Novel Synthetic Route to Dihydropyrenes

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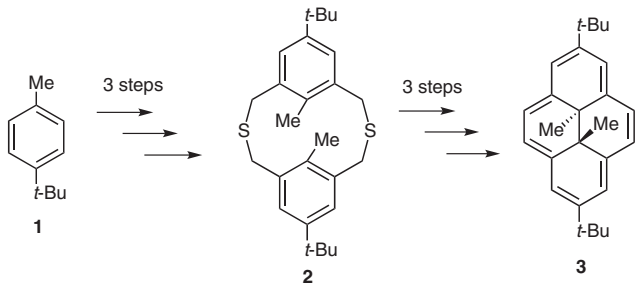
Abstract: We developed a new and short synthetic route to 2,7-di-*tert*-butyl-*trans*-15,16-dimethyldihydropyrene (DHP) via tetrahydroxy[2.2]metacyclophane in four reaction steps with a total yield of 37%. 2,7-Di-*tert*-butyl-*trans*-15,16-dimethyldihydropyrene functionalized by acetoxy groups at 4-, 5-, 9-, 10-positions was synthesized via 5,13-di-*tert*-butyl-8,16-dimethyl-1,2,9,10-tetrahydroxy[2.2]MCP in five reaction steps with a yield of 24%, and its DHP structure was determined by ^{1}H NMR spectroscopy and X-ray crystal-structure analysis.

Key words: cyclophanes, arenes, photochemistry, reduction, oxidations

Dihydropyrene (DHP) derivatives have been attracting considerable interests in various fields[2a–f] due to their photochromic property between DHP and [2.2]metacyclophane-1,9-dienes ([2.2]MCP-diene) since 1967.[1]

The synthetic route to di-*tert*-butyldimethylDHP (**3**), which was the parent compound of DHP, was developed by Tashiro[3] and improved by Mitchell.[4] This route via dithia[3.3]MCP **2** required six reaction steps, and a total yield of 45% was achieved from 4-*tert*-butyltoluene **1** (Scheme 1). Each reaction yield of this route was over 76%, but the long reaction sequence and requirement of highly skilled techniques restricted the practical applications of DHP as advanced materials.

Previously, we have reported facile and one-step synthesis of 5,13-di-*tert*-butyl-8,16-dimethyl-1,2,9,10-tetrahydroxy-[2.2]MCP (**6**) from the bezenedialdehyde derivative **5**.[5a,b] The MCP **6** has the potential to be the intermediate in DHP formation because it has two *trans*-diols at both its bridge positions, the reduction of which would afford a [2.2]MCP-diene, which is an equivalent of **3**.



Scheme 1

However, the benzene-annulated DHP at the [*e*]-position showed a high quantum yield of photoisomerization[6] and possessed suitable properties to qualify as switching materials.[2b,d,e] It is also expected that DHP substituted at the [*e*]-position or 4-, 5-, 9-, 10-positions could be prepared by using **6** as the intermediate in short reaction steps, and these DHP could be investigated for the various purposes. In this paper, we present a simple and short synthetic route to **3** and **9**, which is substituted by acetoxy groups at 4-, 5-, 9-, 10-positions, via **6** as the intermediate.

The synthesis of **3** was shown in Scheme 2. 2,6-Bis(bromomethyl)-4-*tert*-butyltoluene (**4**) and 2,6-di-formyl-4-*tert*-butyltoluene (**5**) were synthesized with yields of 90% and 70%, respectively.[4,5a] Pinacol coupling of **5** in an ice bath afforded **6** in 79% yield, while previously reported methods afforded **6** only in 33% yield at room temperature.[5a,b] The MCP **6** was reduced to **3** using imidazole, chlorodiphenylphosphine, iodine, and Zn powder. This method, which produced *cis*-olefin from *trans*-diol of carbohydrate, has been reported by Zhengchun.[7] A suspension of **6**, imidazole, and chlorodiphenylphosphine in toluene was added to iodine at reflux temperature and stirred for 1 hour. Zinc powder was added, and the mixture was stirred for 8 hours to afford **3** and **7** in 75% and 7% yields, respectively.[8] This synthetic route afforded **3** with a total yield of 37%.

The expected reaction mechanism from **6** to **3** is shown in Scheme 3. As a first step, chlorodiphenylphosphine and imidazole gave imidazolium-solvated complex **8**.[9] The reaction of **6** and **8** was guessed to form cyclic phosphonium ion **9** and iodo-phosphinate **10** as the intermediates.[7,10] The elimination of iodine and diphenylphosphinic acid from iodo-phosphinate **10** provided corresponding olefin.

The synthesis of **12** is shown in Scheme 4. Previously, we have reported the two-step oxidation of **6** to **11** with a yield of 31%.[11] Here, we developed a one-step oxidation of **6** using Ac_2O and DMSO.[12] A solution of **6** in DMSO and Ac_2O was degassed in vacuo, and the reaction mixture was stirred under a nitrogen atmosphere to afford **11** in 98% yield.[13] Treatment of **11** with zinc powder, Ac_2O, and Et_3N[14a,b] afforded **12** functionalized by acetoxy moieties at 4-, 5-, 9-, 10-positions in 50% yield.[15] This synthetic route afforded **12** in 24% yield from **1**.

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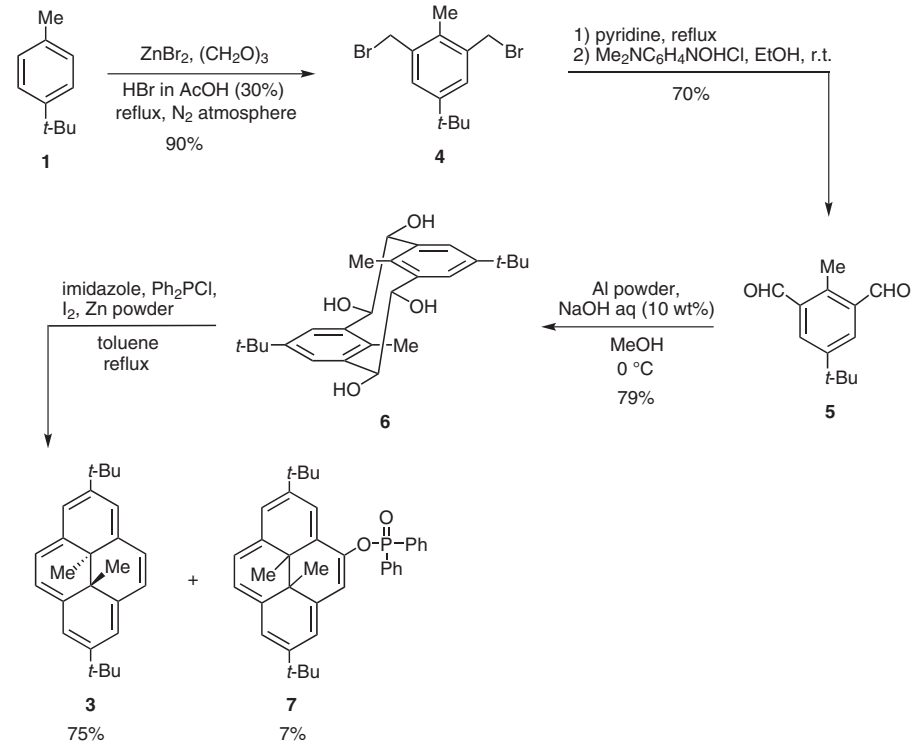
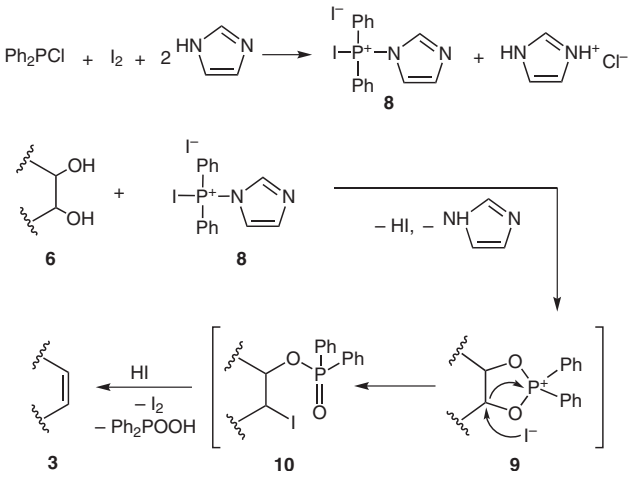


Scheme 2



Scheme 3 Reaction mechanism from vicinal diol to olefin

In ^{1}H NMR spectra, the chemical shifts of two signals of methyl groups in **7** and one signal of **12** were observed at δ = –4.10, –4.17, and –3.28 ppm, respectively. This result estimated that **7** and **12** had DHP forms in which internal methyl groups were influenced by a strong shielding effect. The chemical shifts of the internal methyl protons of **7** shifted to higher magnetic fields than those of **3** (δ = –4.04 ppm)[4] by 0.06–0.13 ppm. In contrast, the signal of internal methyl protons of **12** shifted downfield when compared to those of **3** by 0.75 ppm. These upfield and downfield shifts suggested that the aromaticity of DHP was influenced by the electron-donating[16] or electron-withdrawing groups at 4-, 5-, 9-, 10-positions.

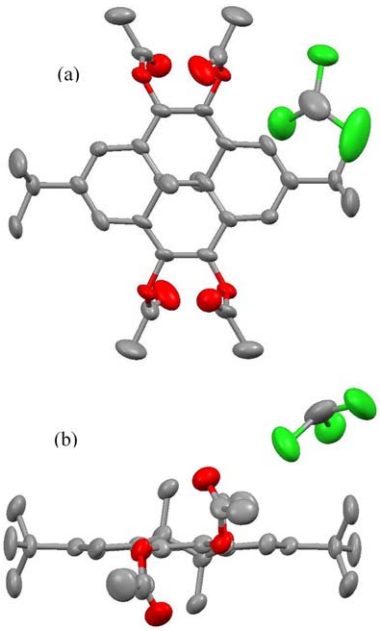
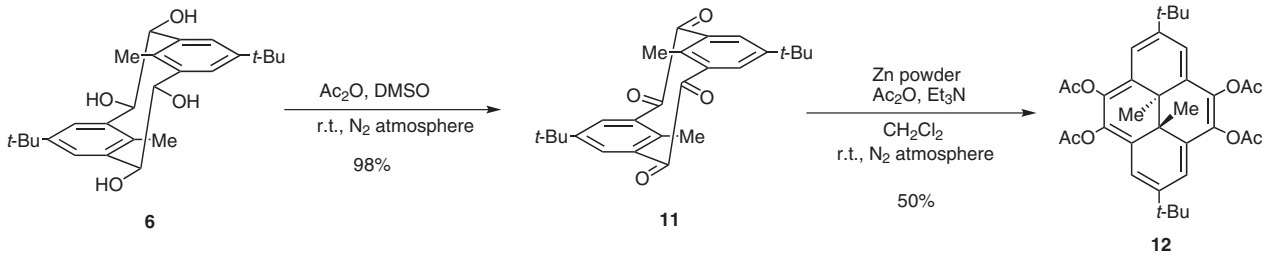


Figure 1 Crystal structure of **12** and chloroform: (a) top view; (b) side view

X-ray crystallography also clarified that **12** formed the DHP structure (Figure 1).[17] A larger alternation of the short and long bonds was observed for the periphery of **12** (1.346–1.432 Å) than the periphery of **3** (1.387–1.402 Å).[18] This result also confirmed that the aromaticity of **12** decreased in comparison to that of **3** due to the acetoxy groups at 4-, 5-, 9-, 10-positions of **12**.

In summary, we developed a new and short synthetic method to **3**. This synthetic route afforded **3** in four reac-



Scheme 4

tion steps with a total yield of 37%. In addition, functionalized DHP **12** was synthesized in five reaction steps from **1** with a total yield of 24%. X-ray structure analysis and ^{1}H NMR spectrum of **12** confirmed the DHP structure of **12** and proved that the aromaticity of **12** decreased in comparison to that of **3**. We believe that these novel synthetic routes to DHP could be useful for practical applications of DHP in various fields.

Acknowledgment

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(8) **Synthesis of 3 from 6**
To a stirred suspension of **6** (100 mg, 0.24 mmol), imidazole (196 mg, 2.88 mmol), and chlorodiphenylphosphine (235 mg, 1.00 mol) in toluene (50 mL) was added iodine (243 mg, 1.00 mmol) portionwise at reflux temperature, and the mixture was refluxed for 1 h. Zinc powder (667 mg, 9.76 mmol) was added, and the mixture was refluxed for 8 h. The mixture was cooled to r.t. and washed with 1 M NaOH (50 mL), H_2O (50 mL), and brine. The organic layer was dried over $MgSO_4$, evaporated in vacuo, and purified by TLC to afford **3** (63 mg, 75%) and **7** (8 mg, 7%) as green powders.
Compound **3**: mp (from *n*-hexane) 201–203 °C (lit.[4] mp 203–204 °C). ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ = –4.04 (s, 6 H), 1.69 (s, 18 H), 8.46 (s, 4 H), 8.54 (s, 4 H).
Compound **7**: mp (from *n*-hexane) 104–105 °C. FT-IR: 697, 732, 1026, 1109, 1130, 1161, 1236, 1360, 1437, 2861, 2906, 2926, 2967 cm^{-1}. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ = –4.17 (s, 3 H), –4.10 (s, 3 H), 1.57 (s, 9 H), 1.60 (s, 9 H), 7.27–7.39 (m, 4 H), 7.40–7.58 (m, 4 H), 8.00–8.22 (m, 2 H), 8.33 (d, *J* = 7.80 Hz, 1 H), 8.38 (d, *J* = 7.84 Hz, 1 H), 8.43 (s. 1 H), 8.45 (s, 1 H), 8.49 (s, 1 H), 8.67 (s, 1 H), 8.82 (s, 1 H). ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ = 29.53, 29.68, 31.81, 31.86, 31.89, 31.96, 36.00, 36.03, 115.85, 120.48, 121.04, 121.59, 122.50, 122.80, 123.26, 124.51, 128.39, 128.70, 131.80, 132.26, 135.14, 136.54, 137.47, 142.10, 144,59, 146.91. HRMS–FAB$^+$: *m/z* calcd for $C_{38}H_{41}O_2P$ + Na: 583.2775; found: 583.2776 [M$^+$ + Na].

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(13) **Oxidation of 6 to 11**
A solution of **6** (1.00 g, 2.40 mmol) in DMSO (100 mL) was degassed in vacuo, Ac_2O (10.0 ml, 97.2 mmol) was added, and the mixture was degassed in vacuo. The reaction mixture was stirred for 20 h under nitrogen at r.t. Then, H_2O (100 mL) was added and the reaction mixture was neutralized by aq NH_3. The reaction mixture was then filtered, and the precipitate was washed with H_2O and cold MeOH, and dried in vacuo to afford **11** (959 mg, 98%) as a yellow powder; mp 233–240 °C (dec.); lit[11] mp 230–240 °C (dec.). ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ = 0.89 (s, 6 H), 1.29 (s, 18 H), 7.58 (s, 4 H).

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(15) **Synthesis of 12 from 11**
To a suspension of **11** (500 mg, 0.25 mmol) and zinc powder (1.61 g, 25.0 mmol) in dry CH_2Cl_2 (50 mL) was added Ac_2O (2.5 mL, 24.3 mmol) and Et_3N (5.0 mmol, 37.5 mmol). The mixture was stirred for 2.5 h under nitrogen at r.t., and then filtered through Celite. The filtrate was washed with 10 wt% aq HCl (50 mL) and sat. aq $NaHCO_3$ (50 mL). The organic layer was dried over $MgSO_4$ and evaporated in vacuo; the residue was recrystallized with hexane–CH_2Cl_2 to afford **12** (203 mg, 50%) as green needles.
Dihydropyrene **12**: mp (from *n*-hexane–CH_2Cl_2): 257–258 °C. FT-IR: 1003, 1215, 1479, 1661, 2957, 3672 cm^{-1}. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ = –3.28 (s, 6 H), 1.61 (s,

18 H), 2.58 (s, 12 H), 8.45 (s, 4 H). ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ = 20.56, 29.90, 31.05, 31.70, 36.25, 116.00, 125.75, 134.93, 147.02, 169.15. MS–FAB$^+$: *m/z* = 576 [M$^+$]. Anal. Calcd for $C_{34}H_{40}O_8$: C, 70.81; H, 6.99. Found: C, 70.55; H, 7.14.

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(17) Single crystals of **12** suitable for X-ray analysis were prepared by recrystallization from $CHCl_3$. Diffraction data were collected on a Regaku AFC'R diffractometer at 25 °C with graphite monochromated Moκ$_a$ (λ = 0.71069 Å) radiation. For structure analysis and refinement, computations were performed using the Crystal Structure crystallographic software package of Rigaku Corporation. The structure was solved by the direct method (SIR92). All nonhydrogen atoms were refined anisotropically. Hydrogen atoms were included, but not refined. The weighting scheme ω = 1/[σ^2 (Fo^2) + (0.2000P)^2 + 0.0000P] where P = (Fo^2 – Fc^2)^2. Supplementary data of **12** have been deposited with the CCDC in the CIF format (deposit No. CCDC671306). X-ray analysis for **12**: $C_{36}H_{42}O_8Cl_6$ ($C_{34}H_{40}O_8$ + 2$CHCl_3$), MW = 815.44, green needles, monoclinic, $P2_1/n$ (# 14), Z = 2, a = 14.220 (4) Å, b = 10.2485 (19) Å, c = 14.012 (2) Å, β = 93.051 (17)°, V = 2039.1 (7) Å^3, D_{calcd} = 1.328 g cm^{-3}, T = 298 K, μ(Moκ$_a$) = 4.669 cm^{-1}, Rigaku AFC7R, Moκ$_a$ (λ = 0.71069 Å), 254 parameters, R1 = 0.1193, wR2 = 0.4244, GOF = 0.901.

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