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FORMATION OF 1-BENZOSUBERONES BY THREE-CARBON RING EXPANSION OF BENZOCYLOBUTENONES [1]

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Abstract: A new method for preparing 1-benzosuberone derivatives by free radical promoted three-carbon ring expansion of benzocyclobutenones is described.

In our effort towards continuous exploration of the Dowd-Beckwith ring expansion reaction,[4] we have developed a new method for making *cis*-fused seven- or eight-membered bicyclic ketones based on the free radical reaction of cyclobutanones (Scheme 1).[5] In this paper we like to report an application of this method in preparation of 1-benzosuberones[6] by three-carbon ring expansion of benzocyclobutenones.

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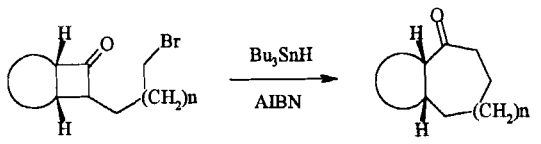
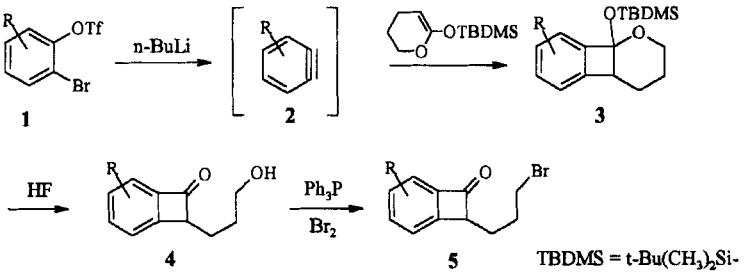


n = 1 or 2

Scheme 1

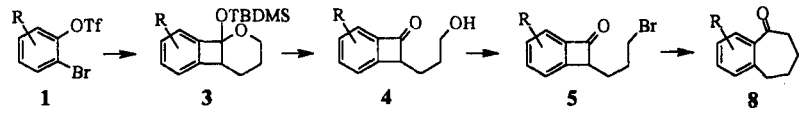
Suzuki's group recently reported a new approach to benzocyclobutenones involving thermal [2 + 2] cycloaddition of benzynes and alkenes (Scheme 2).[7] The arynes **2** (for the R substituents see Table 1) generated *in situ* by halogen-lithium exchange of the *ortho*-haloaryl triflates **1**, underwent cycloaddition with ketene silyl acetal. Hydrolysis of the acetals **3** yielded hydroxalkyl benzocyclobutenones **4**.



Scheme 2

We have taken advantage of Suzuki's method[7] to make radical precursors for ring expansion reaction. Bromoalkyl-substituted benzocyclobutenones **5** were readily prepared by reaction of **4** with Ph_3P/Br_2. With different substrates in hand, we carried out the free radical ring expansion reaction for 1-benzosuberones **8** by slow addition of Bu_3SnH and a catalytic amount of 2,2'-azobisisobutyronitrile (AIBN) to benzocyclobutenones **5** in benzene at 80 °C.[5b] A mechanism for this

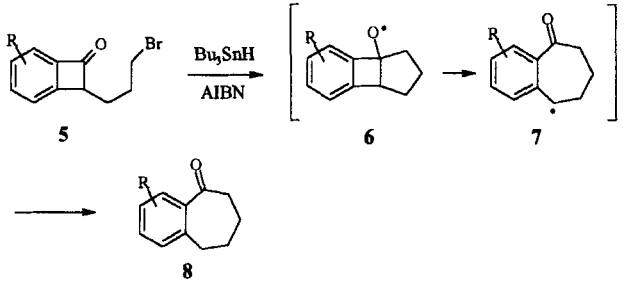
Table 1. Preparation of benzocyclobutenones and ring expansion for 1-benzosuberones



1	**3**	**4**	**5**	**8**
9	**10** (95%)	**11** (93%)	**12** (88%)	**13** (75%)
14	**15** (82%)	**16** (92%)	**17** (72%)	**18** (94%)
19	**20** (89%)	**21** (92%)	**22** (63%)	**23** (90%)
24	**25** (95%)	**26** (94%)	**27** (68%)	**28** (85%)

reaction is proposed (Scheme 3). Release of ring strain in the alkoxy radical **6** and formation of the resonance-stabilized ring-expanded radical **7** provides the driving force for the transformation. The new method leading to 1-benzosuberones is illustrated by the four examples shown in Table 1.

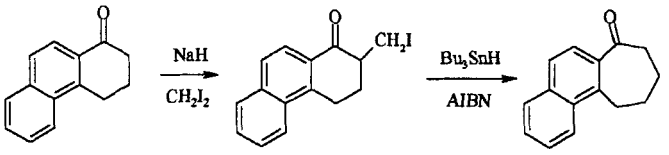
In the step of preparation of benzocyclobutenone, an asymmetric benzyne generated from **19** led to formation **20** as a 1:1 mixture of regioisomers which were non-separable by conventional flash column chromatography, while the



Scheme 3

asymmetric benzyne generated from **24** led to formation of **25** as a single product. Free radical-promoted ring expansion of bromoalkyl benzocyclobutenones **12**, **17**, **22**, and **27** produced good to excellent yield of 1-benzosuberones **13**, **18**, **23**, and **28**, respectively. None of the direct reduction product was observed.

The spectroscopic properties of the ring expansion product **13** are identical with those of an authentic sample of 1-benzosuberone from Aldrich. The structure of **28**, and thereby that of **25**, was established by synthesis of an authentic sample of **28** (Scheme 4). Thus, iodomethylation of 1,2,3,4-tetrahydrophenanthren-1-one[8] followed by free radical ring expansion[9] yielded a compound with spectroscopic properties identical to those of **28**.



Scheme 4

Experimental

All reactions were performed under a nitrogen atmosphere. Benzene for

tinhydride reaction was distilled from blue or purple solution of sodium benzophenone ketyl under nitrogen. Tributyltin hydride (Bu_3SnH) was purchased from Aldrich and used without further purification. 2,2'-Azobisisobutyronitrile (AIBN) was purchased from Alfa. Bromoaryl triflates **9**, **14**, **19**, and **24** were prepared from appropriate commercially available *o*-bromophenols or *o*-bromonaphthol by reacting with trifluoroacetic anhydride (Tf_2O) in the presence of pyridine as base.

NMR spectra were obtained on Bruker AC-300 (300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR) spectrometer. IR spectra were obtained on an IBM IR/32 FTIR spectrometer. MS spectra were obtained using a Hewlett-Packard (5890 series II) gas chromatography equipped with a Hewlett-Packard (5970 series) mass spectrometer. HRMS were obtained on a Varian MAT CH-5DF or a VG-70G spectrometers.

General procedure for making acetals 3 by [2 + 2] cycloaddition of benzynes and ketene silyl acetal:[7a] To a solution of 684 mg triflate **14** (2.2 mmol) and 620 mg of ketene silyl acetal (2.9 mmol) in 4 mL of THF was added 1.95 mL of *n*-BuLi (1.6 M in hexane, 3.1 mmol) at -78 °C. After 40 min, the reaction was quenched with pH 7 phosphate buffer. Ether extraction of the reaction mixture followed by flash column chromatography (40:1 hexanes-ether) gave 586 mg (82%) of **15**. ^1H NMR ($CDCl_3$) δ 0.13 (s, 3H), 0.17 (s, 3H), 0.88 (s, 9H), 1.57 (m, 2H), 1.79, (m, 1H), 2.08 (m, 1H), 3.48 (br t, 1H), 3.76 (m, 1H), 3.89 (m, 1H), 7.00 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 17.9 (s), 20.2 (t), 22.7, 23.7 (t), 25.5 (q), 52.2 (d), 62.4 (t), 98.4 (s), 110.4 (d), 122.5 (d), 140.4 (d), 149.5 (d), 151.3 (dd),

152.6 (dd). MS: m/e (rel. intensity) 326 (1, M^+), 241 (11), 167 (16), 119 (16), 73 (100). HRMS calcd for $C_{17}H_{24}F_2O_2Si$: 326.1515. Found: 326.1512.

Data for **10**: 95% yield. ^1H NMR ($CDCl_3$) δ 0.14 (s, 3H), 0.21 (s, 3H), 0.91 (s, 9H), 1.62 (m, 2H), 1.85, (m, 1H), 2.13 (m, 1H), 3.56 (m, 1H), 3.79 (m, 1H), 3.96 (m, 1H), 7.15-7.35 (4H). IR (neat) 1215 (m), 1428 (m) cm^{-1}. MS: m/e (rel. intensity) 290 (19, M^+), 261 (11), 233 (100), 205 (80), 131 (42), 73 (34). HRMS calcd for $C_{17}H_{26}O_2Si$: 290.1704. Found: 290.1703.

Data for **20** (mixture of 2 regioisomers): 89% yield. ^1H NMR ($CDCl_3$) δ 0.11(s, 3H), 0.12 (s, 3H), 0.18 (s, 3H), 0.19 (s, 3H), 0.89 (s, 9H), 0.90 (s, 9H), 1.58 (m, 4H), 1.80 (m, 2 H), 2.08 (m, 2H), 2.35 (s, $2CH_3$), 3.48 (br t, 2H), 3.78 (m, 2H), 3.93 (m, 2H), 6.95-7.13 (6H). ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 17.9 (s), 20.5, 22.2, 22.7, 23.7 (t), 23.9 (t), 25.8 (q), 31.7 (t), 52.0 (d), 52.3 (d), 62.1 (t), 62.3 (t), 99.0 (s), 99.2 (s), 120.1 (d), 120.7 (d), 122.3 (d), 123.2 (d), 128.2 (d), 130.3 (d), 137.1 (s), 139,3 (s), 141.7 (s), 145.0 (s), 145.7 (s), 148.8 (s). MS: m/e (rel. intensity) 304 (4, M^+), 247 (21), 219 (29), 145 (54), 115 (38), 73 (100). HRMS calcd for $C_{18}H_{28}O_2Si$: 304.1860. Found: 304.1860.

Data for **25**: 95% yield. ^1H NMR ($CDCl_3$) δ 0.02 (s, 3H), 0.05 (s, 3H), 0.93 (s, 9H), 1.61 (m, 2H), 1.93, (m, 1H), 2.18 (m, 1H), 3.65 (t, 1H), 3.74 (m, 1H), 4.04 (m, 1H), 7.33 (d, J=8.2 Hz, 1H), 74.8-7.53 (2H), 7.78-7.90 (3H). ^{13}C NMR ($CDCl_3$) δ 18.1 (s), 20.1 (t), 23.8 (t), 25.8 (q), 53.4 (d), 61.9 (t), 99.5 (s), 120.8 (d), 123.3 (d), 125.2 (d), 126.9 (d), 127.3 (s), 129.4 (d), 130.8 (d), 133.5 (s), 142.8 (s), 143.8 (s). IR (neat) 1242 (m), 1468 (w) cm^{-1}. MS: m/e (rel. intensity)

340 (2, M^+), 283 (7), 255 (7), 207 (14), 181 (15), 152 (15), 73 (100). HRMS calcd for $C_{21}H_{28}O_2Si$: 340.1860. Found: 340.1867.

General procedure for making alcohols 4 by hydrolysis of acetals 3: To a solution of 327 mg of acetal **15** (1.0 mmol) in 3.5 mL of CH_3CN was added 0.2 mL of HF (48%) at 0 °C. After 30 min, the reaction was quenched with $NaHCO_3$ (aq). Ether extraction of the reaction mixture followed by flash column chromatography (2:1 hexanes-ether, then 100% ether) gave 195 mg (92%) of **16**. ^1H NMR ($CDCl_3$) δ 1.72 (m, 2H), 1.92 (m, 2H), 3.70 (t, *J*=6.2 Hz, 2H), 4.25 (t, *J*=7.1 Hz, 1H), 7.15-7.40 (2H). ^{13}C NMR ($CDCl_3$) δ 26.7 (t), 30.0 (t), 62.0 (t), 64.2 (d), 110.2 (d), 112.8 (d), 141.3 (s), 152.4 (dd), 152.9 (d), 155.8 (dd), 189.8 (s). IR (neat) 1767 (s, C=O), 3395 (br, OH) cm^{-1}. MS: m/e (rel. intensity) 194 (4, M^+-H_2O), 181 (8), 167 (100), 151 (90), 133 (88). HRMS calcd for $C_{11}H_{10}F_2O_2$: 212.0649. Found: 212.0651.

Data for **11**: 93% yield. ^1H NMR ($CDCl_3$) δ 1.78 (m, 2H), 1.96 (m, 2H), 3.70 (t, *J*=6.3 Hz, 2H), 4.27 (t, *J*=7.1 Hz, 1H), 7.32-7.60 (4H). ^{13}C NMR ($CDCl_3$) δ 27.1 (t), 30.8 (t), 62.6 (t), 64.9 (d), 121.2 (d), 123.4 (d), 129.5 (d), 135.5 (d), 146.7 (s), 156.4 (s), 193.0 (s). IR (neat) 1763 (s, C=O), 3391 (br, OH) cm^{-1}. MS: m/e (rel. intensity) 176 (2, M^+), 146 (18), 131 (100), 115 (49), 103 (53). HRMS calcd for $C_{11}H_{12}O_2$:176.0838. Found: 176.0844.

Data for **21** (mixture of 2 regioisomers): 92% yield. ^1H NMR ($CDCl_3$) δ 1.78 (m, $2CH_2$), 1.92 (m, $2CH_2$), 2.39 (s, 3H), 2.44 (s, 3H), 3.69 (t, *J*=6.2 Hz, $2CH_2$), 4.20 (t, *J*=6.9 Hz, 2CH), 7.15-7.45 (6H). ^{13}C NMR ($CDCl_3$) δ 21.5 (q), 22.6 (q), 26.7

(t), 26.8 (t), 30.3 (t), 62.0 (t), 63.5 (t), 63.6 (t), 120.5 (d), 120.6 (d), 122.8 (d), 123.6 (d), 130.3 (d), 136.4 (d), 139.1 (s), 143.4 (s), 146.4 (s), 146.7 (s), 153.6 (s), 156.5 (s), 192.4 (s), 193.0 (s). IR (neat) 1752 (s, C=O), 3399 (br, OH) cm^{-1}. MS: m/e (rel. intensity) 172 (1, M^+-H_2O), 160 (10), 145 (100), 115 (57), 91 (48). HRMS calcd for $C_{12}H_{14}O_2$: 190.0994. Found: 190.0992.

Data for **26**: 94% yield. ^1H NMR ($CDCl_3$) δ 1.79 (m, 2H), 2.00 (m, 2H), 3.72 (t, *J*=6.2 Hz, 2H), 4.37 (t, *J*=6.9 Hz, 1H), 7.45-7.70 (3H), 7.91 (d, *J*=8.2 Hz, 1H), 8.03 (d, *J*=8.2 Hz, 1H), 8,09 (d, *J*=8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 26.9 (t), 30.6 (t), 62.4 (t), 63.8 (d), 120.6 (d), 124.1 (d), 125.9 (s), 126.7 (d), 129.2 (2d), 133.6 (s), 137.0 (d), 141.5 (s), 158.7 (s), 191.0 (s). IR (neat) 1742 (s, C=O), 3420 (br, OH) cm^{-1}. MS: m/e (rel. intensity) 226 (5, M^+), 181 (100), 165 (25), 152 (45). HRMS calcd for $C_{15}H_{14}O_2$: 226.0994. Found: 226.0998.

General procedure for making bromides 5: To a solution of 208 mg of Ph_3P (0.8 mmol) in 1.5 mL of CH_3CN was add 126 mg of Br_2 (0.8 mmol) at 0 °C. The mixture was stirred at room temp. for 5 min, then 150 mg of alcohol **16** (0.7 mmol) was added over 10 min at room temp. After 2 h, the reaction mixture was concentrated and extracted with ether to give 138 mg (72%) of bromide **17**. ^1H NMR ($CDCl_3$) δ 2.01 (m, 4H), 3.44 (m, 2H), 4.23 (br, 1H), 7.16-7.42 (2H). ^{13}C NMR ($CDCl_3$) δ 28.9 (t), 30.1 (t), 32.9 (t), 63.6 (d), 110.4 (d), 112.8 (d), 141.6 (s), 152.3 (d), 152.4 (dd), 156.0 (dd), 188.6 (s). IR (neat) 1765 (s, C=O) cm^{-1}. MS: m/e (rel. intensity) 195 (1, M^+-Br), 167 (100), 151 (7), 139 (21), 119 (29). HRMS calcd for $C_{11}H_9F_2O$ (M^+-Br): 195.0622. Found: 195.0624.

Data for **12:** 88% yield. ^{1}H NMR ($CDCl_3$) δ 2.03 (m, 4H), 3.45 (m, 2H), 4.25 (br t, 1H), 7.40-7.70 (4H). IR (neat) 1765 (s, C=O) cm^{-1}. MS: m/e (rel. intensity) 159 (<1, M^+-Br), 131 (100), 115 (11), 103 (33). HRMS calcd for $C_{11}H_{11}O$ (M^+-Br): 159.0810. Found: 159.0818.

Data for **22** (mixture of 2 regioisomers): 63% yield. ^{1}H NMR ($CDCl_3$) δ 1.70-2.10 (m, $4CH_2$), 2.30 (s, 3H), 2.36 (s, 3H), 3.35 (br t, $2CH_2$), 4.09 (br, 2CH), 7.00-7.60 (6H). IR (neat) 1755 (s, C=O) cm^{-1}. MS: m/e (rel. intensity) 145 (M^+-BrCO, 100), 115 (56), 91 (24). HRMS calcd for $C_{12}H_{13}O$ (M^+-Br): 173.0967. Found: 173.0970.

Data for **27:** 68% yield. ^{1}H NMR ($CDCl_3$) δ 2.07 (br, 4H), 3.46 (br, 2H), 4.35 (br, 1H), 7.48-7.70 (3H), 7.91 (d, *J*=8.2 Hz, 1H), 8.03 (d, *J*=8.2 Hz, 1H), 8.09 (d, *J*=8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 29.1 (t), 30.6 (t), 33.4 (t), 63.2 (d), 120.5 (d), 124.2 (d), 125.9 (s), 126.8 (d), 129.3 (2d), 133.7 (s), 137.1 (d), 141.8 (s), 158.1 (s), 189.9 (s). IR (neat) 1752 (s, C=O) cm^{-1}. MS: m/e (rel. intensity) 181 (100, M^+-BrCO), 165 (25), 152 (90). HRMS calcd for $C_{15}H_{13}O$ (M^+-Br): 209.0967. Found: 209.0971.

General procedure for free radical ring expansion: A solution of 130 μL of Bu_3SnH (0.48 mmol) and 3 mg of AIBN (0.02 mmol) in 3 mL of benzene was added to a refluxing solution of 88 mg of **17** (0.32 mmol) in 5 mL of benzene over a period of 4 h. The reaction was refluxed for additional 1 h and then cooled to room temperature. After DBU workup,[10] flash column chromatography (40:1 hexanes-ether) of the crude product afforded 59 mg (94%) of ring expansion

product **18**. ^{1}H NMR ($CDCl_3$) δ 1.74-1.94 (m, 4H), 2.72 (t, *J*=5.9 Hz, 2H), 2.89 (t, *J*=6.0 Hz, 2H), 7.01 (dd, *J*=10.6, 7.3 Hz, 1H), 7.58 (dd, *J*= 10.9, 8.3 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 20.4 (t), 24.9 (t), 31.9 (t), 40.5 (t), 118.0 (d), 118.6 (d), 128.4 (d), 137.0 (dd), 149.0 (dd), 152.3 (dd), 203.0(s). IR (neat) 1682 (s, C=O) cm^{-1}. MS: m/e (rel. intensity) 196 (62, M^+), 167 (64), 140 (100), 127 (86). HRMS calcd for $C_{11}H_{10}F_2O$:196.0700. Found:196.0700.

Data for **13:** 75% yield. ^{1}H NMR, IR, MS of **13** are identical to those of an authentic sample purchased from Aldrich.

Data for **23** (mixture of regioisomers): 90% yield. ^{1}H NMR ($CDCl_3$) δ 1.68-1.95 (m, 4CH_2), 2.35 (s, CH_3), 2.36 (s, CH_3), 2.72 (t, *J*=6.0 Hz, 2CH_2), 2.89 (t, *J*=6.0 Hz, 2CH_2), 6.95-7.70 (6H). IR (neat) 1673 (s, C=O) cm^{-1}. MS: m/e (rel. intensity) 174 (92, M^+), 159 (29), 145 (79), 131 (77), 118 (100). HRMS calcd for $C_{12}H_{14}O$: 174.1042. Found: 174.1048.

Data for **28:** 85% yield. ^{1}H NMR ($CDCl_3$) δ 1.77-2.00 (m, 4H), 2.76 (t, *J*=6.0 Hz, 2H), 2.97 (t, *J*=6.0 Hz, 1H), 7.40-8.15 (6H). IR (neat) 1678 (s, C=O) cm^{-1}. MS: m/e (rel. intensity) 210 (82, M^+), 181 (79), 165 (20), 154 (100), 141 (99). HRMS calcd for $C_{15}H_{14}O$: 210.1045. Found: 210.1050. See also ref. 6 for characterization of **28**.

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References and Notes

1. In memory of Professor Paul Dowd.

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