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SUPPORTING INFORMATION

Title: Baeyer–Villiger Oxidation of the Bicyclo[2.2.2]octanone System Revisited: Searching for a Modular Construction of Heavily Substituted Cyclohexanes Based on *m*-CPBA Mediated Selective Oxygen Insertion
Author(s): Laure Finet, Mohamed Dakir, Isabel Castellote, Siméon Arseniyadis*
Ref. No.: O200700321

Experimental Section

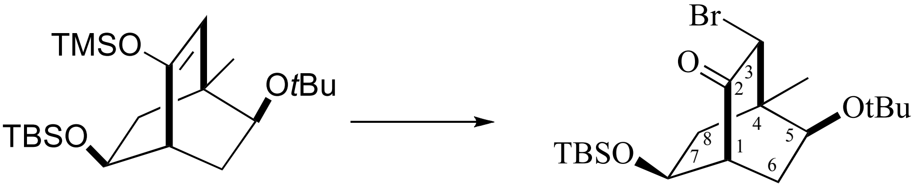
General Remarks: "Usual work up" means washing of the organic layer with brine, drying on anhydrous $MgSO_4$, and evaporating *in vacuo* with a rotary evaporator at aspirator pressure. Melting points were uncorrected. IR spectra were recorded with an FT-IR instrument through NaCl cell windows and absorptions are given in cm^{-1}. NMR spectra were run in $CDCl_3$ unless otherwise noted. Experimental evidence favoring the structures investigated came from a comprehensive range of ^1H and ^{13}C NMR data (500/125 and 300/75 MHz respectively, 1D and 2D experiments) and corroborated by spatial proximity (n.O.e) studies using 1 and D techniques. ^1H chemical shifts are expressed in ppm downfield from TMS using the residual non-deuterated solvent as internal standard ($CDCl_3$ ^1H, 7.26 ppm). ^{13}C chemical shifts are reported relative to $CDCl_3$ triplet centered at 77.0 ppm. Mass spectra acquired in the positive ion mode under electron spray ionization (ES^+) using a mobile phase of methanol, will be abbreviated as ESIMS (MeOH). HR will be added for the high resolution mass measurements (HRESIMS).

Crystallographic data (excluding structure factors) for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 620081 (**43**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Commercially available *m*-chloroperbenzoic acid (Aldrich) was purified by washing with pH 7.4 phosphate buffer and drying under reduced pressure.

Typical procedure for Baeyer-Villiger oxidation: Sodium hydrogen carbonate (0.12 mmol) and *m*-chloroperbenzoic acid (0.3 mmol, washed with phosphate buffer pH = 7.4 and dried carefully under reduced pressure) were added to the appropriate ketone (0.1 mmol) in methylene chloride (1 mL) at 0°C. The mixture was stirred at room temperature (for approximately 17h or as indicated, TLC monitoring). The crude reaction mixture was diluted with methylene chloride and filtered through a plug of Celite. The excess peracid was decomposed by washing with aqueous 5% sodium sulfite. Finally the organic phase was washed with sat. $NaHCO_3$, and worked up as usual.

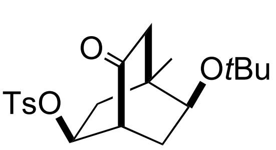
Preparation of the substrates



2c

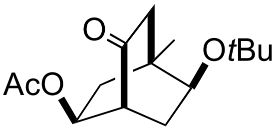
3-Bromo-5-*tert*-butoxy-7-(*tert*-butyl-dimethyl-silanyloxy)-4-methyl-bicyclo [2.2.2] octan-2-one 2c *N*-bromo succinimide (130 mg, 0.73 mmol) was added at 0°C to a solution of the known TMS-enol ether (253 mg, 0.61 mmol) in THF (5 mL). The mixture was stirred at 0°C for 30 min, quenched with sat. aq. $NaHCO_3$ and diluted with EtOAc. Usual work up gave a white solid **2c** (231 mg, 90%): $[\alpha]_D^{20}$ = +26 (*c* 1.2, $CHCl_3$). m. p. 128 °C (CH_2Cl_2). IR (film): ν = 3446, 2973, 2949, 2930, 2897, 2858, 1732, 1472, 1255, 1095 cm^{-1}. ^1H-NMR (300 MHz): δ = 0.00 (2s, 6 H), 0.82 (s, 9 H), 1.03 (s, 3 H), 1.09 (s, 9 H), 1.68 (ddd, J = 2.5, 3.7, 14.8, Hz, 1 H), 1.68 (ddd, J = 2.0, 8.8, 14.9 Hz, 1 H), 1.89 (ddd, J = 0.6, 2.2, 14.9 Hz, 1 H), 2.09 (ddd, J = 2.6, 9.0, 14.8 Hz, 1 H), 2.45 (q, J = 3.4 Hz, 1 H), 3.55 (dd, J = 2.5, 9.0 Hz, 1 H), 3.96 (ddd, J = 2.2, 4.0, 8.8 Hz, 1 H), 4.63 (d, J = 2.0 Hz, 1 H). ^{13}C-NMR (75 MHz): δ = -5.0 (2 C), 17.8, 23.0, 26.6 (3C), 28.5 (3 C), 33.6, 37.8, 41.6, 50.8, 54.1, 68.7, 69.9, 73.8, 207.5. ESIMS (MeOH): 441.1 ($[M+Na]^+$, 100). HRESIMS: calcd. for $C_{19}H_{35}O_3SiBrNa$ *m/z* 441.1437, found 441.1429. Analysis: calcd. for $C_{19}H_{35}BrO_3Si$ (418.15) C 54.40, H 8.41; found C 54.51; H 8.54.

The bicyclic aldol **2a** (124 mg, 0.54 mmol) was dissolved in dry pyridine (4.0 mL), DMAP (cat.) and *p*-toluenesulfonyl chloride (627 mg, 2.19 mmol) were added and the mixture was stirred from 0°C to room temperature for 40 h (TLC monitoring). Cooled to 0°C, diluted with methylene chloride, quenched with a saturated aqueous solution of sodium bicarbonate and worked up as usual afforded after chromatography (heptane-EtOAc 5:1 to 1:1) the required tosylate **10** (153 mg, 75%) and 18 mg (14%) of recovered starting material.



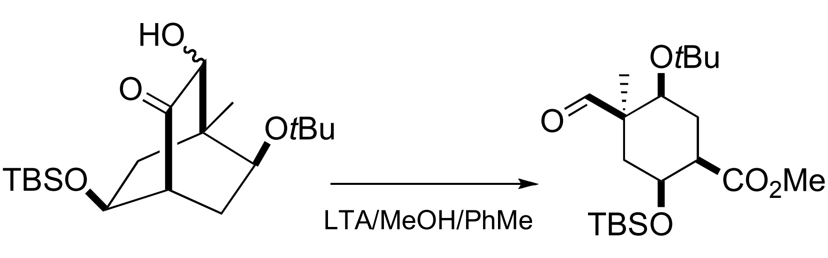
10

Toluene-4-sulfonic acid 5-*tert*-butoxy-4-methyl-7-oxo-bicyclo [2.2.2] oct-2-yl ester 10: $[\alpha]_D^{20}$ = +23 (*c* 1.9, $CHCl_3$). IR (film): ν = 2974, 2931, 2871, 1732, 1363, 1190, 1176, 1084, 910 cm^{-1}. ^1H-NMR (250 MHz): 0.88 (s, 3 H), 1.03 (s, 9 H), 1.61 (ddd, J = 2.4, 3.8, 14.9 Hz, 1 H), 1.68 (ddd, J = 1.0, 2.2, 15.6 Hz, 1 H), 1.84 (dd, J = 1.3, 18.9 Hz, 1 H), 1.86-2.00 (m, 2 H), 2.32 (bq, J = 3.8 Hz, 1 H), 2.37 (s, 3 H), 2.52 (dd, J = 3.0, 18.9 Hz, 1 H), 3.21 (dt, J = 2.0, 7.7 Hz, 1 H), 4.81 (ddd, J = 2.2, 4.1, 9.1 Hz, 1 H), 7.25 (d, J = 8.3 Hz, 2 H), 7.28 (d, J = 8.3 Hz, 2 H). ^{13}C-NMR (63 MHz): 21.6, 23.1, 28.5 (3 C), 34.4, 36.7, 39.0, 43.8, 47.9, 69.0, 73.5, 78.0, 127.6 (2 C), 129.8 (2 C), 133.7, 144.8, 210.9. ESIMS (MeOH): 403.1 ([M + Na]$^+$, 100). HRESIMS: calcd. for $C_{20}H_{28}O_5SNa$ *m/z* 403.1555, found: 403.1547. Analysis: calcd. for $C_{20}H_{28}O_5S$. 0.15 H_2O (380.17): C 62.69, H 7.44; found C 62.65, H 7.51.



11

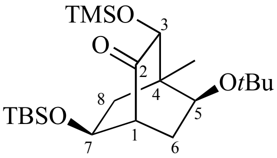
Acetic acid 5-*tert*-butoxy-4-methyl-7-oxo-bicyclo [2.2.2] oct-2-yl ester 11: Acetic anhydride (0.15 mL, 1.59 mmol) was added to a stirred mixture of alcohol **2a** (90 mg, 0.39 mmol) and DMAP (cat.) in pyridine (3 mL) at 0°C under argon. After 1 h 30 min, the mixture was diluted with EtOAc, washed with dilute hydrochloric acid, and worked up as usual. The residue was chromatographed (heptane-EtOAc 5:1) to give the corresponding acetate **11** (85 mg, 82%): $[\alpha]_D^{20}$ = +32 (c 1.6, $CHCl_3$). IR (film): ν = 2974, 2870, 1736, 1732, 1371, 1241, 1088 cm^{-1}. ^{1}H-NMR (400 MHz): δ = 0.95 (s, 3 H), 1.10 (s, 9 H), 1.44 (ddd, J = 0.9, 2.4, 15.2 Hz, 1 H), 1.71 (ddd, J = 2.5, 3.7, 14.7 Hz, 1 H), 1.87 (dd, J = 1.1, 18.9 Hz, 1 H), 1.96 (ddd, J = 3.1, 9.2, 15.2 Hz, 1 H), 1.97 (s, 3 H), 2.12 (ddd, J = 2.6, 8.6, 14.8 Hz, 1 H), 2.49 (q, J = 3.7 Hz, 1 H), 2.60 (dd, J = 3.1, 18.9 Hz, 1 H), 3.33 (ddd, J = 1.4, 2.3, 8.6 Hz 1 H), 5.03 (ddd, J = 2.4, 3.9, 9.2 Hz, 1 H). ^{13}C-NMR (75 MHz): δ = 21.1, 23.4, 28.6 (3 C), 34.5, 36.7, 39.0, 44.0, 47.5, 69.5, 70.7, 73.5, 170.3, 213.2. ESIMS (MeOH): 291.1 ([M + Na]$^+$, 100). HRESIMS: calcd. for $C_{15}H_{24}O_4Na$ *m/z* 291.1572, found: 291.1573. Analysis: calcd. for $C_{15}H_{24}O_4$ (268.17): C 67.14, H 9.01; found C 66.91, H 8.94.



$Pb(OAc)_4$ (1.58 g, 3.56 mmol) was added at 0°C to a solution of **12m** (219 mg, 0.61 mmol) in MeOH-PhMe (40 mL, 1:1). The mixture was stirred at room temperature for 1 h 30 min, filtered through a pad of Celite-$MgSO_4$-silica, the filtrate concentrated and purified by silica gel chromatography using heptane-ethyl acetate, 20:1 to 3:1 as eluent to give **8** (211 mg, 91%) as a colorless oil. This product was also obtained from ozonolysis along with the anomalous ozonolysis product in our previous work.[7]

Preparation of bis-silyl protected 13 and its fully deprotected counterpart 14

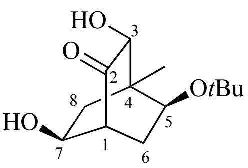
To a stirred solution of **12** (69 mg, 0.19 mmol) in dry CH_2Cl_2 (1 mL) chilled at 0°C, TMS Imidazole (63 μL, 0.43 mmol) was added under argon. The mixture was stirred (0°C to room temperature) for 1 h (TLC monitoring). Upon disappearance of the starting material, dilution with CH_2Cl_2 and usual workup afforded **13** (81 mg, 100%), which was chromatographed (heptane-AcOEt 25:1) and taken for the next step.



13

5-*tert*-butoxy-7-(*tert*-butyl-dimethyl-silanyloxy)-4-methyl-3-(trimethyl-silanyloxy)-bicyclo [2.2.2] octan-2-one 13: $[\alpha]_D^{20}$ = +104 (*c* 1.0, $CHCl_3$). IR (film): ν = 2958, 2930, 2858, 1740, 1250, 1094 cm^{-1}. ^1H-NMR (300 MHz): 0.02 (2s, 6 H), 0.14 (s, 9 H), 0.85 (s, 9 H), 0.91 (s, 3 H), 1.14 (s, 9 H), 1.55 (ddd, J = 1.7, 9.1, 14.3 Hz, 1 H), 1.64 (dt, J = 3.5, 14.6 Hz, 1 H), 1.80 (dd, J = 3.8, 14.3 Hz, 1 H), 2.06 (ddd, J = 3.1, 9.3, 14.6 Hz, 1 H), 2.27 (q, J = 3.2 Hz, 1 H), 3.44 (dd, J = 3.7, 9.3 Hz, 1 H), 3.93 (s, 1 H), 4.00 (dt, J = 3.7, 9.1 Hz, 1 H). ^{13}C-NMR (75 MHz): -4.8, -4.7, 0.35 (3 C), 17.9, 20.0, 25.7 (3 C), 28.7 (3 C), 33.3, 37.6, 41.7, 51.4, 70.1, 70.5, 73.3, 73.6, 212.7. ESIMS (MeOH): 451.2 ($[M + Na]^+$, 100). HRESIMS: calcd. for $C_{22}H_{44}O_4Si_2Na$ *m*/*z* 451.2676, found 451.2654. Analysis: calcd. for $C_{22}H_{44}O_4Si_2$ (428.28): C 61.63, H 10.34; found C 61.75, H 10.54.

TBAF 1M in THF (0.81 mL, 0.81 mmol) was added at -60°C to a solution of **12** (193 mg, 0.54 mmol) in dry THF (3 mL). The mixture was stirred for 1 h from –60°C to –40°C. Ethyl acetate was then added and the mixture was worked up as usual. The residue was purified by chromatography (SiO_2, heptane-EtOAc, 7:1 to1:1) to give 14 (123 mg, 94%) as a white solid.

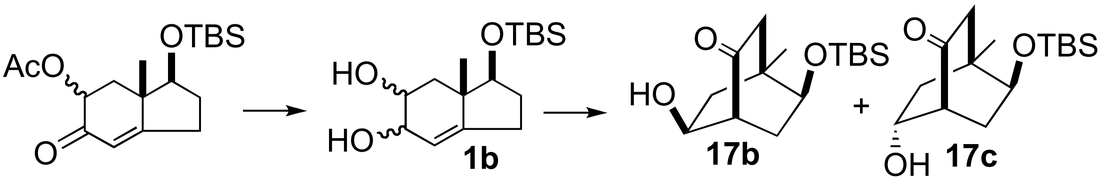


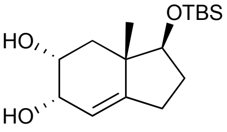
14

5-*tert*-Butoxy-3,7-dihydroxy-4-methyl-bicyclo [2.2.2] octan-2-one 14 : $[\alpha]_D^{20}$= +130 (*c* 1.1, $CHCl_3$). m. p. 129-130 °C (CH_2Cl_2). IR (film): ν = 3376, 2970, 1732, 1365, 1082 cm^{-1}. ^1H-NMR (300 MHz): 1.05 (s, 3 H), 1.15 (s, 9 H), 1.65 (dd, J = 4.4, 14.8 Hz, 1 H), 1.70-1.80 (m, 3 H), 2.13 (ddd, J = 3.0, 9.2, 14.6 Hz, 1 H), 2.49 (q, J = 3.1 Hz, 1 H), 3.03 (b, 1 H), 3.49 (dd, J = 3.7, 9.2 Hz, 1

H), 4.13 (s, 1 H), 4.16 (m, 1 H). ^{13}C-NMR (75 MHz): 19.3, 28.7 (3 C), 32.6, 36.2, 41.9, 50.6, 70.0, 70.4, 73.7, 73.9, 216.1. ESIMS (MeOH): 265.1 ([M + Na]$^+$, 100). HRESIMS: calcd. for $C_{13}H_{22}O_4Na$ *m/z* 265.1416, found 265.1461. Analysis: calcd. for $C_{13}H_{22}O_4$ (242.15): C 64.44, H 9.15; found C 64.41; H 9.21.

Preparation of 17b, 17c from 1b



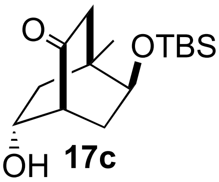


To a magnetically stirred suspension of $LiAlH_4$ (3.77 g, 99.4 mmol) in 200 mL of THF, cooled to nearly 0°C, was added dropwise a solution of acetoxyenone (16.8 g, 49.7 mmol, epimeric mixture) in THF (100 mL). After stirring at this temperature for 30-40 min (TLC monitoring) the mixture was diluted with Et_2O and treated with a small amount of 6N NaOH solution (for each 1 g of $LiAlH_4$ 1ml of water, 1 mL of 6N NaOH and 3 mL more water were added). The organic layer was worked up as usual to give after silica gel chromatography (ethyl acetate-heptane, 3 : 7) 10.5 g (72%) of the desired diols. The stereochemistry at the secondary hydroxyl groups is not important since it is destroyed in the process; we describe an isolated *cis*-diol, among the four existing diastereomers, only for product identification.

(3*S*, 3a*S*, 5*R*, 6*S*)-3-(tert-butyldimethylsilyloxy)-3a-methyl-2,3,3a,4,5,6-hexahydro-1H-indene-5,6-diol $[\alpha]_D^{20}$= -30.69 (*c* = 1.04). IR (film): 3380, 2956, 2857, 1463, 1360, 1256, 1107, 1055, 933, 861 cm^{-1}.^{1}H-NMR (300 MHz): 0.01 (s, 3H), 0.03 (s, 3H), 0.88 (s, 9H), 1.08 (s, 3H), 1.60 (dd, *J* = 2.5, 14.0 Hz, 1H), 1.63 (tdd, *J* = 6.0, 8.7, 12.7 Hz, 1H), 1.87 (dddd, *J* = 4.0, 8.4, 9.6, 12.7 Hz, 1H), 1.92 (dd, *J* = 7.0, 14.0 Hz, 1H), 2.06 (ddd, *J* = 6.0, 9.6, 16.2 Hz, 1H), 2.52 (dddt, *J* = 2.0, 4.0, 12.7, 16.2 Hz, 1H), 3.57 (t, *J* = 8.7 Hz, 1H), 3.91 (dt, *J* = 4.0, 7.0 Hz, 1H), 4.15 (td, *J* = 2.0, 4.1 Hz, 1H), 5.37 (t, *J* = 3.2 Hz, 1H). ^{13}C-NMR (75 MHz): -4.8, -4.4, 18.0, 19.6, 25.7 (3*C*), 26.3, 29.7, 37.5, 43.9, 67.9, 68.3, 79.9, 118.8, 150.2. HRESIMS (MeOH) calculated for $C_{16}H_{30}O_3Si$ Na *m/z* 321.1862, found: 321.1847

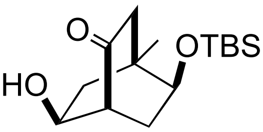
Consecutive domino reaction leading to bicyclic aldols 17

To a solution of the diol **1b** (161 mg, 0.603 mmol, diastereomeric mixture) in anhydrous toluene (5.0 mL) under inert atmosphere, $PhI(OAc)_2$ (232 mg, 0.72 mmol) was added. Stirring was maintained under argon for 24 h, at which point $Pb(OAc)_4$ (319 mg, 0.72 mmol) was added. After an additional 15 h stirring at room temperature, potassium carbonate (416 mg, 3.01 mmol, 5 equiv) in H_2O/MeOH (2/8, 10 mL) was added and after a 12 h room temperature stirring, methanol was removed under reduced pressure, the crude was diluted with EtOAc, washed with brine until pH neutral and worked up as usual. The residue was filtered on silica gel affording a diastereomeric mixture of **17b** + **17c** (121.2 mg, 71%, 4:1 ratio). Silica gel flash chromatography (eluent CH_2Cl_2/acetone, 95/5) afforded pure **17b** (97.2 mg, 57%) and **17c** (23.6 mg, 14 %).



17c

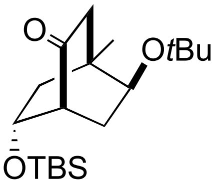
faster eluting isomer 17c: $[\alpha]_D$: +53 (*c* 1.02, $CHCl_3$). m. p. 49-50 °C. IR (film): 3429, 2957, 2857, 1707, 1462, 1360, 1249, 1089, 1050, 1034, 986, 836, 773 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 0.94 (s, 3H), 1.26 (ddd, J = 3.4, 3.4, 14.7 Hz, 1H), 1.44 (dddd, J = 1.4, 2.9, 2.9, 14.4 Hz, 1H), 1.66 (dd, J = 1.5, 18.9 Hz, 1H), 1.72 (br s, 1H), 1.96 (dd, J = 9.4, 14.7 Hz, 1H), 2.40 (dd, J = 3.0, 6.0 Hz, 1H), 2.51 (dd, J = 3.3, 18.9 Hz, 1H), 2.62 (ddd, J=2.9, 8.8, 14.4 Hz, 1H), 3.71 (ddd, J = 1.5, 2.8, 8.8 Hz, 1H), 4.12 (dddd, J = 1.3, 3.4, 3.4, 9.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.0, -4.2, 17.9, 23.1, 25.7, 30.2, 38.0, 41.8, 42.9, 52.0, 65.4, 71.2. ESIMS (MeOH): *m/z* 307.2 ([MNa]$^+$, 100), 323.2 ([MK]$^+$, 40). HRESIMS (MeOH): calcd for $C_{15}H_{28}O_3Na$ *m/z* 307.1693, found: 307.1705. Anal. calcd for $C_{15}H_{28}O_3Si$ (284.46). ½ H_2O: C, 61.39; H, 9.96. Found: C, 61.66; H, 9.83.



17b

faster eluting isomer 17c: 5-(*tert*-Butyl-dimethyl-silanyloxy)-7-β-hydroxy-4-methyl-bicyclo[.2.2.2]octan-2-one 17b: $[\alpha]_D$: +41 (*c* 1.01, $CHCl_3$). m. p. 123-124 °C. IR (film): 3411, 2927, 2857, 1699, 1462, 1446, 1400, 1368, 1250, 1094, 1006, 830 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 3H), 0.01 (s, 3H), 0.84 (s, 9H), 0.94 (s, 3H), 1.44 (ddd, J=0.8, 2.2, 14.8 Hz, 1H), 1.58 (ddd, J=2.2, 3.7, 14.7 Hz, 1H), 1.85 (ddd, J=3.0, 8.8, 14.8 Hz, 1H), 1.95 (dd, J=1.3, 18.8 Hz, 1H), 2.07 (ddd, J=2.5, 8.6, 14.7 Hz, 1H), 2.33 (d, J=1.9 Hz, 1H), 2.41 (dddd, J=0.9, 2.4, 2.4, 3.7 Hz, 1H), 2.54 (dd, J=3.0, 18.8 Hz, 1H), 3.51 (ddd, J=1.5, 2.2, 8.6 Hz, 1H), 4.13 (dddd, J=1.9, 2.2, 2.4, 8.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.0, -4.3, 17.9, 23.2, 25.7, 33.8, 37.5, 40.5, 43.5, 50.9, 68.7, 71.0. ESIMS (MeOH + CH_2Cl_2): *m/z* 307.2 ([MNa]$^+$, 100), 339.2 (([MK]$^+$, 22); HRESIMS (MeOH + CH_2Cl_2): calcd for $C_{15}H_{28}O_3NaSi$ 307.1705, found 307.1677. Anal. calcd for $C_{15}H_{28}O_3Si$ (284.46): C, 63.33; H, 9.92. Found: C, 63.31; H, 9.91.

Preparation of TBS-protected 18a

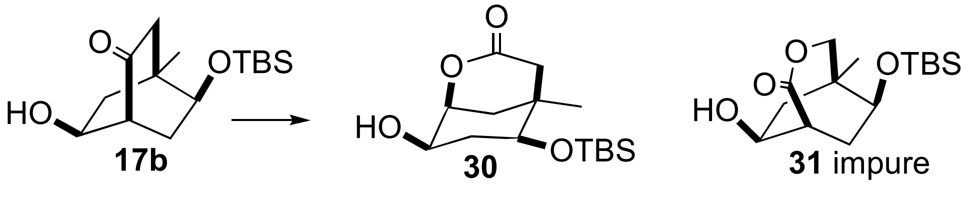


18a

tert-butyldimethylsilyl chloride (1.59 g, 10.6 mmol, 4 equiv) was added to a solution of imidazole (1.44 g, 21.2 mmol, 8 equiv) and the bicyclic aldol **17a** (600 mg, 2.65 mmol) in DMF (8 mL) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 4.5 h (TLC monitoring). After cooling at 0°C, extraction with methylene chloride, washing with 1N HCl, sat $NaHCO_3$ solution and usual workup, the residue was chromatographed (eluent heptane-EtOAc 9:1) to give **18a** (820 mg, 91%).

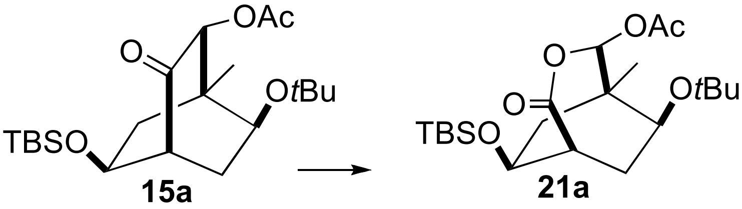
5-tert-Butoxy-7-(tert-butyl-dimethyl-silanyloxy)-4-methyl-bicyclo[2.2.2]octan-2-one 18a: $[\alpha]_D^{20}$ = +36 (c 1.0, $CHCl_3$). IR (film): ν = 2952, 2929, 2855, 1730, 1471, 1462, 1388, 1363, 1257, 1192, 1079, 1051, 1024, 998, 830, 776 cm^{-1}. ^{1}H NMR (500 MHz): δ = 0.00 (s, 3 H), 0.02 (s, 3 H), 0.87 (s, 9 H), 0.91 (s, 3 H), 1.13 (s, 9 H), 1.28 (dt, *J* = 3.3, 14.4 Hz, 1 H), 1.46 (dt, *J* = 1.4, 3.0, 14.0 Hz, 1 H), 1.60 (dd, *J* = 1.7, 18.8 Hz, 1 H), 1.86 (dd, *J* = 9.0, 14.4 Hz, 1 H), 2.30 (dd, *J* = 3.0, 6.1 Hz, 1 H), 2.50 (dd, *J* = 3.3, 18.8 Hz, 1 H), 2.56 (ddd, *J* = 2.9, 8.8, 14.0 Hz, 1 H), 3.48 (ddd, *J* = 1.3, 3.0, 8.7 Hz, 1 H), 4.00 (dtd, *J* = 1.4, 3.2, 9.2 Hz, 1 H). ^{13}C NMR (125 MHz): δ = -4.9, -4.8, 17.9, 23.4, 25.7 (3 C), 28.7 (3 C), 31.0, 37.1, 43.7, 44.4, 52.5, 65.8, 70.0, 73.0, 215.8. ESIMS (MeOH): 363.2 ([M + Na]$^+$, 100). HRESIMS: calcd. for $C_{19}H_{36}O_3SiNa$ m/z 363.2331, found: 363.2296. Analysis: calcd. for $C_{19}H_{36}O_3Si$ (340.24): C 67.01, H 10.65; found C 66.32, H 10.66.

Baeyer-Villiger oxidation of the substrates



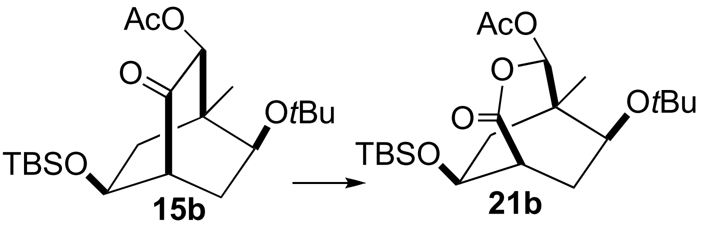
Starting from **17b** (74 mg, 0.314 mmol) and using the general procedure, **30** (46.5 mg, 49%) was obtained, after a 14 h room temperature stirring (silica gel chromatography eluent: heptane-EtOAc 1:1), along with impure **31** (5.4 mg, 4%) and recovered starting material (11 mg, 14.8%).

6-(*tert*-Butyl-dimethyl-silanyloxy)-8-hydroxy-5-methyl-2-oxa-bicyclo[3.3.1]nonan-3-one 30: $[\alpha]_D$: 65 (*c* 1.0, $CHCl_3$). m. p. 188-189 °C. IR (film): 1698, 1313, 1249, 1215, 1130, 993, 835, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 0.96 (s, 3H), 1.29 (ddd, J = 11.6, 11.6, 13.7 Hz, 1H), 1.46 (ddd, J = 1.7, 2.2, 14.6 Hz, 1H), 1.94 (dd, J = 4.6, 14.6 Hz, 1H), 2.02 (dd, J = 0.9, 19.0 Hz, 1H), 2.17 (dddd, J = 1.0, 5.1, 5.1, 13.7 Hz, 1H), 2.25 (br s, 1H), 2.94 (dd, J = 2.4, 19.0 Hz, 1H), 3.37 (ddd, J = 0.7, 5.1, 11.4 Hz, 1H), 3.65 (ddd, J = 2.4, 5.2, 11.9 Hz, 1H), 4.61 (dddd, J = 1.0, 1.7, 2.4, 4.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.8, -3.8, 18.1, 25.9, 26.6, 33.9, 34.8, 36.2, 37.2, 70.6, 73.8, 78.5, 171.6. ESIMS (MeOH): *m/z* 323.1 ($[MNa]^+$, 100). HRESIMS (MeOH): calcd for $C_{15}H_{28}O_4NaSi$ 323.1655, found 323.1644. Anal. calcd for $C_{15}H_{28}O_4Si$ (300.46): C, 59.96; H, 9.39. Found: C, 60.04; H, 9.46.



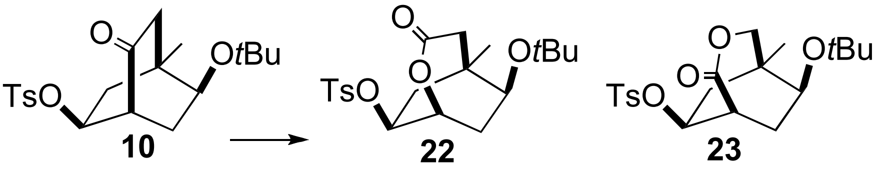
Starting from **15a** (37 mg, 0.09 mmol) and using the general procedure, **21a** (21.5 mg, 56%) was obtained, after a 25 h room temperature stirring (silica gel chromatography eluent: heptane-EtOAc 20:1 to 10:1), along with unreacted starting material **15a** (9.6 mg, 26%).

Acetic acid 8-*tert*-butoxy-6-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-4-oxo-3-oxa-bicyclo[2.2.2]non-2-yl ester 21a: $[\alpha]_D^{20}$ = +13 (*c* 0.7, $CHCl_3$). m. p. 146-147 °C (CH_2Cl_2). IR (film): ν = 2960, 2858, 1752, 1363, 1016 cm^{-1}. ^1H-NMR (300 MHz): δ = 0.00 (2s, 6 H), 0.81 (s, 9 H), 0.98 (s, 3 H), 1.09 (s, 9 H), 1.79 (m, 2 H), 2.02 (s, 3 H), 2.04-2.20 (m, 2 H), 2.97 (m, 1 H), 3.38 (t, J = 8.0 Hz, 1 H), 3.99 (m, 1 H), 6.13 (s, 1 H). ^{13}C-NMR (75 MHz): δ = -4.9, -4.8, 17.9, 20.9, 24.6, 25.6 (3 C), 28.8 (3 C), 31.3, 41.6, 43.6, 49.3, 65.6, 70.1, 73.3, 97.9, 169.1, 172.2. ESIMS (MeOH): 437.2 ($[M + Na]^+$, 100). HRESIMS: calcd. for $C_{21}H_{38}O_6SiNa$ *m/z* 437.2335, found: 437.2328. Analysis: calcd. for $C_{21}H_{38}O_6Si$ (414.24): C 60.83, H 9.24; found C 60.69, H 9.24.



Starting from **15b** (110 mg, 0.27 mmol) and using the general procedure, **21b** (106 mg, 95%) was obtained, after a 2 h room temperature stirring, as a single product (silica gel chromatography eluent: heptane-EtOAc 20:1 to 10:1).

Acetic acid 8-*tert*-butoxy-6-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-4-oxo-3-oxa-bicyclo [3.2.2] non-2-yl ester 21b: $[\alpha]_D^{20}$ = +100 (*c* 1.2, $CHCl_3$). m. p. 94-96 °C (CH_2Cl_2). IR (film): ν = 2930, 2857, 1749, 1225, 1173 cm^{-1}. ^{1}H-NMR (300 MHz): 0.07 (2s, 6 H), 0.89 (s, 9 H), 0.99 (s, 3 H), 1.17 (s, 9 H), 1.66 (dd, *J* = 8.6, 15.2 Hz, 1 H), 1.89 (dt, *J* = 3.0, 15.4 Hz, 1 H), 1.97-2.09 (m, 2 H), 2.10 (s, 3 H), 3.06 (m, 1 H), 3.51 (dd, *J* = 3.5, 8.7 Hz, 1 H), 3.97 (m, 1 H), 6.42 (s, 1 H). ^{13}C-NMR (75 MHz): -4.9 (2 C), 17.9, 21.0, 24.9, 25.6 (3 C), 28.7 (3 C), 32.2, 37.5, 42.3, 48.9, 66.0, 70.3, 74.0, 94.7, 169.1, 171.5. ESIMS (MeOH): 437.2 ($[M + Na]^+$, 100), 453.2 ($[M + K]^+$, 12). HRESIMS: calcd. for $C_{21}H_{38}O_6NaSi$ *m/z* 437.2335, found: 437.2339. Analysis. calcd. for $C_{21}H_{38}O_6Si$ (414.24): C 60.83, H 9.24; found C 60.59, H 9.17.

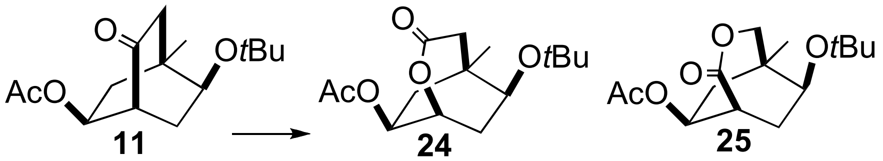


10 → 22 23

Starting from **10** (49 mg, 0.12 mmol) and using the general procedure, **22** and **23** (11.5 mg) were obtained as an unseparable mixture, after a 4 days room temperature stirring, in 24% combined yield and 1:1.5 ratio (silica gel chromatography eluent: heptane-EtOAc 10:1 to 3:1), along with unreacted starting material **10** (33.8 mg, 69%).

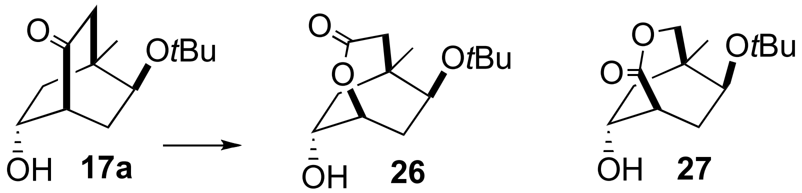
Toluene-4-sulfonic acid 9-*tert*-butoxy-5-methyl-3-oxo-2-oxa-bicyclo [3.2.2] non-7-yl ester 23, Toluene-4-sulfonic acid 8-*tert*-butoxy-1-methyl-4-oxo-3-oxa-bicyclo [3.2.2] non-6-yl ester 22: IR (film): ν = 2963, 2927, 2873, 2856, 1782, 1731, 1598, 1365, 1190, 1176, 882 cm^{-1}. ^{1}H-NMR (300 MHz): δ = 0.89 (s, 3 H, Me'), 0.90 (s, 3 H, Me), 1.10 (s, 18 H, *t*Bu), 1.68 (ddd, *J* = 1.7, 5.2, 15.3 Hz, 1 H, H_6), 1.75 (dd, *J* = 6.1, 15.4 Hz, 1 H, H_7'), 2.00-2.16 (m, 5 H, H_9', H_7', H_6, H_8), 2.30 (ddd, *J* = 5.7, 8.6, 16.2 Hz, 1 H, H_9'), 2.39 (dd, *J* = 1.5, 18.7 Hz, 1 H, H_4), 2.44 (s, 3 H, Ts'), 2.45 (s, 3 H, Ts), 2.98 (ddd, *J* = 1.7, 5.4, 6.6 Hz, 1 H, H_5'), 3.12 (dd, *J* = 2.6, 18.7 Hz, 1 H, H_4), 3.38-3.44 (m, 2 H, H_9, H_8'), 3.71 (dd, *J* = 1.2, 11.9 Hz, 1 H, H_2'), 4.35 (ddd, *J* = 1.8, 3.2, 5.6 Hz, 1 H, H_1), 4.41 (dd, *J* = 1.4, 11.9 Hz, 1 H, H_2'), 4.78-4.87 (m, 2 H, H_7, H_6'), 7.34 (d, *J* = 8.3 Hz, 4 H, Ts), 7.79 (d, *J* = 8.3 Hz, 4 H, Ts). ^{13}C-NMR (75 MHz): δ = 24.2 (Me'), 27.4 (Me), 28.7 (6 C, 2*t*Bu), 32.2 (C9'), 35.0 (C5), 37.3 (C8), 38.4 (C7'), 38.8 (C6), 39.5 (C1'), 43.3 (C4), 46.0 (C5'), 68.7 (C8'), 69.1 (C9), 73.3 (C2), 73.7 (*t*Bu'), 74.0 (*t*Bu), 74.3 (C1), 74.8 (C6'), 75.2 (C7), 127.8 (4C, Ts), 129.9 (4C, Ts), 133.6 (2 C, Ts), 145.1 (2 C, Ts), 171.5 (2 C, C3, C4'). ESIMS (MeOH): 419.1

([M + Na]$^+$, 100). HRESIMS: calcd. for $C_{20}H_{28}O_6SNa$ m/z 419.1504, found: 419.1495. Analysis: calcd. for $C_{20}H_{28}O_6S$ (396.16): C 60.58, H 7.12; S 8.09; found C 64.09, H 8.06, S 5.68.



Starting from **11** (43 mg, 0.16 mmol) and using the general procedure, **24** and **25** (16.6 mg) were obtained as an unseparable mixture, after a 4 days room temperature stirring, in 37% combined yield and 1:1 ratio (silica gel chromatography eluent:heptane-EtOAc 10:1 to 3:1), along with recovered starting material **11** (23.2 mg, 54%).

Acetic acid 9-*tert*-butoxy-5-methyl-3-oxo-2-oxa-bicyclo [3.2.2] non-7-yl ester 24 and Acetic acid 8-*tert*-butoxy-1-methyl-4-oxo-3-oxa-bicyclo [3.2.2] non-6-yl ester 25: IR (film): ν = 2975, 1738, 1731, 1366, 1242, 1049 cm^{-1}. ^{1}H-NMR (300 MHz): δ = 0.84 (s, 3 H, Me), 0.88 (s, 3 H, Me’), 1.10 (s, 18 H, *t*Bu), 1.68 (dd, J = 5.7, 14.9 Hz, 1 H, H_6), 1.75 (dd, J = 5.7, 15.0 Hz, 1 H, H_7’), 1.85 (ddd, J = 1.4, 5.6, 15.3 Hz, 1 H, H_9’), 1.92-2.12 (m, 3 H, H_8, H_7, H_7’), 1.99 (s, 3 H, Ac), 2.02 (s, 3 H, Ac), 2.17 (ddd, J = 6.9, 8.5, 15.3 Hz, 1 H, H_9’), 2.27 (ddd, J = 5.4, 8.6, 16.2 Hz, 1 H, H_8), 2.37 (dd, J = 1.4, 18.6 Hz, 1 H, H_4), 3.03 (ddd, J = 1.5, 5.1, 6.9 Hz, 1 H, H_5’), 3.10 (dd, J = 2.7, 18.6 Hz, 1 H, H_4), 3.41 (m, 2 H, H_9, H_8’), 3.64 (dd, J = 1.2, 11.9 Hz, 1 H, H_2’), 4.41 (dd, J = 1.6, 11.9 Hz, 1 H, H_2’), 4.44 (ddd, J = 1.9, 3.5, 5.4 Hz, 1 H, H_1), 4.89 (ddd, J = 3.4, 5.7, 9.6 Hz, 1 H, H_7), 4.95 (dt, J = 5.4, 9.2 Hz, 1 H, H_6’). ^{13}C-NMR (75 MHz): δ = 21.0 (Me-Ac), 21.1 (Me-Ac), 24.3 (Me'), 27.6 (Me), 28.8 (6 C, 2 *t*Bu), 32.0 (C9'), 34.8 (C5), 37.2 (C8), 37.6 (C7'), 38.2 (C6), 39.4 (C1'), 43.4 (C4), 45.3 (C5'), 67.9 (C6'), 68.9 (2 C, C9, C8'), 69.5 (C7), 73.5 (C2'), 73.7 (*t*Bu), 73.8 (*t*Bu'), 74.3 (C1), 170.5 (Ac), 170.6 (Ac), 172.3 (C3), 173.0 (C4'). ESIMS (MeOH): 307.1 ([M + Na]$^+$, 100). HRESIMS: calcd. for $C_{15}H_{24}O_5Na$ m/z 307.1521, found: 307.1505. Analysis: calcd. for $C_{15}H_{24}O_5$ (284.16): C 63.36, H 8.51; found C 63.61, H 8.45

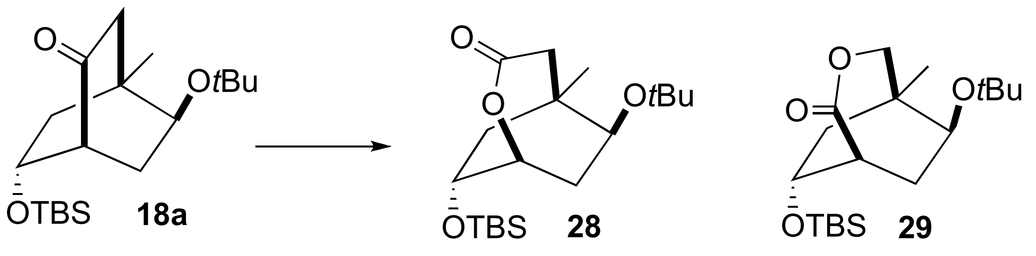


Starting from **17a** (40 mg, 0.17 mmol) and using the general procedure bridgehead migrated **26** (17.2 mg) and methylene migrated **27** (18.8 mg) were obtained in 88% combined yield and 1:1.1

ratio after 4 h room temperature stirring (silica gel chromatography eluent: heptane-EtOAc 2:1 to 1.5:1).

6-tert-Butoxy-8-hydroxy-5-methyl-2-oxa-bicyclo [3.2.2] nonan-3-one 26: $[\alpha]_D^{20}$ = +28 (*c* 0.8, $CHCl_3$). m. p. 86-88 °C (Heptane). IR (film): ν = 3394, 2975, 2929, 1708, 1390, 1067 cm^{-1}. ^1H-NMR (300 MHz): δ = 0.95 (s, 3 H), 1.18 (s, 9 H), 1.45 (ddd, *J* = 2.4, 5.0, 14.7 Hz, 1 H), 2.03 (m, 1 H), 2.18 (dd, *J* = 8.1, 14.7 Hz, 1 H), 2.31 (dd, *J* = 1.1, 18.5 Hz, 1 H), 2.48 (ddd, *J* = 4.3, 8.5, 15.8 Hz, 1 H), 3.01 (dd, *J* = 2.5, 18.5 Hz, 1 H), 3.64 (dd, *J* = 2.9, 8.5 Hz, 1 H), 4.29 (m, 3 H). ^{13}C-NMR (75 MHz): δ = 27.9, 28.8 (3 C), 34.4, 34.5, 42.0, 43.3, 67.1, 70.5, 73.7, 78.0, 173.9. ESIMS (MeOH): 243.2 ($[M+H]^+$, 100), 265.2 ($[M+Na]^+$, 14), 281.1 ($[M+K]^+$, 8). HRESIMS: calcd. for $C_{13}H_{22}O_4Na$ *m/z* 265.1416, found: 265.1407. Analysis: calcd. for $C_{13}H_{22}O_4$. 0.1 H_2O (242.15): C 63.96, H 9.17; found C 63.99, H 9.19.

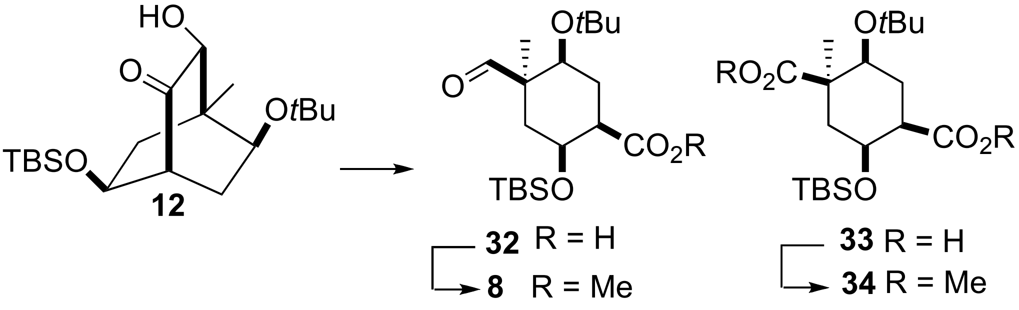
6-*tert*-Butoxy-8-hydroxy-5-methyl-3-oxa-bicyclo [3.2.2] nonan-2-one 27: $[\alpha]_D^{20}$ = +63 (*c* 1.1, $CHCl_3$). m. p. 141-142 °C (Heptane). IR (film): ν = 3383, 2970, 2930, 1719, 1195, 1075 cm^{-1}. ^1H-NMR (300 MHz): δ = 0.89 (s, 3 H), 1.18 (s, 9 H), 1.58 (ddd, *J* = 1.5, 2.8, 15.2 Hz, 1 H), 1.80 (dd, *J* = 5.3, 14.9 Hz, 1 H), 2.20 (dd, *J* = 8.0, 15.2 Hz, 1 H), 2.43 (ddd, *J* = 6.8, 8.2, 14.9 Hz, 1 H), 2.93 (d, *J* = 6.8 Hz, 1 H), 3.34 (b, 1 H), 3.61 (dd, *J* = 1.3, 11.8 Hz, 1 H), 3.72 (ddd, *J* = 1.3, 5.3, 8.2 Hz, 1 H), 4.29 (dt, *J* = 2.8, 8.0 Hz, 1 H), 4.51 (dd, *J* = 1.5, 11.8 Hz, 1 H). ^{13}C-NMR (75 MHz): δ = 24.3, 28.8 (3 C), 29.8, 37.7, 41.1, 48.6, 64.8, 69.1, 73.4, 74.1, 174.5. ESIMS (MeOH): 243.1 ($[M+H]^+$, 4), 265.2 ($[M+Na]^+$, 100), 281.1 ($[M+K]^+$, 8). HRESIMS: calcd. for $C_{13}H_{22}O_4Na$ *m/z* 265.1416, found: 265.1411. Analysis: calcd. for $C_{13}H_{22}O_4$. 0.15 H_2O (242.15): C 63.73, H 9.17; found C 63.99, H 8.99.



Starting from TBS-protected bicyclic aldol **18a** (50 mg, 0.14 mmol) and using the general procedure, **28** (15.6 mg, 30%) and **29** (25 mg, 48%) were obtained, after a 15 h room temperature stirring (silica gel chromatography eluent: heptane-EtOAc 5:1 to EtOAc).

9-*tert*-butoxy-7-(*tert*-butyldimethylsilyloxy)-5-methyl-2-oxabicyclo[3.2.2]nonan-3-one 28: Yellow oil, IR (film): ν = 2953, 2928, 2855, 1730, 1471, 1462, 1388, 1377, 1363, 1252, 1190, 1106, 1083, 1039, 835 cm^{-1}. ^{1}H NMR (300 MHz): δ = 0.05 (s, 3 H), 0.07 (s, 3 H), 0.88 (s, 9 H), 0.91 (s, 3 H), 1.16 (s, 9 H), 146 (dd, *J* = 2.1, 14.8 Hz, 1 H), 1.94 (dd, *J* = 3.3, 14.3 Hz, 1 H), 2.12 (dd, *J* = 7.5, 14.7 Hz, 1 H), 2.26 (d, *J* = 18.5 Hz, 1 H), 2.48 (ddd, *J* = 5.3, 8.5, 15.7 Hz, 1 H), 3.07 (dd, *J* = 2.7, 18.5 Hz, 1 H), 3.67 (ddd, *J* = 1.7, 5.0, 8.5 Hz, 1 H), 4.17 (m, 2 H). ^{13}C NMR (125 MHz): δ = -4.9, -4.8, 17.8, 25.6 (3 C), 28.0 (3 C), 28.8, 34.3, 35.2, 43.4, 43.5, 67.3, 70.0, 73.4, 77.5, 172.4. ESIMS (MeOH): 379.2 ([M + Na]$^+$, 100). HRESIMS: calcd. for $C_{19}H_{36}O_4NaSi$ m/z 379.2281, found: 379.2310. Analysis: calcd. for $C_{19}H_{36}O_4Si$ (356.23): C 64.00, H 10.18; found C 63.87, H 10.13.

9-*tert*-butoxy-7-(*tert*-butyldimethylsilyloxy)-5-methyl-3-oxabicyclo[3.2.2]nonan-2-one 29: Yellow oil. $[\alpha]_D^{20}$ = 65 (c 1.0, $CHCl_3$). IR (film): ν = 2953, 2929, 2856, 1730, 1471, 1369, 1250, 1190, 1053, 998, 836 cm^{-1}. ^{1}H NMR (500 MHz): δ = 0.05 (s, 3 H), 0.06 (s, 3 H), 0.88 (s, 3 H), 0.89 (s, 9 H), 1.16 (s, 9 H), 1.52 (dd, *J* = 1.3, 14.9 Hz, 1 H), 1.74 (dd, *J* = 5.9, 14.6 Hz, 1 H), 2.16 (dd, *J* = 7.2, 14.9 Hz, 1 H), 2.35 (m, 1 H), 2.87 (ddd, *J* = 1.7, 3.5, 7.1 Hz, 1 H), 3.53 (dd, *J* = 1.5, 11.8 Hz, 1 H), 3.78 (ddd, *J* = 1.5, 6.2, 8.0 Hz, 1 H), 4.18 (m, 1 H), 4.53 (dd, *J* = 1.5, 11.8 Hz, 1 H). ^{13}C NMR (125 MHz): δ = -4.9 (2 C), 17.7, 24.5, 25.6 (3 C), 28.8 (3 C), 30.0, 37.8, 42.5, 48.7, 65.8, 68.9, 73.1, 73.7, 173.9. ESIMS (MeOH): 379.2 ([M + Na]$^+$, 100). HRESIMS: calcd. for $C_{19}H_{36}O_4NaSi$ m/z 379.2281, found: 379.2270. Analysis: calcd. for $C_{19}H_{36}O_4Si$. 0.5 H_2O (356.23): C 62.42, H 10.20; found C 62.28, H 9.78.

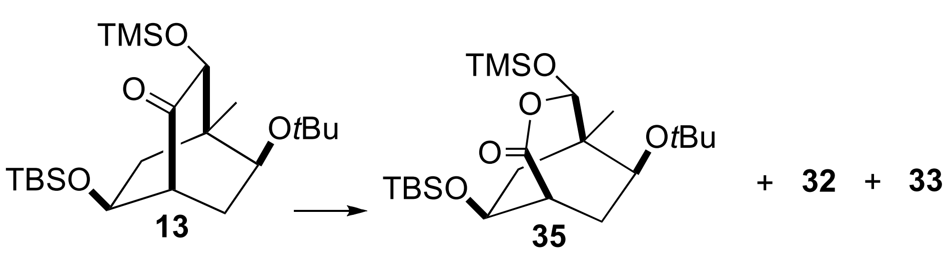


Starting from the acyloin **12** (200 mg, 0.56 mmol) and using the general procedure, acid-aldehyde **32** (29%, 60.5 mg) and diacid **33** (50%, 108 mg) were obtained, after a 1h 30 min room temperature stirring (silica gel chromatography eluent: heptane-EtOAc 3:1). Both structures were methylated with diazomethane for confirmation.

2-*tert*-Butoxy-5-(*tert*-butyl-dimethyl-silanoxy)-1-methyl-cyclohexane-1,4-dicarboxylic acid 33: $[\alpha]_D^{20}$ = +32 (*c* 1.3, $CHCl_3$). m. p. 144-145 °C (CH_2Cl_2). IR (film): ν = 3100, 2975, 2931, 2858, 1750, 1711, 1413, 1062, 1001 cm^{-1}. ^1H-NMR (300 MHz): δ = 0.00 (s, 3 H), 0.14 (s, 3 H), 0.84 (s, 9 H), 1.24 (s, 3 H), 1.30 (s, 9 H), 1.37 (m, 1 H), 1.96 (dt, *J* = 3.3, 13.4 Hz, 1 H), 2.34 (q, *J* = 12.0 Hz, 1 H), 2.49 (dt, *J* = 2.7, 12.0 Hz, 1 H), 2.71 (dd, *J* = 3.8, 14.4 Hz, 1 H), 3.50 (dd, *J* = 3.7, 10.9 Hz, 1 H), 4.32 (bs, 1 H), 10.5 (b, 1 H). ^{13}C-NMR (75 MHz): δ = -5.6, -4.3, 17.8, 25.9 (3 C), 27.0, 27.8, 28.6 (3 C), 41.8, 45.5, 47.5, 66.6, 75.1, 76.9, 176.0, 177.6. ESIMS (MeOH): 411.2 ($[M + Na]^+$, 100). HRESIMS: calcd. for $C_{19}H_{36}O_6SiNa$ *m/z* 411.2179, found: 411.2193. Analysis: calcd. for $C_{19}H_{36}O_6Si$ (388.23): C 58.73, H 9.34; found C 58.79, H 9.36.

Esterification of the free carboxyl functionalities with diazomethane

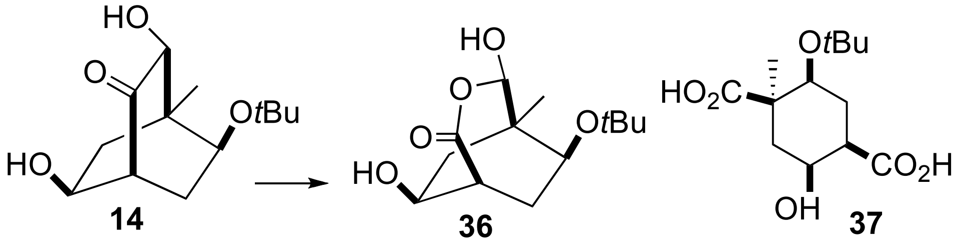
2-*tert*-Butoxy-5-(*tert*-butyl-dimethyl-silanoxy)-1-methyl-cyclohexene-1,4-dicarboxylic acid dimethyl ester 34: $TMSCHN_2$ (0.3 mL, 2M in ether, excess) is added at 0°C to a solution of diacid **33** (29.7 mg, 0.08 mmol) in a mixture of ether (3 mL) and methanol (0.3 mL). After 15 min, the reaction mixture was evaporated and chromatographed (eluent: heptane-EtOAc 20:1 to 10:1) to afford bis-dimethylester **34** (28.2 mg, 88%): $[\alpha]_D^{20}$ = +36 (*c* 1.4, $CHCl_3$). IR (film): ν = 2953, 2930, 2857, 1747, 1464, 836 cm^{-1}. ^1H-NMR (400 MHz): δ = 0.00 (2s, 6 H), 0.82 (s, 9 H), 1.17 (s, 9 H), 1.22 (s, 3 H), 1.44 (dd, *J* = 3.1, 14.3 Hz, 1 H), 1.87 (dt, *J* = 3.6, 13.7 Hz, 1 H), 2.47 (dt, *J* = 3.6, 11.0 Hz, 1 H), 2.51 (dd, *J* = 5.0, 14.3 Hz, 1 H), 2.71 (dt, *J* = 10.1, 10.9, 13.7 Hz, 1 H), 3.23 (dd, *J* = 3.3, 10.0 Hz, 1 H), 3.65 (s, 3 H), 3.66 (s, 3 H), 4.22 (dt, *J* = 3.1, 5.0 Hz, 1 H). ^{13}C-NMR (100 MHz): δ = -5.7, -4.1, 18.0, 25.8 (3 C), 26.0, 28.1, 28.8 (3 C), 42.3, 45.8, 47.7, 51.2, 51.3, 67.4, 73.6, 74.9, 172.8, 174.8. ESIMS (MeOH): 439.2 ($[M + Na]^+$, 100). HRESIMS: calcd. for $C_{21}H_{40}O_6SiNa$ *m/z* 439.2492, found: 439.2513. Analysis: calcd. for $C_{21}H_{40}O_6Si$. 0.25 C_7H_{16} (416.26): C 61.87, H 10.04; found C 61.91, H 10.16.



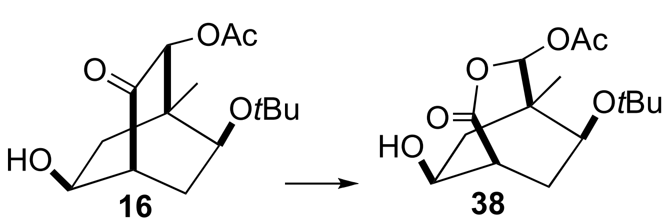
Starting from the bis-silyl protected ketone **13** (22 mg, 0.05 mmol) and using the general procedure, lactone **35** (10 mg, 45%) and a mixture of acid-aldehyde **32** and diacid **33** (7.2 mg, 38%, 1:2) were obtained, after a 22 h room temperature stirring (silica gel chromatography eluent: heptane-EtOAc 3:1).

6-*tert*-butoxy-8-(*tert*-butyl-dimethyl-silanyloxy)-5-methyl-4-(trimethyl-silanyloxy)-3-oxa-bicyclo [2.2.2] nonan-2-one 35: $[\alpha]_D^{20}$= +90 (*c* 0.5, $CHCl_3$). m. p. 81 °C (Ether). IR (film): ν = 2958, 2930, 2858, 1734, 1252, 1136, 842 cm^{-1}. ^{1}H-NMR (300 MHz): δ = 0.06 (s, 6 H), 0.19 (s, 9 H), 0.89 (s, 9 H), 0.96 (s, 3 H), 1.15 (s, 9 H), 1.52 (dd, *J* = 9.0, 15.0 Hz, 1 H), 1.85 (dt, *J* = 2.9, 15.3 Hz, 1 H), 2.00 (ddd, *J* = 5.2, 9.0, 15.3 Hz, 1 H), 2.18 (dd, *J* = 3.5, 15.0 Hz, 1 H), 2.98 (td, *J* = 2.3, 5.5 Hz, 1 H), 3.48 (dd, *J* = 3.9, 9.0 Hz, 1 H), 3.90 (ddd, *J* = 3.5, 5.9, 9.0 Hz, 1 H), 5.48 (s, 1 H). ^{13}C-NMR (75 MHz): δ = -4.9 (2 C), 0.02 (3 C), 18.0, 25.7 (3 C), 28.7 (3 C), 32.8, 36.5, 43.8, 49.2, 66.5, 70.2, 73.6, 99.1, 172.7. ESIMS (MeOH): 467.2 ([M + Na]$^+$, 100). HRESIMS: calcd. for $C_{22}H_{44}O_5Si_2Na$ *m/z* 467.2625, found 467.2619. Analysis: calcd. for $C_{22}H_{44}O_5Si_2$ (444.27): C 59.41, H 9.97; found C 59.52; H 9.95.

Starting from **14** (21 mg, 0.09 mmol) and using the general procedure, **36** and **37** were obtained (and characterized as a mixture), after a 3 h 30 min room temperature stirring, in 78% (12.4 mg) combined yield and 4:1 ratio (silica gel chromatography eluent: heptane/EtOAc 5:1 to EtOAc).



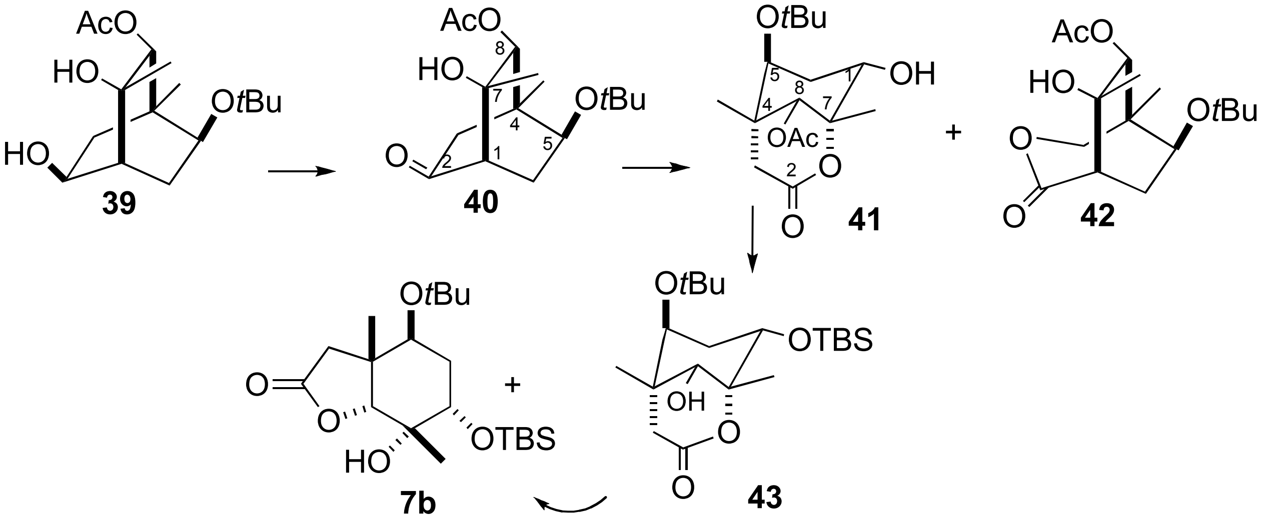
6-*tert*-Butoxy-4,8-dihydroxy-5-methyl-3-oxa-bicyclo [3.2.2] nonan-2-one 36 and 5-*tert*-Butoxy-4-formyl-2-hydroxy-4-methyl-cyclohexane carboxylic acid 37: IR (film): ν = 3442, 2975, 1714, 1192, 1069 cm^{-1}. ^{1}H-NMR (300 MHz): δ= 1.10 (s, 3 H), 1.19 (s, 9 H), 1.74 (m, 1 H), 2.08-2.26 (m, 2 H), 2.35-2.41 (m, 2 H), 3.38 (dd, *J* = 6.3, 10.2 Hz, 1 H), 4.72 (d, *J* = 6.3 Hz, 1 H), 5.32 (s, 1 H). ^{13}C-NMR (63 MHz): 17.8, 29.0 (3 C), 31.3, 39.4, 46.3, 48.0, 72.4, 73.5, 75.9, 99.2, 177.4. ESIMS (MeOH): 281.1 ([**36** + Na]$^+$, 100), 297.1 ([**37** + Na]$^+$, 32).



Baeyer-Villiger oxidation was carried out on bicyclic aldol **16** (30 mg, 0.10 mmol) in methylene chloride (1 mL) for 15 h using the general procedure to give after chromatography (SiO_2, heptane-EtOAc, 1:1) the corresponding lactone **38** (26 mg, 87%). No bridgehead migration was detected.

Acetic acid 8-tert-butoxy-6-hydroxy-1-methyl-4-oxo-3-oxa-bicyclo[3.2.2]non-2-yl ester 38: $[\alpha]_D^{20}$= +13 (c 1.0, $CHCl_3$). m. p. 131°C (heptane). IR (film): ν = 3432, 2972, 1751, 1449, 1364, 1227, 1174, 1100, 1012, 995 cm^{-1}. ^1H NMR (500 MHz): δ = 1.06 (s, 3 H), 1.14 (s, 9 H), 1.80 (dd, *J* = 6.7, 14.6 Hz, 1 H), 2.01 (dd, *J* = 9.1, 14.6 Hz, 1 H), 2.07 (s, 3 H), 2.12 (dd, *J* = 8.4, 14.8 Hz, 1 H), 2.25 (dt, *J* = 8.3, 14.8 Hz, 1 H), 2.39 (b, 1 H), 3.13 (dd, *J* = 4.4, 8.4 Hz, 1 H), 3.45 (t, *J* = 8.4 Hz, 1 H), 4.18 (m, 1 H), 6.17 (s, 1 H). ^{13}C NMR (125 MHz): δ = 20.8, 24.5, 28.7 (3 C), 31.0, 39.9, 43.6, 49.2, 64.9, 69.8, 73.3, 98.0, 168.9, 172.9. ESIMS (MeOH): 323.1 ($[M + Na]^+$, 100). HRESIMS: calcd. for $C_{15}H_{24}O_6Na$ m/z 323.1471, found: 323.1448. Analysis: calcd. for $C_{15}H_{24}O_6$ (300.15): C 59.98, H 8.05; found C 59.31, H 8.24.

Preparation and Baeyer-Villiger oxidation of 40



To a solution of bicyclic aldol **39** (500 mg, 1.66 mmol) in CH_2Cl_2 (20 mL) and pyridine (1.45 mL, 10 equiv) at 0°C is added 2.12 g (5 mmol, 3 equiv) of Dess-Martin periodinane. The reaction is then left at room temperature for 4 hours and followed by TLC monitoring. After completion, the medium is first diluted with ethylacetate and stopped by adding a saturated solution of thiosulfite, the aqueous phase is then extracted three times with ethyl acetate. The combined organic layers are then washed with a saturated solution of $NaHCO_3$, and worked up as usual. The crude residue is then purified by chromatography over silica gel using heptane-Ether 1:1 as eluent, providing ketone **40** (450 mg, 91%) as a white solid.

Acetic acid 7-*tert*-butoxy-3-hydroxy-1,3-dimethyl-5-oxo-bicyclo[2.2.2]oct-2-yl ester 40: $[\alpha]_D^{20}$= +90 (*c* 2.0 $CHCl_3$). m. p. 98-99 °C. IR (film): ν = 3468, 2974, 2970, 1730, 1726, 1371, 1235, 1191, 1069, 1048, 994, 935, 892 cm^{-1}. ^1H-NMR (300 MHz): 0.93 (s, 3 H), 1.15 (s, 9 H), 1.48 (s, 3 H), 1.76 (dt, *J* = 3.3, 15.0 Hz, 1 H), 1.8 (dd, *J* = 1.7, 19.0 Hz, 1 H), 2.07 (ddd, *J* = 3.6, 9.0, 15.0 Hz, 1 H), 2.10 (s, 3 H), 2.30 (t, *J* = 3.2 Hz, 1 H), 2.5 (d, *J* = 19.0 Hz, 1 H), 3.44 (dd, *J* =

3.4, 9.2 Hz, 1 H), 5.05, (d, J = 1.7 Hz, 1 H). ^{13}C-NMR (75 MHz): 19.8, 20.8, 26.7, 28.6 (3 C), 32.1, 41.5, 42.2, 56.0, 70.8, 72.4, 73.9, 75.1, 171.0, 212.1. ESIMS (MeOH): 323.1 ([M + Na]$^+$, 100). HRESIMS calcd. for $C_{16}H_{26}O_5Na$ *m*/*z* 323.1678, found 323.1675. Analysis: calcd. for $C_{16}H_{26}O_5$ (298.18): C 64.41, H 8.78; found C 64.16, H 8.56.

Baeyer-Villiger oxidation was carried out on bicyclic aldol **40** (1.0 g, 3.35 mmol) in $CHCl_2$ (1 mL) for 20 h, using the general procedure to give after chromatography (SiO_2, CH_2Cl_2-Acetone 4:1) two isomeric lactones **41** **(**572 mg) **42** (130 mg) in 67% combined yield and 4.4:1 ratio, along with recovered **40** (300 mg).

Acetic acid 6-tert-butoxy-8-hydroxy-1,5-dimethyl-3-oxo-2-oxa-bicyclo[3.3.1]non-9-yl ester. $[\alpha]_D^{20}$= +75 (c 0.84, $CHCl_3$). m. p. 196-197 °C (heptane). IR (film): ν = 3462, 3019, 2972, 2941, 2874, 1723, 1461, 1372, 1270, 1238, 1215, 1064, 1027, 986 cm^{-1}. ^{1}H NMR (300 MHz): δ = 0.90 (s, 3 H), 1.15 (s, 9 H), 1.34 (s, 3 H), 2.10 (s, 3 H), 2.06-2.18 (m, 3 H), 2.20 and 2.48 (ABquartet, J = 18.9 Hz, 2 H), 3.40 (t, J = 3.0 Hz, 1 H), 3.81 (dd, J = 4.8, 11.6 Hz, 1 H), 5.14 (s, 1 H). ^{13}C NMR (75 MHz): δ = 19.0, 20.6, 22.3, 28.6 (3 C), 34.7, 37.6, 39.3, 70.5 (2 C), 72.8, 74.7, 85.6, 169.9, 170.5. ESIMS (MeOH): 337.2 ([M + Na]$^+$, 100). HRESIMS: calcd. for $C_{16}H_{26}O_6Na$ m/z 337.1627, found: 337.1616. Analysis: calcd. for $C_{16}H_{26}O_6$ (314.17): C 61.13, H 8.34; found C 60.56, H 8.23.

Acetic acid 9-*tert*-butoxy-7-hydroxy-5,7-dimethyl-2-oxo-3-oxa-bicyclo[3.2.2]non-6-yl ester 42: $[\alpha]_D^{20}$= +115 (c = 1.1 $CHCl_3$). m. p. 166-167 °C (CH_2Cl_2). IR (film): ν = 3469, 2970, 2939, 2878, 1747, 1715, 1469, 1374, 1364, 1270, 1229, 1178, 1158, 1095, 1058, 998, 913, 752 cm^{-1}. ^{1}H-NMR (300 MHz): 0.75 (s, 3 H), 1.15 (s, 9 H), 1.33 (s, 3 H), 1.67 (ddd, J = 4.0, 6.5, 15.1 Hz, 1 H), 2.37 (s, 3 H), 2.41 (ddd, J = 3.5, 8.8, 15.1 Hz, 1 H), 3.99 (t, J = 3.5 Hz, 1 H), 3.68 (dd, J = 1.5, 12.2 Hz, 1 H), 3.81 (dd, J = 6.5, 8.8 Hz, 1 H), 4.52 (d, J = 12.2 Hz, 1 H), 5.03 (d, J = 1.5 Hz, 1 H). ^{13}C-NMR (75 MHz): 17.7, 19.9, 27.05, 27.8 (3 C), 31.4, 41.3, 52.4, 67.6, 70.5, 70.8, 73.3, 73.4, 169.2, 172.3. ESIMS (MeOH): 337.1 ([M + Na]$^+$, 100). HRESIMS calcd. for $C_{16}H_{26}O_6Na$ *m*/*z* 337.1627; found 337.1604. Analysis: calcd. for $C_{16}H_{26}O_6$ (314.17): C 61.13, H 8.34; found: C 60.62, H 8.06.

Preparation of the X-ray sample 43 and its translactonization

To a solution of **41** (400 mg, 1.27 mmol) and imidazole (519 mg, 7.62 mmol, 6 equiv) in DMF (2 mL) at 0°C, *tert*-butyldimethylsilyl chloride (572 mg, 3.81 mmol, 3 equiv) was added. The reaction mixture was allowed to warm to room temperature and stirred for 4.5 h (TLC monitoring). After cooling again at 0°C, extraction with CH_2Cl_2, washings with 1N HCl, sat $NaHCO_3$ solution and usual workup the residue was chromatographed (eluent heptane-EtOAc 4:1) to give 498 mg (92%) of the TBS protected lactone.

Acetic acid 6-*tert*-butoxy-8-(*tert*-butyl-dimethyl-silanyloxy)-1,5-dimethyl-3-oxo-2-oxa-bicyclo[3.3.1]non-9-yl ester 41-(C1-OTBS). $[\alpha]_D^{20}$= +41 (c 2.0, $CHCl_3$). m. p. 132-133 °C (heptane). IR (film): ν = 3444, 2973, 2900, 2856, 1751, 1727, 1461, 1367, 1276, 1207, 1107, 1067, 958, 836, 808, 774 cm^{-1}. ^{1}H NMR (300 MHz): δ = 0.04 (s, 3 H), 0.06 (s, 3 H), 0.88 (s, 9 H), 0.92 (s, 3 H), 1.18 (s, 9 H), 1.28 (s, 3 H), 1.52 (ddd, *J* = 2.6, 11.5, 14.6 Hz, 1 H), 1.89 (ddd, *J* = 3.0, 4.8, 14.6 Hz, 1 H), 2.12 (s, 3 H), 2.20 and 2.48 (ABquartet, *J* = 18.9 Hz, 2 H), 3.39 (t, *J* = 2.8 Hz, 1 H), 3.92 (dd, *J* = 4.8, 11.5 Hz, 1 H), 5.12 (s, 1 H). ^{13}C NMR (75 MHz): δ = -4.7, -4.2, 18.0, 19.6, 20.6, 22.3, 25.7 (3 C), 28.7 (3 C), 34.8, 37.7, 39.3, 69.3, 70.8, 73.1, 74.4, 85.3, 170.1, 170.4. ESIMS (MeOH): 451.2 ($[M + Na]^+$, 100). HRESIMS: calcd. for $C_{22}H_{40}O_6SiNa$ m/z 451.2492, found: 451.2465.

To a solution of 150 mg (0.35 mmol) of the TBS-protected lactone thus obtained in 2 mL of methanol, was added 966 mg (7 mmol) of K_2CO_3 and 840 mg (7 mmol) of $MgSO_4$. The mixture was then left under stirring at room temperature (followed by TLC monitoring) and stopped upon appearance of two new spots corresponding to **43** (lower R_f spot) and **7b** (higher R_f spot). MeOH was removed under reduced pressure, the organic residue was highly diluted and extracted with ethylacetate, washed successively with a solution of HCl 1N, $NaHCO_3$ and worked up as usual. The crude organic residue was then purified over silica gel using heptane-Ethylacetate (3:1) as eluent, affording two lactones **7b** (83 mg, 61%) and **43** (42 mg, 31%) in a 2:1 ratio. Recrystallized from ether-heptane, **43** afforded a crystalline material of mp 148-149 °C, suitable for an X-ray diffraction analysis.

6-*tert*-Butoxy-8-(*tert*-butyl-dimethyl-silanyloxy)-9-hydroxy-1,5-dimethyl-2-oxa-bicyclo[3.3.1]nonan-3-one 43: $[\alpha]_D^{20}$= +17 (c 1.0, $CHCl_3$). m. p. 148-149 °C (heptane). IR (film): ν = 3431, 2982, 2853, 1698, 1460, 1291, 1247, 1114, 1060, 1041, 991, 855, 834 cm^{-1}. ^{1}H NMR (300 MHz): δ = 0.04 (s, 3 H), 0.06 (s, 3 H), 0.88 (s, 9 H), 1.06 (s, 3 H), 1.17 (s, 9 H), 1.44 (s, 3 H), 1.51 (ddd, *J* = 2.8, 11.5, 14.5 Hz, 1 H), 1.86 (ddd, *J* = 3.0, 4.8, 14.5 Hz, 1 H), 2.10 and 2.53 (ABquartet, *J* = 18.9 Hz, 2 H), 2.30 (bs, 1 H), 3.37 (t, *J* = 2.8 Hz, 1 H), 3.60 (s, 1 H), 3.84 (dd, *J* =

4.8, 11.5 Hz, 1 H). ^{13}C NMR (75 MHz): δ = -4.7, -4.2, 18.3, 19.4, 22.3, 25.8 (3 C), 28.7 (3 C), 34.8, 37.2, 39.9, 69.4, 70.9, 73.3, 74.1, 86.1, 171.3. ESIMS (MeOH): 409.2 ([M + Na]$^+$, 100). HRESIMS: calcd. for $C_{20}H_{38}O_5SiNa$ m/z 409.2386, found: 409.2354. Analysis: calcd. for $C_{20}H_{38}O_5Si$ (386.25): C 62.14, H 9.91; found C 62.08, H 10.11.

X-Ray data for compound **43**: A mica little plate of 0.45 x 0.45 x 0.10 mm was used for data collection. Empirical formula $C_{20}H_{38}O_5Si$, M = 386, T = 293 K. Monoclinic system, space group $P\ 2_1$, Z = 2, a = 6.728(4), b = 15.470(9), c = 11.216(7) Å, β = 91.87(3)° , V = 1166.8 Å^3, d_{calc} = 1.100 g cm^{-3}, F(000) = 424, μ = 0.124 mm^{-1}, λ(MoKα) = 0.71073 Å. A total of 11902 intensity data was measured with a Nonius Kappa-CCD diffractometer up to θ = 27.51°, reduced to 4159 unique monoclinic reflections. The structure was solved with program *SHELXS86*. Refinement of 246 parameters on F^2, using program *SHELXL97*, leaded to $R_1(F)$ = 0.0744 calculated with the 3087 observed reflections having $I \geq 2$ sigma (I) and $wR_2(F^2)$ = 0.2016 considering all the 4159 data. Goodness of fit = 1.027. Residual electronic density between –0.52 and 0.88 e Å^3 at 0.99 Å near the Si atom. CCDC deposited number : 620081.

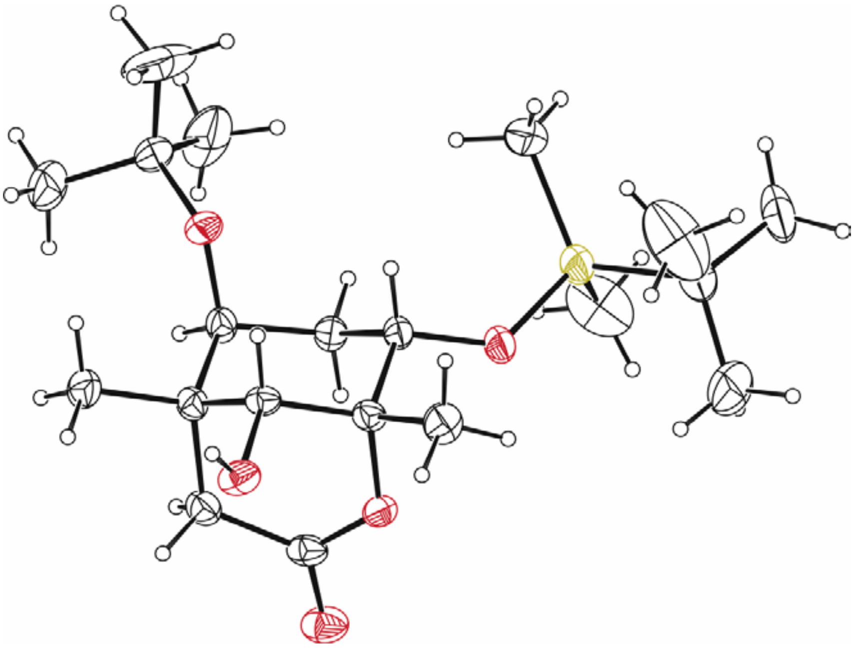
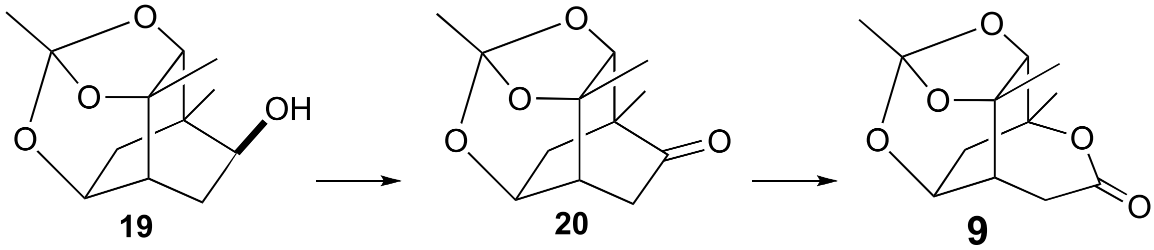


Figure S1: X-ray structure of **43** (ORTEP drawing)

3aR,4S,7R)-4-tert-butoxy-6-(tert-butyldimethylsilyloxy)-7-hydroxy-3a,7-dimethylhexahydrobenzofuran-2(3H)-one 7b: $[\alpha]_D^{20}$= +34 (c 1.0, CHCl$_3$). IR (film): ν = 3521, 2956, 2858, 1789, 1731, 1471, 1390, 1362, 1285, 1253, 1146, 1026, 1005, 836 cm^{-1}. ^{1}H NMR (300 MHz): δ = 0.09 (s, 6 H), 0.90 (s, 9 H), 1.13 (s, 3 H), 1.18 (s, 9 H), 1.27 (s, 3 H), 1.71 (ddd, J = 4.1, 6.7, 13.9 Hz, 1 H), 2.03 (ddd, J = 2.8, 8.1, 13.9 Hz, 1 H), 2.03 (d, J = 16.5 Hz, 1 H), 2.46 (bs, 1 H), 2.77 (d, J = 16.5 Hz, 1 H), 3.80 (dd, J = 2.8, 6.7 Hz, 1 H), 3.84 (dd, J = 4.1, 8.1 Hz, 1 H), 3.90 (s, 1 H). ^{13}C NMR (75 MHz): δ = -4.8, -4.3, 18.0, 23.0, 24.8, 25.8 (3 C), 28.8 (3 C), 34.1, 41.3, 43.7, 68.4, 71.3, 72.2, 74.0, 88.6, 176.6. ESIMS (MeOH): 409.2 ([M + Na]$^+$, 100). HRESIMS: calcd. for $C_{20}H_{38}O_5SiNa$ m/z 409.2386, found: 409.2372.

Lactone **43** (6.0 mg, 0.015 mmol) and K_2CO_3 (20 mg, 0.15 mmol) in CH_3OH (0.5 mL) were stirred at room temperature for 48 h. After evaporation of the solvent in vacuo, **43** was left in the NMR tube ($CDCl_3$) overnight, translactonization was complete, only **7b** being present in the NMR spectra (^{1}H and ^{13}C).

Preparation and Baeyer-Villiger oxidation of 20



19 **20** **9**

Over a solution of the orthoester **19** (108.7 mg, 0.48 mmol) in dry CH_2Cl_2 (5 mL) was added, at 0°C, pyridine (0.40 mL, 10 equiv) and Dess-Martin periodinane (611 mg, 3 equiv). The reaction mixture was stirred at room temperature for 30 minutes, diluted with CH_2Cl_2, washed with $Na_2S_2O_3$, $NaHCO_3$, and worked up as usual. SiO_2 flash chromatography (heptane-AcOEt 7:3) afforded ketone **20** (91 mg, 85%)

$[\alpha]_D^{20}$= -172 (c 1.09, $CHCl_3$). m. p. 148-149 °C. IR (film): ν = 2983, 2968, 2950, 2923, 1727, 1418, 1386, 1274, 1196, 1173, 1118, 988, 935, 895, 849, 736 cm^{-1}. ^{1}H NMR (300 MHz): δ = 1.15 (s, 3 H), 1.29 (s, 3H), 1.63 (s, 3 H), 1.75 (ddd, J = 1.8, 7.2, 14.7 Hz, 1 H), 2.17 (dd, J = 2.2, 18.6 Hz, 1 H), 2.28 (d, J = 14.7 Hz, 1 H), 2.31 (dd, J = 4.0, 18.6 Hz, 1 H), 2.44-2.50 (m, 1 H), 3.58 (dd, J=1.5,1.5 Hz, 1H), 4.39 (dd, J= 5.2, 7.2 Hz, 1H). ^{13}C NMR (75 MHz): δ = 17.3, 20.1, 21.2, 35.7, 36.4, 37.1, 49.0, 70.5, 79.9, 84.9, 119.6, 213.0. MALDI-TOF-MS: m/z 225.1 ([M + H]$^+$, 100). HRMALDI-TOF-MS: calcd. for $C_{12}H_{17}O_4$ 225.1137, found 225.1126. Analysis: calcd. for $C_{12}H_{16}O_4 \cdot 0.3\ H_2O$ (224.10): C 62.76, H 7.29; found C 62.68, H 7.06.

Baeyer-Villiger oxidation was carried out on **20** (70 mg, 0.31 mmol) in $CHCl_2$ (1 mL) for 3 days, using the general procedure to give after chromatography **9** in 88% (65 mg) yield after silica gel chromatography (eluent: heptane-EtOAc 5:1 to EtOAc), along with recovered starting material **20** (5.8 mg, 8%).

$[\alpha]_D^{20}$= -70 (c 1.1 $CHCl_3$). m. p. 185-186 °C. IR (film): ν = 3423, 1712, 1409, 1300, 1264, 1197, 1176, 1111, 1037, 858 cm^{-1}. ^1H NMR (500 MHz): δ = 1.49 (s, 3 H), 1.53 (s, 3 H), 1.57 (s, 3 H), 2.27 (ddd, J = 1.1, 5.9, 16.6 Hz 1 H), 2.39-2.48 (m, 3 H), 2.99 (dd, J = 7.1, 19.2 Hz, 1 H), 3.87 (d, J = 1.2 Hz, 1 H), 4.28 (t, J = 1.2 Hz, 1 H). ^{13}C NMR (75 MHz): δ = 21.1, 21.6, 27.5, 34.0, 36.8, 39.0, 72.0, 79.3, 79.9, 83.5, 119.5, 170.0. ESIMS (MeOH): 263.1 ($[M + Na]^+$, 100). HRESIMS (CH_2Cl_2): calcd. for $C_{12}H_{16}O_5Na$ m/z 263.0891, found: 263.0895.