Construction of Bridged Polycyclic Systems via Radical Cyclizations. Uncovering of a Novel Carbocyclization-Ring Expansion Sequence

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SUPPORTING INFORMATION

EXPERIMENTAL SECTION

General Procedures. All dry solvents were freshly distilled under argon from an appropriate drying agent before use. Bencene, Et_2O and THF were distilled from sodium/benzophenone ketyl. CH_2Cl_2 was distilled from CaH_2. All reactions were conducted in dry solvents under argon atmosphere unless otherwise stated. External bath temperatures were used to record all reaction temperatures. Thin-layer chromatography (TLC) was performed on silica gel plates and components were visualized by observation under UV light, or by treating the plates with a phosphomolybdic reagent followed by heating. Dryings were performed with anhydrous Na_2SO_4. Concentration refers to the removal of volatile solvents via distillation using a Buchi rotary evaporator at water aspirator pressure, followed by residual solvent removal at high vacuum (aprox. 0.5 mmHg). Vinyllithium (0.45 M in Et_2O/pentane) was freshly prepared from vinylbromide by treatment with *t*-BuLi (1.5 M in pentane). Allyllithium (0.35 M in THF) was freshly prepared from allyltriphenyltin and phenyllithium. The TBAF used was 1M in THF. 2,3-Dibromopropene (Aldrich, 80% techn.) was distilled from CaH_2.

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, at 250 MHz and 62.9 MHz, respectively, and in some cases at 300 or 500 MHz (75.4 or 125.7 for ^{13}C NMR) Carbon types were determined from DEPT ^{13}C NMR experiments. The following abbreviations are used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

(1*S**, 2*R**, 4*R**, 5*R**)- 2-Allyl-2-*t*-butyldimethylsilyloxy-1,7-dimethyl-8-oxabicyclo[3.2.1]octan-3-one (7)

Allyllithium (4.1 mL, 1.435 mmol) was added to a –78ºC cooled solution of **6** (370 mg, 1.312 mmol) in THF (12 mL). After 15 min, 2,3-dibromopropene (0.25 mL, 1.93 mmol) was added and the reaction was allowed to reach r.t. and stirred for 12 h. The resulting mixture was poured into brine, extracted with Et_2O, dried, filtered and concentrated. The crude residue was purified by flash cromatography on silica gel (3% EtOAc/hex) to afford 430 mg of **7** [74%, R_f 0.60 (6% EtOAc/ hex), colorless oil].

^1H-NMR δ (ppm): 5.72 (1H, s), 5.62-5.50 (2H, m), 5.05-4.98 (2H, m), 4.26 (1H, d, *J*= 7.2 Hz), 2.89-2.69 (2H, m), 2.62-2.48 (3H, m), 2.26-2.20 (1H, m), 2.02-1.93 (1H, m), 1.71-1.63 (1H, m), 1.25 (3H, s), 0.94 (3H, d, *J*= 7 Hz), 0.83 (9H, s), 0.25 (3H, s), 0.06 (3H, s).

^{13}C-NMR δ (ppm): 210.4 (C), 133.5 (CH), 130.6 (C), 120.2 (CH_2), 118.3 (CH_2), 88.3 (C), 88.0 (C), 74.6 (CH), 55.2 (CH), 41.7 (CH_2), 41.1 (CH_2), 40.2 (CH_2), 35.1 (CH), 26.1 (CH_3), 18.9 (C), 18.5 (CH_3), 14.9 (CH_3), -1.5 (CH_3), -2.9 (CH_3).

LRMS (*m/z*, I): 442 [M^+, 1], 387 [M^+-$C(CH_3)_3$, 62], 385 [M^+-$C(CH_3)_3$, 63], 315 (66), 313 (65), 251 (100), 195 (66), 115 (66).

HRMS: calcd. for $C_{21}H_{35}BrSiO_3$ 442.1538, found 442.1540.

(1*S**, 7*R**, 8*R**, 11*S**)-1-*t*-Butyldimethylsilyloxy-10,11-dimethyl-5-methylene-13-oxatricyclo[5.4.1.1^{8,11}]tridecan-12-one (9)

A solution of TBTH (0.11 mL, 0.423 mmol) and AIBN (10 mg, 20 % mol) in bencene (7 mL) was added via a syringe pump into a refluxing solution of **7** (125 mg, 0.282 mmol) in bencene (8 mL). The addition was completed in 8 h, after which the mixture was poured into brine and extracted with Et_2O. The organic extractes were dryed, filtered and concentrated to give a crude residue that was purified by flash cromatography on silica gel (1% EtOAc/hex) to afford 69 mg of **9** [68%, R_f 0.45 (6% EtOAc/hex), colorless oil].

^{1}H-NMR δ (ppm): 4.88 (1H, s), 4.74 (1H, s), 4.13 (1H, d, *J*= 7.4 Hz), 2.64-2.59 (2H, m), 2.47-2.16 (2H, m), 2.02-1.88 (2H, m), 1.75-1.60 (3H, m), 1.58-1.50 (1H, m), 1.49-1.33 (2H, m), 1.23 (3H, s), 0.91 (3H, d, *J*= 7.1 Hz), 0.83 (9H, s), 0.19 (3H, s), 0.14 (3H, s).

^{13}C-NMR δ (ppm): 211.8 (C), 146.2 (C), 115.0 (CH_2), 89.5 (C), 88.3 (C), 77.4 (CH), 58.8 (CH), 40.1 (CH_2), 39.7 (CH_2), 37.2 (CH_2), 35.5 (CH_2), 34.5 (CH), 26.0 (CH_3), 22.9 (CH_2), 18.8 (C), 18.6 (CH_3), 14.3 (CH_3), -1.8 (CH_3), -2.6 (CH_3).

LRMS (*m/z*, I): 364 [M^+, 8], 307 [M^+-$C(CH_3)_3$, 100], 235 (79), 225 (47), 211 (43), 197 (21), 167 (20), 136 (47), 97 (32).

HRMS calcd. for $C_{21}H_{36}O_3Si$ 364.2433, found 364.2437.

(1*S**, 2*R**, 4*R**, 5*R**)-2-*t*-Butyldimethylsilyloxy-2-ethenyl-1,7-dimethyl-8-oxabicyclo[3.2.1]octan-3-one (10)

Vinyllithium (1.56 mL, 0.70 mmol) was added to a –78ºC cooled solution of **6** (190 mg, 0.637 mmol) in THF (10 mL). After 15 min, 2,3-dibromopropene (0.115 mL, 0.89 mmol) was added, and the mixture reaction was allowed to reach r.t. and strirred overnight. It was poured into brine and extracted with Et_2O. Drying, filtering and concentration of the organic layers gave a crude residue that was flash cromatographed on silica gel (3% EtOAc/hex), to afford 228 mg of **10** as a colorless oil [79%, R_f 0.66 (10% EtOAc/hex)].

^{1}H-NMR δ (ppm): 6.08 (1H, dd, *J*= 12, 18 Hz), 5.56 (1H, s), 5.38 (1H, s), 5.17 (2H, m), 4.18 (1H, d, *J*= 7.3 Hz), 2.76-2.70 (1H, m), 2.66-2.45 (2H, m), 2.23-2.12 (1H, m), 1.95-1.84 (1H, m), 1.64-1.54 (1H, m), 1.08 (3H, s), 0.86 (3H, d, J= 7 Hz), 0.78 (9H, s), 0.16 (3H, s), 0.02 (3H, s).

^{13}C-NMR δ (ppm): 208.2 (C), 135.4 (CH), 130.4 (C), 120.2 (CH_2), 117.7 (CH_2), 89.2 (C), 88.5 (C), 75.0 (CH), 55.1 (CH), 43.0 (CH_2), 40.9 (CH_2), 34.8 (CH), 26.1 (CH_3), 19.2 (C), 18.5 (CH_3), 15.4 (CH_3), -2.0 (CH_3), -2.8 (CH_3).

LRMS (*m/z*, I): 428 [M^+, 1], 373 [M^+-$C(CH_3)_3$, 70], 371 [M^+-$C(CH_3)_3$, 71], 303 (60), 301 (61), 251 (100), 205 (28), 173 (70), 115 (50).

HRMS calcd. for $C_{20}H_{33}BrSiO_3$ 428.1382, found 428.1387.

(1*S**, 2*R**, 4*S**, 5*S**, 6*S**, 7*S**)-6-*t*-Butyldimethylsilyloxy-4,5-dimethyl-9-methylene-12-oxatricyclo[5.3.1.1^{2,5}]dodecan-11-one (11a)

A solution of TBTH (0.19 mL, 0.71 mmol), AIBN (16 mg, 20% mol) and **10** (205 mg, 0.478 mmol) in bencene (12 mL) was refluxed for 2 h. It was poured into brine and extracted with Et_2O, and the organic extracts dried, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (2% EtOAc/hex) to afford 135 mg of **11** as an inseparable mixture of isomers **11a**:**11b** (3:1) [81%, R_f 0.44 (10% EtOAc/hex), white solid].

^{1}H-NMR δ (ppm): 4.84 (1H, s), 4.76 (s) and 4.71 (s) (1H), 4.13 (1H, dd, *J*= 1.8, 7.2 Hz), 3.63 (11a ,s) and 3.57 (11b, d, J= 7.9 Hz) (1H), 2.72-2.53 (3H, m), 2.35-2.26 (1H, m), 1.96-1.50 (3H, m), 1.40-1.19 (2H, m), 1.11 (s) and 1.03 (s) (3H), 0.93-0.88 (3H, m), 0.87 (s) and 0.86 (s) (9H), 0.06-0.03 (6H, m).

^{13}C-NMR δ (ppm):

11a : 214.3 (C), 141.5 (C), 110.9 (CH_2), 86.0 (C), 82.0 (CH), 79.7 (CH), 60.1 (CH), 56.7 (CH), 42.6 (CH_2), 40.8 (CH_2), 39.9 (CH_2), 34.4 (CH), 25.8 (CH_3), 17.7 (CH_3), 17.5 (C), 13.5 (CH_3), -4.3 (CH_3), -4.9 (CH_3).

11b : 214.4 (C), 142.0 (C), 109.9 (CH_2), 88.3 (C), 79.5 (CH), 73.8 (CH), 57.7 (CH), 54.7 (CH), 41.7 (CH_2), 39.0 (CH), 38.7 (CH_2), 34.4 (CH_2), 25.6 (CH_3), 20.1 (CH_3), 18.1 (C), 15.5 (CH_3), -4.6 (CH_3), -5.1 (CH_3).

(1*S**, 2*R**, 4*S**, 5*S**, 7*R**)-4,5-dimethyl-9-methylene-12-oxatricyclo[5.3.1.1^{2,5}]dodecan-6,11-dione (12)

TBAF (0.6 mL, 1M in THF) was added to a solution of **11** (140 mg, 0.40 mmol) in THF (10 mL). After 1 h of being stirred, the reaction mixture was poured into brine and extracted with Et_2O. Drying, filtering and concentration gave a crude residue that was purified by flash cromatography on silica gel (20% EtOAc/hex) to afford 65 mg of a mixture of desilylated products [69%, R_f 0.42 (50 % EtOAc/hex), colorless oil].

This mixture was dissolved in CH_2Cl_2 (20 mL) and PDC (300 mg, 0.78 mmol) was added. After stirring for 3 h at r.t. the reaction was filtered through a pad of celite, extracted with CH_2Cl_2/brine, dried, filtered and concentrated. The crude residue was flash cromatographed on silica gel (15% EtOAc/hex) to afford 42 mg of **12** [64 %, R_f 0.64 (50 % EtOAc/hex), colorless oil].

^{1}H-NMR δ (ppm): 4.90 (1H, br s), 4.78 (1H, br s), 4.46 (1H, dd, *J*= 2.1, 7.3 Hz), 3.39 (1H, m), 2.98-2.68 (4H, m), 2.54 (1H, m), 2.28-2.14 (2H, m), 1.80-1.68 (1H, m), 1.16 (3H, s), 0.94 (3H, d, J= 6.4 Hz).

^{13}C-NMR δ (ppm): 211.7 (C), 204.8 (C), 140.3 (C), 111.9 (CH_2), 88.8 (C), 81.7 (CH), 64.1 (CH), 57.2 (CH), 41.3 (CH_2), 40.2 (CH_2), 39.4 (CH_2), 36.8 (CH), 17.8 (CH_3), 15.8 (CH_3).

LRMS (*m/z*, I): 234 [M^+, 1], 206 (11), 163 (3), 135 (24), 110 (16), 97 (100).

HRMS calcd. for $C_{14}H_{18}O_3$ 234.1256, found 234.1251.

6-(2-Bromoallyl)-2-hydroxy-2-vinyl-1-cyclohexanone (15b):

Vinyllithium (3.4 mL, 1.53 mmol) was added to a –78ºC cooled solution of **14** (300 mg, 1.327 mmol) in THF (14 mL) and stirred for 15 min. Then, 2,3-dibromopropene (0.25 mL, 1.934 mmol) was added and the reaction mixture was allowed to reach r.t. and stirred overnight. TBAF (3 mL, 1 M in THF) was added and the solution was stirred for 2 h. It was poured into brine and extracted with Et_2O, dried, filtered and concentrated. The crude residue thus obtained was purified by flash cromatography on silica gel (5-8% EtOAc/hex) to afford 240 mg of **15b** as an inseparable mixture of isomers [(*cis:trans*) = (0.3:0.7), 70%, R_f 0.48 (20 % EtOAc/hex), colorless oil].

^{1}H-NMR δ (ppm): 6.18-6.03 (1H, m), 5.52 (1H, s), 5.47-5.13 (3H, m), 3.33 (0.3H, cis), 3.11 (1H, br s), 2.94-2.72 (1.7H, m), 2.37-1.56 (6H, m), 1.21-1.14 (1H, m).

^{13}C-NMR δ (ppm):

cis 211.4 (C), 139.1 (CH), 131.7 (C), 118.6 (CH_2), 114.3 (CH_2), 78.3 (C), 44.2 (CH), 41.1 (CH_2), 40.3 (CH_2), 33.0 (CH_2), 19.9 (CH_2).

trans 210.9 (C), 136.8 (CH), 118.9 (CH_2), 117.1 (CH_2), 79.5 (C), 45.0 (CH), 41.6 (CH_2), 40.8 (CH_2), 33.4 (CH_2), 21.5 (CH_2).

(1*S**, 2*R**, 6*S**)-2-Hydroxy-8-methylenebicyclo[4.3.1]decan-10-one (16)

A solution of TBTH (0.24 mL, 0.9 mmol) and AIBN (22 mg, 20% mol) in bencene (6 mL) was syringe pump added onto a refluxing solution of **15** (180 mg, 0.694 mmol, (*cis*:*trans*)=(0.3:0.7) in bencene (15 mL). After completing the addition (approx. 6 h) the reaction mixture was poured into brine, and extracted with CH_3CN. The organic layers were extracted with hexane to remove most of the tin byproducts. Drying, filtering and concentration gave a crude residue that was purified by flajs crhomatography on silica gel (20-30% EtOAc/hex) to afford 19 mg of 16 as a colorless oil [51%, R_f 0.30 (40 % EtOAc/hex)].

^{1}H-NMR δ (ppm): 4.79 (1H, d, J= 1.5 Hz), 4.65 (1H, d, *J*= 1.5 Hz),4.18 (1H, br t, *J*= 5.2 Hz), 2.90-2.66 (3H, m), 2.42-2.16 (4H, m), 2.08-1.91 (3H, m), 1.79-1.62 (2H, m).

^{13}C-NMR δ (ppm): 214.8 (C), 114.4 (C), 111.1 (CH_2), 71.4 (CH), 54.7 (CH), 44.9 (CH_2), 39.1 (CH_2), 38.26 (CH), 38.23 (CH_2), 31.3 (CH_2), 19.2 (CH_2).

LRMS (*m/z*, I): 180 (15), 162 (35), 153 (25), 107 (62), 105 (45), 77 (100).

HRMS calcd. for $C_{11}H_{16}O_2$ 180.1150, found 180.1153.

The stereochemistry of this compound was tentatively assigned on the basis of the broad triplet (*J*=5.2 Hz) observed for the hydrogen in α to the hydroxyl group. The two more stable conformations for each of the epimeric products at that position were calculated using molecular mechanics (MM2) as implemented in the program Chem3D Pro. The observed coupling pattern can only be acomodated by conformations correponding to **16**, as any of the two more stable conformers corresponding to the epimer should origin a higher coupling constant.

(1*S, 6*S**) -8-methylenebicyclo[4.3.1]decan-2,10-dione (17)**

Compound **16** (18 mg, 0.101 mmol) was added to a suspension of PDC (100 mg, 0.266 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at r.t. for 1 h and filtered through a pad of celite. Extraction with CH_2Cl_2, drying, filtering and concentration gave a crude residue that was purified by flash cromatography on silica gel (15-20% EtOAc/hex), to afford 10 mg of **17** [56%, R_f 0.66 (40 % EtOAc/hex), colorless oil].

^{1}H-NMR δ (ppm):4.98 (1H, d, J= 1.7 Hz), 4.89 (1H, d, J= 1.7 Hz), 3.32 (1H, m), 3.09 (1H, dt, J= 2.3, 13.8 Hz), 2.87 (1H, m), 2.89-2.76 (1H, m), 2.70-2.34 (4H, m), 2.20-1.97 (3H, m), 1.81-1.73 (1H, m).

^{13}C-NMR δ (ppm): 213.4 (C), 207.0 (C), 141.5 (C), 113.8 (CH_2), 63.9 (CH), 49.0 (CH), 43.9 (CH_2), 39.3 (CH_2), 38.2 (CH_2), 35.5 (CH_2), 20.1 (CH_2).

LRMS (*m/z*, I): 178 [M^+, 1], 134 (79), 121 (54), 107 (95), 95 (66), 91 (60), 79 (80), 55 (100).

HRMS calcd. for $C_{11}H_{14}O_2$ 178.0993, found 178.0995.