Electronic Supplementary Information (ESI)

pH-Sensitive DNA Cleaving Agents; *In situ* Activation by Ring Contraction of Benzo-fused Cyclobutanols

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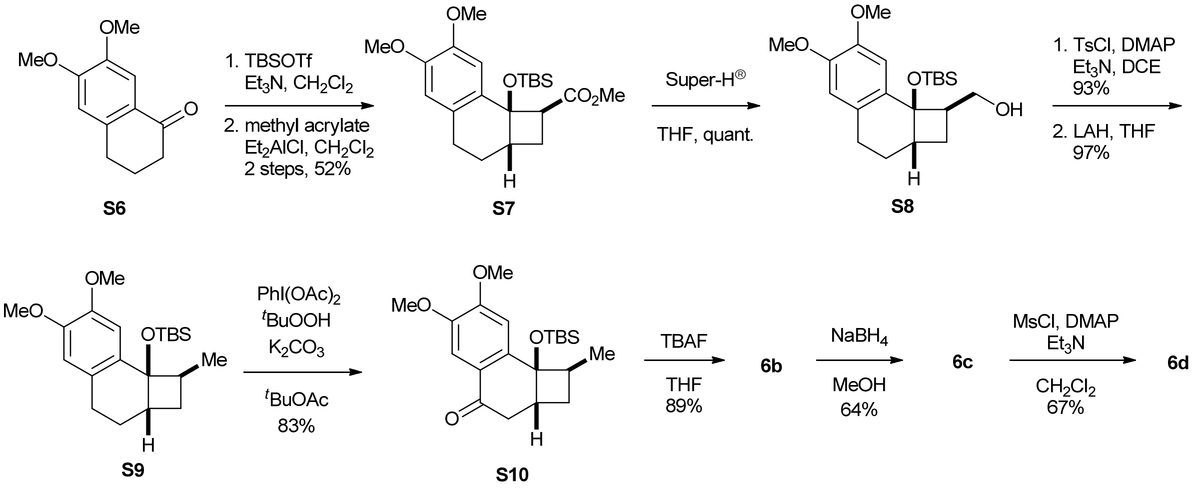
1. General information

All non-aqueous reactions were carried out under a positive atmosphere of argon in dried glassware unless otherwise noted. Solvents and materials were obtained from commercial suppliers and used without further purification. Column chromatography was performed on Merck silica gel 60 (230-400 mesh). Reactions and chromatography fractions were analyzed employing pre-coated silica gel plate (Merck Silica Gel 60 F_{254}). All melting points were measured on YANACO MP-3J micro melting point apparatus and are uncorrected. IR spectra were measured on JASCO FT/IR-4100typeA. The ^{1}H and ^{13}C NMR spectra were recorded on JEOL AL-400 or JEOL ECP-500 with tetramethylsilane as internal standard. Low-resolution and high-resolution mass spectra were recorded on JMS-HX/HX 110A or MS700 mass spectrometer.

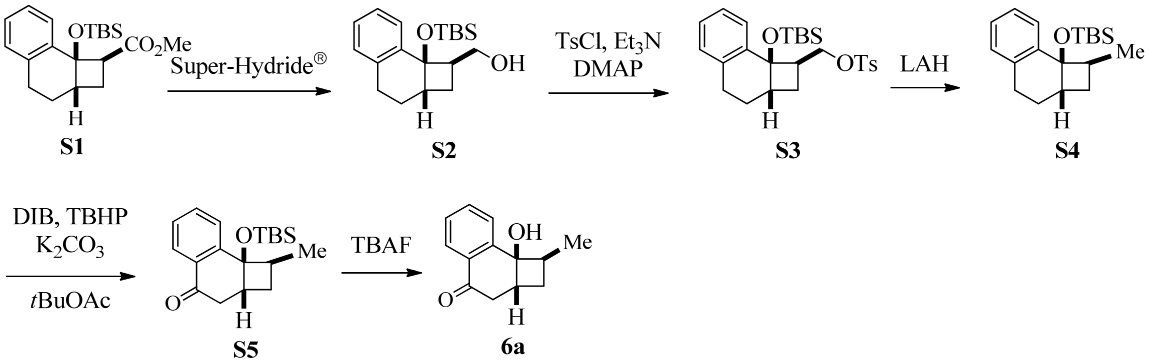
Synthesis and characterization data of fused-cyclobutanols

A procedure for preparation of fused-cyclobutanol 6.

The synthetic procedure underlying **6a-d** is summarized in the following Schemes. Tricyclic cyclobutane **S7** was prepared by silyl enol etherification of **S6**, followed by the $EtAlCl_2$-catalyzed [2+2] cycloaddition.[1] The ester **S7** was reduced to the alcohol **S8** in a quantitative yield. Reductive elimination of the hydroxyl group of **S8** was achieved by tosylation, followed by LAH reduction to give the methylcyclobutane **S9**. Oxidation of the benzyl moiety of **S9** required significant trial and error. Finally, we found that the *tert*-butylhypo radical, which was generated by *tert*-butylhydroperoxide (TBHP) in the presence of diacetoxyiodobenzene (DIB),[2] yielded the desired ketone **S10** in good yield. After desilylation, reduction by $NaBH_4$ stereoselectively gave the alcohol **6c**. Dehydration of **6c** was achieved by the treatment with MsCl at rt to produce **6d**. Compound **6a** was synthesized from **S1**.



A procedure for preparation of fused-cyclobutanol 6a

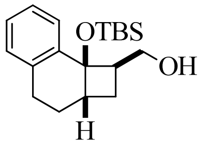


To a solution of **S1** (2.0 g, 5.78 mmol), which was synthesized according as the literature,[1] in THF (58 mL) at 0 °C was dropwise added 1.0 M Super-Hydride® in THF (17.3 mL, 17.3 mmol). After being stirred for 30 min at ambient temperature, the resulting mixture was quenched with H_2O and concentrated in vacuo. The aqueous layer was extracted twice with AcOEt. The combined organic layers were washed with brine and dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane / AcOEt = 13 : 1) to afford **S2** (2.12 g, quant.).

To a mixture of **S2** (464 mg, 1.46 mmol) and DMAP (17.8 mg, 146 μmol) in CH_2Cl_2 (6.0 ml) were added Et_3N (410 μl, 2.92 mmol) and TsCl (307 mg, 1.61 mmol). After being stirred for 5 h at ambient temperature, the resulting mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted twice with AcOEt. The combined organic layers were washed with saturated aqueous NH_4Cl and brine and dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/AcOEt = 22 : 1) to afford **S3** (622 mg, 90%).

To a mixture of LAH (88.9 mg, 2.34 mmol) in Et_2O (6.0 ml) at 0 °C was dropwise added **S3** (526 mg, 1.11 mmol) in Et_2O (5.0 ml). After being stirred for 7 h at ambient temperature, the resulting mixture was quenched with H_2O and 1 N aqueous NaOH, filtered through Celite® and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane) to afford **S4** (260 mg, 78%).

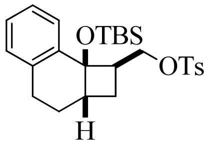
To a mixture of **S4** (254 mg, 839 μmol) and diacetoxyiodobenzene (811 mg, 2.52 mmol) and K_2CO_3 (57.9 mg, 420 μmol) in *t*BuOAc (1.3 mL) at 0 °C was added 5.5 M TBHP (*tert*-butyl hydroperoxide) in nonane (670 μL, 3.36 mmol) via a syringe pump for 30 min. After being stirred for 11 h at 0 °C, the resulting mixture was quenched with saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted twice with AcOEt. The combined organic layers were washed with brine and dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/AcOEt = 40 : 1) to afford **S5** (123 mg, 47%) and **6a** (82.1 mg, 32%). A mixture of **S5** (123 mg, 389 μmol) and 1 M TBAF in THF (584 μL, 584 μmol) was stirred for 1 h at ambient temperature. The resulting mixture was diluted with AcOEt, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane / AcOEt = 2 : 1) to afford **6a** (66.3 mg, 84%).



S2

(1*S**,2a*S**,8b*R**)-8b-*tert*-Butyldimethylsilyloxy-1-hydroxymethyl-1,2,2a,3,4,8b-hexahydrocyclobuta[a]naphthalene (S2)

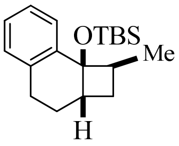
White solids; M.p. 61-62 °C (Hexane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 4.11 (ddd, *J* = 13.2, 7.5, 3.4 Hz, 1H), 3.76 (ddd, *J* = 13.2, 6.9, 4.6 Hz, 1H), 3.15 (dd, *J* = 9.1, 3.4 Hz, 1H), 2.97-2.91 (m, 1H), 2.88-2.74 (m, 2H), 2.50-2.44 (m, 1H), 1.85-1.76 (m, 1H), 1.76-1.71 (m, 1H), 1.58-1.48 (m, 2H), 0.91 (s, 9H), 0.042 (s, 3H), -0.39 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.0, 135.2, 128.3, 128.2, 126.8, 126.7, 75.2, 64.5, 49.0, 40.2, 25.9, 25.5, 21.8, 18.0, 16.8, -2.79, -3.61 ppm; IR (neat) 3467, 2929, 2856 cm^{-1}; LRMS (FAB) *m/z* 319 (M^++1); HRMS (FAB+) calcd for $C_{19}H_{31}O_2Si$ (M+H) 319.2093, found: 319.2095.



S3

(1*R**,2a*S**,8b*R**)-8b-*tert*-Butyldimethylsilyloxy-1-(4-methylbenzenesulfonyl)oxymethyl-1,2,2a,3,4,8b-hexahydrocyclobuta[a]naphthalene (S3).

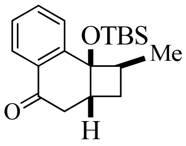
Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.35-7.31 (m, 3H), 7.18-7.12 (m, 2H), 7.05 (d, *J* = 7.2 Hz, 1H), 4.49 (dd, *J* = 9.7, 6.9 Hz, 1H), 4.23 (dd, *J* = 9.5, 8.3 Hz, 1H), 2.74-2.65 (m, 3H), 2.60-2.54 (m, 1H), 2.45 (s, 3H), 1.89-1.82 (m, 1H), 1.78-1.67 (m, 2H), 1.61-1.54 (m, 1H), 0.82 (s, 9H), -0.014 (s, 3H), -0.43 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.5, 141.3, 136.0, 133.2, 129.7, 128.1, 128.0, 127.8, 126.9, 126.6, 74.5, 71.0, 45.6, 40.5, 26.4, 25.8, 24.6, 21.6, 20.8, 18.2, -3.00, -3.57 ppm; IR (neat) 2928, 2855 cm^{-1}; LRMS (FAB) *m/z* 473 (M^++1); *Anal* calcd. for $C_{26}H_{36}O_4SSi$: C, 66.06; H, 7.68; found: C,66.29; H, 7.77.



S4

(1*S,2a*S**,8b*R**)-8b-*tert*-Butyldimethylsilyloxy-1-methyl-1,2,2a,3,4,8b-hexahydrocyclobuta[a]naphthalene (S4).**

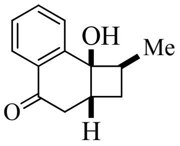
Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.17 (t, *J* = 8.6 Hz, 1H), 7.12 (td, *J* = 7.4, 1.5 Hz, 1H), 7.06 (d, *J* = 7.4 Hz, 1H), 2.78-2.71 (m, 3H), 2.34-2.24 (m, 1H), 1.89-1.82 (m, 1H), 1.75-1.69 (m, 1H), 1.65-1.59 (m, 1H), 1.57-1.51 (m, 1H), 1.20 (d, *J* = 6.8 Hz, 1H), 0.90 (s, 9H), -0.065 (s, 3H), -0.38 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.7, 135.8, 128.0, 127.4, 126.3, 126.2, 74.3, 42.4, 40.2, 26.6, 25.9, 25.0, 24.3, 18.4, 15.6, -2.79, -3.48 ppm; IR (neat) 2927, 2857 cm^{-1}; LRMS (FAB) *m/z* 303 (M^++1); *Anal* calcd. for $C_{19}H_{30}OSi$: C, 75.43; H, 10.00; found: C, 75.53; H, 10.29.



S5

(1S*,2aS*,8bR*)-8b-*tert*-Butyldimethylsilyloxy-1-methyl-1,2,2a,3,4,8b-hexahydrocyclobuta[a]naphthalene-4-one (S5).

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.1 Hz, 1H), 7.61 (t, *J* = 6.8 Hz, 1H), 7.54 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.37 (td, *J* = 8.3, 1.3 Hz, 1H), 3.14-3.08 (m, 1H), 2.81 (dd, *J* = 17.5, 5.8 Hz, 1H), 2.60 (dd, *J* = 17.5, 2.7 Hz, 1H), 2.31-2.23 (m, 1H), 1.60-1.57 (m, 1H), 1.49-1.42 (m, 1H), 1.28 (d, *J* = 7.6 Hz, 3H), 0.90 (s, 9H), -0.013 (s, 3H), -0.40 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.0, 148.8, 134.3, 130.6, 128.6, 127.3, 125.6, 42.4, 38.3, 37.9, 29.6, 25.7, 25.5, 18.2, 15.3, -2.87, -3.57 ppm; IR (neat) 2928, 2857, 1689 cm^{-1}; LRMS (FAB) *m/z* 317 (M^++1); HRMS (FAB) calcd for $C_{19}H_{29}O_2Si$ (M+H) 317.1937, found: 317.1933.

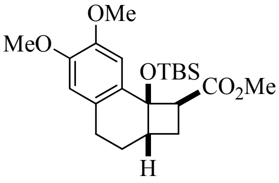


6a

(1*S,2a*S**,8b*R**)-8b-Hydroxy-1-methyl-1,2,2a,3,4,8b-hexahydrocyclobuta[a]naphthalene-4-one (6a).**

Brown solids; M.p. 88-89 °C (Hexane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 3.10-3.04

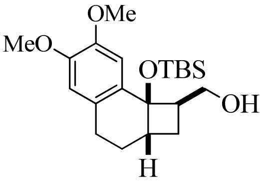
(m, 1H), 2.85 (dd, *J* = 16.9, 5.7 Hz, 1H), 2.58 (dd, *J* = 16.9, 2.5 Hz, 1H), 2.40-2.33 (m, 2H), 1.59 (dd, *J* = 7.4, 2.3 Hz, 1H), 1.53-1.46 (m, 1H), 1.34 (d, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.9, 147.1, 134.8, 130.9, 127.8, 127.5, 125.9, 70.6, 41.4, 39.1, 37.7, 25.4, 14.4 ppm; IR (neat) 3437, 2963, 1674 cm^{-1}; LRMS (FAB) *m/z* 203 (M$^+$+1); *Anal* calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98; found: C, 77.28; H, 7.04.



S7

(1*S,2a*S**,8b*R**)-8b-*tert*-Butyldimethylsilyloxy-6,7-dimethoxy-1-methoxycarbonyl-1,2,2a,3,4,8b-hexahydrocyclobuta[a]naphthalene (S7).**

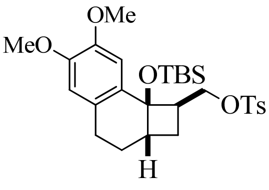
White solids; M.p. 79-80 °C (Hexane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (s, 1H), 6.55 (s, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.14 (dd, *J* = 8.6, 5.1 Hz, 1H), 2.99-2.93 (m, 1H), 2.76-2.63 (m, 2H), 2.34 (ddd, *J* = 11.5, 9.8, 5.5 Hz, 1H), 1.86 (ddd, *J* = 18.3, 9.8, 4.6 Hz, 1H), 1.74 (ddd, *J* = 13.8, 10.9, 5.5 Hz, 1H), 1.56 (dt, *J* = 11.5, 8.0 Hz, 1H), 0.86 (s, 9H), 0.048 (s, 3H), -0.38 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 148.1, 147.8, 133.3, 128.4, 110.3, 110.2, 74.7, 55.7, 55.7, 52.6, 51.5, 40.8, 25.6, 24.0, 18.5, 18.0, -2.97, -3.61 ppm; IR (neat) 2950, 1737 cm^{-1}; LRMS (FAB) *m/z* 407 (M$^+$+1); *Anal* calcd. for $C_{22}H_{34}O_5Si$: C, 64.99; H, 8.43; found: C, 64.83; H, 8.65.



S8

(1*S,2a*S**,8b*R**)-8b-*tert*-Butyldimethylsilyloxy-6,7-dimethoxy-1-hydroxymethyl-1,2,2a,3,4,8b-hexahydrocyclobuta[a]naphthalene (S8).**

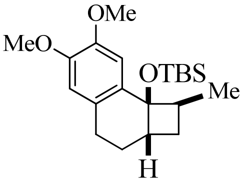
White solids; M.p. 84-85 °C (Hexane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.56 (s, 1H), 4.12 (dt, *J* = 10.6, 3.1 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.75 (ddd, *J* = 14.6, 10.6, 3.5 Hz, 1H), 3.23 (dd, *J* = 9.8, 3.1 Hz, 1H), 2.96-2.89 (m, 1H), 2.77 (ddd, *J* = 17.4, 11.7, 6.0 Hz, 1H), 2.69 (ddd, *J* = 16.4, 6.0, 2.9 Hz, 1H), 2.49-2.44 (m, 1H), 1.83-1.69 (m, 2H), 1.50 (dt, *J* = 11.7, 8.9 Hz, 1H), 1.42 (td, *J* = 9.8, 3.1 Hz, 1H), 0.92 (s, 9H), -0.0052 (s, 3H), -0.36 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.9, 133.8, 127.5, 110.4, 110.1, 75.1, 64.6, 55.7, 55.7, 49.1, 39.9, 25.9, 25.0, 21.5, 18.0, 16.3, -2.77, -3.61 ppm; IR (neat) 3546, 2930, 2855 cm^{-1}; LRMS (FAB) *m/z* 379 (M$^+$+1); *Anal* calcd. for $C_{21}H_{34}O_4Si$: C, 66.62; H, 9.05; found: C, 66.46; H, 9.00.



S8'

(1*R,2a*S**,8b*R**)-8b-*tert*-Butyldimethylsilyloxy-6,7-dimethoxy-1-(4-methylbenzenesulfonyl)oxymethyl-1,2,2a,3,4,8b-hexahydrocyclobuta[a]naphthalene (S8').**

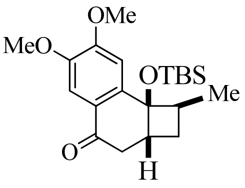
White solids; M.p. 80-81 °C (Hexane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.90 (s, 1H), 6.52 (s, 1H), 4.52 (dd, *J* = 9.7, 8.0 Hz, 1H), 4.14 (dd, *J* = 9.7, 7.4 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 2.66-2.56 (m, 4H), 2.45 (s, 3H), 1.94-1.87 (m, 1H), 1.77-1.65 (m, 2H), 1.57-1.51 (m, 1H), 0.84 (s, 9H), -0.11 (s, 3H), -0.37 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8, 147.7, 144.5, 133.3, 133.1, 129.7, 128.6, 127.9, 110.4, 110.2, 74.9, 70.6, 55.7, 55.7, 45.5, 40.3, 26.3, 25.8, 25.7, 21.6, 20.9, 18,2, -3.04, -3.45 ppm; IR (neat) 2930, 2856 cm^{-1}; LRMS (FAB) *m/z* 533 (M^++1); *Anal* calcd. for $C_{28}H_{40}O_6SSi$: C, 63.12; H, 7.57; found: C, 63.12; H, 7.76.



10

(1*S,2a*S**,8b*R**)-8b-*tert*-Butyldimethylsilyloxy-6,7-dimethoxy-1-methyl-1,2,2a,3,4,8b-hexahydrocyclobuta[a]naphthalene (S9).**

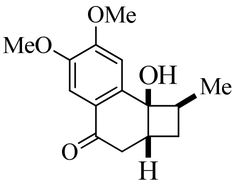
White solids; M.p. 63-64 °C (Hexane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (s, 1H), 6.55 (s, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 2.79-2.63 (m, 3H), 2.30-2.22 (m, 1H), 1.81 (ddd, *J* = 18.6, 8.9, 3.7 Hz, 1H), 1.70 (ddd, *J* = 14.0, 10.0, 4.8 Hz, 1H), 1.60 (dt, *J* = 11.5, 7.4 Hz, 1H), 1.45 (td, *J* = 9.7, 4.8 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), -0.033 (s, 3H), -0.37 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.5, 147.4, 135.7, 127.8, 110.3, 109.8, 73.7, 55.7, 42.6, 39.8, 25.9, 25.9, 24.0, 23.5, 18.4, 15.9, -2.77, -3.49 ppm; IR (neat) 2953, 2927, 2855 cm^{-1}; LRMS (FAB) *m/z* 363 (M^++1); *Anal* calcd. for $C_{21}H_{34}O_3Si$: C, 69.56; H, 9.45; found: C, 69.47; H, 9.56.



S10

(1*S,2a*S**,8b*R**)-8b-*tert*-Butyldimethylsilyloxy-6,7-dimethoxy-1-methyl-1,2,2a,3,4,8b-hexahydrocyclobuta[a]naphthalene-4-one (S10).**

Brown solids; M.p. 73-74 °C (Hexane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 1H), 6.91 (s, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.12-3.05 (m, 1H), 2.77 (dd, *J* = 17.7, 6.0 Hz, 1H), 2.56 (dd, *J* = 17.7, 2.3 Hz, 1H), 2.30-2.23 (m, 1H), 1.54 (ddd, *J* = 11.8, 9.5, 2.3 Hz, 1H), 1.47 (ddd, *J* = 11.8, 10.0, 8.3 Hz, 1H), 1.28 (d, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.016 (s, 3H), -0.36 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.4, 154.4, 148.5, 143.4, 124.4, 109.2, 106.7, 71.4, 55.9, 42.3, 37.8, 25.7, 25.6, 18.2, 15.4, -2.95, -3.55 ppm; IR (neat) 2935, 2857, 1676 cm^{-1}; LRMS (FAB) *m/z* 377 (M^{+}+1); *Anal* calcd. for $C_{21}H_{32}O_4Si$: C, 66.98; H, 8.57; found: C, 66.92; H, 8.53.

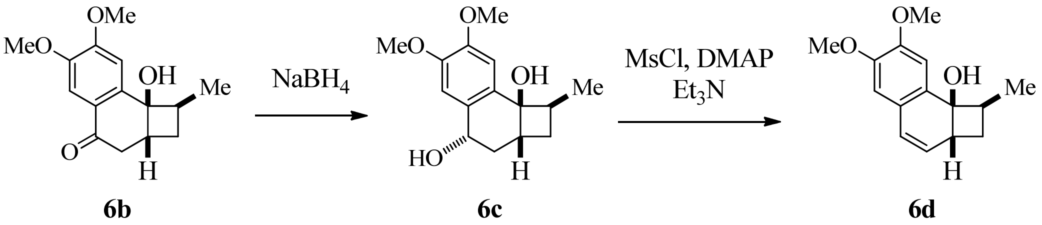


6b

(1S*,2aS*,8bR*)-8b-Hydroxy-6,7-dimethoxy-1-methyl-1,2,2a,3,4,8b-hexahydrocyclobuta[a]naphthalene-4-one (6b).

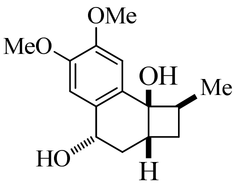
White solids; M.p. 133-134 °C (Hexane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (s, 1H), 6.94 (s, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.07-3.01 (m, 1H), 2.82 (dd, *J* = 17.7, 6.3 Hz, 1H), 2.53 (dd, *J* = 17.7, 2.3 Hz, 1H), 2.41-2.35 (m, 1H), 2.32 (bs, 1H), 1.58 (ddd, *J* = 11.7, 9.7, 2.5 Hz, 1H), 1.52 (ddd, *J* = 11.7, 9.7, 8.0 Hz, 1H), 1.35 (d, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.3, 154.8, 148.8, 141.4, 124.7, 108.4, 107.0, 70.6, 56.2, 56.0, 41.3, 39.3, 37.1, 25.5, 14.5 ppm; IR (neat) 3431, 2961, 1660 cm^{-1}; LRMS (FAB) *m/z* 263 (M^{+}+1); *Anal* calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92; found: C, 68.39; H, 7.08.

Procedure for preparation of fused-cyclobutanols 6c and 6d.



To a solution of **6b** (921 mg, 3.52 mmol) in MeOH (11 mL) at 0 °C was added $NaBH_4$ (334 mg, 8.79 mmol). After being stirred for 20 min at ambient temperature, the resulting mixture was quenched with H_2O and concentrated in vacuo. The aqueous layer was extracted twice with AcOEt. The combined organic layers were washed with brine and dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/AcOEt = 1 : 1.1 to hexane/AcOEt = 1 : 1.5) to afford **6c** (598 mg, 64%).

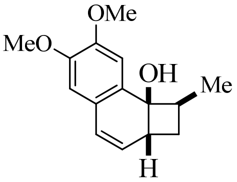
To a mixture of **6c** (222 mg, 841 μmol) and DMAP (10.3 mg, 84.1 μmol) and Et_3N (350 μL, 2.52 mmol) in CH_2Cl_2 (8.4 mL) at 0 °C was dropwise added MsCl (84 μl, 1.09 mmol). After being stirred for 30 min the same temperature, the resulting mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted twice with AcOEt. The combined organic layers were washed with brine and dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by alumina column chromatography (hexane / AcOEt = 4 : 1) to afford **6d** (138 mg, 67%).



6c

(1*S,2a*S**,4*S**,8b*R**)-4,8b-Dihydroxy-6,7-dimethoxy-1-methyl-1,2,2a,3,4,8b-hexahydrocyclobuta[a]naphthalene (6c).**

White solids; M.p. 135-136 °C (Hexane/AcOEt); ^1H NMR (500 MHz, $CDCl_3$) δ 7.04 (s, 1H), 6.84 (s, 1H), 4.81-4.77 (m, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 2.61-2.52 (m, 1H), 2.29 (ddd, J = 13.4, 6.3, 4.6 Hz, 1H), 1.87-1.77 (m, 4H), 1.70 (bs, 1H), 1.60 (bs, 1H), 1.26 (d, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2, 148.6, 133.6, 131.7, 108.6, 108.3, 73.7, 67.4, 56.0, 55.9, 39.4, 39.2, 36.8, 28.4, 14.4 ppm; IR (neat) 3429, 2932 cm^{-1}; LRMS (FAB) *m/z* 265 (M^++1); *Anal* calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; found: C, 68.43; H, 7.48.



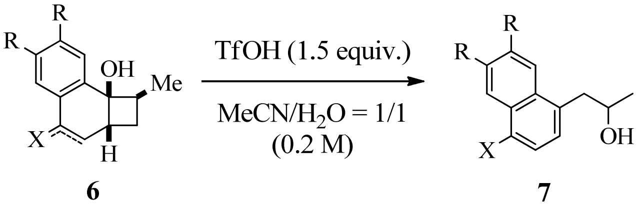
6d

(1*S,2a*S**,8b*R**)-8b-Hydroxy-6,7-dimethoxy-1-methyl-1,2,2a,8b-tetrahydrocyclobuta[a]naphthalene (6d).**

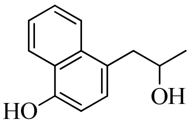
White solids; M.p. 65-66 °C (Hexane/AcOEt); ^1H NMR (500 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.59 (s, 1H), 6.31 (d, *J* = 9.7 Hz, 1H), 5.89 (dd, *J* = 9.7, 5.4 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.11-3.06 (m, 1H), 2.76-2.69 (m, 1H), 1.93 (bs, 1H), 1.87 (ddd, *J* = 10.9, 10.0, 4.9 Hz, 1H), 1.71 (dt, *J* = 10.9, 8.1 Hz, 1H), 1.28 (d, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.9, 148.5, 131.7, 127.4, 125.5, 125.3, 109.8, 109.1, 71.6, 56.1, 55.9, 43.2, 41.8, 31.2, 15.4 ppm; IR (neat) 3501, 2931 cm^{-1}; LRMS (FAB) *m/z* 247 (M^++1); HRMS (FAB) calcd for $C_{15}H_{17}O_2$ (M–OH) 229.1223, found: 229.1227.

Synthesis and characterization data of naphthalenes

A procedure for ring contraction-opening reaction (Typical procedure for Table 1, entry 4).



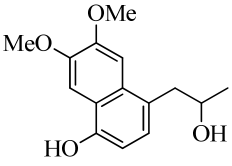
To a solution of **6d** (52.6 mg, 0.214 mmol) in MeCN/H_2O (1 : 1, 1 mL) was dropwise added TfOH (28.4 μL, 0.321 mmol). After being stirred for 1 h at ambient temperature, the resulting mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted twice with AcOEt. The combined organic layers were washed with brine and dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography (Hexane-AcOEt = 2 : 1 to 2 : 3) to afford **7c** (46.5 mg, 88%).



12a

4-(2-Hydroxypropy)naphthalene-1-ol (7a).

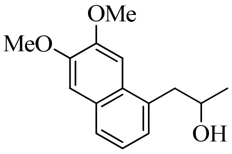
Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.98 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.56-7.48 (m, 2H), 7.19 (d, *J* = 7.4 Hz, 1H), 6.77 (d, *J* = 7.4 Hz, 1H), 5.35 (bs, 1H), 4.18-4.11 (m, 1H), 3.23 (dd, *J* = 14.0, 4.6 Hz, 1H), 3.02 (dd, *J* = 14.0, 8.3 Hz, 1H), 1.53 (bs, 1H), 1.32 (d, *J* =6.3 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.7, 133.2, 127.4, 127.0, 126.5, 124.9, 123.9, 122.4, 108.1, 68.2, 42.5, 23.1 ppm; IR (neat) 3331, 2969 cm^{-1}; LRMS (FAB) *m/z* 203 (M^++1); HRMS (FAB) calcd for $C_{13}H_{14}O_2$ (M) 202.0994, found: 202.0989.



12b

6,7-Dimethyoxy-4-(2-hydroxypropy)naphthalene-1-ol (7b)

Colorless amorphous; M.p. 137-138 °C (Hexane/AcOEt); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.53 (s, 1H), 7.24 (s, 1H), 7.05 (d, *J* = 7.4 Hz, 1H), 6.65 (d, *J* = 7.4 Hz, 1H), 4.19-4.14 (m, 1H), 4.03 (s, 3H), 4.02 (s, 3H), 3.14 (dd, *J* = 14.1, 4.6 Hz, 1H), 3.00 (dd, *J* = 14.1, 8.3 Hz, 1H), 1.60 (bs, 1H), 1.32 (d, *J* =6.3 Hz, 3H) ppm; ^{13}C NMR (126 MHz, CDCl$_3$) δ 149.9, 149.8, 148.7, 129.1, 125.8, 125.3, 120.2, 68.1, 55.9, 55.8, 42.6, 23.1 ppm; IR (neat) 3445, 2929 cm^{-1}; LRMS (FAB) *m/z* 263 (M$^+$+1); *Anal* calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92; found: C, 68.28; H, 6.63.



12c

6,7-Dimethyoxy-4-(2-hydroxypropy)- naphthalene (7c)

Brown solids; M.p. 91-92 °C (Hexane/AcOEt); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.29 (s, 1H), 7.28 (dd, *J* = 8.0, 6.3 Hz, 1H), 7.22 (d, *J* = 6.3 Hz, 1H), 7.14 (s, 1H), 4.24-4.15 (m, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 3.19 (dd, *J* = 14.0, 4.8 Hz, 1H), 3.10 (dd, *J* = 14.0, 8.0 Hz, 1H), 1.62 (bs, 1H), 1.33 (d, *J* =6.0 Hz, 3H) ppm; ^{13}C NMR (126 MHz, CDCl$_3$) δ 149.4, 149.2, 133.1, 129.8, 127.8, 125.9, 125.7, 124.0, 107.1, 102.9, 68.1, 55.8, 55.8, 43.0, 23.2 ppm; IR (neat) 3501, 2962 cm^{-1}; LRMS (FAB) *m/z* 247 (M$^+$+1); HRMS (FAB) calcd for $C_{15}H_{18}O_3$ (M) 246.1256, found: 246.1255.

DNA cleavage assay

DNA-cleaving activities of benzo-fused cyclobutanols were evaluated with pUC19 plasmid DNA. Supercoiled pUC19 DNA (250 ng) was incubated with compounds **6** or **12** (1 μL DMSO solution) in various pH solutions at 37 °C for 24 h (reaction volume: 50 μL). The samples were separated on a 1% TAE agarose gel (100 V, 30 min). Plasmid DNA was visualized with ethidium bromide, and the UV images were obtained with FAS-III system (Toyobo, Osaka, Japan).

Reference

1. K. Takasu, M. Ueno, K. Inanaga, M. Ihara, *J. Org. Chem.,* 2004, **69**, 517.
2. Y. Zhao and Y.-Y. Yeung, *Org. Lett.,* 2010, **12**, 2128.