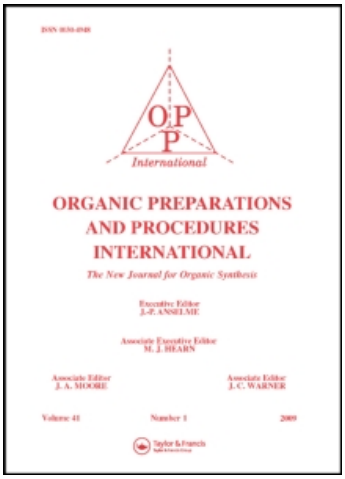

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ELECTROPHILIC SUBSTITUTION OF 7-*tert*-BUTYL-1-SUBSTITUTED PYRENES. A NEW ROUTE FOR THE PREPARATION OF 1,3-DISUBSTITUTED PYRENES

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ELECTROPHILIC SUBSTITUTION OF 7-*tert*-BUTYL-1-SUBSTITUTED PYRENES. A NEW ROUTE FOR THE PREPARATION OF 1,3-DISUBSTITUTED PYRENES†

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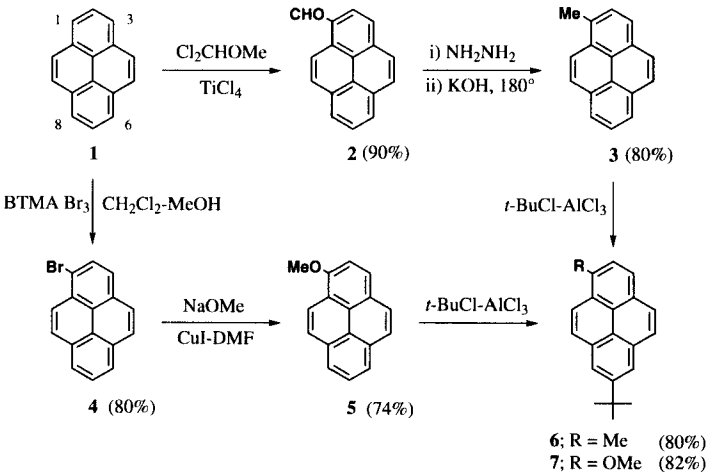
Pyrenes belong to the class of polycyclic aromatic hydrocarbons (PAHs), and are reported to cause cancer or mutations in living organisms,[1] thus making them the largest class of chemical carcinogens today. Pyrenes are formed when organic materials are burned or strongly heated. They are produced in larger amounts under inefficient combustion conditions. Analysis of the complicated mixtures of polycyclic aromatic compounds in the environment is possible only when pure and well-characterized reference materials are available.[2] Reference materials are essential also for the study of the biological effects of polycyclic aromatic compounds and for the establishment of structure-activity relationships. The preparation of 1,3-disubstituted pyrene using the regioselective electrophilic disubstitution is quite difficult in spite of the fact that electrophilic substitution of pyrene itself occurs at 1, 3, 6, and 8 positions.[3-7] For example, Harvey *et al* [7a] reported that the acetylation of pyrene afforded 1,8-diacetylpyrene as a major product along with 1,6- and 1,3-analogues. Therefore, the selective

preparation of 1,3-disubstituted pyrenes by direct electrophilic aromatic substitution is not efficient because of low yields as well as the need for their separation from reaction mixtures. Recently, Hempenius *et al* [6] reported the introduction of methyl groups at 1, 2, and 3 positions, starting from 1*H*-phenalene in ways other than by direct electrophilic substitution of pyrene itself.[8-10] Thus there is substantial interest in investigating the selective introduction of substituents at positions 1 and 3 through electrophilic substitution. The $AlCl_3$-catalyzed acetylation of 2,7-di-*tert*-butylpyrene with acetyl chloride using the *tert*-butyl group as a positional protective group affords only the 4,9-diacetylated product, 4,9-diacetyl-2,7-di-*tert*-butylpyrene.[11] This strategy is also suitable for the preparation of 1,3-disubstituted pyrene. We now report the electrophilic substitution of 7-*tert*-butyl-1-methylpyrene (**6**) and 7-*tert*-butyl-1-methoxypyrene (**7**), which enables the utilization of this method to the preparation of the 1,3-disubstituted pyrenes.

In order to introduce substituents selectively at positions 1 and 3 of pyrene ring by electrophilic substitution, we attempted the preparation of 2-*tert*-butylpyrene in order to protect one of the active positions of pyrene by the *tert*-butyl group.[12] Attempted mono-*tert*-butylation of pyrene with 1.1 equiv. of *tert*-butyl chloride in the presence of various Lewis acids ($AlCl_3$, $TiCl_4$, and $SnCl_4$) led to an inseparable mixture of 2-*tert*-butylpyrene, 2,7-di-*tert*-butylpyrene, and recovered pyrene. The same results were obtained using the sulfuric acid catalyzed *tert*-butylation with *tert*-butyl acetate. The attempted $AlCl_3$-$MeNO_2$ catalyzed dispropotionation of 2,7-di-*tert*-butylpyrene and pyrene in methylene dichloride also led to the same results.

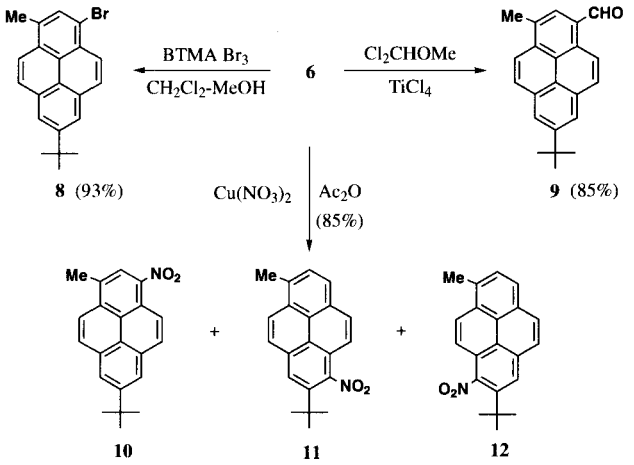
Since introduction of a single *tert*-butyl group on the pyrene ring failed, we undertook the studies shown in the following Scheme.



Thus formylation of pyrene (**1**) with dichloromethyl methyl ether was carried out in the presence of $TiCl_4$ to afford 1-formylpyrene (**2**) in 90% yield, from which 1-methylpyrene (**3**) was obtained in 80% yield by Wolff-Kishner reduction. The $AlCl_3$-catalyzed *tert*-butylation of **3** with *tert*-butyl chloride afforded 7-*tert*-butyl-1-methylpyrene (**6**) in 80% yield. 1-Methoxy analogue (**7**) was

also prepared by bromination of pyrene (**1**) with benzyltrimethylammmonium tribromide (BTMA Br_3),[13] followed by reaction with NaOMe in the presence of CuI and $AlCl_3$-catalyzed *tert*-butylation of **5** with *tert*-butyl chloride.

Formylation of 7-*tert*-butyl-1-methylpyrene (**6**) with dichloromethyl methyl ether in the presence of titanium tetrachloride occurred selectively at the 3-position to afford the corresponding 3-formyl derivative (**9**). The same regioselectivity was observed in the bromination of **6** with BTMA Br_3 to afford 1-bromo-7-*tert*-butyl-3-methylpyrene (**8**) in 93% yield. The relatively facile electrophilic substitution occurs at the 3-position instead of *ortho* to the *tert*-butyl group (6- or 8-position) on the pyrene ring because usually the steric bulk of *tert*-butyl group inhibits substitution towards 6 and 8 positions on the pyrene ring. No substitution at 4,5,9 and 10 positions was observed. This result is also attributable to the high reactivity of 1, 3, 6 and 8-positions.

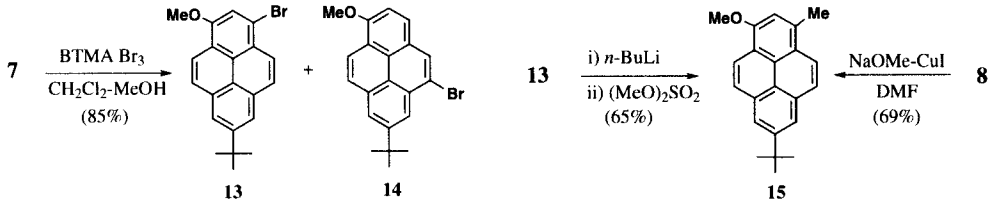


On the other hand, when nitration of **6** with cuprous nitrate in acetic anhydride was carried out at room temperature, 3-nitro derivative **10** was obtained in 53% yield along with a mixture of products **11** and **12** derived from nitration at 6- or 8-position of the pyrene ring, in 20% yield. The nitronium ion attacks on the pyrene ring occurred due to the higher π-basicity of the pyrene ring as compared to a benzene ring even under the relatively mild reaction conditions. The present lower positional selectivity may be governed by the stability of π-complex transition state proposed in the normal aromatic nitration different from that of the σ-complex intermediate for transition state in the bromination or formylation.[14]

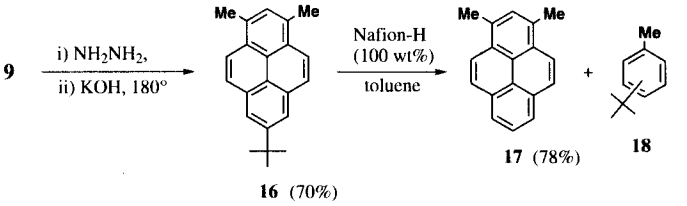
The same regioselectivity was not observed in the bromination of 1-methoxy analogue **7** with BTMA Br_3 to afford a mixture of 3-bromo-7-*tert*-butyl-1-methoxypyrene (**13**) and 5-bromo-7-*tert*-butyl-1-methoxypyrene (**14**) in a ratio of 60:40 in 85% yield, different from bromination of 1-methyl analogue (**6**). This result might be attributable to the increased π-basicity of **7** through the introduction of the methoxy group having a larger electron-releasing character than that of the methyl group. Thus, increased reactivity of substrate **7** may decrease the positional selectivity.

The structures **13** and **14** were readily apparent from their ^{1}H-NMR spectra. For example,

the ^{1}H-NMR spectral data (270 MHz, $CDCl_3$) of **13** shows a singlet at δ 7.73 for a proton at position 2 and 4 sets of doublets with the coupling constant (J = 9.2 Hz) at δ 7.93, 8.02, 8.23 and 8.36, which are



assigned to the protons of positions 4,5,9 and 10 on pyrene ring. In contrast, a different ^{1}H-NMR spectral pattern was observed in compound **14**. These data strongly support the assignment of structures of 3-bromo- (**13**) and 5-bromo-7-*tert*-butyl-1-methoxypyrene (**14**), respectively. Since attempted isolation of pure **13** failed, it was converted to 3-methyl derivative (**15**), which also was prepared by treatment of **8** with NaOMe in the presence of CuI in order to confirm the structure of **13**.



7-*tert*-Butyl-1,3-dimethylpyrene (**16**) was obtained by the reduction of 7-*tert*-butyl-3-methylpyrene-1-carbaldehyde (**9**). When 7-*tert*-butyl-1,3-dimethylpyrene (**16**) was treated with $AlCl_3$-$MeNO_2$, the desired 1,3-dimethylpyrene (**17**) was not obtained. Instead a large amount of resinous materials was formed along with the recovered **16**. However, it was reported[15a] that *tert*-butylbenzene derivatives treated with perfluorinated sulfonic acid resin (Nafion-H) in boiling toluene are dealkylated and *tert*-butyltoluene is formed in excellent yields. Thus, trans-*tert*-butylation of **16**, in the presence of Nafion-H (100 wt%) as a catalyst,[12e,12f,15] was carried out in boiling toluene to afford the desired 1,3-dimethylpyrene (**17**) in 78% yield along with *tert*-butyltoluene (**18**). This method provides good yields, easy isolation of the products, and no concomitant demethylation was observed under the reaction conditions.

We conclude that the electrophilic substitutions of **6** and **7** lead to the first-reported direct introduction of one substituent at the 3-position. The preparative route of **1** → **6** → **17** should be useful for the preparation of 1,3-disubstituted pyrenes. Further application of the present method is currently under study in our laboratory.

EXPERIMENTAL SECTION

All melting points are uncorrected. ^{1}NMR spectra were recorded on a Nippon Denshi JEOL FT-270 NMR spectrometer in $CDCl_3$ with TMS as an internal reference. IR spectra were measured as KBr pellets or as liquid films on NaCl plates in a Nippon Denshi JIR-AQ2OM spectrometer. Mass spectra

were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75 eV using a direct inlet system. Nafion-H catalyst was prepared from commercially available (Du Pont) Nafion-K resin, as described previously.[16]

Caution! Chloromethyl methyl ether is toxic and cancer-suspect compound. The following reactions should be carried out in a good hood. The reagent should not be allowed to come in contact with the skin.

Preparation of Pyrene-1-carbaldehyde (2).- To a stirred solution of pyrene **1** (5.0 g, 25 mmol) and dichloromethyl methyl ether (3.7 g, 32 mmol) in CH_2Cl_2 (200 mL) was added at 0° a solution of titanium tetrachloride (5 mL, 45.6 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 3 hrs at room temperature. The reaction mixture was poured into a large amount of ice-water and extracted with CH_2Cl_2 (2 x 200 mL). The organic layer was washed with water (2 x 300 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatograph- ed over silica gel (Wako, C-300; 200 g) with a hexane and benzene as eluent to give **1** (340 mg, 7.8%) and with benzene as eluent to give a yellow solid, which was recrystallized from hexane to afford the *title compound* **2** (5.1 g, 90%) as pale yellow prisms, mp. 126-127°, lit.[4] 126°.

Preparation of 1-Methylpyrene (3).- To a solution of **2** (50 g, 217 mmol) in toluene (150 mL) and diethylene glycol (150 mL) was added with stirring 100% hydrazine hydrate (40.0 g, 800 mmol). The mixture was heated at reflux for 1 hr. After the toluene and water were removed by distillation, the reaction mixture was cooled to room temperature. To the reaction mixture potassium hydroxide (60.0 g, 1 mol) was added and it was heated at 180° for 3 hrs. After the reaction mixture was cooled to room temperature, it was poured into a large amount of ice-water and extracted with CH_2Cl_2. The organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated. The residue was chromatographed over silica gel (Wako, C-300; 500 g) with a hexane as eluent to give a colorless solid, which was recrystallized from hexane to afford the *title compound* **3** (40.7 g, 80%) as colorless prisms, mp. 68-70°, lit.[4] 70-71°.

Preparation of 1-Bromopyrene (4).- To a solution of pyrene **1** (1.28 g, 6.36 mmol) and $CaCO_3$ (500 mg) in a mixture of CH_2Cl_2 (75 mL) and MeOH (25 mL) was added a solution of BTMA Br_3 (2.73 g, 7.0 mmol) at 0°. After the reaction mixture was stirred for 4 hrs at room temperature, it was poured into water (50 mL). The organic layer was extracted with CH_2Cl_2 (2 x 20 mL). The extract was washed with 10% aqueous sodium thiosulfate (10 mL) and water (10 mL), dried (Na_2SO_4), and concentrated. The residue was column chromatographed over silica gel (Wako, C-300; 200 g) with hexane as eluent to afford colourless solid. Recrystallization from ethanol gave 1-*bromopyrene* **4** (1.44 g, 80.3%) as colorless prisms, mp. 94-96°, lit.[5] 95-96.5°.

Preparation of 1-Methoxypyrene (5).- To methanol (50 mL) was added sodium (2.0 g, 87.0 mmol) and then a mixture of CuI (583 mg, 3.06 mmol) and 1-*bromopyrene* **4** (2.0 g, 7.11 mmol) in DMF (15 mL). After the reaction mixture was heated at reflux for 30 hrs, it was poured into ice-water (100 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The extract was washed with water (2 x 50 mL), dried (Na_2SO_4), and concentrated. The residue was column chromatographed over silica gel (Wako, C-300;

100g) with hexane as eluent to afford the desired 1-*methoxypyrene* **5** (1.22 g, 74%) as a colorless solid, which was recrystallized from hexane to afford the *title compound* **5** as colorless prisms, mp. 87-90°, lit.[4] 93°; NMR ($CDCl_3$): δ 4.14 (3 H, s), 7.50 (1 H, d, *J* = 8.3), 7.80-8.10 (7 H, m), 8.43 (1 H, d, *J* = 8.3).

Preparation of 7-*tert*-Butyl-1-methylpyrene (6).- To a solution of **3** (40.0 g, 187 mmol) and *tert*-butyl chloride (18.5 g, 200 mmol) in CH_2Cl_2 (300 mL) was added at 0° with stirring aluminum chloride (25.0 g, 187 mmol). This mixture was stirred for 2 hrs at room temperature. The reaction mixture was poured into a large amount of ice-water and extracted with CH_2Cl_2 (3 x 200 mL). The extract was washed with water (2 x 200 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed over silica gel (Wako, C-300; 500 g) with a hexane as eluent to give a colourless solid, which was recrystallized from hexane to afford the *title compound* **6** (40.7 g, 80%) as colorless prisms, mp. 99-100°. IR (KBr): 3100, 2950, 1590, 1460, 1380, 1360, 1300, 1220, 1170, 1140, 920 cm^{-1}; NMR ($CDCl_3$): δ 1.58 (9 H, s), 2.95 (3 H, s), 7.70-9.20 (8 H, m); mass spectrum:*m/e* 272 (M^+).

Anal. Calcd. for $C_{21}H_{20}$: C, 92.60; H, 7.40. Found: C, 92.49; H, 7.43

Compound **7** was prepared according to the method described above in 82% yield.

7-*tert*-Butyl-1-methoxypyrene (7) was obtained as colorless oil; NMR ($CDCl_3$): δ 1.57 (9 H, s), 4.16 (3 H, s), 7.49 (1 H, d, *J* = 8.3), 7.85 (1 H, d, *J* = 9.3), 7.92 (1 H, d, *J* = 9.3), 8.02 (1 H, d, *J* = 9.3), 8.07 (1 H, d, *J* = 8.3), 8.12 (1 H, d, *J* = 2.0), 8.14 (1 H, d, *J* = 2.0), 8.41 (1 H, d, *J* = 9.3); mass spectrum:*m/e* 288 (M^+).

Anal. Calcd. for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 92.49; H, 7.43

Preparation of 7-*tert*-Butyl-3-methylpyrene-1-carbaldehyde (9).- To a stirred solution of **6** (60.0 g, 220 mmol) and dichloromethyl methyl ether (50.0 g, 440 mmol) in CH_2Cl_2 (600 mL) was added at 0° a solution of titanium tetrachloride (24 mL, 218.9 mmol) in CH_2Cl_2 (50 mL). This mixture was stirred for 2 hrs at room temperature. The reaction mixture was poured into a large amount of ice-water and extracted with CH_2Cl_2 (2 x 250 mL). The organic layer was washed with water (2 x 300 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed over silica gel (Wako, C-300; 500 g) with a benzene as eluent to give a yellow solid, which was recrystallized from hexane-$CHCl_3$ (1:1) to afford the *title compound* **9** (54.0 g, 82%) as pale yellow prisms, mp. 238-238.5°; IR (KBr): 3050, 2950, 1670, 1570, 1470 cm^{-1}; NMR ($CDCl_3$): δ 1.60 (9 H, s), 3.00 (3 H, s), 8.22 (1 H, d, *J* = 9.3), 8.24 (1 H, d, *J* = 9.3), 8.25 (1 H, d, *J* = 9.3), 8.26 (1 H, s), 8.33 (2 H, s), 9.33 (1 H, d, *J* = 9.3), 10.77 (1 H, s); mass spectrum:*m/e* 300 (M^+).

Anal. Calcd. for $C_{22}H_{20}O$: C, 87.96; H, 6.71. Found: C, 88.00; H, 6.81

Preparation of 1-Bromo-7-*tert*-butyl-3-methylpyrene (8).- To a solution of pyrene **6** (1.73 g, 6.36 mmol) in a mixture of CH_2Cl_2 (75 mL) and MeOH (25 mL) was added a solution of BTMA Br_3 (2.5 g, 6.36 mmol) at 0°. After the reaction mixture was stirred for 2 hrs at room temperature, it was poured into water (100 mL). The organic layer was extracted with CH_2Cl_2 (2 x 50 mL). The extract was washed with 10% aqueous sodium thiosulfate (50 mL) and water (50 mL), dried (Na_2SO_4), and concentrated. The residue was column chromatographed over silica gel (Wako, C-300; 200 g) with

hexane as an eluent to afford colourless solid. Recrystallization from hexane-benzene (1:1) to afford the *title compound* **8** (2.08 g, 93%) as colorless plates, mp. 256-258°; IR (KBr): 2980, 1600, 1500, 1480, 1380, 1230, 1160, 990, 870 cm^{-1}; NMR ($CDCl_3$): δ 1.58 (9 H, s), 2.91 (3 H, s), 8.06 (1 H, s), 8.07 (1 H, d, *J* = 9.2), 8.09 (1 H, d, *J* = 9.2), 8.12 (1 H, d, *J* = 9.2), 8.22 (2 H, s), 8.33 (1 H, d, *J* = 9.2); mass spectrum:*m/e* 350, 352 (M^+).

Anal. Calcd. for $C_{21}H_{19}Br$: C, 71.80; H, 5.45. Found: C, 71.53; H, 5.45

Nitration of 7-*tert*-Butyl-3-methylpyrene (6).- To a solution of **6** (173 mg, 0.636 mmol) in acetic anhydride (50 mL) was added cuprous nitrate (184.4 mg, 0.763 mmol) at room temperature. After the reaction mixture was stirred for 1 hr at room temperature, it was poured into a large amount of ice water (200 mL) and extracted with CH_2Cl_2 (50 cm^3 x 2). The CH_2Cl_2 extract was washed with water and dried (Na_2SO_4), and concentrated. The residue was chromatographed over silica gel (Wako, C-300; 100 g) with hexane as eluent to give as a pale yellow solid a mixture of **10** and **(11+12)** (171 mg, 85%) in the ratio 80:20 (NMR spectrum). Recrystallization from benzene to afford *7-tert-butyl-1-methyl-3-nitropyrene* **(10)** (107 mg, 53%) as pale orange prisms, mp. 240-241°; IR (KBr): 2950, 1590, 1530, 1500, 1320, 1310, 1230, 910, 880 cm^{-1}; NMR ($CDCl_3$): δ 1.61 (9 H, s), 2.95 (3 H, s), 8.19 (1 H, d, *J* = 9.5), 8.23 (1 H, d, *J* = 9.5), 8.26 (1 H, d, *J* = 9.5), 8.33 (1 H, d, *J* = 1.5), 8.34 (1 H, d, *J* = 1.5), 8.47 (1 H, s), 8.83 (1 H, d, *J* = 9.5); mass spectrum:*m/e* 317 (M^+).

Anal. Calcd. for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.89; H, 6.03; N, 4.39

Bromination of 7-*tert*-Butyl-1-methoxypyrene (7).- To a solution of pyrene **7** (1.73 mg, 0.636 mmol) in a mixture of CH_2Cl_2 (7.5 mL) and MeOH (2.5 mL) was added a solution of BTMA Br_3 (0.25 g, 0.636 mmol) at 0°. After the reaction mixture was stirred for 2 hrs at room temperature, it was poured into water (30 mL). The organic layer was extracted with CH_2Cl_2 (2 x 20 mL). The extract was washed with 10% aqueous sodium thiosulfate (20 mL) and water (20 mL), dried (Na_2SO_4), and concentrated. The residue was column chromatographed over silica gel (Wako, C-300; 100 g) with hexane as an eluent to afford as a colourless solid a mixture of **13** amd **14** (200 mg, 85%) in the ratio 60:40 (NMR spectrum). Recrystallization from hexane to afford a small amount of *5-bromo-7-tert-butyl-1-methoxypyrene* **(14)** as colorless prisms, mp. 165-167°; IR (KBr): 2950, 1590, 1500, 1400, 1280, 1100, 1030, 880, 870 cm^{-1}; NMR ($CDCl_3$): δ 1.59 (9 H, s), 4.11 (3 H, s), 7.39 (1 H, d, *J* = 8.4), 7.91 (1 H, d, *J* = 8.4), 7.98 (1 H, d, *J* = 9.2), 8.16 (1 H, d, *J* = 1.8), 8.21 (1 H, s), 8.36 (1 H, d, *J* = 9.2), 8.52 (1 H, d, *J* = 1.8); mass spectrum:*m/e* 366, 368 (M^+).

Anal. Calcd. for $C_{21}H_{19}BrO$: C, 68.67; H, 5.21. Found: C, 68.90; H, 5.21

Although attempted isolation of *3-bromo-7-tert-butyl-1-methoxypyrene* **(13)** pure by fractional recrystallization has failed, the assignment of **13** was performed by ^1H NMR spectral data; NMR ($CDCl_3$): δ 1.57 (9 H, s), 4.14 (3 H, s), 7.73 (1 H, s), 7.93 (1 H, d, *J* = 9.2), 8.02 (1 H, d, *J* = 9.2), 8.23 (1 H, d, *J* = 9.2), 8.27 (2 H, s), 8.36 (1 H, d, *J* = 9.2).

Preparation of 7-*tert*-Butyl-1-methoxy-3-methylpyrene (15).- To a solution of **13** (81.3 mg, 0.221 mmol) in ether (5 mL) was added gradually 15% hexane solution of *n*-butyllithium (0.625 ml, 1.0 mmol) at -78°. After the reaction mixture was stirred for 15 min at -78°, dimethyl sulfate (0.5 mL)

was added and stirred for 30 min. The reaction mixture was worked up by addition of 10% hydrochloric acid and benzene (20 mL). The benzene extract was washed with water (2 x 20 mL), dried over Na_2SO_4, and concentrated. The residue was column chromatographed over silica gel (Wako, C-300; 100 g) with hexane as an eluent to afford as a colourless solid. Recrystallization from hexane afforded the *title compound* **15** (43.4 mg, 65%) as colorless prisms, mp. 160-162°; IR (KBr): 3050, 2980, 1600, 1550, 1520, 1350, 1270, 1220, 1110, 880, 840 cm^{-1}; NMR ($CDCl_3$): δ 1.56 (9 H, s), 2.92 (3 H, s), 4.12 (3 H, s), 7.34 (1 H, s), 7.88 (1 H, d, *J* = 9.2), 7.94 (1 H, d, *J* = 9.2), 8.07 (1 H, d, *J* = 9.2), 8.09 (2 H, s), 8.36 (1 H, d, *J* = 9.2); mass spectrum:*m/e* 302 (M^+).

Anal. Calcd. for $C_{22}H_{22}O$: C, 87.37; H, 7.33. Found: C, 87.27; H, 7.51

Alternative Preparation of 7-*tert*-Butyl-1-methoxy-3-methylpyrene (15).- To methanol (18 mL) was added sodium (580 mg, 25.2 mmol) and then a mixture of CuI (177 mg, 0.93 mmol) and **8** (447.0 mg, 1.27 mmol) in DMF (5 mL). After the reaction mixture was refluxed for 36 hrs, it was poured into ice-water (100 mL) and extracted with CH_2Cl_2 (2 x 70 mL). The extract was washed with water (2 x 40 mL), dried (Na_2SO_4), and concentrated. The residue was column chromatographed over silica gel (Wako, C-300; 100 g) with hexane as eluent to afford a colorless solid. Recrystallization from hexane to afford the *title compound* **15** (264.6 mg, 69%) as colorless prisms.

Preparation of 7-*tert*-Butyl-1,3-dimethylpyrene (16).- To a solution of **9** (20.0 g, 67 mmol) in toluene (50 mL) and diethylene glycol (30 mL), was added hydrazine hydrate (16.0 g, 320 mmol) with stirring. The mixture was heated at reflux for 1 hr. After the toluene and water were removed by distillation, the reaction mixture was cooled to room temperature. Potassium hydroxide (10.0 g, 192 mmol) was added and the reaction mixture was heated at 180° for 3 hrs. After the reaction mixture was cooled to room temperature, it was poured into a large amount of ice-water and extracted with CH_2Cl_2. The organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated. The residue was chromatographed over silica gel (Wako, C-300; 500 g) with a hexane as eluent to give a colourless solid, which was recrystallized from hexane to afford the *title compound* **16** (13.3 g, 70%) as colorless prisms, mp. 221-221.5°, IR (KBr): 2950, 1600, 1450, 1380 cm^{-1}; NMR ($CDCl_3$): δ 1.51 (9 H, s), 2.86 (6 H, s), 7.63 (1 H, s), 7.98 (2 H, d, *J* = 10.1), 8.10 (2 H, s), 8.12 (2 H, d, *J* = 10.1); mass spectrum:*m/e* 286 (M^+).

Anal. Calcd. for $C_{22}H_{22}$: 92.26; H, 7.74. Found: C, 92.53; H, 7.64

Preparation of 1,3-Dimethylpyrene (17).- A solution of **16** (200 mg, 0.70 mmol) in toluene (5 mL) and Nafion-H (200 mg) was refluxed under nitrogen for 12 hrs. After the reaction mixture was cooled to room temperature, it was filtered off and the filtrate was concentrated. The residue was chromatographed over silica gel (Wako, C-300; 50 g) with a hexane as eluent to give a colourless solid, which was recrystallized from hexane to afford the *title compound* **17** (125 mg, 78%) as colorless prisms, mp. 142-143°, IR (KBr): 3050, 2950, 1600, 1450, 1370, 1260, 1180, 1060 cm^{-1}; NMR ($CDCl_3$): δ 2.93 (6 H, s), 7.72 (1 H, s), 7.95 (2 H, d, *J* = 7.7), 8.02 (2 H, d, *J* = 9.2) and 8.13 (2 H, d, *J* = 7.7), 8.20 (2 H, d, *J* = 9.2); mass spectrum:*m/e* 230 (M^+).

Anal. Calcd. for $C_{18}H_{14}$: 93.87; H, 6.13. Found: C, 93.79; H, 6.46

The formation of *tert*-butyltoluene (**18**) was confirmed by GLC (conditions: Shimadzu gas chromatography, GC-14A, Silicone OV-1, 2 m, programmed temperature rise 12°/min; carrier gas nitrogen 25 mL/min).

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EFFICIENT SYNTHESIS OF *EXO*-1-AZABICYCLO[2.2.1]HEPTAN-3-OL

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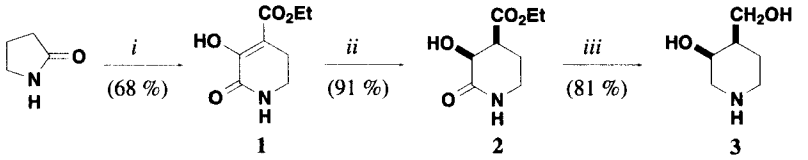
The 1-azabicylo[2.2.1]heptane ring system is found in a number of useful therapeutic agents.[1-4] Since substitution on either of the two-carbon bridges imparts chirality to this ring, an efficient route to the versatile optically active 1-azabicyclo[2.2.1] heptane synthons was required. Enantiomeric (R)-(-)- or (S)-(+)-*exo*-1-azabicyclo[2.2.1]heptan-3-ol (**5**), are such synthons. For example, (-)-**5** is a key intermediate in the synthesis of PD 151832, an m1-selective muscarinic agonist.[5] A previously described cyclodehydration of piperidinediol **3** over basic alumina gave only a modest yield (33%) of racemic **5**.[6] We found this procedure impractical for the procurement of the large quantities of **5** needed and describe here a practical synthesis of racemic **5** on a multigram scale in 86-96% overall yield from **3**.

In our hands, condensation of pyrrolidinone with diethyl oxalate (sequential ring-opening and reclosure under Claisen conditions) on a two hundred-gram scale afforded β-ketoester **1** in 68% yield.[6,7] Catalytic hydrogenation of **1** and recrystallization of the crude product from toluene furnished the *cis* diastereomer of β-hydroxyester **2** as the sole product in excellent yield.



1 **2** **3** (1)

i) $(CO_2Et)_2$, KOEt, $PhCH_3$, Δ, 18 hrs; *ii*) H_2, 10% Rh/C, AcOH; *iii*) LAH, THF, Δ, 48 hrs

Lithium tetrahydoaluminate reduction on the 40 gram scale provided the *cis* diol **3** with no detectable amount of the *trans* diastereomer in 81% yield. An attempt to reduce **2** with borane-tetrahy-