = 16.0 Hz, 1H), 6.89(s, 1H), 7.08(s, 1H), 7.37(d, J = 16.0 Hz, 1H). δ_C($CDCl_3$): 19.18, 21.38, 22.78, 23.02, 25.11, 31.89, 32.09, 32.27, 33.20, 34.16, 35.37, 120.61, 126.70, 126.84, 127.68, 131.31, 132.13, 137.35, 139.49, 141.98, 143.27, 144.26, 156.24, 171.34. ν_{max} (cm^{-1}): 3069, 3015, 2925, 2589, 1666, 1655, 1568, 1495, 1446, 1391, 1361, 1282, 1263, 1247, 978, 894, 766. UV (in CH_2Cl_2): 330 nm. *m/z* (%): 418(M^+, 60), 385(84), 281(100), 195(55), 123(61), 111(75), 69(47), 57(49). HRMS Calcd. for $C_{29}H_{35}O_2$: 418.2853. Found: 418.2834.

2-(5, 6, 7, 8-*Tetrahydro*-3, 5, 5, 8, 8-*pentamethyl*-2-*naphthalenyl*) *boronic acid* (**19**)

tert-Butyl lithium (60 mL, 100 mmol, 1.7 M in pentane) was added to a solution of aryl bromide **5** (17.0 g, 60 mmol) in THF (150 mL) at −78℃ under argon. After stirring at −78℃ for 30 min, it was warmed to room temperature and stirred for 1 h. Then the reaction mixture was cooled to −78℃ and triisopropyl borate (9.4 g, 50 mmol) was added. After stirring at −78℃ for 1 h, the reaction mixture was further stirred at room temperature for 2 h. 2 M HCl was added until the pH was 1. The organic layer was separated. The water phase was extracted with ether (3 × 75 mL). The combined organics were washed with brine, dried over Na_2SO_4 and evaporated to give yellow solids. Recrystallization of the solids from ethanol gave **13** (11.0 g, 75%) as white solid. δ_H($CDCl_3$): 1.32(s, 6H), 1.34(s, 6H), 1.71(s, 4H), 2.81(s, 3H), 7.20(s, 1H), 8.27(s, 1H). ν_{max}(cm^{-1}): 3853, 3555, 3474, 3403, 3022, 2959, 2924, 2816, 1604, 1457, 1392, 1331, 1299, 1265, 1114, 1091, 740.

Methyl 3-(5, 6, 7, 8-*tetrahydro*-3, 5, 5, 8, 8-*pentamethyl*-2-*naphthalenyl*)-2-*thiophenecarboxylate* (**21**)

A mixture of methyl 3-bromo-2-thiophenecarboxylate **20** (3.0 g, 14 mmol) and $Pd(PPh_3)_4$ (1.2 g, 1 mmol) in 40 mL DME was stirred at room temperature for 15 min. Then boronic acid **19** (4.11 g, 15 mmol) and saturated aqueous $NaHCO_3$ (20 mL) were added. The reaction mixture was refluxed for 3 h under argon. After cooling to room temperature, 30 mL of water and 100 mL of ether were added. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, evaporated and purified by flash column chromatography (10% ether — 90% hexane) to give **21** (4.7 g, 98%) as white solid. mp 89—90℃. δ_H($CDCl_3$): 1.25(s, 6H), 1.30 (s, 6H), 1.68(s, 4H), 2.09(s, 3H), 3.70(s, 1H), 7.00(d, J = 5.0 Hz, 1H), 7.08(s, 1H), 7.14(s, 1H), 7.49(d, J = 5.0 Hz, 1H). ν_{max}(cm^{-1}): 3082, 2958, 2857, 1714, 1534, 1387, 1303, 1282, 1266, 1110, 1075, 877, 783, 709. *m/z* (%): 343(M^+ + H, 55.0), 342(M^+, 60.0), 327(63.0), 311(100.0). Anal. $C_{21}H_{26}O_2S$. Calcd: C, 73.65; H, 7.65; S, 9.36. Found: C, 73.84; H, 7.53; S, 9.14.

2-[[3-(5, 6, 7, 8-*Tetrahydro*-3, 5, 5, 8, 8-*pentamethyl*-2-*naphthalenyl*)-2-*thiopheneyl*]-1-*ethenyl*]-1-*cyclopentenyl-carboxylic acid* (**2**)

This compound was prepared in an analogous manner as described for compound **1**. mp 238—239℃. δ_H($CDCl_3$): 1.27(s, 6H), 1.32(s, 6H), 1.70(s, 4H), 1.85(pent, J = 7.0 Hz, 2H), 2.17(s, 3H), 2.62(t, J = 7.0 Hz, 2H), 2.75(t, J = 7.0 Hz, 2H), 6.73(d, J = 16.0 Hz, 1H), 7.00(d, J = 5.0 Hz, 1H), 7.08(s, 1H), 7.19(s, 1H), 7.27(d, J = 5.0 Hz, 1H), 7.87(d, J = 16.0 Hz, 1H). δ_C($CDCl_3$): 20.13, 21.48, 31.93, 32.03, 34.14, 34.25, 34.49, 35.35, 123.35, 124.47, 128.30, 128.41, 128.96, 129.21, 130.73, 132.73, 133.43, 138.17, 142.25, 142.85, 144.49, 154.45, 170.20 ppm. ν_{max}(cm^{-1}): 3053, 2927, 2615, 1719, 1668, 1600, 1492, 1391, 1272, 1094, 908, 733, 689. UV (in CH_2Cl_2): 340 nm. *m/z* (%): 420(M^+, 100), 405(21), 387(45), 279(70), 239(27). HRMS Calcd. for $C_{27}H_{32}O_2S$: 420.2097. Found: 420.2071.

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